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The association of new atherosclerosis markers with coronary collaterals in chronic total occlusion patients

Nadir Emlek[1], Ali Gökhan Özyıldız[2], Elif Ergül[1], Muhammed Mürsel Öğütveren[1], Muhammet Öztürk[1], Cihan Aydın[3]

[1]Department of Cardiology, Recep Tayyip Erdoğan University Faculty of Medicine, Rize, Türkiye
[2]Department of Cardiology, Recep Tayyip Erdoğan University Training and Research Hospital, Rize, Türkiye
[3]Department of Cardiology, Tekirdağ Namık Kemal University Faculty of Medicine, Tekirdağ, Türkiye

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ABSTRACT

Objectives: In the present study, we investigated the relationship between mentioned markers and chronic total occlusion collateral development.

Patients and methods: A total of 243 patients (210 males, 33 females; mean age: 63.3±11.5; range, 51 to 76 years) who underwent coronary angiography due to typical chest pain or myocardial ischemia detected in noninvasive stress tests and diagnosed with ≥1 major coronary artery occlusion between January and September 2020 were included in the cross-sectional observational study. The angiographic collateral index was determined according to the Cohen-Rentrop classification. The patients were divided into two groups according to the sufficiency of collateral development: the well-developed collaterals group (n=155) and the poor-developed collaterals group (n=88).

Results: Statistically significant parameters in univariate logistic regression analysis were evaluated with multivariate (stepwise) logistic regression analysis; as a result, presence of chronic total occlusion in left anterior descending artery (odds ratio [OR]=2.447; 95% confidence interval [CI], 1.160-5.162; p=0.019), total number of occlusions (OR=3.503; 95% CI, 1.445-8.494; p=0.006), left ventricular ejection fraction (OR=1.056; 95% CI, 1.022-1.091; p=0.001), and the atherogenic index of plasma (OR=0.017; 95% CI, 1.022-1.091; p<0.001) were independently associated with well-developed collaterals. Although the triglyceride-glucose index had statistical significance in the univariate analysis, it was not detected as an independent variable in the multivariate analysis. The monocyte-lymphocyte ratio was not significant in the univariate analysis.

Conclusion: Of the new atherosclerosis markers, only the atherogenic index of plasma had an independent association with poor collateral development.

Keywords: Atherogenic index of plasma, chronic total occlusion, coronary collaterals, monocyte-lymphocyte ratio, triglyceride-glucose index.

Coronary angiogenesis and collateral formation are adaptations that act protectively by supplying blood flow in the region where severe myocardial ischemia develops. Infarct size+, frequency of aneurysm formation, and major cardiovascular events are reduced owing to the adaptations.[1,2]

Dyslipidemia is a crucial factor contributing to vascular endothelial dysfunction.[2] Intact vascular endothelium is essential for coronary collateral development. Therefore, vascular endothelial dysfunction may disrupt collateral development. The fact that collateral development is impaired in diabetes mellitus and metabolic syndrome that causes vascular endothelial dysfunction supports this theory.[3-5]

Inflammation and abnormal glucose and lipid metabolisms are critical in atherogenesis and substantial risk factors for cardiovascular diseases.[6,7] Studies have shown that atherogenic index of plasma (AIP), triglyceride-glucose (TyG) index, and monocyte-lymphocyte ratio (MLR) are novel markers for atherosclerosis, insulin resistance, and inflammation, respectively.[8-10] Endothelial dysfunction plays a significant role in initiating the atherosclerosis process; in addition, it is the common ground of atherosclerosis risk factors. Considering the relationship between

Corresponding author: Cihan Aydın, MD. Tekirdağ Namık Kemal Üniversitesi Tıp Fakültesi, Kardiyoloji Anabilim Dalı, 59030 Tekirdağ, Türkiye.
Tel: +90 282 - 250 00 00 e-mail: drcihanaydin@hotmail.com

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coronary collateral development and endothelial dysfunction, new biochemical markers indicate atherosclerosis may be associated with collateral development. In the present study, we aimed to evaluate the relationship of new atherosclerosis-related biochemical markers (AIP, TyG index, and MLR) with the coronary collateral development in chronic total occlusion (CTO) patients.

PATIENTS AND METHODS

The cross-sectional observational study included 243 consecutive patients (210 males, 33 females; 63.3±11.5; range, 51 to 76 years hospitalized in the cardiology department of the Rize Training and Research Hospital between January and September 2020. Patients diagnosed with stable coronary artery disease (CAD) according to the criteria recommended by the European Society of Cardiology and had total occlusion of ≥1 major coronary vessel detected with coronary angiography (CAG) were included in the study.[11] Patients with typical chest pain or with myocardial ischemia detected in noninvasive stress tests were included in the study. Coronary artery bypass grafting, acute coronary syndrome in the last three months, hematological disease, malignancy, severe kidney (estimated glomerular filtration rate <30 mL/min/1.73 m^2) or liver disease, ongoing infection or chronic inflammatory disease, and autoimmune disease were the exclusion criteria.

The presence of classical cardiovascular risk factors, such as age, sex, diabetes mellitus, hypertension, dyslipidemia, and smoking, was questioned. Patients underwent a transthoracic echocardiographic examination. Hypertension was defined as systolic blood pressure ≥140 mmHg or diastolic blood pressure ≥90 mmHg on repeat measurements or use of any antihypertensive drug. Diabetes mellitus was defined as a fasting plasma glucose level of ≥126 or ≥200 mg/dL at any measurement or use of any antidiabetic drug.

Peripheral venous blood samples were obtained from the patients on the day of hospitalization. The levels of blood biochemical parameters, including a lipid panel, fasting glucose, creatinine, and C-reactive protein levels, were measured. The TyG index was calculated as ln[fasting triglycerides (mg/dL) × fasting plasma glucose (mg/dL)/2]. The AIP was calculated by using the following formula: log10 (TG/HDL-C).[7,12] It can be classified according to the values obtained: −0.3 to 0.1 for low risk, 0.1 to 0.24 for medium, and more than 0.24 for high risk of CVD.[13] The MLR was calculated by dividing monocyte count by lymphocyte count.

Standard selective CAG was performed on all patients using the Judkins technique with at least four images for the left coronary system and at least two images for the right coronary artery. Images of CAG were reevaluated for analyzing collateral development by two experienced interventional cardiologists who were blinded to the study. Collateral grading was assessed concerning the vessel with the highest Rentrop grade in case of having more than one CTO-containing vessel. The degree of coronary collateral development was determined according to the Cohen–Rentrop method: Grade 0, no filling of any collateral vessels; Grade 1, side branch filling of the recipient artery without filling of the main artery; Grade 2, partial filling of the main epicardial artery by collaterals; Grade 3, complete filling of the main epicardial artery by collaterals.[14]

The patients were divided into two groups according to collateral development. Patients with Grade 0 to 1 Rentrope were included in the poor-developed collateral group, and patients with Grade 2 to 3 Rentrope were included in the well-developed collateral group. Coronary angiograms of 243 patients were analyzed, and according to the Cohen-Rentrop method, well-developed collaterals were observed in 155 (63.7%) patients, while poor-developed collaterals were observed in 88 (36.2%) patients.

Severe CAD was defined as stenosis of more than 50% in vessels greater than 1.5 mm in diameter. Coronary total occlusion was defined as lesions present for more than three months, in which the artery shows either the complete interruption of antegrade blood flow on angiography or minimal contrast penetration through the lesion without distal vessel opacification.[15]

Statistical analysis

Statistical analysis was performed using IBM SPSS version 20.0 (IBM Corp., Armonk, NY, USA). Continuous variables were tested for normal distribution using the Kolmogorov-Smirnov test, the Shapiro-Wilk test, and visualization methods (histograms and probability plots). Data were expressed as mean±standard deviation (SD) for

Table 1
Baseline characteristics of the groups

Variables	Poor collateral flow (n=88)					Good collateral flow (n=155)					*p*
	n	%	Mean±SD	Mean	25th-75th percentile	n	%	Mean±SD	Mean	25th-75th percentile	
Age (year)			61.5±10.9					64.4±9.9			0.034
Body mass index (kg/m^2)			29.5±3.7					28.2±3.8			0.043
Sex											
Female	8	9.1				25	16.1				0.465
Previous PCI	33	37.5				50	32.3				0.408
Type 2 DM	37	42				44	28.4				0.022
Hypertension	63	71.6				97	62.6				0.099
Current smoking	35	39.8				44	28.4				0.047
Hyperlipidemia	38	43.2				54	34.8				0.125
LAD occlusion	14	15.9				57	36.8				<0.001
CX occlusion	19	21.6				48	31				0.076
RCA occlusion	60	68.2				87	56.1				0.104
Total occlusion number			1.07±0.31					1.3±0.5			0.002
Number of CAD			2.4±1.3					2.9±1.6			0.016
LVEF			47.1±10.3					50.1±10.1			0.027
Atherogenic Index			0.7±0.3					0.5±0.26			<0.001
WBC (10^3/µL)			9.1±2.7					8.6±2.8			0.206
Hemoglobin (g/L)			13.8±1.8					13.8±1.9			0.954
Glucose (Fasting) (mg/dL)			163.7±89.3					140.3±59.1			0.016
Serum creatine (mg/dL)			1.25±0.8					1.04±0.48			0.059
Total cholesterol (mg/dL)			207.1±55.1					201.1±51.6			0.365
LDL cholesterol (mg/dL)			129.8±47.1					128.1±43.1			0.762
HDL cholesterol (mg/dL)			40.7±16.1					43.4±10.1			0.099
Triglyceride (mg/dL)			229.5±162					156.3±92.1			<0.001
Triglyceride/glucose ratio			1.6±1.07					1.2±0.84			0.001
Monocytes/ lymphocyte ratio			0.3±0.2					0.3±0.14			
C-reactive protein				5.7	1.7-12.7				6	2.1-13.5	0.552
Medication						63	40.6				0.532
Acetylsalicylic acid	46	52.3				22	14.2				0.053
P2Y12 inhbitor	20	22.7				60	38.7				0.066
Beta blocker	38	43.2				45	29				0.495
ACE inhbitor	28	31.8				26	16.8				0.639
ARB	19	21.6				41	26.5				0.353
Calcium channel blocker	15	17				54	34.8				0.094
Statin	46	52.3				15	9.7				0.008
Insulin	13	14.8				37	23.9				0.232
OAD	29	33									0.126

SD: Standard deviation; PCI: Percutaneous coronary intervention; DM: Diabetes mellitus; LAD: Left anterior descending coronary artery; CX: Circumflex coronary artery; RCA: Right coronary artery; CAD: Coronary artery disease; LVEF: Left ventricular ejection fraction; WBC: White blood cell; LDL: Low-density lipoprotein; HDL: High-density lipoprotein; ACE: Angiotensin Converting Enzyme Inhb.; ARB: Angiotensin receptor blockers; OAD: Oral antidiabetic agents.

Table 2
Multivariate binary logistic regression analysis

	Univariate			Multivariate		
Variables	OR	95% CI	*p*	OR	95% CI	*p*
Age (year)	1.028	1.002-1.055	0.035			
Body mass index (kg/m^2)	0.932	0.870-0.999	0.047			
Type 2 diabetes mellitus	0.546	0.316-0.946	0.031			
Current smoking*	0.600	0.346-1.042	0.070			
Left anterior descending coronary artery occlusion	3.074	1.592-5.936	0.001	2.447	1.160-5.162	0.019
Number of total occluded vessel	3.362	1.488-7.600	0.004	3.503	1.445-8.494	0.006
Number of coronary artery disease	1.247	1.040-1.496	0.017			
Left ventricular ejection fraction (%)	1.029	1.003-1.056	0.029	1.056	1.022-1.091	0.001
Atherogenic index	0.035	0.011-0.119	<0.001	0.017	0.004-0.069	<0.001
Glucose (fasting)*	0.996	0.992-0.999	0.020			
Triglyceride (mg/dL)	0.994	0.991-0.997	<0.001			
Statin	0.488	0.286-0.832	0.008			
Triglyceride/glucose ratio	0.631	0.469-0.848	0.002			
Constant				0.026		0.001

OR: Odds ratio; CI: Confidence interval; * The marked parameters were not included in the multivariate logistic regression analysis. Forward conditional method was used in multivariate logistic regression analysis.

normally distributed continuous variables and median (interquartile range) for categorical variables. Variables of both groups were compared by the chi-square test, Mann-Whitney U test, and independent samples t-test, where appropriate. Univariate and backward multivariate logistic regression analysis was performed to identify independent predictors for well-developed collaterals. A two-tailed *p* value of <0.05 was considered statistically significant.

RESULTS

There were significant differences between the groups regarding age, body-mass index, diabetes, smoking, left anterior descending (LAD) artery occlusion, the total number of occlusions, number of coronary arteries with severe stenosis, left ventricular ejection fraction, AIP, fasting glucose, and triglyceride levels (Table 1). Although there were differences between the groups in terms of sex, hypertension, creatinine, and high-density lipoprotein cholesterol (HDL-C) levels, this difference was not statistically significant.

The parameters that reached statistical significance were tested with univariate logistic regression analysis, and factors other than smoking were found to be significant (Table 2). All statistically significant parameters in univariate logistic regression analysis were evaluated with multivariate (stepwise) logistic regression analysis; eventually, the presence of CTO in the LAD artery (odds ratio [OR]=2.447; 95% confidence interval [CI], 1.160-5.162; p=0.019), total number of occlusions (OR=3.503; 95% CI, 1.445-8.494; p=0.006), left ventricular ejection fraction (OR=1.056; 95% CI, 1.022-1.091; p=0.001) and AIP (OR=0.017; 95% CI, 1.022-1.091; p<0.001) were independently associated with good collateral development.

DISCUSSION

The present study identified that AIP, one of the new biochemical markers associated with atherosclerosis, has an independent inverse association with well-developed coronary collaterals. Although the TyG index differed significantly between the groups, it had no independent association with coronary collateral development.

The AIP is a new lipid index superior to low-density lipoprotein (LDL)-cholesterol (LDL-C),

HDL-C, total cholesterol, and triglyceride in predicting CAD.[24] Atherogenic index of plasma is a substitute for small dense (sd) LDL particles and is inversely proportional to LDL-C particle size.[25] The rise in AIP indicates a decrease in LDL particle diameter and an increase in sdLDL, which favors the formation of foam cells and atherosclerotic plaque development.[26] Atherogenic index of plasma is independently associated with CTO and is thought to predict the presence and severity of CTO.[27]

High-density lipoprotein cholesterol has cardioprotective effects and improves endothelial function through its anti-inflammatory and antioxidative effects; in addition, it modulates monocyte activation, adhesion, and migration.[28,29] In the present study, HDL-C level was found close to statistical significance in the well-developed collateral group. The HDL-C level might have contributed to well collateral development.

Studies have shown that the TyG index is superior to HOMA-IR (homeostatic model assessment for insulin resistance) in assessing insulin resistance and can be used to predict CAD and adverse cardiovascular events.[30-32] Insulin resistance can directly or indirectly contribute to ventricular and vascular dysfunction due to attenuated proinflammatory response and aggravated atherosclerotic plaque.[33,34] Furthermore, insulin resistance can alter systemic lipid metabolism, leading to dyslipidemia and even accelerating the rupture of fragile plaques by aggravating vascular endothelial damage and inflammation.[35] However, in the current study, although its relationship with collateral development was significant, it was not detected as an independent variable.

Monocyte-lymphocyte ratio, a novel marker of systemic inflammation, is an independent risk factor for CAD and predicts lesion severity.[36] Increased MLR favors body inflammation and oxidative stress, accelerates the formation of foam cells and endothelial damage, suppresses immune responses, and aggregates coronary plaque development.[37,38] In the present study, its relationship with collateral development had no statistical significance.

Melidonis et al.[39] more frequently detected third-degree collateral circulation following complete occlusion of the LAD and right coronary arteries. In the current study, well-developed collaterals were observed much more in the LAD artery CTO cases. We thought that this might be due to the size of the myocardial jeopardy area, which is influential in collateral development, and the ischemic stimulus that it created. We considered that the higher the total number of occlusions and the number of lesions above 50%, the greater the collateral development as a factor affecting the size of the myocardial jeopardy area.

The relatively small study population and the single-center design may limit the interpretation of results. The study's cross-sectional nature limits the direct relationship between cause and effect. More extensive and prospective studies are needed to confirm this relationship.

In conclusion, the use of AIP, one of the new biochemical markers associated with atherosclerosis in patients with CTO, should be at the forefront in predicting poor collateral development. Furthermore, the use of TyG would be beneficial, but MLR was not appropriate. Compared to these parameters, the AIP, which is noninvasive and easily accessible, can help predict the degree of collateral development the best, but more comprehensive randomized controlled studies are needed.

Ethics Committee Approval: The study protocol was approved by the Recep Tayyip Erdoğan University Faculty of Medicine Ethics Committee (Date/no: 18.05.2022/40465587-050.01.04-443). The study was conducted in accordance with the principles of the Declaration of Helsinki.

Patient Consent for Publication: A written informed consent was obtained from each patient.

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

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