Evaluation of the effects of insulin resistance on ECG parameters in obese children

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Abstract. – OBJECTIVE: Obese people are at increased risk of arrhythmia and sudden death, even in the absence of heart dysfunction. Increased insulin resistance, neurohumoral and autonomic changes in obesity can cause atrial and ventricular repolarization abnormalities. This study aimed to investigate the effect on ventricular repolarization parameters and to show the increased risk of ventricular arrhythmia in obese children.

PATIENTS AND METHODS: The data of 50 obese children aged 2-18 who applied to the Pediatric Endocrinology Outpatient Clinic were evaluated prospectively. In 12-lead ECGs, heart rate, Pmax, Pmin, P-wave dispersion (Pwdisp), QTmax, QTmin, QT dispersion (QTd), QTcmax, QTcmin, QTc interval dispersion (QTcd), Tpeak-Tend interval (Tp-e), Tp-e/QT, Tp-e/QTc were calculated electronically.

RESULTS: Tp-e time (0.041 ± 0.004/0.049 ± 0.015/ p=0.018) and Tp parameters were measured in obese children with and without insulin resistance. Tp-e/QT ratio was also found to be high (p=0.035). There is a negative correlation between BMI SDS values and QTcmax and QTcmin values in patients with insulin resistance (p=0.015).

CONCLUSIONS: In our study, the Tp-e interval and Tp-e/QT ratios, which had been revealed in literature to be more sensitive in demonstrating ventricular arrhythmias, were found to be higher in obese individuals with insulin resistance than in those without insulin resistance. Obese individuals with or without insulin resistance should be carefully evaluated in terms of atrial and ventricular depolarization and repolarization parameters with 12-lead ECG during their outpatient controls, and annual 24-hour Holter control should be performed to detect arrhythmias.

Key Words: Obesity, Insulin resistance, Child, Electrocardiography, Ventricular repolarization.

Introduction

The frequency of obesity is gradually increasing in children and adolescents, as well as in adults, leading to related complications, mostly occurring in the cardiovascular system at an earlier age.

There are approximately 800,000 deaths worldwide every year due to sudden cardiac death (SCD). This SCD is often due to malignant ventricular arrhythmias (MVA).

MVA usually results in SCD in individuals with heart diseases. However, healthy hearts can also develop MVA in about 15-20% of cases. In these patients, the development of MVA can be predicted by analyzing the parameters of ventricular repolarization on ECG.

Obesity is one of the risk factors for sudden cardiac death, and its main cause is arrhythmias. Delay of cardiac repolarization increases susceptibility to arrhythmias. Structural and functional changes in atrial and ventricular myocardium caused by obesity can lead to atrial and ventricular depolarization and repolarization abnormalities.

Previous studies have reported that QT, corrected QT (QTc) distance, QT and QTc dispersions (QTcd) with the T wave peak and the end distance (Tp-e interval) and Tp-e/QT ratio can show susceptibility to ventricular arrhythmias. There are few studies on obese children in literature related to these parameters.

The effects of insulin resistance on ventricular repolarization abnormality, which often accompanies obesity, have been studied by animal experiments. It has been shown that the increase in sympathetic tone may also play a role in the increased heterogeneity of ventricular repolarization in relation to insulin resistance.
In this study, we aimed to investigate the effects of obesity and insulin resistance on ventricular repolarization parameters, which are considered to indicate an increased risk of ventricular arrhythmia in children.

**Patients and Methods**

Between October and December 2020, 50 obese children aged 2-18 years were admitted to Izmir Tepecik Training and Research Hospital Pediatric Endocrine Polyclinic with the complaint of being overweight. Patients with a body weight above 99% or +2 Standard Deviation Score (SDS) according to age and gender, as well as those with a body mass index above 95% or +2 SDS, were considered obese and included in the study. Pubertal/prepubertal distinction was made according to Tanner’s stage.

In the study, which was designed prospectively, the sample size was calculated as 0.5 for each variable, 0.5 for type 1 error, and 50 at 95% power according to Prior power analysis.

Exclusion criteria of the study:
- Having blood pressure above the 95th percentile according to age and gender at the time of application;
- Detection of anemia in the hemogram taken at the time of application;
- Presence of cardiac diseases;
- Use of drugs affecting heart rhythm;
- Presence of chronic diseases.

The selection method of patients and the study flow diagram are specified in Figure 1.

In the blood samples taken, total cholesterol (TC), triglyceride (TG), high-density lipoprotein (HDL), low-density lipoprotein (LDL) were determined (TC≥200 mg/dl, TG≥100 mg/dl (2-9 years), TG≥130 mg/dl (10-18 years)]. Patients with LDL levels≥130 mg/dl and HDL levels<40 mg/dl were included. The insulin resistance index homeostasis assessment model (HOMA-IR) was applied using the following equation: [fasting insulin (mU/L) x fasting glucose (mmol/L)/405]. A value of 2.5 or more in prepubertal patients and a value of 4 or more in pubertal patients were accepted as insulin resistance.

**Statistical Analysis**

Data were evaluated in the statistical package program SPSS, v. 26 (IBM Corp., Armonk, NY, USA). The normal distribution of the data of numerical variables was evaluated with the Shapiro-Wilk test of normality and Q-Q graphs. Homogeneity of variances was evaluated with Levene’s test. For non-normally distributed triglyceride, HDL, and LDL variables, patient groups with and without insulin resistance were compared with the Mann-Whitney U test. Comparisons between groups for normally distributed variables were made with an independent two-sample t-test.

The relationship between ECG variables OGTT peak insulin, OGTT 2nd-hour insulin, OGTT total insulin, VA SDS, and BMI SDS variables was evaluated by Pearson’s correlation analysis. A p-value<0.05 was considered statistically significant.

**Results**

A total of 50 patients, of which 25 (50%) with insulin resistance and 25 (50%) without, was included in the study. The age distribution of patients with and without insulin resistance was similar (p=0.087). Body weight SDS, body mass index SDS, and triglyceride values of patients with insulin resistance were found to be statistically higher than those without insulin resistance (p=0.027, p=0.010, p=0.020, respectively). HDL values were found to be higher in patients without insulin resistance.
There was no statistically significant difference in terms of LDL and cholesterol values in both groups ($p=0.056$, $p=0.248$). Systolic blood pressure values in the group with insulin resistance were found to be significantly higher than the group without insulin resistance ($t=2.611$, $p=0.012$). The difference between diastolic blood pressure values was not statistically significant ($p=0.088$) (Table I).

While the $P_{min}$, Tp-e interval and Tp-e/QT values of the patients with insulin resistance were found to be statistically significantly higher than those of the patients without insulin resistance ($p=0.005$, $p=0.018$, $p=0.035$, respectively), a significant difference was not found between the two groups in terms of other ECG parameters ($p>0.05$) (Table II).
There is a negative correlation between BMI SDS and QTcmax in patients with insulin resistance ($r=-0.409$, $p=0.042$).

In patients with insulin resistance, a negative correlation was found between VA SDS values and QTcmax and QTcmin values ($r=-0.576$, $p=0.003$, $r=-0.482$, $p=0.015$, respectively) (Table III).

### Discussion

In our study, it was found that BMI, blood triglyceride, LDL, and cholesterol levels were higher in obese children with insulin resistance compared to obese children without insulin resistance, while HDL levels were lower. This result is in line with previous studies. In individuals with obesity and insulin resistance, only the Pmin value was found to be significantly higher. However, no difference was found in terms of Pwdisp. Additionally, no correlation was found between these parameters and BMI and insulin levels. No significant difference was detected between QT, QTc intervals, and QT and QTc dispersions among obese individuals with and without insulin resistance. Also, no significant difference was found between blood insulin levels and these parameters in children with insulin resistance. In this study, we found that the Tp-e interval and Tp-e/QT ratio were higher in obese individuals with insulin resistance.

Obesity has become an important public health problem in both developed and developing coun-

### Table I. Comparison of demographic characteristics of patients with and without insulin resistance.

<table>
<thead>
<tr>
<th>Insulin resistance</th>
<th>No n = 25</th>
<th>Yes n = 25</th>
<th>$p$-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender, n (%)</td>
<td>11 (44.0)</td>
<td>11 (44.0)</td>
<td>-</td>
</tr>
<tr>
<td>Age (years) (mean±SD)</td>
<td>14 (56.0)</td>
<td>14 (56.0)</td>
<td>-</td>
</tr>
<tr>
<td>VA SDS (max-min)</td>
<td>9.8±3.2 9.6±4.2</td>
<td>9.8±3.2 9.6±4.2</td>
<td>0.087</td>
</tr>
<tr>
<td>BMI SDS (mean±SD)</td>
<td>2.69±0.69 3.18±0.81</td>
<td>2.69±0.69 3.18±0.81</td>
<td>0.027</td>
</tr>
<tr>
<td>Triglyceride [M (Q1-Q3)]</td>
<td>107.0 (70.0-154.5)</td>
<td>151.0 (113.5-210.0)</td>
<td>0.020</td>
</tr>
<tr>
<td>HDL [M (Q1-Q3)]</td>
<td>49.0 (39.0-55.5)</td>
<td>38.0 (36.5-42.5)</td>
<td>0.005</td>
</tr>
<tr>
<td>LDL [M (Q1-Q3)]</td>
<td>85.0 (72.5-116.0)</td>
<td>105.0 (82.0-118.5)</td>
<td>0.256</td>
</tr>
<tr>
<td>Cholesterol (mean±SD)</td>
<td>115.3±36.1</td>
<td>176.5±31.1</td>
<td>0.248</td>
</tr>
<tr>
<td>Systolic blood pressure mean±SD</td>
<td>91.32±10.51</td>
<td>99.04±10.39</td>
<td>0.012</td>
</tr>
<tr>
<td>Diastolic blood pressure mean±SD</td>
<td>74.00±7.94</td>
<td>78.36±9.66</td>
<td>0.088</td>
</tr>
</tbody>
</table>

mean±SD: mean±standard deviation, M: Median, Q1: First quartile value, Q3: Third quartile value.

### Table II. Comparison of ECG parameters of patients with and without insulin resistance.

<table>
<thead>
<tr>
<th>Insulin resistance</th>
<th>Test statistics</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No mean±SD</td>
</tr>
<tr>
<td>Heart rate</td>
<td>91.1±16.7</td>
</tr>
<tr>
<td>$P_{\text{max}}$</td>
<td>0.116±0.028</td>
</tr>
<tr>
<td>$P_{\text{min}}$</td>
<td>0.042±0.008</td>
</tr>
<tr>
<td>$P_{\text{dispersion}}$</td>
<td>0.075±0.029</td>
</tr>
<tr>
<td>QT</td>
<td>0.402±0.034</td>
</tr>
<tr>
<td>QTc</td>
<td>0.318±0.032</td>
</tr>
<tr>
<td>QTc</td>
<td>0.084±0.016</td>
</tr>
<tr>
<td>QTc</td>
<td>0.484±0.036</td>
</tr>
<tr>
<td>QTc</td>
<td>0.382±0.033</td>
</tr>
<tr>
<td>QTc</td>
<td>0.132±0.161</td>
</tr>
<tr>
<td>Tp-e</td>
<td>0.041±0.004</td>
</tr>
<tr>
<td>Tp-e/QT</td>
<td>0.125±0.012</td>
</tr>
<tr>
<td>Tp-e/QTc</td>
<td>0.101±0.010</td>
</tr>
</tbody>
</table>

mean±SD: mean±standard deviation; $t$: Independent two-sample $t$-test.
It is usually seen with increasing frequency in the childhood age group. Sedentary life, ready-to-eat diet, and inactivity are among the leading causes. Its prevalence has increased significantly, especially during the COVID-19 pandemic. This increase in obesity prevalence brings with it an increase in obesity-related co-morbidities. The most important of these co-morbidities are cardiovascular effects. Therefore, taking the necessary precautions, especially in the childhood age group, will prevent possible future complications. The presence of insulin resistance, in addition to obesity, facilitates the emergence of metabolic and cardiovascular complications of obesity.

In a study comparing obese and normal-weight children in terms of cardiovascular risks, it was reported that obese children have more cardiovascular risk factors. It has been demonstrated that increased inflammation is one of the most important mechanisms of cardiovascular co-morbidity. High IL-6 levels due to increased plasma TNF-alpha levels have been demonstrated in obese individuals. TNF is secreted from fat cells and changes insulin signal transmission in skeletal muscle cells, thereby reducing insulin intolerance. Gupta et al showed that children with obesity and glucose intolerance have high TNF and IL-6 levels.

Studies have also shown that a high resting heart rate is positively correlated with cardiovascular mortality. Obese children have been reported to have higher heart rates than normal-weight children in the same age group. It is believed that this condition represents an adaptation mechanism of the organism to the increased adipose tissue, and furthermore, the presence of insulin resistance may contribute to a state in which autonomic functions could be impaired. In our study, obese and non-obese individuals were not compared. However, when obese individuals with and without insulin resistance were compared, no significant difference was found between resting heart rates.

Considering the short follow-up period in our study and the average age of the study group, we predict that there will be a difference in resting heart rates between these groups in the follow-up. The increase in body weight is associated with high blood pressure, and in this case, it causes arrhythmias by causing some structural changes in the left atrium and ventricle in these individuals.

Duncan et al have shown that although systolic and diastolic blood pressure values of obese children are within normal limits, they are higher than non-obese individuals in the same age group. Atrial fibrillation (AF) in children usually occurs due to congenital heart diseases or valvular diseases affecting the left atrium. However, with the increase in the frequency of obesity in the childhood age group, the frequency of AF has increased in obese children without any underlying heart disease. Explaining this condition solely by an increase in left atrial strain is not sufficient. In obese children, concomitant atrial inflammation due to increased adipose tissue also contributes significantly to this situation. P-wave dispersion is an electrocardiographic marker that reveals the heterogeneity of electrical impulse conduction in both atria. In electrophysiological studies, intra-atrial conduction delay leads to prolongation of P-wave duration and Pdip and predisposes to AF. It has been reported that

<p>| Table III. Correlations between BMI SDS and VA SDS values and ECG parameters in patients with insulin resistance. |
|--------------------------------------------------|---------------------------------|---------------------------------|---------------------------------|---------------------------------|---------------------------------|---------------------------------|---------------------------------|---------------------------------|---------------------------------|---------------------------------|</p>
<table>
<thead>
<tr>
<th></th>
<th><strong>BMI SDS</strong></th>
<th>r</th>
<th>p</th>
<th><strong>VA SDS</strong></th>
<th>r</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heart rate</td>
<td>-0.144</td>
<td>0.492</td>
<td></td>
<td>-0.324</td>
<td>0.114</td>
<td></td>
</tr>
<tr>
<td>P</td>
<td>0.132</td>
<td>0.528</td>
<td></td>
<td>-0.111</td>
<td>0.597</td>
<td></td>
</tr>
<tr>
<td>P&lt;sub&gt;max&lt;/sub&gt;</td>
<td>0.034</td>
<td>0.874</td>
<td></td>
<td>-0.090</td>
<td>0.668</td>
<td></td>
</tr>
<tr>
<td>P&lt;sub&gt;min&lt;/sub&gt;</td>
<td>0.120</td>
<td>0.568</td>
<td></td>
<td>0.205</td>
<td>0.327</td>
<td></td>
</tr>
<tr>
<td>QT&lt;sub&gt;dispersion&lt;/sub&gt;</td>
<td>-0.055</td>
<td>0.795</td>
<td></td>
<td>0.081</td>
<td>0.700</td>
<td></td>
</tr>
<tr>
<td>QT&lt;sub&gt;max&lt;/sub&gt;</td>
<td>-0.007</td>
<td>0.973</td>
<td></td>
<td>-0.061</td>
<td>0.772</td>
<td></td>
</tr>
<tr>
<td>QT&lt;sub&gt;min&lt;/sub&gt;</td>
<td>-0.046</td>
<td>0.825</td>
<td></td>
<td>0.166</td>
<td>0.428</td>
<td></td>
</tr>
<tr>
<td>QT&lt;sub&gt;Te&lt;/sub&gt;&lt;sup&gt;max&lt;/sup&gt;</td>
<td>-0.409</td>
<td>0.042</td>
<td></td>
<td>-0.576</td>
<td>0.003</td>
<td></td>
</tr>
<tr>
<td>QT&lt;sub&gt;Te&lt;/sub&gt;&lt;sup&gt;min&lt;/sup&gt;</td>
<td>-0.309</td>
<td>0.132</td>
<td></td>
<td>-0.482</td>
<td>0.015</td>
<td></td>
</tr>
<tr>
<td>QT&lt;sub&gt;Te&lt;/sub&gt;&lt;sup&gt;dispersion&lt;/sup&gt;</td>
<td>0.006</td>
<td>0.977</td>
<td></td>
<td>0.168</td>
<td>0.422</td>
<td></td>
</tr>
<tr>
<td>Tp&lt;sub&gt;e&lt;/sub&gt;interval</td>
<td>-0.008</td>
<td>0.970</td>
<td></td>
<td>-0.083</td>
<td>0.692</td>
<td></td>
</tr>
<tr>
<td>Tp&lt;sub&gt;e&lt;/sub&gt;/QT</td>
<td>0.002</td>
<td>0.992</td>
<td></td>
<td>-0.067</td>
<td>0.751</td>
<td></td>
</tr>
<tr>
<td>Tp&lt;sub&gt;e&lt;/sub&gt;/QT&lt;sub&gt;c&lt;/sub&gt;</td>
<td>0.101</td>
<td>0.633</td>
<td></td>
<td>0.088</td>
<td>0.676</td>
<td></td>
</tr>
</tbody>
</table>

r: Pearson correlation coefficient.
a Pwdisp of 40 ms or more is a risk factor for AF. Changes in the atrium have an effect on increased blood pressure and obesity, as well as increased blood insulin levels due to insulin resistance. In this study, only the Pmin value was found to be significantly higher in obese and insulin-resistant individuals. However, no difference was found in terms of Pwdisp. In addition, no correlation was found between these parameters and BMI and insulin levels. In our study, we think that we may not have detected a significant difference in terms of these parameters due to the small number of patients and the short follow-up period. Considering the results of previous studies, it is clear that long-term follow-up of obese individuals with insulin resistance is necessary in terms of possible atrial fibrillation.

The relationship between obesity and sudden cardiac death has been known for centuries. Sudden death is multifactorial in obese individuals, and one of the leading mechanisms associated with it is ventricular arrhythmias. Prolongations in QT and QTc values indicate that ventricular repolarization is prolonged, while increases in QT and QTc dispersion values indicate that ventricular repolarization is not homogeneous and predisposes to ventricular arrhythmias. Studies conducted in the adult age group have demonstrated that the Tp-e interval and Tp-e/QT ratio is associated with mortality in patients with Brugada syndrome, long QT syndrome, and hypertrophic cardiomyopathy. In addition to the Tp-e interval, Tp-e/QT and Tp-e/QTc ratios were also found to be associated with ventricular arrhythmias and sudden cardiac death. Unlike the Tp-e interval, some studies have demonstrated that the Tp-e/QT ratio, not being influenced by body weight and heart rate, may be a superior parameter in predicting sudden cardiac death and ventricular arrhythmias.

Studies conducted in the adult age group have shown that both the Tp-e interval and the Tp-e/QT ratio increase in both diabetic and obese patients. It paves the way for ventricular arrhythmias by affecting the homogeneous spread of ventricular repolarization in autonomic changes in patients with insulin resistance. In this study, we found that the Tp-e interval and the Tp-e/QT ratio were higher in obese individuals with insulin resistance.

Obesity has become an important public health problem in the pediatric population. Together with obesity, insulin resistance may lead to more susceptibility to adverse outcomes. Considering that atrial and ventricular arrhythmias are the most important causes of morbidity and mortality in obese individuals and diabetic patients with insulin resistance, long-term follow-up of these patients is necessary for possible arrhythmias. Considering that our study is the first to examine these parameters in children with obesity and insulin resistance, we believe that it will be a starting point for future studies.

Limitations

Possible limitations of this study are that our results may be limited to our population and, therefore, have limited applicability to the...
general population. To confirm these results, it is necessary to conduct long-term follow-up of the patients in the study and further studies with the new data to be obtained.

**Conclusions**

Obesity has become an increasingly common public health problem among children in Turkey. In our study, although there is no significant difference in terms of QT, QTc duration and QT and QTcd, the Tp-e interval and the Tp-e/QT ratio, which have been shown to be more sensitive in demonstrating ventricular arrhythmias, were found to be higher in obese individuals with insulin resistance. Therefore, considering that atrial and ventricular arrhythmias are the most important causes of morbidity and mortality in obese individuals and diabetic patients with insulin resistance, long-term follow-up of these patients is necessary for possible arrhythmias. Obese individuals with or without insulin resistance should be carefully evaluated in terms of atrial and ventricular depolarization and repolarization parameters with 12-lead ECG during their outpatient controls, and annual 24-hour Holter control should be performed to detect arrhythmias.

**Ethics Approval**
The study has been approved by the Ethics Committee of Izmir Tepecik Training and Research Hospital (date: 14/09/2020, number: 2020/11-27).

**Informed Consent**
For each patient, informed consent forms were obtained from their parents.

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**Conflict of Interest**
The authors do not have any potential conflict of interest regarding the research, authorship, and data availability or publication of this article.

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**Authors’ Contributions**
K.Y. prepared the manuscript; S.I., I.A., and G.C. collected the clinical data; C.K designed and conducted the study and C.K. edited and revised the manuscript; B.N.D. oversaw the work. All authors read and approved the final manuscript.

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Electrocardiography in obese children


