Hyperhomocysteinemia and metabolic syndrome are risk factors for sub-clinical atherosclerosis in women with systemic lupus erythematosus

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Abstract  Aim of the work: This study aimed to measure serum levels of homocysteine (sHcy) and to study the presence of the metabolic syndrome (MetS) in women with systemic lupus erythematosus (SLE) and to correlate them with disease activity, clinical status and sub-clinical atherosclerosis.

Patients and methods: This study included 30 adult SLE female patients and 20 age and sex matched apparently healthy volunteers as the control group. Disease activity and damage were assessed using the SLE disease activity index (SLEDAI) score and Systemic Lupus International Collaborative Clinics (SLICC) damage index, respectively. The MetS was diagnosed according to the National Cholesterol Education Program’s Adult Treatment Panel III (NCEP-ATPIII). Total sHcy was measured by enzyme immunoassay. B mode ultrasound was done to measure the carotid intima-media thickness (CIMT).

Results: The mean CIMT (0.97 ± 0.26 mm) and sHcy (46.96 ± 22.07 μmol/L) were significantly higher in patients compared to the controls (0.43 ± 0.22 mm and 4.19 ± 1.49 μmol/L, respectively) (p < 0.001). The mean CIMT significantly correlated (p < 0.001) with patient age (r = 0.52), disease duration (r = 0.69), SLEDAI (r = 0.66), SLICC (r = 0.82), sHcy (r = 0.53), total cholesterol (r = 0.51), triglycerides (r = 0.77), low density lipoprotein (r = 0.53), fasting blood sugar (r = 0.75), systolic (r = 0.68) and diastolic (r = 0.64) blood pressure and negatively with C3
We can conclude that SLE itself is considered a risk factor for accelerated atherosclerosis that rises to a 50-fold increase in younger patients [1]. Since the recognition of high cardiovascular disease (CVD) risk and its bimodal pattern of mortality, major advances in comprehensive understanding of the pathways of premature atherosclerosis have been started in SLE patients [2]. Recent advances stress on the interplay between lupus specific inflammatory factors including, inflammatory mediators, auto-antibodies, enhanced endothelial cell activation, corticosteroid-induced atherogenesis, and dyslipidemia associating renal disease together with traditional cardiac risk factors [3].

The metabolic syndrome (MetS); which is a lately defined clustering of CV risk factors characterized by obesity, arterial hypertension, hyperglycemia, insulin resistance, elevation of triglycerides and low high-density lipoprotein (HDL), has been shown during the last decade to be an independent CV mortality predictor [4], with a special concern in women who run a twofold risk to contract severe CVD [5]. MetS is closely related to the inflammatory response, it has been observed that pro-inflammatory cytokines like interleukin-6 (IL-6) and tumor necrosis factor-alpha (TNF-α) facilitate insulin resistance and that patients with MetS present high levels of C-reactive protein (CRP), IL-1β, interleukin-1 receptor antagonist (IL-1Ra), P-selectin, inter-cellular adhesion molecule-1 (ICAM-1) and leptin [6].

Homocysteine (Hcy), a thiol-containing amino acid which is produced during the metabolism of methionine, leads to insulin resistance through the inhibition of insulin-receptor kinase activity in vitro, also in an insulin resistant state, elevated Hcy plasma levels may be the result of hyperinsulinemia, as observed in animal models [7]. Therefore, Hcy may be a cause and/or a consequence of insulin resistance and is considered an indicator of risk for the development of atherosclerosis [8].

It has become inevitable to detect atherosclerosis as early as possible, many physiologic measurements for plaque and endothelial dysfunction are now available, however measurement of the carotid artery intima-media thickness (CIMT), by a non invasive high-resolution B-mode ultrasound technique is now commonly accepted as a surrogate marker for subclinical atherosclerosis [9].

This study aimed to the measure serum levels of Hcy and to study the presence of the MetS in women with systemic lupus erythematosus and to correlate them with disease activity, clinical status and subclinical atherosclerosis.

1. Introduction

Women with systemic lupus erythematosus (SLE) have more than fivefold increase in the risk of coronary heart disease (CHD) events particularly related to premature atherosclerosis that rises to a 50-fold increase in younger patients [1]. Since the recognition of high cardiovascular disease (CVD) risk and its bimodal pattern of mortality, major advances in comprehensive understanding of the pathways of premature atherosclerosis have been started in SLE patients [2]. Recent advances stress on the interplay between lupus specific inflammatory factors including, inflammatory mediators, auto-antibodies, enhanced endothelial cell activation, corticosteroid-induced atherogenesis, and dyslipidemia associating renal disease together with traditional cardiac risk factors [3].

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Homocysteine (Hcy), a thiol-containing amino acid which is produced during the metabolism of methionine, leads to insulin resistance through the inhibition of insulin-receptor kinase activity in vitro, also in an insulin resistant state, elevated Hcy plasma levels may be the result of hyperinsulinemia, as observed in animal models [7]. Therefore, Hcy may be a cause and/or a consequence of insulin resistance and is considered an indicator of risk for the development of atherosclerosis [8].

It has become inevitable to detect atherosclerosis as early as possible, many physiologic measurements for plaque and endothelial dysfunction are now available, however measurement of the carotid artery intima-media thickness (CIMT), by a non invasive high-resolution B-mode ultrasound technique is now commonly accepted as a surrogate marker for subclinical atherosclerosis [9].

This study aimed to the measure serum levels of Hcy and to study the presence of the MetS in women with systemic lupus erythematosus and to correlate them with disease activity, clinical status and subclinical atherosclerosis.

2. Patients and methods

2.1. Participants

This study included 30 female patients who were regularly being followed up at the outpatient clinic and the inpatient unit of the Rheumatology and Rehabilitation department, Benha University Hospitals between November 2012 and March 2013 and met the updated American College of Rheumatology (ACR), revised criteria for the classification of SLE [10] and 20 age and sex matched apparently healthy volunteers as the control group. None of the patients were known to have any symptoms suggestive of a CVD.

All patients were subjected to full history taking, thorough clinical examination recording of the disease duration, duration and doses of current prednisolone and/or disease modifying anti-rheumatic drugs (DMARDs), disease activity evaluated by the SLE disease activity index (SLEDAI) [11] and the cumulative end organ damage in SLE assessed using the Systemic Lupus International Collaborative Clinics/American College of Rheumatology (SLICC/ACR) damage index [12]. The local ethics committee of our institution (Benha University, Faculty of Medicine) approved the study and all participants gave a written informed consent before being enrolled in this study.

2.2. Laboratory investigations

Blood specimens were collected after an overnight fasting analyzed for complete blood count (CBC), erythrocyte sedimentation rate (ESR) by Westergren’s method [13] in mm/ 1st h.

C-Reactive protein (CRP) by Latex agglutination test, Fast- ing blood sugar (FBS) Level, lipid profile [Total cholesterol (TC), triglycerides (TG), high density lipid cholesterol (HDL-C) and low density lipid cholesterol (LDL-C)], blood urea, serum creatinine levels, complete urine analysis (for urinary casts, hematuria, pyuria and albuminuria), 24 h protein in urine, anti-nuclear antibodies (ANA) by the immunofluorescence antibody test, anti-double stranded DNA (ds-DNA) antibodies by indirect fluorescent antibody test, anti phospholipid antibodies were considered positive in the presence of lupus anti-coagulants or anticardiolipin (IgG or IgM) at ≥40 units/ml.

Measurements of serum homocysteine (sHcy): Protein rich meals give higher Hcy values and were avoided late in the day before sampling. Serum samples were allowed to clot for no more than 30 min before centrifugation and separation and kept on ice prior to separation. Total sHcy was then measured with the Axis® Homocysteine Enzyme Immunoassay (EIA)
assay. (Axis-Shield Diagnostics Ltd. The Technology Park Dundee DD2 1XA, United Kingdom). Hyperhomocysteinemia was considered if the sHcy level was $\geq$15 $\mu$mol/L.

2.3. Diagnosis of metabolic syndrome (MetS)

The SLE patients and control subjects were diagnosed to have MetS according to the National Cholesterol Education Program’s Adult Treatment Panel III (NCEP-ATPIII) if they had $\geq$3 of the following: Central obesity (waist circumference $>88$ cm for females), Hypertriglyceridemia (triglycerides $\geq$150 mg/dl), Low HDL (“good”) cholesterol (<50 mg/dl for females), Hypertension (blood pressure $>130/85$ mmHg), and fasting plasma glucose ($\geq$110 mg/dl) [14].

2.4. Sonographic evaluation

Patients and controls underwent carotid ultrasonography and echocardiography on the same day of the study. Carotid scanning was done using Toshiba Xario with a 7.5 MHz probe, the CIMT was measured on each side at the following points: 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). The highest thickness among the six studied segments was recorded. In addition, the number and size of carotid atherosclerosis plaques were also recorded.

Statistical analysis: Collected data were analyzed using the SPSS version 16. Categorical data were presented as number and percentages while continuous variables were presented as mean and SD if parametric, and as median and range if non-parametric. Chi square test, Z-test, Mann Whitney U test, Kruskal-Wallis test and Spearman’s correlation coefficients were used as tests of significance. Two sided p-value $<0.05$ was considered significant.

3. Results

The SLE patients and controls were matched for ages ($p > 0.05$) and all were females. The age ranged from 19 to 50 years (32.9 ± 8.5 years) in the SLE patients and from 18 to 45 years (28.3 ± 7.67 years) in the control group. Patients’ disease durations ranged from 6 months to 20 years with a mean of 3.44 ± 4.01 years. All patients were on daily prednisolone therapy and the dose ranged from 5 to 30 mg/day with a mean of 17.5 ± 5.2 mg/day combined with 200 mg/day hydroxychloroquine. Twelve patients were on azathioprine 150 mg/day and 8 were receiving monthly cyclophosphamide infusions.

Study of the traditional risk factors in SLE patients and controls showed a highly statistically significant difference between both groups regarding most of the classical risk factors (Table 1). Twelve (40%) SLE patients fulfilled the NCEP-ATPIII criteria for the diagnosis of MetS that was statistically significantly higher than that in the control group in whom only 3 (10%) had MetS ($p = 0.04$). Several lupus-specific risk factors were also identified in the SLE patients (Table 2).

The sHcy level ranged between 15.3 and 83.2 $\mu$mol/L with a mean of 46.96 ± 22.07 $\mu$mol/L in SLE patients that was highly significantly higher than that in the control group whose level ranged between 2.2 and 5.4 $\mu$mol/L with a mean of 4.19 ± 1.49 $\mu$mol/L ($p < 0.001$) (Fig. 1). The Hcy was the highest in patients with severe disease activity (71.35 ± 11.85 $\mu$mol/L) and the lowest in those with mild activity (23.93 ± 7.97 $\mu$mol/L). Carotid US examination showed an overall increased CIMT in the SLE patients, ranging between 0.65 and 1.4 mm with a mean of 0.97 ± 0.26 mm compared to the control group (ranging from 0.3 to 0.5 mm with a mean of 0.43 ± 0.22 mm). No plaques were found in the SLE patients or the controls (Fig. 2A and B).

On comparing patients with and without MetS, SLE patients with MetS had a significantly higher sHcy (56 ± 19.31 vs 40.5 ± 21.9 $\mu$mol/L) and CIMT (1.25 ± 0.09 vs 1.25 ± 0.09 mm) ($p = 0.048$ and $p < 0.001$, respectively), (Table 3).

The mean CIMT showed a highly significant correlation ($p < 0.001$) with age ($r = 0.52$), disease duration ($r = 0.69$), SLEDAI ($r = 0.66$) (Fig. 3a), SLICC damage index ($r = 0.82$), sHcy levels ($r = 0.53$) (Fig. 3b), total cholesterol ($r = 0.51$), LDL ($r = 0.53$), TG ($r = 0.77$), FBS ($r = 0.75$), systolic ($r = 0.68$) and diastolic blood pressure ($r = 0.64$), ESR 1st h ($r = 0.61$) and negatively with C3 ($r = -0.54$), HDL ($r = -0.56$), platelets ($r = -0.55$) and white blood cell counts ($r = -0.51$), (Table 4).

Studying the relationship between sHcy and the SLE disease status, there were no significant differences in the mean sHcy levels between SLE patients regarding the presence of clinical features as malar rash ($r = 0.76$), photosensitivity ($r = 0.66$), arthritis ($r = 0.2$) or pulmonary manifestation ($r = 0.23$), except being significantly higher in patients with oral ulcer ($r = 0.015$) and nephritis ($r = 0.016$).

There were significant correlations between sHcy levels and disease duration ($r = 0.56$, $p < 0.001$), SLEDAI ($p < 0.001$) (Fig. 3c) and the SLICC ($p < 0.05$) (Fig. 3d, Table 4).

4. Discussion

Systemic lupus erythematosus (SLE) is a systemic inflammatory disease that mainly affects women. Although treatment has improved during recent decades, patients with SLE appear to have increased morbidity and mortality from CVD [15].

In this study, SLE patients had CIMT cut off point $\geq 0.65$ mm. Our results are near to those found by Marasini et al. [16] that was $\geq 0.7$ mm while in the study conducted by Rua-Figueroa et al. [17] it was $\geq 0.89$ mm and was $\geq 0.9$ mm in that done by Doria et al. [18]. This disparity among studies may be related to the difference in the studied risk factors.

Our results together with several research groups [19–22] have shown that CIMT is significantly increased in SLE patients (0.97 ± 0.26 mm) than that in the control group (0.43 ± 0.22 mm) ($p < 0.001$). As our patients were asymptomatic for CVD, this increased CIMT indicates subclinical atherosclerosis and this confirms the information that measurement of ultrasonographic CIMT is a clinically useful index for identifying early atherosclerosis.

No atherosclerotic plaques were found in the ultrasonographic carotid examination of our SLE patients and this could be traced to the fact that Caucasian SLE patients have milder disease than other ethnicities [23]. Furthermore, this
could be attributed to the small number of patients included in this study.

The current study revealed that atherosclerosis’ classical risk factors were significantly higher in the SLE patients compared to the control group regarding SBP \((p = 0.012)\), DBP \((p = 0.04)\), total cholesterol \((p = 0.001)\), LDL \((p = 0.001)\), TG \((p = 0.001)\), HDL \((p = 0.048)\), and FBS \((p = 0.003)\). These results confirmed those that have been found in previous publications \([24,25]\) although El Saadany et al. \([21]\) found no significant difference between SLE patients and controls for most of these factors except for TG and HDL. On the other hand, Doria et al. \([18]\) showed no significant difference between SLE patients and control group regarding risk factors for coronary heart disease.

In our study CIMT values significantly correlated with most traditional risk factors for atherosclerosis and these results are supportive to those found by other researchers \([18,26,27]\).

The combined effect of these risk factors expressed as MetS could form a more solid risk in the increased IMT with subsequent CVDs \([28]\). Our SLE patient group have significantly increased MetS frequency \((40\%)\) than the control group \((p = 0.04)\). Several studies so far have documented the increased frequency of MetS in patients with chronic rheumatic diseases compared to healthy control populations.

### Table 1  Traditional risk factors for atherosclerosis in the studied groups.

<table>
<thead>
<tr>
<th>Variable</th>
<th>SLE patients ((N = 30))</th>
<th>Controls ((N = 20))</th>
<th>(t)</th>
<th>(p)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>32.9 ± 8.5</td>
<td>28.3 ± 7.67</td>
<td>0.94</td>
<td></td>
</tr>
<tr>
<td>SBP (mmHg)</td>
<td>131.3 ± 24.9</td>
<td>115.5 ± 13.2</td>
<td>2.601</td>
<td>0.012*</td>
</tr>
<tr>
<td>DBP (mmHg)</td>
<td>83.8 ± 13.4</td>
<td>77.0 ± 6.56</td>
<td>2.108</td>
<td>0.04*</td>
</tr>
<tr>
<td>Creatinine (mg/dl)</td>
<td>0.99 ± 0.36</td>
<td>0.52 ± 0.22</td>
<td>5.157</td>
<td>&lt;0.001**</td>
</tr>
<tr>
<td>Cholesterol (mg/dl)</td>
<td>205.3 ± 25.4</td>
<td>165.7 ± 20.9</td>
<td>5.778</td>
<td>&lt;0.001**</td>
</tr>
<tr>
<td>HDL (mg/dl)</td>
<td>43.4 ± 17.5</td>
<td>52.0 ± 8.98</td>
<td>2.026</td>
<td>0.048*</td>
</tr>
<tr>
<td>LDL (mg/dl)</td>
<td>153.2 ± 22.7</td>
<td>128.3 ± 9.54</td>
<td>4.625</td>
<td>&lt;0.001**</td>
</tr>
<tr>
<td>TGs (mg/dl)</td>
<td>182.4 ± 94.4</td>
<td>69.7 ± 15.1</td>
<td>5.274</td>
<td>&lt;0.001**</td>
</tr>
<tr>
<td>FBS (mg/dl)</td>
<td>181.4 ± 132.04</td>
<td>88.3 ± 7.9</td>
<td>3.140</td>
<td>0.003*</td>
</tr>
<tr>
<td>Metabolic syndrome</td>
<td>+ve = 12</td>
<td>40%</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>−ve = 18</td>
<td>10%</td>
<td>3.6</td>
<td>0.04*</td>
</tr>
</tbody>
</table>

SBP = systolic blood pressure; DBP = diastolic blood pressure; HDL = high density-lipoprotein; LDL = low density-lipoprotein; TGs = triglycerides; FBS = fasting blood sugar.

* \(p < 0.05\) = significant.

** \(p < 0.001\) = highly significant.

### Table 2  Laboratory and clinical SLE specific risk factors for atherosclerosis.

<table>
<thead>
<tr>
<th>Variables</th>
<th>SLE patients ((n = 30))</th>
</tr>
</thead>
<tbody>
<tr>
<td>Range Mean ± SD</td>
<td></td>
</tr>
<tr>
<td>ESR (mm/1st h)</td>
<td>15–114</td>
</tr>
<tr>
<td>Urine protein (g/24 h)</td>
<td>0.4–3.7</td>
</tr>
<tr>
<td>C3 (mg/dl)</td>
<td>27–160</td>
</tr>
<tr>
<td>sHcy</td>
<td>15.3–83.2</td>
</tr>
<tr>
<td>+ve anti-ds-DNA (U/ml)</td>
<td>25 (83.3)</td>
</tr>
<tr>
<td>+ve CRP (mg/dl)</td>
<td>5 (16.7)</td>
</tr>
<tr>
<td>SLEDAI</td>
<td></td>
</tr>
<tr>
<td>Mild</td>
<td>10 (33.3)</td>
</tr>
<tr>
<td>Moderate</td>
<td>4 (13.3)</td>
</tr>
<tr>
<td>Severe</td>
<td>3 (10)</td>
</tr>
<tr>
<td>SLICC DI</td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>16 (53.3)</td>
</tr>
<tr>
<td>1</td>
<td>4 (13.3)</td>
</tr>
<tr>
<td>2</td>
<td>3 (10)</td>
</tr>
<tr>
<td>3</td>
<td>0</td>
</tr>
</tbody>
</table>

ESR = erythrocyte sedimentation rate; C = complement; sHcy = serum homocysteine; Anti-ds-DNA abs = anti-double stranded DNA antibodies; CRP = C-reactive protein; APL Ab = antiphospholipid antibodies; SLEDAI = systemic lupus erythematosus disease activity index; SLICC DI = Systemic Lupus International Collaborative Clinics Damage Index.

**Fig. 1** Median and inter-quartile range of the serum homocysteine in systemic lupus erythematosus patients and control.
but otherwise Chung et al. [31] found that the prevalence of MetS was 29.4% in SLE and this was not statistically significantly higher than controls (19.8%). The higher proinflammatory cytokine burden in SLE disease particularly TNFα increases the prevalence of MetS individual components; promotes adverse lipoprotein profile, impairs insulin sensitivity and also impairs endothelium-dependent vasodilatation which could facilitate the hypertension seen in MetS [32,33]. Our study confirmed that SLE patients with MetS have a higher mean CIMT than those without (p < 0.001) which was in agreement with other reports [30,31].

It is settled that atherosclerosis is an inflammatory process and becomes clear that traditional risk factors alone failed to fully account for the premature accelerated development of atherosclerosis in SLE patients [28]. Understanding the SLE-related risk factors for enhanced atherosclerosis shed more light on disease mechanisms, leading to new therapeutic strategies for the treatment of associated CVD [34].

We found that CIMT strongly correlated with the disease duration (r = 0.69), C3 levels (r = −0.54), ESR levels (r = 0.61), SLEDAI (r = 0.66) and SLICC (r = 0.82). These results agreed to those found in other studies [21,35–37]. The association of atherosclerosis with longer disease duration and higher damage scores indicate longer exposure to an inflammatory milieu and define the cumulative impact of the disease rather than individual inflammatory marker and also

<table>
<thead>
<tr>
<th>Variable</th>
<th>No MetS (n = 18)</th>
<th>MetS (n = 12)</th>
<th>t</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>sHcy (μmol/L)</td>
<td>40.5 ± 21.9</td>
<td>56.6 ± 19.31</td>
<td>2.07</td>
<td>0.048*</td>
</tr>
<tr>
<td>CIMT (mm)</td>
<td>0.79 ± 0.02</td>
<td>1.25 ± 0.09</td>
<td>8.8</td>
<td>&lt;0.001**</td>
</tr>
</tbody>
</table>

MetS = metabolic syndrome; sHcy = serum homocysteine; CIMT = carotid intima-media thickness.
* p < 0.05 = significant.
** p < 0.001 = highly significant.
can be used as a surrogate measure of inflammatory burden [38].

The association of homocysteine level and atherosclerosis in SLE patients is challenging [39] and several papers have already illustrated the role of this novel biomarker in the pathogenesis of SLE and as a risk factor for premature atherosclerosis in such patients [40]. Our results revealed a significantly higher sHcy level in the SLE patients (46.96 ± 22.07 μmol/L) compared to the controls (4.19 ± 1.49 μmol/L) and not only that but also it was significantly higher in those SLE patients with MetS (56 ± 19.31 μmol/L) compared to those without (40.5 ± 21.9 μmol/L) (p < 0.048). These results are consistent with other researches [17,30,31,38].

Our study failed to find any relation between mean sHcy levels in the SLE patients and the clinical features except being significantly higher in those with oral ulcer (p < 0.05) and nephritis (p < 0.016) as found by do Prado et al. [41] who found a significant correlation between the total Hcy concentration and renal involvement (p = 0.01). Our results confirmed a direct association between sHcy levels and the disease duration (p < 0.001), SLEDAI scores (p < 0.001), SLICC scores (p < 0.001), SLICC (p < 0.05) and CIMT values. These results were in agreement with many authors [17,37,42,43].

The Hcy contributes to atherosclerosis in many ways including endothelial injury due to release of reactive oxygen species by oxidized Hcy, increased oxidation of LDL and stimulation of smooth muscle cell proliferation [44]. Elevated Hcy concentrations may aggravate the SLE associated imbalance between endothelial damage and regeneration by increasing apoptosis [45].

Finally we can conclude that SLE itself is considered as a risk factor for accelerated atherosclerosis and this is amplified by multiple factors, e.g., active disease, presence of MetS, age of patients and hyperhomocysteinemia. Awareness of the MetS in the already high-risk SLE patients is mandatory to identify a subgroup of patients who confer a higher risk for CVD and it is recommended to measure the CIMT in those patients as may provide a useful marker for detecting subclinical cases and predicting future cardiovascular events.

**Conflict of interest**

All the authors responsible for this work declare no conflict of interest.

**Table 4** Correlations between serum homocysteine and carotid intima-media thickness (CIMT) with clinical and laboratory variables in the SLE patients.

<table>
<thead>
<tr>
<th>Variable</th>
<th>CIMT</th>
<th>sHcy</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>r</td>
<td>p</td>
</tr>
<tr>
<td>Age (years)</td>
<td>0.52</td>
<td>0.003*</td>
</tr>
<tr>
<td>Disease duration (years)</td>
<td>0.69</td>
<td>0.001**</td>
</tr>
<tr>
<td>Steroid dose (mg/d)</td>
<td>0.16</td>
<td>0.413</td>
</tr>
<tr>
<td>SBP (mmHg)</td>
<td>0.68</td>
<td>&lt;0.001**</td>
</tr>
<tr>
<td>DBP (mmHg)</td>
<td>0.64</td>
<td>&lt;0.001**</td>
</tr>
<tr>
<td>Cholesterol (mg/dl)</td>
<td>0.51</td>
<td>0.003*</td>
</tr>
<tr>
<td>HDL (mg/dl)</td>
<td>−0.56</td>
<td>0.001**</td>
</tr>
<tr>
<td>LDL (mg/dl)</td>
<td>0.53</td>
<td>0.002*</td>
</tr>
<tr>
<td>TGs (mg/dl)</td>
<td>0.77</td>
<td>&lt;0.001**</td>
</tr>
<tr>
<td>FBS (mg/dl)</td>
<td>0.75</td>
<td>&lt;0.001**</td>
</tr>
<tr>
<td>ESR (mm/1st hr)</td>
<td>0.61</td>
<td>0.02</td>
</tr>
<tr>
<td>C3 (mg/dl)</td>
<td>−0.54</td>
<td>0.04</td>
</tr>
<tr>
<td>SLEDAI score</td>
<td>0.66</td>
<td>0.001**</td>
</tr>
<tr>
<td>SLICC index</td>
<td>0.82</td>
<td>0.001**</td>
</tr>
</tbody>
</table>

CIMT = carotid intima-media thickness; sHcy = serum homocysteine; SBP = systolic blood pressure; DBP = diastolic blood pressure; HDL = high density-lipoprotein; LDL = low density-lipoprotein; TGs = triglycerides; FBS = fasting blood sugar; ESR = erythrocyte sedimentation rate; C3 = complement 3; SLEDAI = systemic lupus erythematosus disease activity index; SLICC = Systemic Lupus International Collaborative Clinics; ** p < 0.001 = highly significant. * p < 0.05 = significant. ** p < 0.05 = insignificant.

Fig. 3 Correlation between (A) the carotid intima-media thickness (IMT) with the systemic lupus erythematosus disease activity index (SLEDAI) and correlation between the serum homocysteine level with the (B) IMT, (C) SLEDAI and (D) the SLICC/ACR damage index.
Acknowledgment

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References


[34] Bulhnik IE, Teerlink T, Heijst JA, Dijkmans BA, Voskuyl AE. Raised plasma levels of asymmetric dimethylarginine are associ-


