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Relation between impaired coronary microvascular circulation and plasma atherogenic index in patients with ankylosing spondylitis

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ABSTRACT

Aim: The coronary flow reserve (CFR) is a sign of endothelial dysfunction and early-stage coronary artery disease (CAD). Plasma atherogenic index (PAI) is related to subclinical CAD and may be used as a predictor of cardiovascular mortality. Our aim is to determine CFR and PAI in patients with AS and to investigate whether PAI can be used in the detection of early stage CAD.

Methods: The study population comprised 48 patients, who were diagnosed with AS based on modified New York criteria and 35 healthy volunteers. PAI values were calculated with the formula log 10 triglyceride (TG) / high-density lipoprotein (HDL).

Results: No difference was detected between the two groups for the demographic variables, including age, sex and BMI. The comparison of the groups for PAI and CFR demonstrated that PAI levels were observed to be significantly higher and CFR levels were observed to be significantly lower in the AS patients ($p=0.01$, $p<0.001$, respectively). Correlation analysis revealed that CFR and PAI were negatively correlated (PAI- $p<0.0001$ $r=-0.661$). When two groups were formed, one below CFR level 2 and the other above CFR level 2, only PAI was found to increase significantly from the new lipid indices ($p=0.004$).

Conclusion: There is an independent negative correlation between PAI and CFR values. PAI may be useful in identifying AS patients facing high risk of adverse cardiovascular events, and may also enable the early diagnosis of subclinical atherosclerosis.

Keywords: Ankylosing spondylitis, plasma atherogenic index, atherosclerosis, coronary flow reserve

INTRODUCTION

Ankylosing spondylitis (AS) is a rheumatic disease, which is characterized by chronic inflammation that severely affects the axial skeleton. Sacroiliitis being its distinguishing feature, this disease causes spinal ankyloses as a result of both inflammations at tendon attachment points and syndesmophyte formation. Known to vary among populations, the prevalence of this disease ranges between 0.1-2%.[1]

AS may also affect extra-articular structures, including the eyes, lungs and heart. Of all AS patients, 2-10% present with cardiac signs, including early-stage atherosclerosis. While the risk of cardiovascular disease associated with autoimmune diseases is considered to be multifactorial, accelerated atherogenesis caused by systemic inflammatory response is considered to have a significant place among the underlying physiopathological mechanisms.[2,3]

The coronary flow reserve (CFR) is defined as the ratio of the hyperemic diastolic peak flow velocity to baseline diastolic peak flow velocity, and is considered to be a basic indicator of coronary microvascular function. Reduced CFR is a sign of endothelial dysfunction, atherosclerosis and early-stage coronary artery disease (CAD). CFR has been shown to have prognostic value in the assessment of cardiovascular events associated with various systemic diseases.[4-6] CFR can be measured by transthoracic echocardiography. This method is preferred due to its high diagnostic accuracy, versatility, low cost and particularly avoiding exposure to radiation.[7]

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While conventional atherogenic lipid parameters are still used for the assessment of CAD risk, many large-scale epidemiological studies have demonstrated that novel lipid indices, such as the plasma atherogenic index (PAI), offer a better estimation for atherosclerotic CAD risk, compared to conventional parameters.[8-10] The recently popular PAI is a novel lipid index, which is the logarithmically converted ratio of the molar concentrations of triglyceride to high-density lipid cholesterol (HDL-C). Research has shown that PAI is related to atherosclerosis and subclinical coronary artery disease, and may be used as a predictor of cardiovascular mortality.[11,12]

The present study was aimed at determining CFR, as an indicator of subclinical atherosclerosis, and PAI, for the assessment of CAD risk, in patients diagnosed with AS. Furthermore, it was aimed to investigate whether PAI could be used in the detection of early-stage CAD.

METHODS

The study was carried out with the permission of İstanbul Medeniyet University, Göztepe Training and Research Hospital Ethics Committee (Date: 22.07.2020, Decision No: 2020/0459). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki. All patients, who participated in the study, were informed prior to their registration, and both their written and verbal consent were obtained.

Study Population

The study population comprised 48 patients, who were admitted to the rheumatology polyclinic of our hospital and were diagnosed with AS based on modified New York criteria. After their detailed medical history was recorded, the AS patients underwent physical examination. Thirty-five healthy volunteers, who matched the AS patients for age, sex and body mass index (BMI), were included in the study as control subjects.

Individuals under the age of 18, those with a medical history of stroke, and persons with congestive heart failure, CAD, dilated/hypertrophic or restrictive myopathies, severe valvular heart disease, hypertension (HT), diabetes/impaired glucose tolerance, obstructive sleep apnoea, dyslipidaemia, and morbid obesity (BMI >35 kg/m²), as well as smokers, alcoholics (with an excessive alcohol consumption >120 g/day), and individuals with diseases such as renal and hepatic failure that may affect the coronary blood flow, and those with associating systemic diseases were excluded from the study. Furthermore, asthma patients were excluded for safety reasons, and individuals with cardiac arrhythmia and those, for whom it was not possible to perform CFR measurements due to images of suboptimal quality, were also excluded from the study. Persons with a medical history of vasoactive drug use, and those with abnormal basal electrocardiographs (i.e., showing the presence of Q-waves and left branch blockage, an altered ST-segment or myocardial ischaemia-specific T-wave alterations) were also excluded from the study.

Biochemical Parameters and Plasma Atherogenic Index

Venous blood samples were taken from both the AS patients and controls in the morning, after a fasting period of 10-12 hours. Fasting glucose, total cholesterol (TC), high-density lipoprotein (HDL) cholesterol and triglyceride (TG) levels were measured. High-sensitivity C-reactive protein (hsCRP) plasma levels were detected. Low-density lipoprotein (LDL) cholesterol levels were calculated using the Friedewald formula (TC=LDL+HDL+TG/5). PAI values were calculated with the formula log10 TG/HDL. Non-HDL cholesterol levels were calculated by subtracting the HDL level from the TC level. The Castelli risk indices (CRI) I and II were calculated with the formulae TK/HDL and LDL/HDL, respectively. The atherogenic coefficient (AC) was calculated by dividing the non-HDL level by the LDL level. When calculating the PAI, the TG and HDL levels were firstly converted to their molar equivalents, and then the formula log (TG/HDL-C) was applied.

Echocardiographic and Coronary Flow Reserve Assessments

Assessments were made using a Vivid-6 (GE Medical Systems, Horten-Norway) ultrasound device and with secondary harmonic imaging. All data were stored digitally and were analysed by a cardiologist, who was known to be experienced in echocardiography and was blinded to the clinical and laboratory data. The conventional echocardiographic assessment of the AS patients and healthy controls was made according to the standards described by the American Echocardiography Association. The left ventricular mass was calculated with the Devereux formula, using the end-diastolic left ventricular wall thickness and left ventricle diameter. The ejection fraction of the left ventricle was calculated using the modified Simpson's method and apical views.

For the assessment of the CFR, the transducer was positioned at the level of the fourth and fifth intercostal spaces, near the midclavicular line, such that the left anterior descending (LAD) artery was imaged through modified two or four chamber windows while the patients were in the left lateral position. The patients were continuously monitored, both echocardiographically and for heart rate. B mode and Doppler imaging were performed at transducer frequencies of 8 MHz and 1.00-2.50 kHz, respectively. All individuals were given an

infusion of dipyridamole, at a dose of 0.56 mg/kg for 4 minutes. Individuals, for whom the targeted heart rate was not achieved, were administered with an additional dose of 0.28 mg/kg. In the AS patients and healthy controls, CFR was measured with the pulse wave Doppler method, using the basal diastolic current velocity and the peak current velocity after dipyridamole infusion. To determine the diastolic peak flow velocities (DPFV), measurements were performed during at least 3 cycles, more specifically, at rest, during maximal dipyridamole infusion, and 3 minutes after the dipyridamole infusion was terminated. Subsequently, the average was calculated. CFR was defined as the ratio of the hyperaemic diastolic peak velocity to the baseline diastolic peak velocity, and CFR values ≥2.0 were considered to be normal. All echocardiographic procedures were performed by a single researcher. The observer variability of our laboratory was as indicated in previous study.[13]

Statistical Analysis

Statistical analyses were performed using the SPSS software (Version 26, Chicago, IL, USA). The homogenous distribution of the groups was assessed with the Kolmogorov-Smirnov test.

Group comparisons of the variables, for which the groups were determined to display a homogenous distribution, were made with Student's t-test. The results are given as mean±standard deviation. The comparison of the variables, for which the groups did not display a homogenous distribution, was made with the Mann-Whitney U test. These results are given as minimum-maximum values.

Correlations were analysed with Pearson's correlation analysis. For all analyses, a p<0.05

value was considered statistically significant. In bivariate correlation analyses, while an r value <0.30 indicated the absence of a correlation or the presence of a very weak correlation, an r value <0.50 indicated a weak correlation, and r values ≥0.50 indicated a moderate or strong correlation between the variables.

RESULTS

The basal demographic data and clinical and laboratory findings of the AS patients and healthy controls are shown in Table 1. No difference was detected between the two groups for the demographic variables, including age, sex and BMI. CRP levels were significantly higher in the diseased group, whilst CFR levels were significantly lower (Figure 1). While the groups did not differ for the conventional lipid parameters, such as TC, HDL, LDL and non-HDL levels, the AS patients were observed to display significantly higher TR levels (p=0.01).

Table 1. Comparison of demographic, clinical and laboratory values of patient and control groups

	Patients n=48	Control n= 35	p
Age (years)	39.6±9.7	37.7±6.4	0.33
Gender (F, n)	31	21	0.78
BMI (kg/m²)	25.9±3.2	26.3±2	0.32
Glukoz (mg/dl)	93.7±7.3	91.3±5.8	0.11
TC (mg/dl)	184.3±37	180.4±27.5	0.60
TG (mg/dl)	142.4±74	105.2±50.6	0.01
HDL (mg/dl)	42.6 (26-105)	45.14 (30-63)	0.06
LDL (mg/dl)	109.9±29.9	114.6±25	0.45
Non-HDL (mg/dl)	141.8±39	135.2±25.8	0.38
PAI	0.49±0.3	0.32±0.26	0.01
CCI-1	4.6±1.43	4.11±0.86	0.07
CCI-2	2.77±1.01	2.61±0.69	0.43
AC	3.61±1.44	3.11±0.87	0.07
CFR	2.21±0.45	3.01±0.5	<0.001
hsCRP (mg/dl)	7.36 (0.45-19)	2.18 (0.5-6.0)	<0.001

TC; Total cholesterol, HDL; High-density lipoprotein cholesterol, TG; triglyceride, LDL; Low-density lipoprotein, PAI; Plasma atherogenic index, CRI; Castelli risk indice, AC; Atherogenic coefficient, CFR; Coronary flow reserve, hsCRP; High-sensitivity C-reactive protein

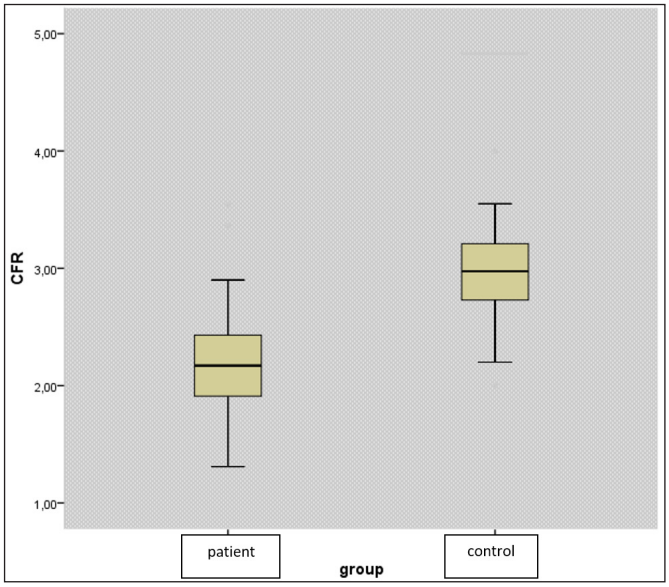

Figure 1. Comparison of CFR levels of AS patients and control groups. CFR; Coronary flow reserve, AS; Ankylosing spondylitis

The comparison of the groups for the novel lipid indices demonstrated no difference to exist for CCI-1, CCI-2 and AC, whilst PAI levels were observed to be significantly higher in the AS patients (p=0.01) (Figure 2).

Correlation analysis revealed that the novel lipid indices, including CFR and TRG, as well as non-HDL and PAI, were negatively correlated, whilst CFR and HDL were positively correlated with each other (PAI - p<0.0001 r=-0.661; CCI-1 - p=0.001 r=-0.483; CCI-2 - p=0.011 r=-0.0362; AC - p=0.001 r=-0.481) (Table 2). The correlation between CFR and PAI is shown in Figure 3.

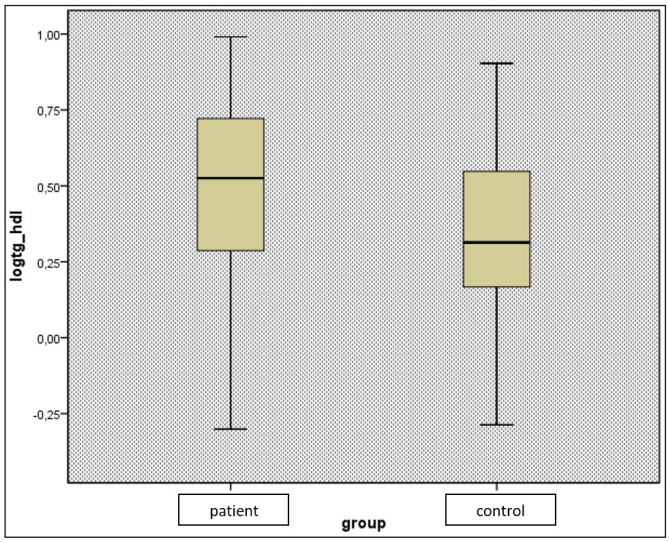

Figure 2. Comparison of PAI levels of AS patients and control groups. PAI; Plasma atherogenic index, AS; Ankylosing spondylitis

Table 2. Correlation analysis of non-CFR parameters between CFR in AS patients

	CFR	
	r values	p values
PAI	-0.661	<0.0001
AC	-0.481	0.001
CCI-1	-0.483	0.001
CCI-2	-0.362	0.011
CRP (mg/dl)	0.299	0.131
TC (mg/dl)	-0.187	0.204
TG (mg/dl)	-0.529	<0.0001
HDL (mg/dl)	0.477	0.002
LDL (mg/dl)	-0.164	0.266
Non-HDL (mg/dl)	-0.347	0.016

CFR; Coronary flow reserve, AS; Ankylosing spondylitis, PAI; Plasma atherogenic index, AC; Atherogenic coefficient, CRI; Castelli risk indice, hsCRP; High-sensitivity C-reactive protein TC; Total cholesterol, TG; triglyceride, HDL; High-density lipoprotein cholesterol, LDL; Low-density lipoprotein

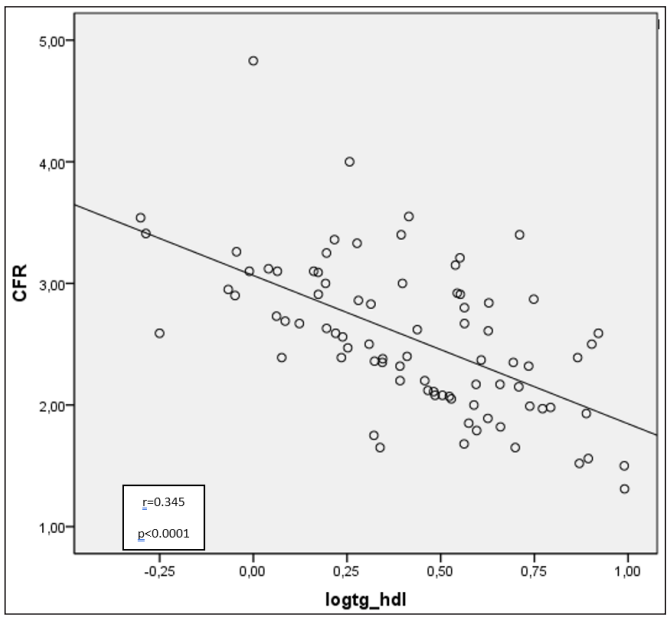

Figure 3. Relationship between PAI and CFR in patients with AS. CFR; Coronary flow reserve, PAI; Plasma atherogenic index, AS; Ankylosing spondylitis

Two groups were established, based on the measurement of the level of CFR as an indicator of atherosclerosis, one including individuals with a CFR level below 2 and the other including those with a CFR level above 2. TR levels were significantly higher and HDL levels were significantly lower in the group with lower CFR levels (p=0.03, p=0.02 and p=0.04, respectively). Of the novel lipid indices only PAI was determined to have significantly increased (p=0.004). No difference was detected for the other demographic parameters, examination findings or lipid parameters/indices (Table 3).

Table 3. Comparison of demographic, clinical and laboratory values between subgroups with low and high CFR levels (cut-off value 2 for CFR)

	CFR <2 (n=16)	CFR >2 (n=32)	p
Age (years)	36.3±11.1	41.2±8.6	0.09
Gender (F n=31)	9	22	0.39
BMI (kg/m²)	25.9±3.7	25.8±2.8	0.94
SBP (mmHg)	127.6±8.2	131.3±5.6	0.09
DBP (mmHg)	78.2±4.1	80.3±4.2	0.13
TC (mg/dl)	187.1±38.2	182.8±36.4	0.70
TG (mg/dl)	188.4±75.4	119.3±62.5	0.02
HDL (mg/dl)	37.1 (26-47)	45.7 (30-105)	0.04
LDL (mg/dl)	110.5±29.5	109.5±30.7	0.91
Non-HDL (mg/dl)	150.9±38.2	137.3±39.2	0.25
PAI	0.66±0.23	0.40±0.30	0.004
AC	4.09±1.13	3.37±1.54	0.10
CCI-1	5.06±1.09	4.37±1.54	0.11
CCI-2	2.97±0.74	2.67±1.12	0.33
hsCRP (mg/dl)	7.99 (0.45-17.9)	5.43 (0.6-19)	0.03

CFR; Coronary flow reserve, SBP; Systolic blood pressure, DBP; Diastolic blood pressure, BMI; Body mass index TC; Total cholesterol, HDL; High-density lipoprotein cholesterol, TG; Triglyceride, LDL; Low-density lipoprotein, PAI; Plasma atherogenic index, CRI; Castelli risk indice, AC; Atherogenic coefficient, CFR; Coronary flow reserve, hsCRP; High-sensitivity C-reactive protein

DISCUSSION

The present study demonstrated that PAI values and CFR levels were higher in the AS patients, compared to the healthy controls. Based on a correlation analysis, PAI values and CFR levels were found to be positively correlated with each other in the AS patients. The results of this study suggest that the PAI values of AS patients could be used as an indicator of subclinical atherosclerosis.

AS is the most common type of spondyloarthropathy with a prevalence ranging from 0.2% to 0.9%. Apart from the skeletal system, this disease is known to affect the cardiovascular system also, and in the event of cardiovascular involvement, the rate of mortality ranges from 20% to 40%.[14] Although increased mortality has not been precisely linked to coronary artery disease, it has been demonstrated that, in AS patients, endothelial functions are impaired and risk factors involved in the pathogenesis of atherosclerosis are altered, these alterations being correlated with the increase observed in

inflammation markers.[15,16] Owing to these mechanisms, the risk of developing atherosclerotic coronary heart disease is high in AS patients.

Endothelial dysfunction is considered to be the first step in the pathogenesis of atherosclerosis. Several mechanisms underlying endothelial dysfunction during inflammatory reactions have been demonstrated. One of these mechanisms is associated with the strong stimulatory effect of oxidised lipoproteins on the expression of cytokine-induced vascular adhesion molecules (VCAM-1), which mechanically links inflammation to the atherogenic process.[17,18] In fact, Gaydukova et al.[19] reported that the plasma levels of vascular adhesion molecules were higher in AS patients, compared to healthy control subjects. Another mechanism is related to the vascular endothelium being a target of tumour necrosis factor alpha (TNF-α), which has a major role in the pathogenesis of chronic inflammatory diseases. Activated endothelial cells are responsible for the secretion of intrinsic chemotactic molecules, and also establish autocrine/paracrine signal cycles localised to the vascular wall and/or of intercellular nature.[20] Furthermore, the genetic regulation of the endothelium reduces the bioavailability of nitric oxide (NO). Thus, the correlation between TNF-α and endothelial dysfunction is associated with a reduced NO level, which is considered to be a critical step.[21] In this respect, it is highly probable that an increased plasma TNF-α level would induce endothelial dysfunction and atherosclerosis. Indeed, Caliskan et al.[22] demonstrated that TNF-α levels significantly increased with AS. A third mechanism involves oxidative stress. It is known that the level of reactive oxygen species (ROS), generated by neutrophils that are related to TNF-α and infiltrate the diseased area, increases in the event of chronic inflammatory diseases.[23] It has been shown in several in vivo animal models that high levels of ROS are associated with reduced NO bioavailability.[24] In previous research conducted by Feijoo et al.[25] and Karakoc et al.[26] oxidative stress markers were determined to have increased in AS patients. A fourth mechanism involves dyslipidaemia, which is an independent determinant of endothelial dysfunction. Although studies are available on the correlation among conventional cardiovascular risk factors, such as endothelial dysfunction and dyslipidaemia, in patients with chronic inflammatory diseases, the results of previous investigations on altered lipid levels are controversial.[27] Nevertheless, it has been reported that while chronic inflammation causes structural changes in lipoproteins, which cannot be detected by standard blood lipid measurements, it also converts LDL into small, dense and pro-atherogenic particles.[28] Moreover, TNF-α contributes to increasing the oxidative modification of LDL. Cure et al.[29] and Caliskan et al.[22] reported that, excluding differences observed in TR levels, TC, HDL and LDL levels did not differ between healthy individuals. In addition, in their meta-analysis by Masi et al.[30] HDL was found to be lower in patients with AS, and no difference was found in other cholesterol levels between patients with AS and healthy individuals. Another fifth mechanism is related to autoantibodies. The production of autoantibodies is involved in the pathogenesis of multiple chronic inflammatory diseases. In patients with such diseases, autoantibodies against normal endothelial and plasma components have been determined, and these auto-antibodies are considered to be involved in the pathogenesis of endothelial dysfunction and atherosclerosis. While this involvement has been clearly demonstrated in systemic lupus erythematosus (SLE), it remains uncertain in some other chronic inflammatory diseases.[24] The present study was aimed at assessing the correlation between endothelial dysfunction and lipid parameters. In this study, we detected that TR levels were significantly higher in the AS patients, compared to the healthy controls. These results were in agreement with those previously reported by Cure et al.[29] and were contradictory to those reported by Caliskan et al.[22] and Masi et al.[30] Despite some controversial results, we ascertained that, in agreement with available literature reports, the TC, HDL and LDL levels of the diseased and control groups were similar.[31] Based on these results, it can be said that there are changes in cholesterol levels of AS patients compared to healthy controls, as in other chronic inflammatory diseases.[27]

Several different methods can be used for the assessment of early-stage atherosclerosis. These methods enable the assessment of the various aspects of the disease as well as the different regions of the arterial tree, and involve the measurement of the intima-media thickness (IMT) of the carotid artery, the flow-mediated dilation (FMD) of the brachial artery, the aortic sclerotic index (AoSI), and the CFR level etc. While each of these parameters can be used as a predictor of cardiovascular events, Gullu et al.[32] claimed that the measurement of the CFR level alone would suffice to determine the treatment to be applied and to follow up the results of treatment. While CFR is used to assess microvascular endothelial functions, it is still not common to use the aforementioned method in the assessment of endothelial function in patients with chronic inflammatory diseases. CFR can be used to assess moderate to severe coronary artery lesions, whilst following a sudden impairment of coronary circulation after stent implantation or acute myocardial infarct, the assessment of the regulation of coronary blood circulation significantly contributes to the determination of prognosis.[33-35] While an impairment of the capacity of the coronary blood circulation to increase indicates the severity of the disease affecting the epicardial arteries, this could also be related to microvascular

dysfunction, as when there is no hemodynamically severe coronary stenosis, maximal increase in blood flow is predominantly determined by the resistance vasculature of the coronary microcirculation. Impaired CFR in the epicardial coronary arteries which appear either normal or mildly diseased in angiographs, have been shown to serve as a predictor for the progression and prognosis of cardiovascular disease.[5] Furthermore, impaired CFR levels have been demonstrated to be associated with bad prognosis in patients diagnosed with coronary microvascular dysfunctions, such as dilated cardiomyopathy and hypertrophic cardiomyopathy.[36, 37] Research on chronic inflammatory diseases and COVID-19 has pointed out to reduced CFR.[38,39] Caliskan et al.[22] determined that CFR decreased in AS patients. Cure et al.[29] reported that, the carotid intima-media thickness, another early-stage predictor of coronary atherosclerosis, was greater in AS patients, compared to the control group. Poddubnyi et al.[40] ascertained that, when compared to controls, reactive hyperaemia of the brachial artery significantly decreased in AS patients. In the present study, we too used the measurement of CFR levels to assess the coronary microvasculature in AS patients and aimed to detect early-stage atherosclerosis in these individuals. Literature reports are available, which indicate impaired CFR levels in AS patients, in agreement with the results of the present study.[22] Our results suggest that AS patients face the risk of developing coronary artery disease.

Impaired lipid parameters predispose individuals to atherosclerosis. The conventional atherogenic lipid profile consists of increased TC, LDL and TG levels, and decreased HDL levels. Some studies suggest that novel lipid indices, including PAI, Framingham's risk scoring, CCI I-II and AC, serve better in the prediction of cardiovascular events, compared to conventional lipid parameters.[41] Owing to its smaller particle size, small dense low-density lipoprotein (sdLDL) penetrates the arterial wall much easier than LDL, forms deposits and undergoes oxidation to generate oxLDL. Several recent studies suggest that sdLDL serves better in predicting atherosclerosis, compared to LDL, and thus, recommend its clinical use.[42] It has been reported that the sdLDL level is correlated with PAI, the measurement of which is both costly and technically complicated.[43] While lipid concentrations may vary during the course of chronic inflammatory diseases such as rheumatoid arthritis (RA), different cholesterol fractions appear to fluctuate in the same direction. PAI is reported to be less affected by fluctuations associated with RA.[44] Recent studies have indicated that PAI could be used as an indicator for the early diagnosis of subclinical atherosclerosis in patients with rheumatic diseases, such as Behçet's syndrome, RA, SLE and familial Mediterranean fever.[29] It is indicated that while PAI values ranging between -0.3 and 0.1 are associated with low cardiovascular risk, a range of 0.1-0.24 indicates moderate risk, and values above 0.24 indicate high risk.[45] In the present study, we detected significantly high PAI values (0.49±0.3). The other lipid indices were also high, but these elevated levels were of no statistical significance. Cure et al.[29] also determined significantly high PAI values in AS patients. The PAI levels detected in the present study showed that the AS patients faced a high risk of developing atherosclerotic cardiovascular disease.

Research conducted on early-stage atherosclerosis in patients diagnosed with chronic inflammatory diseases has revealed a correlation with PAI values. In their research on patients with inflammatory bowel disease, Kul et al.[46] determined that PAI values and CFR levels were inversely correlated with each other. In their study on patients with Behçet's syndrome, Cure et al.[47] determined a strong independent correlation between PAI and carotid intima-media thickness (cIMT) values. In a study carried out in SLE patients, Uslu et al.[48] ascertained that PAI was an independent risk factor for cIMT. Cure et al.[29] assessed early-stage atherosclerosis in AS patients by measuring cIMT, and also investigated the correlation of this parameter with PAI. Based on their results, they revealed a strong independent correlation between PAI and cIMT values, and suggested that PAI would serve as a better indicator for the diagnosis of subclinical atherosclerosis in AS patients, when compared to the TC/HDL ratio. In the present study, we ascertained that the CFR level was correlated with all of the novel lipid indices. Considering levels ≥2 to be normal, the AS patients were assigned to two groups based on CFR measurements, and the group with lower CFR levels was ascertained to display significantly higher levels of the novel lipid indices, excluding PAI. Our results suggest that, compared to the other lipid indices, PAI could serve as a better indicator of early-stage atherosclerosis. It is known that, in individuals under the age of 40, the possibility of predicting early-stage atherosclerosis with cIMT values is lower.[49] Thus, in relatively young individuals, similar to those included in the present study, CFR could serve as a better marker for the diagnosis of early-stage atherosclerosis. In this context, we consider the results of the present study to offer a stronger statement.

PAI appears to be superior to conventional lipid parameters and other novel lipid indices in predicting cardiovascular risk. This is attributed to logarithmically transformed PAI values eliminating distribution irregularity. Furthermore, the determination of PAI values is simple and inexpensive, and PAI values can be used indirectly to assess sdLDL levels.

The present study has some limitations, the first being the enrolment of a small number of AS patients. Secondly, despite the predictive value of CFR in determining the risk of CAD, as a result of the patients enrolled in this study not having been followed up in the long-term, the extent to which the findings of the present study may contribute to daily clinical practice is uncertain. Thirdly, CFR measurements were made only from the LAD. Even if there are low levels of CFR in other arteries, these may be mislabelled as normal values. Fourthly, CRP alone was used as an indicator of inflammation, and this indicator may not represent the whole spectrum of inflammatory activity. Finally, conditions that have the potential to affect CFR in AS patients, such as disease activity, disease duration, and medications used, were not evaluated in this study. This may have caused bias in the study results.

CONCLUSION

A high PAI may be useful in identifying AS patients facing high risk of adverse cardiovascular events, and may also enable the early diagnosis of subclinical atherosclerosis. Nonetheless, further research is required to elucidate the exact mechanisms of early-stage atherogenesis in AS patients and to demonstrate the full impact of atherogenic dyslipidaemia on cardiovascular results in these patients.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was carried out with the permission of İstanbul Medeniyet University, Göztepe Training and Research Hospital Ethics Committee (Date: 22.07.2020, Decision No: 2020/0459).

Informed consent: Written consent was obtained from the patient participating in this study.

Referee Evaluation Process: Externally peer reviewed.

Conflict of Interest Statement: The authors have no conflicts of interest to declare.

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Author Contributions: All the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

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