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ORIGINAL ARTICLE

Increased PCSK9 associated with cIMT in AS: A useful marker for subclinical atherosclerosis in patients with ankylosing spondylitis

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ABSTRACT

Objectives: This study aims to investigate the relationship between proprotein convertase subtilisin/kexin type 9 (PCSK9) levels and subclinical atherosclerosis (SA) in patients with ankylosing spondylitis (AS).

Patients and methods: Between January 2022 and March 2022, a total of 56 patients (33 males, 23 females; mean age: 37.8±9.3 years; range, 20 to 60 years) who were under regular follow-up in our clinic and fulfilled the criteria of the Modified New York Diagnostic Criteria for AS and American College of Rheumatology (ACR) for AS were included. Age- and sex-matched 56 healthy volunteers (25 males, 31 females; mean age: 38.4±8.2 years; range, 20 to 60 years) were also recruited as the control group. Demographic, clinical, and laboratory data were recorded. The PCSK9 level and carotid intima-media thickness (cIMT) were evaluated using appropriate methods.

Results: The mean serum PCSK9 levels in AS patients (609.3±149.9 *vs.* 136.3±120.8 ng/mL, p<0.001) and the mean cIMT values (0.51±0.19 *vs.* 0.43±0.08 mm, p=0.003) were higher than healthy controls. In the multivariate stepwise regression analysis, there was an independent relationship between SA and PCSK9 (β=0.324, p=0.001). Additionally, there was an independent relationship between carotid plaque and PCSK9 (β=0.265, p=0.006). Based on the receiver operating characteristic curve analysis, the optimal PCSK9 cut-off value for plaque was 472.0 ng/mL, sensitivity 90.9%, specificity 65.0% (area under the curve [AUC]=0.759; 95% CI: 0.660-0.857, p=0.005). The optimal PCSK9 cut-off value for SA was 459.5 ng/mL, sensitivity 63.2%, specificity 63.0% (AUC=0.625; 95% CI: 0.512-0.739, p=0.031).

Conclusion: Our study showed that serum PCSK9 levels in patients with AS were higher than that in healthy individuals and were associated with SA and arterial plaque formation. In the light of these findings, PCSK9 may accelerate SA and carotid plaque formation in patients with AS, regardless of the LDL cholesterol level. There may be no relationship between PCSK9 levels and disease activity in patients with AS.

Keywords: Ankylosing spondylitis, carotid intima-media thickness, proprotein convertase subtilisin/kexin type 9, subclinical atherosclerosis.

Ankylosing spondylitis (AS) is a chronic autoimmune inflammatory disease involving large joints, such as the spinal, sacroiliac, and shoulder joints, causing fusion accompanied by frequent human leukocyte antigen-B27 (HLA-B27) positivity.[1] Although the prevalence of AS varies geographically, it ranges between 0.1 and 1.4%.[2] Typically, AS affects young men between the ages of 20 and 40 years. However, the prevalence of AS has recently increased in women.[3]

Ankylosing spondylitis often causes systemic involvement and affects the eyes, skin, kidneys, gastrointestinal system and cardiovascular system.[4] According to previous studies, the

cardiovascular system involvement of AS is seen in 2 to 10% of cases.[5] Asymptomatic atherosclerosis can be also seen at an early age in AS.[6] In addition, aortitis, aortic valve diseases, hypertension, ischemic heart disease, cardiomyopathy, and significant conduction disorders are common in AS.[7]

Early detection of subclinical atherosclerosis (SA) is significant for slowing and preventing the progression of atherosclerotic diseases. Carotid intima-media thickness (cIMT) measurement is a cost-effective method which has long been used to detect SA.[8] The cIMT differs between sexes and shows a progressive increase with advancing age annually.[9] Inflammation and oxidative stress accelerate SA in AS patients.[10] Even at an early age, SA in patients with AS can be detected by cIMT.[11]

Proprotein convertase subtilisin/kexin type 9 (PCSK9) is a serine protease in glycoprotein structure consisting of 692 amino acids, belonging to the family of proprotein convertors released from tissues such as the liver, kidney, small intestine, and central nervous system.[12,13] It binds to low-density lipoprotein (LDL) receptors (LDLRs) on the liver surface and cleaves them.[14] The breakdown of LDLR reduces the clearance of LDL from the blood and predisposes patients to atherosclerosis and coronary artery disease.[15] The PCSK9 inhibitors prevent the breakdown of LDLR, thereby leading to a decrease in LDL levels.[16] In addition, PCSK9 induces atherosclerosis by increasing oxidative stress and cytokine release regardless of LDL levels.[17]

In the literature, there is strong evidence that a high LDL level is related to the etiology of AS, as well as atherosclerosis.[18] Therefore, PCSK9 levels in patients with AS may be significant for both atherosclerosis and the etiology of the disease. A previous study reported that patients with axial spondyloarthritis had lower PCSK9 levels than healthy controls.[19] Review of the literature revals that the relationship between PCSK9 and AS and cIMT is unclear. In the present study, we, therefore, aimed to investigate the level of PCSK9 in patients with AS and whether there was a relationship between PCSK9 and SA in these patients.

PATIENTS AND METHODS

This prospective study was conducted at Necmettin Erbakan University Meram Faculty of Medicine, Department of Rheumatology between January 2022 and March 2022. A total of 56 patients (33 males, 23 females; mean age: 37.8±9.3 years; range, 20 to 60 years) who were under regular follow-up in our clinic and fulfilled the criteria of the Modified New York Diagnostic Criteria for AS and American College of Rheumatology (ACR) for AS[20] were included. Age- and sex-matched 56 healthy volunteers (25 males, 31 females; mean age: 38.4±8.2 years; range, 20 to 60 years) were also recruited as the control group. Known cardiovascular disease (hypertension, acute coronary syndrome, valve disease, and heart failure), diabetes mellitus, hyperlipidemia, acute or chronic kidney disease, thyroid disease, neurological diseases, other rheumatic and autoimmune diseases, malignancy, substance abuse, pregnancy, and patients under 18 years of age were excluded from the study. A written informed consent was obtained from each participant. The study was approved by the Necmettin Erbakan University Non-Pharmaceutical and Medical Device Research Ethics Committee (date: 21.01.2022, no: 2022/3615). The study was conducted in accordance with the principles of the Declaration of Helsinki.

Clinical evaluation

All patients were questioned about their sociodemographic characteristics and habits (smoking and alcohol), drug use, comorbidity history, age at diagnosis, age of onset of symptoms, and family history using a standard questionnaire. In the previous week, weakness, fatigue, neck-back-waist or hip pain and pain, swelling, tenderness and morning stiffness in the joints other than these regions were also questioned. The severity of the symptoms was evaluated separately by the physician and the patient with the Visual Analog Scale (VAS).

Disease activity

Disease activity was evaluated with the Bath Ankylosing Spondylitis Disease Activity Index (BASDAI), which evaluates disease activity based on the last week, and the Bath Ankylosing Spondylitis Functional Index (BASFI), which

is used to describe and monitor the functional abilities of AS patients.

Laboratory evaluation

After fasting for 10 to 12 h, morning fasting blood samples were taken from brachial venous blood. Total cholesterol, LDL cholesterol, high-density lipoprotein (HDL) cholesterol, triglyceride, erythrocyte sedimentation rate (ESR), high-sensitivity C-reactive protein (hs-CRP), aspartate aminotransferase (AST), alanine aminotransferase (ALT), fasting blood glucose, blood urea nitrogen (BUN) creatinine, uric acid, hormones such as thyroid-stimulating hormone and insulin, and PCSK9 were studied using appropriate methods. The hs-CRP levels of over 3.0 mg/L were considered to indicate a high cardiovascular disease risk.[21]

Detection of PCSK9 levels

Serum PCSK9 levels of individuals were determined using sandwich enzyme-linked immunosorbent assay (ELISA) kits with two antibodies (Cloud Clone Corp., Catalog No: SEE189Hu, TX, USA) in accordance with the manufacturer's instructions.

Carotid intima-media thickness measurements

The cIMT values of all participants, both in the patient and control groups, were obtained by a single radiologist with 10 years of experience in a blindly manner using a Siemens S3000 ultrasound device (Siemens Healthcare GmbH. Erlangen, Germany) and a VF-7.3 superficial probe. It was noted by measuring from the anterior wall 2 cm distal to the bilateral common carotid artery bifurcation level. The cIMT values were calculated by taking the average of the values obtained with both measurements as described previously.[22] Since our patients were young, values above the breakpoint cIMT values for age and sex were considered significant for SA.[23-25]

Statistical analysis

Statistical analysis was performed using the IBM SPSS version 20.0 software (IBM Corp., Armonk, NY, USA). Descriptive data were expressed in mean ± standard deviation (SD), median (min-max) or number and frequency, where applicable. The Kolmogorov-Smirnov test was used to determine whether the groups were homogeneously distributed. Analysis of continuous variables was evaluated using the Student t-test and the Mann-Whitney U test, while categorical values were evaluated using the chi-square test. The Pearson correlation or Spearman correlation analyses were used to examine the association between PCSK9 and SA. Independent variables were determined by a multivariate stepwise linear regression test. The diagnostic efficacy of PCSK9 for predicting SA and carotid plaque in patients with AS was evaluated using the receiver operating characteristic (ROC) curve analysis. The optimal PCSK9 cut-off values for the SA and carotid plaque in patients with AS were determined based on the Youden's J statistic. A p value of <0.05 was considered statistically significant with 95% confidence interval (CI).

RESULTS

Baseline demographic and clinical characteristics of the AS patients are given in Table 1.

The mean PCSK9 levels of AS patients (609.3±149.9 *vs.* 136.3±120.8 ng/mL,

Table 1. Baseline characteristics of patients with ankylosing spondylitis (n=56)

	n	%	Mean±SD
Disease duration years			7.1±6.3
BASFI			3.2±1.5
BASDAI			3.9±1.7
Peripheral arthritis	2	3.5	
Enthesitis	5	8.9	
Infliximab	15	26.7	
Adalimumab	7	12.5	
Etanercept	7	12.5	
Golimumab	11	19.6	
Sulfasalazine	2	3.5	
Certolizumab	3	5.3	
Secukinumab	13	23.2	
Colchicine	1	1.7	
Methotrexate	4	7.1	
Systemic steroid	1	1.7	
NSAID	2	3.5	

SD: Standard deviation; BASFI: Bath Ankylosing Spondylitis Functional Index; BASDAI: Bath Ankylosing Spondylitis Disease Activity Index; NSAID: Non-steroidal anti-inflammatory drug.

p<0.001) and the mean cIMT values (0.51±0.19 *vs.* 0.43±0.08 mm, p=0.003) were higher than the PCSK9 levels and cIMT values of healthy controls.

The cIMT values of 26 patients with AS and 12 healthy controls were above the normal range for age and sex, and these high-value individuals were considered to have SA. Carotid plaque was detected in 11 (19.6%) patients with AS, and no plaque was detected in healthy controls (p<0.001). Additionally, the hs-CRP values of AS patients were higher in the control group (p=0.006). The hs-CRP values of 25 patients with AS and 10 healthy controls were >3 mg/L, and these individuals were considered to have an increased cardiovascular disease risk. The lipid parameters of patients with AS were similar to those of healthy controls. All biochemical results of the patient and control groups are given in Table 2.

There was a positive correlation between PCSK9 and cIMT (r=0.328, p=0.015), hs-CRP (r=0.290, p=0.032), and fibrinogen (r=0.341, p=0.011). There was also a positive

Table 2. Sociodemographic characteristics and laboratory results of the patient and control group

	AS (n=56)					Control (n=56)					
Parameters	n	%	Mean±SD	Median	Range	n	%	Mean±SD	Median	Range	*p*
Age (years)			37.8±9.3					38.4±8.2			0.756
Sex Male	33	58.9				25	44.6				0.108
BMI (kg/m^2)			25.8±5.1					26.5±4.0			0.422
PCSK9 (ng/mL)			609.3±149.9					136.3±120.8			<0.001
hs-CRP (mg/L)				2.1	0.1-32.9				1.1	0.3-10.3	0.006
Increased hs-CRP (>3 mg/L)	25	44.6				10	17.8				0.002
cIMT (mm)			0.51±0.19					0.43±0.08			0.003
Increased cIMT	26	46.4				12	21.4				0.004
Plaque	11	19.6				0	0				<0.001
HOMA-IR			2.5±1.9					2.1±1.0			0.201
FPG (mg/dL)			91.2±8.3					90.8±8.4			0.837
BUN (mg/dL)			26.2±7.3					25.6±6.9			0.668
Creatinine (mg/dL)			0.79±0.1					0.85±0.2			0.054
Uric acid (mg/dL)			4.5±1.2					4.9±1.2			0.087
Total cholesterol (mg/dL)			175.6±43.1					188.3±39.1			0.105
Triglyceride (mg/dL)			133.7±76.7					135.8±91.7			0.894
HDL (mg/dL)			49.3±12.8					50.1±12.7			0.752
LDL (mg/dL)			102.6±30.0					111.5±31.6			0.130
AST (U/L)			19.0±6.8					17.9±5.3			0.332
ALT (U/L)			22.0±16.6					19.2±10.3			0.292
Albumin (g/dL)			45.1±3.9					47.0±2.3			0.003
TSH (µg/mL)			2.0±1.6					1.9±1.3			0.696
Hb (g/dL)			13.9±1.9					14.6±1.9			0.056
ESR (mm/h)				9.0	3.0-81.0				6.0	2.0-41.0	0.107
Fibrinogen (mg/dL)			329.4±89.3					277.3±54.9			<0.001

AS: Ankylosing spondylitis; SD: Standard deviation; BMI: Body mass index; PCSK9: Proprotein convertase subtilisin/kexin type 9; hs-CRP: High-sensitive C-reactive protein; cIMT: Carotid intima-media thickness; HOMA-IR: Homeostasis model assessment of insulin resistance; FPG: Fasting plasma glucose; BUN: Blood urea nitrogen; HDL: High-density lipoprotein; LDL: Low-density lipoprotein; AST: Aspartate aminotransferase; ALT: Alanine aminotransferase; TSH: Thyroid-stimulating hormone; Hb: Hemoglobin; ESR: Erythrocyte sedimentation rate.

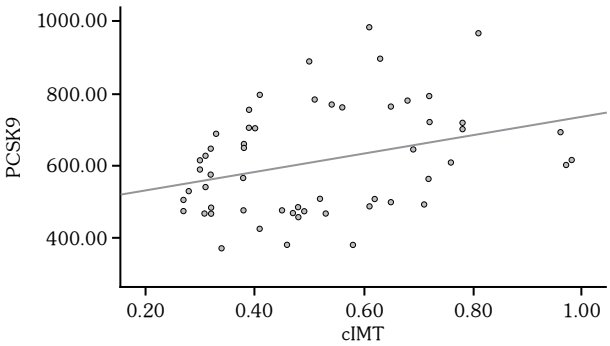

Figure 1. Strong correlation between PCSK9 and cIMT in patients with ankylosing spondylitis.

PCSK9: Proprotein convertase subtilisin/kexin type 9; cIMT: Carotid intima-media thickness.

correlation between cIMT and hs-CRP (r=0.442, p=0.001), age (r=0.689, p<0.001), disease duration (r=0.380, p=0.004), BASFI (r=0.269, p=0.047), BASDAI (r=0.276, p=0.041), and fibrinogen (r=0.451, p=0.001). Figure 1 shows the relationship between PCSK9 and SA. All correlation analysis results are shown in Table 3.

In the multivariate stepwise regression analysis, there was an independent relationship between SA and PCSK9 (beta [β]=0.324, p=0.001). Additionally, there was an independent relationship between carotid plaque and PCSK9 (β=0.265, p=0.006). The regression analysis results are shown in Table 4.

Based on the ROC curve analysis, the optimal PCSK9 cut-off value for plaque was 472.0 ng/mL, sensitivity 90.9%, specificity 65.0% (area under the curve [AUC]=0.759; 95% CI: 0.660-0.857, p=0.005). The optimal PCSK9 cut-off value for SA was 459.5 ng/mL, sensitivity

Table 3. Correlation analysis results of patients with ankylosing spondylitis

	PCSK9		cIMT	
	r	*p*	r	*p*
cIMT	0.328	0.015		
hs-CRP	0.290	0.032	0.442	0.001
ESR	0.199	0.145	0.010	0.942
Age	0.183	0.181	0.689	<0.001
Disease duration	0.089	0.519	0.380	0.004
BASFI	0.102	0.459	0.269	0.047
BASDAI	0.033	0.809	0.276	0.041
HOMA-IR	0.028	0.837	0.055	0.689
FPG	0.083	0.545	0.114	0.419
BUN	0.095	0.492	0.065	0.638
Creatinine	0.052	0.728	0.223	0.102
BMI	0.098	0.477	0.150	0.273
Uric acid	0.123	0.371	0.143	0.297
Total cholesterol	0.155	0.259	0.257	0.059
TG	0.110	0.425	0.202	0.140
HDL	0.003	0.980	-0.052	0.758
LDL	0.036	0.795	0.228	0.094
AST	0.086	0.531	0.056	0.687
ALT	0.066	0.630	0.012	0.929
Hb	-0.050	0.718	0.026	0.853
Albumin	-0.177	0.195	-0.054	0.697
Fibrinogen	0.341	0.011	0.451	0.001

PCSK9: Proprotein convertase subtilisin/kexin type 9; cIMT: Carotid intima-media thickness; hs-CRP: High-sensitive C-reactive protein; ESR: Erythrocyte sedimentation rate; BASFI: Bath Ankylosing Spondylitis Functional Index; BASDAI: Bath Ankylosing Spondylitis Disease Activity Index; HOMA-IR: Homeostasis model assessment of insulin resistance; FPG: Fasting plasma glucose; BUN: Blood urea nitrogen; BMI: Body mass index; TG: Triglyceride; HDL: High-density lipoprotein; LDL: Low-density lipoprotein; AST: Aspartate aminotransferase; ALT: Alanine aminotransferase; Hb: Hemoglobin.

Table 4. Predictive markers for cIMT and carotid plaque in patients with ankylosing spondylitis

Dependent variables	Independent variables	Beta	95% CI	*p*
Increased cIMT	PCSK9	0.324	0.201-0.488	0.001
Carotid plaque	PCSK9	0.265	0.211-0.297	0.006
	Fibrinogen	0.259	0.199-0.276	0.007

cIMT: Carotid intima-media thickness; OR: Odds ratio; CI: Confidence interval; PCSK9: Proprotein convertase subtilisin/kexin type 9.

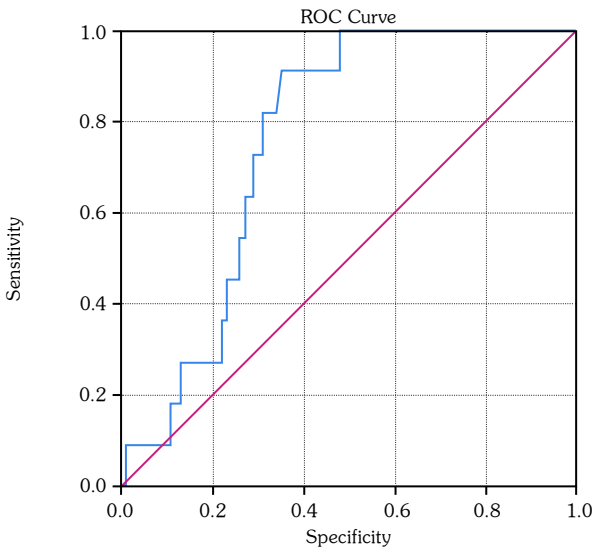

Figure 2. The ROC curve of PCSK9 for predicting carotid plaque.

ROC: Receiver operating characteristic; PCSK9: Proprotein convertase subtilisin/kexin type 9.

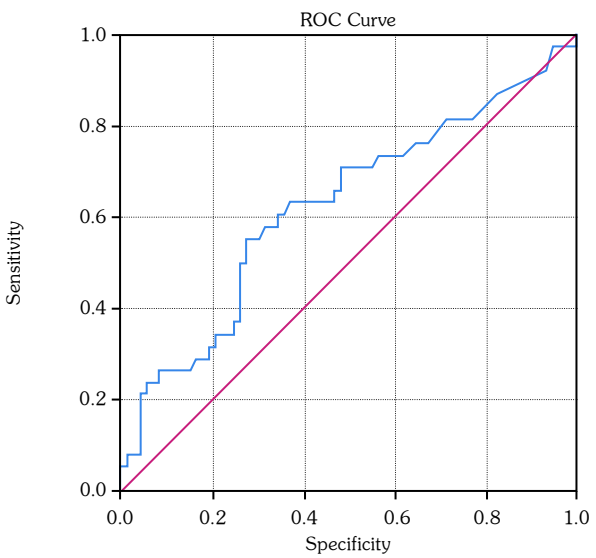

Figure 3. The ROC curve of PCSK9 for predicting cIMT.

ROC: Receiver operating characteristic; PCSK9: Proprotein convertase subtilisin/kexin type 9.

63.2%, specificity 63.0% (AUC=0.625; 95% CI: 0.512–0.739, p=0.031). Figures 2 and 3 show the ROC curves.

DISCUSSION

In the present study, we investigated the level of PCSK9 in patients with AS and whether there was a relationship between PCSK9 and SA in these patients. Our study results showed PCSK9 levels to be significantly higher in patients with AS than in healthy controls. In addition, we found a strong correlation between PCSK9 and cIMT. There was also a highly significant correlation between cIMT and disease activity (BASFI and BASDAI), but not between the PCSK9 and BASFI and BASDAI. In the multivariate regression analysis, PCSK9 was an independent predictor for the existence of SA and carotid plaque.

Cardiovascular involvement is frequent in AS, and mortality due to cardiovascular events has increased in both males and females.[26] In general, SA is common even at early ages in AS.[27] Agents used in the treatment of AS can positively or negatively affect cardiovascular involvement.[27] Increased inflammation and oxidative stress in AS patients may lead to the development of SA at an early age.[28] Cardiovascular disease may occur in patients with AS, although there are no traditional risk factors. Therefore, cIMT measurement should be considered.[29] Previous studies have reported a strong positive correlation between cIMTand disease duration and disease activity index in patients with AS.[30] In the current study, we found the cIMT value of patients with AS to be higher than that of healthy controls. We also showed a significantly positive correlation between cIMT and BASDAI, BASFI, and disease duration.

Low-density protein is atherogenic cholesterol. It is cleared in hepatocytes by binding to LDLR. The PCSK9 binds to LDLR, causing degradation of LDLR. Thus, PCSK9 shows an atherogenic effect.[15] In addition, regardless of the LDL level, PCSK9 induces the development of atherosclerosis and increases platelet activation, oxidative stress and proinflammatory cytokines by stimulating theox-LDL and toll-like receptor 4/nuclear factor kappa-B (TLR4/NF-κB) signaling pathways, thus leading to atherosclerosis.[25,31,32] Vascular plaques have been shown to have ox-LDL in their structure. The PCSK9 accelerates plaque formation in vascular smooth muscle cells, initiated by the association of ox-LDL with the ox-LDL receptor after monocytes/macrophages have entered the vascular stroma.[32,33] In the current study, we detected a strong relationship between carotid plaque and PCSK9 in patients with AS. It has been well documented that PCSK9 levels are closely associated with inflammatory markers, such as increased fibrinogen, leukocyte, and hs-CRP levels.[34] Similarly, we found a strong positive association between PCSK9 and fibrinogen and hs-CRP in our study. Furthermore, hs-CRP is a useful to identify cardiovascular disease risk. In our patients, the number of patients with high hs-CRP and the number of patients with SA detected by increased cIMT were almost the same. However, hs-CRP alone to detect cardiac risk may lead to incorrect results.[21] However, we were unable to detect hs-CRP as an independent predictor for the presence of both SA and carotid plaque in the multivariate analysis. We believe that, combined with PCSK9, hs-CRP may lead to more accurate results in detecting SA in patients with AS. Likewise, fibrinogen plays a role in platelet aggregation and coagulation pathway activation, leading to the development of atherosclerosis. It also increases the risk of plaque rupture by causing fibrous atheroma cap formation.[35] In our study, we found that fibrinogen, such as PCSK9, was highly associated with the presence of carotid plaque in patients with AS. The PCSK9 may also cause SA and plaque formation by increasing the fibrinogen level in patients with AS. Several studies have shown no significant relationship between PCSK9 and lipid parameters.[25,36-38] Consistent with the literature, we found no significant association between PCSK9 and LDL and HDL cholesterol levels in our study. This result suggests that PCSK9 may cause SA and carotid plaque formation with other atherogenic effects, independent of its LDL-lowering impact on patients with AS.

In their study, de Armas-Rillo *et* al.[19] examined 299 axial spondyloarthritis patients and found that PCSK9 levels were lower than those in the control group. The authors found a strong positive association between PCSK9 and disease activity. Although they found no relationship between PCSK9 and cIMT, there was a strong relationship between the presence of carotid plaque and PCSK9. Contrary to their study, we found that PCSK9 levels were higher in patients with AS than in healthy controls. Unlike the aforementioned study, we observed no significant relationship between PCSK9 and BASFI and BASDAI (for disease activity). However, we detected a positive association between PCSK9 and cIMT. The cut-off value of PCSK9 was calculated as 459.5 ng/mL for SA. Similar to de Armas-Rillo et al.,[19] we found a strong relationship between the presence of plaque and PCSK9, and we calculated the 472.0 ng/mL value of PCSK9 as the cut-off value for the existence of plaque with its high sensitivity and specificity value. Of note, unlike our study, the aforementioned study investigated predominantly male individuals, and the mean age and disease duration of the patients were considerably higher than those of our patients. The discrepancy in the results of two studies can be attributed to this fact.

There is a close relationship between PCSK9 and rheumatic diseases.[39] To date, the PCSK9 level in systemic lupus erythematosus (SLE), which is one of the other rheumatic diseases, has been examined in four studies, and controversial results have been reported. In two studies, the PCSK9 value was found to be higher in SLE patients than in healthy individuals.[38-42] One of these studies discovered a positive correlation between PCSK9 and cIMT. A study found PCSK9 levels to be similar to those in healthy individuals,[41] while another study found PCSK9 levels to be lower than those in healthy controls.[40] These studies reported an association between disease activity and PCSK9. In a study examining patients with systemic sclerosis, the PCSK9

level was found to be low; however, the PCSK9 value was found to be high in the presence of skin findings. A correlation was found between PCSK9 and cIMT in patients with this skin lesion.[43] In another study, PCSK9 levels were high in patients with rheumatoid arthritis.[44] The study reported a positive correlation between PCSK9 and atheroma plaque and SA in these patients.[44] Overall, the PCSK9 levels in rheumatic diseases should be examined with more detailed studies.

Limitations of this study include the relatively small number of patients and the fact that the study was conducted in a single center. Another important limitation is the lack of mid- to long-term follow-up results.

In conclusion, our study showed that serum PCSK9 levels in patients with AS were higher than that in healthy individuals and were associated with SA and arterial plaque formation. In the light of these findings, PCSK9 may accelerate SA and carotid plaque formation in patients with AS, regardless of the LDL cholesterol level. There may be no relationship between PCSK9 levels and disease activity in patients with AS. As our study is a pilot study, further large-scale, well-designed, prospective studies are warranted to confirm these findings.

Data Sharing Statement: The data that support the findings of this study are available from the corresponding author upon reasonable request.

Author Contributions: Conception: A.K., A.K., M.H.G.; Design: A.K., Y.A.; Fundings: A.K., Y.A., M.O.; Materials: Y.A., M.O.; Data collection and/or processing: M.H.G., P.D.Y. C.K.; Analysis and/or interpretation: A.K., A.K.; Literature review: M.H.G. A.K.; Writer: M.H.G., A.K, A.K.

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