CORRELATIONS BETWEEN INFLAMATORY MARKERS AND SUBCLINICAL ATHEROSCLEROSIS IN SYSTEMIC LUPUS ERYTHEMATOSUS

-ABSTRACT-

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Keywords

systemic lupus erythematosus; inflammation markers; intima-media thickness; augmentation index; pulse wave velocity.
Atherosclerosis is the most common pathologic process leading to cardiovascular disease (CVD), including myocardial infarction (MI), and stroke. Autoimmune rheumatic diseases (AIRDs) are associated with higher rates of cardiovascular morbidity and mortality, primarily secondary to accelerated atherosclerosis. This phenomenon can be attributed to traditional risk factors for atherosclerosis and use of specific drugs, such as corticosteroids, but also might be the result of other autoimmune and inflammatory mechanisms that are aggravated in AIRDs.

Systemic lupus erythematosus (SLE) is a complex multisystem inflammatory disease caused by autoimmune dysregulation, which mainly affects young women. Young women without SLE are usually free from atherosclerosis. In individuals with SLE the prevalence of CAD ranges from 6% to 10%, and the risk of developing CAD is 4–8 times higher than in the normal population. Moreover, acute MI is reported as a cause of death in 3–25% of individuals with SLE.

The high prevalence of atherosclerosis in SLE, however, cannot be explained by Framingham risk factors alone, and has been attributed to complex interactions between traditional risk factors and factors associated with the disease per se, or its treatment.

Arterial stiffness and endothelium function may serve as a valuable preclinical measure to be counted in the follow-up of these patients prior to a potential cardiovascular event. Two major estimates of vascular function, in particular augmentation index (AIx), indicating systemic arterial stiffness, carotid-femoral pulse wave velocity (PWV), the parameter of regional arterial stiffness, have intensively been explored during last decade in different ways in rheumatic patients.
PATIENTS AND METHODS

We designed a prospective study including 53 patients with systemic lupus
erythematosus, diagnosed using ARA criterias. The study was carried out in
Rheumatology department, Emergency County Hospital, Craiova, during december
2007-may 2011. Imagistic evaluation was performed in the Cardiology department of
Emergencz County Hospital Craiova.

The aim of the study was to evaluate atherosclerosis, inflammatory process,
imune mediated, by laboratory findings and imaging techniques, to identify the
inflammatory profile, and to find the possible correlations between inflammation and
subclinical atherosclerosis; also, another purpose was the one to establish possible
correlations between disease activity index (SLEDAI), inflammation and
atherosclerosis.

The inflammatory status was assessed by measuring hsCRP, homocysteine, IL-6, VSH and fibrinogen. In order to detect subclinical atherosclerosis, we measured
carotid intima media thickness, carotid-femural pulse wave velocity and augmentation
index.

The arterial stiffness was detected by measuring the pulse wave velocity (PWV)
and augmentation index of the pressure waves by performing pulse wave analysis
(PWA).

Intima media thickness was assessed using carotid ultrasonography, and arterial
stiffness was evaluated by applanation tonometry using highfidelity micromanometer
(Sphygmocor v.7.01) AtCor Medical Pty. Ltd 1999–2002).
RESULTS AND DISCUSSIONS

Our study revealed increased values of inflammatory markers, both at the beginning of the study, and after 12 months, showing the persistent inflammatory status in patients with systemic lupus erythematosus. The mean value of VSH was 69.19 mm; DS=14.18; CI95% 65.279 - 73.098, fibrinogen 445.66 mg% (DS 74.56; CI 95% al medi ci 425, 108-466,213mg%); for hs CRP the mean value was 3.493 mg/l, (DS 1.12; CI 95% 3.181-3.804mg/l), 31 de patients (58%) had values that show an increased cardio-vascular risk (>3mg/l). Homocysteine had a mean value of 17.721 µmol/l (DS 2.5374; CI 95% 17.021 - 18.420), most of the patients (51) had values over the ranges. IL-6 had a mean value of 11.209 pg/ml (DS 1.56; CI95% 10.778-11.640). After 12 months, VSH, had a mean value of 36.87 mm (DS 23.5143, 95% CI 30.387-43.349), almost 50% lower than the first value. The mean value of hsCRP was 1.66 mg/l (DS 1.1288, 95% CI 3.181 - 3.804), homocysteine 15.868 µmol/l (DS 3.6135; 95% CI 14.872 - 16.864), IL-6 11.1pg/ml, even higher than the value from the first evaluation.

Carotid intima media thickness (CIMT) had a mean value of 0.87 mm (DS=0.0339; CI95% 0.864 - 0.883), with 12 patients having values over 0.9mm. At 12 months, the mean value of CIMT was 0.9 (DS 0.035 mm), with no significant increase (p=0.81). Augmentation index had an mean initial value of 23.32%(DS=5.82; CI 95% 21.716 - 24.925), with a significant increase at the 12 months evaluation 30.93% (DS 7,61), p<0.0001. Pulse wave velocity had no significant difference- at the moment of diagnosis 9.11±0.49 m/s, at 12 months v, p=0.744.

This study showed that two markers of arterial wall dysfunction, namely aortic AIx (the parameter of systemic arterial stiffness) and to a less extent increased carotid-femoral PWV (the indicator of diminished regional vessel flexibility), were increased in young SLE women with no history of cardiovascular disease and no severe organ damage when compared to healthy controls. It may be assumed that impaired arterial stiffness plays an independent pathogenetic role in atherosclerosis and may be responsible for premature atherosclerosis in SLE and atherosclerotic lesions.

Correlations between inflammation markers and subclinical atherosclerosis

There was a positive, significant correlation between augmentation index and hsCRP (r=0.612; CI 95% 0.4104 - 0.7576; p<0.001), linear regressing showing the same result (r²=0.375; F ratio=30.65; p<0.001). However, the correlation between AIxAo and hsCRP was different regarding the cardiovascular risk: there was a significant positive correlation in patients with hsCRP>3mg/l (r=0.41; CI 95% 0.0654-0.0667) and a inverse correlation in patients with values between 1 and 3mg/l (r=-0.017; CI 95% -0.435-0.407; p=0.94).
AlxAo correlated with IL-6 ($r=0.369; \ CI \ 95\% \ 0.1097 - 0.5813$), statistically significant ($p=0.037$) and with homocysteine ($r=0.526; \ p<0.001$). The multiple correlation coefficient between AlxAo and inflammation markers was 0.6281 by Enter method and 0.6127 by Stepwise method. After 12 months, the multiple coefficient between inflammation markers and AlxAo was 0.5841 by Enter method and 0.5302 by Stepwise method.

The multiple correlation coefficient between CIMT and inflammation markers was 0.85 by Enter method and 0.83 by Stepwise method. After 12 months the value was 0.4863 by Enter method and 0.2817 by Stepwise.

For pulse wave velocity the multiple coefficient markers was 0.91 for both methods. After 12 months there was a weak correlation for cfPWV and IL-6 ($r=0.013$), homocysteine ($r=0.046$), hsCRP ($r=0.05$).

**Correlations between SLEDAI and inflammatory markers**

At the moment of diagnosis, SLEDAI was different in patients with a value of hsCRP over $3 \text{mg/l-}22.52 \pm 3.98$, 25% higher than the ones with hsCRP between 1 and 3 $\text{mg/l-}17.95 \pm 4.18$, statistically significant ($p<0.005$). The correlation coefficient Pearson was 0.5204, $p=0.0001$. After 12 months, there was a highly significant correlation between SLEDAI and hsCRP ($r=0.91; \ p<0.0001$). Linear regression sustained the previous ($r^2=0.83; \ F-\text{Ratio } =248.98; \ p<0.001$). IL-6 values strongly correlated with SLEDAI, both by Pearson coefficient ($r=0.83; \ IC95\% \ 0.7181-0.8973; \ p<0.0001$) and linear regression ($r^2=0.6851; \ F-\text{Ratio } =110.96; \ p<0.001$). A similar correlation coefficient was calculated for homocysteine ($r=0.82, \ p<0.0001$).

**Correlations between SLEDAI and non invasive vascular assessments**

SLEDAI was not significantly different ($p=0.54$) in patients with CIMT more than 0.9mm mm (10.97±7.41), compared with the ones with CIMT <0.9mm (9.45±6.75). SLEDAI was not correlated with CIMT ($r=0.16; \ 95\% \ CI \ -0.1156 - 0.4122; \ p=0.2535$).

Patients with persistent active disease had a higher cfPWV 9.523m/s (DS 0.407; 95%CI 9,342-9,703), but not statistically significant ($p=0.308$), compared with the ones with SLEDAI<8. SLEDAI was not correlated with cfPWV ($r=0.06; \ 95\% \ CI \ -0.2173 - 0.3217; \ p=0.6889$).

The only marker of subclinical atherosclerosis that correlated with SLEDAI was augmentation index ($r=0.46; \ IC95\% \ 0.2134 - 0.6476; \ p<0.001$).

This results are in harmony with the results from the studies focusing on SLE and arterial wall functioning, namely study of Brodski, et al., Roman, et al., Selzer, et al. These studies demonstrated an increased arterial stiffness and signs of premature vascular ageing in SLE patients without manifest cardiovascular disease and without significant atherosclerotic lesions. The authors conclude that other mechanisms beside atherosclerosis might be involved in the pathogenesis of arterial stiffening in SLE patients. The association of arterial stiffening with circulating levels of C-reactive protein and IL-6 implicates chronic inflammation as important mediator of this process.
CONCLUSIONS

- Atherosclerosis is the most common pathologic process leading to cardiovascular disease, and autoimmune rheumatic diseases are associated with higher rates of cardiovascular morbidity and mortality, primarily secondary to accelerated atherosclerosis.
- The results of the study show and confirm the persistent inflammatory status of SLE patients.
- Using applanation tonometry and carotid ultrasonography, the initial assessment of subclinical atherosclerosis showed increased intima media thickness, augmentation index and pulse wave velocity, fact that sustains the early vascular damage in patients with SLE.
- The progression of atherosclerosis was proven by the increased values of the parameters that evaluate subclinical atherosclerosis at 12 months, compared with the initial ones.
- In the cohort of SLE patient's disease damage index and age remains as the most important predicting factors for AIx.
- Augmentation index strongly correlated with inflammation, both at the initial evaluation and after 12 months.
- We can sustain that, for SLE patients, the presence of systemic inflammation has is important promoter for early vascular damage through endothelial dysfunction.
- A strong interrelation was found between SLEDAI and hsCRP.
- The results of the study suggest the fact that the patients with a high active disease and persistent inflammation, will be prone to the development of arterial stiffening, which in turn will be a marker of end-organ damage.
- Non invasive measurement of PWV and AI may allow the detection of early increased arterial stiffness.
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Curriculum Vitae

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Other language(s):
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