



## The Relationship Between Atherosclerosis and the Intima Media Thickness of Carotid Arteries With Serum C-Reactive Protein Levels in Patients With Systemic Lupus Erythematosus

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### ARTICLE INFO

*Article type:*  
Original Article

*Article history:*  
Received: 06 Jun 2012  
Revised: 16 Jun 2012  
Accepted: 26 Jun 2012

*Keywords:*  
Systemic Lupus Erythematosus  
Carotid Intima-Media Thickness  
Atherosclerosis  
C - Reactive Protein

### ABSTRACT

**Background:** Patients with systemic lupus erythematosus (SLE) are more prone to atherosclerosis and cardiovascular diseases due to atherosclerosis and consequently death.

**Objectives:** The aim of this study was to explore a possible relationship between the intima media thickness (IMT) of carotid arteries and the levels of C-reactive protein (CRP) in SLE patients.

**Patients and Methods:** Sixty SLE patients and 60 healthy persons, being matched in age, ethnicity, gender and body mass index, were recruited for the study. The thickness of intima-media of the carotid arteries and the levels of CRP were measured using color Doppler ultrasonography and highly sensitive CRP measurement methods, respectively then findings were compared between the two groups.

**Results:** Ultrasonographic evaluation showed atherosclerosis in 6 (10%) and 3 persons (5%) of the patients and control groups, respectively ( $P = 0.298$ ). The mean thickness of intima-media was not significantly different between the two groups ( $P = 0.31$ ). But the mean level of CRP was significantly higher in patients group ( $P = 0.005$ ).

**Conclusions:** We could not find any relationship between the serum CRP level and the risk of atherosclerosis progression in patients with SLE. Perhaps, SLE alone is not an independent risk factor for atherosclerosis.

### ► Implication for health policy/practice/research/medical education:

According to the results of this study, although the atherosclerotic plaque in carotid arteries of SLE patients seemed to be more prevalent than the control group, statistical analyses did not show significant difference between the two groups. However, further studies on this patient are necessary.

### ► Please cite this paper as:

Zakeri Z, Saneie Sistani S, Bari Z, Ansari Moghaddam A, Imani M, Miradi MR, Sandoughi M. The Relationship Between Atherosclerosis and the Intima Media Thickness of Carotid Arteries With Serum C-Reactive Protein Levels in Patients With Systemic Lupus Erythematosus. *J Health Scope*. 2012;1 (2): 57-60.

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## 1. Background

Systemic lupus erythematosus is a multi-system autoimmune disease involving almost all parts of the body. Heart is one of the main organs involved in the disease, leading to significant morbidities and mortality. The risk of cardiovascular involvement rises from 6% to 45% in women compared with men suffering from SLE (1). , Moreover Autopsy evaluations have shown severe atherosclerosis of the coronary arteries in up to 40% of SLE patients, compared with 2% in non-SLE population (2). Even acute myocardial infarction has been reported in young women with SLE (3). The mortality rate caused by acute myocardial infarction is 10 times higher in SLE patients compared with non-SLE persons being matched in age and sex (4, 5). Furthermore, the presence of atherosclerotic plaque is more prevalent in ultrasonography assessment of carotid arteries in SLE patients (6). The main risk factors for accelerated atherosclerosis in SLE patients include: presence of diabetes mellitus, hypertension, and hyperlipidemia, familial history of cardiovascular diseases, obesity, sedentary life-style and smoking. Other less important risk factors include chronic nephritis, high levels of anti-dsDNA and anti-phospholipid antibodies (7-9). The IMT of more than 1 millimeter in carotid arteries is called an atherosclerotic plaque. It is shown that 0.2 mm increase in IMT can lead to 33% and 28% increased risks of myocardial infarction and cardiac stroke in SLE patients, respectively (6, 10-14). Therefore, it may be concluded that IMT measurement can be considered as a reliable marker for evaluating the presence of atherosclerosis in SLE patients. CRP is an immune marker, increased in inflammatory diseases such as SLE. The increase in CRP levels is proven to be a risk factor for cardiovascular events. Also, the American association of cardiology has recently advised to take highly sensitive CRP (hs-CRP) into account, while evaluating cardiovascular diseases (15, 16). It seems essential to find methods to evaluate the risk of cardiovascular diseases in patients with SLE, in order to prevent or at least diminish the progression of cardiovascular diseases. In the present study we measured the IMT of carotid arteries as an indicator for progression of atherosclerosis in all arteries of the body including coronary arteries. Also, we measured CRP in order to find a possible relationship between the levels of CRP and increased IMT/ atherosclerosis.

## 2. Patients and Methods

Sixty SLE patients, Fifty four females and 6 males, referring to rheumatologic clinics of Zahedan city, in which the disease was confirmed by a rheumatologist, have been recruited for the study. The American College of Rheumatology's "Eleven Criteria of Lupus" was used for the definite diagnosis (17). These patients were considered as the case group. Also 60 healthy people being

**Table 1.** Demographic Parameters of the Participants in Each Group

	Case Group	Control Group	P-value
Age, y	30.8 ± 11.1	31.1 ± 10.2	0.92
Ethnicity, Baluch/Fars	36/24	38/22	0.88
BMI <sup>a</sup> , kg/m <sup>2</sup>	24.7 ± 4.5	24.7 ± 4.4	0.94

<sup>a</sup> Abbreviations: BMI; body mass index

matched with the case group in their age, sex, ethnicity and body mass index (BMI) entered the study as the control group (Table 1). The exclusion criteria were just for choosing control group included: age < 15 years, previous history of cardiovascular or peripheral vascular diseases, smoking, diabetes mellitus, hypertension, hyperlipidemia infectious disease or inflammatory diseases, and familial history of cardiovascular or rheumatologic diseases in first degree relatives. The exclusion criteria were applied by history taking and physical examinations. For exclusion of diabetes and hyperlipidemia, lab tests were performed. Control group were chosen among volunteer medical students or nurses of Imam Ali hospital of Zahedan city. All participants were informed about the study and informed consents were taken from all the participants. The study was approved by the Ethics Committee of Zahedan University of Medical Sciences. Both case and control groups were evaluated by the same ultrasonography's to measure the IMT of right and left common carotid arteries, carotid bulbs and internal carotid arteries (using voluson 730 PRO sonograph, 2007, Austria; and probe: SP6-12). The sonographer was blinded to the study design. The mean and the maximum IMT were recorded for each subject and if the IMT was more than 1 mm, it was considered as an atherosclerotic plaque. Also, the levels of serum CRP were measured by highly sensitive CRP assessment method (immunoturbidimetric assay; Pars-Azmun Company) for all the participants. The laboratory technician was also blinded to the groups' participants. Data was analyzed using T-test and chi-square test (using SPSS software, version 18).

## 3. Results

The mean duration of SLE disease was 1429 days from the diagnosis and the mean duration of corticosteroid treatment was 1049 days (with a mean dose of 6.83 mg/day of prednisolone). After evaluating the presence of atherosclerotic plaque between the 2 groups, 6 persons (10%) in the SLE group and 3 persons (5%) in the control

**Table 2.** Comparing IMT<sup>a</sup> and CRP<sup>a</sup> Levels Between the 2 Groups

	Case Group	Control Group	P-value
Age, y	30.8 ± 11.1	31.1 ± 10.2	0.92
Ethnicity, Baluch/Fars	36/24	38/22	0.88
BMI <sup>a</sup> , kg/m <sup>2</sup>	24.7 ± 4.5	24.7 ± 4.4	0.94

<sup>a</sup> Abbreviations: BMI; body mass index, CRP; C-reactive protein, IMT; intima media thickness

group had been found to have atherosclerotic plaque in their carotid arteries using Doppler ultrasonographic assessment. Despite the fact, these rates did not show any significant difference between the 2 groups ( $P = 0.298$ ) (Table 2). The maximum thickness of intima media of the carotid arteries were  $0.65 \pm 0.28$  mm and  $0.59 \pm 0.23$  mm in the SLE and control groups, respectively, showing no significant difference between the 2 groups ( $P = 0.19$ ). Furthermore, the mean thickness of intima media of the carotid arteries were  $0.48 \pm 0.11$  mm and  $0.46 \pm 0.11$  mm in the SLE and the control groups, respectively. But these rates were not significantly different between the two groups ( $P = 0.31$ ). The mean level of CRP was significantly higher in the SLE patients than the control group ( $3.04 \pm 1.55$  mg/L vs.  $2.37 \pm 0.96$  mg/L, respectively) ( $P = 0.005$ ). Generally the results of our study did not show any significant higher prevalence of atherosclerosis in SLE patients. Also, it did not show any relationship between the presence of atherosclerotic plaque and the level of CRP in the SLE group, when compared with the control group. Furthermore, no significant relationship between the thicknesses of intima-media and serum CRP levels in both groups was observed.

#### 4. Discussions

The main aim of this study was to assess the relationship between CRP levels and IMT and also to determine the prevalence of subclinical atherosclerosis in SLE patients compared with a control group. According to the results of our study, while the prevalence of atherosclerotic plaque in carotid arteries of SLE patients seemed to be higher than the control group, but statistical analyses did not show any significant difference between the two groups. Furthermore we could not introduce SLE disease as an independent risk factor for atherosclerosis. These are in contrast with the results of Fischer and Brzosko study performed in 2009 which reported the prevalence of subclinical atherosclerosis in up to 30-40% of their SLE patients (18). Also, our results are against the findings of an investigation achieved by Manzi in 1999 (19). She reported that SLE patients aged 35-44 years were 50 times more likely to develop atherosclerosis and myocardial infarction than the age-matched controls. However, in our study the mean age of SLE patients was young (30.8 years) and simultaneously we omitted risk factors for atherosclerosis in both case and control groups. But our results did not show any higher prevalence of subclinical atherosclerosis in young SLE patients compared with the control group. The serum level of CRP was significantly higher in SLE patients ( $P = 0.005$ ). Similar to a study performed by Lorenz *et al.* in 2007 (20). Despite the fact our results did not show a significant relationship between increased IMT and serum CRP levels. But some factors might have interfered with the possible relationship. First, we excluded those SLE patients with a

history of cardiovascular diseases. Secondly, most of the patients had been under effective treatment for at least 6 months, which may play an important role in lowering the level of serum CRP and as a result, preventing or at least delaying the progression of atherosclerosis. Furthermore, compared with other studies (3), our patients were almost young. The younger age of SLE patients in our study (30.8 years) indicates that the disease has been diagnosed at early stages and then the treatment had been started quickly. Since inflammatory mechanisms of SLE can predispose atherosclerosis formation, starting treatment and corticosteroids prescription might have decreased inflammation through controlling and lowering the severity and activity of the disease and therefore, might have prevented or at least delayed atherosclerosis formation/progression. In 2005, Rhee emphasized on early controlling of the disease in primary stages in order to prevent atherosclerosis progression (21). Since in our study, most of the patients had used corticosteroids for almost a long time, this might have an effective role in preventing the progression of atherosclerosis or lowering the levels of CRP in our patients. Therefore this might have also influenced a possible relationship between IMT and CRP levels in our patients. According to a study performed by Roman in 2003, better control of the disease activity was correlated with lower carotid atherosclerosis. Also, in the mentioned study, those patients taking higher doses of corticosteroids were less likely to develop atherosclerotic plaque (6). On the other hand, we measured CRP level in a short period of time. But atherosclerosis is a chronic process which takes a long time to progress. This might have also interfered with the relationship between CRP level and the presence of atherosclerosis. Totally, the younger age of our patients at diagnosis, the beginning of effective treatment at primary stages of the disease and the use of corticosteroids might have played a role in lowering the formation of atherosclerotic plaques and the thickness of intima-media. One of the limitations of our study was that we did not consider cytotoxic or other anti-inflammatory drugs as an interfering factor in our patients. According to the results of a study performed by Molad in 2002, an inverse correlation was found between anti-malaria use and the extent of organ failures in SLE patients (6). We also did not investigate a possible relationship between diastolic blood pressure and lupus nephritis with IMT. This is another limitation of our study, since nephritis can be considered as an indicator of vascular involvement (8). Another limitation of our study was the absence of investigating anti-phospholipid antibodies. In 2005, Wagner reported the prevalence of atherosclerosis in up to 50% of SLE patients (22). The difference between the results can be due to differences in ethnicity, life-style and the presence or absence of cardiovascular risk factors, younger age of our patients and shorter duration of the disease

among our patients. In conclusion, since anti-inflammatory, cytotoxic or corticosteroid treatment can interfere with the level of serum CRP and atherosclerosis, it seems better to perform further studies exactly at the beginning of the disease and before initiating the treatment. Also, other investigations on older patients with longer duration of the disease are offered. Besides, further studies on patients receiving immunosuppressive drugs such as azathioprine, mycophenolate or cyclophosphamide may show the effects of these drugs on lowering the risk of atherosclerosis in SLE patients.

## Acknowledgements

None declared.

## Authors' Contribution

Zahra Zakeri (50%), ZohreBari (40%), MahnazSandoughi (10%)

## Financial Disclosure

None declared.

## Funding/Support

None declared.

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