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Atherosclerosis Biomarkers Among Egyptian Patients with Systemic Lupus Erythematosus: Population Based Study

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Abstract

Systemic lupus erythematosus is associated with increased risk of atherosclerosis; endothelial dysfunction is believed one of the most important initial steps of the atherosclerosis process. The aim of this study is to evaluate endothelial microparticles (EMPs) (VCAM-1/CD105) in addition to Carotid intima-media thickness (cIMT), as biomarkers of atherosclerosis, among Egyptian Systemic lupus erythematosus (SLE) patients and its correlation to SLE related risk factors. We compared data obtained from 60 Egyptian SLE patients neither of them had diabetes, hypertension nor smokers, with 30, age and sex matched healthy volunteers. Both patients and controls were subjected to full history taking and clinical examination as well as basic laboratory investigations in addition to VCAM-1 ELISA, CD105 by flow cytometer and Carotid arteries ultrasound to assess intima-media thickness and the presence of plaques. Our results revealed highly significant increase of cIMT, CD105, VCAM-1, total cholesterol and LDL-cholesterol in SLE patients compared to normal controls ($P<0.001$). In comparing SLE patients with increased cIMT with those with normal cIMT, we found significant increase in LDL cholesterol, steroid duration and highly significant increase of steroid cumulative dose and disease duration. Also, SLE patients with positive anti-dsDNA showed significant increase in cIMT ($P<0.05$) in comparison to anti-dsDNA negative patients at the time of sampling. Our results also demonstrated no correlation between Anti-Cardiolipin antibodies (ACL) and cIMT, VCAM-1 or CD105. We found that SLE patients had a significant increase in cIMT, VCAM-1 and CD105 compared with the controls. This significant increase in these atherosclerotic biomarkers was not correlated with indices of disease activity or presence of anti-dsDNA or ACL antibodies but correlated with disease and steroid duration, steroid cumulative dose, age and LDL-C level.

Keywords: Atherosclerosis; Endothelial microparticles; Systemic lupus erythematosus; Biomarkers; ACL antibodies; Steroid

Introduction

The association between atherosclerosis and SLE was first suggested in a case report by Aravanis and colleagues 1964 [1]. Attention was first drawn to the increased risk of atherosclerosis and, in particular, death due to atherosclerosis in patients with SLE by Murray Urowitz and his colleagues in 1976 [2]. Atherosclerotic disease is common in SLE and is the result of multiple pathogenic mechanisms that include traditional risk factors as well as SLE-related factors [3].

Microparticles (MPs) are defined as membrane vesicles released by various cell types (platelets, endothelial cells, monocytes) in circulation after cell activation or apoptosis [4]. All blood cells produce MP, the greatest amount being released by platelets, platelet MP. Endothelial MP (EMP) represents a smaller population of MP in plasma, but has been associated with cardiovascular disease, mainly endothelial dysfunction. EMP includes CD31, CD51, CD54, CD62E, CD105, CD106, CD144, CD146, E-selectina and VE-caderina. Several studies identify plasma levels of EMPs as a surrogate marker of vascular function [5]. Patel and Celermajer even stated that Endothelial dysfunction is believed one of the most important initial steps of the atherosclerosis process [6].

Tushuizen stated that Endothelial cells shed fragments of their plasma membrane known as endothelial microparticles (EMPs) [7]. The protein compositions of endothelial microparticles depend on the stimuli that trigger their release. Endothelial microparticles carry endothelial proteins such as vascular endothelial cadherin, platelet endothelial cell adhesion molecule-1, intercellular cell adhesion molecule (ICAM)-1, endoglin, E-selectin and integrins.

VCAM-1 is the first adhesion molecule expressed before atherosclerotic plaque development [8]. Endoglin (CD105) expression was demonstrated in atherosclerotic vessels predominantly in endothelial cells and smooth muscle cells in various types of blood vessels in mice and humans, suggesting its participation in atherogenesis [9].

The aim of this study was to asses and evaluates cIMT as well as EMPs (VCAM-1 and CD105) among SLE patients and its correlation to SLE related risk factors.

Methods

Clinical and laboratory data were collected from 60 patients with SLE who were selected randomly from the Rheumatology and Immunology outpatient clinic of El-Maadi Armed Forces Hospital and also 30 randomly selected apparently healthy age and sex matched

controls. All SLE patients diagnosed according to 1997 update of the 1982 ACR revised criteria for classification of SLE [10]. Exclusion criteria included hypertension, diabetes mellitus as well as smoking. All patients gave written informed consent and the recommendations of the WHO and of the Declaration of Helsinki were followed in terms of protecting the rights and well-being of the people studied.

Carotid arteries ultrasound was performed for all patients and controls at El-Maadi Armed Forces Hospital Radiology department. Sonographers scanned the right and the left common carotid artery as well as carotid bulb. For each location, the sonographer imaged the vessel in multiple planes and then focused on the interfaces required to measure IMT and also on any areas of focal plaque. We documented the mean of six IMT measurements at the far wall of the CCA over a 1 cm long segment, 1 to 2 cm proximal to the carotid bifurcation for both sides.

We compared the power of the left and right IMT values and documented a mean IMT of the CCA as the mean of the 12 measurements among both sides. Examination was performed by the same operator with an ultrasound scanner (Siemens SONOLINE G40, Siemens Medical Solutions USA, Inc., Mountain View, CA, USA) with 7-MHz linear transducer and a transducer aperture of 38 mm. There are three different definitions of pIMT: a European version (pIMT>0.9), a German version (men 40 to 70 years old, pIMT > 1.0 mm; women 40 to 54 years old, pIMT>0.85 mm and 55 to 70 years old, pIMT>1.0 mm), and an Atherosclerosis Risk in Communities (ARIC) version, defined by the 90th percentile for different age and sex groups out of ARIC cohert [11]. We applied the European version where the IMT was considered "normal" when less than 0.9 mm, "thickened" when the IMT was equal to or more than 0.9 mm and when the thickness was more than 1.3 mm was indicative of atherosclerotic plaque.

Vascular cell adhesion molecule-1 (VCAM-1) estimation was done by ELISA using Human sVCAM-1/CD106 immunoassay lot 329262 manufactured and distributed by R&D systems (USA).

Endoglin (CD105) human conjugated to FITC. Identification and enumeration was done using flow cytometer BD facscalibur, Becton Dickinson four color readers.

Full lipid profile (HDL-C, LDL-C, total cholesterol, total triglycerides) was performed on automated chemistry analyser (Siemens, Dimension EXL200, Germany). Anti-dsDNA ELISA was done manually using INOVA kits while anti-cardiolipin IgM and IgG ELISA using Bioflash kits and Bioflash analyser (USA), in addition to, basic laboratory investigations.

Systemic Lupus Erythematosus Disease Activity Index (SLEDAI) was assessed using a combination of the clinical history, physical examination, organ specific functional tests, and serologic studies [12].

Statistical analysis was done to all data collected from patients and controls included in this study. Data was analyzed by Microsoft Office 2010 (excel) and Statistical Package for Social Science (SPSS) version 20. Parametric data was expressed as mean ± SD, and non-parametric data was expressed as number and percentage of the total. Comparing the mean ± SD of 2 groups was done using unpaired student's t test.

Results

Table 1 demonstrates a comparison between SLE patients and normal controls as regard cIMT, VCAM-1, CD105 and lipid profile. Results revealed highly significant increase of cIMT, VCAM-1, CD105, total cholesterol and LDL-C in SLE patients as compared to normal controls (P<0.001) but no significant difference as regard total triglycerides and HDL-C (P>0.05).

Parameters	Patient group (n= 60) mean ± SD	Control group (n=30) mean ± SD	t-value	P	S
cIMT(mm)	0.657 ± 0.149	0.56 ± 0.11	3.48	0.001	HS
VCAM-1(ng/ml)	1079.2 ± 577.04	531.87 ± 163.89	6.818	0.000	HS
CD105(count/ml)	59,495 ± 21,511.5	31,267 ± 1,871.66	10.088	0.000	HS
Total Cholesterol (mg/dl)	195.96 ± 43.92	166.45 ± 29.03	3.802	0.000	HS
Total Triglycerides (mg/dl)	114.03 ± 55.5	93.07 ± 51.45	1.775	0.081	NS
HDL-C (mg/dl)	49.16 ± 13.27	48.39 ± 3.52	0.42	0.676	NS
LDL-C (mg/dl)	123.22 ± 38.62	87.16 ± 4.08	7.152	0.000	HS

Table 1: Comparison between SLE patients and normal controls as regard cIMT, EMPs (VCAM-1/CD105) and lipid profile.

Table 2 compares between anti-dsDNA positive and anti-dsDNA negative SLE patients. Results revealed significant increase of cIMT in anti-dsDNA positive group (P<0.05) and no significant difference as regard VCAM-1 and CD105 (P>0.05).

Table 3 demonstrates a comparison between two subgroups; ACL positive and ACL negative SLE patients. There was no significant difference as regard cIMT, VCAM-1 and CD105 (P>0.05) between both subgroups.

Table 4 demonstrate a comparative study between SLE patients with increased cIMT and those with normal cIMT. Results revealed no significant difference as regard VCAM-1, CD105 (count/ml), total cholesterol, total triglycerides, HDL-C and SLEDAI (P>0.05) and showed a significant increase as regard LDL-C and steroid duration (P<0.05) and high significant difference as regard age, steroid cumulative dose and disease duration (P<0.001).

Table 5 illustrates a comparative study between SLE patients with no or mild activity (SLEDAI ≤ 5) and SLE patients with high activity

(SLEDAI>5) revealed no significant difference as regard VCAM-1, CD105 and cIMT (P>0.05).

Parameters	Anti-dsDNA	Anti-dsDNA +ve patients (n=40)	t-value	P	S
	-ve patients (n=20) mean ± SD	mean ± SD			
cIMT(mm)	0.593 ± 0.121	0.690 ± 0.153	2.689	0.010	S
VCAM-1 (ng/ml)	1052.4 ± 415.89	1092.6 ± 647.23	-0.291	0.772	NS
CD105 (count/ml)	64,954 ± 22,246.12	56,766 ± 20,881.27	1.371	0.179	NS

Table 2: Comparison between anti-dsDNA positive and negative patients in SLE group as regard cIMT and EMPs (VCAM-1/CD105).

Parameters	ACL -ve patients (n=50) mean ± SD	ACL +ve patients (n=10) mean ± SD	t-value	P	S
cIMT (mm)	0.66 ± 0.16	0.65 ± 0.12	0.208	0.838	NS
VCAM-1 (ng/ml)	1062.3 ± 569.19	1163.8 ± 639.83	-0.466	0.649	NS
CD105 (count/ml)	58,091 ± 20,120.24	66,517 ± 27,636.2	-0.917	0.379	NS

Table 3: Comparison between Anti-cardiolipin +ve or –ve SLE patients as regard cIMT and EMPs (VCAM-1/CD105).

Parameters	SLE patients with normal cIMT (n=48) mean ± SD	SLE patients with increased cIMT including plaque (n=12) mean ± SD	t-value	R	S
VCAM-1 (ng/ml)	1090.5 ± 570.86	1034.2 ± 625.11	0.284	0.78	NS
CD105 (count/ml)	57,221 ± 19,375.22	68,590 ± 27,662.58	-1.344	0.201	NS
Total Cholesterol (mg/dl)	193.1 ± 43.81	207.42 ± 44.36	-1.002	0.33	NS
Total Triglycerides (mg/dl)	113.4 ± 57.87	116.58 ± 46.94	-0.2	0.843	NS
HDL-C (mg/dl)	49.35 ± 13.30	48.36 ± 13.69	0.227	0.823	NS
LDL-C (mg/dl)	118.12 ± 39.045	143.60 ± 30.35	-2.446	0.023	S
Age (years)	32.64 ± 10.83	42.91 ± 12.58	2.845	0.006	HS
Steroid duration (months)	90.92 ± 66.96	166.33 ± 96.85	-2.549	0.023	S
Cumulative steroid dose (gm)	29.48 ± 21.01	49.95 ± 26.95	2.849	0.006	HS
Disease duration (Months)	92.20 ± 67.42	178.33 ± 92.51	3.663	0.001	HS
SLEDAI	7.52 ± 6.17	12.17 ± 12.35	-1.264	0.229	NS

Table 4: Comparison between SLE patients with normal cIMT and patients with increased cIMT as regard EMPs (VCAM-1/CD105) and lipid profile as well as SLE related risk factors.

Discussion

The IMT measurement in the carotid artery in its extracranial part can serve as an early marker of atherosclerotic changes and a risk factor for atherosclerotic organic complications and this very thickening of the complex triggers a long process of building the atherosclerotic plaque, whose fracturing in the future activates a cardiovascular incident [13].

According to the concept of parallel atherosclerosis development, early atherosclerotic changes observed in the lumen of peripheral arteries are a reflection of a generalized atherosclerotic process in other vessels and for that reason, measurement of the intima-media complex is presently a recognized evaluation method both of the initial and advanced atherosclerotic changes and also a control method of the applied pharmacotherapy efficiency [14].

Parameters	SLE patients with SLEDAI ≤ 5 (n=23) mean ± SD	SLE patients with SLEDAI >5 (n=37) mean ± SD	t-value	P	S
cIMT(mm)	0.665 ± 0.139	0.653 ± 0.158	0.322	0.748	NS
VCAM-1 (ng/ml)	1033.8 ± 427.948	1107.4 ± 657.003	-0.525	0.601	NS
CD105 (count/ml)	61,632 ± 23,146.874	58,167 ± 20,645.533	0.587	0.56	NS

Table 5: Comparison between SLE patients with no or mild activity (SLEDAI ≤ 5) and SLE patients with high activity (SLEDAI>5) as regard cIMT and EMP (VCAM-1/CD105).

In the present study, our results revealed highly significant increase as regard cIMT in SLE patients as compared to normal controls (P<0.001) (0.657 ± 0.149 and 0.56 ± 0.11, respectively) and this observation suggests a faster atherosclerotic process in patients with SLE. Our results were supported by Colombo study which showed that patients with SLE have an increased mean cIMT value compared with a healthy control [15]. This is in agreement with Cacciapaglia who stated that patients with SLE presented a higher mean IMT of the common carotid artery than healthy subjects (0.7 ± 0.2 mm vs. 0.5 ± 0.1 mm, P<0.0001) [16]. In favor of our results, additional two meta-analyses and reviews published by Au and Tyrrell which revealed a higher cIMT compared with healthy controls in SLE patients [17,18]. In disagreement with our work, Gallelli their study did not show significant differences regarding the cIMT versus the control group [19].

Approximately thirteen percent (13.3%) (8/60 patients) of our SLE patients had thickened cIMT more than 0.9 mm and 4 patients (6.6%) had carotid plaques. This is less than what was reported in a study by Doria (2003) who found that 28% from lupus patients were found to have thickened cIMT of more than 0.9 mm and also, [20] less than the study conducted by Frerix who stated that with a population of 100 patients with SLE reveals the existence of subclinical atherosclerosis measured by the cIMT in 26.5% of patients with SLE [11]. On the other hand, a previous study on Egyptian SLE patients by Rizk (2012) stated that subclinical carotid plaque was found in only 5% of the patients while in another study on SLE and the risk of carotid atherosclerosis among non-Egyptians by Souza 50% of the patients had carotid plaque [21,22].

Atherosclerotic plaque lesions can be found frequently in absence of intima-media thickening in SLE patients [11]. This was the case in our study where the four patients with plaques had normal cIMT.

The mean of the cIMT for SLE patients in our study which was 0.657 mm agrees with Skeoch who found that the mean of cIMT for SLE patients in their study was 0.633 mm but slightly higher than Roman who found that the mean cIMT for SLE patients was 0.61 mm [23,24].

Petri and Hamper stated that subclinical atherosclerosis detected by cIMT measurement in various lupus populations and has ranged from 8% to 40%, depending on the technique and the patients demographic background, which can explain this variation [25].

Our results demonstrated no correlation between cIMT and SLEDAI. This agrees with Sazliyana who stated that there was no correlation between disease activity measured by SLEDAI and thickened cIMT, since atherosclerosis itself is the result of a chronic insult to the vessel wall, perhaps measuring disease activity at the current study time point is not a good indicator of the overall activity or severity of lupus activity throughout the course of the disease [26]. Our results disagree with Kisiel who stated that IMT was associated with SLEDAI [27]. This could be explained by different technical methods used and/or absence of standardization. Our results also disagree with Nassef who found that there was a statistically significant correlation between IMT and SLEDAI [28].

Also, cIMT of patients with SLE did not correlate with the presence of antiphospholipid syndrome and/or the presence of anticardiolipin antibodies in the present study. Our results agree with Sazliyana who stated that no association was found between thickened cIMT and the presence of antiphospholipid syndrome and/or the presence of anticardiolipin antibodies [26].

Comparative study between patients with normal cIMT and patients with increased cIMT in SLE group revealed significant difference as regard steroid duration (P<0.05) and high significant difference as regard steroid cumulative dose and disease duration (P<0.01). This agrees with Doria and her colleges who stated that in patients with SLE some non-traditional risk factors for atherosclerosis were identified, the most important of which was the cumulative prednisone dose [20].

In our study, VCAM-1 mean ± SD for SLE patients was 1,079.2 ± 577.04 (ng/ml) while that of the control group was 531.87 ± 163.89 (ng/ml) which showed significant increase as compared to normal control group (P<0.001). The mean of VCAM-1 for SLE patients was similar to that reported by Young and his colleges (2008) where it was 1077.4 ng/ml (887.9-1203.3), but they reported higher levels of the mean value for their control group [29]. Our results agree with Robak and his colleges (2009) who stated that the serum concentration of VCAM-1 was detectable in all SLE patients [30]. VCAM-1 was higher in patients with SLE than in the control group. Our results also agree with Kassem who stated that there was significant elevation of VCAM-1 in SLE patients than healthy controls [31]. On the other hand, Skeoch and his colleges found no significant difference in VCAM-1 levels in SLE patients and controls [23]. This could be explained by different assay methods, variation in studied patients as regard age, gender and nationality, also the number of the studied cases can affect the statistical results.

In this study, a comparative study between patients with normal cIMT and patients with increased cIMT in SLE group revealed no significant difference as regard VCAM-1 (P>0.05).

Also, in this study the correlation between VCAM-1 in all 60 patients enrolled in this study revealed no significant correlation with

cIMT. These results might denote that VCAM-1 is not the only player in the atheroma formation in carotid arteries. Our results agree with the study of Roman and his colleges, who stated that adhesion molecules (VCAM and ICAM) were not associated with the presence or absence of carotid plaque in SLE [24]. But our results disagree with Rubio-Guerra who suggest that systemic levels of ICAM-1 and VCAM-1 are associated with IMT and correlated with the degree of atherosclerosis [32].

Comparative study between SLE patients with no or mild activity (SLEDAI ≤ 5) and SLE patients with high activity (SLEDAI>5) revealed no significant difference as regard VCAM-1, the results were 1033.8 ng/ml and 1107.4 ng/ml, respectively (P>0.05). Our findings agree with Skeoch and his colleges who studied 178 patients and 69 controls with a median age of 53 and 50 years old, respectively [23]. They found no association between VCAM-1 and disease activity. Our findings also agree with Robak and his colleges who stated that they did not find any statistically significant differences in numbers of circulating EMPs and their particular subpopulations between patients with active and non-active type of SLE [30]. But our results disagree with Kassem who stated that regarding their relations to disease activity VCAM-1 significantly increased with disease activity and correlate positively with circulating endothelial cells microparticles count and such variation in results may reflect small sample sizes and heterogeneity of populations studied [31].

In the present study, the mean ± SD of CD105 in SLE patients group was 59,495 ± 21,511.5 while that in the control group was 31,267 ± 1,871.66. Comparative study between both groups revealed high significant elevation in SLE group in comparison with the control group (P<0.001). Similar results were reported by Duval who measured the EMP in the plasma of SLE patients and healthy individuals and found significant elevation of EMP in SLE patients in comparison with the control [32,33].

In the present work CD105 showed no significant difference in their levels in SLE patients with ACL antibodies or with anti-dsDNA. Also, there was no significant difference between patients with normal IMT and patients with increased IMT as regard CD105 level.

In our study, a comparative study between SLE patients with no or mild activity (SLEDAI ≤ 5) and SLE patients with high activity (SLEDAI>5) revealed no significant difference as regard CD105 (P>0.05). Our results agree with Bassyouni who stated that they failed to detect any association between the disease activity as assessed by SLEDAI and s-Endoglin concentrations [34].

Conclusion

Our results show that SLE patients had a significant increase in cIMT, VCAM-1 and CD105 compared with the controls. This significant increase in these atherosclerotic biomarkers was not correlated with indices of disease activity or presence of anti-dsDNA nor ACL antibodies but correlated with duration of steroids, duration of the disease, steroid cumulative dose, age and LDL-C level. We can conclude that the increase in these atherosclerotic biomarkers could be attributed to immune complex-mediated autoimmune inflammation and its effect upon endothelial system.

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