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Evaluation of the Triglyceride-Glucose Index with Different Generations of Beta-Adrenergic Blockers

Farklı Nesil Beta-Adrenerjik Blokerlerde Trigliserit-Glukoz İndeksinin Değerlendirilmesi

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ABSTRACT

Background: Beta-blockers (β-blockers) work by blocking β-adrenergic receptors and differ in their metabolic effects and side effects. We aimed to compare the metabolic effects of different generations of β-blockers by evaluating the triglyceride-glucose (TyG) index in patients treated with this group of drugs.

Materials and Methods: Subjects using β-blockers were divided into three groups according to first-generation, second-generation, and third-generation β-blockers. The TyG index values of the subjects were calculated.

Results: There were no differences in age, sex, presence of hypertension, coronary artery disease, or use of medications among the three groups. Glucose, triglycerides, hemoglobin A1c and TyG index were significantly different between three groups of patients. A post-hoc analysis revealed group differences between the third-generation, second-generation, and first-generation, β-blockers. Patients taking third-generation β-blockers had the lowest TyG index and the lowest triglyceride and glucose levels. Univariable and multivariable linear regression analyses showed that age and the β-blocker group were independent predictors of TyG index values.

Conclusion: The use of third generation β-blockers was associated with better metabolic profiles.

Keywords: Triglyceride, glucose, β-blocker, metabolic profile

ÖZ

Amaç: Beta-blokerler (β-blokerler) β-adrenerjik reseptörleri bloke ederek çalışır ve kardiyovasküler hastalıklarda en sık kullanılan ilaçlar arasındadır. Metabolik etkileri ve yan etkileri bakımından farklılık gösterirler. Bu çalışmada amacımız β-blokerler ile tedavi edilen hastalarda trigliserid-glukoz indeksini (TyG) değerlendirerek farklı nesil β-blokerlerin metabolik etkilerini karşılaştırmayı amaçladık.

Gereç ve Yöntemler: β-bloker kullanan hastalar birinci, ikinci ve üçüncü nesil β-blokerlere göre üç gruba ayrıldı. Bu hastaların TyG indeks değerleri hesaplanarak karşılaştırıldı.

Bulgular: Üç grup arasında yaş, cinsiyet, hipertansiyon varlığı, koroner arter hastalığı veya ilaç kullanımı açısından fark yoktu. glukoz, trigliserit, hemoglobin A1c ve TyG indeksi üç hasta grubu arasında anlamlı derecede farklıydı. Post-hoc analiz, üçüncü nesil, ikinci nesil ve birinci nesil β-blokerler arasında grup farklılıkları olduğunu ortaya koydu. Üçüncü nesil β-bloker kullanan hastalar en düşük TyG indeksinin yanı sıra en düşük trigliserit ve glukoz seviyelerine sahipti. Tek değişkenli ve çok değişkenli doğrusal regresyon analizleri, yaşın ve β-bloker grubunun TyG indeks değerlerinin bağımsız belirleyicileri olduğunu gösterdi.

Sonuç: Üçüncü nesil β-blokerlerin kullanımı daha iyi metabolik profil ile ilişkilidir.

Anahtar Kelimeler: Trigliserid, glukoz, β-bloker, metabolik profil

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Introduction

Beta-blockers (β-blockers) exert their actions by blocking β-adrenergic receptors (1). However, they differed in terms of metabolic actions and side effects. Traditionally, β-blockers are divided into three groups with respect to their pharmacological features. First generation β-blockers non-selectively act on β-1 and β-2 receptors, whereas second generation β-blockers show greater affinity for β-1 receptors. More recently introduced third generation β-blockers differ by their cardioselective actions and have additional vasodilating properties by blocking alpha (α)-1 and activating β-3-adrenergic receptors (1). Various studies have investigated the metabolic adverse effects of these drugs. Metoprolol, atenolol, and propranolol, considered as conventional β-blockers, have negative effects on insulin sensitivity and glucose metabolism. They are found to be linked to heightened risk of new-onset diabetes mellitus (2). On the contrary, β-blockers with vasodilating actions have more favorable cardiometabolic effects (3,4).

Insulin resistance, reduced response to the circulating insulin, is closely associated with two common conditions, namely, metabolic syndrome and type 2 diabetes mellitus (5). Insulin, by affecting the insulin receptor tyrosine kinase, brings about a series of reactions in different cell types such as glucose uptake in skeletal muscle, inhibition of gluconeogenesis in liver, and suppression of lipolysis in adipocytes (6). Insulin resistance with resultant hypertriglyceridemia, low levels of high-density lipoprotein-cholesterol (HDL-C), high blood pressure level, proinflammatory status, and endothelial dysfunction make a large contribution to cardiovascular disease pathogenesis (7-11). Several methods have been used to diagnose insulin resistance with different sensitivities and complexities (12). The hyperinsulinemic-euglycemic glucose clamp is considered the best method (13) for the identification of insulin resistance, but it is expensive and requires expertise. The triglyceride-glucose (TyG) index is a novel biomarker that has been suggested to predict the insulin resistance status of the body in patients with or without diabetes (14,15). Clinical significance of this index has been shown in several diseases such as acute and chronic coronary syndromes, heart failure, cerebrovascular disease, and populations with high cardiovascular risk (16-20). The present study was aimed at measuring the metabolic effects of different generations of β-blockers by evaluating the TyG index in patients who were under treatment with this group of drugs.

Materials and Methods

We retrospectively screened the hospital files of the patients who applied to our cardiology clinic at a tertiary care hospital. We enrolled consecutive patients who met the inclusion criteria applied in our outpatient clinic from 1 June 2022 to 1 June 2023. Patients diagnosed with acute coronary syndrome, diabetes mellitus, thyroid diseases, hepatic or renal failure, malignancy, or inflammatory diseases were excluded from the study. Additionally, those using triglyceride-lowering drugs were not included. Patients' clinical characteristics, demographic features and biochemical variables were obtained from the hospital records. After the application of exclusion criteria 712 patients were enrolled in the study. Patients were using six different β-blockers, namely metoprolol, atenolol, carvedilol, propranolol, bisoprolol, and nebivolol. We divided the patients into three groups according to first, second, and third generations of β-blockers. These groups consisted of 162, 303 and 242 patients, respectively.

Since our study was retrospective, we used the patients' blood results from the hospital's electronic records. We collected information regarding their glucose, triglyceride, and HgbA1c levels. The multiplication of glucose and triglyceride values was divided by two. The natural logarithmic transformation of the obtained results gave the TyG index values.

No artificial intelligence assistance was used during the preparation of the manuscript. The Demiroğlu Bilim University Clinical Research Ethics Committee approved the study (approval number: 44140529, dated: 31.01.2023) and it was conducted in accordance with the Declaration of Helsinki.

Statistical Analysis

The normality of the data was analyzed using the Kolmogorov-Smirnov test. Data showing normal distribution are expressed as the mean and standard deviation; otherwise, they are expressed as the median and interquartile range. A one-way analysis of variance or a Kruskal-Wallis test was used to compare the three groups, depending on the distribution of the data. Post-hoc analysis between groups was performed using Bonferroni correction. Categorical variables were compared by using a chi-square test. To identify predictors of the TyG index, a univariate linear regression analysis was performed. Because the TyG index was multicollinear with triglyceride and glucose levels in the presence of diabetes mellitus, we did not use these variables in the linear regression analysis. Variables

with statistically significant results were then entered into a multivariable linear regression analysis. A p-value less than 0.05 was considered significant.

Results

Median age of the study population was 59.00 (55.00-62.00) years, 366 51.4% of them were male, 367 51.5% of them were hypertensive, 365 51.3% patients had coronary artery disease, 252 35.4% of them were taking angiotensin converting enzyme inhibitors (ACE-I), 111 15.6% of them were taking angiotensin receptor blockers (ARB), 339 47.6% of them were using calcium channel blockers (CCB), 94 13.2% of them were using thiazide type diuretics and 365 51.3% of them were using statins. Median fasting glucose and triglyceride levels of the study group were 97.00 (94.00-100.00) mg/dL and 131.00 (120.00-147.00) mg/dL, respectively. Median hemoglobin A1c (HbA1c) and TyG index values were 5.70 (5.60-5.90) and 8.73 (8.64-8.90), respectively. Average duration of β-blockers use was found to be 42.00 (24.00-53.00) months.

When comparing first, second, and third generation β-blockers, there were no differences in age, sex, presence of hypertension, coronary artery disease, or use of medications including ACE-I, ARB, CCB, thiazide-type diuretics, and statins. Glucose, triglyceride, HbA1c, and TyG index were significantly different between the three groups of patients. A post-hoc analysis revealed group differences between the third-generation, second-generation, and first-generation β-blockers. Patients taking third-generation β-blockers had the lowest TyG index, as well as the lowest triglyceride and glucose levels. Table 1 shows a comparison of the three groups' clinical and biochemical variables.

Univariable and multivariable linear regression analyses showed that age and the β-blocker group were independent predictors of TyG index values (Tables 2 and 3).

Table 1. Comparaison of three groups

	First generation group (n=162)	Second generation group (n=303)	Third generation group (n=242)	p-value	
Age (years)	59.00 (55.00-62.00)	59.00 (56.00-63.00)	58.00 (54.00-62.00)	0.083	
Gender (n,%)				0.162	
Female	84 (51.9)	154 (50ç8)	108 (43.7)		(Group 3-2) p=0.097
Male	78 (48.1)	149 (49.2)	139 (56.3)		(Group 3-1) p=0.107
					(Group 2-1) p=0.833
Hypertension (n,%)	86 (53.1)	164 (54.1)	117 (47.4)	0.261	
					(Group 3-2) p=0.117
					(Group 3-1) p=0.258
					(Group 2-1) p=0.830
CAD (n,%)	79 (48.8)	150 (49.5)	136 (55.1)	0.332	
					(Group 3-2) p=0.195
					(Group 3-1) p=0.212
					(Group 2-1) p=0.879
ACE-I (n,%)	66(40.7)	102 (33.7)	84 (34)	0.269	
					(Group 3-2) p=0.932
					(Group 3-1) p=0.167
					(Group 2-1) p=0.130
ARB (n,%)	23 (14.2)	44 (14.5)	44 (17.8)	0.489	
					(Group 3-2) p=0.295
					(Group 3-1) p=0.334
					(Group 2-1) p=0.924
Ca-channel blockers (n,%)	68 (42)	149 (49.2)	122 (49.4)	0.263	
					(Group 3-2) p=0.959
					(Group 3-1) p=0.141

Table 1. Continued

	First generation group (n=162)	Second generation group (n=303)	Third generation group (n=242)	p-value	
					(Group 2-1) p=0.138
Thiazide diuretics (n,%)	18 (11.1)	39 (12.9)	37 (15)	0.515	
					(Group 3-2) p=0.476
					(Group 3-1) p=0.262
					(Group 2-1) p=0.581
Statin (n,%)	79 (48.8)	150 (49.5)	136 (55.1)	0.332	
					(Group 3-2) p=0.195
					(Group 3-1) p=0.212
					(Group 2-1) p=0.879
Glucose (mg/dL)	104.00 (95.00-109.00)	97.00 (93.00-99.75)	96.00 (93.00-98.00)	<0.001	
					(Group 3-2) p=0.002
					(Group 3-1) p<0.001
					(Group 2-1) p<0.001
Triglyceride (mg/dL)	136.12±17.19	133.94±17.00	127.81±11.43	<0.001	
					(Group 3-2) p<0.001
					(Group 3-1) p<0.001
					(Group 2-1) p<0.001
HbA1c	5.74±0.15	5.71±0.35	5.66±0.15	<0.001	
					(Group 3-2) p<0.001
					(Group 3-1) p<0.001
					Group 2-1) p=0.001
TyG index	8.81±0.17	8.77±0.15	8.71±0.11	<0.001	
					(Group 3-2) p<0.001
					(Group 3-1) p<0.001
					(Group 2-1) p<0.001

ACE-I: Angiotensin converting enzyme inhibitor, ARB: Angiotensin receptor blocker, CAD: Coronary artery disease, HbA1c: Hemoglobin A1c, TyG index: Triglyceride-glucose index

Table 2. Univariable linear regression analysis for TyG index

	β	p-value	95% CI
Age	0.190	<0.001	0.004-0.009
Beta-blocker group	-0.481	<0.001	-0.122--0.093
Gender	-0.042	0.269	-0.040-0.011
Hypertension	-0.030	0.427	-0.036-0.015

CI: Confidence interval, TyG index: Triglyceride-glucose index

Table 3. Multivariable linear regression analysis for TyG index

	β	p-value	95% CI
Age	0.146	<0.001	0.003-0.007
Beta-blocker group	-0.467	<0.001	-0.119--0.090

CI: Confidence interval, TyG index: Triglyceride-glucose index

Discussion

Our study showed that patients who were treated with the third generation of β-blockers had better metabolic profiles and lower values of the TyG index compared to patients who were treated with other types of β -blockers. Additionally, the use of third-generation β-blockers was an independent predictor of lower TyG values.

Both selective and non-selective β-blockers have been linked to the occurrence of insulin resistance and new-onset diabetes mellitus (21). Since this group of drugs is usually used in patients with high cardiovascular risk, their adverse effects have become important for clinicians. Over time, β-blockers with additional vasodilating and distinct metabolic activities have been developed, making them desirable in clinical practice.

Non-vasodilating β-blockers comprise first and second-generation β-blockers and their effects are mainly mediated through a decrease in cardiac output (22). They do not affect peripheral resistance, and administration of them is associated with unfavorable side effects. Several studies have been conducted in order to compare the metabolic side effects of different β-blockers. A post-hoc analysis of the Atherosclerosis Risk in Communities study has shown that patients who are treated with non-vasodilating β-blockers are at 28% higher risk of getting diabetes mellitus compared to patients who do not use them (21). Likewise, in the Losartan Intervention for Endpoint reduction study, the risk of diabetes mellitus development was 25% lower in patients who were treated with losartan in comparison to patients who were treated with atenolol (23). Carvedilol, a third generation β-blocker with non-selective β-adrenoceptor and α blocker activity, has been shown to improve insulin sensitivity and increase HDL-C levels (24). In a study in which carvedilol was compared with metoprolol, carvedilol has been associated with an increment of 8.5% in insulin sensitivity, where metoprolol decreased insulin sensitivity by up to 14% (24) In the GEMINI trial, carvedilol showed a more favorable metabolic effect in comparison to metoprolol. In that study, carvedilol decreased insulin resistance by 9.1%, whereas insulin resistance did not show any difference in patients treated with metoprolol (25). Nebivolol exerts its effects by blocking β-1 adrenergic receptors and increasing NO production, which might be the cause of more favorable metabolic effects of the drug (26). In comparison to nebivolol, metoprolol significantly reduced the insulin sensitivity index in patients with metabolic syndrome (27). In a study conducted by Poirier et al. (28), atenolol reduced insulin sensitivity by 20%, and insulin sensitivity was not preserved with atenolol.

The TyG index has been validated in numerous studies as a superior tool for the prediction and identification of insulin resistance compared to the homeostasis model assessment of insulin resistance model (29). Its utility for both prognosis and diagnosis has been demonstrated across multiple studies. Higher TyG index levels were associated with an increased risk of chronic kidney disease, type 2 diabetes mellitus, diabetic retinopathy, non-alcoholic fatty liver disease, dementia, and ischemic stroke (30). Zhang and Hou (31) examined NHANES data to investigate the relationship between the TyG index and heart failure. They discovered a significant J-shaped dose-response relationship between the TyG index and heart failure risk. In a study of the general population, Liu et al. (32) analyzed the dose-response relationship between the TyG index and cardiovascular disease and mortality, reporting that elevated TyG index levels were linked to a higher incidence of coronary artery disease and myocardial infarction. In the present study, we investigated the TyG index in patients who applied to our cardiology outpatient clinic. Our results showed that patients who were treated with the third generation of β-blockers had significantly lower levels of TyG index in comparison to patients who were treated with other types of β-blockers. In our study, third-generation β-blockers consisted of nebivolol and carvedilol. Comparison of these drugs showed that the TyG index was not different (p=0.352). Second-generation β-blockers consisted of atenolol, metoprolol, and bisoprolol. When these drugs were compared in a separate analysis, the analysis showed that there was a a difference between bisoprolol and atenolol groups. Patients using bisoprolol exhibit lowered TyG index values compared to patients who were using atenolol (8.81±0.18 vs. 8.72±0.12, demonstrating a statistically significant difference, p=0.004).

Study Limitations

Our sample size was small, and the study was conducted on a single-center population. We did not conduct long-term follow-ups of the patients, so we could not assess the prognostic value of the TyG index or whether its prognostic utility was superior to that of glucose and triglyceride values.

Conclusion

Use of third generation β-blockers was associated with better metabolic profile.

Ethics

Ethics Committee Approval: The Demiroğlu Bilim University Clinical Research Ethics Committee approved the study (approval number: 44140529, dated: 31.01.2023) and it was conducted in accordance with the Declaration of Helsinki.

Informed Consent: All patients gave informed consent before study participation.

Footnotes

Authorship Contributions

Concept: D.E., A.A., Design: D.E., F.N.T.Ç., Data Collection or Processing: D.E., C.Y., A.A., F.N.T.Ç., Analysis or Interpretation: D.E., C.Y., A.A., F.N.T.Ç., Literature Search: C.Y., Writing: D.E., C.Y.

Conflict of Interest: No conflict of interest was declared by the authors.

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