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Triglyceride glucose index is related with cardiac autonomic dysfunction in patients with metabolic syndrome

Aim	Cardiac autonomic dysfunction is encountered in approximately 25% of patients with metabolic syndrome (MetS). 24 hr Holter-ECG based heart rate variability (HRV) and heart rate turbulence (HRT) parameters are used to evaluate cardiac autonomic function. We aimed to investigate the relationship between a novel insulin resistance marker, triglyceride glucose (TyG) index and cardiac autonomic dysfunction in patients with MetS.
Material and methods	We examined a total of 400 non-diabetic subjects, 136 with MetS and 264 without MetS. All underwent TyG index calculations, and 24 hr Holter-ECG recordings for the measurement of HRV and HRT parameters.
Results	HRV and HRT parameters were lower or higher in patients with MetS than in subjects without MetS, indicating cardiac autonomic dysfunction. We observed significant correlations between TyG index and measures of cardiac autonomic function. Multiple linear regression analysis showed that the TyG index was an independent predictor of almost all HRV and HRT parameters.
Conclusion	This study demonstrates the independent relationship between cardiac autonomic dysfunction and the TyG index, a novel marker of insulin resistance in non-diabetic patients with MetS.

Keywords	Autonomic dysfunction; insulin resistance; triglyceride glucose index
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Introduction

Cardiac autonomic dysfunction is a major chronic complication of diabetes mellitus [1]. However, it has been reported to be significantly present in patients with prediabetes and metabolic syndrome (MetS), with a prevalence of 11% and 24%, respectively [2]. Cardiac autonomic dysfunction is caused by impairment of the autonomic nerve fibers regulating heart rate (HR), myocardial contractility, cardiac electrophysiological function, and vasoconstriction and vasodilatation [3]. Impaired cardiac autonomic function increases morbidity and cardiovascular mortality by leading to potentially life-threatening conditions, such as silent myocardial ischemia and infarction, arrhythmias, orthostatic hypotension, cardiomyopathy, and perioperative cardiovascular instability [3, 4].

MetS, also known as insulin resistance syndrome, is a combination of disorders, including central obesity, impaired fasting plasma glucose (FPG), atherogenic dyslipidemia, and high blood pressure (BP) [5]. The triglyceride glucose (TyG) index is a new marker that has been shown to have a high sensitivity and specificity in identifying insulin resistance [6]. TyG has been described as a biochemical surrogate of insulin resistance, and it has been found to be superior to "homeostatic model assessment for insulin resistance" (HOMA-IR) for predicting MetS [7].

The 24 hr Holter-ECG parameters of HR variability (HRV) and HR turbulence (HRT) are useful for assessing cardiac autonomic function [8, 9]. The most used methods for the diagnosis of cardiac autonomic dysfunction are based on examination of HRV, which is the physiological variation in the time interval between heartbeats [8]. HRT is a reliable indicator of baroreceptor sensitivity following an episode of isolated premature ventricular beats (PVBs) [9]. A decrease in HRV is known to be the first finding of reduced cardiac autonomic function [10]. Similarly, HRT analysis has been found to be useful for early diagnosis of cardiac autonomic neuropathy [11].

In this study we investigated the relationship between the TyG index and cardiac autonomic dysfunction using both HRV and HRT parameters in patients with and without MetS.

Material and Methods

This study was conducted between August, 2021 and January, 2022 and examined about 800 subjects. The study was designed and performed in accordance with the principles of the Helsinki Declaration and was approved by the local clinical research ethics committee (2021/26; Decision no: 06). All subjects gave informed consent prior to enrollment.

Exclusion criteria were: diabetes, obstructive coronary artery disease, heart failure or having signs and symptoms of heart failure, cardiomyopathies, moderate or severe valvular heart disease, hyper/hypothyroidism, use of any anti-arrhythmic drugs that may affect HRV and HRT indices (including beta blockers, verapamil and diltiazem), absence of sinus rhythm, or any PVBs on 24 hr Holter-ECG recordings. Considering these exclusion criteria, the remaining 400 patients were divided into two groups based on the presence of MetS as defined in the revised Adult Treatment Panel III of National Cholesterol Education Program [5]. Accordingly, 164 patients who met the MetS criteria formed the MetS group, and 236 subjects who did not formed the control group.

TyG index

FPG and lipid profile were determined from venous blood samples taken after at least 8 hrs of night-time fasting. The TyG index was calculated according to the formula:

$$\text{TyG index} = \ln[\text{fasting triglycerides (mg/dl)} \times \text{FPG (mg/dl)}/2]$$ [6].

Holter-ECG measurements

For 24 hr Holter-ECG recordings, 3-channel digital recorders were used (CardioDay 2.5 Holter-ECG, GE Healthcare, USA). In addition to the drugs specified in the exclusion criteria, it was ensured that drugs such as anesthetics, sedatives, and analgesics that could affect HRV and HRT parameters were not used for 1 wk before Holter-ECG recording. The recordings were required to be at least 22 hrs in duration and to be of sufficient quality to permit evaluations to be made appropriately. These recordings were evaluated by a reviewer who had no knowledge of the subjects' data. Before the HRV and HRT analyses, the entire recording was checked for PVBs.

HRV, defined as physiological cyclic fluctuations in the time interval between consecutive heartbeats, includes the following parameters: the standard deviation (SD) of the normal-to-normal (NN) interval (SDNN), the SD of the average NN interval (SDANN) calculated over 5-min periods, the mean of the 5-min SD of the NN interval (SDNN index) calculated over 24 hrs, the square root of the mean squared differences of successive NN intervals (RMSSD), and the division of the number of interval differences of successive NN intervals of more than 50 ms by the total number of NN intervals (pNN50) [8]. The mean RR interval was also calculated.

HRT is a baroreflex-mediated biphasic reaction of HR in response to PVBs. Turbulence onset (TO), which is a measure of the expected normal early sinus acceleration after a PVB, and the turbulence slope (TS), which is a measure of late sinus deceleration after a PVB, constitute the two components of HRT. TO values less than 0% and TS values greater than 2.5 ms/RR are considered normal. Another HRT parameter, HRT category (HRTc), was calculated to determine if the TO and TS values were normal. If both TO and TS values are normal, it means that HRTc is 0. If both TO and TS are abnormal, it means that HRTc is 2. If HRTc is 1, this means either TO or TS is abnormal [9]. All evaluations and measurements were made in accordance with the standards set by the Task Force of the European Society of Cardiology and by the North American Society of Pacing and Electrophysiology [8, 9].

Statistical analysis

Statistical calculations were performed with SPSS for Windows, version 11.5 (SPSS Inc., Chicago, IL, USA). The Kolmogorov Smirnov test was used to determine if continuous variables were normally distributed. Categorical variables are presented as the number of cases with percentages, and continuous variables are presented as mean±SD, if normally distributed, or as median (25/75% interquartile ranges), if not normally distributed. The chi-square test was used for inter-group comparisons. Comparison of continuous variables was made with either the student's t test or the Mann–Whitney U test according to their distribution characteristics. Likewise, correlation analysis between Holter-ECG parameters and the TyG index was performed with the Pearson or Spearman's tests. The best predictor (s) affecting HRV and HRT parameters were evaluated using multiple linear regression analysis after adjusting for all possible confounding factors. Standardized coefficient of regression and levels of significance for each independent variable were calculated. All tests of significance were two-tailed. Statistical significance was defined as $p<0.05$.

Results

Study population

The clinical, laboratory, and echocardiographic findings are shown in Table 1. Body mass index, waist circumference, number of patients with hypertension, systolic BP, diastolic BP, and left ventricular wall thickness were significantly higher in patients with MetS. As expected, FPG, HbA1c, total cholesterol and triglyceride values were higher in the MetS group, while HDL cholesterol was lower.

24 hr Holter-ECG findings

Data obtained from the Holter-ECG recordings are presented in Table 2. There were no differences between recording times, mean RR intervals and mean HRs in both groups. SDNN, SDNN index, SDANN, RMSSD, pNN50 and TS values were lower in the MetS group. Lower values of these parameters indicate a higher possibility of cardiac

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Table 1. Baseline characteristics, echocardiographic and laboratory findings

Variable	MetS group (n=164)	Control group (n=236)	p-value
Age, yrs	58 (48/69)	55 (44/68)	0.123
Gender, male/female	70/94 (42.7/57.3)	116/120 (49.2/50.8)	0.202
Currently smoking	44 (26.8)	55 (23.3)	0.422
Hypertension	65 (39.6)	68 (28.8)	0.024
Body mass index, kg/m^2	30.9 (27.2/33.4)	27.7 (25.3/30.3)	<0.001
Waist circumference, cm	96 (89/103.8)	91 (83/98)	<0.001
Fasting plasma glucose, mg/dl	109 (100/143.2)	94 (86.2/108)	<0.001
Total cholesterol, mg/dl	201 (171/229)	188 (156/221)	0.043
HDL cholesterol, mg/dl	42 (37/46.7)	48 (42/55)	<0.001
LDL cholesterol, mg/dl	122 (97/147)	115 (94/146)	0.320
Triglycerides, mg/dl	166 (118/208)	104 (79/134)	<0.001
HbA1c, %	5.9 (5.7/6.2)	5.4 (5/5.9)	<0.001
Triglyceride glucose index	9.138±0.543	8.561±0.474	<0.001
Systolic blood pressure, mmHg	130 (120/140)	120 (110/130)	<0.001
Diastolic blood pressure, mmHg	80 (70/85)	75 (70/80)	<0.001
LV ejection fraction, %	65 (60.2/67)	65 (60/67)	0.195
Interventricular septum thickness, mm	11.3±1.74	10.9±1.83	0.024
LV posterior wall thickness, mm	10.6±1.55	10.1±1.70	0.009
Left atrial diameter, mm	35 (32/38)	34.5 (31/38)	0.087

Data are number (%), mean±SD, or as median (25/75% interquartile range). HDL, high-density lipoprotein; LDL, low-density lipoprotein; LV, left ventricular; MetS, metabolic syndrome.

autonomic dysfunction. TO was higher in patients with MetS. This is associated with a higher probability of cardiac autonomic impairment. While HRTc 0 subjects were mostly in the control group, the frequency of HRTc 2 was about 5 times higher in the MetS group (Table 2).

Correlation analysis

Correlations between the TyG index and HRV/HRT parameters are presented in Table 3. There were significant correlations only in the MetS group.

Multiple linear regression analysis

Table 4 presents independent variables of parameters indicating HRV and HRT. After multiple linear regression analysis, age, FPG and TyG index were found to be independent predictors of almost all HRV and HRT parameters. Age was an independent predictor of SDNN, SDNN index, SDANN, TO and TS. TyG index had also independent associations for the same parameters except for

Table 2. Comparisons of 24 hr Holter-ECG findings, HR variability, and HR turbulence

Variables	MetS group (n=164)	Control group (n=236)	p-value
Recording duration, hrs	23.19 (22.58/23.57)	23.16 (22.50/23.56)	0.465
Mean RR interval, ms	773 (724/881.6)	797.1 (729/893.3)	0.389
Mean HR, bpm	75.4±10.8	74.7±10.7	0.490
HR variability parameters			
SDNN, ms	105 (80.25/131.75)	119.5 (98/150.75)	<0.001
SDNN index, ms	42 (32/53)	49 (40/60.75)	<0.001
SDANN, ms	96 (71.5/117.75)	107 (87.25/136)	<0.001
RMSSD, ms	21.5 (15.25/30)	27 (20/36.75)	<0.001
pNN50, %	3.01 (1/9)	5.7 (2/11)	0.002
HR turbulence parameters			
Turbulence onset, %	–0.002 (–1.550/0.993)	–1.212 (–3.312/–0.004)	<0.001
Turbulence slope, ms/RR	3.24 (1.76/6.20)	6.57 (3.52/13)	<0.001
HR turbulence category			
0	67 (40.9)	168 (71.2)	<0.001
1	51 (31.1)	55 (23.3)	0.082
2	46 (28)	13 (5.5)	<0.001

Data are number (%), mean±SD, or as median (25/75% interquartile range). MetS, metabolic syndrome; pNN50, the proportion of adjacent RR intervals differing by >50 ms in the 24 hr recording; RMSSD, the square root of the mean squared differences of successive NN intervals; SDANN, the SD of the average NN intervals calculated over a 5-min period for the entire recording; SDNN, the SD of all NN intervals; SDNN index, the mean of the deviation of the 5-min NN intervals for the entire recording.

Table 3. Correlation coefficients between triglyceride glucose index and parameters of HR variability and HR turbulence

HR variability parameters	MetS group (n=164)		Control group (n=236)	
	r	p-value	r	p-value
SDNN, ms	-0.315	<0.001	-0.081	0.213
SDNN index, ms	-0.298	<0.001	-0.062	0.345
SDANN, ms	-0.285	<0.001	-0.101	0.122
RMSSD, ms	-0.263	<0.001	-0.085	0.191
pNN50, %	-0.160	0.040	-0.099	0.128
HR turbulence parameters				
Turbulence onset, %	0.204	0.009	0.015	0.817
Turbulence slope, ms/RR	-0.252	0.001	-0.120	0.066
HR turbulence category	0.365	<0.001	0.006	0.922

MetS, metabolic syndrome; pNN50, the proportion of adjacent RR intervals differing by >50 ms in the 24 hr recording; RMSSD, the square root of the mean squared differences of successive NN intervals; SDANN, the standard deviation of the average NN intervals calculated over 5-min period of the entire recording; SDNN, the standard deviation of all NN intervals; SDNN index, the mean of the deviation of the 5-min NN intervals over the entire recording.

Table 4. Results of multiple linear regression analysis for determining the best predictors affecting parameters of HR variability and HR turbulence in patients with metabolic syndrome

Variables	SDNN	SDNN index	SDANN	RMSDD	pNN50	TO	TS
Age Beta (standardized) p-value	 -0.266 <0.001	 -0.242 <0.001	 -0.271 <0.001	 –	 –	 0.228 <0.001	 -0.335 <0.001
Triglycerid glucose index Beta (standardized) p-value	 -0.188 <0.001	 -0.175 0.002	 -0.163 0.003	 –	 –	 –	 -0.153 0.004
Fasting plasma glucose Beta (standardized) p-value	 -0.125 0.023	 -0.119 0.035	 -0.135 0.014	 -0.221 <0.001	 -0.214 <0.001	 0.257 <0.001	 -0.187 <0.001
Constant Unstandardized B p-value	 275.152 <0.001	 111.700 <0.001	 252.220 <0.001	 38.026 <0.001	 12.663 <0.001	 -5.568 <0.001	 38.753 <0.001
Adjusted R^2	0.150	0.125	0.144	0.046	0.043	0.120	0.208

pNN50, the proportion of adjacent RR intervals differing by >50 ms in the 24 hr recording;
RMSSD, the square root of the mean squared differences of successive NN intervals; SDANN, the SD of the average NN intervals calculated over 5-min period of the entire recording, SDNN, the SD of all NN intervals, SDNN index, the mean of the deviation of the 5-min NN intervals over the entire recording; TO, turbulence onset; TS, turbulence slope.

TO. FPG was an independent determinant of all examined HRV and HRT parameters (Table 4).

Discussion

We examined whether TyG index is associated with cardiac autonomic dysfunction, using HRV and HRT parameters obtained from 24 hr Holter-ECG recordings, in patients with versus without MetS. Our main findings are as follows:

1) While the time-domain HRV parameters and the TS component of HRT were lower in patients with MetS, the TO component of HRT and HRTc were higher, indicating an association between cardiac autonomic dysfunction and MetS;
2) Patients with MetS had higher TyG index values than those without MetS;
3) TyG index values were negatively correlated with SDNN, SDNN index, SDANN, RMMSD, pNN50 and TS, and positively correlated with TO and HRTc. These correlations were present only in the MetS group;
4) Age, TyG index and FPG were significant independent predictors of the impairment on almost all impaired HRV and HRT parameters.

The new insight gained in this study is that higher TyG index values may be a potential predictor of cardiac autonomic dysfunction in patients with MetS.

MetS, with insulin resistance at the center of its pathophysiology, consists of a complex set of risk factors, such as impaired FPG and atherogenic dyslipidemia including increased triglycerides [5]. It has been shown that the TyG index, which is a product of plasma triglyceride and FPG levels, is a useful biomarker for determining insulin resistance [6]. To date, HOMA-IR is the most widely used index of insulin resistance, but the TyG index has been proposed as a reliable alternative marker. Recently, Son et al. showed that the TyG index was superior to HOMA-IR in predicting MetS, and they found 8.718 to be a cut-off point for predicting the prevalence of MetS [7]. In the current study, the mean/median values of the TyG index were 9.138/9.158 for the MetS group and 8.561/8.513 for the control group. The values were higher and lower, respectively, than the cutoff value of above mentioned study.

Previous studies have shown a relationship between insulin resistance and altered cardiac autonomic function in patients with MetS [12, 13]. Although the link between insulin resistance and the mechanisms causing cardiac autonomic impairment is complex, mitochondrial dysfunction has been stated as the leading factor [3]. Increased mitochondrial production of free radicals due to hyperglycemia-induced oxidative stress and to many other factors damages the autonomic nerve fibers innerving the heart and blood vessels [3]. The first sign of impaired cardiac autonomic function is a decrease in HRV, which is apparent at the subclinical stage [10]. Reduced HRV can be evaluated with a series of simple clinical tests called cardiovascular autonomic reflex tests (CARTs) or more easily with digital 24 hr Holter-ECG [3]. Studies comparing Holter-based analysis and CARTs have found a high correlation between both techniques [14]. In our study, Holter-based HRV and HRT parameters were found significantly lower or higher, respectively, in the MetS group than in the control group, indicating cardiac autonomic dysfunction. We observed that the values of RMSSD and pNN50, which mainly assess parasympathetic function, and SDNN and its derivatives, which reflect both parasympathetic and sympathetic function [3], decreased in patients with MetS. More exciting, however, is that our study

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revealed the association of these Holter-based parameters with the TyG index in patients with MetS. Previously, the relationship between TyG index and cardiac autonomic neuropathy had been demonstrated in type 2 diabetic patients [15]. In contrast, we showed that the TyG index is an independent risk factor for cardiac autonomic dysfunction in non-diabetic patients with MetS. Similarly, in an ancillary study of the Atherosclerosis Risk in Communities Study, Poon et al. showed an inverse relationship between insulin resistance and cardiac autonomic function in older subjects (average age 78 yrs) without diabetes by using 48-hr ambulatory ECG [16]. In that study, the TyG index quartiles from first to fourth were equal to (7.25, 8.24), (8.25, 8.54), (8.55, 8.81) and (8.82, 9.93), respectively. Although subjects were not grouped according to the presence of MetS, they found that higher TyG index values (i.e., quartile 4 vs quartile 1) were associated with lower HRV values [16]. This is consistent with our findings. Since it was already known that aging itself impairs cardiac autonomic functions [17] it was valuable to demonstrate the relationship between TyG index and cardiac autonomic dysfunction in the younger population included in our study.

HRT parameters, TO and TS, have been previously shown to be adversely affected in non-diabetic patients with MetS [18]. Our findings are consistent with the results of previous studies, and they show the relationship between HRT parameters and insulin resistance. Since neuropathy affects the longest nerve fibers first, the first manifestations of cardiac autonomic dysfunction are those associated with vagus nerve damage [3]. Because TO and TS are significantly vagal dependent, they may become abnormal from early phases of the autonomic impairment [19]. We found higher TO and HRTc values and lower TS values in patients with MetS, and these values were independently correlated with the TyG index in which higher values may indicate cardiac autonomic dysfunction from the early stages of the disorder.

Cardiac autonomic dysfunction is an important public health problem, as it causes silent myocardial ischemia and infarction, arrhythmias, orthostatic hypotension, cardiomyopathy, and perioperative cardiovascular instability, resulting in increased morbidity and mortality [3, 4]. Considering that the MetS is often a prediabetic state, this and similar previous studies have shown that cardiac autonomic dysfunction is a condition directly related to insulin resistance and is present even before the onset of overt diabetes [16]. Since insulin resistance is a modifiable risk factor and can be improved with lifestyle-based and medical interventions [20, 21], it could be an important target for primary prevention of cardiac autonomic neuropathies. Accordingly, TyG index, a novel marker of insulin resistance, may be used both for screening and for early diagnosis of cardiac autonomic dysfunction.

Study limitations

The fact that CARTs were not performed to diagnose cardiac autonomic neuropathy can be considered a major limitation of this study. However, the correlation between CARTs and Holter-based tests is quite strong [14]. Another limitation was the use of only time-domain analyzes of the Holter-based HRV tests, but many time and frequency domain variables obtained during the 24 hr period were found to be highly correlated with each other [8]. In addition, we could not provide a cutoff TyG index value to predict the presence of this disorder in patients with MetS. The reason for this is that cardiac autonomic dysfunction could not be determined as a categorical value, that is, either present or absent, as we did not use CARTs. Future studies that overcome these limitations will increase the power of the TyG index in recognizing cardiac autonomic dysfunction in patients with MetS.

Conclusion

This study demonstrated an independent relationship between impaired cardiac autonomic function and the TyG index, an easily accessible, inexpensive, and sensitive marker of insulin resistance. Accordingly, higher TyG index values may be a potential predictor of cardiac autonomic dysfunction in non-diabetic patients with MetS.

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