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Investigation of the relationship between hypertension and asymptomatic organ damage in patients with Sjogren's disease

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Abstract

The study aimed to compare the development of asymptomatic cardiovascular (CV) organ damage in hypertensive patients with and without Sjogren syndrome (SS), a condition characterized by inflammatory processes that lead to vascular damage. Forty hypertensive patients with SS (aged 18–65) and 40 age- and sex-matched hypertensive patients without this syndrome were included into the study. Carotid intima-media thickness was measured from area of 1 cm length proximal to both carotid bulbs. Left ventricular mass index was determined via echocardiography, and microalbuminuria was calculated from spot urine samples. Hypertensive retinopathy was assessed through fundoscopy. Asymptomatic organ damage was found in 51.2% of all participants: 61% in the Sjogren group and 39% in controls, with a statistically significant difference between groups and sexes ($P = .041$). Carotid intima-media thickness was higher in the Sjogren group (0.815 mm vs 0.607 mm in controls), and left ventricular mass index was significantly elevated in the Sjogren group (92.54 g/m² vs 83.07 g/m², $P = .016$). All patients with Sjogren disease had at least stage 1 hypertensive retinopathy, while 14 patients in the control group had not. Microalbuminuria values were higher in the Sjogren group but the difference was not statistically significant ($P = .082$). Hypertensive patients with SS exhibit more asymptomatic organ damage compared to those without the syndrome. Close monitoring and CV screening with measurement of tools which are reflecting subclinical atherosclerosis are recommended for prevention and early detection of overt CV diseases in this population.

Abbreviations: AOD = asymptomatic organ damage, BMI = body mass index, CIMT = carotid intima-media thickness, CV = cardiovascular, DBP = diastolic blood pressure, HR = hypertensive retinopathy, HT = hypertension, LVMI = left ventricular mass index, MALB = microalbuminuria, RA = rheumatoid arthritis, SBP = systolic blood pressure, SS = Sjogren syndrome.

Keywords: asymptomatic organ damage, hypertension, Sjogren disease

1. Introduction

Sjogren syndrome (SS) is a chronic, autoimmune, rheumatological disease which occurs in individuals with genetic predisposition triggered by environmental factors. Multiple factors, all of which have not been completely elucidated, play roles in its etiopathogenesis. Lymphocytic infiltration in exocrine glands, especially salivary glands and lacrimal glands, and dysfunctions of them caused by these infiltration are essential. SS may also involve many other organs and systems.[1] Inflammation and the clinical pictures arise as results of it cause significant problems in SS and in all other rheumatological diseases. Endothelial damage caused by inflammation predisposes to the emergence of a procoagulant state and development of vascular events via atherosclerosis even at low disease activity in other rheumatological diseases but also in SS. Atherosclerosis is recognized as an inflammatory process occurring in the vessel wall. Detection of the atherosclerotic process triggered by endothelial damage in the subclinical atherosclerosis stage, before it leads to obvious clinical events, creates a window of opportunity to prevent future cardiovascular (CV) and cerebrovascular events.[2–4]

Some tools are developed to obtain the subclinical atherosclerosis successfully. Carotid intima-media thickness (CIMT) is an important indicator of subclinical atherosclerosis.[5] Left ventricular mass index (LVMI) is a sign of asymptomatic CV organ damage that occurs before the development of atherosclerotic heart disease and heart failure.[6] Microalbuminuria (MALB) is an indicator of early phase of CV diseases.[7,8] Hypertensive retinopathy (HR) is another amplifier of subclinical atherosclerosis and associated with an increased risk of CV mortality.[9–11] All these parameters could be used to identify increased risk of CV events in Sjogren disease and other inflammatory rheumatological diseases as they are robust markers of subclinical atherosclerosis.

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All data generated or analyzed during this study are included in this published article [and its supplementary information files].

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In this study, we aimed to compare the development of asymptomatic CV organ damage (AOD) in hypertensive patients with and without SS. There is not a study focused on this issue in the literature. With this study, we intended to reveal whether the risk of subclinical atherosclerosis increases in the presence of Sjogren disease in hypertensive patients, and if so, to what extent the risk increases.

2. Material and method

2.1. Study design and study population

Forty hypertensive patients with Sjogren disease and 40 participants with essential hypertension over the age of 18 years were included in the study. Exclusion criteria were: having diabetes mellitus types 1 and 2, active or chronic infection, active or history of any malignancy, history of taking chemo/radiotherapy, chronic obstructive and restrictive lung diseases, another rheumatologic disease other than SS, surgical operation within the last 3 months, undergone eye surgery history, acute prerenal, renal or postrenal kidney injury, chronic renal disease stages 2 to 5, aortic valve disease or previous aortic valve surgery, coronary artery disease, previous coronary or peripheral bypass/graft surgery, and out of age between 18 and 65 years. After obtaining the approval of the ethics committee (decision no: 2023/126), 40 hypertensive patients with Sjogren disease who applied to BAIBU Medicine Faculty Rheumatology department outpatient clinic for follow-up visit between April 2022 and October 2023 who met the inclusion criteria were included in the study as patient group. Forty hypertensive patients without a diagnosis of Sjogren disease who applied to the cardiology outpatient clinic for routine follow-up visit were included in the study as control group, if they have met the inclusion criteria.

2.2. Methods of measurements

Demographic characteristics of the patients were recorded. The results of hemogram, biochemical tests, and autoantibodies are also recorded. ECG findings, left ventricular wall thickness, and diastolic filling parameters measured by a cardiologist in the supine position.

2.2.1. CIMT measurement. CIMT measurements were performed with an ultrasonography device (GE Healthcare, M4S-RS, Tokyo, Hino-Shi, 2017, Japan) using a B-mode ultrasonography technique with a frequency of 7.5 mHz. All measurements of the CIMT were made in the longitudinal plane at the point of maximum thickness of the far wall of the common carotid artery along a 1 cm section of the artery proximal to the carotid bulb. The CIMT was defined as the distance between the inner echogenic line representing the intima blood interface and the adventitia-media border (outer echogenic line). We made 3 measurement from left and right side. Arithmetic mean of the highest values measured on the right and left is accepted as CIMT.

2.2.2. LVMI measurement. Echocardiography was performed by an technician blinded to the patients' clinical data. A Vivid 7 cardiac ultrasound system (GE Medical Systems; Horten, Norway, 2017) equipped with a 2.5 to 3.5 MHz phased array. Left ventricular mass (LVM) was calculated from 2D echocardiographic measurements using the Devereux formula:

$$\mathrm{LVM} = 1.04 \times [(\mathrm{IVST} + \mathrm{PWT} + \mathrm{LVDd})\,3\,(\mathrm{LVDd})\,3]\,13.6.$$

The obtained LVM values were indexed to body surface area and are presented as the LVM index (LVMI).

2.2.3. HR measurement. For fundoscopic examination, 1 drop of tropicamide 1% solution was dripped into each eye 15 minutes prior to examination. Fundoscopic examination was performed by an ophthalmologist by using a biomicroscopy device (Topcon SL-3C, Topcon Corp., Japan). Retinopathy staging was in accordance with 2013 European Society of Hypertension and European Society of Cardiology Hypertension guidelines, as follows: grade I: arteriolar narrowing (either focal or general in nature); grade II: arteriovenous nicking; grade III: retinal hemorrhages, microaneurysms, hard exudates, and cotton wool spots; grade IV: grade III signs plus papilledema and/or macular edema.

2.2.4. MALB measurement. Albumin in spot urine/creatinine in spot urine ratio was calculated and values > 30 mg/g were accepted as microalbuminuria.

2.3. Statistical analysis

Descriptive statistics of the obtained data were given as mean ± standard deviation, median (interquartile range) or number (percentage) depending on the type of variable measured. Quantitative data were compared by one-way ANOVA and post hoc Tukey test if they fit the normal distribution, and by nonparametric Kruskal–Wallis and post hoc Dunn test if they did not fit the normal distribution. Pearson chi-square or Fisher exact test was used to analyze categorical data. The results were interpreted at 0.05 statistical significance level and 95% confidence interval. Data analysis was performed with SPSS Statistics 27 program.

3. Results

The mean age of patients with Sjogren disease was 53.2 years and body mass index (BMI) was 27.9 kg/m^2. Twenty-one of the patients were male and 19 were female. The mean systolic blood pressure (SBP) was 143.3 mm Hg and diastolic blood pressure (DBP) was 82.2 mm Hg in patients with Sjogren disease. There was an increased systolic blood pressure, while DBP was normal. The time elapsed since the diagnosis of hypertension (HT) was 2.95 years in patients with Sjogren disease and 3.05 years in the control group. There was no significant difference between the glomerular filtration rates of the patient group and the control group (95.6 and 96.3 mL/min, respectively). Mean CIMT was 0.815 mm in patient group and 0.607 mm in the control group. LVMI was 92.54 g/m^2 in the Sjogren group and 83.07 g/m^2 in the control group (P = .016). CIMT and triacylglycerol levels were higher in the Sjogren group. The differences between the patient group and the control group in terms of age, gender, BMI, SBP, DBP, LVMI, high-density lipoprotein-cholesterol, low-density lipoprotein-cholesterol, and total cholesterol levels were not statistically significant.

AOD was detected in a total of 41 participants (51.2%). Of those with AOD, 61% (25 people) were in the patient group and 39% (16 people) were members of the control group (P = .041) (Table 1). AOD was found in 13 men and 12 women among Sjogren disease group and in 5 men and 11 women among the control group.

When we analyzed those with asymptomatic organ damage (AOD), there was no significant difference between patient and the control group in terms of age, BMI, SBP, DBP, LVMI, MALB, high-density lipoprotein-cholesterol, low-density lipoprotein-cholesterol, TAG, glomerular filtration rates, and duration of HT. Total cholesterol and CIMT values were significantly higher in Sjogren disease group with AOD (P = .033, P = .022, respectively) (Table 2). No significant correlation was found between AOD and age, SBP, DBP, and BMI.

All patients with Sjogren disease had at least stage 1 HR, whereas 14 people in the control group did not have. The numbers of people with stage 1, 2, and 3 HR were higher in the SS patient group than in the control group (22/18, 15/7, 3/1, respectively). Among those with AOD, the number of people

with stage 1, 2 and 3 HR was 8/7, 14/7, 3/1 in the Sjogren patients/control group, respectively (Fig. 1). There was a moderate positive correlation between HR and being diagnosed with Sjogren disease ($R = 0.41$). There was also a positive correlation between CIMT value and HR ($R = 0.46$). No significant correlation was found between HR and age, SBP, DBP, and BMI.

Table 1

Asymptomatic organ damage.

	Asymptomatic organ damage*	
	Positive (n, %)	Negative (n, %)
Sjogren group	25 (62.5)	15 (37.5)
Control group	16 (40)	24 (60)

* $P = .041$.

Mean LVMI was higher in SS patient group than in the control ($P = .016$). LVMI was also higher in patients with AOD than in the control group with AOD, but the difference was not significant ($P > .05$) (Table 3). LVMI was moderately and positively correlated with having Sjogren disease ($R = 0.42$), increasing HT years ($R = 0.36$), MALB level ($R = 0.44$), and HR ($R = 0.43$). There was a moderate and positive correlation between CIMT value and having HR ($R = 0.46$) and was a slightly positive correlation with LVMI ($R = 0.27$). There was a positive correlation between the CIMT value and having Sjogren disease ($R = 0.36$). The mean MALB value was 23 mg/g in patients with SS and 13 mg/g in the control group ($P = .082$). The mean MALB was 31 mg/g in patients with AOD and 24 mg/g in the control group with AOD ($P = .466$). There was a positive correlation between the occurrence of microalbuminuria and having SS ($R = 0.22$), increasing years of HT ($R = 0.25$), and CIMT values ($R = 0.49$). The strongest correlation with microalbuminuria was found between having HR ($R = 0.52$). The standardized coefficient

Table 2

Comparison of those with asymptomatic organ damage.

Parameter	Sjogren	Control	*P*-value	Parameter	Sjogren	Control	*P*-value
Age (years)	51.96	52.13	.231	LDL (mg/dL)	127.2	118.8	.666
BMI (kg/m²)	28.55	27.75	.301	TAG (mg/dL)	143.2	136.4	.123
SBP (mm Hg)	141.6	140.3	.993	GFR (mL/min)	95.9	96.8	.716
DBP (mm Hg)	83.2	80.0	.692	HT (years)	3.48	5.06	.849
LVMI (g/m²)	97.42	86.35	.725	TC (mg/dL)	190.4	179.6	**.033**
MALB (mg/day)	31.4	24.0	.466	CIMT (mm)	1.000	0.706	**.022**
HDL (mg/dL)	53.0	54.6	.786				

BMI (kg/m²) = body mass index, CIMT (mm) = carotid intima-media thickness, DBP (mm Hg) = diastolic blood pressure, GFR (mL/min) = glomerular filtration rate, HDL (mg/dL) = high-density lipoprotein-cholesterol, HT (years) = hypertension duration, LDL (mg/dL) = low-density lipoprotein-cholesterol, LVMI (g/m²) = left ventricular mass index, MALB (mg/day) = microalbuminuria, SBP (mm Hg) = systolic blood pressure, TAG (mg/dL) = triacylglycerol, TC (mg/dL) = total cholesterol.

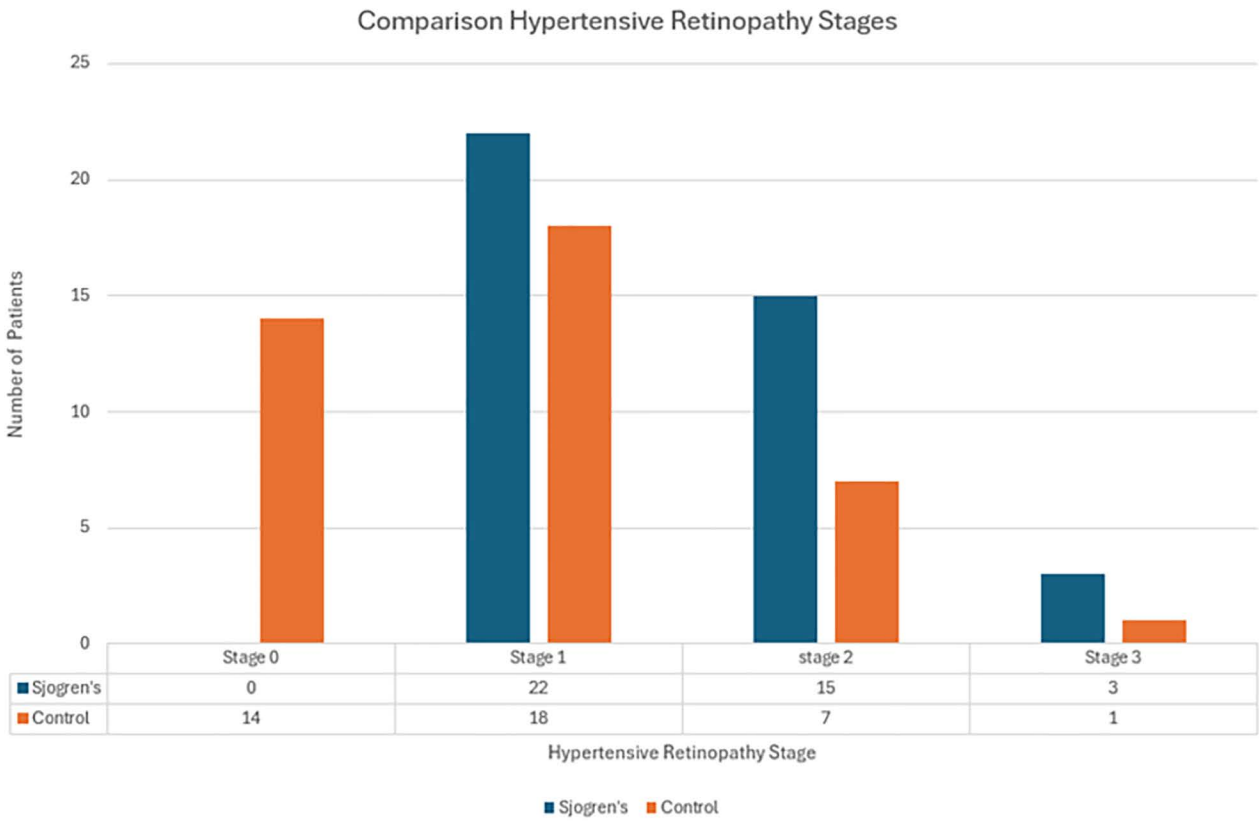

Figure 1. Comparison of groups according to hypertensive retinopathy status.

Table 3

Comparison of the groups in terms of LVMI values.

	Mean LVMI (g/m^2)	
	AOD (+)	**Total**
Sjogren	97.42	92.54
Control	86.35	83.07
P	.725	**.016**

AOD = asymptomatic organ damage, LVMI = Left ventricular mass index.

beta value between LVMI and HT year was 0.286 and it is 0.258 for microalbuminuria.

4. Discussion

In this study, we investigated the association between SS and asymptomatic CV organ damage. To assess AOD, we performed tests and measurements to detect CIMT, LVMI, MALB, and HR. We found that 61% of patient with Sjogren disease and 39% of age, sex, smoking, and BMI-matched controls had AOD ($P = .041$).

CV diseases are the leading causes of death worldwide. The main event leading to the development of CV diseases is atherosclerosis, which is recognized as an inflammatory process occurring in the vessel wall.[12,13] Atherosclerosis is a process that starts in intrauterine life and continues throughout life. Various diagnostic tools have been developed to detect atherosclerosis and AOD before CV events develop and their validity has been demonstrated by scientific studies. Values obtained by many ultrasonographic, echocardiographic, radiological imaging and measurement methods, and biomarkers of which levels can be measured in serum are used for the detection of AOD. Measurements for the detection of AOD, treatment modalities and elimination of all risk factors are the correct medical approach to be adopted to prevent the development of CV events in the subclinical period.[14] CIMT, LVMI, HR, MALB are parameters that reflect AOD well.[5,15–21] Some scoring systems such as MADIT-II, FADES, PACE, SHOCKED also can be used for predicting patients under risk.[22] In our study, we used these parameters because of the noninvasive manner of them for evaluating AOD and because they are cheap, easily accessible and reproducible.

In rheumatological diseases, increased levels of cytokines such as tumor necrosis factor alpha and interleukin-6; endothelial damage and dysfunction; impaired blood flow; increased procoagulant substances such as adhesion molecules, fibrinogen, coagulation factors, especially factor 8, and decreased anticoagulant substances predispose to thrombotic events.[2,23] Mameli A et al demonstrated a 3-fold increased risk of venous thromboembolism in patients with rheumatoid arthritis (RA).[24] Increased risk of venous thrombosis has also been demonstrated in patients with SLE and vasculitis.[25,26] Ungprasert et al showed a 2-fold increased risk of thrombosis in patients with Sjogren disease in their meta-analysis.[27] This shows us that the main event constituting the pathophysiology of CV events occurring in rheumatological diseases is the accelerated atherosclerotic process triggered by increased inflammation, which is a condition specific to these disease group, in addition to conventional risk factors, and that increased thrombosis risk also plays an important role in the development of CV diseases. The overlap of inflammatory processes triggering both atherosclerosis and thrombosis supports this conclusion.

One of the most important triggers of atherosclerotic processes leading to the development of CV diseases is chronic inflammation.[2,23] The relationship between inflammation and atherosclerosis is well known.[13,28] Patients with RA have been shown to have 30 to 60% increased risk of CV events. Endothelial damage and initiation of coagulation by monocyte activation triggered by tumor necrosis factor alpha and tissue factor increase have been blamed for this result.[24,29] Bartoloni E et al and Berardicurti O et al have shown an increased frequency of CV events in patients with Sjogren disease as in RA.[30,31] Casian et al have shown increased both subclinical and clinical CV disease risk in Sjogren disease.[32] Endothelial dysfunction development is in question at the beginning of the atherosclerotic process. Pırıldar T et al have demonstrated endothelial dysfunction in patients with Sjogren disease by proving decreased endothelium-dependent vasodilatation.[4] Studies with markers such as ankle-brachial index, pulse wave velocity, CIMT, plasma asymmetric dimethylarginine levels, coronary flow reserve have revealed increased risk of subclinical atherosclerosis in patients with SS.[33–35] Santos et al showed that increased inflammatory markers, increased disease activity (ESSDAI), extraglandular involvement, hypergammaglobulinemia, low C3 and glucocorticoid use were factors associated with the development of CV disease in SS.[36]

CIMT is an important reflector of the subclinical atherosclerotic process and is a good predictor of future CV events.[5] Del Rincon et al demonstrated the relationship between elevated serum inflammation markers C-reactive protein and erythrocyte sedimentation rate and increased CIMT values, which is an indicator of subclinical atherosclerosis.[37] Increased CIMT values have been shown to be present in many rheumatological diseases such as SLE and RA and this has been shown to be associated with an increased risk of CV disease.[38–40] Vaudo G et al revealed that the mean CIMT value was 0.82 mm in Sjogren disease group and 0.63 mm in the control ($P < .001$).[41] It has been previously demonstrated that Sjogren disease is an independent risk factor for subclinical atherosclerosis determined by CIMT.[42] In our study, we found a mean CIMT value of 0.81 mm in Sjogren disease group without AOD and 0.60 mm in the control ($P = .001$). We measured a mean CIMT value of 1.000 mm in SS patients with AOD and 0.706 mm in the control group with AOD ($P = .022$). In addition, when we evaluated CIMT thickness and hypercholesterolemia, which is an important component of the atherosclerotic process, we found that TAG levels were higher in the SS patient group. Total cholesterol values were higher in SS patients with AOD than in those without AOD.

LVMI is an important predictor for CV diseases.[43,44] Vassiliou et al found LVMI higher in patients with Sjogren disease than healthy controls. They showed that high LVMI was associated with xerostomia, purpura, low C3, and anti-Ro positivity.[45] In our study, LVMI was found to be higher in patients with Sjogren disease than in the control group, and there was high statistical significance ($P = .016$).

One of the major risk factors of atherosclerosis and CV events is hypertension. In a prospective study, it is proved that hypertension is related to LVMI as an important CV event risk factor.[46] In addition to neurohumoral mechanisms, inflammatory processes such as increased mitochondrial oxidative stress play an important role in the development and maintenance of hypertension.[47,48] In their prospective study, Sesso HD et al showed that the risk of developing HT was higher in healthy subjects with high baseline C-reactive protein values.[49] Midtbø et al showed that HT was associated with AOD in patients with RA independent of the level of inflammation.[50] In our study, we measured mean SBP as 143.3 mm Hg and DBP as 82.2 mm Hg in patients with SS. There was an increased SBP, while DBP was normal.

There was no significant difference between the systolic and DBP values of the SS patients and the control group. HR is a reflection of systemic vascular disease, indicating structural changes in the coronary and cerebral microcirculation. It has been shown to be associated with increased subclinical atherosclerosis, is a mirror of damage in target organs such as kidney and heart, and is associated with an increased risk of CV

mortality.[9–11] In our study, 14 patients in the control group had no HR, whereas SS patients had at least stage 1 HR. Patients with stage 1, 2, and 3 HR were also more common in SS group than in controls. There was a moderate correlation between SS and having HR ($R = 0.41$).

Microalbuminuria is an early warning parameter for CV diseases.[7,8] In this study, we found that microalbuminuria levels in SS patients with AOD were higher than those in the control group, although not reaching statistical significance. A weak correlation was found between being diagnosed with SS and having microalbuminuria. The strongest correlation with microalbuminuria was found between HR.

The limitations of our study include the small number of participants. The fact that not all methods showing AOD were performed and whole serum biomarkers were not measured can also be counted among the limitations. If we had measured microalbuminuria in 24-hour urine, we can say that we would have obtained more sensitive results than spot urine albumin/creatinine measurement. The most powerful aspect of our study is the comparison of 2 groups (Sjogren disease + HT/essential HT) which were not compared in terms of AOD before. We believe that our study will shed light on the literature on the early detection and treatment of CV diseases, which are the most important causes of morbidity and mortality in SS and other rheumatological diseases especially concomitant diagnosis of HT and other risk conventional factors.

In conclusion, in this study, we found that patients with SS + HT had increased AOD compared to patients with essential HT. The most important reason for this result is that inflammatory processes that play roles in the pathophysiology of SS also play roles in the pathophysiology of accelerated atherosclerosis. In the follow-up and treatment of patients with SS, subclinical atherosclerosis and related clinical pictures should be evaluated during follow-up visits to reduce morbidity and mortality risks. In the future, we think this issue should be investigated in depth with larger patient cohorts, with grouping SS patients according to a disease activity indexes and with using same and also different methods and tools for detecting subclinical atherosclerosis.

Author contributions

Conceptualization: Muhammet Fatih Bayraktar, Güvenç Toprak, Murat Taşçı.
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