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EXPLORING THE NEXUS OF SUBCLINICAL ATHEROSCLEROSIS AND SYNDECAN-4 LEVELS IN PATIENTS WITH SYSTEMIC LUPUS ERYTHEMATOSUS

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Abstract

Aim: Systemic lupus erythematosus (SLE) is a persistent inflammatory autoimmune disorder. In an endeavor to juxtapose disease activity against the acknowledged occurrence of subclinical atherosclerosis in patients with SLE, this study sought to evaluate the interrelation between carotid intima-media thickness (CIMT), SLE disease activity index (SLEDAI), and Syndecan-4 (SDC4) levels.

Material and Methods: This study assembled a cohort comprising 70 patients with SLE aged 18 years and older, devoid of concomitant systemic diseases, was assembled, alongside a control group consisting of 68 healthy volunteers attending the rheumatology outpatient clinic. The assessment quantifying SDC4 levels using enzyme-linked immunosorbent assay method. CIMT measurements were conducted for both the patient and control groups. SLEDAI scores, as well as sociodemographic and laboratory data for both groups, were systematically extracted from the hospital's digitalized medical records system.

Results: SDC4 levels within the patient cohort (8.211±9.069) exhibited a statistically significant reduction compared to the SDC4 levels in the control group (26.221±24.653). Furthermore, the CIMT values for the patient group (0.558±0.116) demonstrated a statistically significant variance in contrast to the CIMT values of the control group (0.49±0.117). Remarkably, a noteworthy correlation emerged between SDC4 and CIMT. Additionally, a significant association was identified between SDC4 levels and body mass index ($p<0.05$). Further correlations were discerned between SDC4 levels and SLEDAI in the patient group. Correspondingly, a statistically significant correlation was observed between CIMT and SLEDAI in the patient group.

Conclusion: Despite the statistically significant elevation in CIMT, an essential indicator of subclinical atherosclerosis, within our patient group compared with the control group, we posit that SDC4 levels may not be reliable predictors of atherosclerosis.

Keywords: Atherosclerosis, body mass index, carotid intima-media thickness, Syndecan-4, systemic lupus erythematosus, systemic lupus erythematosus disease activity index

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INTRODUCTION

Systemic lupus erythematosus (SLE) is a chronic connective tissue disorder of undetermined etiology characterized by immunological dysregulation, autoimmune features, and multi-organ system involvement (1). The clinical manifestations of SLE encompass a spectrum of fever, joint swelling, and erythematous skin rashes, and include involvement of vital organs and systems, including but not limited to the kidneys, central nervous system, and lungs.

Atherosclerosis, a condition associated with inflammation, autoimmunity, chronic illness, and dyslipidemia, is well-recognized in the context of SLE, with established links to systemic inflammatory markers, such as C-reactive protein (CRP), fibrinogen, cytokines, chemokines, adhesion molecules, and proteases (2). Cardiovascular complications constitute a leading cause of mortality in patients with SLE (3), with a higher incidence of cardiovascular diseases than in the general population (4). Pignoli et al. (5) highlighted the significance of carotid intima-media thickness (CIMT) as a sonographic marker indicative of early atherosclerosis linked to widespread vascular pathology.

The protein Syndecan-4 (SDC4) encoded by SDC4 in humans has a molecular weight of approximately 20 kDa (6) and is recognized as a well-characterized plasma membrane proteoglycan. Syndecans play a pivotal role in cellular functions by interacting with the intracellular domain of membrane-covering core proteins, the actin cytoskeleton, and signaling molecules within the cell cortex (7). Typically present on the surface of fibroblasts and epithelial cells, Syndecan exhibit binding capabilities with fibroblast growth factors (FGF), facilitating their transport to the FGF receptor on the same cell (8). Studies have elucidated the specific role of SDC4 in determining endothelial alignment, providing atheroprotective signaling, and regulating myofibroblast migration following mechanical stretch or injury (9). A recent study on mice in which SDC4 gene expression was deleted showed that atherosclerosis was accelerated. In this study, ApoE/mice (n=10) and male SDC4/ApoE/mice (n=10) were fed a high-cholesterol diet for 12 weeks. SDC4 −/− ApoE −/− mice have higher lipid contents and a more severe plaque burden. The most important result of the study was that downregulation of SDC4 is not only a consequence of atherogenesis but also a promoter of atherogenesis (10). Notably, SDC4 levels were found to correlate with the extent of myocardial damage observed in myocardial infarction (11). It has been determined that mice genetically suppressed SDC4 protein synthesis are fertile and do not exhibit any morphological defects. It was observed that these mice had a delay in the formation of granulation tissue and that the angiogenesis rates were lower than those of normal mice. This situation raised the question of whether SDC4 is critical for the continuation of life (13).

Previous research indicated an association between SDC4 and atherosclerotic diseases, with increased susceptibility to atherosclerosis observed in SLE. Poor endothelial alignment is an indicator of susceptibility to atherosclerosis *in vivo* (14). The attachment of monocytes and T lymphocytes to the injured endothelium and their subsequent migration to the intima are among the first and most important steps in lesion development. The co-localization of CD4+ T cells and macrophages in the lesion, overexpression of human leukocyte antigen class II molecules, and co-stimulatory molecule CD40 and its ligand indicate the contribution of cell-mediated immunity to atherogenesis (15). Increased oxidative stress, as identified in vitro through endothelial progenitor cell cultures from patients with SLE, is implicated in elevating SDC4 levels (16).

Building on this background, the present cross-sectional study aimed to investigate, for the first time *in vivo*, the relationship between serum SDC4 levels, subclinical atherosclerosis, and SLE disease activity. Employing CIMT as an indicator of subclinical atherosclerosis and the SLE disease activity index (SLEDAI) scale to assess disease activity, this study aimed to elucidate the interplay between SDC4 and these markers in patients with SLE. By comparing SDC4 levels in healthy volunteers and the patient group, our research aimed to establish novel insights into the relationship of SDC4 with CIMT, an established indicator of atherosclerosis, and SLEDAI, a measure of disease activity in SLE patients.

MATERIALS AND METHODS

Approval for our study was received from Necmettin Erbakan University Meram Faculty of Medicine Pharmaceutical and Non-medical Device Research Ethics Committee (approval number: 2020/2928, date: 04/12/2020). For our cross-sectional study, patients diagnosed with SLE, aged 18 years or older, and devoid of any other known systemic diseases were recruited from the rheumatology outpatient clinic of Necmettin Erbakan University Meram Faculty of Medicine. The control group consisted of individuals who sought medical help with non-rheumatological complaints and had no history of heart or systemic diseases. Informed consent was obtained from each participant after providing comprehensive information disclosure.

For the purpose of study inclusion, individuals aged over 18 years must have been diagnosed with SLE for a minimum of 2 months in accordance with the 2019 European League Against Rheumatism/American College of Rheumatology classification criteria. In contrast, the control group was intended to comprise

healthy adults aged 18-65 years. The exclusion criteria include excluding patients with a medical history of coronary artery disease, diabetes, hypertension, and morbid obesity [body mass index (BMI) of 35 or above], given their potential contribution to heart attack. Additionally, participants from all groups who were admitted to the hospital for acute coronary syndrome or stroke within 6 months were excluded from the analysis framework. The 6-month period between April and October 2021 was selected for inclusion in the study. During the study period, 72 patients were included in the patient group and 69 in the control group. The sample group of 50 people was selected using the G*Power program for the 95% confidence interval. Eight patients and 5 control group participants who did not meet the inclusion criteria were excluded from the study.

Bilateral measurements of the internal carotid artery were made by the radiology team involved in the study, and the highest intima media thickness value was recorded.

A 10 mL peripheral blood sample was obtained from the antecubital brachial vein of all participants. The blood samples were allowed to clot at room temperature for 20 min and subsequently subjected to cold centrifugation at 3000 rpm for 20 min. Serum samples were stored at -86 ºC. Carotid ultrasound examinations, using the B (brightness)-mode gray technique, were performed on all participants on the same day as blood collection. A blind radiologist assessed the carotid arteries of both patients and the control group by measuring the CIMT in millimeters.

Serum samples were examined using the sandwich enzyme-linked immunosorbent assay (ELISA) technique with BT LAB Human SDC4 ELISA kits. The specified standard curve range was 0.1-35 ng/mL, with a sensitivity of 0.053 ng/mL. There was no normal SDC4 level range reported by the manufacturer. The ELISA plate was pre-coated with Human SDC4 antibody, followed by the addition of SDC4 from the sample to form a bound complex with the coated antibodies. A biotinylated Human SDC4 Antibody was then introduced and attached to the SDC4 in the sample. Subsequent addition of Streptavidin-HRP formed a complex with a biotinylated SDC4 antibody. After incubation and a washing step to remove unbound Streptavidin-HRP, a substrate solution was added, resulting in color development proportionate to the quantity of Human SDC4. The reaction was halted by adding an acidic stop solution, and absorbance was measured at 450 nm. The recorded results are expressed in ng/mL.

Statistical Analysis

The G*Power program (version 3.1.9.7) was used for sample size calculation. A population of at least 50 individuals is recommended to obtain a 95% confidence interval. Data analysis was conducted using SPSS version 21.0 software. The normal distribution of variables was assessed using the Kolmogorov-Smirnov test. Descriptive statistics, including mean, standard deviation, minimum, maximum, frequency, and percentage, were employed to present comprehensive data summaries. The correlation between continuous variables within each case group was evaluated using Spearman's correlation test. For the univariate analysis of dependent and independent variables, the chi-square test was used. Model summaries and parameter estimates were generated using linear regression to express the relationship between the dependent variable and a set of independent variables. Statistical significance was determined using p-values below 0.05.

RESULTS

The cohort under investigation comprises 57 females, representing 89% of the total sample, while the control group comprises 56 females, representing 87%. The mean ages of the patient group was determined to be 36.36±13.42, and 34.78±11.798 for the control group. Although the mean age was similar between the patient and control groups (p=0.749), female sex was similarly dominant in both groups. Furthermore, the mean BMI of the patient group was calculated as 26.11±4.28, whereas the mean BMI for the control group was observed to be 25.01±3.71. Renal involvement (lupus nephritis, etc.) of SLE patients was not examined in this study. Patients' medication and serology status are summarized in Table 1. There was a statistically significant difference between the CIMT value of the patient group (0.558±0.116) and the CIMT value of the control group (0.49±0.117) (p=0.001).

The median SDC4 level in the patient group was determined to be 4.085 (2.893-9.702), whereas the corresponding mean in the control group was 18.405 (5.180-42.25). Upon comparative analysis between the patient and control groups, a statistically significant difference in SDC4 levels was observed, with the

Table 1. Medication choices and serologies of patients

Rituximab, n (%)	62 (97%)
Cyclophosphamide, n (%)	63 (98%)
Mycophenolate mofetil, n (%)	53 (83%)
Azathioprine, n (%)	39 (61%)
Corticosteroid, n (%)	19 (30%)
Hydroxychloroquine, n (%)	19 (30%)
C3+C4 mg/dL	14 (22%)
Anti-ds DNA n (%)	42 (66%)

patient group exhibiting a markedly lower level compared with the control group, with a p-value of 0.001 (Figure 1). The laboratory outcomes of the groups are presented in Table 2.

Because the SDC4 data and CIMT values of the control group did not comply with the normal distribution, a correlation test was performed using Spearman's rho analysis. No correlation was detected between CIMT and SDC4 levels in the control group (p=0.327).

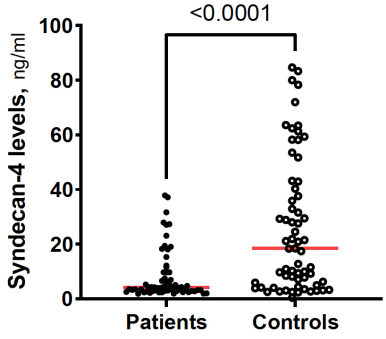

Figure 1. Distribution of Syndecan-4 levels between the patient and control groups

Cumulatively, Figure 2 presents the outcomes derived from linear regression analysis, aimed at delineating conceivable relationships between the pivotal factor SDC4 and patient attributes with disease severity grading.

DISCUSSION

SLE is a chronic disease that increases the risk of cardiovascular disease in the long term. In our study, we aimed to demonstrate subclinical atherosclerosis in SLE patients at an early stage by comparing CIMT values, disease activity indexes and serum SDC4 levels. We also tried to identify statistically significant differences by comparing the SDC4 and carotid intima levels between the healthy volunteers and the patient group.

In an experimental study that inspired this study, the relationship between SDC4 and atherosclerosis was examined. In this *in*

Table 2. Laboratory results of the groups

	Patients	Controls	p-value
WBC, $^{x}10^{9}$/L	6.87±3.07	6.83±1.82	0.926
ANC, $^{x}10^{9}$/L	4.62±2.52	3.95±1.31	0.063
ALC, $^{x}10^{9}$/L	1.5 (1.06-2.13)	0.4 (0.32-0.49)	0.001
AMC, $^{x}10^{9}$/L	0.41 (0.31-0.55)	0.41 (0.32-0.48)	0.359
Hemoglobin, gr/L	12.47±1.98	13.42±1.19	0.001
Platelet, $^{x}10^{9}$/L	237 (191-297)	259 (227-301)	0.043
RDW, fL	14.8 (13.4-16.4)	13.3 (12.9-14)	0.001
MPV, fL	10.31±1.42	13±2.1	0.311
Creatinine, mg/dL	0.76 (0.67-0.92)	0.75 (0.65-0.84)	0.353
AST, U/L	14.8 (12.8-20.4)	14.5 (11.5-17.9)	0.145
ALT, U/L	14.1 (9.9-20.5)	11.8 (9.1-15.6)	0.105
Erythrocyte sedimentation rate, mm/h	15 (6.2-26)	9 (5.3-13.7)	0.002
C-reactive protein level, mg/L	3.14 (1.92-10.57)	0.93 (0.49-2.40)	0.001
Calcium, mg/dL	9.33 (9.06-9.6)	9.29 (9-9.55)	0.502
Ferritin, ng/mL	29.44 (13.01-102.87)	27.02 (12.87-54.92)	0.342
Triglyceride, mg/dL	138.4 (83.5-196)	73.45 (63.12-99.6)	0.001
LDL, mg/dL	89.27±26.84	95.06±29.91	0.250
HDL, mg/dL	47.6±14.61	57.47±12.30	0.001
VLDL, mg/dL	27.37±14.33	18.10±9.61	0.001
TSH, mIU/mL	2.61±1.28	1.93±1.13	0.002
CIMT, mm	0.55±0.11	0.49±0.11	0.001

WBC: White blood cells, ANC: Absolute neutrophil count, ALC: Absolute lymphocyte count, AMC: Absolute monocyte count, RDW: Red cell distribution width, MPV: Mean platelet volume, AST: Aspartate aminotransferase, ALT: Alanine transaminase, LDL: Low-density lipoproteins, HDL: High-density lipoproteins, VLDL: Very low-density lipoproteins, TSH: Thyroid-stimulating hormone, CIMT: Carotid intima-media thickness

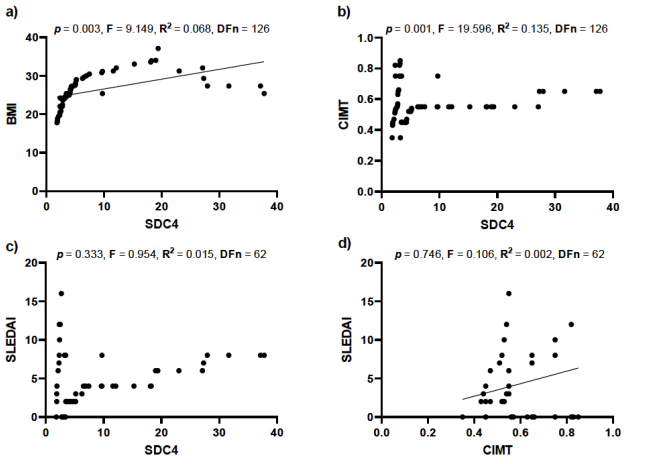

Figure 2. Linear regression results: a) between SDC4 and BMI, (b) between SDC4 and CIMT, c) between SDC4 and SLEDAI, and d) between CIMT and SLEDAI
BMI: Body mass index, CIMT: Carotid intima-media thickness, SLEDAI: Systemic lupus erythematosus disease activity index, SDC4: Syndecan-4

vitro study, in which SDC mRNA responses were monitored, mechanical damage was created to cultured rat aortic smooth muscle cells using a balloon catheter. Serum levels of SDC4 mRNA increase after basic FGF and arterial injury in vascular smooth muscle cells (VSMC) (12). In an *in vitro* study, cardiomyocyte-specific overexpression of SDC4 caused activation of calcineurin-NFAT signaling and intensified cardiac hypertrophy in mice (13). Early detection of subclinical atherosclerosis in patients with SLE plays a vital role in preventing cardiovascular events that do not yet show clinical signs. Cardiovascular complications caused by SLE are the leading cause of mortality and morbidity due to this disease. CIMT measurement, which provides early detection of subclinical atherosclerosis, is performed by ultrasonography, which is quickly accessible, inexpensive, noninvasive, and does not contain ionizing radiation. It has been determined in studies that SDC4 plays important roles in cardiac injury and restructuring process (10). It has been shown that the differentiation of fibroblasts with deleted SDC4 genetic expression into myofibroblast is impaired (14).

However, when the literature is reviewed in general, the relationship between the *in vivo* functions of SDC4 and atherosclerosis has been shown in a limited number of studies. In a study examining the effects of SDC4 on atherosclerosis and cellular alignment in intravascular blood flow, it was found that in hypercholesterolemic mice, stopping the replication step of SDC4 [S4(-/-)] via viral vector greatly increased the atherosclerotic plaque burden, with the appearance of plaque in areas of normal resistance (9). SDC4 has been shown to promote the formation of FGF-2 signaling and subsequently suppress mineralization in VSMC by downregulating transforming growth factor-β signaling (19).

The importance of T-lymphocytes in the development of subclinical atherosclerosis in patients with SLE was also emphasized. During the development of atherosclerotic lesions, the arterial wall is invaded by leukocytes, especially monocytes and T-lymphocytes. This may be important for demonstrating the relationship between lymphocytes and subclinical atherosclerosis in autoimmune disease. We considered the association between T lymphocytes in atherosclerotic plaques and peripheral lymphocytosis as a weak statistical possibility. In our study, the lymphocyte count was significantly higher in the patient group than in the control group. In the control group, lymphopenia was unexpectedly detected in comparison with the population average.

ATP-binding cassette transporters A1 and G1 (ABCA1, ABCG1) are members of the ATP-binding cassette transporter family, and they promote the efflux of intracellular lipids into the extracellular compartment and reverse transport of intracellular lipids to high-density lipoproteins (HDL), thereby inhibiting foam cell formation (20). Deletion of SDC4 expression increased the proinflammatory capacity of mouse macrophages via this pathway. These studies identified SDC4 as a very potent atherosclerosis-inhibiting protein. The increased atherosclerotic plaque burden in mice with SDC4 loss supports this. Studies have determined that SDC4 plays an important role in heart damage and restructuring process (10). In our study, the fact that SDC4 levels were significantly lower in the SLE group than in the control group does not directly support that the atherosclerosis burden increased in the SLE group. Because, as we will explain in detail later, this situation may be caused by the immunosuppressant treatment the patients receive. In our study, we examined whether there is a relationship between subclinical atherosclerosis and SDC4 protein in patients with SLE using CIMT measurement. The CIMT level was found to be significantly higher in our patient group than in the control group. Serum SDC4 levels were associated with blood pressure and cardiovascular parameters in healthy older women, but not with proinflammatory cytokines or arterial elasticity. Significant correlations were detected between SDC4 and MMP-9, heart rate, left ventricular ejection time, systemic vascular resistance, and blood pressure. However, no significant correlation was detected with serum tumor necrosis factor-alpha and interleukin-6 levels, which are proinflammatory markers.

According to the results of this study, systemic inflammation may not cause SDC4 to distribute to the extravascular area

in healthy individuals with aging (21). SDC4 coexistence was examined in a study in which serum osteoprotegerin levels were measured to evaluate oxidative stress in patients with SLE. *In vitro*, the application of osteoprotegerin to endothelial progenitor cells cultured in the peripheral blood of patients with SLE significantly induced the apoptosis of these cells. It was determined that osteoprotegerin treatment increased SDC4 mRNA levels. It is thought that SDC4 may play a role in the development of premature atherosclerosis in patients with SLE by being expressed when oxidative stress increases (15). In a meta-analysis including a total of 80 studies (6085 SLE patients and 4794 controls) evaluating subclinical atherosclerosis in SLE patients, SLE patients had a higher CIMT and increased carotid artery disease compared with controls. plaque prevalence was determined. Additionally, this meta-analysis found that traditional cardiovascular risk factors (age, HDL, and triglyceride of SLE patients) steroids and triglyceride, and lupus-related risk factors (expressed by duration, erythrocyte sedimentation rate, SLEDAI, and steroids) had a significant impact on CIMT and carotid plaque prevalence. In our study, we found no significant correlation between CIMT and SLEDAI values (p=0.746).

A 4-year prospective follow-up study was conducted to evaluate the relationship between BMI and subclinical atherosclerosis in patients with SLE. In this study, CIMT, cumulative steroid doses, and BMI were assessed in 61 Korean female patients with SLE. The average CIMT value of the patients was found to be 0.39±0.09 mm (CIMT value in our study was 0.558±0.116). Additionally, these patients received fewer non-steroidal anti-inflammatory drugs and a higher 4-year cumulative dose of glucocorticoids. The results showed that lower BMI and 4-year cumulative glucocorticoid dose were associated with the progression of subclinical atherosclerosis (22). Although the cumulative steroid dose was not calculated in our study, BMIs were correlated with CIMT.

It has been shown in a longitudinal study that the use of immunosuppressant drugs is effective against plaque progression, regardless of the presence of traditional cardiovascular risk factors (23). Medical treatment methods for SLE have many effects on the prevention of subclinical atherosclerosis. Corticosteroids (CS) have anti-inflammatory properties that should theoretically reduce the risk of atherogenesis, but due to their side effects, such as hypertension, hyperglycemia, dyslipidemia, and obesity, it is possible that these drugs may create paradoxical situations that accelerate atherosclerosis. Hydroxychloroquine (HQ) is an anti-malarial drug that is frequently used for treating SLE. Anti-platelet effects may reduce thrombovascular events, whereas hypocholesterolemic effects may improve lipid profiles (24). Mycophenolate mofetil (MMF), an immunosuppressant, has also attracted attention due to its cardioprotective properties. A high PREDICTS score increases the likelihood of future atherosclerosis in SLE by 28-fold.

In a 12-week study in which Azathioprine, HQ, and MMF treatment were randomized, the PREDICTS atherosclerosis risk score, which is a predictor of cardiovascular events, was found to be significantly lower in the MMF-treated group than in the MMF-treated group (25). Therapeutic drugs used for treating SLE can affect the development of atherosclerosis both positively and negatively (26). In our study, a significant proportion of patients received HQ and CS treatment. Patients receiving MMF, which has been shown to significantly reduce the risk of atherosclerosis, were in the minority. In our study, SDC4 levels were significantly lower in the patient group than in the control group, which may be related to the immunosuppressive treatment the patients received.

Our study patients generally comprised a patient population that did not disrupt follow-up and treatment. Our control group consisted of randomly selected healthy volunteers. We identified patients with asymptomatic subclinical atherosclerosis in our control group despite strict compliance with the inclusion and exclusion criteria. Although patients were excluded from our study, we observed that CIMT was high in the control group with high SDC4 levels. Additionally, we did not detect a significant statistical relationship between the SDC4 levels examined in the control and CIMT groups. We conclude that SDC4 levels are not reliable indicators of subclinical atherosclerosis. Therefore, more studies are needed to clarify the relationship between SDC4 and subclinical atherosclerosis. There is an increased incidence of coronary artery disease and obesity, particularly in the Central Anatolian region where this study was conducted. In our study, the average BMI of the control group was that of the obese group. According to the results of a meta-analysis including 10 studies investigating BMI in adult individuals in our country, the average BMI was 28.2 kg/m^2 in women and 26.5 kg/m^2 in men (27). In our study, the BMI of the control group was below the general country average. In a study conducted on healthy Turkish adults, the CIMT was found to be 0.458±0.116 mm in men and 0.47±0.104 mm in women (28). In our study, the CIMT value of the control group was determined as 0.49±0.117 mm, which was similar to the average for the population. In the patient group, the CIMT was higher than the population average (0.558±0.116 mm).

In a study conducted abroad measuring the CIMT to indicate atherosclerosis in patients with SLE, the average CIMT of the patient group was 0.91 mm. In this study, the highest CIMT

values (1.02±0.27 mm) were observed in patients with lupus nephritis. This value is considerably higher than the CIMT average (0.558±0.116 mm) obtained in the patient group in our study.

SDC4 is a glycocalyx component, and its increased levels in serum reflect glycocalyx damage. Studies on SDC4 levels in coronary artery disease have led to the investigation of SDC4 levels in ischemic stroke. Serum SDC4 levels of 65 patients diagnosed with cryptogenic stroke and 36 healthy volunteers were examined. SDC4 levels were found to be 0.81 (0.78-0.87) (ng/mL) in the patient group and SDC4 levels were 0.79 (0.78-0.88) (ng/mL) in the control group. There was no statistical difference between the SDC4 levels of the patient and control groups (p=0.68). In addition, the CIMTs of the patient and control groups were similar, 0.8 (0.7-1.15) versus 0.8 (0.7-0.9) (p=0.42) (29). In our study, similar to this study, SDC4 serum levels were thought to have a meaningless effect on endothelial dysfunction *in vivo*. There is a need for large-scale population studies on this subject.

Anemia is common in patients with SLE. Autoimmune hemolytic anemia, iron deficiency anemia, CKD, and anemia due to drug myelotoxicity can also be observed in patients with SLE. The other causes of anemia are pure erythroid aplasia, pernicious anemia, myelofibrosis, sideroblastic anemia, hemophagocytic syndrome, aplastic anemia, and thrombotic microangiopathic anemia (30). In our study, hemoglobin values were found to be significantly lower in the patient group than in the control group.

In patients with SLE, on of cardiovascular disease, high-sensitivity CRP (hsCRP) and CRP levels may increase depending on disease activity. In a prospective cohort study evaluating CV mortality in patients with SLE, the serum parameter most associated with CV mortality was hsCRP (31). In our study, hsCRP was not studied. However, the CRP levels of our patient group were significantly higher than those of the control group.

Endocan is a protein whose plasma levels in vascular endothelial cells may reflect endothelial dysfunction. Endocan is a protein expressed in endothelial cells and is associated with subclinical atherosclerosis in patients with SLE (32). We referred to this study because it is similar to our study design and deals with a different endothelial protein. In this study, the CIMT was 0.70 (range: 0.45-1.20) mm in patients with SLE and 0.40 (0.25-0.60) mm in controls. The results were found to be similar to our averages.

Study Limitations

In our single-center study, although the number of cases and controls was sufficient, we experienced limitations in the randomization of participants based on sociodemographic characteristics. The patient group mainly consisted of female patients. Although unequal numbers of patients were included in the patient and control groups, the numbers of patients and control groups were equal due to the exclusion criteria of the study. This led to a statistically unexpected outcome. The patient group generally consisted of a population with an average age of very young who did not skip check-ups and received regular treatment. Contrary to our hypothesis, subclinical atherosclerosis did not progress as quickly as expected in the young group. We believe that the most important reason for this is that patients have easy access to effective treatment. Our patients had access to regular treatment. Our patient population generally consisted of a group that did not interrupt follow-up and visited the outpatient clinic regularly for checkups. In the control group, patients with a high risk of subclinical atherosclerosis were identified despite meeting the exclusion criteria. We think that this is related to the carbohydrate-rich diet in the region where the study was conducted. We believe that large-scale multicenter studies are needed to evaluate SDC4 levels in identifying subclinical atherosclerosis in patients with SLE. We believe that our study will shed light on this issue.

CONCLUSION

We did not find a relationship between SDC4 levels and the progression of subclinical atherosclerosis in patients with SLEs. We believe that SDC4 levels may be related to SLEDAI disease activity in patients with SLE, and further research is needed on this subject. We did not detect any significant correlation between SDC4 levels and CIMT, which reflects subclinical atherosclerosis, in the control group. Although we found that SDC4 levels were positively correlated with CIMT levels in patients with SLE, no significant difference was detected in the control group. We found that the SLEDAI was positively correlated with CIMTs. We believe that this is due to SLE accelerating atherosclerosis processes.

Ethics

Ethics Committee Approval: Approval for our study was received from Necmettin Erbakan University Meram Faculty of Medicine Pharmaceutical and Non-medical Device Research Ethics Committee (approval number: 2020/2928, date: 04/12/2020).

Informed Consent: Informed consent was obtained from each participant after providing comprehensive information disclosure.

Authorship Contributions

Concept: A.Y., C.K., A.K., Data Collection or Processing: A.Y., C.K., Analysis or Interpretation: A.Y., C.K., A.Ç., Literature Search: A.Y., A.Ç., Writing: A.Y., A.Ç., A.K.

Conflict of Interest: One author of this article, Adem Küçük, is a member of the editorial board of the Rheumatology Quarterly. However, he did not take part in any stage of the editorial decision of the manuscript. The editors who evaluated this manuscript are from different institutions. The other authors declared no conflict of interest.

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