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ORIGINAL ARTICLE

Importance of Plasma N-Terminal Pro B-Type Natriuretic Peptide, Epicardial Adipose Tissue, and Carotid Intima-Media Thicknesses in Asymptomatic Obese Children

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Abstract This study aimed to analyze the variations of N-terminal pro B-type natriuretic peptide, epicardial adipose tissue thickness, and carotid intima-media thickness in childhood obesity. The study participants consisted of 50 obese children in the study group and 20 nonobese children referred for evaluation of murmurs who proved to have an innocent murmur and were used as control subjects. All the subjects underwent transthoracic echocardiographic examination for determination of left ventricular systolic function and mass index, myocardial tissue rates, and myocardial performance index. Epicardial adipose tissue thickness and carotid intima-media thickness also were measured during echocardiography. Serum N-terminal pro B-type natriuretic peptide levels were measured at the time of evaluation. The left ventricle mass index was 40.21 ± 10.42 g/m^2 in the obese group and 34.44 ± 4.51 g/m^2 in the control group ($p > 0.05$). The serum N-terminal pro B-type natriuretic peptide level was 109.25 ± 48.53 pg/ml in the study group and 51.96 ± 22.36 pg/ml and in the control group ($p = 0.001$). The epicardial adipose tissue thickness was 5.57 ± 1.45 mm in the study group and 2.98 ± 0.41 mm in the control group ($p = 0.001$), and the respective carotid intima-media thicknesses were 0.079 ± 0.019 cm and 0.049 ± 0.012 cm ($p = 0.001$). The left ventricular systolic and diastolic functions showed no statistically significant correlations with N-terminal pro B-type natriuretic peptide levels, carotid intima-media thickness, or epicardial adipose tissue thickness values. The results show that measurement of serum N-terminal pro B-type natriuretic peptide level, carotid intima-media thickness, and epicardial adipose tissue thickness in asymptomatic obese children is not needed.

Keywords Cardiac dysfunction · Child · Echocardiography · N-terminal pro B-type natriuretic peptide · Visceral adipose tissue

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Childhood and especially adolescent obesity is accompanied with an increased cardiovascular disease risk profile in adulthood [7]. Hypertension, hypercholesterolemia, dyslipidemia, cardiomyopathy, and coronary heart disease are known cardiovascular complications of obesity, together with insulin resistance, diabetes mellitus, and sleep apnea, which often accompany obesity [10, 11, 20].

Obesity may cause cardiac dysfunction even in the absence of childhood hypertension, as reported previously [8]. In addition, both systolic and diastolic dysfunction may ensue [21, 38]. In recent years, researchers have focused on possible risk factors in obese children to allow for early diagnosis of cardiovascular complications and institution of preventive measures.

In this study, carotid intima-media thickness, epicardial adipose tissue thickness, and serum N-terminal pro B-type natriuretic peptide levels of obese children were assessed, similar to assessment for the early diagnosis of cardiovascular complications in adults [19]. The correlations within these parameters and with myocardial performance indices were analyzed, and their possible role in the management of childhood obesity was investigated.

Materials and Methods

Case Selection

The study was conducted prospectively between November 2007 and March 2008. For the series, 50 obese children (age, 125.58 ± 28.66 months; range 66–166 months) and 20 healthy control children (age, 121.30 ± 40.33 months; range, 59–190 months) were enrolled. The 20 healthy age- and sex-matched children selected to be control subjects had been referred for cardiac murmurs detected by auscultation that later proved to be innocent murmurs by clinical and laboratory methods. Children with anemia, chronic conditions, psychiatric illnesses, or administration of medications for any reason were excluded from the study.

A body mass index (BMI) at the 97th percentile determined a diagnosis of obesity, in accordance with the definition of the International Task Force on Obesity in Childhood and population-specific data [4, 6]. Blood pressure was measured by the same investigator using a standard validated protocol. Hypertension was defined as blood pressure values above the 95th percentile for height, age, and sex [30].

The study was conducted in accordance with the guidelines proposed in the Helsinki Declaration and approved by the local ethics committee. Informed written consent was obtained from the parents of each subject.

Echocardiographic Evaluation

Transthoracic echocardiographic examinations was performed using a Acuson Sequoia C256 equipment (Siemens Medical Solutions, Mountain View, CA, USA) with 3.5- and 5-MHz transducers. In all echocardiographic studies, left ventricular systolic functions and left ventricular mass indices were assessed using M-mode, whereas myocardial tissue rates and myocardial performance indices were studied using tissue Doppler methods. The two-dimensional colored Doppler, pulsed-wave Doppler, continuous-wave Doppler, and pulsed-wave tissue Doppler assessments were performed using all possible echocardiographic windows with the subjects lying supine or in the left lateral semirecumbent position.

Concurrent electrocardiographic (ECG) monitoring was provided during echocardiographic studies. In the ECG studies, the period from the beginning of the Q-wave to the end of the T-wave was considered to be ventricular systole and the remainder of the cycle to be ventricular diastole.

The M-mode echocardiographic measurements were performed according to the recommendations of the American Society of Echocardiography from the section obtained at the level of the posterior mitral valve [31]. The left ventricular mass and the left ventricle mass index were calculated using the method of Woythaler and colleagues, which is a modification of the method of Devereux and Reichek. According to this calculation, left ventricular mass is 1.04 ([left ventricular diameter at end diastole + end-diastolic interventricular septum thickness −left ventricular posterior wall thickness at end-diastole]^3 − [left ventricular diameter at end diastole)^3 − 13.6], and left ventricle mass index is the left ventricular mass/body surface area, in which body surface area is 4 × weight + 7/90 + weight [7].

Doppler imaging was performed using a 3-MHz transducer, a pulsed Doppler sample volume of 2–4 mm, and a Nyquist limit adjusted to a velocity rate of 15 to 20 cm/s. The gain was minimized to allow for a clear tissue signal with minimal background noise.

Using the apical four-chamber view, the sample volume was placed at the mitral and tricuspid valve annuli at the left and right ventricular free walls, respectively. The flow samples were recorded while the patients were at rest for at least five cardiac cycles to avoid the influence of respiration. Measurements were obtained from five consecutive beats, and means were calculated.

The thickness of the epicardial adipose tissue was measured from the right ventricular free wall in the parasternal long axis view. The epicardial adipose tissue was identified as an echo-free space in the pericardial layers on the two-dimensional echocardiography, and its thickness was measured perpendicularly on the free wall of the right ventricle at end diastole for three cardiac cycles [15, 16].

To standardize the set point of measurement between different observers, the aortic annulus was used as the anatomic reference. The measurement was performed at a point on the free wall of the right ventricle along the midline of the ultrasound beam perpendicular to the aortic annulus. The average value from three cardiac cycles was used for the statistical analyses.

In both groups, the carotid intima-media thickness was measured from the common carotid artery at a point 5 mm proximal to its bifurcation, as often preferred in the literature [36]. The transducer was placed perpendicular to the common carotid artery, and its long axis was adjusted parallel to the flow direction. Images obtained from the anterior wall were magnified threefold, and measurements were made with an electronic caliper. Measurements also were made in the axial and longitudinal planes. The measurements from three consecutive beats were averaged and recorded as the carotid intima-media thickness [35].

The inter- and intraobserver variability of the two independent investigators performing the examinations were calculated, and the correlation coefficients were found to be 0.98 and 0.94, respectively.

N-Terminal Pro B-Type Natriuretic Peptide Measurement

In both groups, blood samples of 0.5 ml were obtained from the antecubital vein using a heparinized syringe, and N-terminal pro B-type natriuretic peptide measurements were made using the Roche Cardiac Reader dry system equipment by putting a volume of 150 µl on the strip.

Statistical Analysis

Differences among the study groups were analyzed using Student's *t* test. Correlations were analyzed using Pearson's correlation coefficient. All *p* values less than 0.05 were considered statistically significant.

Results

This study investigated 50 obese children and 20 healthy age- and sex-matched control children. The two groups did not differ significantly in terms of age (125.58 ± 28.66 vs. 121.30 ± 40.33 months) or height (147.5 ± 14.32 vs. 139.00 ± 18.32 cm) ($p > 0.05$ for both). However, the groups differed significantly in terms of body weight (59.80 ± 19.94 vs 34.87 ± 12.95 kg) and BMI (26 ± 4.5 vs. 17 ± 2.6) ($p = 0.001$ for both). The study and control groups did not differ significantly with regard to heart rate (78.95 ± 5.04 vs. 78.95 ± 7.46 beats/min; $p > 0.05$) or average hemoglobin value (12.8 ± 1.04 vs. 12.5 ± 1.1 g/dl; $p > 0.05$). However, the average systolic and diastolic blood pressure values differed significantly between the study and control groups ($p = 0.001$ for both) (Fig. 1).

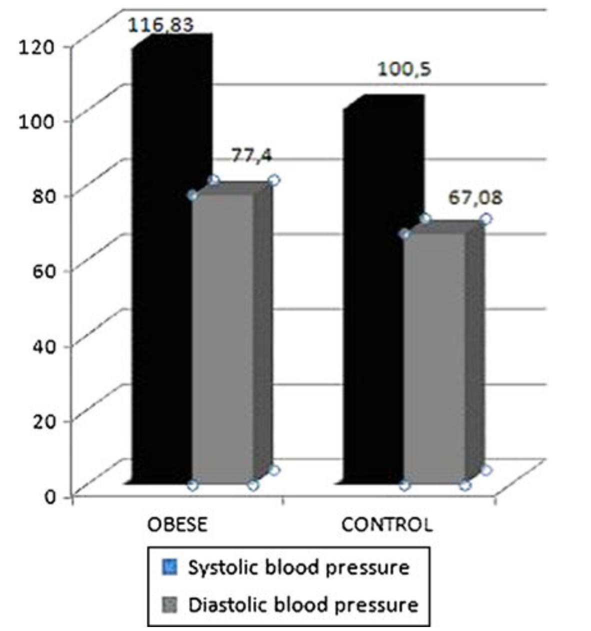

Fig. 1 Average systolic and diastolic blood pressures for the two groups

The average left ventricular mass index was greater in the obese group than in the control group, but this difference did not reach statistical significance (40.21 ± 10.42 vs. 34.44 ± 4.51 g/m^2; $p > 0.05$). The M-mode measurements for both groups are shown in Table 1. The N-terminal pro B-type natriuretic peptide values averaged 109.25 ± 48.53 pg/ml in the obese group and 51.96 ± 22.36 pg/ml in the control group ($p = 0.001$) (Fig. 2).

The epicardial adipose tissue thickness averaged 5.57 ± 1.45 mm in the obese group and 2.98 ± 0.41 mm in the control group ($p = 0.001$) (Fig. 3). The average carotid intima-media thickness was 0.079 ± 0.019 cm in the obese group and 0.049 ± 0.012 cm in the control group ($p = 0.001$; Fig. 4).

The results of the tissue Doppler imaging studies from the mitral and tricuspid annulus for both groups are summarized in Table 2. In the obese group, a statistically significant positive and strong correlation was observed between body weights ($p = 0.09$ and $r = 0.68$), systolic and diastolic blood pressures ($p = 0.09$ and $r = 0.52$), left ventricular mass indices ($p = 0.09$ and $r = 0.58$), and epicardial adipose tissue thicknesses ($p = 0.08$ and $r = 0.058$) (Figs. 5 and 6). On the other hand, no statistically significant correlations between the serum N-terminal pro B-type natriuretic peptide levels, fractional shortening and ejection fraction values, mitral and tricuspid annular myocardial performance indices, or carotid intima-media thickness measurements were found.

Statistically significant correlations were not observed between the serum N-terminal pro B-type natriuretic peptide levels and the left ventricular mass index values of the obese subjects. Also, no statistically significant correlations between these two parameters and the systolic and diastolic blood pressures, ejection fraction and fractional shortening values, myocardial performance index values, epicardial adipose tissue thicknesses, or carotid intima-media thicknesses were found ($p > 0.05$).

Although a statistically significant positive and moderate correlation was detected between epicardial adipose tissue and the carotid intima-media thicknesses ($p = 0.04$ and $r = 0.47$; Fig. 7), no significant correlations were detected between these two parameters and fractional

Table 1 M-mode echocardiographic measurements in the study and control groups

	Obese	Control	p Value
Interventricular septal diastolic dimension	0.78 ± 0.17	0.61 ± 0.1	0.001
Left ventricular internal dimension at diastole	4.19 ± 0.6	3.88 ± 0.39	>0.05
Left ventricular internal dimension at systole	2.46 ± 0.38	2.47 ± 0.3	>0.05
Left ventricular posterior wall diastolic dimension	0.76 ± 0.16	0.63 ± 0.1	0.005
Fractional shortening	41.36 ± 6.4	37.58 ± 8.9	>0.05
Ejection fraction	72.35 ± 6.8	64.65 ± 6.7	0.001
Left ventricle mass index	40.21 ± 10.42	34.44 ± 4.51	>0.05

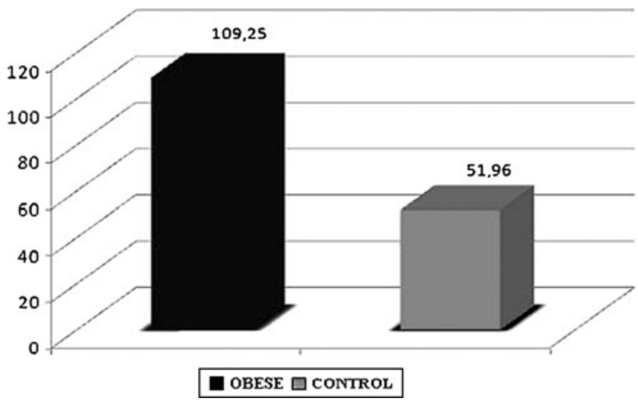

Fig. 2 Average N-terminal pro B-type natriuretic peptide levels for the two groups

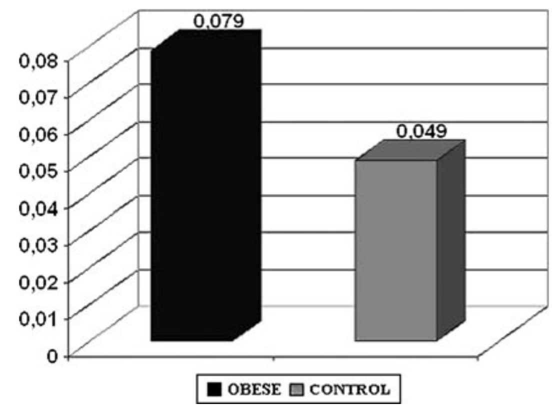

Fig. 4 Mean carotid intima-media thicknesses for the two groups

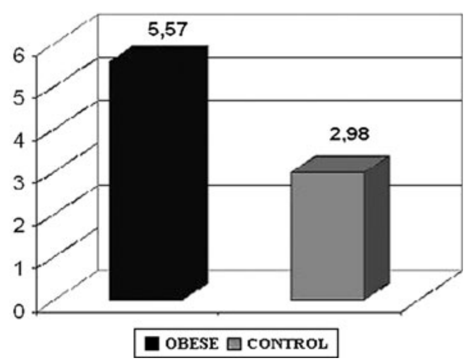

Fig. 3 Average epicardial adipose tissue thicknesses for the two groups

shortening and ejection fraction values and myocardial performance index values ($p > 0.05$).

Obese children with normal and elevated systolic and diastolic blood pressures (109.09 ± 9.4 mmHg systolic and 67.27 ± 4.26 mmHg diastolic vs 120 ± 11.9 mmHg systolic and 80 ± 7.5 mmHg diastolic) were further compared for serum N-terminal pro B-type natriuretic peptide levels, left ventricle mass index values, average epicardial adipose tissue, and carotid intima-media thicknesses, and no significant correlations were noted ($p > 0.05$) (Table 3).

Discussion

Childhood obesity is known to cause changes in cardiac structure and function [1]. Starting from childhood, myocardial mass parallels the increase in BMI. It is reported that left ventricular hypertrophy occurs in obesity and that this hypertrophy is related to an increased risk of cardiovascular disease, mortality, and morbidity [26, 28, 38].

Left ventricular systolic functions usually are evaluated through measurements of ejection fraction and fractional shortening. Studies have repeatedly shown that these values are rather increased in the early stages of obesity. Consequently, these values are shown to be greater in obese children than in nonobese control children [21, 23].

For patients with aortic stenosis and coarctation, overnormal contractility secondary to increased afterload is reported unless there are irreversible changes in the ventricular myocardium [12]. In our study, it was speculated that increased load was the major reason for the elevated ejection fraction and fractional shortening values in obese children.

In the current study, the left ventricular mass index was higher in the obese group than in the control group, but this difference was not statistically significant because it is known that left ventricle hypertrophy affects diastolic

Table 2 Tissue Doppler echocardiography measurements in the study and control groups

	Mitral valve			Tricuspid valve		
	Obese	Control	p Value	Obese	Control	p Value
Diastolic early wave peak velocity (cm/s)	0.24 ± 0.05	0.27 ± 0.04	>0.05	0.23 ± 0.04	0.25 ± 0.04	>0.05
Diastolic late wave peak velocity (cm/s)	0.15 ± 0.04	0.14 ± 0.03	>0.05	0.16 ± 0.05	0.15 ± 0.04	>0.05
Systolic wave peak velocity (cm/s)	0.16 ± 0.03	0.16 ± 0.03	>0.05	0.19 ± 0.03	0.20 ± 0.03	>0.05
Isovolumic relaxation time (ms)	59.72 ± 9.57	49.44 ± 5.99	0.001	60.39 ± 9.83	46.44 ± 4.39	0.001
Isovolumic contraction time (ms)	72.35 ± 12.46	58.26 ± 5.02	0.001	66.90 ± 10.61	58.60 ± 6.38	0.05
Ejection time (ms)	263.03 ± 26.41	252.05 ± 10.95	>0.05	253.87 ± 23.70	248.12 ± 15.68	>0.05
Myocardial performance index	0.50 ± 0.08	0.42 ± 0.01	0.001	0.50 ± 0.08	0.42 ± 0.01	0.001

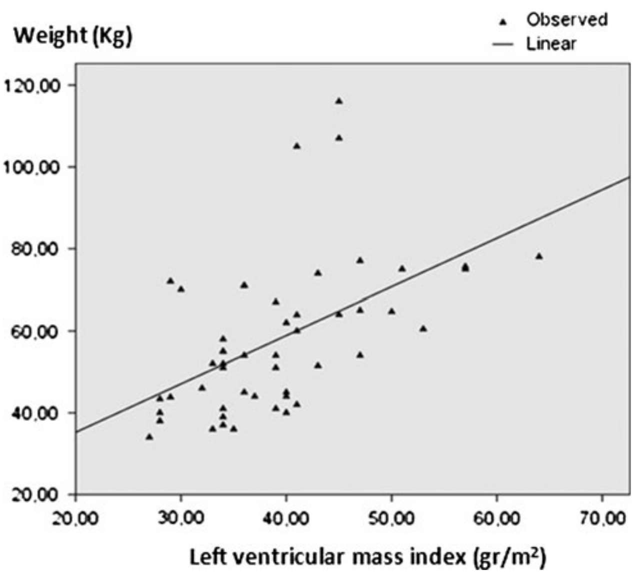

Fig. 5 Correlation between weight and left ventricular mass index in the obese group

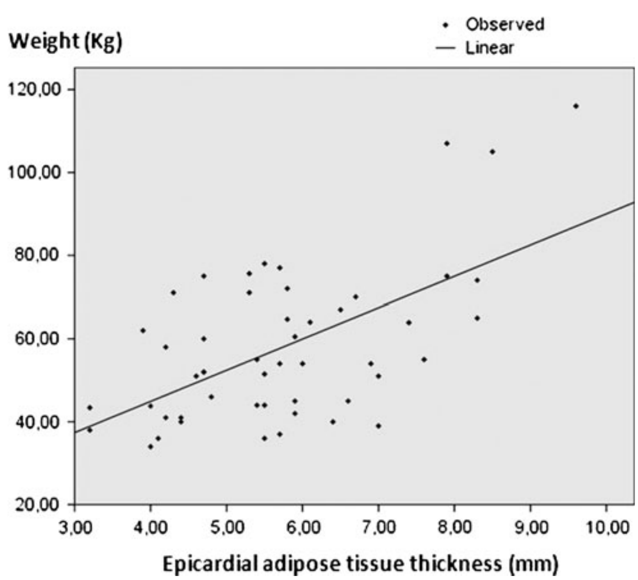

Fig. 6 Correlation between weight and epicardial adipose tissue thickness in the obese group

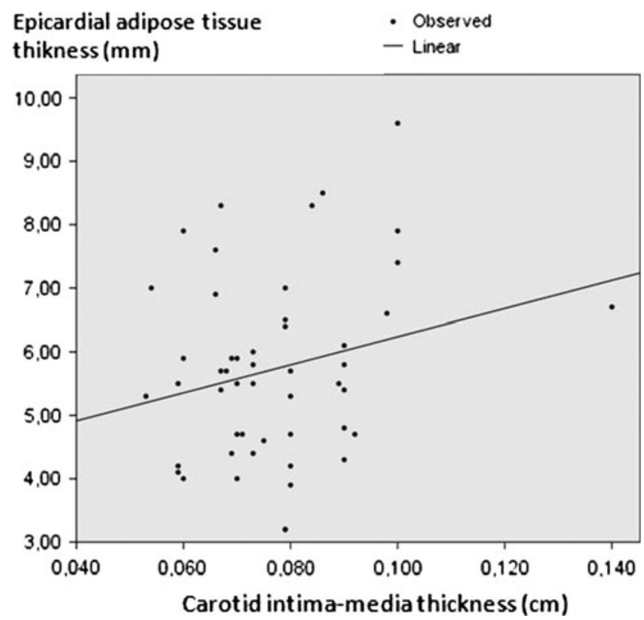

Fig. 7 Correlation between epicardial adipose tissue and carotid intima-media thickness in the obese group

function negatively. On the other hand, in obese patients with no ventricle hypertrophy, cardiac functions may deteriorate. Moreover, this deterioration may be seen in each ventricle [14, 24, 25, 33].

In the current study, the mitral and tricuspid valve pulsed-wave Doppler analyses failed to show a statistically significant difference between the two groups in terms of diastolic early wave peak velocity, diastolic late wave peak velocity, ratio of average diastolic early wave peak velocity to average diastolic late wave peak velocity, and average deceleration time. In the tissue Doppler imaging analysis of the two groups, the average isovolumic relaxation time and isovolumic contraction values were greater in the obese group than in the control group, as were the average myocardial performance indices. The systolic wave peak velocity averages were normal in obese children, implying normal systolic functions. In obese cases, some parameters of diastolic function were normal, possibly due to the

Table 3 Comparison of the plasma N-terminal pro B-type natriuretic peptide levels, left ventricular mass index values, carotid intima-media, and epicardial adipose tissue thicknesses in obese subjects with normal and elevated blood pressures

	Hypertension	*n*	Mean	*p* Value
N-terminal pro B-type natriuretic peptide	Absent	38	104.37 ± 43.69	>0.05
	Present	12	115.97 ± 56.92	>0.05
Left ventriular mass index	Absent	38	41.40 ± 9.78	>0.05
	Present	12	38.59 ± 11.71	>0.05
Carotid intima-media thickness	Absent	38	0.073 ± 0.013	>0.05
	Present	12	0.088 ± 0.023	>0.05
Epicardial adipose tissue thickness	Absent	38	5.55 ± 1.08	>0.05
	Present	12	5.60 ± 1.93	>0.05

relatively young ages of the children. Another reason could be that the study subjects were not classified as morbidly or excessively obese.

Obesity is an important risk factor for atherosclerotic cardiovascular disease. In an adult study, the epicardial fat thickness measured using transthoracic echocardiography significantly correlated with the severity of coronary artery stenosis in patients with known coronary artery disease [18]. Obesity seems to be a predisposing factor for the accumulation of excess epicardial fat [32]. Our data showed a strong correlation between epicardial fat thickness and body weight in obese cases. However, this study found no statistically significant correlations between epicardial adipose tissue thickness and systolic and diastolic blood pressures, left ventricular mass index values, and mitral and tricuspid annular myocardial performance index values in obese cases.

Carotid intima-media thickness measurement is a widely used method for the early diagnosis of atherosclerosis [5]. Di Salvo et al. [8] showed that carotid intima-media thickness was not greater in obese children than in non-obese control children. Iannuzzi et al. [17] reported that carotid intima-media thickness was increased in children with metabolic syndrome but that this increase was not statistically significant. Thus, numerous studies have shown that carotid intima-media thickness is increased in obese children, and it is widely agreed that this increase in childhood is related to atherosclerosis in adulthood [2, 3, 13, 29, 39, 40]. In our study, too, the carotid intima-media thickness was significantly greater in the obese children than in the control children.

It is reported that carotid intima-media thickness is related to decreased myocardial blood flow [34]. In a study performed with adults using magnetic resonance imaging, the carotid intima-media thickness was associated with regional systolic and diastolic myocardial dysfunction [11]. Parrinello et al. [27] reported an association between carotid intima-media thickness and diastolic dysfunction in hypertensive adults. Our study found no statistically significant correlations between the carotid intima-media thickness and the mitral and tricuspid annular myocardial performance index values.

Serum N-terminal pro B-type natriuretic peptide levels are found to be increased in cases with left ventricular systolic and diastolic dysfunction [22]. Kim et al. [20] studied adults with hypertrophic cardiomyopathy and found a positive correlation of the serum N-terminal pro B-type natriuretic peptide levels with the end-diastolic thickness of the interventricular septum and the left ventricular mass index. The serum N-terminal pro B-type natriuretic peptide levels were higher in cases with diastolic dysfunction than in normal control subjects.

Other adult studies have found the reliability of the N-terminal pro B-type natriuretic peptide to be comparable with tissue Doppler echocardiography and even higher than that of conventional echocardiography because this method had the best negative predictive value among the three methods and also exhibited a strong correlation with the left ventricular filling index measured invasively. Consequently, it was reported that this method is reliable for detecting patients with isolated diastolic dysfunction [9, 37].

To the best of our knowledge, serum N-terminal pro B-type natriuretic peptide levels in obese children have not been reported in the literature to date regardless of the presence of systolic and/or diastolic dysfunction. In this study, the average serum N-terminal pro B-type natriuretic peptide levels were found to be significantly higher in obese children than in the control group. However, in the obese children, no statistically significant correlations were observed between the serum N-terminal pro B-type natriuretic peptide values and body weight, carotid intima-media thickness, epicardial adipose tissue thickness, systolic and diastolic blood pressures, and left ventricular mass index values. Contrary to the studies performed with adults, no statistically significant correlations were detected between the mitral and tricuspid annular myocardial performance index values and serum N-terminal pro B-type natriuretic peptide levels in obese children compared with nonobese control children.

Conclusion

Our results show that obese children are subject to cardiac structural and functional changes even during the asymptomatic period. Consequently, these changes affect systolic and diastolic functions and increase the left ventricular mass index, serum N-terminal pro B-type natriuretic peptide values, epicardial adipose tissue thickness, and carotid intima-media thickness. The diastolic functions were observed to be more sensitive to these changes than the systolic functions. This situation must be considered in the cardiologic evaluation of obese children, and their diastolic functions must be interpreted carefully. The myocardial performance index, computed with the Doppler and tissue Doppler methods, can be an important parameter for the early detection of cardiac dysfunction in obese children. On the other hand, measurements of the serum N-terminal pro B-type natriuretic peptide level, carotid intima-media thickness, and epicardial adipose tissue thickness for the evaluation of the systolic and diastolic functions are unnecessary.

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