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ELEVATED TRIGLYCERIDE GLUCOSE INDEX IS RELATED TO THE PRESENCE OF HEART FAILURE

YÜKSEK TRİGLİSERİD GLUKOZ İNDEKSİ KALP YETMEZLİĞİ VARLIĞIYLA İLİŞKİLİDİR

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ABSTRACT

Objective: Previous studies have shown a significant association between insulin resistance (IR) measured by using different methods and heart failure (HF). In recent years, the triglyceride glucose (TyG) index has been used to measure IR, and there are several reports showing that the TyG index indicates conditions such as metabolic syndrome (MetS) and atherosclerotic process. However, there is no study investigating the association of the TyG index with HF. Therefore, we aimed to evaluate the role of the TyG index in HF presence and its relationship with HF severity in this study.

Materials and Methods: Sixty-nine subjects matched for age and gender were analyzed retrospectively. The TyG index was used to measure IR and was calculated by the formula Ln [fasting triglycerides (mg/dl) x fasting glucose (mg/dl)/2]. The severity of HF was assessed by New York Heart Association (NYHA) functional class, left ventricular ejection fraction (LVEF) and N- terminal prohormone brain natriuretic peptide (NT-proBNP).

Results: HF patients had higher TyG index (9.11±0.59 vs. 8.55±0.55; p<0.001) but there was no correlation between TyG index with HF severity identified by NYHA functional class, LVEF and NT-proBNP. The ROC curve showed the cut-off point of the TyG index in determining HF as 9.19 with 71% sensitivity and 51% specificity (AUC:0.745, p<0.001).

Conclusion: TyG index may be a useful marker for diagnosis of HF, but is not correlated with HF severity.

Keywords: Heart failure, insulin resistance, triglyceride glucose index

ÖZET

Amaç: Önceki çalışmalar, farklı yöntemler kullanılarak ölçülen insülin direnci (IR) ile kalp yetmezliği (KY) arasında önemli bir ilişki olduğunu göstermiştir. Son yıllarda, trigliserid glikoz (TyG) indeksi IR'ni ölçmek için kullanılmaktadır ve TyG indeksinin, metabolik sendrom (MetS) ve aterosklerotik süreç gibi durumları gösterdiğine dair birkaç rapor vardır. Ancak TyG indeksinin KY ile ilişkisini araştıran herhangi bir çalışma yoktur. Bu nedenle, biz bu çalışmada TyG indeksinin KY varlığındaki rolünü ve KY şiddeti ile ilişkisini değerlendirmeyi amaçladık.

Gereç ve Yöntem: Yaş ve cinsiyet uyumlu 69 hasta geriye dönük olarak incelendi. IR'ni ölçmek için TyG indeksi kullanıldı ve Ln [açlık trigliseridleri (mg/dl) x açlık glikozu (mg/dl)/2] formülüyle hesaplandı. KY'nin şiddeti, New York Kalp Derneği (NYHA) fonksiyonel sınıfı, sol ventriküler ejeksiyon fraksiyonu (LVEF) ve N-terminal prohormon beyin natriüretik peptidi (NT-proBNP) ile değerlendirildi.

Bulgular: KY hastaları daha yüksek TyG indeksine sahipti (9,11±0,59'a karşı 8,55±0,55; p<0,001). Ancak NYHA fonksiyonel sınıfı, LVEF, NT-proBNP ile tanımlanan KY şiddeti ile TyG indeksi arasında herhangi bir korelasyon yoktu. ROC eğrisi, KY'nin belirlenmesinde TyG indeksinin kesme noktasını %71 duyarlılık ve %51 özgüllük ile 9,19 olarak gösterdi (AUC:0,745, p<0,001).

Sonuç: TyG indeksi, KY tanısı için yararlı bir belirteç olabilir ancak KY ciddiyeti ile ilişkili değildir.

Anahtar Kelimeler: Kalp yetmezliği, insülin direnci, trigliserid glikoz indeksi

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INTRODUCTION

Heart failure (HF) is one of the leading causes of mortality and morbidity worldwide. Although the pathophysiological mechanisms underlying HF are still not fully understood, previous animal and human studies have shown a significant relation between HF and insulin resistance (IR) (1). Currently, real-life data studies have reported that HF is associated with hyperglycemia or chronic hyperglycemic conditions such as IR, diabetes and that the incidence of HF is higher in patients with these conditions (2).

The triglyceride glucose (TyG) index has been derived from fasting triglyceride and glucose, and several studies have shown the relationship between the TyG index with hypertension, diabetes, metabolic syndrome (MetS), arterial stiffness and coronary artery calcification. In addition, the TyG index may be an indicator for determining the presence and severity of coronary artery disease, carotid atherosclerosis and ischemic stroke according to the recent study results (3-5). However, no study investigating the relationship between the TyG index and HF has yet been reported in the literature. Hence, we aimed to evaluate the role of the TyG index in patients with HF in this study.

MATERIALS AND METHODS

Study population

In this study, age and gender matched 69 subjects who were admitted to our cardiology outpatient clinic were analyzed retrospectively. Acute coronary syndrome, acute myocarditis/pericarditis, malignancy, acute and chronic infections, autoimmune diseases, severe hematological disorders, systemic inflammatory diseases, chronic renal failure (glomerular filtration rate calculated by Cockcroft-Gault formula <50 mL/min/1.73 m^2), severe liver failure and pregnancy were defined as exclusion criteria. The subjects aged 18-90 years with a diagnosis of HF for at least 6 months and left ventricular ejection fraction (LVEF) <40% were included in the patient group (n=34). The New York Heart Association (NYHA) functional classification was determined by cardiologists who were blind to the patients' clinical data. The subjects aged 18-90 with LVEF>50%, but no known history of heart disease or clinical findings were included in the control group (n=35). This study was approved by our institutional ethical committee in accordance with the Declaration of Helsinki (2021/01, protocol no:020-4331).

Data collection and definitions

Previously recorded data such as demographic, medical history, medications and the laboratory findings including fasting blood glucose (FBG), renal function tests, lipid parameters, complete blood counts and serum N- terminal prohormone brain natriuretic peptide (NT-proBNP) concentrations were re-analyzed. The TyG index was calculated by the formula Ln [fasting triglycerides (mg/dl) xfasting glucose (mg/dl)/2] (6). LVEF calculated by modified biplanar Simpson method of the study population was scanned retrospectively.

Hypertension was defined in accordance with the criteria of World Health Organization (WHO) (7). The diagnosis of diabetes was based on the American Diabetes Association criteria (8). National Cholesterol Education Programme guidelines were used for the definition of dyslipidemia (9).

Statistical analysis

Statistical analysis was performed using SPSS version 21.0 software (SPSS, Inc., Chicago, Ill., USA). In expressing the values, number (percentage) for categorical variables and mean ± standard deviation for continuous variables were used. Kolmogorov-Smirnov test was done to determine the normal distribution. Student's t-test or chi-square test was performed to compare variables between groups where appropriate. The relationship between TyG index and other variables was evaluated using Pearson's correlation analysis. In the advanced stage, the association between the TyG index with variables, including HF severity indicators, was assessed by multiple logistic regression after the adjustment for any potential confounding. Curve analysis receiver operating characteristics analysis (ROC) was used to predict the ability of the TyG index to detect the presence of HF.

RESULTS

The baseline characteristics of the study population are presented in Table 1. The incidences of comorbidity such as hypertension, diabetes, hyperlipidemia and vital signs including systolic blood pressure, diastolic blood pressure, and heart rate did not differ between the groups. Laboratory parameters including FBG, HbA1c, sodium, creatinine, triglyceride, HDL-C, white blood cells (WBC), albumin and NT-proBNP showed significant differences in the groups ($p<0.05$). However, there was no significant difference in total cholesterol, LDL-C and hemoglobin levels. The TyG index was higher in HF patients compared to controls (9.11±0.59 vs 8.55±0.55; $p<0.001$). The ROC curve generated from the TyG index resulted in the area under the curve (AUC) of 0.745 to indicate HF presence and and the cut-off point calculated based on this curve was 9.19 with 71% sensitivity and 51% specificity (Figure 1).

In Pearson's correlation analysis, a significant relationship was found between the TyG index with systolic blood pressure, total cholesterol, creatinine, as well as its components FBG and triglycerides (Table 2). However, the TyG index was not significantly correlated with body mass index, diastolic blood pressure, heart rate, LVEF, hemoglobin A1c (HbA1c), LDL-C, HDL-C, hemoglobin, WBC, albumin and, NYHA functional class, LVEF or NT-proBNP

Table 1: Baseline characteristics and medications of study population

Variables	Subjects with HF (n=34)	Subjects without HF (n=35)	p
Mean age (years)	64.17±9.57	62.57±9.22	0.481
Males, n (%)	16 (47)	16 (46)	0.911
Body mass index (kg/m^2)	28.06±4.98	28.42±4.55	0.751
Hypertension, n (%)	15 (44)	13 (37)	0.555
Diabetes, n (%)	14 (41)	9 (26)	0.173
Hyperlipidemia, n (%)	12 (35)	6 (17)	0.086
Current smoking, n (%)	3 (9)	7 (20)	0.187
Systolic blood pressure (mmHg)	119.00±13.24	120.43±14.67	0.672
Diastolic blood pressure (mmHg)	75.94±10.35	74.29±8.23	0.463
Heart rate (beats/minute)	75.21±13.33	69.83±11.62	0.078
LVEF (%)	26.60±4.55	59.26±3.58	<0.001
Atrial fibrillation, n (%)	10 (29)	-	-
NYHA III-IV, n (%)	20 (58)	-	-
Ischemic etiology, n (%)	19 (56)	-	-
ACEI/ARB, n (%)	25 (74)	12 (34)	0.001
Beta-blockers, n (%)	31 (91)	3 (9)	<0.001
Statins, n (%)	12 (35)	2 (6)	0.002
Antiplatelets, n (%)	32 (94)	9 (26)	<0.001
Diuretics, n (%)	23 (67)		
Digitalis, n (%)	9 (26)		

LVEF: left ventricular ejection fraction, NYHA: New York Heart Association, ACEI: Angiotensin-converting enzyme inhibitor, ARB: Angiotensin receptor blocker, HF: heart failure

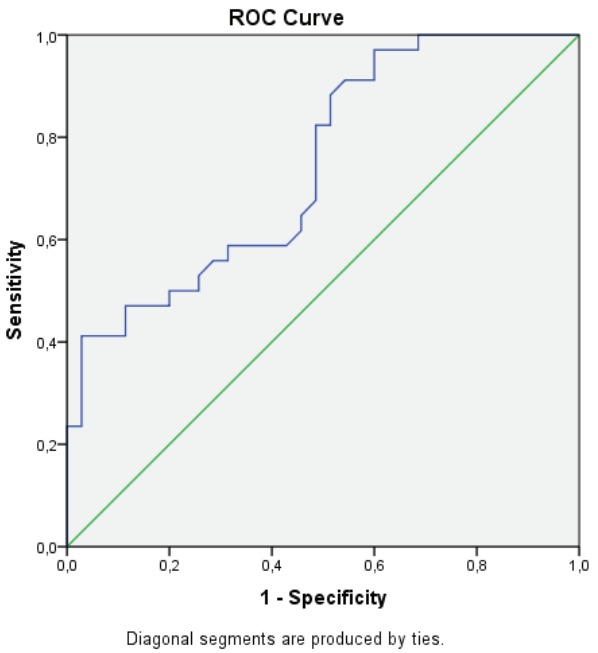

Figure 1: Receiver operator characteristic curve (ROC) of TyG index in predicting the presence of heart failure
TyG index: triglyceride glucose index

used in predicting HF severity and prognosis (Table 2, Figure 2). In addition, TyG index did not differ significantly in HF subgroups divided as ischemic and non-ischemic (Figure 3). In the multiple logistic regression analysis, it was found that none of the variables used in the model was independently associated with the TyG index, but the combination of these variables could strongly indicate a high TyG index as presented in Table 3 (95% CI:3.366-8.157; p<0.001).

DISCUSSION

In this study, we found that the patients with HF had a higher TyG index, but did not correlate with parameters indicating HF severity, including LVEF, NT-proBNP, and NYHA functional class. After adjusting the confounding factors by multiple logistic regression analysis, we observed that none of the clinical variables alone was associated with the TyG index, but their combination strongly indicated the high TyG index.

IR is defined as the impairment of cells' ability to respond to the action of insulin in the transport of glucose from the bloodstream to target tissues (10). IR is related to dyslipidemic conditions and patients with IR are typ-

Table 2: The laboratory data of study population

Variables	Subjects with HF (n=34)	Subjects without HF (n=35)	p
FBG (mg/dl)	117.02±28.56	97.26±12.59	<0.001
HbA1c	6.45±1.05	5.59±0.80	<0.001
Creatinine (mg/dl)	0.96±0.17	0.75±0.13	<0.001
Sodium (mEq/L)	139.14±3.54	140.63±1.97	0.003
T-chol (mg/dl)	189.71±46.63	193.20±41.54	0.743
TG (mg/dl)	167.35±78.06	119.69±55.32	<0.001
LDL-C (mg/dl)	109.97±30.98	116.48±33.98	0.408
HDL-C (mg/dl)	40.67±7.48	52.57±13.38	<0.001
Hemoglobin (g/dl)	13.61±1.29	14.16±1.25	0.076
WBC (cells/μL)	9.23±2.00	6.98±1.54	<0.001
Albumin (g/dL)	4.25±0.26	4.57±0.23	<0.001
NT-proBNP (pg/ml)	613.71±433.70	97.32±49.78	<0.001
TyG index	9.11±0.59	8.55±0.55	<0.001

FBG: fasting blood glucose, HbA1c: hemoglobin A1c, T-chol: total cholesterol, TG: triglycerides, LDL-C: low-density lipoprotein cholesterol, HDL-C: high-density lipoprotein cholesterol, WBC: white blood cells, NT-proBNP: N-terminal prohormone brain natriuretic peptide, TyG index: triglyceride glucose index, HF: heart failure

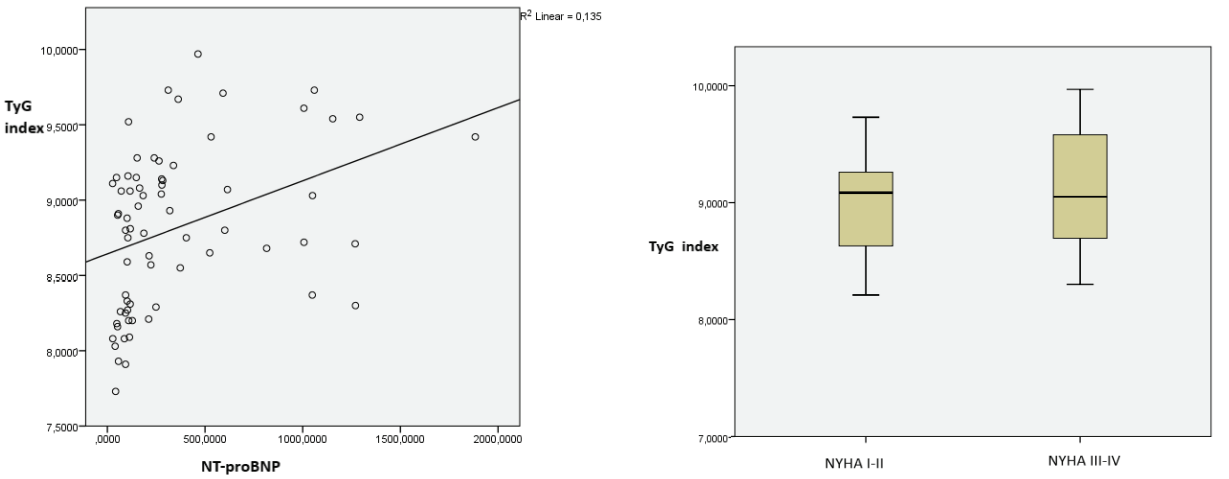

Figure 2: The relationship between TyG index with NT-proBNP and NYHA functional class
TyG index: triglyceride glucose index, NT-proBNP: N- terminal pro hormone brain natriuretic peptide, NYHA: New York Heart Association

ically characterized by high triglycerides, small dense LDL particles and low HDL-C levels. Also, triglycerides and triglyceride-rich lipoproteins play a major role in atherosclerosis, which is the main etiologic factor of HF by reducing of endothelial function, increasing of proinflammatory cytokines expression, inducing of monocyte-platelet activation and raising of fibrinogen levels (11,12). However, there is increasing evidence of the direct effects of IR on heart failure itself (13). The major responsible mechanisms are listed as follows: (i) TNF-α is a pre-inflammatory cytokine associated with HF and it has been reported that TNF-α may affect the glucose metabolism. Indeed, a study showed that patients with IR had higher TNF-α levels compared to insulin-sensitive patients; (ii) In IR, both plasma and cardiac free fatty acids (FFA) and triglycerides concentrations increase and their accumulation in myocardial cells may result in apoptosis and fibrosis due to lipotoxic effects. Moreover, FFA may trigger IR by activation of Toll-like Receptor 4 and the innate immune response; (iii) Activa-

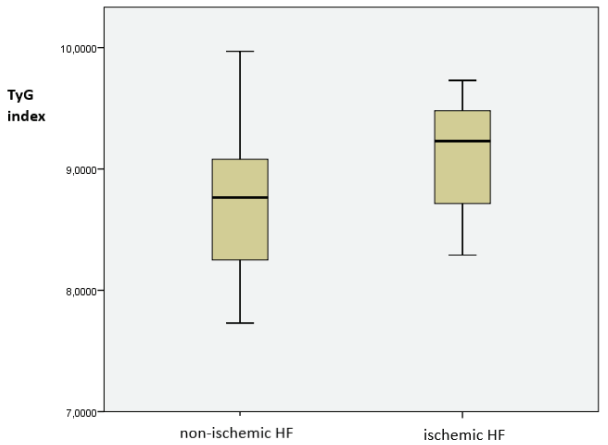

Figure 3: The TyG index levels according to underlying etiology in heart failure
TyG index: triglyceride glucose index, HF: heart failure

Table 3: Correlation between the TyG index and clinical variables

Variables	r	p
Systolic blood pressure	0.364	0.034
FBG	0.553	<0.001
Creatinine	0.420	0.010
T-chol	0.345	0.045
TG	0.567	<0.001

FPG: fasting blood glucose, T-chol: total cholesterol, TG: triglycerides, TyG index: triglyceride glucose index

tion of the renin-angiotensin II-aldosterone (RAAS) and sympathetic nervous system have been associated with impairment of glucose metabolism, and the interaction between IR and RAAS may contribute to HF through abnormal aldosterone release by triggering of TNF-α and IL-6 (iv) IR causes to endothelial dysfunction by reducing NO release in endothelial cells, and this may result in hypoxia and inhibition of angiogenesis, leading to myocardial cell apoptosis (v) The other culprit mechanisms are mitochondrial dysfunction and endoplasmic reticulum stress. Hyperglycemia may trigger inflammatory responses through mitochondrial dysfunction in oxidative stress, resulting in cell apoptosis. In addition, it has been

Table 4: Multiple logistic regression analysis for TyG index

Model	Unstandardized coefficients		Standardized coefficients	t	p	95.0% Confidence interval for B	
	B	Std.Error	ßeta			Lower bound	Upper bound
Constant	5.761	1.148	-	5.018	<0.001	3.366	8.157
LVEF	0.004	0.011	0.128	0.359	0.721	-0.018	0.026
FBG	0.007	0.003	0.401	2.075	0.051	0.000	0.013
T-chol	0.002	0.003	0.194	0.685	0.501	-0.004	0.008
TG	0.002	0.001	0.346	1.952	0.065	0.000	0.004
Systolic blood pressure	0.004	0.008	0.101	0.463	0.648	-0.013	0.020
Diastolic blood pressure	-0.004	0.010	-0.080	-0.353	0.727	-0.025	0.018
HbA1c	0.074	0.099	0.161	0.745	0.465	-0.133	0.280
Creatinine	0.022	0.504	0.078	0.441	0.664	-0.830	1.275
LDL-C	0.001	0.004	0.038	0.158	0.876	-0.007	0.008
HDL-C	0.006	0.013	0.093	0.454	0.655	-0.021	0.033
Hemoglobin	0.044	0.068	0.118	0.647	0.525	-0.098	0.185
NT-proBNP	0.000	0.000	-0.036	-0.131	0.897	-0.001	0.001
Ischemia	-0.095	0.202	-0.100	-0.471	0.643	-0.517	0.327
NYHA III-IV	0.165	0.238	0.172	0.694	0.496	-0.331	0.661

LVEF: left ventricular ejection fraction, FBG: fasting blood glucose, T-chol: total cholesterol, TG: triglycerides, HbA1c: hemoglobin A1c LDL-C: low-density lipoprotein cholesterol, HDL-C: high-density lipoprotein cholesterol, NT-proBNP: N- terminal prohormone brain natriuretic peptide, NYHA: New York Heart Association, TyG index: triglyceride glucose index

reported that miR 19a-3p, 144-5p, miR-34a and miR-21 polymorphisms responsible for glycolipid metabolism disorders are associated with myocardial dysfunction (11,14-16). Considering the effects of glycolipid disorders on HF, the TyG index derived from triglycerides, and glucose is likely to indicate the presence of HF.

In the first studies investigating the relationship between HF and hyperglycemia, IR was measured using the euglycemic-hyperglycemic clamp method, and one study showed impaired insulin-mediated glucose uptake into skeletal muscle and liver muscle tissue in HF patients (15). In later studies, IR was measured by non-invasive methods such as the homeostatic model assessment of insulin resistance (HOMA-IR) score. In a study using HOMA-IR, HF patients had a higher IR than healthy volunteers. Another study conducted with 12,606 subjects, Atherosclerosis Risk in Communities (ARIC) study, showed the relationship between HOMA-IR and increased risk of HF (17,18). Unlike these studies, we used the TyG index for the first time to evaluate IR in HF patients and confirmed the relationship between HF presence and IR with a different method.

Several studies have reported the relationship between HF severity and IR. In a study, HF patients with IR had a worse 6-minute walking test than patients without IR (19). In another study, the relationship between insulin sensitivity and HF severity was evaluated with peak VO_2, which is used to determine functional exercise capacity, and lower peak VO_2 levels were observed in patients with reduced insulin sensitivity (20). However, we could not find any correlation between TyG index and HF severity in our study. In contrast to these studies, we used the NYHA functional classification, which is more subjective and based on patients' symptoms due to retrospective design. Also in these studies, the use of digoxin and diuretics, which improve functional capacity, was higher and the mean age was lower compared to our patients. In addition, the decrease in physiological functional capacity with aging may lead to defining the NYHA as class more exaggerated in our patients. Moreover, IR may reduce the glucose uptake into skeletal muscle, which may increase fatigue by reducing skeletal muscle strength, and this may be more pronounced in older ages. Finally, prolongation of HF exposure time may increase the severity of diastolic dysfunction in our patients, and it may contribute to progression of HF symptoms independently from IR (21).

The other parameter used for evaluation of HF severity was LVEF in this study. In addition, we investigated the importance of etiology in the TyG index, but we failed showing the correlation between the TyG index and these parameters. Indeed, one study did not show any relationship between IR with LVEF and HF etiology (22). In another study, abnormalities in insulin metabolism were found to be similar in patients diagnosed with ischemic or dilated cardiomyopathy, and it has been claimed that IR may develop as a part of a neurohormonal and metabolic response in HF rather than atherosclerotic disease (15). In addition, there was no correlation between the TyG index and variables with confounding effects such as blood pressure, age, and body mass index in multiple logistic regression analysis in our study. The absence of any relationship between these parameters and IR in the study conducted by Suskin et al supports our study results (19). However, many mechanisms may be responsible for the relationship between HF and IR, and it is not clear which mechanism explains this relationship more, and in our study, multiple logistic regression analysis showed the interaction of many factors with each other for high TyG index in HF.

There are also studies investigating the relationship between IR and NT-proBNP levels in hyperglycemic patients. A study found lower BNP levels in HF patients with diabetes than in non-diabetic HF patients, and lower levels of NT-proBNP were associated with less HF symptoms and HF severity. The researchers explained this status as beta-adrenergic receptor antagonism may increase plasma BNP levels and its increased levels may lead to a decrease in IR (19,23). In another study, there was an inverse association between NT-proBNP and HOMA-IR, and the insulin sensitivity index was an independent predictor of plasma NT-proBNP levels in HF patients. This has been associated with the lipolytic effects of BNP, and it has been hypothesized that decreased natriuretic peptide signals may cause IR and MetS by increasing lipid accumulation in adipose tissue and skeletal muscle (24). Unlike these studies, we could not find any association between the TyG index and NT-proBNP. The different result of our study at this point may be due to the heterogeneous distribution of comorbidities closely related to IR and MetS, such as hypertension, diabetes, hyperlipidemia or the differences in visceral fat accumulation or the intensive use of beta blockers.

There were some limitations to be addressed in our study. The study was a relatively small sample, and most patients were under HF treatment, which could affect glucose metabolism. HOMA-IR was not analyzed and compared with the TyG index as insulin levels could not be measured. Due to the lack of data, confounding factors such as exercise and diet habits, participation in a cardiac rehabilitation program, and cardiorespiratory fitness were not included in this study.

In conclusion, TyG index can be used for diagnosis in patients with HF symptoms, but not for HF severity. Howev-

er, larger studies are needed to determine the relationship between TyG index and HF.

Ethics Committee Approval: This study was approved by the Non-Invasive Clinical Research Ethical Committee of the, Pamukkale University (Date: 05.01.2021 No: 01).

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