Association between the corrected QT interval, carotid artery intima-media thickness, and hepatic steatosis in obese children

Ghaniya Daar, Halil İbrahim Serin, Hüseyin Ede**, Haşim Hüsrevşahi****

Departments of Pediatrics, *Radiology, **Cardiology, ***Pediatric Cardiology, Faculty of Medicine, Bozok University; Yozgat-*Turkey*

Abstract

Objective: Childhood obesity is related to subclinical atherosclerosis. Carotid intima-media thickness (CIMT) and hepatosteatosis are parameters that reflect subclinical atherosclerosis and are shown to be associated with obesity. However, their relation with the corrected QT interval (QTc) has not been thoroughly studied in children. Here, we aimed to research the relation between QTc, hepatic steatosis, and CIMT among obese children.

Methods: Fifty-three obese and 53 age- and sex-matched non-obese children aged 6–16 years were included in this prospective cross-sectional study. The QTc of each subject was accordingly obtained from lead II on a 12-lead resting electrocardiogram. Thus, CIMT measurement and abdominal ultrasonographic examination were performed. The data for obese and non-obese children were analyzed and compared.

Result: The age and gender distribution of the subjects were statistically similar. The CIMT value of the obese group was higher than that of the non-obese group ($p<0.001$). The obese group had a higher frequency of hepatosteatosis at grade 1 or 2 than the non-obese group ($p<0.001$). The QTc values were also found to be more prolonged in the obese group than in the other group ($p<0.001$). With Student's t-test and Mann-Whitey U test accordingly.

Conclusion: We demonstrated that obese children had higher CIMT and QTc values as well as more frequent hepatosteatosis, and that the presence of hepatosteatosis or increased CIMT had an association with prolonged QTc values in obese children. Therefore, with the aim of detecting cardiovascular effects of obesity, it may be beneficial to perform the measurements of QTc in the presence of hepatosteatosis and/or increased CIMT among obese children. *(Anatol J Cardiol 2016; 16: 524-8)*

Keywords: obesity, children, QT interval, carotid intima-media thickness, hepatosteatosis

Introduction

Obesity in childhood is a common health problem, particularly in developed countries. It has been shown that childhood obesity has a strong correlation with an increased risk of the development of atherosclerotic cardiovascular diseases (1-3). It is one of the main causes of mortality and morbidity. Another important issue in obese children is sudden cardiac death. Sudden cardiac death without obvious structural abnormalities has been reported in obese children (4). Atherosclerosis-related cardiovascular events and arrhythmias may be some of the possible causes. Prolongation of the corrected QT interval (QTc) may be one of the potential reasons. A prolonged QTc can result in fatal cardiac arrhythmias such as ventricular tachycardia and fibrillation. Güven et al. (5) reported that the QTc values of obese children were longer than those of healthy ones. However, the mechanisms leading to sudden cardiac death among obese children still remain to be elucidated. The preferred method to determine the QTc is from 12-lead ECG via visual interpretations with calipers and then calculating the QTc with the help of Bazett's formula, but an automated 24-h ambulatory Holter can also be used to measure the QTc. Both methods have pros and cons when used for calculating QTc values but have nearly similar results in the evaluation of cardiovascular outcomes (6).

Carotid intima-media thickness (CIMT) is a non-invasive diagnostic tool for detecting subclinical atherosclerosis in cardiovascular structures. Increased CIMT in obese children was found to be strongly associated with cardiovascular risk factors (7). A prolonged QTc was found to be associated with increased CIMT in obese children (5). This suggests a possible relation among obesity, subclinical atherosclerosis, and ventricular repolarization impairment.

Another impairment because of obesity is the development of non-alcoholic fatty liver disease (NAFLD). This is the leading

Address for Correspondence: Dr. Hüseyin Ede, Bozok Üniversitesi Tıp Fakültesi, Kardiyoloji Anabilim Dalı, Adnan Menderes Bulvarı No:44 66200 Yozgat-*Türkiye*
Phone: +90 505 671 11 04 Fax: +90 354 212 3739 E-mail: huseyinede@gmail.com
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cause of chronic liver disease in children worldwide (8). Hepatic tissue is one of the major ectopic sites where lipids may be stored easily in obese subjects. Ectopic fat accumulation takes place, particularly when the energy-storing capacity of fatty tissue is overloaded, resulting in increased net lipid deposition in non-adipose organs, thereby leading to lipotoxicity and insulin resistance (9).

As shown in adults, children and adolescents with hepatic steatosis manifest impaired glucose and lipid metabolism (10). Therefore, NAFLD appeared to be the hepatic component of metabolic syndrome and a cardiovascular risk factor (11). The relation between QTc and hepatic steatosis has not been thoroughly studied in children. Therefore, herein, we aimed to study the relation among QTc, hepatic steatosis, and CIMT in obese children.

Methods

Subjects

A prospective cross-sectional study was conducted between August 2013 and September 2014 at the Bozok University Training and Research Hospital. Informed consent of each subject and their caregivers and an approval from the local Ethical Committee were obtained. Otherwise healthy children aged between 6 and 16 years who were admitted to the pediatric department were enrolled in the study. Subjects with obesity owing to endocrinologic disorders or endogenous reasons, cancer, active infection, active inflammatory disease, connective tissue disorder, diabetes mellitus, arterial hypertension, kidney failure [glomerular filtration rate (GFR) of <60 mL/min/1.73 m^2 calculated using GFR=0.55 x height in cm/serum creatinine in mg/dL (12), hypo- or hyperthyroidism, liver function disorders (transaminase levels more than two times the upper limit of normal level), cigarette use, and alcohol use were excluded. Following exclusion, subjects were classified into obese and non-obese groups in accordance with the criteria described below. None of the subjects in the obese and non-obese groups were under any type of treatment that is known to affect the QTc value. To avoid any potential bias in the study, all anthropometric measurements and electrocardiographic and ultrasonographic evaluations were performed by independent health professionals who were blinded to the subjects' data, as described elsewhere in the text.

All children were weighed on a standing scale without shoes, and their standing height was measured with a stadiometer between 09:00 and 12:00 AM. Following the height and weight measurements, the body mass index (BMI) was calculated for every subject using weight (in kg) divided by the square of the height (in m). The World Health Organization definition (obese=two standard deviations above the mean BMI for age and sex) was used for defining obesity among school-age children and adolescents. Fasting serum glucose (normal range of 70–110 mg/dL At our institution) and serum insulin levels (normal range of 3–17 mIU/L at our institution) of each subject were measured accordingly.

QTc measurement

A 12-lead ECG was performed in the resting position on all the subjects at a standard paper speed of 25 mm/s and a sensitivity of 10 mm/mV. The recording was manually analyzed in lead II by an observer who was certified in ECG analysis and blinded to the clinical data. Each QTc was measured from the beginning of the QRS complex to the end deflection of the T wave. The preceding RR interval was obtained for each QTc. Three distinct QTc were determined according to Bazett's formula, which is used to correct variations in heart rate. The mean value of the three calculated QTc values was used to determine the QTc of each subject for analysis. QTc values at an excess of 440 ms were considered to be prolonged.

Evaluation of hepatic steatosis

Hepatic steatosis was evaluated by the same radiologist who was blinded to the clinical data via an Aloka Prosound A6 (Hitachi Aloka Medical, Japan) ultrasonography equipped with a 7.5 MHz linear array imaging probe. Grading of hepatic steatosis was defined as follows: normal hepatic texture (grade 0): normal liver echogenicity; mild steatosis (grade 1): mild and diffuse increase in fine parenchymal echogenicity but the borders of the diaphragm and portal vein were visualized to be normal; moderate steatosis (grade 2): moderate and diffuse increase in fine parenchymal echogenicity but the diaphragm and portal vein borders were visualized to be mildly damaged; and severe steatosis (grade 3): the diaphragm, portal vein borders, and posterior portion of the right lobe are weakly differentiated or cannot be completely visualized with fine echoes (13).

CIMT measurement

Carotid Doppler ultrasonography was performed by the same radiologist who was blinded to the clinical data via an Aloka Prosound A6 (Hitachi Aloka Medical, Japan) equipped with a 7.5-MHz linear array imaging probe. All measurements were performed while the patient was lying supine, the head was directed away from the side of interest, and the neck was slightly extended. To maximize the lumen diameter, the transducer was located at the longitudinal plane. At a location of 1 cm proximal to the carotid bifurcation, the images were magnified to achieve a higher resolution of detail. The CIMT of the far wall was calculated as the distance between the lumen–intima interface and the media–adventitia interface. Measurements were obtained from five contiguous sites at 1-mm intervals bilaterally and the average of all measurements of the patient was used for statistical analyses.

Statistical analyses

The SPSS for Windows 18.0 package program was used for statistical analyses. Continuous variables with a normal distribu-

tion were expressed as the mean±SD, whereas those without a normal distribution were shown as the median [interquartile range (IQR), 25^{th}–75^{th} percentile]. Categorical variables were shown as frequencies (%). The normality of variables was analyzed by the Kolmogorov–Smirnov test. Except for QTc all other variables were not normally distributed. Pearson's chi-squared or Fisher's exact tests were used to analyze categorical variables. The significance of difference between the groups with respect to QTc was tested using Student's t-test, whereas the Mann–Whitney U-test was used for continuous variables without a normal distribution to analyze the difference between the groups. Spearman correlation analysis was used to establish the association between continuous variables. A p value of <0.05 was considered to be statistically significant.

Results

The study was conducted between August 2013 and September 2014 at the Bozok University Training and Research Hospital where 53 obese children (22 boys, 31 girls) and 53 non-obese children (24 boys, 29 girls) were enrolled in the study consecutively. The age and gender distribution were statistically similar across the groups (p value of 0.647 and 0.695, respectively) (Table 1). The median BMI values of the obese and non-obese groups were 27.4 (26.2–30.4) and 16.5 (14.5–19.5) kg/m^2, respectively (p<0.001; z score, -8.837). The median CIMT value of the obese group was higher than that of the non-obese group (p<0.001; z score, -7.714). Similarly, the QTc value of the obese group was more prolonged than that of the non-obese group (p<0.001). Among the 106 subjects, 11 children (10 obese, 1 non-obese) had a prolonged QTc value. The obese group had a higher frequency of prolonged QTc compared to the non-obese group (p=0.008). Some 81.1% of the obese group (n=43) and 7.5% of the non-obese group (n=4) were found to have either grade 1 or 2 hepatosteatosis in their ultrasonographic examinations (p<0.001). The median age of subjects without hepatosteatosis (n=59) was similar to that of subjects with hepatosteatosis of grade 1 or 2 (n=47) [10 years (IQR 8–10) vs. 12 years (IQR 10–14), respectively; p=0.097; z score, -1.658], but subjects with hepatosteatosis of any degree had a higher CIMT value compared to subjects without hepatosteatosis [0.65 mm (IQR 0.60–0.80) vs. 0.95 mm (IQR 0.90–1.10), respectively; p<0.001; z score, -8.122]. Similarly, the average QTc value of subjects with hepatosteatosis was higher than that of subjects without hepatosteatosis (422±20 vs. 398±21 ms, respectively; p<0.001). We also found that the QTc value was well correlated with the CIMT value among children aged 16 years and below (p<0.001, r=0.476).

The serum insulin level of obese children was significantly higher than that of non-obese children, whereas the serum glucose levels of both obese and non-obese children were statistically similar (Table 1). In correlation analyses, CIMT values were significantly correlated to serum insulin levels (r=0.482; p<0.001) but not to serum glucose levels (r=0.072; p=0.478). Similarly to these findings, QTc values were statistically associated with serum insulin levels (r=0.382; p<0.001) but not to serum glucose levels (r=0.060; p=0.553). Subjects with hepatosteatosis of grade 1 or above (n=47) had significantly higher serum insulin compared to subjects without hepatosteatosis (n=59) (p<0.001; z score, -4.411) but similar serum glucose levels (p=0.195; z score, -1.294). In subgroup analyses performed for obese subjects, obese subjects with hepatosteatosis of grade 2 (n=15) [16.3 mIU/L (IQR 10.4–22.0)] had higher serum insulin compared to obese subjects without hepatosteatosis (n=10) [11.6 mIU/L (IQR 6.4–14.8)] but the relation did not reach the level of significance (p=0.052; z score, -1.942).

Table 1. Clinical data of the subjects

	Obese group (n=53)	Non-obese group (n=53)	
Age, years	11 (8–14)	10 (9–14)	*P*=0.647 z score: -0.458
Male/female, %	22/31 (42/58)	24/29 (45/55)	*P*=0.695
Height, cm	150 (133–160)	138 (127–160)	*P*=0.185 z score: -1.325
Weight, kg	64 (47–73)	31 (26–49)	*P*<0.001 z score: -6.825
BMI, kg/m^2	27.4 (26.2–30.4)	16.5 (14.5–19.5)	*P*<0.001 z score: -8.837
CIMT, mm	0.95 (0.90–1.1)	0.65 (0.59–0.79)	*P*<0.001 z score: -7.714
QTc value, ms	419±20	399±23	*P*<0.001
Hepatic steatosis, %			
Grade 0	10 (18.9)	49 (92.5)	*P*<0.001
Grade 1	28 (52.8)	4 (7.5)	
Grade 2	15 (28.3)	0 (0)	
Grade 3	0 (0)	0 (0)	
Glucose, mg/dL	90 (86–97)	90 (84–94)	*P*=0.384 z score: -0.871
Insulin, mIU/L	11.5 (8.8–17.8)	5.6 (3.4–9.7)	*P*<0.001 z score: -5.006

Student's t test for QTc, Mann-Whitney U test for the other continuous varibales, chi-square or Fisher's exact tests. BMI - body mass index; CIMT - carotid intima-media thickness; QTc - corrected QT interval. QTc values are expressed as the mean±SD, whereas other continuous variables are expressed as the median (interquartile range 25^{th}–75^{th} percentile).

Discussion

In this study, we found that obese children had higher CIMT values, a higher frequency of hepatosteatosis, and more prolonged QTc values compared to non-obese children. In addition,

we found that both an increase in CIMT and the presence of hepatosteatosis were significantly correlated to prolonged QTc values in obese children.

Obesity is an emerging health problem among children globally and, according to US data, the prevalence of obesity in the country tripled, making it a public health problem. It is estimated that about 30% of American children are overweight (14). It has a strong relation with atherosclerotic cardiovascular diseases. An increase in CIMT is a sign of subclinical atherosclerosis. Its clinical importance has been strongly proven in the adult population. Another important issue in obese children is sudden cardiac death. Atherosclerosis-related cardiovascular events and arrhythmias may be some of the possible causes. Sudden cardiac death without obvious structural abnormalities has been reported in obese children (4). QTc prolongation can be one of the potential reasons for arrhythmic deaths. In this study, we demonstrated the relation between CIMT and QTc in obese children.

Hepatic steatosis is another impairment because of obesity. It is the leading cause of chronic liver disease in children worldwide (8). Fat accumulation in the liver results in lipotoxicity and insulin resistance (9). As is known, insulin resistance is directly related to atherosclerotic impairment in the cardiovascular system. In this study, we aimed to show the relation between hepatic steatosis, CIMT, and QTc in children.

QTc can be measured using either a resting-state 12-lead electrocardiogram or 24-h ambulatory Holter data. Both methods have been shown to be reliable in obtaining information about QTc (5, 6). Here we used a simple resting 12-lead electrocardiogram to obtain data related to QTc.

In the study by Güven et al. (5), the relationship between CIMT and QTc was researched. They found that the presence of metabolic syndrome among obese children did not affect either CIMT or QTc values. However, they found that QTc was more prolonged among obese children compared to non-obese healthy children. This meant that obesity itself had more impact on the QTc value rather than the presence of metabolic syndrome (5). Here we classified our study population into obese and non-obese children groups without any further subgrouping of obese subjects. In our study we also found increased CIMT values and QTc values in obese subjects compared to non-obese subjects ($p<0.001$ for both analyses). In addition, QTc values were well correlated to CIMT values in all the study population ($p<0.001$; $r=0.476$). These findings imply that obesity may be related to significant impairment in vascular structures.

In the literature, pathology studies have revealed that atherosclerosis is an early-onset process starting from childhood, with fatty streaks found in the aorta and the coronary and carotid arteries of children (15-17). Early evaluation of vascular impairment is therefore crucial to prevent future vascular events because subclinical atherosclerosis can be reversed if diagnosis and intervention are conducted early. Torun et al. (17) found that subclinical atherosclerosis was more prominent among children with NAFLD. In obese children, the likelihood of having atherosclerosis was more than six times higher in children with hepatic steatosis than in those without fatty liver (17, 18). Therefore, the presence of fatty liver increases the risk of having atherosclerosis. The other sign of subclinical atherosclerosis is an increase in CIMT. In our study (n=106) we also found that CIMT was well correlated with the grade of hepatic steatosis ($p<0.001$; $r=0.811$). Among all children, patients with hepatic steatosis of any degree (n=47) had higher CIMT compared to patients with normal liver (n=59), whereas they did not differ in age or gender distribution ($p=0.097$ and 0.812, respectively). In obese children, subjects with grade 2 hepatosteatosis (n=15) had significantly higher CIMT values than subjects with normal liver (n=10) [1.10 mm (IQR 0.95–1.15) vs. 0.80 mm (IQR 0.80–0.90), respectively; $p<0.001$; z score, -3.693]. All these findings support the existing data in the literature. Therefore, it was observed that subjects with hepatic steatosis had a greater atherosclerotic burden and this tendency seemed to increase further in obese subjects.

The relationship between hepatic steatosis and QTc in children has not been studied before. However, the presence and severity of ultrasonographically detected NAFLD was found to be associated with an increased QTc interval among diabetic adult patients (19). Therefore, we searched for the relationship between the QTc value and hepatic steatosis in children. We found that hepatic steatosis was well correlated with the QTc value among all children ($p<0.001$; $r=0.551$). For obese subjects, patients with hepatic steatosis of any degree (n=43) had a more prolonged QTc compared to those without (n=10) (423±20 vs. 404±12 ms, respectively; $p=0.006$; z score, -2.751). Similarly, obese children with grade 2 hepatosteatosis had a more prolonged QTc than obese children with normal liver (435±19 vs. 404±12 ms, respectively; $p<0.001$; z score, -3.719). The number of cases with prolonged QTc was also higher in children with hepatosteatosis compared to children without ($p=0.002$). All these findings imply that obese children had a higher risk of fatty liver and those with hepatosteatosis had a higher risk of prolonged QTc.

Increased insulin resistance among morbidly obese young adults was found to be related to higher CIMT (20). We also found that higher serum insulin was correlated with higher CIMT values among children. A similar correlation was not found between glucose and CIMT, as the study included non-diabetic children with relatively lower BMI. Similarly, prolonged QTc values were associated with increased serum insulin levels. Hepatosteatosis is related to the formation of both hepatic insulin resistance and type 2 diabetes but its role in obese children has not been investigated extensively (21). Here, we showed that children with hepatosteatosis of grade 1 or above had significantly higher serum insulin compared to children without hepatosteatosis. However, the relation was weak among obese children. This may be because of the smaller number of obese subjects with hepatosteatosis of grade 2 in the study, as

it was known that the severity of hepatosteatosis was well correlated to the degree of insulin resistance (21).

Study limitations

The number of obese and non-obese children was too low to perform subgroup analyses. Also, the study population did not include cases of grade 3 hepatosteatosis. This may be because of the inclusion of moderately obese children in the randomization process rather than morbidly obese children. The study was cross-sectional; therefore, further follow-up studies are needed to detect the long-term outcome of prolonged QTc among obese children.

Conclusion

We demonstrated that obese children had a tendency to have higher CIMT and QTc values and more frequent hepatosteatosis compared to non-obese children and that both increased CIMT and the presence of hepatosteatosis were strongly correlated to prolonged QTc values in obese children. Therefore, we concluded that it may be beneficial to carry out measurements of QTc in the presence of hepatosteatosis and/or increased CIMT among obese children with the aim of detecting cardiovascular effects of obesity.

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