RESEARCH ARTICLE / *Araştırma Makalesi*

Association Between Plasma Levels of Fibrinogen and the Presence and Severity of Coronary Artery Ectasia

Plazma Fibrinojen Düzeyleri ile Koroner Arter Ektazisinin Varlığı ve Ciddiyeti Arasındaki İlişki

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Abstract

Objective	The aim of this study was to investigate the plasma fibrinogen levels in patients with isolated coronary artery ectasia (CAE).
Materials and Methods	The study population included 154 patients, of whom 52 had isolated CAE, 52 had stable coronary artery disease (CAD) and 50 had normal coronary arteries (NCA). The severity of isolated CAE was determined using the Markis classification. All the subjects underwent complete physical examinations, including a detailed medical history, complete blood count and biochemical parameters. Plasma fibrinogen levels also were measured in all subjects.
Results	The baseline characteristics of the three groups were similar. Plasma fibrinogen levels were significantly higher in the CAE group and CAD group than in the NCA group (383.3 ± 53.0 mg/dl and 400.8 ± 50.6 mg/dl vs 324.0 ± 56.4 respectively, p < 0.001). No difference was found between the CAE and CAD groups. The fibrinogen level was significantly higher in the type 1 Markis subgroup than in the type 2 and type 3 subgroups (P <0.001). In multivariate logistic regression analyses, fibrinogen level was independently and significantly associated with isolated CAE. Receiver operating characteristic curve analysis revealed that fibrinogen levels > 325 mg/dl identified patients with isolated CAE.
Conclusions	Plasma fibrinogen is an easily measurable systemic inflammatory biomarker that is independently associated with CAE presence and severity. This suggests that fibrinogen may be involved in the pathophysiology of CAE.
Keywords	coronary artery ectasia; fibrinogen; coronary artery disease

Öz

Amaç	*Bu çalışmanın amacı izole koroner arter ektazisi (KAE) olan hastalarda plazma fibrinojen düzeylerini araştırmaktı.*
Gereç ve Yöntemler	*Çalışma popülasyonunda 52'si izole KAE, 52'sinde koroner arter hastalığı (KAH) ve 50'sinde normal koroner arter (NKA) bulunan 154 hasta vardı. İzole KAE ciddiyeti Markis sınıflandırması kullanılarak belirlendi. Tüm hastalardan ayrıntılı tıbbi öykü alındı ve eksiksiz fizik muayene yapıldı. Tam kan sayımı ve biyokimyasal parametreler değerlendirildi. Tüm hastaların plazma fibrinojen düzeyleri de ölçüldü.*
Bulgular	*Üç grubun temel özellikleri benzerdi. Plazma fibrinojen düzeyleri KAE grubunda ve KAH grubunda NKA grubuna göre anlamlı derecede yüksekti (sırasıyla 383.3 ± 53.0 mg / dl ve 400.8 ± 50.6 mg / dl vs 324.0 ± 56.4, p <0.001). KAE ve KAH grupları arasında anlamlı fark saptanmadı. Fibrinojen düzeyi, tip 1 Markis alt grubunda, tip 2 ve tip 3 alt gruplarına göre anlamlı derecede yüksekti (p <0.001). Çok değişkenli lojistik regresyon analizlerinde fibrinojen düzeyi bağımsız ve anlamlı bir şekilde KAE ile ilişkili bulundu. İşlem karakteristik eğrisi analizinde, fibrinojen seviyelerinin >325 mg / dl olmasının KAE hastalarını tanımladığı saptandı.*
Sonuç	*Plazma fibrinojeni; KAE varlığı ve şiddeti ile bağımsız bir şekilde ilişkili olan, kolayca ölçülebilen sistemik inflamatuar bir biyobelirteçtir. Bu sonuçlar, fibrinojenin KAE patofizyolojisinde rol oynayabileceğini göstermektedir.*
Anahtar Kelimeler	*koroner arter ektazi; fibrinojen; koroner arter hastalığı*

Introduction

Coronary artery ectasia (CAE) has been defined as localized or diffuse dilation of the coronary arteries exceeding 1.5-fold of the normal adjacent segment in coronary angiographic assessment.[1] The prevalence was reported to be as high as 7.4% in coronary angiography with concomitant atherosclerotic coronary artery disease (CAD), and the right coronary artery is the most severely affected vessel.[2] Isolated CAE without the presence of CAD occurs in a very small percentage (~1%) of all CAE patients.[1-3] Previous clinical studies have suggested that vascular inflammation and atherosclerosis may play major roles in the development of CAE. However, the main pathophysiological mechanism is still unclear.[4] CAE may be a variant of CAD and is associated with inflammation. CAE pathogenesis may be associated with more severe pro-inflammatory status.[5] The morbidity and prognostic significance of the disease are also still not fully understood. Patients with CAE may be completely asymptomatic; however, patients may also complain of typical chest pain, show abnormal cardiovascular stress test results, or present with acute coronary syndrome (ACS) and even sudden cardiac death.[6] Therefore, determining the factors associated with the presence and severity of CAE may help to better manage these patients.
Fibrinogen, a soluble plasma glycoprotein produced by the liver, is not only a component of the coagulation cascade, but also a biomarker involved in inflammatory processes. In addition, it plays a crucial role in the formation of atherosclerotic plaques with pro-inflammatory and pro-thrombotic effects.[7] The prognostic role of fibrinogen in CAD has been evaluated in many studies. The very first studies showed that mortality and future cardiovascular events increased with increased fibrinogen levels, regardless of conventional risk factors.[8,9] Recent studies showed an association between increased plasma fibrinogen and CAD severity and complexity.[10]

The relationship between fibrinogen and CAE is not yet well-established. As CAE seems to be a form of atherosclerosis, and inflammation plays a crucial role in atherosclerotic vascular processes, fibrinogen-mediated inflammation may also be involved in CAE. We investigated the relationship between plasma fibrinogen levels and CAE in patients undergoing coronary angiograph evaluation.

Materials And Methods

Study design and patient selection

This single-center study was cross-sectional and observational in nature. The study was conducted in the tertiary cardiovascular unit of a university hospital and approved by the local University Ethics Committee (approval date: 03.09.2018; approval number: 2018/161). Oral and written informed consent was obtained from all participants before the study started.

All patients were consecutively selected among patients who underwent coronary angiography for suspected coronary artery disease (CAD) in the catheterization laboratory of the Düzce university medical school, education and Research Hospital between January 2018 and December 2018. A total of 3,100 patients were studied, among whom 1,485 were excluded because they either presented with ACS (unstable angina pectoris, NSTEMI and STEMI) or had implanted stents. In total, 137 patients were excluded for not providing informed consent, and 126 were excluded based on the exclusion criteria. Of the remaining 1,352 patients, 52 (3.8%) were found to have CAE without of unknown origin; these patients comprised the CAE group. Fifty patients with angiographically normal coronary arteries (NCA) is comprised the control group. Fifty-two consecutive patients with stable CAD is also comprised the CAD group.

The indication of CAG was either typical chest pain or positive/equivocal results of noninvasive screening tests (myocardial perfusion scintigraphy/treadmill exercise test) for myocardial ischemia and ACS. We selected 52 (16 males and 36 females; mean age, 60.56 ± 11.74 years) consecutive patients diagnosed with isolated CAE without any atherosclerotic lesions (CAE group) and 50 (22 males

and 28 females; mean age, 59.85 ± 10.32 years) consecutive patients with angiographically normal coronary arteries (control group). Finally, the stable CAD group consisted of 52 (31 males and 19 females; mean age, 59.55 ± 9.90 years) consecutive subjects who were selected from catheterized patients during the same study period and who had >50% stenotic lesions on a coronary angiogram.

The exclusion criteria were as follows: (I) ACS presentation, (II) stent implantation in the elective setting, (III) presence of concomitant atherosclerotic disease, (IV) presence of secondary coronary aneurysms (Kawasaki disease or any known collagen vascular disease), (V) presence of significant organic valvular heart disease, (VI) presence of peripheral arterial disease, (VII) presence of atrial fibrillation, (VIII) presence of congestive heart failure and congenital heart disease, (IX) presence of any chronic disease (thyroid dysfunction, any chronic hematological disease, obstructive or restrictive chronic lung disease, any autoimmune or neoplastic disease, chronic kidney (creatinine > 1.5 mg/dL) or hepatic failure (aspartate transaminase or alanine transaminase more than one third of the normal value), chronic or current infections, or receiving active treatment with antiplatelets (except acetylsalicylic acid), anticoagulants, fibrinolytics or steroids (oral or inhaled). Patients with plasma D-dimer levels above the normal range were also excluded.

Study Protocol

A detailed medical history was obtained from all subjects and a complete physical examination was performed. Body mass index (BMI) was calculated according to World Health Organization criteria. A 12-lead electrocardiogram was performed in all patients before CAG, while transthoracic echocardiography was performed in the study group and controls after CAG. The diagnosis of diabetes mellitus was established by fasting blood glucose ≥ 126 mg/dL, hbA1C levels > 6.5% and/or antidiabetic drug usage. Fasting blood glucose was defined as impaired at 100 to 126 mg/dL. The diagnosis of hypertension was established if systolic blood pressure was ≥ 140 mm Hg or diastolic blood pressure was ≥ 90 mm Hg, measured at least twice separately, or based on antihypertensive drug usage. Hyperlipidemia was defined as a total cholesterol level ≥ 200 mg/dL or a history of statin use except in the last 3 months. Patients who were smokers before hospitalization at any stage of life were classified as smokers. Family history of CAD was accepted as positive if any member of the patient's immediate family (siblings or parents) had a nonfatal or fatal myocardial infarction and/or coronary revascularization before 55 years of age.

Coronary Angiography

Coronary angiography was performed using the Judkins technique without nitroglycerin, and 5F Tiger 3.5 or 4 diagnostic catheters (Terumo Interventional Systems, Somerset, NJ, USA) were implanted through the radial arteries. Iodiksanol (Visipaque®) was used as a contrast agent during coronary angiography in all subjects. Two experienced interventional cardiologists, who were blinded to the laboratory measurements and clinical status of the participants, analyzed the CAG images. CAE was diagnosed when a segment of a coronary artery was dilated at least 1.5 times more than the adjacent segment.[1] CAE was classified according to the system proposed by Markis et al. the severity of CAE was graded according to the following criteria: type 1, diffuse ectasia of two or three vessels; type 2, diffuse ectasia in one vessel and localized ectasia in another vessel; type 3, diffuse ectasia in one vessel only; and type 4, localized or segmental ectasia.[3,4] The location of ectatic coronary segments, number of coronary vessels with ectasia, and Markis classifications were recorded.

Patients with coronary lesions with a stenosis diameter >50% in >1.5-mm vessels were diagnosed with CAD. Complexity of CAD was evaluated using the SYNTAX score.11 Coronary lesions with >50% diameter stenosis in >1.5-mm vessels were scored separately and added together to provide the cumulative SYNTAX score, which was prospectively calculated using the SYNTAX score algorit-

hm on the baseline diagnostic angiogram. The online current version was used in the calculation of the SYNTAX scores.[12] Two experienced interventional cardiologists analyzed the SYNTAX score, and the final judgment was made by consensus in cases of disagreement. The final score was calculated from the individual lesion scores by analysts who were blinded to study protocol.

Laboratory Measurements

Blood for biochemical analyses and hematologic parameters was obtained from the antecubital veins following an overnight fast just after CAG. All biochemical tests and complete blood counts were performed using an automatic hematology analyzer (AU5800; Beckman Coulter, Brea, CA, USA) within 1 h after venous puncture. The plasma fibrinogen levels were determined by the clotting method of Clauss with Stago Compact Max (Diagnostica Stago, Asnieres, France).[13] The plasma hs-CRP levels were measured by the nephelometric method using commercially available kits. Fasting blood glucose, total cholesterol, high-density lipoprotein, triglyceride and low-density lipoprotein levels were measured by the hexokinase method, enzymatic method, accelerator selective detergent method, glycerol phosphate oxidase method and Friedewald formula, respectively, using the AU5800 autoanalyzer. Urea and creatinine levels were measured using the spectrophotometric method.

Statistical Analyses

Statistical analyses were performed using SPSS software (ver. 20.0; SPSS Inc., Chicago, IL, USA). The variables were investigated using visual (histograms and probability plots) and analytical methods (Shapiro-Wilk tests) to determine whether they were normally distributed. Descriptive data are presented as means and standard deviations for normally distributed variables. Mean, standard deviation, lowest median value, highest frequency value and ratio value were used. The Kolmogorov-Smirnov test was used to assess the distribution of the data. Analysis of variance followed by Tukey post-hoc analysis, Kruskal-Wallis tests and Mann-Whitney U tests was used to analyze the quantitative data. The $\chi 2$-test was used to analyze the qualitative data. A P value <0.05 was considered significant. The ability to predict the presence of CAE based on fibrinogen levels was analyzed using receiver operating characteristic (ROC) curve analysis. Sensitivity and specificity values were determined when a significant cut-off value was detected. A 5% type 1 error level was significantly predictive of the test variables when evaluating the area under the curve.

Results

The demographic and clinical data of the patients are presented in Table 1. No statistically significant differences in age, gender, BMI or medical treatment were observed among the groups. No statistically significant differences in cardiovascular risk factors, such as dyslipidemia, hypertension, diabetes mellitus, smoking, or family history, were detected among the groups. However, there were significantly more smokers in the CAD group than in the control and CAE groups. There was no significant difference between the CAE and control groups according to smoking.

Patients' angiographic characteristics are also presented in Table 1. The types of CAE according to the Markis classification of coronary ectasia were as follows, in decreasing order of severity: 20 (38.40%) patients with type 1 CAE, 11 (21.10%) with type 2 CAE, 11 (21.10%) with type 3 CAE, and 10 (19.20%) with type 4 CAE. Complexity of CAD was evaluated with the SYNTAX score, and the mean SYNTAX score was 11.85 ± 7.05 in the CAD group.

Laboratory parameters are presented in Table 2. The white blood cell (WBC) counts, neutrophil counts, monocyte counts, uric acid levels, total cholesterol levels, low density lipoprotein (LDL) levels, triglyceride levels and gamma glutamyl transferase (GGT) levels were significantly higher in CAD and CAE patients than control patients. In addition, the patients with CAD had significantly greater

Table 1. Demographic, clinical and angiographic characteristics of the study population					
Variables		NCA (n = 50)	CAE (n = 52)	CAD (n=52)	p value
Age (years)		59.85 ± 10.32	60.56 ± 11.74	59.55 ± 9.90	0.512 (NS)
Gender	Male	22 (44%)	16 (30.8%)	31 (62%)	0.718 (NS)
	Female	28 (56%)	36 (69.2%)	19 (38%)	
Body Mass Index (kg/m2)		28.54 ± 4.10	29.53 ± 4.41	27.4 ± 4.15	0.052 (NS)
Diabetes Mellitus		10 (20%)	14 (25.44%)	19 (38%)	0.131 (NS)
Hypertension		25 (50%)	35 (67.32%)	33 (66.02%)	0.139 (NS)
Dyslipidemia		10 (20%)	13 (25%)	12 (24.05%)	0.819 (NS)
Family History of CAD		7 (14.00%)	12 (23.01%)	11 (22.09%)	0.457 (NS)
Smoker		10 (20%)	15 (28.80%)	33 (66.02%)	0.000
Medical Treatment					
ASA		18 (36.00%)	28 (53.80%)	33 (63,40%)	0.098 (NS)
Statin		5 (10.01%)	10 (19.20%)	18 (34.60%)	0.061 (NS)
ACEI		12 (24.01%)	17 (32.70%)	18 (34.60%)	0.115 (NS)
ARB		7 (14.00%)	7 (13.50%)	9 (17.30%)	0.840 (NS)
β-blocker		3 (6.00%)	13 (25.00%)	16 (30.70%)	0.216 (NS)
CCB		3 (6.00%)	10 (19.20%)	7 (13.40%)	0.671 (NS)
OAD		4 (8.00%)	5 (9.60%)	7 (13.40%)	0.803 (NS)
Insulin		2 (4%)	2 (3.80%)	2 (3.80%)	0.910 (NS)
Marcis Classification					
Type - 1			20 (38.45%)		
Type - 2			11 (21.18%)		
Type - 3			11 (21.15%)		
Type - 4			10 (19.20%)		
SYNTAX Score				11.85 ± 7.05	

NCA: normal coronary artery, CAE: coronary artery ectasia, CAD: coronary artery disease, ASA: Asetil salisilic asit, ACE_I: Angiotensin converting enzyme inhibitors, ARB: Angiotesin reseptor blocers, BB: Beta blocer, CCB: Calsium chanel blocers, OAD: Oral andidiyabetic drug, NS: non-sense

total cholesterol levels, low density lipoprotein (LDL) levels compared to the others. However, there were no significant difference in the WBC counts, monocyte counts, uric acid levels, triglyceride levels and GGT levels between the CAE and CAD groups. The hs-CRP level was significantly higher in CAD patients compared with others, but no significant difference was found in CAE and control groups. The neutrophil level was significantly higher in the CAE groups than in the other groups. However, there was no significant difference in the neutrophil level between the control and CAD groups. There were no statistically significant differences among the three groups in any other laboratory parameters.

The plasma level of fibrinogen is also shown in Table 2. As shown in Figure 1, patients with isolated CAE had significantly higher fibrinogen levels than in the control patients.

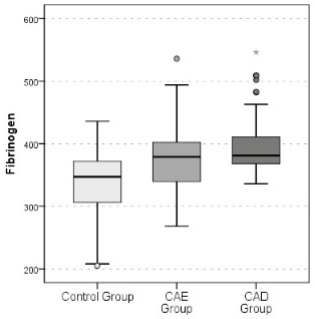

Figure-1. The comparison of fibrinogen levels between the groups, 383.3 ± 53.0 mg/dL in coronary artery ectasia group, 400.8 ± 50.6 mg/dL coronary artery disease group and 324.0 ± 56.4 mg/dL in normal

Table 2. Laboratory findings of the study population (mean value ± standard deviation)				
Variables	NCA (n = 50)	CAE (n = 52)	CAD (n=52)	p value
WBC (103 /μL)	6.60 ± 1.60	7.50 ± 1.70	7.70 ± 1.50	0.015
Neutrophil (103 /μL)	4.00 ± 1.30	4.50 ± 1.60	4.00 ± 1.00	0.013
Monocyte (103 /μL)	0.46 ± 0.17	0.62 ± 0.28	0.61 ± 0.21	<0.001
Lymphocyte (103 /μL)	2.00 ± 0.60	2.50 ± 1.10	2.20 ± 0.60	0.160
Eosinophil (103 /μL)	0.01 ± 0.01	0.01 ± 0.00	0.01 ± 0.00	0.920
Basophil (103 /μL)	0.01 ± 0.00	0.01 ± 0.00	0.02 ± 0.00	0.874
Hemoglobin (103 /μL)	13.70 ± 1.70	13.60 ± 1.30	13.40 ± 1.60	0.154
Platelet (103 /μL)	271.55 ± 69.90	253.95 ± 69.65	258.90 ± 64.30	0.307
Urea (mg/dL)	27.85 ± 11.45	30.45 ± 15.00	30.10 ± 13.10	0.109
Creatinin (mg/dL)	0.80 ± 0.16	0.87 ± 0.27	0.89 ± 0.74	0.415
Uric Acid (mg/dL)	4.90 ± 1.35	5.80 ± 1.55	6.40 ± 4.20	0.001
FBG (mg/dL)	106.25 ±38.85	105.15 ± 38.95	108.55 ± 35.40	0.754
HbA1c (%)	6.14 ± 0.96	6.36 ± 0.85	6.45 ± 4.26	0.578
AST (U/lt)	21.25 ± 8.15	22.85 ± 6.10	23.84 ± 12.65	0.301
ALT (U/lt)	22.35 ± 9.15	24.75 ± 10.50	23.76 ± 22.05	0.094
GGT (U/lt)	26.45 ± 8.75	34.50 ± 12.20	32.67 ± 13.03	0.001
T. Cholesterol (mg/dL)	180.84 ± 41.96	199.95 ± 38.65	223.45 ± 44.75	<0.001
LDL (mg/dL)	108.45 ± 32.25	123.85 ± 33.25	143.75 ± 39.05	<0.001
HDL (mg/dL)	47.56 ± 13.04	42.65 ± 8.55	44.59 ± 9.91	0.142
Triglyceride (mg/dL)	123.20 ± 67.95	167.95 ± 79.85	171.35 ± 87.35	0.032
hsCRP (mg/dL)	2.38 ± 2.42	2.82 ± 1.78	3.18 ± 1.89	0.002
Fibrinogen (mg/dL)	324.05 ± 56.45	383.35 ± 53.05	400.85 ± 50.65	<0.001

NCA: normal coronary artery, CAE: coronary artery ectasia, NS: non-sense, WBC: white blood cells,
Hgb: hemoglobin, Plt: platelet, AST: aspartate transaminase, ALT: alanine transaminase,
FBG: Fasting blood glucose, HbA1c: hemoglobin A1c, Cr: creatinine, T. Cholesterol: total cholesterol,
LDL: low-density lipoprotein, HDL: high-density lipoprotein, TG: triglyceride

However, no differences were detected between the CAE and CAD groups. Plasma level of fibrinogen was found to be significantly associated with the Markis classification of CAE (Table 3 and Figure 2). The fibrinogen level in type 1 was significantly higher than in type II and type III. However, no statistically significant difference in fibrinogen level was found among types II, III and IV.

As shown in Figure 3, ROC curve analysis was performed on the isolated CAE cases and controls to detect the fibrinogen cut-off value for predicting patients with isolated CAE. The ROC curve for fibrinogen revealed that values over 325 mg/dL were correlated with CAE (92.3% sensitivity; 63.4% specificity; positive predictive value: 65.5%; negative predictive value: 50%; area under the curve: 0.767; 95% CI: 0.6780 - 0.857; P < 0.001) (Figure 3).

Based on univariate logistic regression analyses, fibrinogen level, white blood cell count, monocyte count, neutrophil count, lymphocyte count, uric acid, LDL level, triglyceride level and GGT level were significantly associated with isolated CAE. When these parameters were included in multivariate logistic regression analyses, fibrinogen level, monocyte count and GGT level were independently and significantly associated with isolated CAE (Table 4).

Table 3. Comparison of fibrinogen levels according to severity of CAE					
Marcis Classification	CAE (n=52)	median value	mean value ± standard deviation	p value	Post. Hoc.
Type - I	20	396	417.05 ± 47.75	<0.001*	
Type - II	11	352	358.85 ± 44.65		Type-I > Type-II*
Type - III	11	345	346.65 ± 44.35		Type-I > Type-III*
Type - IV	10	376	383.05 ± 42.65		
CAE: coronary artery ectasia, *Statistically significant					

Table 4. Multiple logistic regression analysis showing independent predictors of isolated coronary artery ectasia						
Marcis Classification	Univariate Model			Multivariate Model		
	OR	%95 CI	p value	OR	%95 CI	p value
Fibrinogen	1.02	1.01 - 1.03	0.000	1.03	1.02-1.04	<0.001
White Blood Cell	1.00	1.00 - 1.00	0.032			
Lymphocyte	2.04	1.12 - 3.72	0.019			
Neutrophil	1.27	0.95 - 1.69	0.101			
Monocyte	56.1	4.5 - 696.6	0.002	138.5	4.8 - 4019.5	0.004
Uric Acide	1.63	1.19 - 2.22	0.002			
Total Cholesterole	1.01	1.00 - 1.02	0.023			
Low Density Lipoprotein (LDL)	1.02	1.00 - 1.03	0.023			
Triglyceride	1.01	1.00 - 1.01	0.005			
Gama-Glutamil Transpherase (GGT)	1.07	1.03 – 1.11	0.001	1.09	1.03 - 1.14	0.001

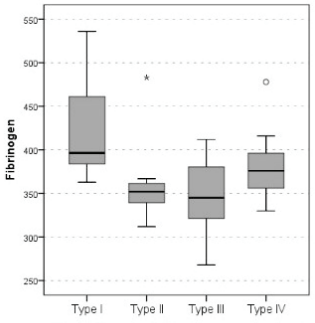

Figure-2. The fibrinogen distribution according to the Markis classification.

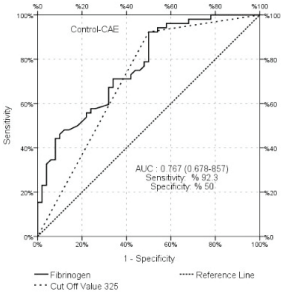

Figure – 3. The ROC curve for fibrinogen revealed that cut-off value over 325 mg/dL was correlated with coronary artery ectasia (92.3% sensitivity, 50% specificity; area under the curve: 0.767, 95% CI: 0.6780 - 0.857, P < 0.001).
95% CI indicates: 95% confidence interval; ROC: receiver operating characteristic.

Discussion

To our knowledge, this is the first study showing the association between CAE and fibrinogen. Patients with CAE had significantly higher plasma fibrinogen levels than those with angiographically normal coronary arteries. We also found that the plasma fibrinogen level was significantly related to the Markis classification of CAE severity.

Although the exact pathogenic mechanisms underlying CAE remain unclear, it has been suggested that CAE is a variant of atherosclerosis with excessively expansive positive remodeling of a coronary artery.[14] The most prominent mechanism for this inappropriate remodeling is diffuse intimal and medial destruction, degeneration of the extracellular matrix, and weakening of the vascular tunica

media associated with severe chronic inflammation.[15] Recent studies have demonstrated that increases in chronic inflammatory cell count, inflammatory cytokine levels and inflammation-related soluble adhesion molecules induced injury to the vascular wall in patients with CAE. Dogan et. al. reported that serum levels of IL-6 were higher in CAE patients compared to normal controls.[16] In addition, CRP, an easier, cheaper and more accessible inflammatory biomarker, was found to be higher in CAE patients than normal controls.[17,18] Adhesion molecules are known to promote inflammation by facilitating the activity of immune system cells. Plasma levels of these molecules, such as intercellular adhesion molecule-1 (ICAM-1), vascular adhesion molecule-1 (VCAM-1) and E-selectin, were found to be significantly higher in CAE patients.[19] Another study showed increased total and differential leukocyte (monocyte) counts in CAE.[20] Moreover, Yildirim et al. showed higher mean fluorescence intensity of CD45 and CD11b on the active monocyte surface of patients with CAE compared to normal controls.[21] They concluded that increased levels of CD11b and CD45 adhesion molecules could be an indicator of the chronic inflammatory response in CAE.[21] Considering all of these studies, CAE appears to be associated with a chronic pro-inflammatory process.

Fibrinogen is a soluble plasma glycoprotein that is usually known as the acute phase reactant. It is the precursor of fibrin and acts as the main determinant of blood viscosity, fibrin formation, coagulation regulation, fibrinolysis and platelet aggregation.[22] Additionally, it was found to be a major pro-inflammatory biomarker of the chronic low-grade inflammatory status characterizing atherosclerosis.[23] Fibrinogen has been found to be an independent predictor for cardiovascular events even after adjusting for traditional cardiovascular risk factors.[24] De Luca et al. revealed an association between elevated plasma fibrinogen levels and atherosclerotic CAD.[25]

Fibrinogen plays an important role in the formation of atherosclerotic plaques.[7,26] Various lines of evidence indicate direct involvement of fibrinogen in atherogenesis. It adheres to arterial walls, turns into fibrin and supports the binding and production of HDL.[23,27] It facilitates the migration of inflammatory adhesion molecules to the endothelial surface.[28] Similarly, it triggers the proliferation and migration of arterial SMCs (smooth muscle cells).[29] In addition, it mediates the binding of monocytes to endothelial cells via ICAM-1 and MAC-1 and it also interacts with leukocytes through macrophage-1 (MAC-1) and alpha X beta 2 receptors.[30-34] As a result, it increases the levels of soluble ICAM-1 in the circulation. It also increases leukocyte and platelet aggregation on the endothelial surface, enhances leukocyte phagocytosis, increases leukocyte activation, and delays apoptosis.[26,35] Finally, it indirectly increases the expression of neutrophil activation factors. In the present study, it was demonstrated that CAE and plasma fibrinogen may be related. Plasma fibrinogen levels were higher in patients with CAE than in those with angiographically normal coronary arteries. Furthermore, there seems to be a correlation between CAE severity and plasma fibrinogen level. Plasma fibrinogen levels were found to be higher in patients with more severe CAE. Fibrinogen, which has a multifaceted relationship with CAD, is an important indicator of inflammatory activity; it is easily accessible and relatively inexpensive. In the context of this study, it is important to determine the predictive value of plasma fibrinogen for CAE cases.

Although this study focused mainly on the association between fibrinogen and CAE, the results were also important regarding the pro-inflammatory status of CAE patients. Previous studies have demonstrated the association between monocytes and inflammatory activity in CAE. Kocaman et al. showed higher monocyte counts in CEA compared to normal controls.[20] In another study, Yıldırım et al. found increased circulating levels of monocyte adhesion molecules, an indirect indicator of activated monocytes, in CAE compared to controls.[21] In the present study, increased plasma fibrinogen levels and monocyte counts appeared to be associated with a pro-inflammatory condi-

tion in CAE, which supports the hypothesis of increased inflammatory activity in the pathogenesis of CAE. Serum GGT may be a predictor of inflammation, as well as fibrinogen and C-reactive protein, and may also be an important biomarker for oxidative stress.36 In this context, GGT activity has been shown to be associated with atherosclerotic CAD.[37] Moreover, serum GGT levels were found to be higher in CAE than in controls.[38,39] The results of our study regarding serum GGT levels were consistent with those of previous studies, and can be explained by the increased inflammation and oxidative stress associated with CAE.

Earlier studies identified an increased incidence of acute cardiovascular events in CAE compared to normal controls.[3,4] CAE may cause increased coronary events via reduced blood flow, thrombosis and/or thromboembolism.40 Reduced flow within the ectatic coronary segment itself may promote the activation of the coagulation cascade, which was described by Virchow's triad. Thrombosis is mediated both by endothelial- and platelet-derived pro-inflammatory and pro-thrombogenic mechanisms, and may be further aggravated by embolism in CAE.[40] Once thrombosis occurs in the CAE segment, owing to positive feedback mechanisms, more inflammatory mediators and cells aggregate and thrombus can develop in an uninterrupted loop.[2,40] As per our hypothesis, fibrinogen plays a key role as a multifunctional biomolecule, and is presumably one of the main determinants of the pro-inflammatory and prothrombotic process triggered by CAE. Based on the results of this study, we cannot confirm fibrinogen is the only factor associated with the pathophysiology of isolated CAE. However, it appears to be an important biomarker for a pro-inflammatory and prothrombotic condition in patients with CAE.

There is no clear explanation for why some patients develop only a small segmental ectasia in one vessel, while others develop diffuse ectasia in all of the coronaries. However, it is believed that the disease status is severe when it compromises all of the vessels.[3] Our study assessed CEA severity according to the Markis classification. Significantly higher fibrinogen levels were observed in the most severe CEA group (Markis-I) than in the other two groups (Markis–II and Markis-III). However, no significant difference was found between the most severely affected group (Markis-I) and the least severely affected group (Markis-IV). This unexpected result may have been due to the study's small sample size.

The current study had several limitations, including the small sample size and the fact that all of the patients were Caucasian. None of the patients underwent intravascular ultrasonography (IVUS) to detect atherosclerotic remodeling in ectatic coronary arteries. Therefore, the coexistence of nonobstructive CAD (< 30%) in patients with "isolated" CAE cannot be unequivocally established. However, patients with isolated CAE do not routinely undergo IVUS in clinical practice, and CAE is usually diagnosed by visual coronary angiography. The observational and cross-sectional design of our study makes it difficult to comment on the causal relationship between plasma fibrinogen levels and CAE. Overall, we believe this study will serve as a valuable base for future prospective and confounder-controlled studies.

Conclusion

Our study revealed that increased fibrinogen levels were associated with CAE, indicating the crucial role of inflammation in the pathophysiology of the disease. Especially high fibrinogen levels were observed in severely affected patients. In addition to fibrinogen, monocyte count and GGT were found to be independently associated with CAE. However, more studies with larger cohorts are needed to validate these findings.

Authors' Note

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