Relation between Heart Valves Calcification and Carotid Atherosclerosis in Systemic Lupus Erythematosus

MOHAMED ABDEL GHANY, M.D.; MONA M. SOLIMAN, M.D.*; ENAS F. ABU ELHAMD, M.D. and YEHIA KISHK, M.D.

The Departments of Cardiology and Medicine*, Faculty of Medicine, Assiut University

Abstract

Objectives: Detection of relation between heart valves calcification and carotid intima-media thickness as predictors of premature atherosclerosis in patients with SLE.

Methods: 40 pre menopausal women 28.57 ± 8.24 (18-46) years with SLE satisfying the updated revised criteria for the classification of SLE, were included in the study.

Traditional risk factors for atherosclerosis and disease-related factors as disease duration and duration of steroid therapy were recorded. Patients were subjected to carotid Duplex assessment and echocardiography examination.

Results: IMT was increased in 27 (67.5%) patients, with relatively younger age of onset (mean age 28.57 ± 8.24 years), a significant positive correlation between thickened IMT and age, duration of disease, duration of steroid therapy, total cholesterol level, triglycerides level (\( p \)-value < 0.05) (\( r \)-value = 0.6, 0.63, 0.68, 0.35, 0.04, 0.36 respectively).

Prevalence of mitral valve leaflet calcification was (77.7%), mitral annular calcification was (47.5%), aortic valve calcification was (87.5%).

Thickened IMT was present in 21 patient (67.7%) with mitral valve leaflet calcification, 13 patient (68.4%) with mitral annular calcification, 25 patient (71.4%) with Aortic valve calcification and in 12 patient (70.6%) with both mitral and aortic calcification but these associations were statistically insignificant (\( p \)-value > 0.05).

Conclusion: Increased IMT in SLE patients is associated with disease-related risk factors, disease duration, duration of steroid therapy. High prevalence of heart valves calcification in SLE indicate that SLE is a significant risk factor for premature LV valve calcification.

There was no statistically significant correlation between increased IMT and valve calcification, this may be due to smaller size of our sample and relatively younger age of our patients.

Key Words: Heart valves – Calcification – Carotid atherosclerosis – Erythemasus.

Introduction

SYSTEMIC Lupus Erythematosus (SLE) is a chronic inflammatory disease characterized by widespread immunological abnormalities and multiorgan involvement, SLE affects mainly young women, a group usually free of atherosclerosis [1,2].

Atherosclerosis is a chronic autoimmune inflammatory disease, characterized by lipoproteins metabolism alteration that leads to formation of pro-inflammatory and pro-oxidative and immune response [3].

Premature atherosclerosis in SLE was first noted in necropsy studies by Bulkley and Roberts [4] and subsequently confirmed in a survival study by Urowitz et al. [5,6].

Since then, early clinical and subclinical atherosclerotic features have been demonstrated in SLE by several groups with reports up to 30% of deaths in SLE patients being due to coronary artery disease [7].

Premature atherosclerosis and coronary heart disease (CHD) has also emerged as a major cause of morbidity and mortality in patients with SLE. Overall SLE patients have a 5-6 folds increased risk of CHD and this excess risk is especially pronounced in younger women where the excess risk may be >50-folds. Several studies have also demonstrated that SLE patients have a higher prevalence (about 30%) of subclinical atherosclerosis compared with controls [8,9].

In patients with SLE, the prevalence of coronary-artery atherosclerosis is elevated and the age at onset is reduced. Early detection of atherosclerosis may provide an opportunity for therapeutic
intervention. Also studies found relative risks of 5 to 7 for myocardial infarction in SLE patients compared to healthy controls [10].

The pathogenesis of premature atherosclerosis in lupus is multifactorial and includes traditional CV risk factors, lupus-related factors and inflammatory risk factors [11].

The Toronto Lupus Cohort Study reported that SLE patients with CV events have a greater total number of traditional CV risk factors including hypertension, diabetes, dyslipidaemia, tobacco use and sedentary lifestyle than lupus patients without events [6].

Lupus related factors including disease activity, duration, autoantibodies, lupus nephritis, premature menopause, corticosteroid therapy, play important role in accelerated atherosclerosis in SLE [12,13].

The determination of classic and new risk factors, together with specific autoantibody titers and the use of Doppler carotid ultrasound, are useful methods to detect early atherosclerosis [10,14].

Valvular calcification is generally considered a manifestation of atherosclerosis. Particularly, aortic valve calcification (AVC) and mitral annular calcification (MAC) were reported to be associated with both cardiovascular risk factor [34] and coronary artery calcification (CAC) [14-16].

Recent epidemiological studies have also demonstrated that the combined presence of both AVC and MAC is associated with cardiovascular mortality than is AVC or MAC alone [17].

There is limited data regarding the correlation between heart valves calcification & IMT as markers of premature atherosclerosis in patients with SLE. Our aim, was to detect the relation between heart valves calcification and carotid intima-media thickness as predictors of premature atherosclerosis in patients with SLE [18,19].

**Patients and Methods**

This study was Cross-sectional study, it was conducted at Cardiology Department, Assiut University on 40 SLE patients, those patients were either outpatient attender or inpatient from Internal Medicine and Rheumatology & Rehabilitation Departments from January 2011 to January 2012.

Forty premenopausal females who fulfilled the updated American College of Rheumatology Classification Criteria for SLE were included in the present study [20].

**Exclusion criteria:**
- Male patients.
- Post menopausal females.
- Age \( \geq 65 \) years.
- Chronic renal impairment (serum creatinine \( \geq 3 \)mg/dl).
- Other connective tissue disease.

- **Clinical Assessments:**
  All SLE patients were subjected to full history taking, full clinical examination, assessment of risk factors such as Hypertension (was defined as systolic arterial pressure above 140mmHg and/or diastolic arterial pressure above 90mmHg), Dyslipidemia, DM (diagnosed as random blood glucose \( > 200 \)mg/dl or fasting blood glucose \( > 126 \)mg/dl).

- **Lipogram:**
  Lipid levels were measured by routine technique after fasting period of at least 8 hours. Dyslipidemia was diagnosed if plasma cholesterol exceeded 6.21mmol/l, plasma LDL cholesterol exceeded 3.36mmol/l, plasma triglycerides exceeded 2.26mmol/l.

- **Duplex Ultrasoundography:**
  Carotid arteries of the patients were evaluated using high resolution B-mode ultrasound equipment Philips, HDI 5000 (sonos) equipped with a linear probe (5-12MHz) with the use of standardized protocol [20]:
  - **Measurement of IMT:**
    It was done in the far wall of the distal CCA. It was measured as the distance between the lumen-intima interface and the media-adventia interface. At least three measurements were taken and the maximum was considered on each side. IMT is considered abnormal if \( \geq 0.07 \)cm (this value was used by most of studies). Plaque was defined as a maximum IMT \( \geq 1.5 \)mm [21].

- **Transthoracic Echocardiography**
  Complete two-dimensional (2D) and Doppler color flow examinations were performed with the Philips, HDI 5000 (Sonos) equipped with Harmonic 53 transducer.

  MAC was defined as an intense echo-producing structure located at the junction of the atrioventricular groove and posterior mitral valve leaflet on the parasternal long-axis, apical 4-chamber view, or the parasternal short-axis view [18].

  AVC was defined as focal areas of increased echogenicity and thickening of the aortic valve
The echocardiographic study also included the assessment of left and right-side atrial and ventricular size, contractility and function as well as the detection of valvular stenosis or regurgitation by color Doppler.

- Statistical Analysis:
  Data were analysed by statistical package for the social sciences (SPSS, version 16.0). The following statistics were carried out:
  - Descriptive statistics:
    The ranges, means, standard deviations were calculated for interval and ordinal variables and the frequencies and percentages for categorical variables [23].
  - Comparisons:
    Comparisons between the different groups of patients were made by two-sample t-tests for continuous variables and by chi-square analysis for categorical variables.
  - Correlation:
    The univariate correlation between IMT and all included variables was assessed by Pearson correlation coefficient ($r$) which were calculated to detect the strength and significance of association between pair of variables measured on the interval, ordinal, dichotomous scale in each patient group separately.
  - The probability of significance ($p$-value):
    The probability ($p$-value) less than 0.05 was taken as the limit of statistical significance.

Results

- Patient characteristics:

Demographic data of the patients:
  Table (1) shows the clinical characteristics, lipid profile and IMT measures of our patients.

| Table (1): Patients characteristic of SLE patients. |
|----------------------------------|------------------|------------------|
| Demographic data of the patients: | Mean±SD (range)   |
| Age                             | 28.57±8.24 (18-46) |
| Duration of disease (months)    | 44.17±26.69 (12-120) |
| Duration of steroid (months)    | 40.50±24.97 (12-120) |
| Cholesterol (mg/dl)             | 200.27±32.59 (146-322) |
| Triglycerides (mg/dl)           | 174.52±49.97 (64-312) |
| HDL (mg/dl)                     | 42.05±8.10 (25-72) |
| LDL (mg/dl)                     | 110.72±25.44 (72-217) |
| Mean IMT (mm)                   | 0.79±0.2 (0.4-1.5) |
| Right IMT (mm)                  | 0.79±0.2 (0.2-1.5) |
| Left IMT (mm)                   | 0.83±0.2 (0.5-1.4) |

HDL: High density lipoprotein.
IMT: Intima media thickness.
LDL: Low density lipoprotein.

- Carotid ultrasound findings:
  Thicked IMT was found in 27 patients (67.5%) only one patient (2.5%) had carotid plaque (Table 2).

- Heart valves calcification:
  Mitral valve leaflet calcification was present in 31 patients (77.7%), mitral valve annular calcification was present in 19 patients (47.5%), aortic valve Calcification was present in 35 patients (87.5%) and both mitral and aortic valve calcification were present in 17 patients (42.5%) (Table 2).

<table>
<thead>
<tr>
<th>Table (2): Duplex Ultrasound and Echocardiographic findings.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal IMT</td>
</tr>
<tr>
<td>Thickened IMT</td>
</tr>
<tr>
<td>Plaque</td>
</tr>
<tr>
<td>MVL Calcification</td>
</tr>
<tr>
<td>MVA Calcification</td>
</tr>
<tr>
<td>AVL Calcification</td>
</tr>
<tr>
<td>Both Mitral and Aortic Calcification</td>
</tr>
</tbody>
</table>

MVL: Mitral valve leaflet.
MVA: Mitral valve annular.
AVL: Aortic valve leaflet.

- Comparative study:
  In this study, patients with thickened IMT were older than patients with normal IMT with a mean age of (30.25±8.66 years) versus (25.7 ±6.2 years) ($p$-value >0.05).

  Also patients with thickened IMT had longer mean duration of the disease compared to patients with normal IMT (50.33±25.62 months) versus (31.38±25.11 months) ($p$-value <0.05). Also patients with thickened IMT have longer mean duration of steroid therapy in comparison to patients with normal IMT (47.11±24.66 months) versus (26.76±20.14 months) ($p$-value <0.05) (Table 3).

  There was statistically significant association between thickened IMT and mean levels of total cholesterol (209.51 ±33.19mg/dl) ($p$-value <0.05) as well as mean triglycerides level (188.25 ±51.04mg/dl) ($p$-value <0.05) (Table 3).

  Also, there was increase in the mean IMT (0.98±0.10mm) in patients with risk factor (2 patients) than mean IMT (0.77±0.18mm) in patients without risk factor (38 patients) ($p$-value >0.05).
SLE patients with heart valve calcification, either on the mitral valve or the aortic valve or both, have higher mean IMT than patients without calcification (0.82±0.2 versus 0.73±0.1) (0.8±0.1 versus 0.67±0.08) (0.83±0.25 versus (0.77±0.13) respectively (p-value >0.05) (Table 4).

In comparison between SLE patients with normal and thickened IMT regarding heart valve calcification, it was found that thickened IMT was present in 21 patients (67.7%) with mitral valve leaflet calcification, 13 patients (68.4%) with mitral annular calcification, 25 patients (71.4%) with Aortic valve calcification and in 12 patients (70.6%) with both mitral and aortic calcification, but these associations were statistically insignificant (Table 5).

**Correlations**

There was significant positive correlation between mean IMT and the following (Table 6):
- Age (p-value <0.01).
- Duration of disease (p-value <0.01).
- Duration of steroid therapy (p-value <0.01).
- Total cholesterol level (p-value <0.01).
- Triglyceride level (p-value <0.01).
- Low density lipoprotein (p-value <0.01) and significant negative correlation with high density lipoprotein (p-value <0.01).

**Multiple regressions**

In our study only total cholesterol was a predictor of Thickened IMT, (p-value 0.01), confidence interval 1.015-1.187, odds ratio 1.098.

### Table (3): Comparison between SLE patients with normal and thickened IMT regarding patients characteristics.

<table>
<thead>
<tr>
<th>Variables</th>
<th>SLE patients with normal IMT (13)</th>
<th>SLE patients with thickened IMT (27)</th>
<th>t</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean±SD</td>
<td>Mean±SD</td>
<td></td>
<td>-----</td>
<td>--------</td>
</tr>
<tr>
<td>Total cholesterol</td>
<td>181.07±21.74</td>
<td>209.51±33.19</td>
<td>–2.8</td>
<td>0.008**</td>
</tr>
<tr>
<td>Triglycerides</td>
<td>146.00±34.11</td>
<td>188.25±51.04</td>
<td>–2.6</td>
<td>0.01*</td>
</tr>
<tr>
<td>HDL</td>
<td>43.00±5.38</td>
<td>41.59±9.11</td>
<td>0.5</td>
<td>0.6</td>
</tr>
<tr>
<td>LDL</td>
<td>101.23±17.29</td>
<td>115.29±29.68</td>
<td>–1.67</td>
<td>0.1</td>
</tr>
<tr>
<td>Age (years)</td>
<td>25.7±6.2</td>
<td>30.25±8.66</td>
<td>–1.9</td>
<td>0.06</td>
</tr>
<tr>
<td>Duration of disease (months)</td>
<td>31.38±25.11</td>
<td>50.33±25.62</td>
<td>–2.2</td>
<td>0.03*</td>
</tr>
<tr>
<td>Duration of steroid (months)</td>
<td>26.76±20.14</td>
<td>47.11±24.66</td>
<td>–2.5</td>
<td>0.01*</td>
</tr>
</tbody>
</table>

HDL: High density lipoprotein. IMT: Intima media thickness. **significant correlation if p-value <0.05.

### Table (4): Correlation between M.IMT and heart valve calcifications.

<table>
<thead>
<tr>
<th>IMT</th>
<th>Patients with calcification</th>
<th>Patients with out calcification</th>
<th>t</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>MVL</td>
<td>Mean±SD</td>
<td>Mean±SD</td>
<td></td>
<td></td>
</tr>
<tr>
<td>MVA</td>
<td>0.82±0.2</td>
<td>0.73±0.1</td>
<td>0.1</td>
<td>0.2</td>
</tr>
<tr>
<td>AVL</td>
<td>0.8±0.1</td>
<td>0.67±0.08</td>
<td>1.69</td>
<td>0.09</td>
</tr>
<tr>
<td>Both mitral and aortic</td>
<td>0.82±0.23</td>
<td>0.77±0.14</td>
<td>0.9</td>
<td>0.37</td>
</tr>
</tbody>
</table>


### Table (5): Comparison between SLE patients with normal and thickened IMT regarding heart valve calcification.

<table>
<thead>
<tr>
<th>IMT Calcific</th>
<th>Thicken IMT</th>
<th>Normal IMT</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>MVLCalcification</td>
<td>21 (67.7%)</td>
<td>10 (32.3%)</td>
<td>0.9</td>
</tr>
<tr>
<td>MVAcalcification</td>
<td>13 (68.4%)</td>
<td>6 (31.6%)</td>
<td>0.9</td>
</tr>
<tr>
<td>AVLcalcification</td>
<td>25 (71.4%)</td>
<td>10 (28.6%)</td>
<td>0.1</td>
</tr>
<tr>
<td>Both Mitral annular and Aortic Calcification</td>
<td>12 (70.6%)</td>
<td>5 (29.4%)</td>
<td>0.07</td>
</tr>
</tbody>
</table>


### Table (6): Correlation between carotid M.IMT and disease variables.

<table>
<thead>
<tr>
<th>Disease variables</th>
<th>Correlation (r)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>0.60</td>
<td>0.000**</td>
</tr>
<tr>
<td>Duration of disease</td>
<td>0.63</td>
<td>0.000**</td>
</tr>
<tr>
<td>Duration of steroid</td>
<td>0.68</td>
<td>0.000**</td>
</tr>
<tr>
<td>Cholesterol</td>
<td>0.35</td>
<td>0.000**</td>
</tr>
<tr>
<td>Triglycerides</td>
<td>0.40</td>
<td>0.000**</td>
</tr>
<tr>
<td>HDL</td>
<td>–0.33</td>
<td>0.000**</td>
</tr>
<tr>
<td>LDL</td>
<td>0.36</td>
<td>0.000**</td>
</tr>
</tbody>
</table>

HDL: High density lipoprotein. LDL: Low density lipoprotein.
Discussion

Atherosclerosis is a major cause of morbidity and mortality in SLE. In this study, we demonstrated that increased IMT, as a measure of atherosclerosis, is prevalent in SLE patients (67.5%). This high prevalence of premature atherosclerosis in our study may be attributed to difference in ultrasound equipment or even using the same equipment with different frequency or different resolution could result in such variability, common carotid artery IMT using ultrasound with high frequency may allow more accurate results than that of limited resolution. Different scanning and reading protocols could also influence the results.

Different sites and methods of carotid measurement may account for different results. Some studies focused on the common carotid IMT [8,24], others on the internal carotid IMT, and others on the average IMT in the common carotid artery, carotid bulb and internal carotid artery [7].

In this study, we use the average IMT in the common carotid artery, carotid bulb and internal carotid artery then the mean IMT of both right and left carotid arteries were calculated.

Another important factor is that the cut off point between normal and high IMT was different between studies. In Doria et al. study [20] normal IMT was defined when complex intima-media is ≤0.09 cm, therefore IMT values ≥0.09 cm were considered indicative of thickened intima. In our study, IMT is considered abnormal if ≥0.07 cm (this value was used by most of studies [28]).

High prevalence of premature atherosclerosis in this study in association with low prevalence of traditional risk factor in the study (7.5%) may be indicative of the impact of other factors which had not been assessed in our study, other than traditional risk on pathophysiology of premature atherosclerosis including inflammatory and non traditional risk factors such as CRP, Homocysteine, pro inflammatory cytokines, CD40-CD40 ligand. Also may be due to the effect of lupus related factor as disease activity, disease duration, corticosteroid therapy, auto antibodies and lupus nephritis [11].

In the present study, atherosclerotic plaque was detected in only one patient (2.5%) in other studies, a prevalence rates of 13%, 19%, and 50% of SLE patients who had an atherosclerotic plaque were reported by Marasisi et al. [25], El-Magadmi et al. [8] & Souza et al. [26] respectively.

The main explanation for such variability is most likely due to difference in the characteristics of the group. Our patients were much younger, with shorter disease duration than patients evaluated in other studies [24,26].

Another important factor is that only premenopausal females were included in our study in order to avoid the strong confounding effect of pre-versus post-menopausal estrogen level on the risk of vascular disease. The prevalence of plaque had been higher (50-67%) in studies that included middle-aged and post menopausal women, and this reflects the influence of age [27].

Difference in plaque definition may account also for such difference. In this study plaques were defined as Intima-media thickness ≥1.5 mm [17].

In Roman et al., study [24], plaque was defined as focal protrusion of more than 50% of the surrounding wall.

Our patients were much younger (mean age 28 years) with shorter disease duration 44.17 ±26.69 months i.e. 12-120 months younger than patients studied by El Magadm et al. [8] and Roman et al. [24] with a mean age of 37 ±14 years with a mean disease duration of 98 months (33-178). This may explain low prevalence of risk factors in our patients.

The relatively earlier age at onset of our sample may be attributed to methodological differences between the studies or alternatively may reflect a tendency of SLE to occur at an earlier age in our patients in comparison with Western populations as reported for Rheumatoid Arthritis [28].

Also in our study, there is higher mean levels of total cholesterol and triglycerides in patients with thickened IMT than patients with normal IMT (209.51±33.19 versus 181.07±21.74) (188.25±51.04 versus 146.00±34.11) respectively.

El Magadmi et al. [8], found that high levels of total cholesterol, triglycerides, LDL and low level of HDL cholesterol in patients with SLE in comparison with control.

In another study Karina de Leeuw et al. [29], lipid levels were found in control subjects higher than SLE patients.

Altered lipids profile seen in our patients may be attributed to corticosteroid therapy. In our study, patients with thick IMT had longer duration of corticosteroid therapy than patients with normal IMT. Some authors have proposed that the use of
glucocorticoids in SLE patients may contribute to higher levels of serum triglycerides, cholesterol and LDL cholesterol [30].

Insignificant association found in our study between the levels of HDL and LDL in patients with normal and thickened IMT may be due to smaller size of our sample.

In our study, a positive significant correlation was found between thickened IMT and duration of steroid therapy. Bulkley and Roberts [4] found evidence of atherosclerosis in over 50% of autopsy specimens from patients with SLE who had treated with corticosteroid for more than 12 months.

Doria et al. [7], found an association between the cumulative dose of prednisone and plaque.

In the light of these results, it can be concluded that steroid exposure is clearly an important factor in the process of atherosclerosis.

Regarding heart valve calcifications, in this study, mitral valve leaflet calcifications were found in 31 patients (77.7%), mitral annular calcification (MAC) found in 19 patients (47.5%), aortic valve calcification (AVC) in 35 patients (87.5%) and both mitral and aortic calcifications were found in 17 patients (42.5%). This finding is particularly impressive in light of the relatively young age of our patients (28.57 ± 8.24 years) compared to Molad et al. [31] (mean age 45.9 ± 14.7 years), and non-SLE patients with either MAC or AVR in other studies (mean age >70 years) [18,22].

Our findings are consistent with previous echocardiographic studies in SLE patients, which demonstrated valve calcification in 0.04-14% [32,33].

Thus, this study suggests that SLE is a significant risk factor for premature LV valve calcifications.

Also, our study demonstrated significant positive correlation between presence of aortic valve calcifications (AVC) and duration of disease, duration of steroid therapy and LDL levels but no significant correlation found with other valve calcifications.

Molad et al. [31] were the first to provide evidence of high prevalence of valve calcification in patients with SLE, and a positive correlation with vascular atherosclerosis. They also, revealed a significant positive correlation between the presence of MAC and patient age, higher score of SLE damage Index, duration of SLE. Also they found significant positive correlation between MAC, AVC and levels of serum creatinine, and IgA anticoagulipin antibody, also significantly and positively correlated with diabetes mellitus, and hypercholesterolemia.

Difference between the two studies may be due to methodological difference, smaller size of our sample which lead to low prevalence of traditional risk factor as DM, HTN. In our study we did not measure serum creatinine, IgA anticoagulipin antibody.

The initial aim of our study was to compare the possible association of carotid IMT and heart valve calcification, however our analysis found that SLE patients with heart valve calcification, either on the mitral or the aortic valves or both, have higher mean IMT than patients without calcification (0.82±0.2 versus 0.73±0.1) (0.8±0.1 versus 0.67±0.08) (0.83±0.25 versus (0.77±0.13) respectively, but this was statistically insignificant.

This study also found that thickened IMT is present in 21 patients (67.7%) with mitral valve leaflet calcification, 13 patients (68.4%) with mitral annular calcification, 25 patients (71.4%) with Aortic valve calcification and in 12 patients (70.6%) with both mitral and aortic calcification, but these associations were statistically insignificant.

Up to our knowledge, this study was the first to detect a relation between carotid IMT and heart valve calcification as markers of premature atherosclerosis in SLE patients, so it was the first study to show high prevalence of thickened IMT in patients with heart valve calcification in SLE patients but we failed to prove any statistically significant correlation between them. This may be due to smaller size of our sample and relatively younger age of our patients.

Premature atherosclerotic cardiovascular and cerebrovascular diseases are leading causes of morbidity and mortality patients with SLE compared to age- and sex-matched individuals in the general population [31], so detection of a relation between IMT and heart valve calcification may provide early therapeutic intervention for management of SLE patients with premature atherosclerosis.

Our study suggests that other studies on larger series of SLE patients are needed to put light on our result and detect if there is a significant relation between IMT and heart valve calcification or not and detection of a relation between both markers together and result of coronary angiography.
References

1. BRUCE I.N.: ‘Not only... but also’: Factors that contribute to accelerated atherosclerosis and premature coronary heart disease in systemic lupus erythematosus. Rheumatology, 44: 1492-1502, 2005.


