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High-Sensitivity C-Reactive Protein in Systemic Lupus Erythematosus Patients without Cardiac Involvement: Relation to Disease Activity and Intima-Media Thickness

Authors
Mona H. EL Zohri, Mohamed A. Tohammy, Ahmed A.Obiedallah, Effat AE Tony, Huda M Kamel, Mohamed Z Abd Elrhman*
Departments of Internal Medicine and *Clinical Pathology, Faculty of Medicine, Assiut University, Egypt

Abstract

Objectives: *measuring hs-CRP in SLE patients without clinical cardiac involvement and finds its relation to disease activity and carotid intima media thickness (CIMT), to detect a possible subclinical atherosclerosis.*

Methods: *40 SLE patients without cardiac involvement and 20 controls. Disease activity was evaluated using SLEDAI. A SLEDAI of 6 or more is consistent with active disease. CIMT increased if > 0.7 mm.*

Results: *hs-CRP in SLE patients was significantly higher than controls. 29 patients had high risk level of hs-CRP(> 3 mg/L) , 5 patients had average risk (1-3mg/L) , 6 patients had a low risk (< 1 mg/L) compared to the controls. Hs-CRP was significantly higher in patients with positive antids DNA compared to those with negative results, (P 0.003, r 0.5). Hs-CRP significantly correlated with SLEDAI, (P 0.001, r 0.49). CIMT in SLE patients was significantly increased (0.81± 0.42 mm), (>7 mm) compared to controls (0.54± 0.15 mm). 90% of SLE patients with increased CIMT have high risk hs-CRP, 10% of SLE patients with increased CIMT have averege risk hs-CRP compared to those at lower levels (0 %), while 55% of SLE patients with normal CIMT have high risk hs-CRP, 15% of SLE patients with normal CIMT have averege risk hs-CRP, 30% of SLE patients with normal CIMT have a low risk hs-CRP. A significant correlation between hs-CRP and CIMT (p 0.019, and r 0.39).*

Conclusion: *hs-CRP may be a useful marker of disease activity and increased CIMT in SLE.*

Keywords: *Systemic lupus erythematosus-High-sensitivity C-reactive protein- Carotid Intima Media Thickness- Subclinical atherosclerosis.*

Introduction

Systemic lupus erythematosus (SLE) is a chronic disorder where treatment is typically life-long. SLE is with progressive accumulation of irreversible organ damage, which may be a predictor of further morbidity and early mortality [1]. The main causes of death remain active lupus, infection and cardiovascular disease. Atherosclerosis develops prematurely among SLE patients in the setting of chronic inflammatory disease, together with a contribution from increased traditional cardiovascular risk factors [2].

In Egyptian SLE patients, metabolic syndrome was considered a risk factor for the subclinical atherosclerosis and increased carotid intima-media

thickness (CIMT). Accelerated atherosclerosis in SLE is the result of a complex between the traditional cardiac risk factors and non-traditional SLE biomarkers of inflammation [3].

The non-traditional AS biomarkers included The CRP, leptin and homocysteine, The C-reactive protein (CRP) is an acute phase reactant synthesized mainly by hepatocytes in response to cytokines such as IL-6, IL1β and TNFα. Elevation of CRP is an essential component of the acute phase response to a variety of cellular insults such as infection, inflammation, tissue trauma and malignancies [4].

The inflammatory process associated with SLE is characterized by a low level of the acute-phase proteins such as CRP. The CRP increase during lupus flares is small, although SLE patients can produce large amounts of CRP, usually in response to bacterial stimulation [5].

CRP elevation is associated with increased risk of developing coronary artery disease (CAD) and having a heart attack [6]. The CRP level is a well-recognized nontraditional or novel cardiovascular risk factor, and its effect is independent from other risk factors (smoking, obesity, hypertension, diabetes, family history) [7]. The CRP level is a stronger predictor of the first cardiovascular event than the LDL-cholesterol level in patients with no known history of CAD [8].

The development of high sensitivity C-reactive protein (hs- CRP), with several folds improvement in sensitivity, allows it to detect low levels of chronic inflammation. Conventional CRP assay typically measures levels above 3mg/L. But high-sensitivity CRP assay can now detect CRP at a level as low as 0.3mg/L [9];[10]. However, hsCRP level did not correlate with SLE disease activity scores. Some studies demonstrated that hsCRP levels correlated significantly with SLE activity [11].

Although hsCRP level has been demonstrated to be an independent risk factor of cardiovascular disease in the general population[12] and is of clinical importance as an independent marker for CAD in SLE patients, with stratifications corresponding to low (< 1 mg/L), moderate (1-3 mg/L), and high (> 3 mg/L) levels of cardiovascular risks [13]. H-sCRP levels were found to be higher in the African-Americans than other racial groups, suggesting that racial differences may confound the relationship between hsCRP and cardiovascular risk [11]. Racial differences in other cardiovascular risk factors in SLE would further complicate this relationship, such as the increased frequency of arterial thrombosis in Chinese and African American SLE patients [14].

Intima-media thickness of the carotid artery (CIMT) and its increase is associated with several cardiovascular risk factors. CIMT is an important biomarker of subclinical atherosclerosis. Measurement seems to be applicable in patients with intermediate risk hs CRP in order to readjust cardiovascular risk. Both parameters (CIMT & hs CRP) contribute independently to risk assessment for future cardiovascular events [15].

Aim of the work

Assessment of hs-CRP level in SLE patients without clinical cardiac involvement and find its relation to clinical, laboratory features and disease activity in addition to its correlation with CIMT, to detect a possible subclinical atherosclerosis.

Patients and Methods

Patients

Our study was done in Rheumatology unit, Internal Medicine Department, Assiut University Hospitals, Egypt. It is a case control study. Sixty (60) persons divided into two groups: patient group and control group.40 patients with SLE without cardiac involvement, every patient were fulfilled at least 4 from 11 criteria of the updated American College of Rheumatology (ACR) revised criteria for classification of SLE [16]. The control group consists of twenty (20) healthy subjects' age and sex matched.

Exclusion criteria

- Patients with cardiac involvement. (Excluded by ECG and echocardiography).

- Patients with history of diabetes mellitus, hypertension & hyperlipidemia.
- Patients with recent infection within the preceding month.
- Patient who refuses to be enrolled in the study.

Ethical Considerations

In accordance of the policy of the faculty of medicine, Assiut University, This study is not indicated for approval from the Ethical Committee of the faculty of medicine.

Methods

1. **Full history taking including age, sex, duration of the disease and type of treatment.**
2. **Complete clinical examination, Disease activity was evaluated using the Systemic Lupus Erythematosus Disease Activity Index (SLEDAI) [17, 18]. A SLEDAI of 6 or more has been shown to be consistent with active disease [19].**
3. **Laboratory investigations:**

- Complete blood count (CBC).
- Erythrocyte sedimentation rate (ESR).
- Urine analysis.
- 24 hours urinary protein (g/24hours).
- Serum uric acid.
- Lipogram.
- FBS: fasting blood sugar.
- Kidney function: Serum creatinine &blood urea.
- Liver functions: -Serum albumin, AST: Aspartate transaminase, ALT: Alanine transaminase, ALP: Alkaline phosphatase.
- Complement 3& 4.
- Anti-dsDNA antibody.
- Antinuclear antibodies, ANA.
- High sensitivity C-reactive protein, Hs-CRP (mg/l) using Particle-enhanced immunoturbidimetric assay.

4. **Ultrasonographic scanning of the carotid artery was performed by using an echographic system to detect CIMT. CIMT was increased if it > 0.7 mm.**
5. **Echocardiography and ECG.**

Statistical Analysis

Statistical analysis was conducted using Statistical Package for Social Sciences version 16.0 for Window software (SPSS Inc.). Mean and standard deviations were used to express quantitative data. For continuous variables, testing between 2 groups was performed by the Mann-Whitney *U* test. Categorical variables were compared by Pearson's Chi-Square test when very small proportions were analyzed. Correlations among continuous variables were calculated by the Spearman rank correlation coefficient (*rs*). *P* values of less than 0.05 were considered statistically significant. *P* values of more than 0.05 were considered statistically insignificant.

Results

Forty SLE patients 37 female and 3 male had a mean age of (26.13 ±9.21) years and a disease duration of a mean (3.68± 3.12) years. Twenty age and sex matched subjects formed the control group. Thirty six patients were receiving oral corticosteroids and four patients were receiving cyclophosphamide.

The patients had no cardiac involvement by history or clinical examination and the electrocardiograms were normal. Patients with pulmonary manifestations with suspicion of cardiac involvement were performed an echocardiography which was essentially normal. The pulmonary manifestations were in the form of a mild pleural rub. Three patients had antiphospholipid syndrome with a history of DVT in two.

Demographic, Clinical and laboratory features of the SLE patients are seen in Tables 1 and 2. The hs-CRP in the SLE patients was significantly higher. 29 patients had high risk level of hs-CRP(> 3 mg/L) , 5 patients had average risk (1-3mg/L) , 6 patients had a low risk (< 1 mg/L) compared to the control group in which one patient had high risk ,one had average risk and 18 had low risk level of hs-CRP.

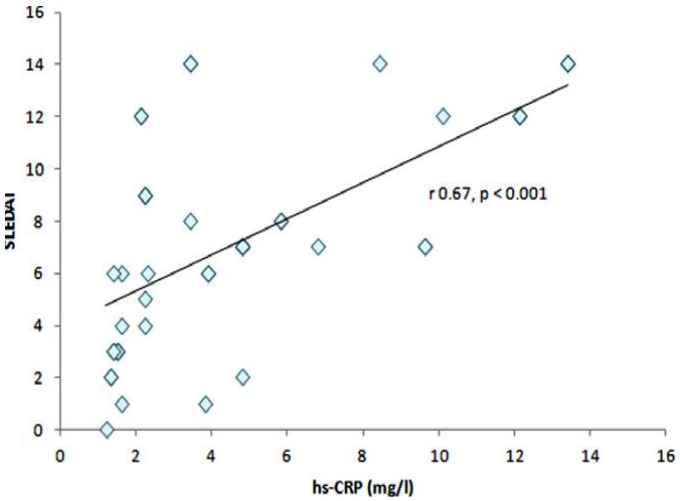
There was no difference in the level of hs-CRP according to the presence or absence of clinical manifestations of SLE (Table 3). However, it was significantly higher in those with positive antids DNA compared to those with negative results (P 0.003, r 0.5), (Table 3).

There was no significant correlation between the hs-CRP and the dose of corticosteroids, (P 0.73, r 0.07), (Table 3).

The hs-CRP significantly correlated with the SLEDAI in the SLE patients (P 0.001, r 0.49). 84.4% of patients with active SLE were having a high risk level of Hs-CRP, 6.2% was average risk, 9.4% was with a low risk ,while in patients with inactive SLE, 25% of patients have a high risk level of Hs-CRP , 37.5% have average risk of Hs-CRP and 37.5% have a low risk of Hs-CRP (Table 4) .

The CIMT in the patients with SLE was significantly increased (0.81± 0.42 mm), (>7 mm) compared to the control (0.54± 0.15 mm). 90% of The SLE patients with increased CIMT have high risk hs-CRP level , 10% of The SLE patients with increased CIMT have averege risk hs-CRP level compared to those at lower levels (0 %), while 55% of The SLE patients with normal CIMT have high risk hs-CRP level , 15% of The SLE patients with normal CIMT have averege risk hs-CRP level, 30% of The SLE patients with normal CIMT have low risk hs-CRP level (Table5).

There was a significant correlation between the hs-CRP level and CIMT in the SLE patients (p 0.019, r 0.39) (Table5).



(Figure 1): Correlation of the hs-CRP with SLEDAI in the SLE patients.

(Table 1): Demographic and Clinical features of the SLE patients.

Feature		SLE patients	
		number	percentage
sex	female	37	92.5%
	male	3	7.5%
Age (years)	(Mean)	26.13±9.21	
Disease duration (years)	(Mean)	3.68 ±3.12	
BMI (kg/m^2)	(Mean)	28.02±3.64	
SLEDAI	active	32	80.0%
	inactive	8	20.0%
Kidney affection (proteinuria, casts, Haematuria, Pyuria)		28	70.0%
fever		17	42.5%
arthritis		14	35.0%
arthralgia		7	17.5%
fatigue		12	30.0%
alopecia		9	22.5%
Oral ulcer		6	15.0%
myositis		6	15.0%
Malar rash		6	15.0%
pleurisy		5	12.5%
New rash		5	12.5%
Discoid rash		3	7.5%
Lupus headache		2	5.0%
Lupus enteritis		2	5.0%
Raynauds		2	5.0%
peripheral neuropathy		2	5.0%
vasculitis		1	2.5%
psychosis		1	2.5%
lower limb edema		3	7.5%
Prednisolone		36	90.0%
cyclophosphamide		4	10.0%

SLEDAI: Systemic lupus erythematosus disease activity index, BMI: body mass index , Results are presented mean±SD or No (%).

Table 2: Laboratory investigations of the SLE patients.

Laboratory investigation		SLE patients		Normal value
		number	percentage	
antidsDNA	positive	17	42.5%	30-75 (IU/mL)
	negative	23	57.5%	
ANA positivity	positive	12	30.0%	1.0 -1.2 (AI)
	negative	28	70.0%	
Hs-CRP	high risk	29	72.5%	> 3 (mg/L)
	averag risk	5	12.5%	1-3 (mg/L)
	low risk	6	15.0%	< 1 (mg/L)
compelement3	high	20	51.3%	>135 (mg/dl)
	normal	10	25.6%	75-135 (mg/dl)
	low	9	23.1%	< 75 (mg/dl)
		mean±SD		
C4 (mg/dl)				
CIMT (mm)				4 - 7 (mm)
Hemoglobin (g%)				
Platelets (·10^3 /mm ^{3})		0.15 ±0.1		
WBCs (·10^3 /mm^3)		0.81± 0.42		
FBS (mg/dl)		9.94 ±2.19		
Creatinine (mg/dl)		282.16±127.46		
Cholesterol (mg/dl)		8.23 ±4.06		
Triglycerides (mg/dl)		96.38±10.7		
HDL (mg/dl)		0.55 ±0.15		
LDL (mg/dl)		184.2±47.58		
AST (U/L)		155.29±69.04		
ALT (U/L)		47.67±13.12		
ALP (IU/L)		152.11±30.91		
Albumin (g/dl)		36.3 ±15.91		
Urine protein (g/24 h)		33.22±16.15		
		104.87±51.84		
		3.4± 0.7		
		0.37 ±0.43		

Hs-CRP: high sensitivity C-reactive protein, CIMT : carotid intima media thickness, AST: Aspartate transaminase, ALT: Alanine transaminase, ALP: Alkaline phosphatase, HDL: High density lipoprotein, LDL: Low density lipoprotein, C: complement, FBS: fasting Blood sugar, ANA: Antinuclear antibodies, Anti-ds-DNA: anti-double stranded DNA.
Results are presented as mean±SD or No (%).

Table 3: Correlation between HSCRP and clinical manifestations, investigation, drug therapy in SLE patients.

clinical manifestations	P value	r value	Investigation and drug therapy	P value	r value
fever	0.69	0.06	Antids DNA	0.003*	0.5
arthritis	0.82	0.139	Hemoglobin	0.002*	-0.56
arthralgia	0.59	0.339	Prednisolone	0.73	0.07
alopecia	0.76	0.07			
Malar rash	0.68	0.06			

P value significante < 0.05 r value (-1 : +1)

Table 4: Correlation between HSCRP and activity in SLE patients.

		SLE activity measured by SLEDAI	
		Active (32 patients)	inactive (8 patients)
Hs-CRP	high risk (29 patient)	27 patients (84.4%)	2 patients (25.0%)
	averag risk (5 patients)	2 patients (6.2%)	3 patients (37.5%)
	low risk (6 patients)	3 patients (9.4%)	3 patients (37.5%)

Hs-CRP: high sensitivity C-reactive protein, SLEDAI: Systemic lupus erythematosus disease activity index. SLEDAI active 6 or more, SLEDAI in active less than 6

Table 5: Correlation between HSCRP and carotid intima media thickness in SLE patients.

		CIMT in SLE patients		P value	r value
		increase > 0.7 mm (20 patients)	Normal (20 patients)		
Hs-CRP	high risk (29 patient)	18 patients (90.0%)	11 patients (55.0%)	0.019*	0.39
	averag risk (5 patients)	2 patients (10.0%)	3 patients (15.0%)	0.019*	0.39
	low risk (6 patients)	0 patients (0%)	6 patients (30.0%)	0.019*	0.39

Hs-CRP: high sensitivity C-reactive protein, CIMT: carotid intima media thickness.

Discussion

Morbidity and mortality secondary to premature CVD in SLE remain significant issues and pathogenesis has not been fully explored [20]. Yet, it has been reported that hs-CRP represents a risk factor for CVD in lupus patients [21] And it has been hypothesized that CRP itself could be the link between disease activity and CVD [22].

In this study, the hs- CRP was significantly higher in SLE patients than in controls. This was in accordance with the study of de Leeuw et al., who found CRP significantly higher even in inactive SLE patients [23]. Another study found hs-CRP to be significantly higher in SLE [24].

Although cardiovascular disease has been acknowledged as a primary cause of morbidity and mortality in SLE, cardiac manifestations are often mild and subclinical[25]. When very sensitive methods of investigation are used, the prevalence of cardiac involvement was found to be >50% [26] and asymptomatic manifestations can be recognized by echocardiography and measurement of hs-CRP, has been used in the assessment of disease activity in numerous rheumatic conditions including SLE [10]. The hs-CRP may be useful to monitor the course of the disease and predict its intermediate outcome [9]. In the present study, the hs-CRP significantly correlated with SLEDAI. This in agreement with Ter Borg et al who found that SLE exacerbations were accompanied by CRP levels >10 mg/L in about 60% of patients [27]. But disagree with the study of Barnes et al., who found that hs-CRP was not associated with SLEDAI which makes its value as a marker of disease activity questionable, yet it is useful in the assessment of cardiovascular risk [10].

Furthermore, in other studies such as that of Williams et al., a high proportion of uninfected lupus patients had clinically significant CRP elevation which did not correlate with disease activity [28]. Moreover, some patients with inactive lupus and without infection were had CRP levels >10 mg/L [29]. It was found that in SLE patients the ESR and CRP values modestly correlated with each other and weakly with disease activity suggesting that their roles as markers of inflammation in routine care may be in order [30].

In the present study, hs- CRP was found to be higher in those with positive anti ds- DNA, and positively correlated with SLEDAI and this in agreement with the study of Sjo¨ wall et al [31].

In this study there was no significant difference in the hs-CRP level according to the presence or absence of clinical manifestations of SLE. However, Gheita et al., was found CRP to be significantly elevated in a subset of SLE patients with pericardial effusion [32]. We found no significant correlation of hs-CRP with most of the studied parameters except negatively with the Hb. This in agreement with Panafidina et al., who found a significant correlation of hs-CRP with anemia [33]. In another study, hs-CRP did not correlate with any of the laboratory parameters, except negatively for C3 and C4 [24].

In this study the serum level of hs-CRP significantly correlated with the CIMT in the SLE patients. In agreement with Panafidina et al., A slight increase in hs-CRP is thought to reflect the presence of subclinical inflammation in the vascular wall, connected with atherosclerotic process and is found to moderately correlate with the CIMT [33]. And also in agreement with Gheita et al., CIMT is significantly increased in SLE patients with high serum level of hs-CRP [34]. The hs-CRP was associated with aortic valve thickening and calcification in SLE [35].

Inflammation is pivotal in atherosclerosis and minor CRP response reflects low-grade vascular inflammation. The connection of CRP with cardiovascular disease in SLE has been suggested [36]. The circulating concentration of liver-derived CRP rises rapidly in response to infections and tissue injury, and its measurement is widely employed as a marker of ongoing inflammation. With sensitive methods, the detection of small elevations of hs-CRP is even more valuable as a prognostic marker in cardiovascular diseases [37]. This disagree with the study of Mok et al., where there was no significant association between hsCRP and carotid atherosclerosis [38]. Also disagree with the study of Anania et al., where there was high serum level of hsCRP especially during active SLE or infection, may not accurately reflect cardiovascular risk this might have contributed to the negative relationship between hsCRP and subclinical atherosclerosis [39].

In this study, 90% of patients were receiving oral corticosteroids. There was no significant correla-

tion between the dose of corticosteroids and hs-CRP. The role of corticosteroids in lupus-associated atherogenesis is rather controversial, as these agents may themselves be directly atherogenic, but they may also indirectly prevent premature atherosclerosis by controlling disease activity [40].

Conclusions

SLE patients without traditional major cardiovascular risk factors may have increased risk of future cardiac events and measuring hs-CRP may be useful as a marker of disease activity, increased IMT and subclinical atherosclerosis in SLE especially those with positive Anti-dsDNA.

Conflict of interest

The authors declare that they have no conflict of interest.

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