ENDOTHELIAL DYSFUNCTION IN LUPUS NEPHRITIS

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Summary
Systemic lupus erythematosus (SLE) is associated with a high risk of atherosclerosis. Endothelial dysfunction is the first step in its pathogenesis. SLE-secondary renal involvement (lupus nephritis – LN) represents one of the most severe manifestations of the disease, with a major impact on the prognosis, morbidity and mortality it induces (subsequent to chronic kidney disease and cardiovascular disease, respectively). The aim of the study is to assess endothelial dysfunction in SLE patients versus patients with SLE-secondary renal involvement, using vascular echography. The study was conducted on a group of 30 patients, all women, subdivided into two subgroups: subgroup A – 15 SEL patients and subgroup B – 15 SEL patients with associated LN. Kidney function was determined by assessing the values of proteinuria, haematuria and creatinine clearance. SLE activity was assessed using SLE Disease Activity Index (SLEDAI). Endothelial dysfunction was assessed by flux-mediated vasodilation (FMD), using brachial artery ultrasound. Statistical analysis showed the following results: subgroup A – mean age 36.26±6.98 years, creatinine clearance 103.73±9.71 ml/min, SLEDAI 9.73±2.63, FMD% - 9.38±1.24% (p=0.02); subgroup B – mean age 39.4±6.96 years, creatinine clearance 70.13±24.74 ml/min, SLEDAI 15.33±3.73, FMD% - 7.43±0.98 (p=0.02). Statistical analysis showed a direct correlation between FMD values and renal function parameters in both subgroups. The patients with SLE and LN have a more severe endothelial dysfunction than the patients without renal impairment.

Key words: systemic lupus erythematosus, lupus nephritis, endothelial dysfunction

Introduction
Systemic lupus erythematosus (SLE) is an autoimmune disorder of unknown etiology defined by a chronic inflammatory process and the production of a wide range of antibodies, most importantly anti-nuclear antibodies (Mason et al., 2008).

Women are more susceptible to the disease than men, the women/men ratio being 9/1 (Mok et al., 2003). The incidence of the disease is 2-8 cases/100,000 people/year, and its prevalence is estimated to approximately 51 cases/100,000 people (Bertsias et al., 2012).

SLE-secondary renal involvement (lupus nephritis, LN) is one of the most severe manifestations of the disease with a major impact on the prognosis, morbidity and mortality it induces (subsequent to chronic kidney disease and cardiovascular disease, respectively). Estimates show that LN is diagnosed in approximately 40 – 70% of SLE patients (Bertsias et al., 2012).

Endothelial dysfunction is characterized by a shift of the actions of the endothelium toward reduced vasodilation, a proinflammatory state, and prothrombic properties. It is associated with most forms of cardiovascular disease, such as hypertension, coronary artery disease, chronic heart failure, peripheral artery disease, diabetes, and chronic renal failure (Endemann et al., 2004).

Several recent studies demonstrated the high incidence of atherosclerosis within young SLE patients. Atherosclerosis is considered the second mortality peak in SLE. In the population segment represented by women aged between 35 –
45 years, ischaemic cardiac disease occurs 50 times more often in SLE patients than in the healthy population of the same age. This high incidence cannot be attributed solely to traditional risk factors; there are also additional factors induced by SLE inflammatory pathology and also by its treatment.

Systemic inflammation, autoantibodies directed to double stranded DNA (dsDNA), ribonucleoproteins (nRNP), endothelial cells, phospholipids, circulating immune complexes, activated complement products, lupus nephropathy, dyslipidemia represent some factors related to SLE which contribute to the appearance of endothelial dysfunction (Hahn, 2003).

Chronic kidney disease is associated with a low degree of inflammation, endothelial dysfunction and platelet activation, even in patients with moderate kidney failure (Landray et al., 2004).

The association of three pro-inflammatory conditions: LES, LN and atherosclerosis, all responsible for the development of endothelial dysfunction, can provide valuable information to better understand the various unknown aspects about the pathogeny of the three disorders.

A non-invasive method for the assessment of endothelial function is flow-mediated vasodilation (FMD) on brachial artery, using vascular ultrasound.

The aim of the study is to assess endothelial dysfunction in SLE patients versus patients with SLE-secondary renal involvement, using vascular echography.

Materials and methods

The study was carried out on 30 patients diagnosed with SLE (all women), hospitalised in the Medical Department of the Timisoara Clinical Railways Hospital. The study group was divided into two groups: subgroup A – 15 SEL patients and subgroup B – 15 SEL patients with associated LN.

All the patients met the ARA diagnostic criteria for SLE. The exclusion criteria were pregnancy, SLE-associated haemorrhagic diathesis, uncontrolled hypertension and the patient’s refusal.

The clinical and biological assessment of the patients was performed the moment the patients were included in the study group.

SLE degree of activity was assessed based on the SLE Disease Activity Index (SLEDAI).

Index of renal involvement:
- proteinuria (the Turbidimetry method, normal values NV<200mg/24h)
- haematuria (the Addis-Hamburger method, NV H<1000 red blood cells/minute)
- creatinine clearance (ml/min/1.73 mp) = urine creatinine (mg/dl) x urine volume (ml)/serum creatinine (mg/dl) x collection time (minute = 1440 minutes/24hs).

Measurements of flow-mediated dilation (FMD) in brachial artery:

Endothelial function was assessed by means of flow-mediated vasodilation on brachial artery, using B-mode ultrasonography (ALOKA ProSound 4000, with linear transducer of 7.5 MHz). Before the test, the patient was relaxed at a stable room temperature between 20 – 25 ºC; smoking was prohibited. The diameter of the brachial artery was measured incident with the R wave of the electrocardiograph trace (Di). Then, ischemia was induced by inflating the pneumatic cuff to a pressure 50 mmHg above systolic one, in order to obliterate the brachial artery and induce ischaemia. After 5 minutes, the cuff was deflated and the diameter was measured after 60 seconds post-deflation (Df).

FMD was calculated with the formula: FMD = [(Df – Di)/Di] × 100

Statistical analysis:

All the values were presented as mean ± standard deviation. The statistical analysis was done using Pearson’s test (for correlation) and Student’s t-test (for the comparison of FMD between the two
groups). p < 0.05 was considered statistically significant.

Results and discussion

Demographical and clinical-biological characteristics of the two subgroups are shown in Table 1.

Table 1

<table>
<thead>
<tr>
<th>Assessed parameters</th>
<th>Subgroup A SLE</th>
<th>Subgroup B SLE+LN</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nr. patients</td>
<td>15</td>
<td>15</td>
</tr>
<tr>
<td>Male/Female</td>
<td>0/15</td>
<td>0/15</td>
</tr>
<tr>
<td>Age</td>
<td>36.26 ± 6.98</td>
<td>39.4 ± 6.96</td>
</tr>
<tr>
<td>Creatinine clearance (ml/min)</td>
<td>103.73 ± 9.71</td>
<td>70.13 ± 24.74</td>
</tr>
<tr>
<td>Proteinuria (mg/24h)</td>
<td>&lt;10mg/dL</td>
<td>2867 ± 1188.43</td>
</tr>
<tr>
<td>Haematuria (red blood cells/min)</td>
<td>NEGATIVE</td>
<td>1406.67 ± 652.09</td>
</tr>
<tr>
<td>SLEDAI</td>
<td>9.73 ± 2.63</td>
<td>15.33 ± 3.73</td>
</tr>
</tbody>
</table>

The mean FMD value in subgroup B (SLE + LN) is lower than the mean FMD value in subgroup A (SLE)

Table 2

<table>
<thead>
<tr>
<th>Assessed parameters</th>
<th>Subgroup A SLE</th>
<th>Subgroup B SLE+NL</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>FMD (%)</td>
<td>9.38 ± 1.24</td>
<td>7.43 ± 0.98</td>
<td>0.02</td>
</tr>
</tbody>
</table>

Figure 1

Statistical analysis shows a direct correlation between FMD value and kidney-function parameters in both subgroups

Table 3

<table>
<thead>
<tr>
<th>Assessed parameters</th>
<th>Correlation coefficient Subgroup A</th>
<th>Correlation coefficient Subgroup B</th>
</tr>
</thead>
<tbody>
<tr>
<td>Creatinine clearance</td>
<td>r = 0.61; p=0.03</td>
<td>r = 0.57; p=0.02</td>
</tr>
</tbody>
</table>

The endothelial dysfunction, assessed by vascular ultrasonography on brachial artery, is presented in Figures 2, 3 (FMD = 8.94 %).
Systemic lupus erythematosus (SLE) is a chronic, inflammatory, multisystem disorder. SLE represents the prototype of the autoimmune disease (Mason et al., 2008).

The clinical picture is extremely varied, reflecting the chronic inflammation of the various organs and systems. The most common targets of LES are the skin, joints and kidneys, but practically any organ or system may present LES-induced morphofunctional anomalies.

One of these anomalies is atherosclerosis. It is a well-known fact that ischaemic cardiac disorder is 50 times more common in SLE patients than in the healthy population of the same age, and it occurs early in the development of the disease and progresses rapidly (Tani et al., 2006).

Atherosclerosis, with its multiple locations, has become the main cause of morbidity and mortality among the general population. It is defined by the presence of atheroma plaques in the vascular walls. The atherogenic process has a long-term sub-clinical stadial progression. Normal endothelium is an important location for the control of vascular functions. It is involved in modulating vascular tonus, limiting leukocyte adhesion, regulating vascular permeability, inhibiting adhesiveness and platelet aggregation, maintaining the balance between coagulation and fibrinolysis (De Caterina, 2000; Vita et al., 2002).

The first step in the atherogenetic process, preceding any clinical sign, is represented by endothelial dysfunction (Vita et al., 2002). The latter is defined as a disruption of the entire spectrum of the normal endothelial functions: the increase or decrease of plasma concentrations of any chemical mediator released by the endothelial cells and/or the alteration of any endothelial functional change. Endothelial function is, however, reversible, by therapeutic control of its inducing factors. Its persistence, though, leads to a progressive deterioration of the arterial wall (De Caterina, 2000).

The association between two pro-atherogenic factors such as SLE and chronic kidney disease, due to their pro-inflammatory condition, leads to the increase of cardiovascular events.

Conclusions

Patients with SLE and LN have a more severe endothelial dysfunction compared to patients without renal involvement, therefore they have a higher
incidence of morbidity and mortality caused by cardiovascular events.

Endothelial dysfunction is the first step in the atherogenic process, flux-mediated vasodilation being the non-invasive, repeatable objectifying method, applicable to all patients.

References
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