FULL LENGTH ARTICLE

Assessment of left ventricular mass index could predict metabolic syndrome in obese children

Usama M. Alkholy [a,*], Ihab A. Ahmed [a], Nehad A. Karam [a], Yasser Fathy Ali [a], Ahmed Yosry [b]

[a] Department of Pediatrics, Zagazig University, Zagazig
[b] Department of Cardiology, Zagazig University, Zagazig

[a,b] Egypt

Background: Childhood obesity is a major risk factor for cardiovascular diseases in children and adults.

Objectives: The purpose of this study was to evaluate the serum leptin level and the cardiac changes in normotensive obese children and to study the relationship between left ventricular mass index (LVMI) and serum leptin with the parameters of metabolic syndrome (MS) in obese children.

Methods: This study was conducted in al Jeddani Hospital and Ibn Sina College Hospital in Saudi Arabia in the period from July 2012 to December 2013, and included 82 obese children. Their mean age was 10.2 ± 2.8 years; they were divided into 25 obese children with MS and 57 obese children without MS, and 40 healthy age- and sex-matched children were also included in the study as a control group. All children were subjected to clinical assessment including standing height, body weight, body mass index (BMI), waist circumference (WC), and blood pressure measurements. All children received an echocardiographic examination (2-dimensional, M-mode, Doppler, and tissue Doppler echocardiograpy) and laboratory assessment of serum leptin level, fasting glucose, fasting insulin, the homeostatic model assessment for insulin resistance (HOMA) index, total cholesterol, triglycerides, and high- and low-density lipoprotein profile.

Results: BMI, BMI standard deviation score, WC, fasting glucose, fasting insulin, HOMA index and the serum leptin level were significantly higher in obese children compared to control group ($p < 0.05$). The LVMI were increased in the obese compared to the control group ($p < 0.001$) while left ventricle systolic and diastolic functions did not differ in obese versus control group ($p > 0.05$). There was a significant positive correlation between both LVMI and serum leptin level in comparison to BMI, WC, fasting glucose, fasting insulin, HOMA, triglycerides, and low-density lipoprotein in all obese children, especially the MS group. However, there was a significant negative correlation between both LVMI and serum leptin level in comparison to high-density lipoprotein.

Conclusion: Assessment of LVMI as routine echocardiographic examinations and serum leptin level might be a feasible and reliable method for the evaluation of obesity and its related cardiovascular risks during childhood that can predict metabolic syndrome and insulin resistance.

Keywords: Left ventricular mass index, Metabolic syndrome, Obese children, Serum leptin

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* Corresponding author at: Consultant of Pediatrics, Al jedaani Hospital Alameer Metab street, Jeddah, Mekah 21462, Saudi Arabia.
E-mail address: usamaalkoly@yahoo.com (U.M. Alkholy).

P.O. Box 2925 Riyadh – 11461KSA
Tel: +966 1 2520088 ext 40151
Fax: +966 1 2520718
Email: sha@sha.org.sa
URL: www.sha.org.sa

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Introduction

Obesity is currently regarded as a public health problem that affects both children and adults [1]. It has been shown that obesity is associated with the development of early myocardial and coronary artery changes in children and adolescent [2]. Therefore, prior to the onset of left ventricular systolic dysfunction, emergence of diastolic dysfunction in obese children might lead to diagnosis in a very early stage of the disease [3]. Obesity affects cardiovascular parameters such as left ventricular mass (LVM) and cardiac function as well as metabolic parameters such as insulin levels and glucose tolerance [4]. Tissue Doppler echocardiography (TDE) is a recent echocardiographic imaging technique that allows evaluation of regional myocardial systolic and diastolic function [5]. Metabolic syndrome (MS) is characterized by central obesity, insulin resistance, hyperglycemia, dyslipidemia, and hypertension [6]. Adipose tissue serves not only as an energy storage organ, but also as an endocrine organ by releasing factors into the circulation that have sites of action [7]. Leptin is a peptide hormone that is predominantly produced in adipose tissue [8]. In addition to its effect on neuroendocrine, immune, and reproductive systems, leptin regulates food intake, body weight, and energy homeostasis [9]. Increased adiposity was shown to be associated with hyperleptinemia, which subsequently causes endothelial dysfunction, hypertension, and cardiovascular diseases [10]. Leptin is proposed as biomarker in children for predicting MS, Type 2 diabetes, or cardiovascular disease [11]. This study aimed to assess the LVM index (LVMI) and serum leptin level in obese nonhypertensive children and their prediction to metabolic syndrome.

Patients and methods

A cross-sectional study that comprised 82 obese children and 40 healthy children was conducted in al Jeddani Hospital and Ibn Sina College Hospital in Saudi Arabia from July 2012 to December 2013. The obese group consisted of 82 children (47 boys and 35 girls) aged 6–14 years. Their mean ± standard deviation age was 10.2 ± 2.8 years and mean body mass index (BMI) 32.8 ± 4.6 kg/m^2. The obese children had BMI $\geqslant$95th percentile for age and sex based on the standards of the Centers for Disease Control and Prevention.

Abbreviations

LVMI	left ventricular mass index
BMI	body mass index
WC	waist circumference
HOMA	homeostatic model assessment
TDE	tissue Doppler echocardiography
LVM	left ventricular mass
MS	metabolic syndrome
HOMA-IR	homeostatic model assessment for insulin resistance
LV	left ventricle
FGIR	fasting glucose insulin ratio
HDL	high density lipoprotein
SDS	standard deviation score
EM	early diastolic myocardial velocity

The control group consisted of 40 children (22 boys and 18 girls) aged 6–14 years. Their mean age was 10.6 ± 2.7 years and their mean BMI was 18.7 ± 2.9 kg/m^2. The control participants were recruited from a population of nonobese healthy children who presented to the hospital for minor illnesses. The obese patients were divided into the MS group (n = 25) and non-MS group (n = 57) according to the International Diabetes Federation consensus definition of MS in children and adolescents [12]. A local ethical committee was approved from our hospital (al Jeddani Hospital). Informed consent was obtained from parents of patients and controls. Children were excluded if they had: previous cardiac disease or taken medication known to affect cardiac function (antihypertensive drugs); an earlier major illness, including type 1 diabetes; taken medications; had a condition that is known to influence their growth, insulin action, or insulin secretion (e.g., glucocorticoid therapy, hypothyroidism, and Cushing's disease); or liver disease or impaired liver functions (see Figs. 1 and 2).

Anthropometric measures

For each child, the height and weight were measured. The height was measured to the nearest 0.1 cm using a Holtain portable anthropometer (manufacturer, address), and the weight was determined to the nearest 0.01 kg using a Seca scale balance (manufacturer, address) with the patient dressed in minimal clothes and without shoes. The BMI was calculated as weight (in kg) divided by height (in m) squared. Waist circumference (WC) was measured at the level of the umbilicus with the child standing and breathing normally. Each measurement was taken as the mean of three consecutive measurements, using standardized equipment and following the

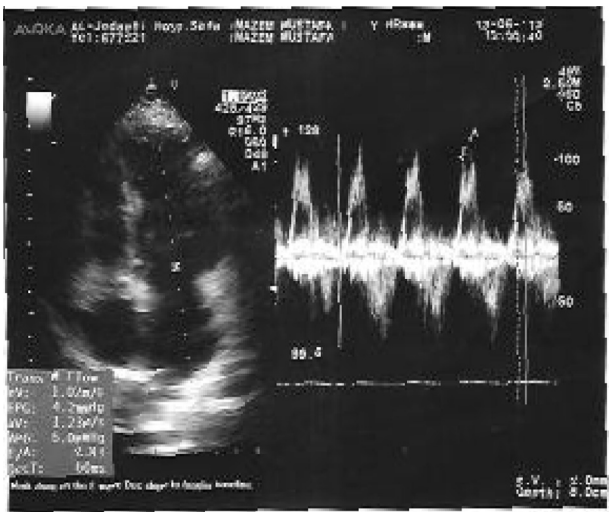

Figure 1. Doppler echocardiography showing reversed E/A ratio of the mitral valve flow.

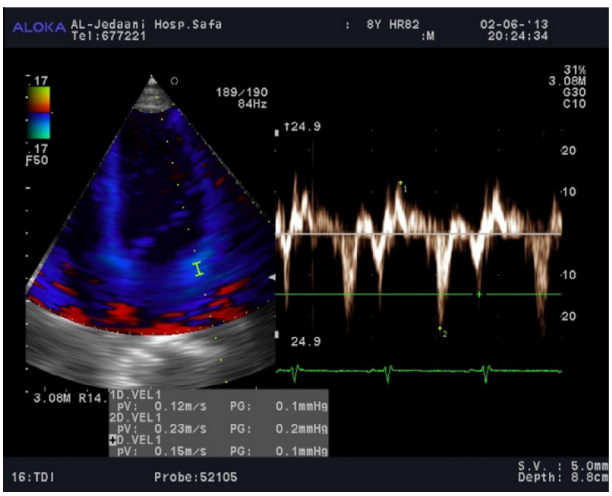

Figure 2. Tissue Doppler echocardiography on the lateral mitral annulus showing normal early diastolic myocardial velocity.

recommendations of the International Biological Program.

Biochemical measurements

Fasting venous blood samples were collected in plain tubes using a standard venipuncture aseptic technique. The samples were allowed to clot and sera were separated by centrifugation and stored in aliquots at −80 °C until assayed. Fasting glucose was measured using a quantitative enzymatic colorimetric commercial kit provided by Stanbio according to the glucose oxidase method [14]. The human leptin assay utilized ^{125}I-labeled human leptin and human leptin antiserum to determine leptin levels [15]. The detection limit of the assay was 0.5 ng/mL. Plasma concentrations of total cholesterol, high-density lipoprotein, low-density lipoprotein, and triglycerides were measured using routine enzymatic methods with Olympus 2700 Analyzer (Tokyo, Japan). Insulin levels were measured using a chemiluminescence immunoassay. The homeostatic model assessment for insulin resistance (HOMA-IR) index was calculated according to the following equation HOMA-IR = fasting insulin concentration (μU/mL) × fasting glucose concentration (mM)/22.5 [7].

Definitions of MS

Based on the MS criteria proposed by the International Diabetes Federation [12], patients were diagnosed as having MS when their WC was ⩾90th percentile and when at least two of the following factors were present: (1) raised concentration of triglycerides: ⩾150 mg/dL (1.7 mM) or receiving specific treatment for high triglycerides; (2) reduced concentration of high-density lipoprotein (HDL) cholesterol: <40 mg/dL (1.03 mM) or receiving specific treatment for this lipid abnormality; (3) raised blood pressure (BP): systolic BP ⩾130 mmHg or diastolic BP ⩾85 mmHg or receiving treatment for previously diagnosed hypertension; and (4) raised fasting plasma glucose concentration 100 mg/dL (5.6 mM) or known type 2 diabetes mellitus.

Echocardiographic measurements

All studies were performed using SCD-Alpha 7 Aloka Color Doppler Ultrasound Machine with UST-9120 (Manufacturer, address) equipped with tissue Doppler imaging technology. All patients underwent a complete two-dimensional, M mode, color Doppler imaging and TDE. During standard echocardiographic studies, diameters of left atrium, dimensions of left ventricle (LV), thickness of interventricular septum and posterior wall, LV fractional shortening, and ejection fraction were determined using parasternal long-axis approach. Ejection fraction is the fraction of the end-diastolic volume that is ejected with each beat; that is, it is stroke volume (SV) divided by end-diastolic volume (EDV) [16]:

$$E_f\% = \frac{\mathrm{SV}}{\mathrm{EDV}} \times 100$$

Under the guidance of two-dimensional and M-mode echocardiography, via parasternal long-axis view, left atrial systolic diameter, LV end-systolic diameter, LV end-diastolic diameter, LV posterior wall, and interventricular septum thickness were measured. The LVM was calculated using the for-

mula of Devereux et al. [17], by the following equation: LVM = 0.8 [1.04 × (interventricular septal thickness + posterior wall thickness + end-diastolic diameter)^3 − (end-diastolic diameter)^3] + 0.6. The LVMI was calculated as LVM divided by the body surface area and measured by g/m^2 [by the formula LVMI = LVM/height (m)$^{2.7}$].

LV diastolic functions were evaluated using Doppler echocardiography and TDE. With apical four-chamber view, the sample volume was placed on mitral valve cusps (LV inflow region), and direction of the Doppler waves were adjusted so as to parallel blood flow. Then peak early (E) and late (A) transmitral filling velocities and E/A ratio were measured. By using TDE, the LV diastolic function was evaluated by the early (Em) diastolic myocardial velocities by recording the mitral Doppler signals in the apical four-chamber view, with the sample volume placed at the lateral walls of mitral annulus.

Statistical analysis

SPSS version 9 (SPSS, Chicago, IL, USA) was used for data analysis. All data were expressed as mean ± standard deviation. The Student *t* test for quantitative independent variables was used for analysis of difference between two groups. Pearson's correlation test was used. Analysis of two independent variables was done using a non-parametric test (Mann–Whitney test). In all tests, $p < 0.05$ was considered significant.

Results

The baseline and laboratory characteristics of 82 obese children and 40 control group are reported in Table 1. BMI, BMI standard deviation score (SDS), heart rate, fasting blood glucose, fasting serum insulin levels, HOMA-IR, total cholesterol, triglycerides, low-density lipoprotein (LDL), serum leptin level, and waist circumference were significantly higher in obese children compared with the control group. Obese children had significantly lower HDL level compared with the control group. The systolic BP and diastolic BP showed no significant difference between both groups. Also, the serum leptin level in obese girls was significantly higher than in obese boys.

Table 2 shows that the LVMI of obese children was significantly higher compared with the control group ($p < 0.001$), while ejection fraction and fractional shortening of the left ventricle did not differ significantly in obese versus control group ($p > 0.05$). The diastolic function of the left ventricle in obese children (mitral E wave, A wave, E/A ratio, and Em signal) showed no significant statistical difference when compared with the control group. Doppler echocardiography and TDE measurements did not differ significantly between the two groups ($p = 0.35$).

Table 3 shows the clinical and laboratory results, and LVMI in obese children with MS ($n = 25$) and without MS ($n = 57$). MS children had significantly higher LVMI, serum leptin, fasting serum insulin,

Table 1. Clinical and laboratory characteristics of the studied children.

	Obese children $n = 82$	Control group $n = 40$	p
Age (y)	10.2 ± 2.8	10.6 ± 2.7	0.45
Male/female	47/35	22/18	0.8
BMI (kg/m^2)	32.8 ± 4.6	18.7 ± 2.9	<0.001
BMI-SDS	2.8 ± 0.6	2.1 ± 1.1	<0.001
Duration of obesity	3.8 ± 3.2	—	—
Heart rate (beats/min)	90 ± 14	75 ± 13	0.001
Systolic BP (mmHg)	112 ± 16	110 ± 15	0.05
Diastolic BP (mmHg)	78 ± 12	74 ± 8	0.058
Waist circumference (cm)	88.4 ± 13.8	56.2 ± 12.8	0.001
Total cholesterol (mg/dL)	168.9 ± 44.4	142.6 ± 38.8	0.001
Triglycerides (mg/dL)	118.6 ± 48.9	80.9 ± 34.8	0.001
LDL cholesterol (mg/dL)	128.9 ± 33.2	81.2 ± 26.4	0.001
HDL cholesterol (mg/dL)	40.1 ± 9.8	50.9 ± 8.8	0.001
Fasting glucose (mg/dL)	89.4 ± 15	81.6 ± 12	0.004
Fasting insulin (μU/mL)	18.2 ± 10.2	8.6 ± 3.8	<0.001
FGIR	4.7 ± 1.3	8.9 ± 3.6	<0.001
HOMA-IR	4.06 ± 2.2	1.8 ± 0.8	<0.001
Serum leptin level (ng/mL)	20.2 ± 6.2	5.2 ± 2.4	<0.001
Boys	17.9 ± 6.6	4.4 ± 3.8	<0.001
Girls	24.1 ± 1.9	6.9 ± 2.8	<0.001

BMI = body mass index; BP = blood pressure; FGIR = fasting glucose insulin ratio; HDL = high density lipoprotein; HOMA-IR = homeostatic model assessment for insulin resistance; SDS = standard deviation score.

Table 2. Comparisons of echocardiographic data between obese and control group.

Characteristic	Obese	Non-obese	*p*
Ejection fraction (%)	65.96 ± 6.28	67.44 ± 5.94	0.21
Fractional shortening (%)	35.2 ± 4.8	36.66 ± 4.34	0.1
Mitral E wave (m/s)	0.92 ± 0.18	0.91 ± 0.14	0.75
Mitral A wave (m/s)	0.57 ± 0.14	0.58 ± 0.18	0.73
Mitral E/A	1.60 ± 0.28	1.57 ± 0.29	0.88
Em (cm/s)	18.9 ± 5.2	19.8 ± 4.8	0.35
LVMI ($g/m^{2.7}$)	56.6 ± 14.1	42.7 ± 12.6	<0.001

Em = early diastolic myocardial velocity; LVMI = left ventricular mass index.

Table 3. Clinical and laboratory data, and left ventricular mass index (LVMI) in obese children with and without metabolic syndrome (MS).

	MS group *n* = 25	Non-MS group *n* = 57	*p*
BMI (kg/m^2)	32.8 ± 4.4	31.2 ± 4.6	0.14
BMI-SDS	2.7 ± 0.6	2.6 ± 0.5	0.43
Systolic BP (mmHg)	116 ± 12	107 ± 14	0.006
Diastolic BP (mmHg)	78 ± 10	75 ± 12	0.27
Waist circumference (cm)	86.8 ± 13.6	84.6 ± 13.9	0.5
Triglycerides (mg/dL)	138.6 ± 35.8	102.9 ± 32.2	0.001
HDL cholesterol (mg/dL)	41.8 ± 8.8	44.8 ± 12.8	0.29
LDL cholesterol (mg/dL)	107.6 ± 35.4	104.6 ± 32.4	0.7
Fasting glucose (mg/dL)	88.6 ± 14	86.6 ± 13	0.53
Fasting insulin (μU/mL)	25.2 ± 11.8	15.8 ± 8.8	<0.001
FGIR	3.4 ± 1.1	5.7 ± 1.4	<0.01
HOMA-IR	5.4 ± 3.8	3.5 ± 2.4	<0.01
LVMI (g/m^2)	60.8 ± 17.4	50.6 ± 17.6	0.017
Serum leptin level (ng/mL)	21.8 ± 7.9	16.5 ± 7.0	<0.01
Boys	18.9 ± 4.8	15.3 ± 5.8	<0.01
Girls	24.8 ± 1.9	18.9 ± 6.8	<0.01

BP = blood pressure; BMI = body mass index; FGIR = fasting glucose insulin ratio; HDL = high density lipoprotein; HOMA-IR = homeostatic model assessment for insulin resistance; LVMI = left ventricular mass index; SDS = standard deviation score.

Table 4. Correlation between serum leptin and various parameters in obese children with and without metabolic syndrome (MS).

	Leptin in obese children with MS		Leptin in obese children without MS	
	r	*p*	*r*	*p*
BMI	0.724	<0.001	0.625	<0.001
Systolic BP	0.128	0.06	0.168	0.07
Diastolic BP	0.154	0.07	0.178	0.08
Waist circumference	0.822	<0.001	0.804	<0.001
Total cholesterol	0.188	0.08	0.190	0.08
Triglycerides	0.084	0.422	0.094	0.482
LDL cholesterol	0.166	0.123	0.202	0.148
HDL cholesterol	−0.026	0.812	−0.036	0.654
Fasting glucose	0.482	<0.01	0.422	<0.01
Fasting insulin	0.435	0.01	0.388	0.01
HOMA-IR	0.328	0.01	0.358	0.01
LVMI	0.345	<0.01	0.335	<0.01

BP = blood pressure; BMI = body mass index; FGIR = fasting glucose insulin ratio; HDL = high density lipoprotein; HOMA-IR = homeostatic model assessment for insulin resistance.

HOMA, and triglycerides compared to non-MS children, while no significant difference between the MS and non-MS children regarding BMI, BMI-SDS, WC, fasting blood glucose, total cholesterol, LDL, and HDL levels was found ($p > 0.05$).

Table 4 shows that, in both MS and non-MS groups, the serum leptin had a positive correlation with BMI, WC, triglycerides, fasting glucose, fasting insulin, HOMA-IR, and LVMI, but showed a negative correlation with HDL. There was no cor-

Table 5. Correlations between left ventricular mass index (LVMI) and cardiovascular risk factors in obese children with and without metabolic syndrome (MS).

	LVMI in obese children with MS		LVMI in obese children without MS	
	r	*p*	*r*	*p*
BMI	0.344	0.005	0.196	0.008
BMI-SDS	0.358	<0.005	0.560	0.001
Systolic BP	0.330	0.017	0.248	0.021
Diastolic BP	0.242	0.012	0.216	0.024
Waist circumference	0.220	0.015	0.260	0.004
Triglycerides	0.394	0.001	0.312	<0.01
HDL cholesterol	0.047	0.350	0.060	0.11
Fasting insulin	0.322	0.009	0.359	<0.001
FGIR	0.355	0.014	0.312	<0.001
HOMA-IR	0.324	0.011	0.343	<0.001

BP = blood pressure; BMI = body mass index; FGIR = fasting glucose insulin ratio; HDL = high density lipoprotein; HOMA-IR = homeostatic model assessment for insulin resistance; SDS = standard deviation score.

relation found between serum leptin in either group with blood pressure, total cholesterol, or LDL.

Table 5 shows the correlations between LVMI and other measurements in obese children and those of MS. When LVMI was considered as a continuous variable in the whole population of obese children, it was found positively correlated with BMI-SDS, WC, systolic BP, diastolic BP, triglycerides, fasting insulin levels, HOMA-IR and fasting glucose insulin ratio, and negatively correlated with HDL cholesterol.

In receiver operating characteristic analysis, the results showed that an LVMI value of >38 g/m^2 was the best cut-off value in predicting metabolic syndrome in obese children with a sensitivity of 95% and a specificity of 84% (Fig. 3).

Discussion

Obesity is an important risk factor for atherosclerotic cardiovascular disease. Risk factor control in young people might retard the progression of atherosclerosis [2]. Therefore, it is very important to study the structural and functional cardiac changes and assess the serum leptin level in obese children and study their relations to parameters of MS in children.

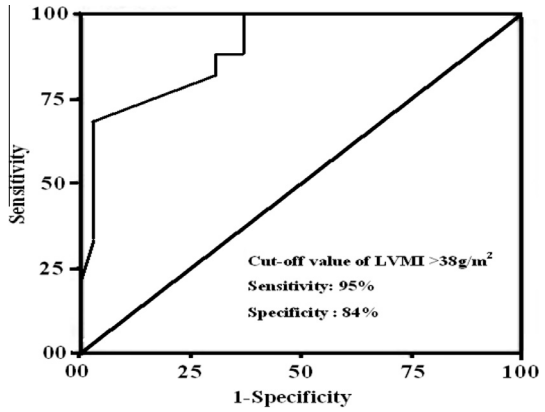

Figure 3. Receiver operating characteristic curve of left ventricular mass index cut-off value in predicting metabolic syndrome.

In this study, the obese group showed significant increase in the mean level of triglycerides, total cholesterol, LDL, fasting glucose level, fasting insulin level, and HOMA-IR when compared to the control group. However, the level of HDL showed a significant decrease in obese children when compared to control group. This can be explained and supported by studies that found that both obesity and type 2 diabetes are associated with dyslipidemia and insulin resistance [18], although most obese, insulin-resistant individuals do not develop hyperglycemia unless there is impaired B cell function [19].

In our study, assessment of systolic function by measuring ejection fraction and fractional shortening showed normal results with no significant statistical difference between obese children and control group, and even between MS obese children and non-MS obese children. Similarly, most echocardiographic studies that assessed systolic function in obese individuals showed normal results [20,21]. Chinali et al. [22] and Pascual et al. [23] reported that a reduction of indices of systolic function was only found in patients with a considerable degree of obesity, suggesting that left ventricular function is affected late in the course of obesity.

The diastolic functions in our obese children (through echo Doppler and TDE) showed no significant statistical difference when compared to control group. Some studies have specifically investigated the impact of obesity on diastolic function in children found normal results by using

echo Doppler [24–27]. In contrast to most results, Harada et al. [28] found altered transmitral and pulmonary venous velocities in 21 obese children using pulse wave Doppler, suggesting a reduction in early diastolic filling. Mehta et al. used TDE to measure the diastolic function in obese children, and revealed impaired diastolic function [29]. Other studies using TDE to assess the effects of childhood obesity on diastolic function have reported similar findings [24,25,30,31].

In this study, the LVMI in obese children was significantly higher when compared to control group and also more significant in MS obese children when compared to non-MS obese children. Moreover, a significantly positive correlation was detected between LVMI and parameters of MS syndrome and also with those of insulin resistance this suggests that MS may have a harmful effect on myocardial structure [32]. Some studies found a relationship between insulin resistance and LVM whereas others found no relationship at all [18,22,33–36]. The association of MS with cardiac hypertrophy might be explained also by non-hemodynamic factors, such as insulin resistance and the accompanying compensatory hyperinsulinemia, which are considered to be the major pathophysiological features underlying the MS [37].

This study demonstrates that leptin levels were significantly higher in obese children when compared with the control group. This finding was confirmed by other studies [38,39]. Our study confirms previous findings of higher leptin levels in obese girls [40,41]. This is attributed to inhibitory effect of testosterone on leptin production [42]. Despite good correlation of leptin and BMI, we observed significant variability in leptin levels in individuals with similar BMI. This may be related to differences in body composition and fat distribution. Maffie et al. described significant heterogeneity in leptin concentration in individuals with similar BMI [43]. In our study, a positive correlation was seen between serum leptin with the triglycerides, fasting insulin, fasting glucose, and HOMA-IR and negative correlation was seen with HDL. These observations indicate a role of leptin resistance in the pathogenesis of dyslipidaemia. Leptin levels are shown to predict the development of MS independent of baseline obesity [44]. Some studies found no significant relationship between leptin and lipids [38,45], whereas another study found that lipids showed significant correlation with leptin levels [46].

Lastly, in this study, the serum leptin was positively correlated with LVMI. This confirms other studies that showed same results in adolescence and young adults [47,48], although some studies showed no correlation between leptin and LVM [49], or that even higher leptin level was associated with lower LVM [50].

Conclusion

The main findings in the current study are: (1) serum leptin was significantly higher in obese children with MS; (2) obese children with MS had insulin resistance; (3) LVMI was significantly correlated with both serum leptin level and insulin resistance in obese children with MS; and (4) a value of $\geqslant 38\ g/m^2$ LVMI was the optimal cut-off in predicting MS in obese children. We suggest that assessment of LVMI as a routine echocardiographic examination of obese children might be used in predicting the presence of MS and insulin resistance.

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