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Relation of homeostasis model of insulin resistance and body mass index with cardiac repolarization inhomogeneity in overweight and obese patients

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Abstract

In obese individuals, asymptomatic minimal myocardial dysfunction can be encountered even in the absence of structural of functional cardiac alterations. Novel electrocardiographic (ECG) parameters are used to predict arrhythmias related to this situation. We aimed to evaluate body mass index (BMI) and homeostasis model of insulin resistance (HOMA-IR) levels and investigate their relationship with the novel ECG parameters. The study was conducted with 250 individuals in five groups (normoweight, overweight, class I obese, class II obese, and class III obese) each including 50 subjects. The ECGs of the individuals were retrospectively reviewed. Corrected QT (QTc), QTc dispersion (QTcd), Tpeak-Tend (Tp-e) interval, Tp-e dispersion (Tp-ed), and Tp-e/QT and Tp-e/QTc ratios were calculated and their relationship with BMI and HOMA-IR was investigated. ECG parameters indicating ventricular repolarization inhomogeneity were significantly different in overweight individuals compared with the normoweight individuals. Comparing overweight and obese subjects, it was determined that QTc, QTcd and Tp-ed parameters were significantly associated with obesity and showed positive correlations with BMI and HOMA-IR. There was a positive relationship of BMI and HOMA-IR with the novel parameters indicating ventricular repolarization abnormality. Novel and simple ECG parameters including QTc, QTcd, and Tp-ed might be beneficial in monitoring of such patients for critical cardiac events, such as ventricular tachycardia or sudden cardiac death.

Keywords: Obesity, electrocardiography, QTc dispersion, Tp-e dispersion

Introduction

Obesity can enhance the risk of coronary atherosclerosis by well-defined and generally accepted mechanisms such as dyslipidemia, hypertension and type-2 diabetes mellitus and may also lead to arrhythmias [1-3]. Sudden death has been reported more commonly in obese individuals than in non-obese individuals [4,5]. Electro physiological studies have demonstrated that obese individuals have increased electrical activity, which triggers ventricular arrhythmias in the absence of ventricular dysfunction or clinical heart failure [6,7]. The association of prolonged corrected QT (QTc) interval, QT dispersion (QTd), and QTc dispersion (QTcd) with sudden cardiac death and all-cause mortality has been demonstrated by epidemiological studies [8,9]. Prolonged QTc interval may be helpful in predicting cardiovascular events and risk of mortality. Body mass index (BMI) is the method used most frequently in clinical measurement of obesity and has been found to be directly associated with QTc [9].

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Tpeak-Tend (Tp-e) interval, Tp-e dispersion (Tp-ed), and Tp-e/QT and Tp-e/QTc ratios measured on electrocardiography (ECG) are the novel parameters that have been reported in the literature and recently used to evaluate ventricular arrhythmogenicity in several diseases. Tp-e/QT and Tp-e/QTc ratios in particular are considered more reliable in assessing ventricular repolarization as they are not affected by changes in heart rate [10,11].

To the best of our knowledge, there has been yet no study in the literature demonstrating the relationship between homeostasis model of insulin resistance (HOMA-IR) value, which is a reliable test in assessing insulin resistance, and these novel parameters. The present study aimed to evaluate BMI and HOMA-IR levels and investigate their relationship with the novel ECG parameters.

Material and Methods

Study population

Medical records of the patients followed-up in our endocrinology and metabolism disorders clinic between December 2015 and December 2017 were retrospectively reviewed. Two hundred and

fifty subjects were included in the study. The individuals were classified according to their BMI values as class III obesity (BMI > 40 kg/m2), class II obesity (BMI = 35-39.9 kg/m2), class I obesity (BMI = 30-34.9 kg/m2), overweight (BMI = 25-29.9 kg/m2), and normoweight (BMI = 18.5-24.9 kg/m2) in line with the recommendations of the World Health Organization. HOMA-IR was used to identify the presence of insulin resistance. HOMA-IR was calculated using the following formula: Fasting blood glucose (mg/dL) x insulin (μIU/mL)/405. HOMA-IR value ≥ 2.7 was considered significant for insulin resistance.

Individuals who had no structural abnormality and had normal ejection fraction on the echocardiography were included in the study. On the other hand, patients with coronary artery disease, cerebrovascular event, peripheral vascular disease, valvular heart problems, cardiomyopathy, history of atrial and ventricular arrhythmia, hypertension, thyroid dysfunction, diabetes mellitus, electrolyte disorder, history of chronic diseases, and anemia were excluded from the study. The study protocol was approved by the Institutional Ethics Committee of Dumlupinar University.

Electrocardiography

Electrocardiography measurements were performed using 12-lead ECG at a speed of 25 mm/s and a voltage of 10 mm/mV while the patient was in supine position. ECG recordings were manually interpreted by three independent cardiologists, who were blind for patients' clinical information. QT interval was measured from the starting point of QRS complex to the point where the descending limb of T-wave intersected the isoelectric line. QTc was calculated as QT/√RR (Bazzet formula) [12]. Tp-e interval was measured from the peak point of T-wave to the point where the descending limb of T-wave intersected the isoelectric line. QTcd was calculated as the difference between the longest QTc and the shortest QTc, whereas Tp-e dispersion was calculated as the difference between the maximum and minimum Tp-e intervals. Tp-e/QT and Tp-e/QTc ratios were calculated using these measurements.

Laboratory assessments

From the blood samples of the patients drawn after 8-10-hour overnight fasting period, levels of blood glucose, insulin, hemoglobin A1c (HbA1c), total cholesterol, high-density lipoprotein cholesterol, low-density lipoprotein cholesterol, triglyceride, thyroid-stimulating hormone (TSH), and free T4 and complete blood count were recorded. Level of fasting blood glucose was measured using the glucose hexokinase method (Beckman Coulter Ireland Inc.).Insulin serum concentrations were determined by the Beckman Access Ultrasensitive Insulin Assay, which is a simultaneous one-step immunoenzymatic ("sandwich") assay performed by the automated Access Immunoassay System (Beckman Coulter DXI 600, Fullerton, CA, USA). HbA1c values were measured using high-performance liquid chromatography (Tosoh Bioscience, South San Francisco, CA, USA). Levels of total cholesterol, high-density lipoprotein cholesterol, low-density lipoprotein cholesterol, and triglyceride were determined using an automatic analyzer (Beckman Coulter AU 2700, Brea, CA, USA). TSH and free T4 were determined by immunoenzymatic method (Beckman Coulter DXI 600 , Fullerton, CA, USA) based on chemiluminescence detection principle.

Statistical analysis

Statistical analysis was performed using the Predictive Analytics Software for Windows version 18.0 (SPSS Inc., Chicago, IL, USA) . The Kolmogorov-Smirnov test was used for normality analysis of the distribution of numerical data. Descriptive data were expressed as mean±standart deviation. For the comparison of two independent groups, the Student's t-test was used for normally distributed variables and the Mann-Whitney U test was used for non-normally distributed variables. When more than two independent groups were compared, the difference between the groups was analyzed using the one-way ANOVA for each variable. The Tukey's post hoc test was performed to determine the significance of differences. In addition, the chi-square test was used to compare categorical variables. The Pearson's correlation test was used for correlation analyses. A p value of less than 0.05 was considered statistically significant.

Results

The study population comprised 50 class III obese patients (34 females, 16 males, mean age, 39.5±10.8 years), 50 class II obese patients (34 females, 16 males, mean age, 38.7±10.3 years), 50 class I obese patients (32 females, 18 males, mean age, 40.5±10.1 years), and 50 overweight patients (29 females, 21 males, mean age, 39.0±10.9 years) and age- and gender-matched 50 healthy normoweight individuals (29 females, 21 males, mean age, 35.8±10.3 years).

There were no significant differences among the study groups in terms of demographic, clinical, and laboratory characteristics including age, systolic blood pressure, diastolic blood pressure, and levels of blood glucose, TSH, and free T4. As was expected, there were significant differences among the groups in terms of BMI, insulin level, HOMA-IR, Hba1c level, and lipid parameters (Table 1).

The mean QT, QTc, QTcd, Tp-e, Tp-ed, Tp-e/QT, Tp-e/QTc, and heart rate values in the normoweight and overweight groups are demonstrated in Table 2. All ECG parameters excluding heart rate were significantly different between these groups; the ECG parameters were significantly higher in the overweight group ($p=0.002$, $p<0.001$, $p<0.001$, $p<0.001$, $p<0.001$, $p<0.001$, and $p<0.001$, respectively). Intra-group comparison of overweight patients as class I obese, class II obese, and class III obese using ANOVA F-test revealed significant differences in terms of the ECG parameters including QTc, QTcd, and Tp-ed ($p=0.01$, $p=0.04$, $p=0.049$, respectively). Proportional increase in these parameters with weight is presented in Table 3. The whole study population was divided into two groups according to the HOMA-IR level as <2.7 (n=140) and >2.7 (n=110) and these groups were compared. Similar to the groups established based on the BMI values, QTc, QTcd, and Tp-ed were significantly higher in the group with HOMA-IR >2.7 ($p<0.001$, $p<0.001$, $p<0.001$, respectively). The Pearson's correlation analysis, which was performed to determine the correlation of HOMA-IR and BMI values with the ECG parameters, revealed strongly positive correlations of QTc, QTcd, and Tp-ed parameters with HOMA-IR and BMI values (Table 5).

Table 1. Demographic, clinical and laboratory characteristics of study participants

Variables	Normoweight (18.5-24.9 kg/m²)	Overweight (25-29.9 kg/m²)	Class I obesity (30-34.9 kg/m²)	Class II obesity (35-39.9 kg/m²)	Class III obesity (>40 kg/m²)	P-value
Female/male (n)	29/21	29/21	32/18	34/16	34/16	
Smoker/nonsmoker (n)	9/41	11/39	8/42	8/42	10/40	
Age (years)	35.8±10.3	39.0±10.9	40.5±10.1	38.7±10.3	39.5±10.8	0.24
SBP (mm Hg)	118±9.7	116±10.4	121±10.5	120±9.8	121±9.9	0.08
DBP (mm Hg)	68.6±5.5	67.9±7.8	71.0±7.6	71.3±7.4	69.5±7.1	0.74
BMI (kg/m2)	22.0±2.0	27.2±1.2	32.4±1.4	37.5±1.4	45.1±4.5	<0.001
İnsulin (uIU/mL)	6.2±3.5	8.5±4.8	12.8±6.2	13.4±8.7	14.4±7.1	<0.001
Glucose (mg/dl)	92.2±6.4	95.5±7.5	93.2±8.1	95.6±8.5	95.8±9.2	0.08
HOMA-IR	1.4±0.8	2.0±1.2	3.0±1.6	3.1±2.0	3.4±1.7	<0.001
HbA1c (%)	5.2±0.3	5.2±0.4	5.3±0.3	5.5±0.3	5.5±0.3	<0.001
TSH (uIU/mL)	1.8±0.9	1.9±0.8	2.0±0.9	2.2±0.9	2.3±1.1	0.09
Free T4 (ng/dl)	0.84±0.10	0.82±0.13	0.81±0.12	0.79±0.09	0.83±0.12	0.25
LDL-C (mg/dl)	103.5±23.1	123.2±29.0	113.8±26.7	119.7±26.1	118.3±29.9	0.009
HDL-C (mg/dl)	52.2±10.7	45.2±11.3	46.8±9.2	46.3±10.0	48.8±10.4	0.02
TC (mg/dl)	174.0±26.5	199.4±32.7	187.0±32.2	198.4±34.9	196.6±32.6	0.001
Triglyceride (mg/dl)	91.4±40.8	143.3±72.2	137.8±73.5	166.0±93.7	144.6±57.0	<0.001

SBP: Systolic blood pressure, DBP: Diastolic blood pressure, BMI: Body mass index, HOMA-IR: Homeostatic Model of Assessment-Insulin Resistance, HbA1c: Hemoglobin A1c, TSH: Thyroid stimulating hormone, LDL-C: Low-density lipoprotein cholesterol, HDL-C: High-density lipoprotein cholesterol, TC: Total cholesterol. Data are shown as means ± s.d. P values were calculated by an ANOVA F-test

Table 2. Comparison of the electrocardiographic parameters in the normoweight group and overweight group

Groups	QT (ms)	QTc (ms)	QTcd (ms)	Tp-e (ms)	Tp-ed (ms)	Tp-e/QT	Tp-e/QTc	Heart rate (bpm)
Normoweight (18.5-24.9 kg/m²)	366.6±24	398.7±19	37.4±11	81.6±12	35.0±9	0.22±0.03	0.20±0.02	72.7±10.3
Overweight (25-29.9 kg/m²)	381.4±23	418.6±17	49.3±12	95.4±15	43.6±12	0.24±0.03	0.22±0.03	76.6±11.1
P-value	0.002	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	0.07

Data are shown as means ± s.d. P values were calculated by student t-test.

Table 3. Comparison of the electrocardiographic parameters in the overweight group and obese groups

Groups (bpm)	QT (ms)	QTc (ms)	QTcd (ms)	Tp-e (ms)	Tp-e disp (ms)	Tp-e/QT	Tp-e/QTc	Heart rate
Overweight (25-29.9 kg/m²)	381.4±23	418.6±17	49.3±12	95.4±15	43.6±12	0.24±0.03	0.22±0.03	76.6±11.1
Class I obesity (30-34.9 kg/m²)	378.8±22	425.3±18	53.3±15	92.4±14	47.2±12	0.24±0.04	0.22±0.03	75.4±9.6
Class II obesity (35-39.9 kg/m²)	383.6±23	432.0±21	54.0±15	92.6±13	46.2±13	0.24±0.03	0.21±0.03	76.7±10.7
Class III obesity (>40 kg/m²)	376.4±20	433.1±20	57.7±16	91.8±12	49.6±10	0.24±0.02	0.21±0.02	80.1±10.1
P-value	0.38	0.01	0.04	0.53	0.049	0.5	0.06	0.12

Data are shown as means ± s.d. P values were calculated by an ANOVA F-test

Table 4. Comparison of the electrocardiographic parameters in the HOMA-IR < 2.7 group and HOMA-IR > 2.7 group

Groups	QT (ms)	QTc (ms)	QTcd (ms)	Tp-e (ms)	Tp-ed (ms)	Tp-e/QT	Tp-e/QTc	Heart rate (bpm)
HOMA-IR < 2.7 (n: 140)	376.9±23	414.2±23	46.3±15	89.4±15	41.8±13	0.23±0.03	0.21±0.03	74.1±10.5
HOMA-IR > 2.7 (n: 110)	378.0±22	430.9±18	55.4±15	92.5±12	47.5±10	0.24±0.02	0.21±0.02	79.1±10.1
P-value	0.7	<0.001	<0.001	0.08	<0.001	0.82	0.82	<0.001

HOMA-IR: Homeostatic Model of Assessment-Insulin Resistance Data are shown as means ± s.d. P values were calculated by student t-test

Tablo 5. Pearson correlation analysis between ECG parameters and BMI and HOMA-IR

Variables	QTc (ms)		QTcd (ms)		Tp-e (ms)		Tp-e disp (ms)		Tp-e/QT		Tp-e/QTc	
	r	p	r	p	r	p	r	p	r	p	r	p
BMI (kg/m²)	0.501	<0.001	0.39	<0.001	0.16	0.008	0.35	<0.001	0.13	0.03	0.001	0.98
HOMA-IR	0.37	<0.001	0.28	<0.001	0.11	0.07	0.22	<0.001	0.14	0.02	0.01	0.8

BMI: Body mass index, HOMA-IR: Homeostatic Model of Assessment-Insulin Resistance

Discussion

Potential risk factors of cardiac arrhythmia such as ischemic heart disease, atrial dilatation, systolic and diastolic heart failure, and sleep apnea are significantly more common in obese individuals [13,14]. Moreover, obesity-related minimal asymptomatic myocardial dysfunction may accompany even in the absence of structural or functional cardiac changes [15]. This asymptomatic myocardial dysfunction can increase electrical activity, which triggers ventricular arrhythmias, and can lead to sudden cardiac death [16-18]. Increased QTc and QTcd parameters with increasing BMI have been confirmed in many studies and associated with delayed ventricular repolarization [9,10,19,20]. In line with the literature, , a statistically significant positive correlation of QTc and QTcd parameters with BMI and HOMA-IR was obtained in the present study. Increase in these parameters is a potential marker of ventricular arrhythmias and sudden cardiac death [14,15].

Tp-e, Tp-ed, and ratios of Tp-e/QT and Tp-e/QTc have been defined as the novel electrocardiographic markers of ventricular repolarization abnormality. Electrophysiological studies have demonstrated that prolonged Tp-e interval is correlated with induction or spontaneous development of ventricular tachycardia. The ratios of Tp-e/QT and Tp-e/QTc are also considered as a sensitive index for arrhythmogenesis [12,21-23]. To our knowledge, in the literature, there are two recent studies demonstrating the relation of BMI with these novel parameters in limited number of patients. Braschi et al. [24] compared 60 overweight/obese patients with 60 normoweight individuals in terms of the new ECG parameters and reported no significant relationship between the groups regarding QTd, Tp-e, Tp-ed, and Tp-e/QT ratio. A recent study by Hussain et al. [25] compared Tp-e, Tp-ed, and Tp-e/QT ratio among 34 normoweight, 30 overweight, and 32 obese patients and, likewise, reported no statistically significant relationship. Contrary to these studies, the present study, which was performed in a larger patient group, determined significant differences between normoweight and overweight groups in terms of Tp-e, Tp-ed, Tp-e/QT, and Tp-e/QTc parameters; these parameters were significantly higher in the overweight group. In intra-group comparison of overweight patients as class I obese, class II obese, and class III obese using ANOVA F-test, a significant difference was determined only for Tp-ed parameter in addition to QTc and QTcd parameters. The correlation analysis also revealed a strong correlation between QTc, QTcd, and Tp-ed parameters and BMI.

Various theories have been suggested to explain the relation of obesity with delayed ventricular repolarization. The most striking one is the insulin resistance, which is the common comorbidity in obese patients [26,27]. In the study by Laitinen et al. (28), the relationship of insulin resistance and hyperinsulinemia with prolonged QT was demonstrated even in the absence of myocardial infarction or diabetes mellitus [28]. Another study has propounded that insulin leads to prolonged QT by hyperpolarizing the plasma membranes of both stimulatable and non-stimulatable tissues [29]. Hyperinsulinemia may result in hypokalemia, which is an important factor for the development of cardiac arrhythmias, by causing potassium to shift into the cell [26]. As far as we know, there is no study in the literature demonstrating the relationship between HOMA-IR -indicator of insulin resistance- and the novel ECG parameters. In the present study, only Tp-ed, a novel parameter, in addition to QTc and QTcd parameters was significantly higher in the group with HOMA-IR >2.7. Similar to the correlation with BMI, there was also a strong correlation between the parameters of QTc, QTcd, and Tp-ed and HOMA-IR.

One of the limitations of the present study was the manual measurement of the parameters which might have limited the accuracy of the outcomes. Although manual measurement has been scientifically accepted, digital measurement by converting the paper ECG tracing to digital form using an optical scanner has been reported as an alternative method. Another limitation of the present study was the fact that subclinical ischemic cardiac disease might have been overlooked because performing coronary angiography in all patients was practically not possible.

Conclusion

There was a positive relationship of BMI and HOMA-IR with the novel parameters indicating ventricular repolarization abnormality. Ventricular repolarization inhomogeneity was observed to be increase in the patients with BMI >25 kg/m2 and HOMA-IR >2.7. Regular monitoring of these patients for critical cardiac events, such as ventricular tachycardia, would be beneficial.

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Competing interests
The authors declare that they have no competing interest

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Ethical approval
Before the study, permissions were obtained from local ethical committee

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