ARAŞTIRMA MAKALESİ / *RESEARCH ARTICLE*

Relationship Between Nonobstructive Coronary Arteries and Metabolic Parameters

Nonobstrüktif Koroner Arterlerle Metabolik Parametreler Arasındaki İlişki

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ABSTRACT

Aim: *The atherogenic index of plasma (AIP) and triglyceride-glucose (TyG) index are strongly associated with atherogenesis of the coronary artery. However, the relationship between these metabolic parameters and ischaemia with nonobstructive coronary artery diseases (INOCA) is unknown. Therefore, we aimed to investigate the relationship between AIP and TyG index and INOCA patients.*

Material and Method: *A total of 529 patients were enrolled in this study and assigned to the INOCA group (n=264) and control group (n=265). The clinical data and calculated AIP, TyG index, were collected. Multivariate logistic regression was set up to assess the AIP and TyG indices for INOCA.*

Results: *The optimal cut-off value of TyG for predicting INOCA was 8.87 with a sensitivity of 52.24% and a specificity of 70% ([AUC]: 0.634 [95% CI: 0.592–0.675, p=0.023]). The optimal cut-off value of AIP for predicting INOCA was 0.54 with a sensitivity of 45.15% and a specificity of 70.57% ([AUC]: 0.590 [95% CI: 0.547–0.632, p=0.025]). When the ROC curves of TyG and AIP are compared, it is seen that TyG is a better predictor ([Difference between areas]: 0.045 [95% CI: 0.0180–0.0711, p=0.001]).*

Conclusion: *AIP and TyG index were significantly higher in the INOCA group when compared to the control group. In addition, the main finding was that when the metabolic parameters TyG index and AIP were compared with each other, the TyG index provided a stronger prediction and was found to be an independent risk factor for INOCA.*

Key words: *atherogenic index of plasma; triglyceride-glucose index; ischaemia with no obstructive coronary arteries (INOCA); coronary artery disease*

ÖZET

Amaç: *Plazmanın aterojenik endeksi (AIP) ve trigliserit-glikoz (TyG) endeksi, koroner arter aterosklerozu ile güçlü bir şekilde ilişkilidir. Ancak bu metabolik parametreler ile nonobstrüktif koroner arter hastalıkları (INOCA) arasındaki ilişki bilinmemektedir. Bu nedenle AIP ve TyG endeksinin INOCA hastaları ile ilişkisini araştırmayı amaçladık.*

Materyal ve Metot: *Bu çalışmaya toplam 529 hasta dâhil edildi ve INOCA grubuna (n=264) ve kontrol grubuna (n=265) atandılar. Klinik veriler ve hesaplanan AIP, TyG endeksi kayıt edildi. INOCA için AIP ve TyG endekslerini değerlendirmek üzere çok değişkenli lojistik regresyon kullanıldı.*

Bulgular: *INOCA'yı öngörmek için TyG'nin optimal kesme değeri %52,24 duyarlılık ve %70 özgüllük ile 8,87 idi ([AUC]: 0,634 [%95 GA: 0,592–0,675, p=0,023]). INOCA'yı öngörmek için AIP'nin optimal kesme değeri, %45,15 duyarlılık ve %70,57 özgüllük ile 0,54 idi ([AUC]: 0,590 [%95 GA: 0,547–0,632, p=0,025]). TyG ve AIP'nin ROC eğrileri karşılaştırıldığında TyG'nin daha iyi bir öngörücü olduğu görülmektedir ([Alanlar arasındaki fark]: 0,045 [%95 GA: 0,0180–0,0711, p=0,001]).*

Sonuç: *AIP ve TyG endeksi INOCA grubunda kontrol grubuyla karşılaştırıldığında anlamlı derecede yüksekti. Ayrıca temel bulgu olarak, TyG endeksi ve AIP metabolik parametreleri birbirleriyle karşılaştırıldığında TyG endeksinin daha güçlü bir öngörü sağladığı ve INOCA için bağımsız bir risk faktörü olduğu tespit edildi.*

Anahtar kelimeler: *plazmanın aterojenik endeksi; trigliserit-glikoz endeksi; obstrüktif koroner arterlerin olmadığı iskemi (INOCA); koroner arter hastalığı*

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Introduction

Most individuals who have anginal symptoms do not have obstructive coronary artery disease (CAD)[1]. There are more women in this group than men. Up to 59–89% of these individuals referred to as "Ischaemia with No Obstructive Coronary Arteries (INOCA)" appear to have coronary vascular dysfunction, which includes both epicardial coronary vasospasm and coronary microvascular dysfunction[2,3]. While the exact pathophysiology of INOCA remains unknown, some research has shown that endothelial dysfunction and micro circular coronary anomalies are key factors[4].

Important components of atherogenesis include inflammation and abnormal glucose and lipid metabolism, which also serve as strong risk factors for cardiovascular disease[5,6]. Research has demonstrated that the triglyceride-glucose (TyG) index and atherogenic index of plasma (AIP) are novel indicators of inflammation, insulin resistance, and atherosclerosis, respectively[7,8].

Although the association of AIP and TyG index with coronary artery disease has been reported, its association with INOCA patients has not been reported in the literature. Therefore, we aimed to investigate the relationship between the atherogenic index of plasma (AIP) and TyG index to INOCA patients.

Method

Study Population

Of 529 patients: 264 were diagnosed with INOCA after coronary angiography at Kafkas University School of Medicine cardiology department between October 2020 and July 2023, and 265 patients were in the control group. Individuals who met the following criteria were classified as INOCA patients: normal coronary angiography, ischaemia on myocardial perfusion scintigraphy, and classic angina-like chest pain with normal 12-lead ECG at rest. Patients in the control group had similar demographics for age and sex, normal echocardiography, no signs of ischaemia during the treadmill exercise test or myocardial perfusion scintigraphy, and patients who had normal coronary angiography results after being suspected of having coronary artery disease.

The patients with coronary artery disease at coronary angiography and surgical or mechanical revascularization were excluded from the study.

Age, sex, hypertension, diabetes, smoking, and family history were recorded as baseline characteristics. The study protocol was approved by the local ethics committee (Ethics Committee of the Dean of the Faculty of Medicine of Kafkas University – numbered ethics committee approval numbered 80576354–050–99/216).

Blood Samples

Biochemical and complete blood counts were obtained retrospectively from intravenous blood samples before coronary angiography. Patients had fasted for twelve hours before the blood samples were taken in the morning. Blood samples were performed after 12 hours of fasting. Plasma total, high density lipoprotein cholesterol (HDL-C), low density lipoprotein cholesterol (LDL-C), triglycerides were determined using Cobas Integra 700/800 (F. Hoffmann-Laroche Ltd, Basel; Switzerland) or Cobas6000, module c501 (Roche Diagnostics, Basel, Switzerland) and blood cell count by ADVIA 120 or 2120 (Bayer Health Care, Tarrytown, NY, USA). The TyG index was calculated as ln [fasting triglycerides (mg/dL) × fasting glucose (mg/dL)/2]. The AIP was determined by the ratio of levels of TG and HDL-C relating to the logarithmic transformation as: log10 [TG (mmol/L)/HDL-C (mmol/L)][9].

Angiographic Analysis

Nitroglycerin was not utilized when performing coronary angiography (Siemens Medical Solutions, Erlangen, Germany) using the standard Judkins procedure. Two seasoned doctors who were blind to the study performed the examination of the angiograms. When evaluating angiograms, visually smooth contours devoid of any anomalies in the wall were regarded as normal.

Statistical Analysis

Version 18.0 of the IBM Statistical Package for Social Sciences (SPSS) program for Windows (IBM Inc., Chicago, IL) was utilized in the data analysis technique. The normality of the continuous variable distribution was examined using the Kolmogorov-Smirnov test. Continuous variables were denoted by averages, whereas categorical variables were indicated by standard deviations and percentages, respectively. The chi-square test was employed for categorical data, and independent sample t and Mann-Whitney U-tests were applied based on distribution patterns to determine

Table 1. *Clinical characteristics of subjects*

	Control group (n: 265)		INOCA group (n: 264)		All patients (529)		p
Age (years)	48	±11	55	±9	52	±11	0.001
Gender, n (%) (Female)	152	(57.4)	107	(39.9)	328	(61.5)	0.049
Smoking, n (%)	89	(33.6)	94	(44.3)	196	(36.8)	0.129
Family CAD history, n (%)	37	(14)	122	(45.7)	181	(34)	0.001
Hypertension, n (%)	59	(22.3)	89	(42.0)	179	(42.2)	0.001
Diabetes, n (%)	20	(7.5)	56	(20.9)	76	(14.3)	0.001
Hemoglobin (g/dL)	14.63	±1.72	14.91	±1.67	14.34	±1.70	0.001
Platelet (10^3/mL)	267.38	±72.35	250.79	±66.52	259.04	±69.90	0.003
Lymphocyte (10^3/mL)	2.42	±0.91	2.57	±0.875	2.494	±0.950	0.012
Eosinophil (10^3/mL)	0.160	(0.090–0.300)	0.160	(0.100–0.235)	0.160	(0.100–0.270)	0.945
Monocyte (10^3/mL)	0.470	(0.380–0.570)	0.510	(0.420–0.670)	0.490	(0.400–0.620)	0.001
Neutrophil (10^3/mL)	4.50	(3.53–5.57)	4.20	(3.50–5.24)	4.32	(3.50–5.40)	0.082
Glucose (mg/dL)	101	±28	114	±42	107	±36	<0.001
Total Cholesterol (mg/dL)	175	±39	195	±45	185	±43	<0.001
Triglyceride (mg/L)	120	(90–150)	145	(103–200)	134	(98–180)	<0.001
LDL-C (mg/dL)	102	±38	118	±46	110	±43	<0.001
HDL-C (mg/dL)	48	±12	47	±12	47	±12	0.348
Urea (mg/dL)	25	(17–31)	16	(11–24)	20	(13–29)	0.001
Creatine (mg/dL)	0.70	(0.60–0.84)	0.80	(0.68–0.90)	0.74	(0.64–0.94)	0.001
hsCRP (mg/L)	3	(1–5)	4	(3–8)	4	(2–7)	0.001
EF (%)	63.29	±5.57	60.90	±7.55	62.09	±6.74	0.001
AIP	0.41	(0.25–0.59)	0.50	(0.32–0.68)	0.45	(0.28–0.64)	<0.001
TyG index	8.68	±0.58	8.97	±0.61	8.83	±0.62	<0.001

INOCA: ischaemia with non-obstructive coronary arteries, CAD: coronary artery disease, LDL-C: low density lipoprotein cholesterol. HDL-C: high density lipoprotein cholesterol, hsCRP: high sensitive C-Reactive protein, EF: ejection fraction, AIP: atherogenic index of plasma, TyG: triglyceride-glucose.

differences in continuous variables across groups. Multivariate logistic regression analysis was used to identify factors whose p-value was less than 0.05. This allowed for the evaluation of the independent predictors of INOCA. As a result, the logistic regression model contained all significant factors following the univariate analysis.

Results

A total of 529 patients with an average age of 52±11 years (328[61.5%] patients were female) were included in the study. The patients were divided into two groups according to the diagnosis of INOCA. The baseline demographic, biochemical, and haematological data of the patients according to the groups are presented in Table 1.

Levels of triglyceride, glucose and AIP, TyG index were all greater in the INOCA patients. Smoking status, count of eosinophil and neutrophil, level of HDL-c did not significantly differ across the groups.

Familial coronary artery disease history was statistically significantly higher in INOCA patients than in the control group. From blood and biochemistry parameters; hemoglobin (Hgb), total cholesterol (TC), LDL-C, creatine, high sensitive C-reactive protein (hsCRP), counts of lymphocyte and monocyte were found to be statistically significant on the side of the INOCA group. On the other hand level of urea, count of platelet and ejection fraction (EF) were found to be higher on the side of the control group. While female gender was more in the control group, the INOCA group was older. Additionally, the presence of diabetes mellitus (DM) and hypertension (HT) was higher in the INOCA group.

Univariate logistic regression analysis revealed significant correlations between INOCA; age, HT, family CAD history, TyG, DM, hemoglobin, monocyte, platelet, urea, creatine and hsCRP (Table 2). Further analysis of these variables using the multivariate logistic regression analysis indicated that age (Odds Ratio [OR]: 1.070, 95% confidence interval [CI]: 1.048–1.093; p<0.001), HT (OR: 1.825, 95% CI: 1.176–2.833; p=0.007), family CAD history (OR: 2.276, 95% CI: 1.330–3.894; p=0.003) and TyG (OR: 1.577, 95% CI: 1.086–2.289; p=0.017) were independent predictors for the INOCA (Table 2).

Table 2. *Multivariate logistic regression model adjustment of INOCA*

	Univariate			Multivariate		
	Univariate OR, 95% CI		p	Multivariate OR, 95% CI		p
Age	1.072	(1.053–1.092)	0.001	1.070	(1.048–1.093)	<0.001
HT	2.938	(2.016–4.281)	0.001	1.825	(1.176–2.833)	0.007
Family CAD history	2.862	(1.858–4.410)	0.001	2.276	(1.330–3.894)	0.003
TyG index	2.311	(1.698–3.147)	<0.001	1.577	(1.086–2.289)	0.017
DM	1.157	(0.570–2.349)	0.687	-	-	-
Hemoglobin	1.000	(0.998–1.002)	0.998	-	-	-
Monocyte	3.218	(0.931–11.123)	0.065	-	-	-
Platelet	0.997	(0.994–1.000)	0.029	-	-	-
Urea	0.941	(0.922–0.960)	0.001	-	-	-
Creatine	1.948	(0.929–4.085)	0.078			
hsCRP	0.991	(0.970–1.013)	0.435			

OR: odds ratio, CI: confidence interval, HT: hypertension, CAD: coronary artery disease, TyG: triglyceride-glucose, DM: diabetes mellitus, hsCRP: high sensitive C-Reactive protein.

The optimal cut-off value of TyG for predicting INOCA was 8.87 with a sensitivity of 52.24% and a specificity of 70% ([AUC]: 0.634 [95% CI: 0.592–0.675, p=0.023]) (Fig. 1). The optimal cut-off value of AIP for predicting INOCA was 0.54 with a sensitivity of 45.15% and a specificity of 70.57% ([AUC]: 0.590 [95% CI: 0.547–0.632, p=0.025]) (Fig. 1). When the ROC curves of TyG and AIP are compared, it is seen that TyG is a better predictor ([Difference between areas]: 0.045 [95% CI: 0.0180–0.0711, p=0.001]).

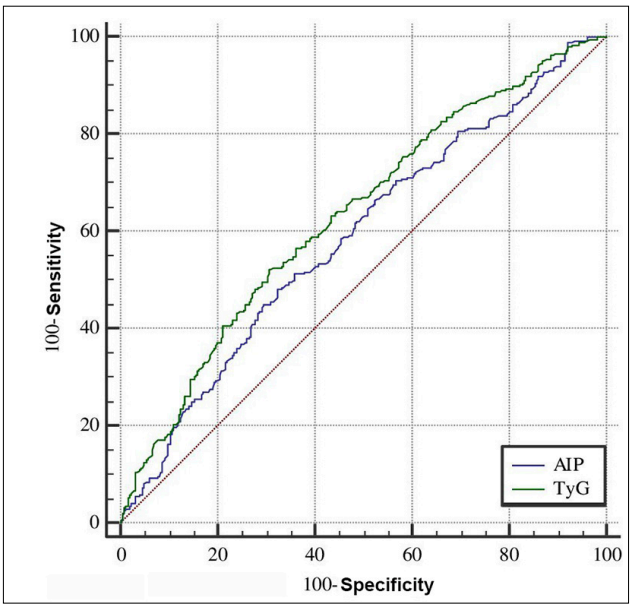

Figure 1. *Receiver operating characteristic curve analysis of AIP and Tyg to predict INOCA (AIP: atherogenic index of plasma, TyG: triglyceride-glucose index).*

Discussion

To our knowledge, this is the first study to determine the relationship between metabolic parameters such as AIP and TyG index and INOCA. We have found that AIP and TyG index were significantly higher in the INOCA group when compared to the control group. In addition, the main finding was that when the metabolic parameters TyG index and AIP were compared with each other, the TyG index provided a stronger prediction and was found to be an independent risk factor for INOCA.

Ischaemia with no obstructive coronary arteries appears to be caused by a variety of processes, some of which may operate alone or in combination[10]. While these may include, in some cases, congenital heart disease, myocarditis, hypertension, severe aortic stenosis, anemia, type II myocardial infarction, shunts, certain medications, heart failure or cardiogenic shock, Prinzmetal variant angina (coronary spasm), myocardial diseases, coronary anomalies, myocardial bridging, and other causes, the underlying mechanisms and appropriate diagnostic and management approaches are typically evident in these situations. One proposed mechanism contributing to INOCA is coronary microvascular dysfunction (CMD), defined as epicardial, microvascular endothelial or nonendothelial dysfunction that limits myocardial perfusion, most often detected as reduced coronary flow reserve (CFR)[11]. Coronary microvascular dysfunction can be iatrogenic, arise in the presence of cardiac disease or obstructive CAD but not in the absence of either. Patients even in the absence of flow-limiting stenosis are at risk of cardiac mortality if they have coronary vasomotor dysfunction[12].

Abnormal lipid metabolism, insulin resistance and the inflammatory response play important roles in the progression of coronary atherosclerosis, calcified plaque

formation and deterioration[6,13]. One significant risk factor for atherosclerosis is the plasma's atherogenic lipoprotein composition. The high and positive correlation between the AIP, cholesterol esterification rates, lipoprotein particle size, and residual lipoproteinemia has led to its proposal as a measure of plasma atherogenicity[14,15]. The AIP is a new comprehensive lipid index superior to LDL-C, HDL-C, TC, and triglyceride as a predictor for CAD[16]. Furthermore, previous studies have shown that AIP is more closely related to cardiovascular (CV) risk than individual lipoprotein cholesterol fractions or other atherogenic indices[17,18]. Foam cell production and the development of atherosclerotic plaque are aided by an increase in the AIP, which signifies a decrease in LDL particle diameter and an increase in the fraction of small dense LDL (sdLDL)[19].

According to studies, the TyG index may be utilized as a predictor of CAD and adverse cardiovascular events and is a more accurate measure of insulin resistance than Homeostatic Model Assessment for Insulin Resistance (HOMA-IR)[20,21]. In relation to coronary artery calcification, coronary artery stiffness, and the potential to predict the degree of coronary stenosis, the TyG index may have an impact on the development of atherosclerotic plaques at all stages of coronary artery disease (CAD) [22]. Furthermore, insulin resistance can change the way that systemic lipid metabolism functions. This can cause dyslipidemia, which aggravates vascular endothelial damage and inflammation as well as makes it more likely that susceptible plaques will burst[23]. Although our study does not claim that this relationship is stronger than obstructive coronary artery diseases, the relationship of these two indices, which have been proven to be related to atherosclerosis, was revealed for the first time in the literature with INOCA patients.

In conclusion, the TyG index was found to be a helpful indicator for INOCA prediction in the current investigation.

Limitations of the study

There are many restrictions on our investigation. We did not measure coronary flow velocity during cholinergic provocation in this single-center investigation with a limited sample size, and although the doppler wire evaluation is in accordance with recognized standards, it was not the basis for the diagnosis of microvascular spasm[24]. One of the most important limitations of our study is that we did not compare INOCA patients with obstructive coronary artery patients.

Conclusions

Ischaemia with no obstructive coronary arteries is a significant health issue that is linked to poor prognosis, insufficient therapy, and underdiagnosis. Multicenter research with a greater patient sample size is nonetheless required in this area. To address the unsolved concerns in the diagnosis and treatment of these individuals, prospective, well-designed, continuing research is required. Elevated TyG index may predict INOCA and independent risk factor. Although our study does not claim that this relationship is stronger than obstructive coronary artery diseases, the relationship of these two indices, which have been proven to be related to atherosclerosis, was revealed for the first time in the literature with INOCA patients.

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Authors' Contribution

The authors share the responsibility for the manuscript.

Data Availability

The datasets generated during and/or analyzed during the current study are available from the corresponding author upon reasonable request.

Conflict of Interest

The authors declare no potential conflicts of interest regarding this article.

Disclaimer

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