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Metabolic syndrome and insulin resistance comorbidity in systemic lupus erythematosus:

Effect on carotid intima-media thickness

Abstract: *Objective:* The aim of the present study was to assess the effect of metabolic syndrome (MetS) and insulin resistance comorbidity on the carotid intima-media thickness (IMT) in SLE patients and their relation to clinical manifestations, disease activity and damage. *Methods:* The study included 92 SLE patients (mean age 30.18±8.27 years) and 30 matched control. Disease activity and damage were assessed by the SLEDAI and SLICC Indeces respectively. The Health assessment questionnaire II (HAQII) and Quality of life (QoL) index were assessed in the patients. Levels of insulin, glucose, creatinine and lipid profile were measured in patients and control. Insulin sensitivity was estimated using the homeostatic model assessment index (HOMA-B) for beta cell function and (HOMA-IR) for peripheral tissue insulin resistance. The carotid IMT was measured by ultrasonography. *Results:* The SLE patients had high HOMA-IR and HOMA-B. The IMT was significantly increased (0.82±0.29 mm) compared to the control (0.45±0.2 mm).The HOMA-IR, SLEDAI, SLICC, HAQII and IMT were significantly higher and the QoL lower in those with MetS (n =34) compared to those without (n=58) while the HOMAB was comparable. There was a significant correlation between the IMT and the SLEDAI, SLICC and WHR. *Conclusion:* Insulin sensitivity and IMT are altered in SLE patients especially those with MetS co-morbidity with an associated increase in disease activity and damage. Effective management of MetS would aid in controlling SLE activity, damage and future development of cardiovascular events especially in the absence of symptoms of cardiovascular disease.

Keywords: SLE; metabolic syndrome; HOMA-IR ;HOMA-B; IMT

Introduction

Although the prognosis for patients with systemic lupus erythematosus (SLE) improved after the advent of immunosuppressive treatment [1], arterial vascular disorders have become increasingly important causes of morbidity and mortality [2]. Features of accelerated atherosclerosis may appear early in the course of the disease. The pathogenesis of the vascular complications in SLE has not been fully elucidated [3]. The metabolic syndrome (MetS), a concurrence of disturbed glucose and insulin metabolism, overweight, dyslipidemia and hypertension, is closely associated with the subsequent development of type 2 diabetes mellitus and cardiovascular disease (CVD) [4]. Moreover, insulin resistance (IR) has been confirmed as an independent risk factor for CVD [5] and roughly doubled the risk of coronary heart disease (CHD), irrespective of the presence of type 2 diabetes mellitus [6].

It has been found that lupus patients had significantly more common diabetes mellitus and glucose intolerance than in the general population [7-9] and MetS is highly prevalent [10]. Considerable evidence suggests that hyperglycaemia is associated with excessive oxidation [11] and with mild but chronic inflammation [12]. Several inflammatory and immunologic factors significantly contribute to the accelerated or premature development of atherosclerosis observed in patients with systemic autoimmune diseases [13] including SLE [14,15] with an increased incidence of CVD [16].
Classic risk factors, hypertension and diabetes mellitus, are more prevalent in SLE and persistent hypercholesterolemia independently predicts patients who will develop CHD [17]. In addition, IR is more pronounced in SLE [18] and 28% have MetS [19]. A deranged lipid metabolism and use of immune-suppressive medications account partially for the accelerated process of atherosclerosis in SLE [20].

The aim of the present study was to assess the effect of metabolic syndrome and insulin resistance comorbidity on the carotid intima-media thickness (IMT) in asymptomatic SLE patients and their relation to clinical manifestations, disease activity and damage.

Patients and Methods

Ninety-two SLE patients with a mean age of 30.18 ±8.27 years, fulfilling the updated ACR revised criteria for the classification of SLE [21], were consecutively recruited from the rheumatology and internal medicine departments and out patient clinics of Cairo University Hospitals during the period from May 2011 till January 2012. Thirty age and sex matched healthy volunteers served as controls with a mean age of 28 ±5.37 years. The study was approved by the local university ethical committee and the study performed in accordance with the ethical standards of the 1964 Helsinki declaration. All patients gave their informed consent prior to their inclusion in the study.

Tab 1: Demographic feature, laboratory investigations, disease indeces of SLE patients with and without metabolic syndrome and control

Features (mean±SD)	With MetS (n=34)	Without MetS (n =58)	p-value	Control (n=30)
Age (years)	31.26±9.14	29.55±7.73	0.36	28±5.37
Male:Female	2:32	6:52		3:27
Disease duration (years)	6.28±2.6	5.57±3.41	0.26	-
Corticosteroid dose (mg/day)	15.29±12.67	13.1±11.54	0.41	-
Laboratory investigations				
ESR (mmHg/1st hour)	53.03±22.41	46.57±22.07	0.18	9.57±2.57
Hb (g/dl)	10.45±1.65	10.73±1.6	0.43	16.09±18.71
WBC count ($x10^3/mm^3$)	7.54±6.08	7.52±5.02	0.985	8.67±1.25
Platelets($x10^3/mm^3$)	368.5±93.15	331.71±96.91	0.076	330.33±52.16
Creatinine (mg/dl)	0.83±0.34	0.73±0.3	0.195	0.63±0.12
Urine protein (g/24 hr)	0.61±0.4	0.46±0.34	0.07	0.06±0.013
C3 (mg/dl)	0.83±0.4	0.94±0.43	0.25	-
C4 (mg/dl)	0.14±0.11	0.19±0.16	0.1	-
Disease indeces				
HAQII	1.5±0.44*	1.25±0.53	0.017	-
QoL	6.35±1.54*	7.41±1.26	0.001	-
SLEDAI	9.88±5.39*	7.29±4.05	0.022	-
SLICC/DI	5.03±2.44*	3.78±2.05	0.015	-

ESR: Eryhtrocyte sedimentation rate, Hb: hemoglobin, WBC: White blood cell, C3, C4: Complement, HAQ: Health assessment Questionnaire, QoL: Quality of life, SLEDAI: Systemic Lupus Erythematosus Disease Activity Index, SLICC/DI: Systemic Lupus International Collaborating Clinics/Damage Index.

* = significantly different from SLE patients without metabolic syndrome at $p < 0.05$

Tab 2: Clinical manifestations of SLE patients with and without MetS

Manifestation No. (%)	With MetS (n=34)	Without MetS (n =58)
Mucocutaneous	24 (70.59)	39 (67.24)
Arthritis	19 (55.88)	27 (46.55)
Nephritis	17 (50)	28 (48.28)
Hematological	26 (76.47)	43 (74.14)
Neuropsychiatric	22 (64.71)	36 (62.07)
Gastrointestinal	5 (14.71)	7 (12.07)
Cardiovascular	11 (32.35)	8 (13.79)
Pulmonary	8 (23.53)	19 (32.76)
Serositis	12 (35.29)	24 (41.38)

Study population

Full history taking, thorough clinical examination and laboratory investigations were performed for all the patients and their current drug therapy was also reported. Standard CHD risk factors as well as anthropomorphic measurements including body mass index (BMI) and waist: hip ratio (WHR) was clinically assessed. Blood pressure was recorded as the mean of two measurements obtained 5 min apart after participants had rested in a supine position for 10 min. Disease activity and damage were assessed using the SLEDAI [22] and SLICC/ACR DI [23] respectively. The general well-being was assessed using the quality of life (QoL) index [24] and the functional capacity using the Health Assessment Questionnaire II (HAQ II) [25].

The Adult Treatment Panel (ATP III) criteria [26] were used to define the presence of the MetS in the patients with SLE. The metabolic syndrome was present if patients had 3 or more of the following: waist circumference > 88 cm (for females); serum triglycerides ≥ 150 mg/dl; HDL < 50 mg/dl; elevated blood pressure of ≥ 130 mm Hg systolic, ≥ 85 mm Hg diastolic, or on antihypertensive therapy; fasting blood glucose (FBG) ≥ 110 mg/dl. An informed consent was obtained from all patients and controls. Blood specimens were collected from patients and control after an overnight fast for the measurement of levels of insulin, glucose, creatinine and lipid profile (total cholesterol, triglycerides, HDL-c, LDL-c).

Analytical methods

The separated serum was divided into aliquots; part was used for determination of FBG, triglyceride, total cholesterol, high and low density lipoprotein cholesterol (HDL-c and LDL-c respectively) using commercially available kits. The other part was kept frozen at -80° C for further measurements. Serum fasting insulin was assessed by the ELISA kit provided by BioSource, Nivelles, Belgium. Insulin sensitivity was estimated using the homeostatic model assessment (HOMA) index which is an arithmetic way of deriving indices of pancreatic endocrine function (beta cell function, HOMA-B) and peripheral tissue insulin resistance (HOMA-IR) from fasting plasma samples. HOMA-IR and HOMA-B are derived using the formulae: HOMA-IR = [insulin (mU/l) × glucose (mmol/l) / 22.5]. HOMA-B = [20 × insulin (mU/l)] / [glucose (mmol/l) – 3.5)]. HOMA-IR exceeding 2.0 was considered to indicate insulin resistance.

Measurement of intima-media thickness

In order to estimate early-stage atherosclerosis ultrasonographic scanning of the carotid artery was performed using an echographic system (ATL HDI 5000, USA) with an electric linear transducer (mid- frequency 7.5 MHz). The detection limit of this echosystem using 7.5 MHz was 0.1 mm. Scanning of the extracranial common carotid artery, the carotid bulb, and the internal carotid artery (ICA) in the neck was performed bilaterally from two different longitudinal (i.e.anterolateral and posterolateral) and cross-sectional scanning. Characteristic patterns showed two parallel echogenic lines separated by a hypoecho-genic space.

Tab 3: Metabolic features and intima media thickness of SLE patients with and without metabolic syndrome and control

Metabolic Features (mean±SD)	With MetS (n=34)	Without MetS (n =58)	p-value	Control (n=30)
Waist circumference (cm)	92.26±8.18*	81.55±9.9	<0.001	84.33±9.49
Waist Hip Ratio (WHR)	1.01±0.08*	0.88±0.16	<0.001	0.93±0.16
Body mass index (kg/m^2)	26.79±4.12	25.4±3.09	0.09	24.74±2.29
Systolic BP (mmHg)	137.35±16.2*	121.72±15.23	<0.001	112±9.97
Diastolic BP (mmHg)	89.26±9.7*	80.17±11.01	<0.001	72±8.05
Fasting blood glucose (mg/dl)	104.62±13.43*	94.22±10.7	<0.001	95.73±5.85
Insulin (µIU/ml)	10.74±3.59	10.5±3.25	0.75	7.81±0.93
HOMA-IR	2.94±0.96*	2.41±0.7	0.007	1.86±0.28
HOMA-B	145.92±82.26	139.35±68.74	0.7	83.97±6.62
Cholesterol (mg/dl)	216.47±42.09*	188.57±48.57	0.005	113.43±52.4
Triglycerides (mg/dl)	189.85±41.16*	135.22±39.17	<0.001	72.13±30.21
HDL-c (mg/dl)	56.74±24.93	66.31±23.1	0.07	70.63±12.47
LDL-c (mg/dl)	165.47±47.64*	135.36±40.9	0.003	68.07±33.85
Intima-media thickness (mm)	0.91±0.33*	0.77±0.26	0.046	0.45±0.197

HOMA: homeostatic model assessment; B: beta cell function, IR: insulin resistance, HDL: high density lipoprotein, LDL: low density lipoprotein * = significantly different from SLE patients without metabolic syndrome at $p < 0.05$

Tab 4: Correlation of the HOMA-IR, HOMA-B and IMT with the studied parameters in the SLE patients

Variables	HOMA-IR		HOMA-B		IMT	
	r	p	r	p	r	p
Waist circumference (cm)	0.08	(0.45)	-0.06	(0.55)	0.21	**(0.047)**
Waist Hip Ratio (WHR)	0.04	(0.71)	-0.006	(0.95)	0.21	**(0.042)**
Body mass index (kg/m^2)	0.09	(0.41)	0.23	**(0.03)**	-0.12	(0.27)
Fasting blood glucose (mg/dl)	0.05	(0.63)	-0.68	**(<0.001**	0.13	(0.22)
Insulin (µIU/ml)	0.89	**(< 0.001)**	0.72	**(< 0.00**	-0.03	(0.75)
Cholesterol (mg/dl)	0.09	(0.4)	0.06	(0.57)	-0.02	(0.83)
Triglycerides (mg/dl)	0.08	(0.44)	-0.07	(0.49)	0.09	(0.38)
HDL-c (mg/dl)	-0.17	(0.12)	-0.07	(0.52)	0.01	(0.91)
LDL-c (mg/dl)	0.13	(0.23)	0.24	**(0.03)**	-0.04	(0.7)
HAQII	0.08	(0.42)	0.03	(0.79)	0.09	(0.41)
QoL	-0.13	(0.2)	0.06	(0.6)	0.01	(0.91)
SLEDAI	-0.03	(0.79)	-0.1	(0.36)	0.35	**(0.001)**
SLICC/DI	0.002	(0.98)	-0.05	(0.61)	0.34	**(0.001)**
Intima-media thickness (mm)	0.005	(0.96)	-0.08	(0.43)	-	-

HOMA: homeostatic model assessment; B: beta cell function, IR: insulin resistance, HDL: high density lipoprotein, LDL: low density lipoprotein, HAQ: Health assessment Questionnaire, QoL: Quality of life, SLEDAI: Systemic Lupus Erythematosus Disease Activity Index, SLICC/DI: Systemic Lupus International Collaborating Clinics/Damage Index. Bold numbers are considered significant at $p < 0.05$

The IMT was defined as the distance from the leading edge of the first echogenic line to the leading edge of the second line. The first line represented luminal-intimal transition and the second one medial-adventitial transition. The site of the greatest thickness including a plaque lesion was sought along the arterial walls. Three determinations of IMT were conducted at the site of thickest point and two adjacent points (located 1cm upstream and1cm downstream from the thickest point). These three determinations were averaged (mean IMT).

Statistical analysis

Statistical Package for Social Science (SPSS) program version 15 was used for analysis of data. Data was presented as mean ± SD. Mann-Whitney test was used for analysis of 2 quantitative data. Spearman's correlation was used for detection of relation between 2 variables. Multiple regression analysis was performed for dependant variables to detect the risk among many independent variables. p-value was considered significant if < 0.05.

Results

The study included 92 SLE patients with a mean age of 30.18±8.27 years [median 27 (range 18-51 years)] and a mean disease duration of 5.83±3.14 years [median 5 (range 0.5-15 years)]. The patients were 8 males and 84 females. 30 age and sex matched control were also included. At the time of the study, corticosteroids were received by 84 SLE patients (13.91±11.95 mg/day) for duration of 3.6±3.35 years and hydroxychloroquine received by 43. None of the patients was known to have any symptoms suggestive of a CVD. The demographic, laboratory, disease activity, clinical and metabolic features in SLE patients and control are shown in table 1,2 and 3. The clinical manifestations or organ involvement of the patients tended to be increased in those with MetS but showed no significant difference from those without. The number of disease flares requiring therapeutic intensification tended to be higher in those with Mets with a slightly higher mean daily dose of corticosteroids received. The IMT of a patient and control are presented in figure 1. Plaque was present in 10 patients, 6 with MetS and 4 without.

The ANA was positive in 89 and the anti-dsDNA in 55 (59.8%) of the SLE patients. The anti-ds-DNA was positive in 24/34 (70.6%) of those with MetS and 31/58 (53.4%) of those without. Only the C3 level was significantly consumed in those with a positive anti-ds DNA (0.82±0.41 g/l) compared to those with a negative test (1.01±0.4 g/l) (p 0.034). There were no significant differences in the studied parameters according to the gender of the patients. The WC, WHR, blood pressure, FBS, insulin, HOMA-IR, HOMA-B, 24 hr urinary protein, ESR, lipid profile and IMT were significantly different in the SLE patients with or without MetS compared to the control ($p < 0.001$).

In the SLE patients, correlation of the HOMA-IR, HOMA-B and IMT with the studied parameters are shown in table 4.

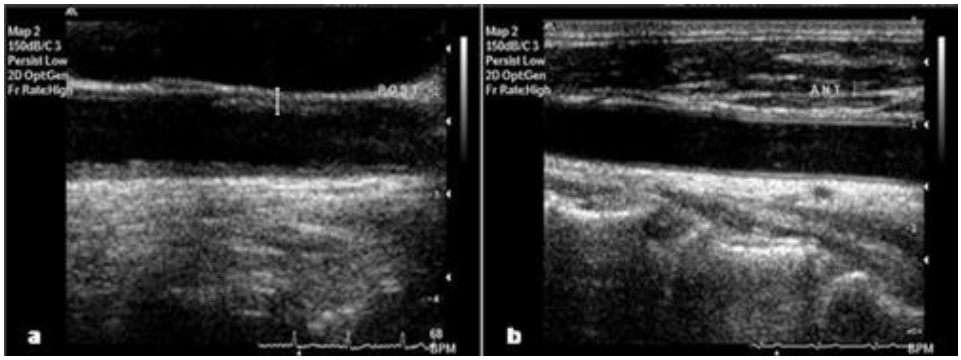

Figure legend: Figure 1: Increased (a) and normal (b) intima-media thickness (IMT) of the common carotid artery (CCA) in SLE patient and control respectively by Doppler ultrasonography. The thickness is denoted by the white line from the cursor.

Moreover, in those with MetS, there were significant correlations between the IMT and SLEDAI (r 0.45, p 0.008); SLICC and WHR (r 0.39, p 0.024); HOMA-IR with C3 (r 0.34, p 0.048) and C4 (r 0.42, p 0.013). In those without MetS the IMT significantly correlated with the SLICC (r 0.37, p 0.004) and WHR (r 0.27, p 0.04). In the SLE patients, according to the multiple regression analysis, the risk of increased IMT was determined by the SLICC (p 0.03) among other variables including the age, disease duration, BMI, HOMAIR and HOMAB. The SLEDAI was a significant independent risk factor for increased IMT among other factors including the age, disease duration, BMI, HOMAIR, HOMAB, C3, C4, HAQII and QoL. Such findings were not present when analyzing the factors in SLE patients with and without MetS.

Discussion

The present study showed a significantly increased carotid IMT in SLE patients confirming previous reports of CVD morbidity and increased prevalence of carotid plaques [3, 27-29]. These patients were asymptomatic for CVD indicating subclinical atherosclerosis. Traditional risk factors for atherosclerosis were present suggesting an increased CVD risk. These findings were in accordance with other results [30,31]. In the present study, the insulin level, insulin resistance (HOMA-IR), HOMA-B, cholesterol and LDL were significantly higher and the HDL lower in SLE patients than in control. This is in agreement with other studies [10,32,33] that reported a higher prevalence of insulin resistance and MetS in SLE.

In the current study, the IMT, SLEDAI and SLICC were significantly increased in SLE patients especially those with MetS and the IMT correlated with disease activity. It has been reported that insulin resistance was more striking in the severely affected SLE patients [32]. Traditional risk factors failed to fully account for premature accelerated development of atherosclerosis in SLE patients [12]. The combined effect of factors expressed as MetS could form a more solid risk in the increased IMT with subsequent CVDs. Oxidative injury contributes to the increased IMT and plaque formation in SLE [33] and the development of autoimmune-mediated atherosclerosis was supported in the study of *Lopez, et. al.*, [13].

Insulin resistance (HOMA-IR) showed no correlation with the studied parameters in the present SLE patients or with the corticosteroid dose. Insulin resistance in the context of SLE was not found to be related to current or recent steroid therapy. It may therefore represent an additional CHD risk factor in SLE patients [34]. Insulin sensitivity was lower in SLE and was not related to the steroid dose or disease activity. Hyperinsulinaemia and insulin resistance may therefore play a pivotal role in atherogenesis in lupus [17].

In the present study, it stands to reason that the SLE patients with MetS had a significantly higher WC, WHR, BMI, blood pressure,cholesterol, triglycerides and compared to those without. The study of *Chung, et. al.*, [32] showed that in SLE, the MetS was associated with higher levels of inflammation providing a link to the increased cardiovascular risk. The SLEDAI, SLICC/DI, HAQII and IMT were higher and the QoL lower in the present SLE patients with MetS. There was no significant correlation between the studied measures of MetS or insulin resistance with SLE indeces or IMT. It has been reported that neither lupus disease activity nor damage scores were associated with the MetS [32]. Insulin resistance (HOMA-IR) in the present study was significantly higher in the SLE patients with MetS. Insulin resistance is considered to be fundamental to the increased cardiovascular risk attributed to MetS in SLE patients [32]. Understanding of SLE-related risk factors for enhanced atherosclerosis could throw more light on disease mechanisms, leading to new therapeutic strategies for treatment of associated cardiovascular diseases [15] & insight into the disease mechanisms [35].

As patients with SLE live longer due to improved therapies and preventive measures, death and disability from cardiovascular events are increasing. Preventative strategies need to address all potential risk factors. A more thorough understanding of the interplay between inflammation, autoimmunity and atherogenesis is possible by the study of SLE [17, 35,36]. Results of the present study support the hypothesis that autoimmunity may contribute to and accelerates atherosclerosis.

The significance of the gender- and age-matched control population is limited in this study, because SLE patients without MetS showed many subclinical features of MetS, although they were not observed in control population. Therefore, the effect of MetS on carotid IMT, the aim of the present study, has been elucidated, but the effect of SLE on carotid IMT has not. Thus, this point is considered as a limitation of this study. It is suggested that a longitudinal study is performed to have an overview on the outcome of SLE in the presence of MetS.

It could be concluded that SLE patients with metabolic syndrome are at increased risk of insulin resistance, IMT and atherosclerosis. The conjoined presence of MetS in SLE forms a significant impact on the disease activity and damage.

Considering the association with MetS and measuring the carotid IMT are recommended in SLE patients and may form useful markers for detecting subclinical cases and predicting future cardiovascular events.

The authors declare that they have no conflict of interest

References

1. Mok CC, Wong RW, Lai KN. Treatment of severe proliferative lupus nephritis: the current state. Ann.Rheum.Dis. 2003;62:799-804.
2. Cervera R, Khamashta MA, Font J, Sebastiani GD, Gil A, Lavilla P, Mejía JC, Aydintug AO, Chwalinska-Sadowska H, de Ramón E, Fernández-Nebro A, Galeazzi M, Valen M, Mathieu A, Houssiau F, Caro N, Alba P, Ramos-Casals M, Ingelmo M, Hughes GR, European Working Party on Systemic Lupus Erythematosus. Morbidity and mortality in systemic lupus erythematosus during a 10-year period: a comparison of early and late manifestations in a cohort of 1,000 patients. Medicine (Baltimore). 2003;82(5):299-308.
3. 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):2399-406
4. Liese AD, Mayer-Davis EJ, Haffner SM. Development of the multiple metabolic syndrome. an epidemiologic perspective. Epidemiol.Rev.1998;20:157-172.
5. Bonora E, Formentini G, Calcaterra F, Lombardi S, Marini F, Zenari L, Saggiani F, Poli M, Perbellini S, Raffaelli A, Cacciatori V, Santi L, Targher G, Bonadonna R and Muggeo M. HOMA-estimated insulin resistance is an independent predictor of cardiovascular disease in type 2 diabetic subjects: prospective data from the Verona Diabetes Complications Study. Diabetes Care. 2002; 25(7):1135-41
6. Howard G, O'Leary DH, Zaccaro D, Haffner S, Rewers M, Hamman R, Selby JV, Saad MF, Savage P, Bergman R. Insulin sensitivity and atherosclerosis. The Insulin Resistance Atherosclerosis Study (IRAS) Investigators. Circulation. 1996 15;93(10):1809-17.
7. Petri M, Spence D, Bone LR, Hochberg MC. Coronary artery disease risk factors in the Johns Hopkins Lupus Cohort: prevalence, recognition by patients, and preventive practices. Medicine Baltimore1992; 71: 291-302.
8. Petri M, Yoo S-S. Predictors of glucose intolerance in systemic lupus erythematosus [abstract]. Arthritis Rheum.1994; 37 Suppl:S323.
9. Bruce IN, Urowitz MB, Gladman DD, Ibanez D, Steiner G. Risk factors for coronary heart disease in women with systemic lupus erythematosus: the Toronto Risk Factor Study. Arthritis Rheum.2003; 48: 3159-67.
10. Sada KE, Yamasaki Y, Maruyama M, Sugiyama H, Yamamura M, Maeshima Y, Makino H. Altered levels of adipocytokines in association with insulin resistance in patients with systemic lupus erythematosus. J Rheumatol. 2006;33(8):1545-52.
11. Nourooz-zadeh J, Tajaddini-Sarmadi J, McCarthy S, Betteridge DJ, Wolff SP. Elevated levels of authentic plasma hydroperoxides in NIDDM. Diabetes1995;44:1054-58.
12. Berliner JA, Navab M, Fogelman AM, Frank JS, Demer LL, Edwards PA, Watson AD, Lusis AJ. Atherosclerosis: basic mechanism of oxidation, inflammation and genetics. Circulation 1995;91: 2488-96.
13. Lopez LR, Salazar-Paramo M, Palafox-Sanchez C, Hurley BL, Matsuura E, Garcia-De La Torre I. Oxidized low-density lipoprotein and β2-glycoprotein I in patients with SLE and increased carotid intima-media thickness: implications in autoimmune-mediated atherosclerosis. Lupus, 2006;15,80–86.
14. Kobayashi K, Lopez LR, Shoenfeld Y, Matsuura E. The role of innate and adaptive immunity to oxidized low-density lipoprotein in the development of atherosclerosis. Ann N Y Acad Sci. 2005; 1051:442-54.
15. Zampieri S, Iaccarino L, Ghirardello A, Tarricone E, Arienti S, Sarzi-Puttini P, Gambari P, Doria A. Systemic lupus erythematosus, atherosclerosis, and autoantibodies. Ann N Y Acad Sci. 2005; 1051: 351-61.
16. van Leuven SI, Kastelein JJ, D'Cruz DP, Hughes GR, Stroes ES. Atherogenesis in rheumatology. Lupus. 2006;15(3):117-21.
17. Bruce IN. 'Not only...but also': factors that contribute to accelerated atherosclerosis and premature coronary heart disease in systemic lupus erythematosus. Rheumatology (Oxford). 2005; 44(12):1492-502.
18. Ryan MJ, McLemore GR, Hendrix ST. Insulin resistance and obesity in a mouse model of systemic lupus erythematosus. Hypertension. 2006;48 (5):988-93.
19. Bellomio V, Spindler A, Lucero E, Berman A, Sueldo R, Berman H, Santana M, Molina MJ, Góngora V, Cassano G, Paira S, Saurit V, Retamozo G, Alvarellos A, Caerio F, Alba P, Gotero M, Velozo EJ, Ceballos F, Soriano E, Catoggio L, García MA, Eimon A, Agüero S; SLE Study Group of the Argentinean Society of Rheumatology. Metabolic syndrome in Argentinean patients with systemic lupus erythematosus. Lupus. 2009;18(11):1019-25.
20. George J, Harats D, Gilburd B, Levy Y, Langevitz P, Shoenfeld Y. Atherosclerosis-related markers in systemic lupus erythematosus patients: the role of humoral immunity in enhanced atherogenesis. Lupus. 1999;8(3):220-6.
21.Hochberg MC. Updating the American College of Rheumatology revised criteria for the classification of SLE [letter].Arthritis Rheum.1997;40:1725.
22. Bombardier C, Gladman DD, Urowitz MB, Caron D, Chang CH. Derivation of the SLEDAI. A disease activity index for lupus patients. The Committee on Prognosis Studies in SLE. Arthritis Rheum.1992;35:630-40.
23. Gladman D, Ginzler E, Goldsmith C, Fortin P, Liang M, Urowitz M, Bacon P, Bombardieri S, Hanly J, Hay E, Isenberg D, Jones J, Kalunian K, Maddison P, Nived O, Petri M, Richter M, Sanchez-Guerrero J, Snaith M, Sturfelt G, Symmons D, Zoma A. The development and initial validation of the Systemic Lupus International Collaborating Clinics/American College of Rheumatology damage index for systemic lupus erythematosus.Arthritis Rheum1996;39:363-9

24. Spitzer WO, Dobson AJ, Hall J, Chesterman E, Levi J, Shephard R. Measuring the quality of life of cancer patients. J Chron Dis. 1981;34:585-597.
25. Wolfe F, Michaud K, Pincus T. Development and validation of the health assessment questionnaire II: A revised version of the health assessment questionnaire. Arthritis Rheum.2004, 50:3296–3305.
26. National Cholesterol Education Program Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults: Third report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III) JAMA. 2001;285:2486-97
27.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.
28. Vlachoyiannopoulos PG, Kanellopoulos PG, Ioannidis JP, Tektonidou MG, Mastorakou I, Moutsopoulos HM. Atherosclerosis in premenopausal women with antiphospholipid syndrome and systemic lupus erythematosus: a controlled study. Rheumatology2003;42: 645-51.
29. Medina G, Casaos D, Jara LJ, Vera-Lastra O, Fuentes M, Barile L, Salas M. Increased carotid artery intima-media thickness may be associated with stroke in primary antiphospholipid syndrome. Ann Rheum Dis. 2003;62(7):607-10
30. Esdaile JM, Abrahamowicz M, Grodzicky T, Li Y, Panaritis C, du Berger R, Côte R, Grover SA, Fortin PR, Clarke AE, Senécal JL. Traditional Framingham risk factors fail to fully account for accelerated atherosclerosis in systemic lupus erythematosus Arthritis Rheum. 2001;44(10):2331-7
31. 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):1071-7
32. Chung CP, Avalos I, Oeser A, Gebretsadik T, Shintani A, Raggi P, Michael Stein C. High prevalence of the metabolic syndrome in patients with systemic lupus erythematosus: association with disease characteristics and cardiovascular risk factors. Ann Rheum Dis. 2007;66 (2):208-14.
33. Svenungsson E, Jensen-Urstad K, Heimbürger M, Silveira A, Hamsten A, de Faire U, Witztum JL and Frostegård J. Risk factors for cardiovascular disease in systemic lupus erythematosus. Circulation. 2001;104 (16):1887-93.
34. El Magadmi M, Ahmad Y, Turkie W, Yates AP, Sheikh N, Bernstein RM, Durrington PN, Laing I, Bruce IN: Hyperinsulinemia, insulin resistance, and circulating oxidized low density lipoprotein in women with systemic lupus erythematosus J Rheumatol. 2006;33(1):50-6.
35. Frostegård J. Autoimmunity: oxidized LDL and cardiovascular disease. Autoimmun Rev. 2002;1(4):233-7.
36. McMahona M, Hahna BH. Atherosclerosis and systemic lupus erythematosus: mechanistic basis of the association. Curr Opin Immunol. 2007;19(6):633-9.