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Left and right ventricular function by echocardiography, tissue Doppler imaging, carotid intima-media thickness, and asymmetric dimethyl arginine levels in obese adolescents with metabolic syndrome

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Abstract

Purpose: The aim of our study was to assess left ventricle and right ventricle systolic and diastolic functions in obese adolescents with metabolic syndrome using conventional echocardiography and pulsed-wave tissue Doppler imaging and to investigate carotis intima-media thickness, and asymmetric dimethyl arginine levels. *Methods:* A total of 198 obese adolescents were enrolled in the study. The obese patients were divided into metabolic syndrome group and non-metabolic syndrome group. All subjects underwent laboratory blood tests, including asymmetric dimethyl arginine, complete two-dimensional, pulsed, and tissue Doppler echocardiography, and measurement of the carotid intima-media thickness. *Results:* Obese adolescents were characterised by enlarged left end-diastolic, end-systolic and left atrial diameters, thicker left and right ventricular walls compared with non-obese adolescents. The metabolic syndrome group had normal left ventricle systolic function, impaired diastolic function, and altered global systolic and diastolic myocardial performance. In the metabolic syndrome obese group patients, left ventricle mass was found positively correlated with body mass index, waist and hip circumferences, diastolic blood pressure, age, and waist-to-hip circumference ratio. The carotid intima-media thickness was found positively correlated with waist and hip circumferences and total cholesterol levels. Asymmetric dimethyl arginine levels were found positively correlated with systolic blood pressure, waist-to-hip circumference ratio, and diastolic blood pressure. *Conclusions:* The results of this study demonstrate that metabolic syndrome in adolescence is associated with significant changes in myocardial geometry and function. In addition, it has been associated with a high level of asymmetric dimethyl arginine concentration and thicker carotid intima-media thickness reflecting endothelial dysfunction.

Metabolic syndrome is a cluster of risk factors including abdominal obesity, hypertension, insulin resistance, dyslipidaemia, which directly increase the risk of cardiovascular disease. Myocardial and vascular structural alterations may influence both left[1] and right ventricular[2] function as well as an increased risk of atherosclerosis.[3] Increased carotid intima-media thickness of the common carotid artery measured by carotid artery ultrasound has been a useful non-invasive marker of atherosclerosis in patients with metabolic syndrome.[3]

Nitric oxide is the main vasorelaxing and antithrombotic factor produced by endothelial cells through the action of endothelial nitric oxide synthase. Asymmetric dimethyl arginine is the major endogenous inhibitor of nitric oxide synthase leading to endothelial dysfunction and atherosclerotic vascular disease.[4] Increased plasma asymmetric dimethyl arginine concentrations mainly occur following inhibition of the enzyme responsible for asymmetric dimethyl arginine catabolism, dimethylarginine dimethylaminohydrolase, through oxidative stress triggered by several cardiovascular risk factors.[5] It has been shown in adults that patients with metabolic syndrome had higher plasma asymmetric dimethyl arginine levels and tissue Doppler imaging values than the controls, reflecting the presence of endothelial dysfunction.[6]

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The aim of our study was to assess left ventricle and right ventricle systolic and diastolic functions in obese adolescents with metabolic syndrome using conventional echocardiography and pulsed-wave tissue Doppler imaging and to investigate asymmetric dimethyl arginine levels. We also studied left ventricle and right ventricle structural remodelling, and cardiovascular risk profiles in obese adolescents with metabolic syndrome.

Materials and method

A total of 198 obese adolescents, consisting of 118 females and 80 males with mean age of 13.9 ± 1.5 years; range 12–17; mean body mass index 31.1 ± 3.8 kg/m^2, were recruited from obese adolescents admitted to the paediatric endocrinology unit between June 2013 and June 2014. The obese group was divided into two subgroups; one group is patients with metabolic syndrome consisting of 60 females and 40 males, with mean age of 14.0 ± 1.4 years; mean body mass index 32.4 ± 3.5 kg/m^2; and the other is non-metabolic syndrome consisting of 58 females and 40 males, with mean age of 13.9 ± 1.3 years; mean body mass index 29.9 ± 3.6 kg/m^2. Control adolescents – 52 females, 50 males; mean age 14.0 ± 1.3 years, range 12–17; mean body mass index 19.5 ± 2.3 kg/m^2 – were selected from non-obese healthy adolescents.

Metabolic syndrome was defined according to the modified WHO criteria adapted for children. Subjects were diagnosed as having metabolic syndrome if they met three of four WHO criteria, which are *obesity* where body mass index is >95th percentile for age and sex; *dyslipidaemia* caused by high triglycerides (>136 mg/dl) in children ⩾10 years of age, low high-density lipoprotein cholesterol (<35 mg/dl), or high total cholesterol (>95th percentile); *hypertension* where systolic blood pressure is >95th percentile for age and sex and height; and *abnormal glucose homeostasis* caused by fasting hyperinsulinemia, impaired fasting glucose, or impaired glucose tolerance).[7]

Patients with clinical or laboratory signs of any systemic disease, including type 1 or type 2 diabetes mellitus; taking medications; or that had conditions known to affect insulin action or insulin secretion, for example glucocorticoid therapy, hypothyroidism, and Cushing disease; CHD; valvular heart disease; chronic renal failure; and smokers were excluded from the study. The study protocols were approved by our hospital's ethics committee (approval number: 0.28.00.00/130-304). Signed informed consent forms were obtained from the parents of the adolescents.

Height and weight were measured with an empty bladder in post-absorptive conditions. Body mass index was calculated as weight in kilograms divided by the square of height in meters. Patients with body mass index ⩾95th percentile according to reference curves for Turkish adolescents were accepted as obese.[8] Waist circumference was measured midway between the lowest rib and the top of the iliac crest at the end of gentle expiration. Hip circumference was measured over the great trochanters. Pubertal developmental stage was assessed by a single paediatric endocrinologist using the Tanner criteria. Staging for sexual maturation was >2 in all patients; Tanner stages II–IV. After resting for ⩾5 minutes, systolic and diastolic blood pressures were measured in the sitting position, using a mercury-gravity manometer and a cuff appropriate for body size.

Blood samples were obtained in the morning by venipuncture after an overnight fast, that is ⩾12 hours fasting. Serum concentrations of total cholesterol, high-density lipoprotein cholesterol, and triglycerides were measured using routine enzymatic methods with an Abbott Diagnostics c16000 chemistry analyser (Abbott Diagnostics, Lake Forest, IL, United States of America). Serum insulin levels were measured using the IMMULITE immunoassay (Siemens Healthcare Diagnostics, Camberley, United Kingdom). Insulin resistance was estimated by homeostasis model assessment of insulin resistance using the formula: fasting insulin concentration (mU/ml) × fasting glucose concentration (mmol/L)/22.5.[9]

Measurement of asymmetric dimethyl arginine levels was accomplished by high-performance liquid chromatography, using the method described by Chen et al.[10]

Carotis ultrasound studies were performed by a single radiologist, who was blinded to the clinical and laboratory status of the patients, using high-resolution B-mode ultrasonography (Logiq 7) and a high-resolution linear-array vascular transducer (14 MHz). An optimal two-dimensional image of the common carotid artery was obtained in which the near and far wall intima-media complex was well visualised. After a 10-minute rest, the M-mode cursor was placed 1 cm proximal to the beginning of the carotid artery bulb during end-diastole. Carotid intima-media thickness was calculated by taking the mean value of three measurements. There was no evidence of carotid plaque formation in all obese and control groups.

All echocardiographic and Doppler examinations were performed by a single expert paediatric cardiologist, who was blinded to the clinical and laboratory results of the study group. ProSound Alpha 7 (Aloka, Hitachi-Aloka Medical, Tokyo, Japan) with a 3-MHz phased-array transducer was used for each study subject. Conventional echocardiographic evaluation from the parasternal long-axis view included left ventricle end-diastolic and end-systolic diameter, septal and left ventricle posterior wall thicknesses in diastole and systole, right ventricle free wall thicknesses in diastole and systole, the left ventricle ejection fraction, and left ventricle fractional shortening. Teichholz's M-mode formula was used to calculate the left ventricle ejection fraction and left ventricle fractional shortening. All data were determined according to the recommendations of the American Society of Echocardiography.[11] Relative posterior wall thickness was calculated as (interventricular septal thickness in diastole + left ventricle posterior wall thickness in diastole)/left ventricle end-diastolic diameter. Left ventricular mass was calculated using the Devereux[12] formula and indexed to height.[2,7]

Transmitral and transtricuspid flow patterns were obtained by pulsed-wave Doppler echocardiography from the apical four-chamber view with the sample volume placed at the mitral and tricuspid valves leaflets tips. Peak early (E_m, E_t) and late (A_m, A_t) diastolic velocities, the $(E/A)_m$ and $(E/A)_t$ ratios, isovolumetric relaxation times, isovolumetric contraction times, and ejection times were measured. The Doppler-derived index of combined systolic and diastolic myocardial performance (Tei index; [isovolumetric relaxation time + isovolumetric contraction time]/ejection time) was used to quantify global left and right ventricle functions.[13]

A 5-mm pulsed-wave Doppler tracing was placed at the septal and lateral segments of the mitral valve, and lateral segment of the tricuspid valve and peak myocardial systolic (s_m, s_t), early (e'_m, e'_t), and late diastolic (a'_m, a'_t) velocities were measured from the apical four-chamber view. $(E/e')_m$ and $(E/e')_t$ ratios of the left and the right ventricle were determined by using previously estimated Doppler values.

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Table 1. Clinical features of healthy controls and obese adolescents.

Variable	Healthy controls	Obese Non-MS	Subjects MS
Subjects (female/male)	102	98	100
Age (years)	14.0 ± 1.3 (12–17)	13.9 ± 1.3 (12–17)	14.0 ± 1.4 (12–17)
BMI (kg/m^2)	19.5 ± 2.3 (16.1–24.5)	29.9 ± 3.6 (25.1–39.7)$^{\gamma}$	32.4 ± 3.5 (26.5–39.9)$^{\delta\star}$
Waist circumference (cm)	73 ± 7 (56–93)	95 ± 10 (68–128)$^{\gamma}$	99 ± 11 (69–132)$^{\delta\star}$
Hip circumference (cm)	88 ± 7 (71–106)	106 ± 10 (70–144)$^{\gamma}$	112 ± 9 (94–157)$^{\delta\star}$
Waist circumference/hip circumference ratio	0.82 ± 0.06 (0.67–1)	0.89 ± 0.10 (0.71–1.71)$^{\gamma}$	0.88 ± 0.07 (0.52–1.05)$^{\delta}$
Systolic BP (mmHg)	102 ± 8 (80–120)	114 ± 9 (100–150)$^{\gamma}$	125 ± 12 (100–150)$^{\delta\star}$
Diastolic BP (mmHg)	63 ± 7 (40–80)	73 ± 7 (60–100)$^{\gamma}$	78 ± 9 (65–100)$^{\delta\star}$
Heart rate (beats/min)	89 ± 12 (61–117)	89 ± 11 (62–125)	90 ± 14 (58–133)
Total cholesterol (mg/dl)	152 ± 23 (104–213)	166 ± 27 (111–246)$^{\gamma}$	163 ± 31 (98–269)$^{\delta}$
Triglycerides (mg/dl)	86 ± 30 (24–154)	100 ± 36 (25–192)$^{\gamma}$	167 ± 78 (54–398)$^{\delta\star}$
Low-density lipoprotein cholesterol (mg/dl)	86 ± 19 (38–138)	96 ± 23 (49–168)$^{\gamma}$	91 ± 30 (22–171)
High-density lipoprotein cholesterol (mg/dl)	50 ± 8 (33–74)	48 ± 8 (30–70)	38 ± 7 (25–62)$^{\delta\star}$
Fasting glucose (mg/dl)	81 ± 5 (69–92)	88 ± 11 (62–125)$^{\gamma}$	94 ± 10 (81–146)$^{\delta\star}$
Fasting insulin (U/ml)	7.3 ± 2.4 (2–15)	14.5 ± 9.0 (3–59)$^{\gamma}$	25.2 ± 15.8 (7–102)$^{\delta\star}$
HOMA-IR	1.4 ± 0.4 (0.4–3)	3.1 ± 2.0 (0.7–12.8)$^{\gamma}$	6.1 ± 4.9 (1.6–36)$^{\delta\star}$
ADMA	0.35 ± 0.22 (0.1–1.00)	0.54 ± 0.23 (0.16–1.29)$^{\gamma}$	0.60 ± 0.25 (0.16–1.57)$^{\delta}$

ADMA = asymmetric dimethylarginine; BMI = body mass index; BP = blood pressure; HOMA-IR = homeostasis model assessment of insulin resistance; MS = metabolic syndrome
Data are expressed as mean ± SD (range)
*$p < 0.05$, obese subjects with non-MS versus obese subjects with MS
$^{\gamma}p < 0.05$, controls versus obese subjects with non-MS
$^{\delta}p < 0.05$, controls versus obese subjects with MS

The left and right ventricle Tei index was calculated according to the formula: (Isovolumic relaxation time + Isovolumic contraction time)/Ejection time.

Right ventricle global systolic function was assessed as the tricuspid annular plane systolic excursion, which was measured as the difference between the distance among the tricuspid annulus and right ventricle apex end-diastole and end-systole of the same cardiac cycle.[14]

Continuous variables are expressed as mean ± SD (range). Normality assumptions were assessed before conducting parametric tests. When all groups were compared for parameters, analyses of variance were used; post-hoc analysis was performed using Tukey's honestly significantly different test. Bivariate associations of continuous variables were assessed using Pearson's correlation coefficients.

Stepwise multivariate linear regression was then used to determine which determinants independently explained a significant ($p < 0.05$) fraction of the variance of the dependent variables. A p-value <0.05 was considered to indicate statistical significance. Statistical analyses were performed using SPSS version 15.0 for Windows (SPSS, Inc., Chicago, IL, United States of America).

Results

The characteristics of the patients and healthy controls are listed in Table 1. Metabolic syndrome was present in 100 of 198 of all obese adolescents (50.5%). There was no statistically important difference in heart rate between the obese subjects metabolic or non-metabolic syndrome and controls. The metabolic syndrome obese group had significantly higher body mass index, waist and hip circumferences, and systolic and diastolic blood pressure than the non-metabolic syndrome obese and control groups.

The levels of serum triglyceride, fasting glucose, and insulin were significantly higher and levels of high-density lipoprotein cholesterol were significantly lower in the metabolic syndrome obese group compared with controls. The control group had significantly lower homeostasis model assessment of insulin resistance values than the metabolic and non-metabolic syndrome obese groups. We also found that asymmetric dimethyl arginine levels were significantly lower in the control group than the metabolic syndrome and non-metabolic syndrome obese groups.

Two-dimensional, M-mode, and pulsed-wave Doppler conventional echocardiographic findings and carotid intima-media thickness results of the patients and controls are listed in Table 2. Left ventricle M-mode measurements were significantly larger in the metabolic and non-metabolic syndrome obese groups compared with controls. The metabolic syndrome obese group had significantly higher interventricular septal thickness in systole and left ventricle posterior wall thickness in diastole than the non-metabolic syndrome obese and control groups. The left atrial and aortic diameters were significantly higher in the metabolic syndrome group than the control group. By conventional echocardiography, the left ventricle ejection fraction and left ventricle shortening fraction were similar in the obese and control groups.

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Table 2. Conventional echocardiographic findings and carotid intima-media thickness measurements in controls and obese adolescents.

	Controls (n = 102)	Non-MS (n = 98)	MS (n = 100)
Left ventricle			
LV end-diastolic diameter (mm)	42.8 ± 4.1 (34–55)	44.0 ± 3.5 (35–53)[¥]	44.6 ± 4.2 (35–56)[δ]
LV end-systolic diameter (mm)	26.8 ± 3.7 (19–35)	27.2 ± 3.7 (18–35)	28.0 ± 3.6 (18–40)[δ]
Interventricular septal diameter in diastole (mm)	7.2 ± 0.6 (5–9)	8.4 ± 1.1 (6–13)[¥]	9.3 ± 1.5 (7–14)[*δ]
Interventricular septal diameter in systole (mm)	8.3 ± 1.1 (6–12)	9.3 ± .1.3 (7–14)[¥]	10.0 ± .1.4 (6–14)[*δ]
LV posterior wall diameter in diastole (mm)	6.7 ± 1.2 (4–12)	7.9 ± 1.2 (6–14)[¥]	8.0 ± 1.1 (6–12)[δ]
LV posterior wall diameter in systole (mm)	10.9 ± 2.2 (8–18)	12.1 ± 2.4[¥](8–29)[¥]	12.5 ± 1.8 (9–16)[δ]
LV ejection fraction (%)	67 ± 3.8 (60–79)	67 ± 4.0 (60–80)	67 ± 4.5 (60–83)
LV fractional shortening (%)	37 ± 3.3 (31–48)	37 ± 3.0 (32–48)	37 ± 5.1 (30–51)
Relative wall thickness (mm)	3.26 ± 0.37 (2.40–4.10)	3.72 ± 0.51 (2.64–5.29)[¥]	3.90 ± 0.58 (2.80–5.36)[*δ]
LV mass (g)	99 ± 28.6 (44–213)	124 ± 26.0 (68–209)[¥]	133 ± 34.2 (75–234)[*δ]
LV mass index ($g/m^{2.7}$)	28 ± 5.7 (15–48)	35 ± 7.7 (17–67)	36 ± 9.0 (23–68)
Left atrial dimension (mm)	25 ± 3 (18–37)	28 ± 2.7 (21–34)[¥]	30 ± 3.6 (22–41)[δ]
Aortic dimension (mm)	19 ± 2.2 (15–26)	21 ± 2.7 (16–33)[¥]	22 ± 2.9 (11–29)[δ]
Right ventricle			
RV free wall diameter in diastole (mm)	4.19 ± 0.64 (3–6)	5.67 ± 0.87 (4–8)[¥]	5.80 ± 0.82 (4–7)[*δ]
RV free wall diameter in systole (mm)	5.39 ± 0.81 (3–7)	7.05 ± 0.95 (5–9)[¥]	7.60 ± 0.88 (6–10)[δ]
Tricuspid annular plane systolic excursion (mm)	22.8 ± 2.8 (17–29)	24.5 ± 2.7 (19–32)[¥]	25.4 ± 2.89(19–33)[*δ]
CIMT (mm)	0.370 ± 0.025 (0.32–0.45)	0.421 ± 0.042 (0.32–0.58)[¥]	0.444 ± 0.052 (0.34–0.65)[*δ]

CIMT = carotid intima-media thickness; LV = left ventricle; MS = metabolic syndrome; RV = right ventricle
Data are expressed as mean ± SD (range)
*$p < 0.05$, obese subjects with non-MS versus obese subjects with MS
[¥]$p < 0.05$, controls versus obese subjects with non-MS
[δ]$p < 0.05$, controls versus obese subjects with MS

The right ventricle free wall thicknesses in systole and diastole were significantly higher in the metabolic and non-metabolic syndrome obese groups than the controls. Tricuspid annular plane systolic excursion was completely preserved in all groups. The metabolic and non-metabolic syndrome obese groups had significantly higher carotid intima-media thickness and left ventricle mass than the controls.

The parameters of the left ventricle myocardial systolic function obtained by the tissue Doppler – s'_{septal} and $s'_{lateral}$ – seemed normal in interventricular septum and left ventricle lateral wall in all groups. The parameters of the left ventricle diastolic function such as E/A_{mitral} were lower in the metabolic and non-metabolic syndrome obese groups than the controls, but E/e'_{septal} and $E/e'_{lateral}$ values were similar in each group. The left ventricle Tei index was also significantly higher in subjects in the metabolic and non-metabolic syndrome obese groups than the controls. The parameters of the right ventricle myocardial systolic function seemed normal in interventricular septum and right ventricle lateral wall in all groups. However, the parameters of the right ventricle diastolic function such as $E/A_{tricuspid}$ and $E/e'_{tricuspid}$ were lower and higher, respectively, in the metabolic and non-metabolic syndrome groups as compared with the controls. The right ventricle Tei index was also significantly higher in the metabolic and non-metabolic syndrome obese groups than the controls (Table 3).

In the metabolic syndrome obese group, left ventricle mass was positively correlated with body mass index, waist and hip circumferences, diastolic blood pressure, age, and waist to hip circumference ratio. In addition, carotid intima-media thickness was positively correlated with waist and hip circumferences, total cholesterol levels, left ventricle mass, and E/e'_{septal} (Table 4), and asymmetric dimethyl arginine was positively correlated with systolic and diastolic blood pressure and, waist to hip circumference ratio in the metabolic syndrome obese group (Table 5).

To evaluate which variables independently influenced left ventricle mass, a multiple regression analysis model was performed in the metabolic syndrome obese group. A multiple stepwise regression was conducted to disclose the independent contributions of age, the ratio of waist-to-hip circumference, systolic and diastolic blood pressures, homeostasis model assessment of insulin resistance, total cholesterol, high-density lipoprotein cholesterol, asymmetric dimethyl arginine and regional tissue Doppler imaging myocardial performance indexes of left ventricle mass. The independent variables for left ventricle mass were age (β: 0.344, p: 0.006), and diastolic

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Table 3. Comparison of left and right ventricular systolic and diastolic functions by pulse wave Doppler and tissue Doppler imaging measurements in controls and obese adolescents.

	Controls (n = 102)	Non-MS (n = 98)	MS (n = 100)
Left ventricle			
Mitral peak early diastolic wave (E) (m/s)	0.94 ± 0.13 (0.59–1.35)	0.94 ± 0.15 (0.66–1.40)	0.91 ± 0.14 (0.57–1.30)
Mitral peak late diastolic wave (A) (m/s)	0.53 ± 0.12 (0.31–0.81)	0.53 ± 0.11 (0.32–0.96)	0.53 ± 0.11 (0.29–0.83)
Mitral peak early diastolic wave/peak late diastolic wave ratio $(E/A)_{mitral}$	1.84 ± 0.35 (1.18–2.90)	1.79 ± 0.30 (1.18–2.87)	1.74 ± 0.27 (1.26–2.46)$^{\delta}$
Septum peak myocardial systolic velocity (s'_{septal}) (cm/s)	10.6 ± 1.5 (7.8–18.4)	10.9 ± 1.7 (7.5–16.6)	11.1 ± 1.8 (8.0–18.2)$^{\delta}$
Septum peak myocardial early diastolic velocity (e'_{septal}) (cm/s)	15.8 ± 2.1 (5.6–22.1)	15.4 ± 1.9 (11.8–20.4)	15.4 ± 1.8 (10.9–21.2)
Lateral peak myocardial systolic velocity ($s'_{lateral}$) (cm/s)	11.4 ± 2.0 (7.6–21.5)	11.1 ± 1.8 (8.0–17.3)	11.6 ± 1.7 (8.6–17.0)
Lateral peak myocardial early diastolic velocity ($e'_{lateral}$) (cm/s)	19.2 ± 3.2 (11.1–27.2)	18.8 ± 3.1 (10.9–27.2)	18.6 ± 2.3 (13.6–24.1)
LV global performance index	0.650 ± 0.113 (0.3–1.2)	0.776 ± 0.160 (0.4–1.1)$^{\gamma}$	0.767 ± 0.167 (0.4–1.2)$^{\delta\star}$
Right ventricle			
Tricuspid peak early diastolic wave (E) (m/s)	64.8 ± 8.3 (44–82)	65.5 ± 11.0 (44–90)	66.4 ± 9.9 (46–101)
Tricuspid peak late diastolic wave (A) (m/s)	38.8 ± 8.4 (22–60)	40.6 ± 9.2 (26–84)	40.9 ± 8.2 (25–73)
Tricuspid peak early diastolic wave/ peak late diastolic wave ratio $(E/A)_{tricuspid}$	1.72 ± 0.3 (1.2–2.6)	1.65 ± 0.3 (0.88–2.3)	1.66 ± 0.3 (1.09–2.4)
Tricuspid peak myocardial systolic velocity ($s'_{tricuspid}$) (cm/s)	14.8 ± 1.9 (10.6–21.0)	14.3 ± 2.6 (9.1–22.4)	14.2 ± 3.1 (9.1–22.4)
Tricuspid peak myocardial early diastolic velocity ($e'_{tricuspid}$) (cm/s)	17.5 ± 3.8 (12.5–32.0)	16.3 ± 2.8 (8.4–24.4)	16.7 ± 3.1 (8.8–28.0)*
RV global performance index	0.60 ± 0.10 (0.28–0.91)	0.72 ± 0.12 (0.36–1.03)$^{\gamma}$	0.75 ± 0.12 (0.33–1.00)*

LV = left ventricle; MS = metabolic syndrome; RV = right ventricle
Data are expressed as mean ± SD (range)
*$p < 0.05$, obese subjects non-MS versus obese subjects with MS
$^{\gamma}p < 0.05$, controls versus obese subjects with non-MS
$^{\delta}p < 0.05$, controls versus obese subjects with MS

blood pressure (β: 0.122, p: 0.036) in the metabolic syndrome group.

Discussion

A considerable number of studies exist, which show the harmful effects of metabolic syndrome and its components on the structure and function of the heart. On the contrary, it was shown in previous studies that asymmetric dimethyl arginine values, which negatively influence vascular haemodynamics in metabolic syndrome patients, were found high. In addition, it is known that the measurement of carotid intima-media thickness is a useful method in assessing the development of atherosclerosis. However, there are no studies on asymmetric dimethyl arginine and carotid intima-media thickness that relate to the structure and function of the heart in adolescents with metabolic syndrome. Our study is the first study in literature to assess the effects of metabolic syndrome on the right and left ventricular structure and function and carotid intima-media thickness as well as asymmetric dimethyl arginine levels.

The present study demonstrates that patient with metabolic syndrome have significantly changed left and right ventricles geometry and diastolic functions. Furthermore, we found increased carotid intima-media thickness and asymmetric dimethyl arginine levels in metabolic syndrome obese adolescents compared to non-metabolic syndrome group and controls.

In obesity, which is the main parameter of the metabolic syndrome, left and right ventricular dilatation and hypertrophy have been shown in previous studies.[15,16] The Bogalusa Heart Study revealed that obesity was associated with left ventricle dilatation and hypertrophy, and they also found that body mass index was the only independent predictor of left ventricle structure.[17] In our study, we found that left ventricle diameters, left ventricular mass, relative posterior wall thickness, and right ventricle free wall thickness were significantly higher in metabolic and non-metabolic syndrome obese groups compared with controls. Moreover, we also identified positive correlation between body mass index, waist and hip circumference measurements, and left ventricular mass and right ventricle free wall thicknesses.

Hypertension, often present in metabolic syndrome, has an adverse effect on intima-media and increase afterload of the heart. Tadic et al[18] reported that left ventricle relative posterior wall thickness, left ventricular mass index, and right ventricle free wall thickness were significantly higher in non-dippers hypertensive patients irrespective of the presence of metabolic syndrome. Despite that, the meta-analysis by Li et al[19] reported that the metabolic syndrome patients combined with hypertension showed higher left ventricular mass, and relative posterior wall thickness when compared to those with hypertension alone. In addition, they claimed that metabolic syndrome played an important role in the development of left ventricular hypertrophy, and metabolic syndrome amplified hypertension-related cardiac changes. In our study, metabolic and non-metabolic syndrome

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Table 4. Pearson's correlation between carotid intima-media thickness and cardiac geometry and functions in obese adolescents.

	Non-MS		MS	
Variable	r	P	r	p
Left ventricle				
LV mass (g)	0.427	0.000*	0.221	0.029*
LV mass index ($g/m^{2.7}$)	0.267	0.008*	0.128	0.208
Left atrial dimension (mm)	0.178	0.080	0.165	0.106
LV ejection fraction (%)	0.103	0.312	−0.181	0.075
Septum peak myocardial systolic velocity (s'_{septal}) (cm/s)	−0.046	0.654	−0.031	0.759
Lateral peak myocardial systolic velocity ($s'_{lateral}$) (cm/s)	−0.060	0.556	0.113	0.270
Mitral peak early diastolic wave/peak late diastolic wave ratio $(E/A)_{mitral}$	−0.103	0.311	−0.103	0.311
Peak early diastolic velocity/septum peak myocardial early diastolic velocity ratio (E/e'_{septal})	−0.062	0.750	0.436	0.014*
Peak early diastolic velocity/lateral peak myocardial early diastolic velocity ratio ($E/e'_{lateral}$)	0.363	0.000*	0.155	0.127
LV myocardial performance index	0.052	0.612	0.115	0.259
Right ventricle				
RV free wall diameter in diastole (mm)	0.424	0.000*	0.089	0.384
Tricuspid annular plane systolic excursion (mm)	0.187	0.065	0.018	0.862
Tricuspid peak myocardial systolic velocity ($s'_{tricuspid}$) (cm/s)	0.094	0.357	0.086	0.401
Tricuspid peak early diastolic wave/peak late diastolic wave ratio $(E/A)_{tricuspid}$	−0.069	0.501	0.087	0.397
Tricuspid peak early diastolic velocity/peak myocardial early diastolic velocity ratio ($E/e'_{tricuspid}$)	0.109	0.285	0.064	0.530
RV myocardial performance index	0.072	0.491	−0.005	0.959

*Statistically significant ($p < 0.05$)
LV = left ventricle; RV = right ventricle

obese groups had significantly higher systolic and diastolic blood pressure than the controls. Furthermore, we found that there is a positive correlation between systolic and diastolic blood pressure and left ventricular mass, and right ventricle free wall thickness in metabolic and non-metabolic syndrome obese groups, which agreed with the previous studies.

There are conflicting results regarding the effects of insulin resistance on the heart structure. In African-American adolescents, Gidding et al[20] found that, in cases, where patients with severe obesity and chronic hypertension were excluded, a weak relationship of left ventricle relative wall thickness with insulin resistance was estimated by homeostasis model assessment of insulin resistance. Karamitsos et al[21] found normal systolic function but impaired diastolic function in both ventricles in the patient with type 1 diabetes mellitus, and were unable to find any correlations between diabetes and right ventricle structure. In turn, some researchers[22–24] stated that it had a negative effect on the ventricle structure. In our study, the homeostasis model assessment of insulin resistance values in obese groups were higher as compared to the control group; however, no correlations between homeostasis model assessment of insulin resistance and left ventricular mass were found in the study groups.

In the majority of studies, systolic function of the left ventricle was reported to be in the normal range in metabolic syndrome. Mangner et al[15] found comparable left ventricle ejection fraction, decreased tissue Doppler-derived systolic peak velocity, and regional basoseptal strain in obese children compared with non-obese children. Faganello et al[25] found that left ventricle systolic function measured as stress-corrected mid-wall shortening and s′ was frequently impaired in type 2 diabetes mellitus patients without coronary artery disease; however, the coexistence of metabolic syndrome is not associated with more severe left ventricle systolic dysfunction. In our study, it was seen that left ventricle myocardial normal $s_{septal,\ lateral}$ values and systolic function measured by ejection fraction and tissue Doppler imaging were preserved in the obese and control groups. In addition, tricuspid lateral wall myocardial $s_{tricuspid}$ and tricuspid annular plane systolic excursion were found to be within normal ranges in obese and control groups. While Karakurt et al[26] measured lower tricuspid annular plane systolic excursion values in metabolic syndrome, Tadic et al[2] found that the right ventricle tricuspid annular plane systolic excursion, $s_{tricuspid}$ and right ventricle ejection fraction values were normal in metabolic syndrome and reported preservation of the systolic functions.

In contrary to the preservation of systolic functions, it was stated that there was left ventricle diastolic dysfunction with metabolic syndrome. Ayalon et al[1] reported that preclinical left ventricle diastolic dysfunction could occur independently of left ventricle hypertrophy in metabolic syndrome with lower E/A ratio and mean e′. While Tadic et al[27] found non-dipping pattern and metabolic syndrome separately cause left ventricle diastolic dysfunction in hypertensive patients, Akçay et al[28] found lower

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Table 5. Pearson's correlation between asymmetric dimethyl arginine and cardiac geometry and functions in obese adolescents.

	Non-MS		MS	
Variable	r	p	r	P
Left ventricle				
LV mass (g)	0.222	0.057	0.089	0.444
LV mass index ($g/m^{2.7}$)	0.185	0.115	0.087	0.451
Left atrial dimension (mm)	0.015	0.897	0.175	0.128
LV ejection fraction (%)	−0.025	0.832	−0.046	0.693
Septum peak myocardial systolic velocity (s'_{septal}) (cm/s)	0.010	0.934	0.057	0.620
Lateral peak myocardial systolic velocity ($s'_{lateral}$) (cm/s)	0.039	0.739	0.031	0.788
Mitral peak early diastolic wave/ peak late diastolic wave ratio $(E/A)_{mitral}$	0.090	0.172	−0.012	0.083
Peak early diastolic velocity / septum peak myocardial early diastolic velocity ratio (E/e'_{septal})	0.136	0.492	0.098	0.618
Peak early diastolic velocity/lateral peak myocardial early diastolic velocity ratio ($E/e'_{lateral}$)	0.080	0.498	0.057	0.625
LV myocardial performance index	0.445	0.143	0.474	0.914
Right ventricle				
RV free wall diameter in diastole (mm)	0.110	0.352	0.060	0.605
Tricuspid annular plane systolic excursion (mm)	−0.102	0.388	−0.018	0.876
Tricuspid peak myocardial systolic velocity ($s'_{tricuspid}$) (cm/s)	0.053	0.655	0.192	0.094
Tricuspid peak early diastolic wave/peak late diastolic wave ratio $(E/A)_{tricuspid}$	0.021	0.152	0.128	0.269
Tricuspid peak early diastolic velocity/peak myocardial early diastolic velocity ratio ($E/e'_{tricuspid}$)	0.132	0.261	−0.155	0.177
RV myocardial performance index	0.861	0.195	0.127	0.271

*Statistically significant ($p < 0.005$)
LV = left ventricle; RV = right ventricle

E/A ratio, higher E/e′ and myocardial performance index values in normotensive prediabetics. Furthermore, Karakurt et al[26] found that adult metabolic syndrome patients with preserved left ventricle ejection fraction had low E, E/A ratio in right ventricle, and high right ventricle global myocardial performance index as compared to the control group and identified diastolic dysfunction. In our study, we found lower E/A_{mitral} and higher myocardial performance index in obese adolescents, but nearly similar values in $E/e'_{lateral}$ and E/e'_{septal} in obese groups as compared to the controls.

Similarly with left ventricle diastolic dysfunction, Tadic et al[18] reported that metabolic syndrome, hypertension with non-dipping pattern, and their interaction had a huge impact on right ventricle wall thickness, parameters of right ventricle diastolic function (E/At, E/e′t, e′/a′t), as well as right ventricle global function estimated by the myocardial performance index. Gokdeniz et al[29] assessed right ventricle in metabolic syndrome patients with strain and reported deterioration in right ventricle systolic and diastolic functions in comparison with the control group. In our study, we also found right ventricle diastolic dysfunction in obese adolescents with lower $E/A_{tricuspid}$, and higher $E/e'_{tricuspid}$ and right ventricle global myocardial performance index than the controls.

High carotid intima-media thickness measurement in children with metabolic syndrome was shown in studies.[3,30] Elshorbagy et al[31] identified a significant increase in carotid intima-media thickness in metabolic syndrome patients as compared to the non-metabolic syndrome obese and control groups. Hirata et al[32] demonstrated in a study, which included 1727 subjects, that an elevated number of metabolic syndrome components, with or without central obesity, was associated with higher intima-media thickness and, hypertension had the strongest association with higher intima-media thickness. Alp et al[33] found that carotid artery intima-media thickness was strongly associated with Tei index values. In our study, we found significant increased carotid intima-media thickness in metabolic syndrome group as compared to the non-metabolic syndrome obese and control groups. Moreover, carotid intima-media thickness is correlated with waist and hip circumference measurements, total cholesterol, left ventricular mass and E/e'_{septal} ratio in metabolic syndrome patients.

Increased plasma asymmetric dimethyl arginine concentrations cause impaired nitric oxide synthesis leading to endothelial dysfunction and atherosclerotic vascular disease.[4] Bai et al[34] showed a significant association of asymmetric dimethyl arginine with carotid intima-media thickness. Palomo et al[35] found that asymmetric dimethyl arginine levels were significantly increased in the metabolic syndrome group and the levels of asymmetric dimethyl arginine were modestly but significantly correlated only with waist circumference among components of metabolic syndrome. Similar to Palomo et al,[35] we found that asymmetric dimethyl arginine levels were significantly higher, both in metabolic and non-metabolic syndrome obese groups compared to the

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controls. Furthermore, we found a correlation between asymmetric dimethyl arginine and waist/hip ratio, systolic and diastolic blood pressure in metabolic syndrome group.

Limitations

There are some limitations to our study. As this was a cross-sectional study design, it does not allow us making conclusions about the causal relationships among variables and potential reversibility of the changes with weight loss over time. Therefore, the clinical significance of these changed values in obese persons remains unknown and will require extensive longitudinal follow-up to ultimately determine their predictive value. In addition, our healthy controls were patients who were free from any metabolic syndrome factors but referred to our department for echocardiography. For this reason, they were perfectly healthy subjects. This resulted by design in baseline differences of clinical characteristics between participants with metabolic and non-metabolic syndrome. It is therefore possible that residual confounding could in part account for our findings.

Conclusion

The results of the present study demonstrate that left and right ventricular structure, diastolic, and global functions are significantly influenced by the metabolic syndrome, but that the left and right ventricular systolic functions are completely preserved in patients with metabolic syndrome. Conducting the study with a longitudinal design in the future should explain what prognostic significance the structural and functional changes of the left and right ventricle have in patients with the metabolic syndrome. Moreover, asymmetric dimethyl arginine concentrations have been found to be significantly higher in obese adolescents. In light of this data, asymmetric dimethyl arginine might be proposed as a cardiovascular risk marker to be used extensively in populations that are at risk.

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Conflicts of Interest. None.

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