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Association between disease activity, asymmetric dimethylarginine, tumor necrosis factor-alpha, interleukin-10 and neopterin with echocardiography and blood pressure monitoring findings in patients with systemic lupus erythematosus

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Abstract

Pulse wave velocity (PWV) and augmentation index (AIx) have been repeatedly showed to be correlated with premature atherosclerosis. The increased arterial stiffness and endothelium dysfunction may cause premature aging of the arteries in patients with systemic lupus erythematosus (SLE). However, the association of PWV and its markers, AIx, has not been linked to SLE Disease Activity Index (SLEDAI), Asymmetric dimethylarginine (ADMA) and inflammatory cytokines in SLE women. 57 women diagnosed with SLE and 31 healthy women were consequently included in the study and both groups were compared according to age, body mass index (BMI), serum lipid profile, creatinine, cardiac parameters, blood pressure. Tumor Necrosis Factor-Alpha (TNF-α), Interleukin 10 (IL-10), neopterin, and ADMA were assayed. In SLE women, PWV was significantly higher (p=0.04), and AIx was not different from controls (p=0.136). In linear multiple stepwise regression analysis, when patients and controls were both considered, PWV was weakly related to age (p=0.001), waist circumference (p=0.003), LDL-cholesterol (p=0.018), ADMA (p=0.042). Although, when the individual SLE setting was analyzed, PWV was not related to organ damage measured by SLEDAI (p=0.4), ADMA (p=0.361), TNF-α (p=0.893), IL-10 (p=0.686), and neopterin (p=(0.444)). PWV was significantly related to mean blood pressure (MBP) (p=0.001), age (p=0.001), disease duration (p=0.001) and glucocorticoid (p=0.014). Our data suggest that controlling MBP and appropriate indications of low doses steroids can partially slow down the process of early atherosclerosis in female patients diagnosed with SLE.

Keywords: Arterial stiffness, asymmetric dimethylarginine, interleukin 10, neopterin, systemic lupus erythematosus, tumor necrosis factor-alpha

Introduction

In systemic lupus erythematosus (SLE), the risk of developing cardiovascular disease has increased dramatically [1-4]. Early changes in the arterial vessel wall caused by inflammatory and immunologically mediated mechanisms accelerate the development of atherosclerosis in young patients with SLE [1]. Clinical atherosclerosis can be diagnosed by ultrasonography measurements of carotid intima-media thickness in SLE, but subclinical atherosclerosis may not always be diagnosed [1]. Nevertheless, endothelial function and vascular stiffness that can be assessed by ultrasonography techniques may be useful to show or exclude subclinical atherosclerosis [1-4]. Early diagnosis of subclinical atherosclerosis in SLE patients may play an essential role in preventing the development of major vascular diseases.

Atherosclerosis in SLE is a multi-factor process involving inflammatory, immunologically mediated mechanisms, oxidative stress, and endothelial dysfunction (1-4). Changes in the arterial vessel wall in young SLE patients have accelerated the development of atherosclerosis at an early age [1-4]. It is essential to recognize early vessel wall changes to prevent the development of cardiovascular complications.

Our aim of this study was to determine cardiac involvement in patients with SLE with transthoracic echocardiography and 24-hour blood pressure monitoring findings, and to determine the association between these findings, disease activity and inflammatory parameters such as Asymmetric dimethylarginine (ADMA), Tumor Necrosis Factor-Alpha (TNF-alpha), Interleukin-10 (IL-10) and neopterin is known as a cardiac involvement risk factor in SLE

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Materials and Method

Fifty-seven SLE patients who applied to Selcuk University Medicine Faculty Rheumatology and Internal Medicine clinic between the ages of 18-65 were included in the study. As a control group, 31 healthy women have included the study. In the cardiology clinic, both patients and the control group were assessed for cardiac involvement by monitoring 24-hour blood pressure and transthoracic echocardiography. Control group women with cardiovascular risk factors, active infection, and malignancy were not included in the study. Informed consents were obtained. Selcuk University Ethical committee approval for the study was obtained (The ethical committee number: 2013/97). We routinely studied white blood cell (WBC), hemoglobin (HB), platelet, glucose, total cholesterol, HDL-C, LDL-C, erythrocyte sedimentation rate (ESR), C-reactive protein (CRP) and 24-hour urine protein. TNF-alpha and IL-10 were assayed by enzyme-linked immunosorbent assay (ELISA). Neopterin and ADMA were tested by High-Performance Liquid Chromatography (HPLC) instrument.

Arterial stiffness detection was performed with ambulatory blood pressure monitoring devices. Ambulatory blood pressure monitoring and arterial stiffness were performed in all patients and control groups with oscillometric type Mobile O Graph NG (I.e.M GmbH Stolberg Germany). All patients, two-dimensional and color Doppler echocardiographic examinations were performed, and necessary measurements were calculated.

Ethics

This study was approved by the institutional review board of the hospital and was performed in compliance with all principles of the Helsinki Declaration. As the data were prospective, informed consent was obtained from the patients.

Statistics

*I*n statistical analysis, the statistical package program of IBM Statistics 17.0 (SPSS) was used. Normal distribution of continuous variables was measured by the Kolmogorov-Smirnov test. Mann Whitney U test was used for comparison of nonhomogeneous distributed variables. The independent t-test was used to evaluate the standard dispersive continuous variables. Correlation analysis was performed by Pearson correlation test. P-values of less than 0.05 were considered as statistically significan*t*

Results

The study consisted of 57 patients and 31 controls, totally 88 subjects. There was no significant difference in age, waist circumference, systolic blood pressure and diastolic blood pressure in the patient and control groups (p>0.05, for all). Body mass index was statistically higher in the control group than in the patient group (p=0.006). WBC (p<0.001), total cholesterol (p<0.001) and LDL (p=0.002) were statistically significantly lower, but ESR (p=0.028) was significantly higher in the patient group compared to the control group. Neopterin was found in the control group at 3.58 (1.54-8.99) nm/l, and in the patient group at 5.9 (3.56-37.4) nm/l (p=0.001). ADMA, Symmetric dimethylarginine (SDMA) and N-methyl-L-arginine (L-NMMA) were statistically significantly higher in the patient group than the control group (p <0.05, for all). Arginine/Asymmetric Dimethylarginine ratio was statistically significantly lower in the patient group than in the control group (p=0.006). TNF-alpha, IL-10, Citrulline, and Arginine were not statistically significant in the control and patient groups (p> 0.005, for all) (Table 1).

Table1. Demographic characteristics laboratory parameters and echocardiographic findings of the study groups

	Study Groups		P
	Control group	Patient group	
	Mean ±SD		
Age (year)	37.7±1.9	36.5±1.41	0.62
Waist circumference (cm)	87.39±2.4	87.33±1.83	0.54
Low-Density Lipoprotein(mg/dl)	125±5.9	103±3.9	**0.002**
Hemoglobin (g/dl)	13.15±0.18	13.23±0.2	0.81
White Blood Cell (K/uL)	7,11±0.31	5,61±0.21	**<0.001**
Erythrocyte sedimentation rate(m/h)	14.4±1,7	22.3±2.4	**0.028**
Total Cholesterol (mg/dl)	206±8.14	172±4.8	<0.001
Homocysteine	13.53±0.8	14.6±1.2	0.51
Systolic Blood Pressure (mm/Hg)	109.8±1.7	109.2±1.7	0.77
Central diastolic blood pressure (mmHg)	64.95±1.6	65.7±1.2	0.97
Cardiac output (l/min)	3.96±0.05	3.89±0.05	0.35
Ejection fraction (%)	67.5±076	68.35±0.76	0.51
Left atrium diameter (cm)	3.07±0.07	3.28±0.05	**0.023**
Aortic diameter (cm)	2.55±0.03	2.52±0.03	0.56
Diastolic Blood Pressure (mm/Hg)	66.8±1.5	66.7±1.2	0.165
Central systolic blood pressure (mmHg)	103(81-124)	100(83-132)	0.878
Asymmetric dimethylarginine	0.36±0.01	0.48±0.02	**<0.001**
Symmetric dimethylarginine	0.37±0.1	0.55±0.03	**<0.001**
N-methyl-L-arginine	0.052±0.002	0.072±0.003	**<0.001**
Arginine	211.1±10.9	239±10.6	0.88
Arginine/Asymmetric Dimethylarginine Ratio	588.6±23.7	508±16.3	**0.006**
	Median (Min-Max)		
Neopterin (nm/l)	3.58 (1.54-8.99)	5.9 (3.56-37.4)	**0.001**
C- reaktive protein (mg/dl)	3.5 (3.2-14.1)	3.3 (2.7-36.2)	0.7
Creatinine (mg/dl)	0.7 (0.6-0.8)	0.7 (0.6-1.3)	0.12
Tumor necrosis factor alpha (pg/l)	1.24 (1.1-2)	1.23 (1.06-3.28)	0.32
Sitruline (pg/l)	63.2(36-120)	76.5 (20-141)	0.15
Central diastolic blood pressure (mmHg)	66.5 (53-89)	67 (51-94)	0.97
End-systolic diameter (mm)	28 (16-37)	27 (20-36)	0.29
Posterior wall diastolic thickness (mm)	8 (6-11)	8 (7-12)	0.53
Intraventricular septum diastolic thickness (mm)	9 (7-11) (25-117)	9 (7-13)	0.81
Body Mass Index	28.3 (17.7-38.9)	24.5 (16.4-39.9)	**0.006**

According to echocardiographic findings, left atrium diameter was measured as 3.07±0.07 cm in the control group and 3.28±0.05 cm in the patient group (p=0.023). From echocardiography findings;

central systolic blood pressure, central diastolic blood pressure, cardiac output, posterior wall diastolic thickness, intraventricular septum, diastolic thickness, ejection fraction, and aortic diameter were not statistically significant in the control and group of patients (p>0.005 for all) (Table 1).

Pulse Wave Velocity (PWV) was found 5.56±0.50 m/s in the control group and 5.93±0.86 m/s in the patient group (p=0.04). PWV was 6.19±1 m/s in patients not using Acetylsalicylic acid (ASA) and 5.64±0.54 m/s in patients using ASA (p=0.011). PWV was 6.06±0.90 m/s in patients using steroids and 5.39±0.25 m/s in patients not using steroids, these results were statistically significant (p=0.014) There was no statistically significant difference in augmentation index (AIx) between patient and control group (p=0.136).

There was a positive correlation between PWV and age, weight, BMI and duration of disease, and these values were statistically significant (r=0.876, p<0.001; r=0.312, p=0.003; r=0.261, p=0.014; r=0.611 p<0.001, respectively)

Discussion

This study showed increased vessel damage in SLE patients despite appropriate treatment. This vascular injury was evaluated the relation of ADMA, IL-10, TNF-α, neopterin, and SLEDAI values and it was determined that the increase of ADMA in the patient group compared to control group might be related to the development of vascular stiffness. However, this association could not be detected in SLE patients. Thus, the association of PWV value in the patient group with the inflammation parameters could not be determined. Perhaps, the most favorable result in the study was the association of PWV with low-dose steroid use. Low-dose steroid use has been shown to reduce PWV and to be statistically significant, indicating that appropriate anti-inflammatory therapy in SLE patients may have a role in preventing vascular stiffness.

In systemic lupus erythematosus patients, the risk of developing cardiovascular disease has increased dramatically [1-4]. Early changes in the arterial vessel wall caused by inflammatory and immunologically mediated mechanisms accelerate the development of atherosclerosis in young patients with SLE [1]. Pulse wave velocity (PWV) and augmentation index (AIx) have been repeatedly shown to be correlated with premature atherosclerosis [5]. In many studies, independent of cardiovascular risk factors, the PWV value was found to be higher in patients with SLE compared to the control group [5,6]. In our study, the PWV value was statistically significantly higher in SLE patients. In contrast, the AIx value was not significant. Also, we found that PWV decreased significantly in SLE patients with steroid and ASA use, and was significantly higher with age and disease duration.

In a study, a strong correlation with the arterial stiffness index of ADMA was determined, and ADMA has been reported to increase independently in arterial stiffness [7]. In another study, ADMA values were higher in SLE patients. However, statistically significant was found only in African-American SLE patients. The same study also reported that the risk of coronary atherosclerosis could be increased independently of the average lipid profile and cardiovascular risk factors in SLE patients [8]. Bultink et al. reported that SLE patients' ADMA levels were higher in those with cardiovascular disease history [9]. In our study, there was a significant difference between PWV and ADMA in the general population. We also found it increased PWV in SLE patients, although patients without cardiovascular risk factors were included in the study, and SLEDAI values are low. Similar to the study of Kiani et al., we found that SLE disease may independently cause endothelial dysfunction, which may be associated with an increased risk of atherosclerosis. In our study, vascular stiffness was assessed by PWV, and PWV value was similar to literature with age and disease duration. We also found that low-dose steroid use significantly reduced PWV and could reduce vessel stiffness in SLE patients.

One study evaluated the PWV and AIx values to assess arterial stiffness and correlated them with CRP, sedimentation, IL-6, and fibrinogen values. Correlation of both PWV and AIx values with inflammation parameters was determined, and inflammation has been claimed to be a risk factor for vascular stiffness in SLE patients [10]. In another study, the severity of chronic inflammatory diseases was found to be higher than the healthy group, which correlated with the disease duration, CRP, IL-6, serum cholesterol level and age at diagnosis [11]. In our study, inflammation parameters such as TNF-alpha and IL-10 affecting arterial stiffness were evaluated, and we investigated whether elevated monocyte and macrophage activation might be related to vascular stiffness in SLE patients, and we examined serum neopterin value for this. In patients with SLE, TNF-α levels were found to be lower than the control group, and the difference was statistically significant. However, the correlation between this value and PWV did not reveal any association. No difference was found in IL-10 value in the patient and control groups, and IL-10 was not associated with PWV. Also, when the relationship between CRP, ESR, homocysteine values, and PWV as inflammation parameters were examined, there was no significant relationship with PWV.

Neopterin is now considered to be a biochemical marker of activation of the cellular immune system. In many studies, neopterin levels were found to be significantly higher in patients with SLE compared to the control group and according to disease activation status [12-14]. These results suggest that neopterin may be a useful activator in SLE patients. In our study, neopterin levels were statistically significantly higher between SLE patients and control group. However, there was no significant correlation between neopterin value and PWV.

The limitations of our study is that the entire patient group is female and all of the patients are taking medication for a specified period.

Conclusions

There is an increased risk of atherosclerosis in SLE independent of the traditional risk factors. Pulse wave analysis, which is one of the most basic methods used to assess vascular stiffness, is an independent predictor of cardiovascular disease. Chronic inflammation in SLE; secondary endothelial damage leads to vascular inflammation and atherosclerosis. Endothelial dysfunction and arteriosclerosis in SLE reveal subclinical atherosclerosis and can be calculated using ambulatory blood pressure monitoring devices. Early diagnosis of subclinical ATS in SLE is the major can help us identify vascular complications. Appropriate anti-

inflammatory therapy in patients with SLE may delay the development of vascular stiffness in patients. Further studies with more patients will be useful in assessing vascular stiffness in SLE patients.

Competing interests

The authors declare that they have no competing interests.

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Ethical approval

The study was approved by Ethics Committee of Selçuk University School of Medicine.

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