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The relationship between serum VCAM-1 level and lupus nephritis in patients with systemic lupus erythematosus

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ABSTRACT

Introduction: Nephritis is a frequent inflammatory autoimmune complication in systemic lupus erythematosus (SLE). Detecting the nephritis state of SLE patients using non-invasive biomarkers seems to be necessary.

Objectives: This study aimed to evaluate role of vascular cell adhesion molecule-1 (VCAM-1) as a noninvasive method in the assessment of lupus nephritis.

Patients and Methods: This study was conducted at Imam Reza hospital in Mashhad, Iran, during 2017-2018. A total of 114 SLE patients diagnosed based on the lupus diagnosis criteria including the clinical and paraclinical symptoms that were referred to the rheumatology or nephrology clinics and were enrolled in the study. After obtaining informed consent, a blood sample was taken to determine serum VCAM-1 levels. All patients were evaluated for glomerular hematuria and proteinuria in addition to testing for serum C3, and C4, anti-nuclear antibody (ANA) and anti-ds DNA levels. The serum urea and creatinine levels as well as 24-hour urine protein were measured. Finally, the patients were designed into two groups of SLE with and without nephritis. A renal biopsy was performed in lupus patients with nephritis to determine the class of the disease. The association between serum levels of VCAM-1 and activity of SLE disease [systemic lupus erythematosus disease activity index (SLEDAI)], anti-dsDNA serum level, glomerular hematuria, proteinuria, and lupus nephritis class were evaluated.

Results: According to statistical analysis there was no significant relationship between SLEDAI and VCAM-1 levels was detected ($P > 0.05$). Additionally, no significant relationship between VCAM-1 levels and lupus nephritis classes was detected ($P > 0.05$); however the serum VCAM-1 levels were significantly lower in patients with hematuria ($P = 0.021$).

Conclusion: There is no correlation between serum VCAM-1 levels and classes of lupus nephritis. Our data however requires further investigation on its clinical implications.

Implication for health policy/practice/research/medical education:
In a study on 114 patients with systemic lupus erythematosus, we observed no relationship between systemic lupus erythematosus disease activity index (SLEDAI) and vascular cell adhesion molecule-1 (VCAM-1) levels, whereas the serum levels of VCAM-1 were significantly lower in patients with hematuria. There was no correlation between serum VCAM-1 levels and classes of lupus nephritis.

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Introduction

Systemic lupus erythematosus (SLE) is a common chronic inflammatory illness which can affect many organs; however, the kidney is the most common organ that suffers from the complications of the disease. About 50% of patients with SLE develop lupus nephritis (1). Unfortunately, half of these patients are diagnosed with advanced stages of glomerulonephritis (2). It has been shown that the mortality rate in SLE patients increases following glomerulonephritis (3). In addition,

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glomerulonephritis worsens the quality of life in SLE patients (4).

The clinical manifestations of lupus nephritis can be assessed using a urinalysis. Therefore, all SLE patients should first be evaluated for renal involvement by performing a urinalysis. However, urinalysis is not sufficient for the management of the disease. Therefore, all patients with evidence of kidney involvement in urinalysis should undergo renal biopsy (5). Further, serial biopsy sampling is needed to assess the response to treatment. Although kidney biopsy is the gold standard to diagnose kidney involvement, it is an invasive procedure and may lead to important side effects. Bleeding is one of the most common complications of kidney biopsy (6) while infection is the second most common complication (7). Some studies have shown that intestinal rupture can lead to peritonitis as another complication of kidney biopsy (8). Acute renal obstruction, septicemia, and death are also among the other complications of renal biopsy which can occur within two hours after biopsy (9). Therefore, although kidney biopsy is an excellent method for evaluating lupus nephritis, it is still an invasive procedure and has dangerous complications (8). Exploring less invasive novel biomarkers for early identifying of lupus nephritis is needed.

Vascular cell adhesion molecule-1 (VCAM-1) contains immunoglobulin domains. A recent proteomic study has shown that human renal glomerular endothelial cells treated with cytokines involving in the pathogenesis of lupus nephritis secret VCAM-1 increasingly (10).

Objectives

VCAM-1 expression in an animal model has been shown to increase in lupus nephritis (11). It seems that VCAM-1 can signal the progression of nephritis and potentially replace the invasive methods to screen lupus nephritis. In this study, the aim was to assess the applicability of VCAM-1 in the diagnosis of lupus nephritis.

Patients and Methods

Study population

Between 2016 and 2018 all adult patients diagnosed with SLE in our outpatient clinics were included in this study according to the 1997 American College of Rheumatology (ACR) criteria for diagnosis of SLE (12). Participants with a history of recent trauma, malignancy, recent surgery, recent pregnancy, recent breastfeeding, and recent infectious diseases were excluded.

Blood samples were taken to assess the SLE activity (anti-nuclear antibody, anti-dsDNA, and complements C3, C4, VCAM-1, CRP (C-reactive protein) and also serum creatinine). The concentrations of VCAM-1 were measured, using ELISA (enzyme linked immunoabsorbent assay). Glomerular filtration rate (GFR) was calculated based on MDRD formula. Urine samples were also obtained to evaluate hematuria, proteinuria, and 24-hour urine protein. Systemic lupus erythematosus disease activity index (SLEDAI) was assessed in all patients. Patients were designed into two groups (lupus nephritis, and non-renal nephritis). Patients with glomerular hematuria or excretion of greater than 500 mg protein in the urine per day were considered as lupus nephritis group. Each group consisted of 57 patients according to a previous study (13). The lupus nephritis group underwent a renal biopsy to determine the class of lupus nephritis in each patient.

Ethical issues

The study followed the tenets of the Declaration of Helsinki. The institutional ethical committee at Mashhad University of Medical Sciences y of Medical Sciences approved all study protocols (IR.MUMS.FN.REC.1396.777). Accordingly, informed consent was taken from all patients before any intervention. This study was obtained from the thesis of Ensieh-Sadat Musavi at this university (Thesis # 960588).

Statistical analysis

The data were analyzed as mean and standard deviation (SD). Independent *t* test and Mann-Whitney U test were done for comparison of quantitative variables in two groups in case of normal distribution of data. Chi-square test and Fisher's exact test were conducted for the qualitative variables of two group's comparison. *P* values <0.05 were considered significant. All tests were done using SPSS 16.0 (Chicago, IL, USA).

Results

A total of 114 lupus patients were entered in the research, half of whom (57 participants) had lupus nephritis. The average age of patients was 37.66±9.56 years in non-lupus nephritis group and 31.25±10.28 years in the group with lupus nephritis ($P=0.001$). Additionally, the mean of activity and chronicity indices in the lupus nephritis group were 3.24 and 1.14, respectively. Demographic information is shown in Table 1.

A significant difference was observed in the history of blood pressure and the consumption of anti-SLE drugs between the two groups (Table 1).

The SLEDAI score was significantly higher in lupus patients with nephritis ($P=0.0001$). Moreover, GFR was significantly lower in lupus patients with nephritis compared to lupus patients without lupus nephritis ($P=0.041$). However, no significant difference was observed in the levels of VCAM-1 between the two groups (Table 2).

Table 1. Demographic and clinical information of SLE patients (lupus nephritis and non-lupus nephritis groups)

		Lupus nephritis	Non-lupus nephritis	*P* value
Age (y) (mean ± SD)		31.25 ± 10.28	37.66 ± 9.56	0.0001
Gender, No. (%)	Male	3 (5.3)	5 (8.8)	0.358
	Female	54 (94.7)	52 (91.2%)	
History of blood pressure, No. (%)	Positive	26 (45.6)	12 (21.1)	0.005
	Negative	45(78.9)	31(54.4)	
Consumption of anti-SLE drugs, No. (%)	Positive	32(56.1)	42(73.7)	0.03
	Negative	32(56.1)	15(26.3)	

Table 3 shows that no pyuria was found among the patients without lupus nephritis; however, 36.8% of the patients with renal SLE had pyuria ($P=0.001$). The C3 and anti-dsDNA were significantly higher in lupus patients with nephritis ($P<0.05$); however, no significant differences were observed for C4, anti-nuclear antibody (ANA), and CRP values.

Among lupus patients with nephritis, serum levels of VCAM-1 were significantly higher in those with hematuria compared to those without hematuria ($P=0.021$). There was no significant relationship between serum VCAM-1 and quantity of proteinuria. Additionally, VCAM-1 and Anti-dsDNA were not significantly associated with the lupus nephritis group (Table 4).

Lupus nephritis patients were designed into six groups based on glomerular involvement. Five patients (8.8%) were in class 2. In class 3, 4, and 5 there were 28 (49.1%), 9 (15.8%), and 4 (7%) patients, respectively. None was classified in class 6.

No relationship was found between the classification of lupus nephritis and serum levels of VCAM-1 ($P>0.05$, Table 5).

Table 2. Comparison of SLEDAI, serum creatinine, GFR, and VCAM-1 (levels between studied groups

	Non-lupus nephritis	Lupus nephritis	*P* value
SLEDAI score	4.85±5.72	16.89±8.92	0.001
Creatinine (mg/dL)	1.11±1.33	1.45±1.15	0.152
GFR (mL/min)	90.10±23.08	77.92±38.00	0.041
VCAM-1(µg/mL)	4.01±1.44	3.85±1.42	0.535

Abbreviatopns: VCAM-1, vascular cell adhesion molecule-1; SLEDAI, Systemic lupus erythematosus disease activity index; GFR, glomerular filtration rate.

Discussion

In this study, we evaluated the potency of VCAM-1 in the diagnosis of lupus nephritis. Our results revealed that VCAM-1 serum levels were not different between the patients with and without lupus nephritis. Additionally, VCAM-1 serum levels did not increase significantly as glomerulonephritis developed. However, among the patients with lupus nephritis, VCAM-1 was significantly higher in those with hematuria compared to those without hematuria. There are few studies about the association between serum VCAM-1 levels and lupus nephritis. Previous researches have reported that VCAM-1 serum levels were significantly higher in patients with lupus nephritis. They showed, the higher the class of glomerulonephritis, the higher the serum VCAM-1 levels was (14,15), which confirm the association between serum VCAM-1 levels and lupus nephritis. All of these findings contradict the results of our study. Although, the application of serum levels of VCAM-1 for diagnosis

Table 3. Comparison of pyuria, ANA, anti-dsDNA, C3 and C4 levels between studied groups

		Lupus nephritis, No. (%)	Non-lupus nephritis, No. (%)	*P* value
Pyuria	Positive	21 (36.8)	0 (0)	0.001
	Negative	36 (63.2)	57 (100)	
ANA	Positive	52 (91.2)	54 (94.7)	0.463
	Negative	5 (8.8)	3 (5.3)	
Anti-dsDNA	Positive	48 (84.2)	29 (50)	0.001
	Negative	9 (15.8)	28 (49.1)	
C3	Normal	33 (57.9)	46 (80.7)	0.008
	Decreased	24 (42.1)	11 (19.3)	
C4	Normal	43 (75.4)	45 (78.9)	0.655
	Decreased	14 (24.6)	12 (21.1)	
CRP	Positive	7 (12.3)	9 (15.8)	0.590
	Negative	50 (87.7)	48 (84.2)	

Abbreviatopns: CRP, C-reactive protein; ANA, anti-nuclear antibody.

Table 4. Comparison of serum VCAM-1 based on proteinuria and hematuria in lupus nephritis group

		VCAM-1 Mean±SD	*P* value
Proteinuria	Negative	3.27±1.48	0.752
	Positive	3.89±1.43	
Hematuria	Negative	4.35±1.24	0.021
	Positive	3.48±1.44	
Anti-dsDNA	Negative	4.21±1.68	0.054
	Positive	3.79±1.27	

Table 5. Serum VCAM-1 levels and classification of lupus nephritis

Classification of lupus nephritis	VCAM-1 (mean±SD)	*P* value
Class 1	4.04±1.11	>0.05
Class 2	3.36±0.59	
Class 3	3.87±1.37	
Class 4	3.99±1.77	
Class 5	2.94±0.49	

of lupus nephritis has received less attention; its urinary levels have been more investigated as a noninvasive method. The urinary VCAM-1 levels have been found to be significantly higher in SLE patients with nephritis and were significantly correlated with SLEDAI index (15).

Urinary VCAM-1 levels have been shown to be associated with poor prognosis of lupus nephritis and were correlated with anti-dsDNA, C3 and C4 levels. VCAM-1 level was significantly higher in patients who were taking cyclophosphamide (16). A direct relationship was observed between the urinary VCAM-1 level and SLEDAI index (r=0.324, $P<0.05$) and it was also inversely correlated with lupus nephritis clinical indices (SDI score) (r=-0.27, $P<0.05$). This means that elevated urinary levels of VCAM-1 indicate more kidney damage following afflicting with lupus. In addition, urinary VCAM-1 levels were significantly higher in lupus patients with a progressive class of glomerulonephritis (16).

Urinary VCAM-1 levels in lupus patients have been reported to be directly related to the SLEDAI index. Moreover, the low-clearance of creatinine and albuminuria was reported to be associated with urinary VCAM-1 levels (17). In addition to VCAM-1, another member of this family, intercellular adhesion molecule 1(ICAM-1), has also been studied. The potency of ICAM-1 in the identifying of lupus nephritis is still controversial (17, 18).

Conclusion

The results of our study revealed that there was no association between VCAM-1 serum levels and lupus nephritis. Further studies with a larger sample size are needed to obtain more robust evidence on the association of VCAM-1 and lupus nephritis.

Limitations of the study

Our research was not without certain limitations. First, it was a single-center research with a relatively small population. Second, the research is cross-sectional and was not designed to identify whether serial serum VCAM-1 levels can predict the progression of nephritis in lupus patients. Thus, there is a need to do further investigations on serial of serum VCAM-1 analysis and its association with activity of disease and treatment response.

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Authors' contribution

ESM, ZM, FS and HMM were the principal investigators of the study. SM, KS and AZ were included in preparing the concept and design. AZ and FS revised the manuscript and critically evaluated the intellectual contents. All authors participated in preparing the final draft of the manuscript, revised the manuscript and critically evaluated the intellectual contents. All authors have read and approved the content of the manuscript and confirmed the accuracy or integrity of any part of the work

Conflicts of interest

The authors declare no conflict of financial interest.

Ethical considerations

Ethical issues (including plagiarism, data fabrication, double publication) have been completely observed by the authors.

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