

Relationship between the triglyceride glucose index and collateral index in patients with coronary chronic total occlusion

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ABSTRACT

Objectives: This study aims to investigate the relationship between the triglyceride glucose (TyG) index and coronary collateral circulation (CCC) in patients with coronary chronic total occlusion (CTO).

Patients and methods: Between July 2018 and December 2019, a total of 228 consecutive patients (186 males, 42 females; mean age: 62.2±9.7 years; range, 18 to 80 years) with stable or unstable angina pectoris who had CCO in at least one coronary artery were retrospectively analyzed. The TyG index was calculated. Coronary collateral circulation was evaluated using the Rentrop grading system. The patients were divided into two groups as low-grade CCC (Group 1, n=101) and high-grade CCC (Group 2, n=127).

Results: There was no significant difference in the body mass index, left ventricular ejection fraction, height, weight, the frequency of dyslipidemia, hypertension, diabetes mellitus, and smoking between the groups ($p>0.01$). In the multivariate logistic regression analysis, high TyG index (odds ratio [OR]: 1.345; 95% confidence interval [CI]: 1.120-2.184; $p<0.001$) and uric acid levels (OR: 0.249; 95% CI: 0.105-0.491; $p=0.013$) were the independent predictors of poor CCC.

Conclusion: Our study results suggest that a high TyG index is related to poor collateral circulation.

Keywords: Atherosclerosis, coronary collateral circulation, coronary occlusion, dyslipidemia, glucose.

Cardiovascular diseases are among the leading causes of mortality and morbidity worldwide.^[1] Coronary chronic total occlusion (CTO) is a condition in which the coronary artery is completely occluded for at least three months and there is no blood flow through the occluded vessel.^[2] It is approximately detected in 20% of patients with coronary artery disease (CAD).^[3] When the blood flow decreases due to stenosis in a coronary artery, the collateral vessels progressively open and begin to transport blood to the ischemic or infarcted myocardium.

The presence of coronary collateral circulation (CCC) is important for the prevention of ventricular dysfunction and ventricular aneurysm formation. The mechanism of CCC formation has not been clarified, yet. Vascular growth factors and blood cells such as monocytes, neutrophils, and lymphocytes are implicated in the CCC formation.^[4] A good CCC is important for the prognosis of the patient in the long-term. The triglyceride glucose (TyG) index is considered a basic indicator of insulin resistance which can be important for predicting CCC grade. The TyG index, a consequence of triglycerides and

fasting plasma glucose (FPG), is a good sign of insulin resistance.^[5]

The TyG index is significantly related to a raised risk of developing type 2 diabetes mellitus, arterial stiffness, coronary artery calcification, hypertension, and adverse cardiovascular events.^[6-9] In many studies, the relationship between the TyG index and atherosclerosis has been proven.^[10,11] Alizargar and Bai^[12] reported that the TyG index was significantly related to the total amount of carotid plaque and the increased intima-media thicknesses of carotid arteries in hypertensive and normotensive patients.

In previous studies, higher TyG index levels were related to poor prognosis in patients with acute

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ST-elevation myocardial infarction.^[13] However, the relationship between CCC and TyG index in patients with CTO has not been studied in any study to date. In this study, we aimed to investigate the relationship between the TyG index and CCC in patients with CTO.

PATIENTS AND METHODS

This single-center, retrospective study was conducted at Namık Kemal University Health Practice and Research Hospital, Department of Cardiology between July 2018 and December 2019. Our center is a respected health center in the Thrace region where 4,000 coronary angiography procedures are performed annually. Angiography was performed in 3,800 patients in our clinic and CTO was detected in 290 patients. Patients with severe renal insufficiency (creatinine >2 mg/dL), elevated triglyceride levels (≥ 400 mg/dL), active infection, and malignancy were excluded from the study. Patients taking triglyceride-lowering medications were also excluded. Finally, a total of 228 consecutive patients (186 males, 42 females; mean age: 62.2 ± 9.7 years; range, 18 to 80 years) with stable or unstable angina pectoris were included. Baseline demographic and clinical characteristics of the patients were obtained from the hospital database. A written informed consent was obtained from each patient. The study protocol was approved by the Namık Kemal University, Faculty of Medicine Ethics Committee (Date/No: 25/07/2021/2021,242,10,06). The study was conducted in accordance with the principles of the Declaration of Helsinki.

The fasting blood samples were obtained from all patients during hospitalization after 12 h of fasting. We performed a complete blood count with an automatic blood analyzer and biochemical values were measured with an automatic device via the standard laboratory techniques.

Blood pressure (BP) was measured three times using an automatic BP monitor on both arms, with the arm placed at heart level after a 10-min rest period, and an average of three measurements were taken. Patients with an average of these three measurements $>140/90$ mmHg or those taking antihypertensive drugs were considered hypertensive. Patients with an FPG level of ≥ 7.0 mmol/L (126 mg/dL) or hemoglobin A1c (HbA1c) of $\geq 6.5\%$ or using antidiabetic medication were defined as diabetic. Hyperlipidemia was defined as being on lipid-lowering therapy or

having a total cholesterol level above 220 mg/dL. The TyG was calculated as follows: $[\text{fasting triglycerides (mg/dL)} \times \text{fasting glucose (mg/dL)}] / 2$.^[14]

Coronary angiography

Coronary angiography images of the patients were evaluated by two independent invasive cardiologists who were blinded to clinical data of the patients. Stenosis of $\geq 50\%$ more in the coronary arteries was considered significant. Each coronary artery was visualized in at least two different projections. The CCC was evaluated according to the Rentrop classification as described previously. The Rentrop classification was as follows: Grade 0= no visible collateral, Grade 1= filling in collateral via collateral vessels without visualizing the side branch epicardial segment, Grade 2= epicardial partial filling coronary artery, and Grade 3= complete filling of the epicardial coronary artery.^[15] The patients whose coronary angiography reports were examined were divided into two groups under the Rentrop classification: Group 1 (Grade 0-1) and Group 2 (Grade 2-3). These groups were compared in terms of the calculated TyG index and other biochemical parameters.

Statistical analysis

Statistical analysis was performed using the IBM SPSS version 22.0 software (IBM Corp., Armonk, NY, USA). Continuous variables were presented in mean \pm standard deviation (SD) or median (min-max), while categorical variables were presented in number and frequency. The variables were analyzed using the chi-square or Fischer exact test. The distribution of the data was checked using the Kolmogorov-Smirnov test. The Student t-test was used for continuous data conforming to the normal distribution. Non-parametric variables were analyzed using the Mann-Whitney U test. Receiver operating characteristic (ROC) analysis was performed to determine the optimal cut-off value of the TyG index in the prediction of CCC. The correlation analysis between the TyG index and the CCC was performed using the Spearman correlation test. Multivariate logistic regression analysis was used to identify independent predictors of the CCC. A *p* value of <0.05 was considered statistically significant. coronary collateral index (CCI).

RESULTS

Baseline characteristics and laboratory results of the patients are summarized in Tables 1 and 2,

Table 1
Baseline characteristics of patients

Variables	Group 1 (n=101)			Group 2 (n=127)			Total (n=228)			p
	n	%	Mean±SD	n	%	Mean±SD	n	%	Mean±SD	
Age (year)			61.9±9.7			62.4±9.7			62.2±9.7	0.71
Sex										
Male	84	83.2		102	80.3		186	81.6		0.58
Female	17	16.8		25	19.7		42	18.4		0.58
Height (meter)			1.7±0.2			1.7±0.07			1.7±0.2	0.45
Dyslipidemia	70	69.3		94	74		164	71.9		0.43
Hypertension	50	49.5		73	57.5		123	53.9		0.23
Weight (kg)			80.6±10.2			80.3±10.4			78.8±1	0.82
Smokers	65	64.4		70	55.1		135	59.2		0.15
Diabetes mellitus	49	48.5		47	37		96	42.1		0.08†
Body mass index (kg/m ²)			28.1±4.6			28.1±4.7			28.1±4.6	0.92
Ejection fraction (%)			49.2±9.4			50.7±10.0			50.0±9.7	0.24
Vessel with chronic total occlusion										
LAD	64	63.4		83	65.4		147	64.5		0.95
Cx	31	30.7		37	29.1		68	29.8		0.95
RCA	6	5.9		7	5.5		13	5.7		0.95
Medical treatment										
Beta blocker	66	65.3		71	55.9		137	60.1		0.14
Calcium channel blocker	9	8.9		12	9.4		21	9.2		0.88
ACE-I	49	48.5		66	52		115	50.4		0.60
Diuretic	11	10.9		16	12.6		27	11.8		0.69
Acetyl salicylic acid	73	73.3		83	65.4		156	68.4		0.26
Clopidogrel	10	9.9		11	8.7		21	9.2		0.74
Oral antidiabetic	28	27.7		28	22		56	24.6		0.32
Insulin	21	20.8		24	18.9		45	19.7		0.72
Statin	66	65.3		82	64.6		148	64.9		0.90
Number of vessels with coronary artery disease										
One vessel	24	23.8		25	19.7		49	21.5		0.41
Two vessel	61	60.4		80	63		141	61.8		0.41
Three vessel	16	15.8		21	16.5		37	16.2		0.41

SD: Standard deviation; LAD: Left anterior descending coronary artery; Cx: Circumflex coronary artery; RCA: Right coronary artery; ACE-I: Angiotensin-converting enzyme inhibitors.

Table 2
Laboratory data of patients

	Group 1 (n=101)			Group 2 (n=127)			Total (n=228)			p
	Mean±SD	Median	Min-Max	Mean±SD	Median	Min-Max	Mean±SD	Median	Min-Max	
Glucose (mg/dL)		134	83-371		90	70-176		106.5	68-371	<0.001
Hemoglobin (g/dL)	13.5±1.4			13.5±1.5			13.5±1.5			0.88
Blood urea nitrogen (mg/dL)		17.28	8-46		15.88	6-40		17.56	6-46	0.56
Creatinine (mg/dL)		1	0.6-1.7		0.9	0.3-1.7		0.96	0.3-1.7	0.34
Uric acid (mg/dL)		8.3	3.4-11		5.9	2.3-7.9		6.48	2.3-11	<0.001
Total cholesterol (mg/dL)	199.2±47.6			183.7±45.9			190.6±47.2			0.01
HDL-cholesterol (mg/dL)		40	23-75.71		42	18-87		41	18-87	0.016
LDL-cholesterol (mg/dL)	148.8±40.4			115.9±43.7			130.5±45.7			<0.001
Triglyceride (mg/dL)	194.3±81.2			113.2±27.8			149.1±70.5			<0.001
White blood cell count (×10 ³ /μL)	8.0±2.2			8.2±2.3			8.1±2.3			0.62
Neutrophil count (×10 ³ /μL)	4.8±1.7			5.1±2.1			5.0±2.0			0.46
Lymphocyte count (×10 ³ /μL)	2.2±0.9			2.2±0.9			2.2±0.9			0.92
Monocyte count (×10 ³ /μL)		0.53	0.3-1.44		0.59	0.27-2		0.6±0.3		0.63
Mean platelet volume (fl)	8.5±1.1			8.1±1.1			8.2±1.1			0.10
Platelet count (×10 ³ /μL)	278.4±83.1			274.7±7			276.2±7			0.77
Glomerular filtration rate	81.0±18.1			81.5±17.4			81.3±17.7			0.87
Triglyceride glucose index	9.5±0.5			8.6±0.3			9.0±0.6			0.001

SD: Standard deviation; HDL: High density lipoprotein; LDL: Low-density lipoprotein.

Table 3
Multivariate logistic regression analysis of variables related to CCC

Variables	Odds ratio	95% CI	<i>p</i>
Total cholesterol (mg/dL)	1.037	0.929-1.157	0.517
LDL-cholesterol (mg/dL)	0.874	0.753-1.194	0.077
Triglyceride glucose index	1.345	1.120-2.184	<0.001
HDL-cholesterol (mg/dL)	1.060	0.880-1.278	0.539
Uric acid (mg/dL)	0.249	0.105-0.491	0.013

CCC: Coronary collateral circulation; CI: Confidence interval; LDL: Low-density lipoprotein; HDL: High density lipoprotein.

respectively. Of a total of 228 patients, Group 1 consisted of 101 patients (mean age: 63.9±9.9 years) and Group 2 consisted of 127 patients (mean age: 62.1±9.4 years) ($p=0.710$). The body mass index, left ventricular ejection fraction, height, and weight of the patients were similar in both groups. The frequency of dyslipidemia, hypertension, diabetes mellitus, and smoking were also similar between the groups. The vessels with chronic total occlusion, the number of vessels with CAD, and the medical treatment of both groups were similar.

Furthermore, the laboratory parameters of the two groups were similar, except for the glucose, uric acid, triglyceride, TyG index, and lipid parameters. However, uric acid ($p<0.001$), glucose ($p<0.001$),

triglyceride ($p<0.001$), low-density lipoprotein cholesterol ($p<0.001$), TyG index levels ($p<0.001$), and total cholesterol ($p=0.01$) were higher in Group 1 than Group 2. High-density lipoprotein cholesterol was lower in Group 1 than Group 2 ($p=0.016$).

In the multivariate logistic regression analysis, high TyG index (odds ratio [OR]: 1.345; 95% confidence interval [CI]: 1.120- 2.184; $p<0.001$) and uric acid levels (OR: 0.249; 95% CI: 0.105-0.491; $p=0.013$) were the independent predictors of poor CCC.

The result of the ROC analysis and area under the curve (AUC) for the TyG index to predict low degree of CCC were as follows: cut-off 8.93, AUC: 0.955, 95% CI: 0.931-0.978, $p<0.001$ with 88.1% sensitivity and 88.2% specificity (Figure 1).

In the correlation analysis, a high degree of negative correlation was observed between the TyG index and the CCI ($r=-0.782$, $p<0.001$).

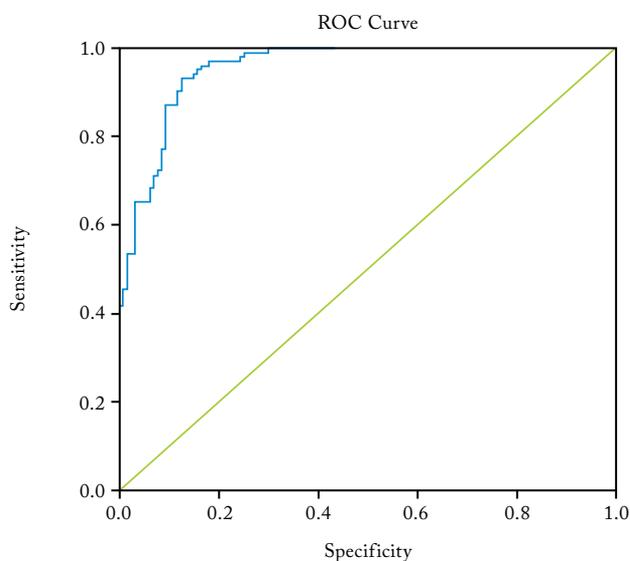


Figure 1. Receiver operating characteristic curve analysis of the triglyceride glucose index levels for the prediction of coronary collateral circulation grade.

ROC: Receiver operating characteristic.

DISCUSSION

In our study, we examined the relationship between the coronary collateral index and TyG index in patients with stable or unstable angina pectoris who underwent coronary angiography procedures. To the best of our knowledge, there is no study regarding the TyG index and CTO. Early identification of diabetic patients with acute coronary syndrome (ACS) is important to reduce future cardiovascular events. Insulin resistance is an increasingly common metabolic disorder caused by an impaired physiological response to insulin. For many years, insulin resistance and hypertriglyceridemia have been related to metabolic disorders, type 2 diabetes, and atherosclerotic cardiovascular diseases.^[16-19] In the onset of diabetes, insulin resistance develops first. Causes of insulin resistance include reduction

of glycogen synthesis in skeletal muscles by glucose transporter type-4 (GLUT 4), impaired insulin receptor binding or intracellular signal transduction, as well as the presence of high amounts of circulating free fatty acids. Patients with type 2 diabetes have insulin resistance and decreased β -cell function. Hyperglycemia causes islet cells to be constantly exposed to oxidative stress. Islet cells in the pancreas have a weaker antioxidant capacity. Long-term glucose toxicity and lipotoxicity cause β -cell failure.

Insulin resistance is related to the chronic increase of plasma glucose and triglycerides.^[19] The TyG index, which is an indicator of insulin resistance, is related to cardiovascular mortality and morbidity in patients with and without diabetes in many studies.^[20] The sensitivity and specificity of the TyG index for determining insulin resistance were 84.0% and 45.0%, respectively, in the study reported by Simental-Mendia et al.^[21] Zhao et al.^[22] revealed that the TyG index could be a better predictor of cardiovascular risk than FPG or HbA1C for patients with ACS.

In their study, da Silva et al.^[23] found that the TyG index could be used as a marker in determining the intensity of atherosclerosis in patients with symptomatic CAD. Mao et al.^[24] revealed that the TyG index could be a detached predictor of CAD severity as assessed by the SYNTAX score in patients with ACS. Luo et al.^[25] also observed that a TYG increase index could be a potent indicator of the worst prognosis in patients with acute ST-segment elevation myocardial infarction cured with percutaneous coronary intervention for one-year follow-up. In a cross-sectional study, patients with type 2 diabetes, but without a CAD history were found to have a higher TyG index related to an increased risk of significant coronary artery stenosis.^[26] In another study involving Korean adults, the TyG index was associated with the progression of coronary artery calcification.^[27]

Recent studies have revealed that insulin resistance takes part in macrophage, endothelial, and vascular smooth muscle cell destruction, which contributes to plaque progression.^[28] Impaired glucose tolerance, increased insulin resistance increases oxidative stress in the long-term and damages vascular endothelial cells. Moreover, insulin resistance, hyperglycemia, and dyslipidemia increase plasminogen activator inhibitor-1 levels, resulting in reduced fibrinolytic activity and raised thrombotic events.^[29,30] Again, in

several studies, insulin resistance causes both structural and functional deterioration such as increased intima-media thickness, coronary artery calcification, and arterial stiffness in the vessel wall.^[31]

In different studies, cardiovascular diseases and complications were found to be higher in diabetic patients.^[32,33] On the other hand, a higher level of TyG index can expedite atherosclerosis in patients with CABG that causes graft failure, as insulin resistance has a proinflammatory and procoagulatory effect, and TyG index is related to endothelial dysfunction. In previous studies, increased insulin resistance levels were associated with the decreased circulation at the microvascular level.^[34]

Insulin resistance was associated with an increased infarct area of single-photon emission computed tomography and myocardial perfusion imaging in a study that included non-diabetic patients with ST-segment elevation myocardial infarction.^[35] In our study, the TyG index was found to be higher in the group with poor CCC. This situation may have been the result of endothelial dysfunction as a result of the proinflammatory and procoagulatory effects of IR.^[36,37]

The main limitation to this study is that it was conducted with a small group of patients in a single center. In addition, the retrospective nature of our study, including a small group of patients, reduces the power of the study. The findings may not cover other demographic groups. The TyG index of patients was calculated only once during hospitalization. Also, we could not reach the HbA1c results of all patients. Therefore, we did not include HbA1c results in the table as the statistical data. Calculating the changes in the TyG index during follow-up may be better in predicting the prognosis. Further multi-center, large-scale prospective studies are required to confirm our results.

In conclusion, high TyG index levels are related to poor collateral circulation in patients with CTO. A high TyG index is an important predictor of a low CCC grade. Based on these findings, TyG index can be a beneficial marker for prognosis in patients with type 2 diabetes and ACS undergoing percutaneous coronary intervention. For CTO interventions, these and similar markers can be a guide in the patient selection.

Declaration of conflicting interests

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