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Research Article

Myocardial Performance Index and Carotid Intima-Media Thickness in Children with Metabolically Healthy and Metabolically Unhealthy Obesity

Civilibal Tang et al. Cardiovascular Changes in Children with Obesity

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What is already known on this topic?
Obesity in children increases cardiovascular risk factors. MPI and cIMT are established measures of subclinical cardiovascular abnormalities. Studies have shown that obesity impacts MPI and cIMT but hasn't clearly identified BMI and WC as specific predictors.

What this study adds?
Unlike previous research, our findings identify BMI and WC as independent predictors of increased MPI and cIMT, highlighting obesity severity as a risk factor. Utilizing advanced diagnostics like tissue Doppler imaging for MPI and high-resolution ultrasonography for cIMT, we provide robust evidence advocating their early incorporation in clinical practice.

Abstract
Objective: This study aimed to compare the myocardial performance index (MPI) and carotid intima-media thickness (cIMT) of children who are metabolically healthy obese (MHO) and metabolically unhealthy obese (MUO) with children without obesity.
Methods: This study included 62 obese patients between 6 and 17 years of age and 30 age- and gender-matched healthy children. Two groups of obese patients were created: MUO (n=30) and MHO (n=32).
Results: Compared to controls, the MPI and cIMT of the obese groups were significantly greater. However, there was no significant difference in MPI and cIMT between the MUO and MHO groups. Additionally, there were independent associations between higher MPI and body mass index-SDS (BMI-SDS) (β=0.312, p=0.002) and between higher cIMT and waist circumference-SDS (WC-SDS) (β=0.371, p=0.003).
Conclusion: The primary outcome of the study indicates that while both MPI and cIMT values are elevated in obese children compared to non-obese controls, there is no significant difference between MUO and MHO groups. This suggests that obesity itself, irrespective of metabolic health, is associated with increased cardiovascular risks. BMI-SDS and WC-SDS are useful markers for identifying children at cardiovascular risk, emphasizing the need for early intervention in pediatric obesity.
Keywords: BMI, childhood obesity, waist circumference

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Introduction

Childhood obesity is a global problem leading to various endocrine, metabolic, and cardiovascular comorbidities. Changes in eating habits and a decrease in physical activity parallel to modern life have turned obesity into an endemic disease (1).
Adults with obesity who have none of the risk factors such as dyslipidemia, insulin resistance (IR), and hypertension are called metabolically healthy obese (MHO). In contrast, those who have one or more of these risk factors are defined as metabolically unhealthy obese (MUO) (2, 3). First described and investigated in adults with obesity, these phenotypes have also been extensively studied and confirmed in children and adolescents with obesity (3). Obesity plays an important role in the development of metabolic syndrome (MS). However, not all adults and children with severe obesity have MS or MUO.
The most common cardiovascular disorders due to obesity are increased left ventricular mass, myocardial dysfunction, and increased carotid intima-media thickness (cIMT) (4, 5). These early subclinical cardiovascular diseases (CVD) have been shown in both pediatric and adult obese (6-9). However, the impact of obesity-related conditions such as insulin resistance, dyslipidemia, and arterial hypertension on the development of these CVDs is not yet clear in children.
In recent years, tissue Doppler imaging (TDI) has been more frequently preferred to evaluate early changes in left ventricular systolic and diastolic function. Myocardial performance index (MPI) measured with this method is less affected by age, heart rate, or preload compared to conventional pulsed wave Doppler (cPWD) echocardiography (10, 11). The cIMT is a well-known marker of the atherosclerotic process and is a valuable indicator for long-term follow-up of children at high risk of atherosclerosis (12, 13).
It has been widely shown that MPI and cIMT are increased in adults with obesity. However, to our knowledge, there are limited studies investigating the relationship of obesity-related metabolic factors with the increase in MPI and cIMT in children and adolescents. This study aimed to compare MPI and cIMT of metabolically healthy and metabolically unhealthy obese and to evaluate the effects of obesity-related metabolic factors.

Materials and methods

Study design

This study included 62 obese patients between 6 and 17 years of age in our pediatric endocrinology outpatient clinic. The patients with obesity were divided into two groups MUO (n=30) and MHO (n=32). The control group comprised 30 age- and gender-matched healthy children and adolescents.

A power analysis was conducted to ensure that our sample size was adequate for detecting significant differences in myocardial performance index (MPI) and carotid intima-media thickness (cIMT) between metabolically healthy obese (MHO) and metabolically unhealthy obese (MUO) children, as well as non-obese controls. Based on previous studies in similar populations, an effect size (Cohen's d) of 0.5 was estimated for the cardiovascular measures. Using a two-sided alpha level of 0.05 and a desired power of 0.80, G*Power software calculations indicated that a minimum of 27 participants per group would be required to achieve sufficient statistical power.

This study was approved by the Local Ethics Committee (decision no: 2019/57, date: 22.03.2019). Written informed consent was obtained from the parents of patients and controls. The research related to human use has complied with all the relevant national regulations, and institutional policies and by the tenets of the Helsinki Declaration.

Patients with missing data, secondary obesity, any kind of chronic disease or systemic diseases, and use of medications known to alter blood pressure or lipid or glucose metabolism were excluded. Control subjects were selected from healthy children admitted to the hospital for mild illnesses with a BMI between the 25th and 75th percentile.

Height was measured to the nearest millimeter by a wall-mounted stadiometer, and weight was measured to the nearest 100 g by SECA digital scale with minimal clothes and without shoes. Body mass index (BMI) was calculated by dividing the body weight in kilograms by height in meters squared. On the BMI reference curve, which was prepared for Turkish children and adjusted for age and gender, those with BMI values at or above the 95th percentile were defined as "obese" (14). Waist circumference (WC) was measured using a nonelastic tape at the level of the umbilicus with the child standing and breathing normally. Waist measurements were evaluated using the percentile curves for WC of healthy Turkish children (15). Standard deviation scores (SDS) of BMI and WC were computed using the least mean square (LMS) method and the references for Turkish children (15, 16).

Blood pressure measurements

Blood pressure (BP) measurements were made three times at 2-minute intervals on the right arm, in a sedentary patient after at least five minutes of rest, by auscultation method (ERKA®, Germany) with appropriate cuff size according to the age and constitution of the child. The last two BPs were averaged for analysis. Systolic BP (SBP) and diastolic BP (DBP) measurements of all patients were evaluated according to the American Academy of Pediatrics 2017 (AAP-2017) hypertension guideline and based on these data, we calculated the blood pressure SDS-score (16). SBP and/or DBP values that were >90th percentile were defined as elevated blood pressure, and values ≥95th percentile were defined as hypertension.

Biochemical measurements

Glucose, insulin, triglycerides, total cholesterol, low-density lipoprotein (LDL)-cholesterol, and high-density lipoprotein (HDL)-cholesterol were measured in blood samples taken in the morning after a 12-hour fasting. Blood glucose levels were measured by the glucose oxidase method and serum lipid profiles were measured using routine enzymatic methods. Insulin measurements were made by the immunofluorometric method (Modular E170 analyzer, Roche Diagnostics, Mannheim, Germany). The homeostasis model assessment of insulin resistance (HOMA-IR) was calculated to estimate insulin resistance using the following formula: (HOMA-IR= fasting plasma glucose (mg/dL) x fasting plasma insulin (μU/mL)/405).

Assessment of metabolic status

The definition of MHO in children and adolescents is controversial and heterogeneous. There are two commonly used definitions for pediatric metabolic syndrome; modified National Cholesterol Education Program (NCEP) criteria and modified International Diabetes Federation (IDF) criteria (17, 18). Metabolic risk factors in both definitions are similar, but the cut-offs of the components are different. Moreover, the definitions are not clear for children under 10 years of age. For this reason, Damanhoury et al (3). collaborated with 46 international experts, they published a classification on the definitions of MHO and MUO in children in 2018.

According to this classification, standard MUO phenotype was defined as the presence of at least one of the following risk factors: SBP and/or DBP> 90th percentile, fasting blood glucose >100 mg/dl, HDL cholesterol <40 mg/dl, triglycerides >100 mg/dl (children <10 years) or >130 mg/dl (children>10 years); individuals who did not meet any of the above-mentioned criteria were considered as MHO. Additionally, following the suggestions of some authors, we included insulin resistance, defined by the homeostasis model assessment of insulin resistance (HOMA-IR) with thresholds >2.5 for prepubertal and >3.0 for pubertal (Tanner stage ≥2) participants, in our classification criteria (19, 20). Detailed cut-off values and thresholds applied in this study, especially for age-specific thresholds (Table 1).

Echocardiographic measurements

Echocardiographic assessments were performed using the General Electric Medical Systems ViVid 7 Pro dimension echocardiography device (GE Vingmed Ultrasound AS, Horten, Norway) equipped with tissue Doppler imaging technology. All measurements were performed according to American Society of Echocardiography guidelines (21). Participants were examined in the left lateral position by the same experienced pediatric cardiologist blinded to clinical and laboratory outcomes. TDI was obtained from the apical four-chamber view, where the sample volume was placed at the septal and lateral sides of the mitral annulus.

For the calculation of MPI, systolic myocardial velocity (Sm), ejection time (ET), and isovolumetric contraction time (IVCT) as systolic parameters, and early (Em) and late (Am) diastolic velocities, the Em/Am ratio, and the isovolumetric relaxation time (IVRT) as diastolic parameters were measured by TDI. We measured the IVRT from the end of the S-wave to the beginning of the E-wave and IVCT from the beginning of the first positive deflection after the Q-wave to the onset of the S-wave. ET was measured from the beginning to the end of the S-wave. The MPI (IVRT + IVCT/ET) was calculated to assess the LV global (systolic+diastolic) function. The results recorded from three cardiac cycles were averaged.

Vascular assessment

The cIMT was measured using B-mode high-resolution ultrasonography (Toshiba Aplio 300 Ultrasound, Japan). Measurements were performed in the supine position, with the neck slightly hyperextended, and 1 to 2 cm proximal to the bifurcation of both common carotid arteries. The SDSs for cIMT were calculated using the LMS method and height-specific normative values (22).

Statistical Analysis

All statistical evaluations were performed using the SPSS software version 26.0 (IBM Inc., Armonk, NY, USA). The visual (histogram, probability plots) and analytic methods (Kolmogorov–Smirnov) were used to evaluate the distribution of continuous variables. Discrete variables are expressed as counts (percentage), continuous variables with normal distribution were calculated as mean±SD, and continuous variables with non-normal distribution as median. Differences in the means of MUO, MHO, and control subjects were initially tested by ANOVA. To identify specific group differences, post-hoc comparisons were conducted using the Tukey HSD test. Associations between variables were assessed by Pearson or Spearman's analysis, depending on the distribution type of the variable. The variables that showed a p-value of 0.05 in the univariate analysis were tested in a stepwise linear regression analysis for the assessment of risk factors. A $p<0.05$ was considered statistically significant for all statistical evaluations.

Results

Of the 62 children with obesity included in the study, 32 (51.6%) were MHO and 30 (48.4%) patients had MUO. The control group consisted of 30 healthy normal-weight children. There were no significant differences between the groups regarding age and gender. Post-hoc comparisons using the Tukey HSD test revealed that BMI, BMI-SDS, WC, WC-SDS, DBP, and DBP-SDS were similar in MUO and MHO

groups, but significantly higher than the controls. SBP, SBP-SDS, and HOMA-IR were significantly different between the three groups, while glucose and LDL levels were similar. Triglyceride was significantly higher and HDL lower in the MUO group compared to the other two groups (Table 2).

When tissue Doppler imaging and carotid ultrasonography findings are evaluated, while the ET and Em/Am values of the three groups were statistically significantly different, the Sm, IVCT, Em, and IVRT were similar. The MPI and cIMT means of obese groups were significantly higher than controls. However, there were no differences between MPI and cIMT in MUO and MHO patients (Table 3).

All clinical and laboratory results were analyzed by univariate analysis to identify cardiometabolic risk factors affecting LV diastolic dysfunction (increase in MPI) and subclinical atherosclerosis (increase in CIMT) in patients with obesity (Table 4). Both MPI and cIMT were positively correlated with BMI-SDS, WC-SDS, SBP-SDS, and DBP-SDS. Additionally, MPI was found to be positively related to HOMA-IR, and cIMT was found to be negatively correlated with HDL. Finally, we found an independent association between high MPI and BMI-SDS (β=0.312, p=0.002), and between CIMT and WC-SDS (β=0.371, p=0.003) in stepwise linear regression analysis (Table 5).

Discussion

This study showed that MPI and cIMT increased in children both with MUO and MHO and that BMI and WC were important predictors of these increases. Our findings reinforce the idea that the severity of obesity in children may be the important risk factor for increased MPI and cIMT, independent of metabolic abnormalities.

Left ventricular hypertrophy, systolic/diastolic dysfunction, and increased carotid intima-media thickness, have been recognized as subclinical indicators of cardiovascular disease (CVD) in children and adults with obesity (9, 13, 23-25). Detection of cardiovascular structure and functional changes during the subclinical period in obese patients is important in clinical follow-up and in determining the prognosis. Our knowledge about subclinical LV diastolic dysfunction and atherosclerosis in children with obesity is more limited than in adults. The strongest aspect of this study is the comparison of MPI and cIMT measurements of children with (MUO) and without (MHO) hypertension, hyperglycemia, insulin resistance, or dyslipidemia.

In children and adults with obesity, cardiac structural and functional changes are frequently investigated using the cPW-TDI echocardiography method (6, 8). However, there are limited studies on MPI, which is an indicator of diastolic dysfunction measured by the TDI method. Obesity-related increased preload volume causes significant impairments in diastolic myocardial velocities (1, 26). Similar to previous studies, we detected a significant increase in Am wave velocity and therefore a significant decrease in the Em/Am ratio. In addition to the low Em/Am ratio, we found that the MPI was significantly higher in the MUO and MHO groups compared to individuals without obesity. This increase was caused by the shortening of ET without significant changes in tissue Doppler-derived IVRT and IVCT.

TDI-derived MPI is a relatively new parameter used to evaluate systolic and diastolic myocardial function. Also, MPI reflects an increase in LV filling pressure and a decrease in compliance (10, 27, 28). Our data are consistent with previous MPI studies in children with obesity (26, 29-31).

The cause of this myocardial dysfunction remains unclear, although the severity and duration of obesity, chronic volume overload, insulin resistance, and hemodynamic and metabolic changes have all been implicated (32). LV systolic and diastolic dysfunction secondary to obesity has been associated with metabolic syndrome-related hypertension, dyslipidemia, and insulin resistance accompanying obesity. Some studies have shown that subclinical myocardial dysfunction revealed by MPI is correlated with BMI and insulin resistance (11, 29, 31). In our study, although MPI was significantly higher in children with MUO and MHO than in children without obesity, it was observed that there was no difference between these two obese groups. Additionally, regression analysis showed that the high MPI of our children with obesity was independently associated only with BMI-SDS. Therefore, we can suggest that the increase in MPI in children with obesity may be related to the severity of obesity rather than metabolic abnormalities and that the risk of left ventricular myocardial dysfunction is higher in children with morbid obesity.

Childhood obesity is associated with changes in cardiac structure and function, as well as various markers of subclinical atherosclerosis such as endothelial dysfunction, carotid intima-media thickening, and increased arterial stiffness. Similar to our results, elevated cIMT has been documented in numerous investigations involving children with obesity (13, 33, 34). This finding is indicative of the presence of subclinical atherosclerosis in patients with obesity.

There is no consensus on the results regarding the increase in cIMT in patients with and without metabolic syndrome. Although some studies report higher cIMT in children with MS, studies also reporting that cIMT is not different between obese children with and without MS (13, 35). In agreement with the studies of Zhao et al. (33) and Parello et al. (34), we found that cIMT values of obese groups were higher than controls, but cIMT was not different between obese groups with MUO and MHO. Therefore, we believe that obesity may be an important risk factor for increased cIMT even in the absence of metabolic abnormalities. The lack of difference in MPI and cIMT between MHO and MUO groups may be influenced by factors such as the overall degree of obesity, genetic predispositions, lifestyle factors, and underlying subclinical inflammation that can affect cardiovascular outcomes regardless of metabolic health status.

On the other hand, although increased cIMT was positively correlated with BMI-SDS, WC-SDS, SBP-SDS, and DBP-SDS and was negatively associated with HDL-cholesterol in the present study, we determined that WC-SDS was the only independent factor responsible for high cIMT. Similar to our study, Sonmez et al. also reported that a high CIMT was independently associated with higher waist circumference in children with obesity (13). Therefore, we believe that obesity may be an important risk factor for increased cIMT even in the absence of metabolic abnormalities.

BMI and WC are the most common anthropometric measures for predicting abdominal obesity. In recent years, an increasing number of studies support the use of WC instead of BMI in children with obesity (36, 37). Besides, derived waist circumference cut points for children to identify cardiovascular risk factors have been suggested in some countries (38, 39).

This study has some limitations. First, our study is a cross-sectional study with a relatively small number of cases. Further prospective, long-term studies with larger number of patients are needed to determine the effects of obesity on myocardial functions and atherosclerosis. Lack of obesity duration and weight status history is another limitation.

Conclusions

We demonstrated the increased MPI and cIMT that markers of subclinical diastolic dysfunction and atherosclerosis in children with obesity. The similarity of these two markers between MUO and MHO patients and the detection of an independent relationship between MPI and BMI-SDS, and cIMT and WC-SDS indicate that MPI and cIMT in children are affected by the severity of obesity rather than metabolic abnormalities. Our results demonstrate the diagnostic value of MPI and cIMT for routine and widespread use in children with obesity due to their ease of application and reproducibility. Moreover, BMI and WC appear to be valuable and easy indicators of early cardiovascular disease in children with obesity. Long-term multicenter prospective studies will provide better insight into early screening of cardiovascular risk factors in children with obesity.

Author Contributions

Author 1: Conceptualization (lead); writing – original draft (lead); formal analysis (lead); writing – review and editing (equal). Author 2: Methodology (lead); writing – review and editing (equal). Author 3: Software (lead); writing – review and editing (equal). Author 4: Conceptualization (supporting); Writing – original draft (supporting); writing – review and editing (equal). All authors were involved in the final approval of the submitted version and agreed to be accountable for all aspects of the work.

Declaration of Conflicting Interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article

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Table 1. Metabolic Risk Factor Cut-off Values Used for Classification of MUO

Parameter	Age Group	Threshold
Systolic or Diastolic BP	All ages	>90th percentile
Fasting Blood Glucose	All ages	>100 mg/dL
HDL Cholesterol	All ages	<40 mg/dL
Triglycerides	<10 years	>100 mg/dL
Triglycerides	≥10 years	>130 mg/dL
HOMA-IR	Prepubertal	>2.5
HOMA-IR	Pubertal (Tanner ≥2)	>3.16

BP: Blood pressure, HDL: high density lipoprotein, LDL: low density lipoprotein, HOMA-IR: homeostatic model assessment for insulin resistance

Table 2. Demographic and anthropometric characteristics and laboratory findings of the study groups

	MUO (n=30)	MHO (n=32)	Control (n=30)	p
Age (year)	13.3±2.4	13.2±3.1	12.3±2.3	0.160
Male n (%)	16 (53.3)	17 (53.1)	16 (53.3)	0.992
BMI (*kg/m²*)	33.3±5.7	29.8±4.4	19.3±2.2**	<0.001
BMI-SDS	2.22±0.92	2.50±0.73	0.02±0.57**	<0.001
WC (cm)	97.9±13.8	98.1±12.9	76.8±8.9**	<0.001
WC-SDS	2.12±0.71	2.26±0.79	0.65±0.82**	<0.001
SBP (mmHg)	131.8±14.3	125.6±12.6	108.9±7.3	<0.001*
SBP-SDS	1.87±0.70	1.44±0.84	0.40±0.37	<0.001*
DBP (mmHg)	86.2±10.8	82.0±9.1	67.2±5.3**	<0.001
DBP-SDS	1.83±0.71	1.61±0.68	0.48±0.40**	<0.001
Triglycerides (mg/dl)	134.1±76.3**	101.9±42.1	96.0±22.0	0.013
HDL (mg/dl)	39.2±6.8 **	49.3±9.9	49.3±9.8	<0.001
LDL (mg/dl)	81.9±20.5	80.0±20.1	74.6±18.9	0.422
Glucose (mg/dl)	84.0±7.1	82.9±4.4	83.2±5.9	0.759
HOMA-IR	5.30±2.25	2.47±0.79	1.57±0.48	<0.001*

*The results of all groups were statistically different from each other.
**The results were significantly different from the other two groups
MUO: metabolically unhealthy obese, MHO: metabolically healthy obese, BMI: body mass index, SDS: standard deviation scores, WC: waist circumference, SBP: systolic blood pressure, DBP: diastolic blood pressure, HDL: high density lipoprotein, LDL: low density lipoprotein, HOMA-IR: homeostatic model assessment for insulin resistance

Table 3. Comparison of tissue Doppler imaging and carotid ultrasonography findings

	MUO (n=30)	MHO (n=32)	Control (n=30)	p
Systolic parameters				
Sm (cm/s)	9.90±1.01	9.83±1.05	9.76±1.12	0.717
ET (ms)	253.0±34.5	262.1±36.5	288.3±34.2	0.001*
IVCT (ms)	33.2±9.6	33.3±8.0	33.0±10.8	0.990
Diastolic parameters				
Em (cm/s)	18.0±4.2	18.0±4.0	17.5±2.7	0,818
Am (cm/s)	12.8±4.7	13.9±3.1	9.9±1.8**	<0.001
Em/Am ratio	1.50±0.35	1.32±0.23	1.81±0.24	<0.001
IVRT (ms)	24.3±5.0	26.1±6.0	23.4±2.7	0.083
MPI	0.23±0.07	0.23±0.06	0.20±0.05**	0.004
cIMT (μm)	389.0±57.3	385.9±55.7	369.3±48.9**	0.003

*The results of all groups were statistically different from each other.
**The results were significantly different from the other two groups
MUO: metabolically unhealthy obese, MHO: metabolically healthy obese, Sm: systolic myocardial velocity, ET: ejection time, IVCT: isovolumetric contraction time, Em: early diastolic velocity, Am: late diastolic velocity, IVRT: isovolumetric relaxation time, MPI: myocardial performance index, cIMT: carotid intima media thickness

Table 4. Risk factors of myocardial performance index and carotid intima-media thickness

	MPI		cIMT	
	R	p	r	p
BMI-SDS	0.289	0.003	0.239	0.010
WC-SDS	0.262	0.006	0.248	0.008
SBP-SDS	0.185	0.049	0.194	0.032
DBP-SDS	0.195	0.031	0.222	0.017
HOMA-IR	0.237	0.011		
HDL			-0.210	0.022

Spearman's correlation analysis (only significant correlations shown)
MPI: myocardial performance index, cIMT: carotid intima media thickness, BMI: body mass index, SDS: standard deviation scores, WC: waist circumference, SBP: systolic blood pressure, DBP: diastolic blood pressure, HOMA-IR: homeostatic model assessment for insulin resistance, HDL: high density lipoprotein.

Table 5. Independent predictors of myocardial performance index and carotid intima-media thickness in all obese patients.

Dependent variable	Independent variable	β-Coefficient	SE	P value
MPI	BMI-SDS	0.312	0.011	0.002
cIMT	WC-SDS	0.371	0.041	0.003

MPI: myocardial performance index, cIMT: carotid intima media thickness, BMI: body mass index, SDS: standard deviation scores, WC: waist circumference