The Turkish Journal of Pediatrics 2024; 66(6): 690-702
https://doi.org/10.24953/turkjpediatr.2024.4558

Original Article

Evaluation of metabolic syndrome components, serum uric acid levels and epicardial adipose tissue thickness in pubertal children by severity of obesity

Gönül Büyükyılmaz[1], Yasemin Özdemir Şahan[2]

[1]Department of Pediatric Endocrinology, Ankara Bilkent City Hospital, Ankara; [2]Department of Pediatric Cardiology, Ankara Bilkent City Hospital, Ankara, Türkiye.

ABSTRACT

Background. We aimed to evaluate how the parameters used in the diagnosis of metabolic syndrome (MetS) and parameters such as epicardial adipose tissue (EAT) thickness, insulin resistance (IR), and serum uric acid (SUA) are affected according to the severity of obesity.

Methods. A total of 120 obese patients aged 10-18 years were classified as class 1-2-3 according to their body mass index (BMI) score. SUA was measured and oral glucose tolerance tests were performed on all patients. MetS components were determined according to the International Diabetes Federation 2007 criteria. IR was calculated using homeostatic model assessment for insulin resistance (HOMA-IR) and whole body insulin sensitivity index (WBISI).

Results. HOMA-IR was higher in the class 3 group than in the class 1 ($p<0.001$) and class 2 groups ($p<0.01$). WBISI was lower in the class 3 group than in the class 1 ($p=0.015$) and class 2 groups ($p<0.01$). EAT thickness was higher in the class 3 group than in the class 1 ($p<0.01$) and class 2 groups ($p<0.01$). No significant difference was found between class 1 and 2 groups for HOMA-IR, WBISI, and EAT thickness variables. The frequency of the MetS components was similar between the class of obesity groups ($p=0.702$). SUA and EAT thickness were significantly higher in the group with 2 and/or more MetS components than in the group with no MetS component. EAT thickness was positively and moderately correlated with SUA levels (Rho=0.319, $p<0.001$).

Conclusions. A more significant increase in cardiovascular disease risk factors, especially after class 2 obesity suggests that obese people should be followed closely and necessary interventions made for the prevention and progression of obesity. SUA and EAT thickness, an important risk factor affecting the obesity-related comorbidities, are positively correlated with each other and can be used in the follow-up of obese children.

Key words: obesity, epicardial adipose tissue, uric acid, metabolic syndrome, insulin resistance.

Obesity is one of the important childhood health problems, and its increasing prevalence can cause many serious obesity-related comorbidities such as insulin resistance (IR), type-2 diabetes mellitus (T2DM), metabolic syndrome (MetS), and cardiovascular diseases (CVD).[1,2] Although obesity is defined in terms of body mass index (BMI) determined by age and sex, BMI alone may not classify the risks of having obesity-related comorbidities. The utility of BMI in assessing obesity has been criticized for its inability to distinguish between fat, muscle, and skeletal weight. Individuals with similar BMI may have very different metabolic profiles.[3] However, Ortega et al.,[4] reported that BMI strongly predicts cardiovascular mortality

✉ Gönül Büyükyılmaz ▪ gonulgulal@hotmail.com

Received 10th Jun 2024, revised 26th Aug 2024, accepted 12th Sep 2024.

and may be more important than total adiposity measures evaluated by complex, expensive methods.

Studies have also reported that regional, visceral, and organ-specific adiposity play an important role in the development of obesity-related comorbidities.[5] As people gain weight, fat accumulates mainly in the subcutaneous tissue. However, as weight gain continues, excess fat tends to accumulate in ectopic areas such as the liver, pancreas, kidney, muscle, and also heart.[6,7] The pathophysiological mechanisms underlying the transition from subcutaneous fat accumulation to ectopic fat accumulation have not yet been elucidated. Ectopic fat stores may contribute to obesity-related comorbidities, and this association may be relevant to clinical entities such as "metabolically healthy" obesity phenotypes.[8] Epicardial adipose tissue (EAT), which is one of the ectopic fat deposits, is a fat tissue deposit located mainly around the epicardial coronary vessels, on the right ventricle surface and on the anterior wall of the left ventricle, between myocardium and visceral pericardium.[9] Studies have shown a strong correlation between EAT thickness and anthropometric and imaging measurements of visceral adipose tissue.[10,11]

Although EAT serves important physiological functions, it has been shown in adults that excessive EAT is associated with coronary artery disease, MetS, IR, and impaired fasting glucose (IFG).[12,13] While the assessment of MetS in adults is based on criteria set by national or international organizations, assessment among children and adolescents is still unclear. Most assessments are based on adaptations based on adult criteria. Numerous biomarkers, including adipokines and inflammatory markers, have been discovered, better aiding the understanding of pathophysiology and detecting MetS early. Serum uric acid (SUA) is one of them. Studies have found that high SUA levels are associated with the risk of MetS.[14] Evaluation of EAT thickness by echocardiography has been developed as an indirect marker of CVD and metabolic changes in adults. However, studies in children are limited. Therefore, the main aim of this study is to evaluate how the parameters used in the diagnosis of MetS and parameters such as EAT thickness, IR, and SUA are affected according to the severity of obesity.

Materials and Methods

Participants

Patients aged 10-18 years with Tanner stage 3 and above who were examined and observed for obesity in Ankara Bilkent City Hospital pediatric endocrinology and pediatric cardiology clinics between September 2019 and December 2022 were included in this retrospective study. Adolescents with a BMI at or above the 95th percentile for children of the same age and sex and without chronic disease involving the endocrine, cardiac, or any other system were included in the obese group. Screening tests for T2DM in youth should be considered after the onset of puberty or > age ten years, whichever is earlier, in youth with BMI ≥ 85th percentile for age and sex with one or more of the following: family history of type 2 DM, race or ethnicity associated with higher risk, signs of insulin resistance or, low birth weight (small for gestational age) or high birth weight, maternal history of DM or gestational DM.[15] Oral glucose tolerance test (OGTT) was performed on patients who met these criteria. Patients with dyslipidemia, being investigated for high blood pressure, and a family history of early coronary artery disease were evaluated by pediatric cardiology. Obese patients who were assessed by cardiology and had an OGTT were included in the study. Previous studies reported that 1-hour OGTT glucose of > 155 mg/dL showed lower insulin sensitivity, impaired β-cell function, and worse cardiovascular risk profile and, therefore, are at greater risk of developing T2DM and cardiovascular disease.[16] OGTTs are performed at standard 0, 30, 60, 90, and 120 minutes in our department. All our patients were at Tanner stage 3 and above. The pubertal transition is a time during which rapid and dynamic changes

occur in various metabolic systems, including hormonal regulations, changes in body fat and its distribution, as well as increased insulin resistance. Insulin sensitivity changes with pubertal stages. It reaches its lowest point midway through maturation (Tanner stage 3), approaching near pre-pubertal levels at the end of maturation (Tanner stage 5).[17] To minimize differences that may arise from pubertal changes, those at Tanner stage 3 and above group were included. The control group, which is suitable for the obese group in terms of age, gender, and puberty was compared to the obese group in terms of EAT thickness. EAT thickness is routinely examined in patients undergoing echocardiography in the pediatric cardiology outpatient clinic. The healthy control group was composed of patients referred to pediatric cardiology with complaints such as chest pain and murmur, whose cardiological examination was normal, and whose BMI was below the 85th percentile for age and gender.

Patients with endocrine and syndromic causes of obesity, and using drugs that affect insulin action and secretion were excluded from the study. The study was approved by the Clinical Research Ethics Committee of Ankara Bilkent City Hospital with a decision no 23-4512 dated July 12, 2023.

Anthropometric and clinical measurements

The height and weight of all participants were measured. Weight measurement was made with electronic scales (measuring accuracy of 0.1 kg) with thin clothes without shoes. Height was measured with a Harpenden stadiometer (0.1 cm measurement accuracy), standing upright, with feet together and parallel, and with the shoulder and gluteal region touching the wall. BMI was calculated by dividing weight (kg) by height squared (m^2). Standard deviation score (SDS) of height, weight, and BMI were calculated. Obesity was diagnosed in patients with a BMI greater than the 95th percentile for age and gender.[18] Obesity is further divided into three classes according to the severity of obesity[18,19]: If BMI is ≥95th percentile to <120% of the 95th percentile according to age and gender, class 1; if BMI is ≥120% to <140% of the 95th percentile according to age and gender, class 2; if BMI is ≥140% of the 95th percentile for age and gender, class 3.

Tanner staging system was used in pubertal staging. Systolic blood pressure (SBP) and diastolic blood pressure (DBP) were measured three times after 10 minutes of rest in the supine position. The mean of the three measurements was calculated. Individuals were considered hypertensive if the mean of the measurement was 95th percentile and above or SBP ≥130 mmHg or DBP ≥85 mmHg.[20,21]

Laboratory tests

Plasma glucose (PG), aspartate aminotransferase (AST), alanine aminotransferase (ALT), g-glutamyl transferase (GGT), SUA, total cholesterol (TC), triglyceride (TG), and high-density lipoprotein (HDL) cholesterol, and low-density lipoprotein (LDL) cholesterol were measured for the obese group after 12 h of fasting by enzymatic colorimetric assays (Atellica Solution CH90, Siemens, Germany). Insulin levels were measured by chemiluminescence immunoassay (Siemens Healthineers, Erlangen, Germany).

Obese patients underwent the OGTT after 12 hours of fasting. Participants were given 1.75 g/kg glucose (maximum 75 g) in an average of 5 minutes. Venous blood samples were taken at 0, 30, 60, 90, and 120 minutes for plasma glucose and insulin. The results were evaluated according to the American Diabetes Association criteria[22]:

- Fasting plasma glucose (FPG) <100 mg/dL (5.6 mmol/L) and 2-h PG <140 mg/dL (7.8 mmol/L), normal glucose tolerance.
- FPG 100–125 mg/dL (5.6–6.9 mmol/L), IFG.
- 2-h PG 140–199 mg/dL (7.8–11.0 mmol/L), impaired glucose tolerance (IGT).

- FPG ≥126 mg/dL (7.0 mmol/L) and 2-h PG ≥200 mg/dL (11.1 mmol/L), diabetes mellitus.

IR was calculated using the homeostasis model assessment of fasting insulin resistance (HOMA-IR): FPG (mmol/L) X fasting insulin (mIU/L) /22.5.

Insulin sensitivity was calculated using whole-body insulin sensitivity index (WBISI).

$$\mathrm{WBISI} = \frac{10000}{\sqrt{G_0 \times I_0 \times G_{\mathrm{mean}} \times I_{\mathrm{mean}}}}$$

where G_0 stands for fasting glucose, I_0 for fasting insulin, G_{mean} for the mean PG concentration during the OGTT, and I_{mean} for the mean plasma insulin concentration during the OGTT.[23]

The criteria developed by the International Diabetes Federation (IDF) were used as MetS criteria[21]: Since waist circumference was not measured, other criteria of the MetS were evaluated.

- 10 to 16 years old: TG ≥150 mg/dL (1.7 mmol/L); HDL <40 mg/dL (1.03 mmol/L); SBP ≥130 mmHg or DBP ≥85 mmHg, or treatment for hypertension, or a SBP level of at least 95th percentile for sex, age and height; FPG levels ≥100 mg/dL (5.6 mmol/L) or known T2DM
- > 16 years old (adult criteria): TG ≥150 mg/dL (1.7 mmol/L); HDL <40 mg/dL (1.03 mmol/L) in males, < 50 mg/dl (1.29 mmol/L) in females; SBP ≥130 mmHg or DBP ≥85 mmHg, or treatment for hypertension; FPG levels ≥100 mg/dL (5.6 mmol/L) or known T2DM

Echocardiographic examination

All patients were evaluated by a single experienced pediatric cardiologist with the same ultrasound system (iE33, Philips, The Netherlands, Eindhoven) equipped with a broadband (1-5 MHz) X5-1 transducer. EAT, identified as the echo-free space between the outer wall of the myocardium and the visceral layer of the pericardium, was measured from the left lateral decubitus position of the participants. The measurements from its thickest part were performed on each parasternal long-axis and short-axis view by directing the ultrasonic beam perpendicular to the right ventricular free wall from the reference point of the aortic annulus on the parasternal long-axis and the reference point of the interventricular septum and papillary muscle tip on the parasternal short axis section at the end of systole. The average value of three cardiac cycles from each echocardiographic view was computed. In addition, apical 4-chamber, parasternal long axis, and parasternal short axis images of all echocardiographies performed in our hospital are routinely recorded in the system.

Statistical analysis

All analyses were carried out with SPSS 25.0 (IBM, USA). The findings of the study are expressed as frequency and percentages. Normality analysis was carried out using the Kolmogorov-Smirnov and Shapiro-Wilk tests. The variables without normal distribution are presented as median and interquartile range (IQR) with 25-75 percentiles, while variables with normal distribution are expressed as mean±standart deviation. Categorical variables were compared with the chi-square test using Yate's correction. Numerical variables with and without normal distribution were compared using the independent samples t-test and Mann-Whitney U test, respectively. One-way ANOVA and Kruskal-Wallis tests were used to compare numerical variables between more than two groups. Post-hoc multiple comparisons were made with Bonferroni or Dunnett's T3 tests according to equality of variances. Spearman correlation analysis was performed to determine the variables associated with EAT thickness and the obesity class. The correlation of SUA and EAT thickness with the scatter plot graphic is shown in Fig. 1. Multiple linear regression analysis using the backward method was performed to determine variables associated with EAT thickness. ROC analysis was

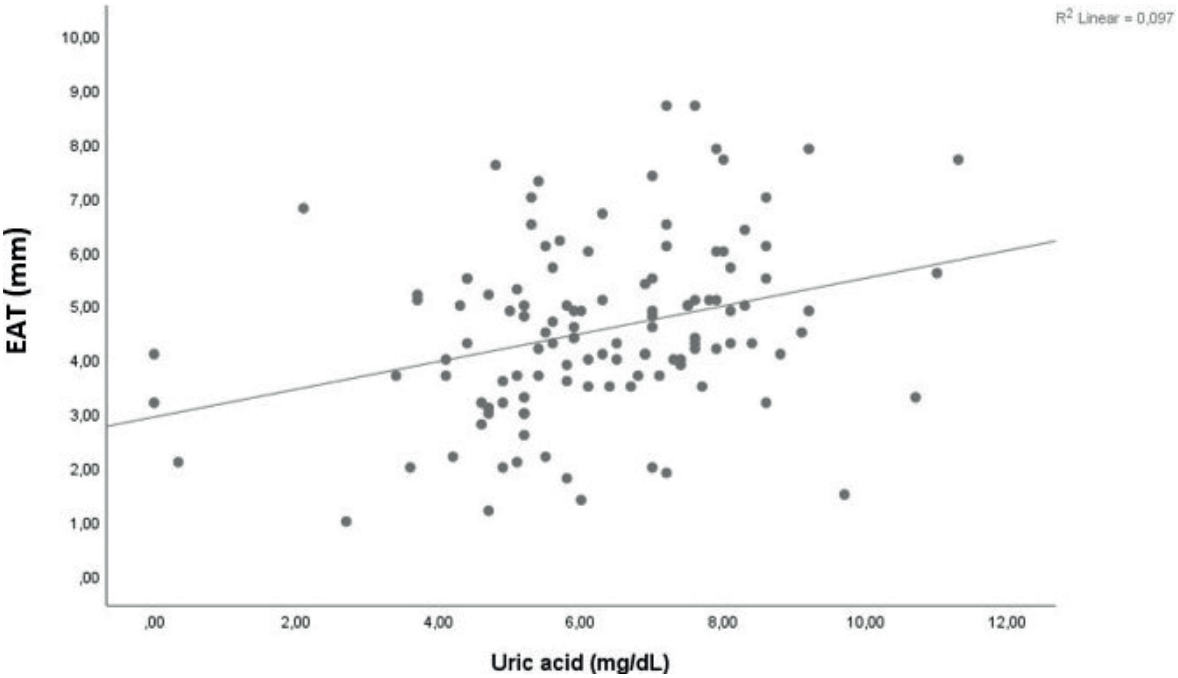

Fig. 1. Scatter plot of epicardial adipose tissue (EAT) thickness and serum uric acid level.

conducted to determine the possible association of BMI SDS and EAT thickness. The confidence interval was set at 95%, and the margin of error accepted was set to 5%. Therefore, the p <0.05 was considered significant.

Results

One hundred twenty obese patients (55 males and 65 females) with a mean age of 14.9±1.8 years were studied. Their median BMI SDS was 2.9 (Q1-Q3: 2.5-3.3). The control group included 95 normal-weight children (43 males and 52 females) with a mean age of 14.9±1.7 years. Their median BMI SDS was -0.25 (Q1-Q3: -0.73-0.44). EAT thickness was found to be statistically significantly higher in obese patients than in the healthy control group (p<0.001).

Demographic, clinical features and laboratory parameters of obese patients classified as class 1-2-3 according to the severity of obesity are presented in Table I. While the rate of males was higher in the class 1 group, the rate of females was higher in classes 2 and 3. The frequency of the female gender increased in line with the BMI category. HOMA-IR, WBISI, and EAT thickness were significantly different between classes of obesity groups. No significant difference was found between classes 1 and 2 for HOMA-IR and WBISI variables (p>0.05). Therefore, HOMA-IR was higher in the class 3 group than in the class 1 (p<0.001) and the class 2 group (p<0.01). WBISI was lower in the class 3 group than the class 1 (p=0.015) and the class 2 group (p<0.01). EAT thickness was higher in the class 3 group than in the class 1 (p<0.01) and the class 2 group (p<0.01). However, no difference was found between the classes 1 and 2 (p=0.889). A significant difference was found between groups when EAT thickness was compared between the control, class 1, 2, and 3 groups (p<0.001). Post hoc analysis showed that differences existed between the control group-class 1 group (p<0.001), control group-class 2 group (p<0.001), and control group-class 3 group (p<0.001).

Each component of MetS was compared between the class of obesity groups. The groups were similar regarding high TG levels, low HDL levels, and high blood pressure. IFG or the presence of DM could not be compared because

Table I. Comparison of demographic, clinical features and laboratory findings according to class of obesity.

	Class 1 (n=41)	Class 2 (n=47)	Class 3 (n=32)	P
Demographic and clinical features				
Female/male (n)	15/26	27/20	23/9	<0.01
Age (years)	15.0±1.9	14.9±1.9	14.9±1.7	0.941
BMI (kg/m^2)	30.7 (30.1-31.5)	33.9 (32.6-34.9)	39.6 (36.4-42.7)	<0.001
BMI SDS	2.4 (2.2-2.5)	2.9 (2.8-3.1)	3.6 (3.4-4.1)	<0.001
SBP (mmHg)	125.0 (120.0-135.0)	125.0 (120.0-135.0)	121.5 (120.0-130.5)	0.346
DBP (mmHg)	66.0 (60.0-76.3)	80.0 (70.0-90.0)	70.0 (67.3-80.0)	0.187
Laboratory parameters				
Urea (mg/dL)	23.9±5.3	22.9±4.9	21.9±3.9	0.430
Creatinine (mg/dL)	0.7±0.1	0.7±0.1	0.7±0.1	0.664
Uric acid (mg/dL)	6.1 ±2.0	6.2±1.8	6.2±1.9	0.638
ALT (U/L)	36.5 (25.0-51.5)	26.0 (21.0-39.0)	35.0 (23.3-51.0)	0.129
AST (U/L)	23.5 (16.0-30.3)	22.0 (15.0-28.0)	24.5 (17.0-31.3)	0.304
GGT (U/L)	25.0 (17.8-31.3)	19.0 (15.0-25.0)	21.0 (16.8-27.3)	0.227
Fasting plasma glucose (mg/dL)	90.7±7.3	90.9± 7.5	89.9 ±12.8	0894
Fasting insulin (mIU/L)	19.0 (8.9-44.0)	21.0 (6.0-52.0)	32.0 (15.0-107.0)	<0.001
Total cholesterol (mg/dL)	170.5± 32.9.0	164.1±29.0	166.0±34.6	0.635
HDL (mg/dL)	42.1±8.7	42.7±9.3	39.7±8.4	0.252
LDL (mg/dL)	103.1±27.2	94342.7±25.0	96.9±21.9	0.316
TG (mg/dL)	110.0 (88.0-149.5)	115.0 (88.0-158.0)	138.5 (92.5-184.3)	0.146
HOMA-IR	4.3 (3.2-6.2)	4.5 (3.5-7.0)	7.1 (5.2-9.7)	<0.001
EAT thickness (mm)	4.0±1.3	4.2±1.7	5.2±1.4	<0.01
WBISI	2.8 (1.6-2.9)	2.1 (1.4-2.9)	1.4 (1.1-1.8)	<0.01

Data presented as mean±standard deviation, or median (Q1-Q3).
ALT: Alanine aminotransferase; AST: Aspartate aminotransferase; BMI: Body mass index; DBP: Diastolic blood pressure; EAT: Epicardial adipose tissue; GGT: g-glutamyl transferase; HDL: High-density lipoprotein; HOMA-IR: Homeostatic model assessment for insulin resistance; LDL: Low-density lipoprotein; SBP: Systolic blood pressure; SDS: Standard deviation score; TG: Triglyceride; WBISI: Whole body insulin sensitivity index.

of the low number of cases in the groups (Table II). The frequency of metabolic syndrome components was similar between the class of obesity groups (p=0.702) (Table III). In the subgroup analysis, the proportion of patients without MetS components was significantly lower in the class 3 obesity group than in class 1 and 2 (p=0.034).

The comparisons of demographic and clinical variables regarding number of abnormal MetS components are shown in Table IV. AST level was found to be higher in the 2 and/or more MetS component group than the 1 MetS component group (p=0.013) and the group without MetS component (p<0.01). The SUA levels were different among groups. It was significantly higher in the group with 2 and/or more MetS components than in the groups with no MetS component (p<0.01) and 1 MetS component (p=0.024). WBISI value was significantly different between groups (p=0.045). WBISI was lower in the 2 and/or more MetS component group than in the groups with no MetS component (p=0.025) and 1 MetS component (p=0.039). The EAT thickness level was higher in the group with 2 and/or more MetS components than in the group without a MetS component (p=0.047); therefore, EAT thickness was statistically similar to that of the group with 1 MetS component. Also, no significant difference was found between 1 MetS component group and the group without any MetS component (p>0.05).

Table II. Prevalence of each component of metabolic syndrome according to class of obesity.

MetS Components	Class 1 (41)	Class 2 (47)	Class 3 (32)	P
Triglycerides ≥ 150 mg/dL	10 (24.3)	12 (25.5)	14 (43.7)	0.099
HDL-cholesterol < 40 mg/dL, 16+ age in females < 50 mg/dL	22 (53.6)	21 (44.6)	18 (56.2)	0.590
Hypertension	7 (17.1)	8(17.0)	8 (25)	0.619
Impaired FBG or T2DM	3 (7.3)	4 (8,5) 1(2.1)	3 (9.4) 3 (9.4)	-

Data presented as number (percentage).
FBG: Fasting blood glucose; HDL: High-density lipoprotein; MetS: Metabolic syndrome; T2DM: Type 2 diabetes mellitus.

Table III. Comparison of frequency of metabolic syndrome components between class of obesity groups.

Number and frequency of MetS components	Class 1 (41)	Class 2 (47)	Class 3 (32)	All	p
0	15 (36.5)	18 (38.3)	4 (12.5)	37 (30.8)	
1	16 (39.1)	16 (34.1)	14 (43.8)	46 (38.4)	0.702
2 and/or more	10 (24.4)	13 (27.7)	14 (43.8)	37 (30.8)	

Data presented as number (percentage).
MetS: metabolic syndrome.

Table IV. Comparison of demographic, clinical features and laboratory findings regarding number of abnormal metabolic syndrome components.

	No component (n=37)	1 component (n=46)	2 and/or more component (n=37)	p
Female/male (n)	25/12	26/20	14/23	0.157
BMI SDS	2.9±0.5	3.0±0.6	3.0±0.6	0.377
ALT (U/L)	25.5 (21.3-39.0)	30.5 (19.3-57.8)	36.0 (27.8-56.3)	0.08
AST (U/L)	19.0 (13.8-23.3)	21.0 (16.3-29.8)	26.0 (21.8-32.0)	<0.01
GGT (U/L)	19.0 (15.0-24.0)	20.0 (16.0-31.0)	24.5 (17.0-43.5)	0.085
Uric acid (mg/dL)	5.7±1.4	6.1±2.0	7.1±1.6	<0.01
HOMA-IR	5.6 (3.9-6.4)	5.3 (3.7-7.5)	6.8 (3.7-9.0)	0.060
WBISI	1.9 (1.4-2.7)	1.8 (1.3-2.5)	1.3 (1.1-1.9)	0.045
EAT thickness (mm)	4.1±1.6	4.5±1.6	5.0±1.5	0.047

Data presented as mean±standard deviation, or median (Q1-Q3).
ALT: Alanine aminotransferase; AST: Aspartate aminotransferase; BMI: Body mass index; EAT: Epicardial adipose tissue; GGT: g-glutamyl transferase; HOMA-IR: Homeostatic model assessment for insulin resistance; SDS: Standard deviation score; WBISI: Whole body insulin sensitivity index.

Correlation analysis of variables with the class of obesity and EAT thickness in the patient group are shown in Table V. There was a weak positive correlation between the class of obesity and EAT thickness (Rho=0.216 p=0.018), a moderate positive correlation between the class of obesity and HOMA-IR (Rho=0.342, p<0.001), and finally, a moderate negative correlation between the class of obesity and WBISI (Rho=-0.329, p<0.001). EAT thickness was weakly and negatively correlated with WBISI (Rho=-0.282, p<0.01), positively and weakly correlated with GGT (Rho=0.229, p=0.012), positively and moderately correlated with SUA (Rho=0.319, p<0.001). The simple scatter plot of EAT thickness and SUA is demonstrated in Fig. 1.

Multiple linear regression analysis revealed that male gender (p<0.001) and BMI SDS (p<0.01) were positively associated with EAT thickness, while WBISI (p=0.021) was negatively associated with it (Table VI). Age, SBP, DBP, total cholesterol, LDL, HDL, TG, HOMA-IR, and uric acid levels were not associated with

Table V. Correlation analysis of variables with class of obesity, epicardial adipose tissue thickness in patient group (n=120).

	Class of obesity		EAT thickness	
	Rho	P	Rho	P
Class of obesity	1.000	-	0.216	0.018
SBP	0.102	0.268	0.253	<0.01**
DBP	0.173	0.058	0.147	0.109
EAT thickness	0.216	0.018	1.000	-
HOMA-IR	0.342	<0.001**	0.102	0.268
WBISI	-0.329	<0.001	-0.283	<0.01**
GGT	-0.066	0.474	0.229	0.012*
Uric acid	0.034	0.710	0.319	<0.001***
Total cholesterol	-0.053	0.567	0.019	0.832
LDL	-0.101	0.268	-0.012	0.894
HDL	-0.108	0.237	-0.142	0.120
TG	0.165	0.070	0.117	0.200

DBP: Diastolic blood pressure; EAT: Epicardial adipose tissue; GGT: g-glutamyl transferase; HDL: High-density lipoprotein; HOMA-IR: Homeostatic model assessment for insulin resistance; LDL: Low-density lipoprotein; SBP: Systolic blood pressure; TG: Triglyceride; WBISI: Whole body insulin sensitivity index.
* p<0.05, **p<0.01, ***p<0.001

Table VI. Multiple linear regression analysis of factors associated with epicardial adipose tissue thickness.

Backward model final step*	Unstandardized Coefficients- B	t	p	95% Confidence Interval for B	
Variables				Lower	Upper
Constant	-0.481	-0.323	0.747	-0.3429	2.467
Gender	1.170	3.868	<0.001	0.571	1.769
BMI SDS	0.834	3.177	<0.01	0.314	1.354
SBP	0.022	1.966	0.052	0.000	0.044
WBISI	-0.343	-2.340	0.021	-0.633	-0.053

*Adjusted R^2: 0.528
BMI: Body mass index; SDS: Standard deviation score; WBISI: Whole body insulin sensitivity index.

EAT thickness (p>0.05). ROC analysis showed no significant predictive value for BMI SDS value when the EAT thickness cut-off value was 3.55 (p=0.564, sensitivity 50.0%, specificity 58.2%).

Discussion

The current study evaluated MetS components, EAT thickness, and SUA according to the severity of obesity in pubertal children. In addition, liver function tests, EAT thickness, SUA, HOMA-IR, and WBISI were examined to determine how they changed according to the MetS risk. Especially class 3 obesity in adolescent children was found to be associated with a high prevalence of abnormal levels of cardiometabolic risk factors. There was no difference between class 1 and 2 obesity in terms of both EAT thickness and cardiometabolic risk factors. As MetS components increased, higher EAT thickness, SUA, and impaired IR were detected.

Although the general statement that obese people have a higher risk of CVD and MetS than people with normal body weight is still valid, the severity of visceral adiposity is considered to be a more substantial cardio-metabolic risk factor

than body weight.[24] Therefore, neither BMI nor its derivatives alone may be very reliable for cardiometabolic risk markers. In a study by Skinner et al.[19], the risks of low HDL level, high SBP, high DBP, high TG level, and high glycated hemoglobin level were greater among children and young adults with class 3 obesity than those with class 1 obesity. Another study reported that increased BMI has a significant negative effect on IR, glycemia, lipids, and BP.[25] In our study, which is slightly different from the literature, the severity of obesity did not have a different effect on glycemia, lipids, and BP. In the class 3 group, both IRs were significantly higher, and the number of obese patients without the MetS component was significantly lower compared to the class 1 and 2 groups.

Despite the importance of determining EAT thickness for its possible predictive value for CVDs and the associations of EAT thickness with indirect measures linked to excess adiposity, little research has combined the indirect (BMI, waist circumference, or blood pressure) and direct (echography) measures in pediatric populations.[26] It was reported that age, sex, and BMI could be among the most significant factors related to EAT thickness.[27] In addition, while EAT thickness has been shown to be positively correlated with BMI;[28,29] we found a positive correlation between the class of obesity and EAT thickness. We also showed that male gender and BMI SDS were positively associated with EAT thickness. For the first time it was shown in our study that EAT thickness was found to be statistically significantly higher in the class 3 group than in the class 1 and 2 group, but no significant difference was found between class 1 and 2. The fact that EAT thickness is similar in the class 1 and 2 groups and the metabolic picture is similar supports the idea that EAT also increases in the class 3 group, and the metabolic picture is more prone to deterioration. These results suggest that visceral fat distribution underlying the concept of metabolic healthy obesity is a stronger predictor of metabolic health and increased fat mass.[30] It also suggests that EAT thickness may increase more rapidly after class 2 obesity.

Studies on the relationship between EAT and obesity-related comorbidities in children are rare, and conflicting results have been found. Higher EAT thickness has been reported in adult studies in patients with MetS.[31] Mazur et al.[32] evaluated 52 obese children, and no significant difference was found in EAT thickness between obese children with and without MetS. They suggested that this discrepancy between results in adults and children may be due to the difference in metabolic activity of EAT in younger subjects and duration of exposure to obesity, which is shorter in children than in adults, hence may not be long enough to advance the chronic inflammation process.[32] Eren et al.[33] showed no statistical difference between EAT thickness in obese patients with and without MetS, and no correlation was found between EAT and ALT, TG, FPG, insulin, and HOMA-IR. In the study by Abacı et al.,[34] while EAT thickness showed a significant correlation with age, BMI, intima-media thickness, and SBP values, it was not significantly correlated with BMI SDS, glucose, insulin, HOMA-IR, TC, TG, LDL, HDL, and DBP. Despite these, Akyol et al.[35] found higher EAT thickness in the obese children with MetS than in the obese group without MetS and lean children. Although our study could not measure the waist circumference, obese patients could not be divided into MetS and non-MetS. However, they were evaluated regarding the presence of MetS components, and EAT thickness was found to be higher as the number of MetS components increased. While a correlation was found between EAT thickness and severity of obesity and SBP in our study, no correlation was found between DBP, lipid profile, HOMA-IR, and EAT thickness.

The relationship between EAT thickness and WBISI, which we have not seen before in the literature, was evaluated. Although the euglycemic hyperinsulinemic clamp is the best method for assessing insulin sensitivity, it is a complex test and rarely used in a clinical setting.[36] Therefore, different tests are used to evaluate insulin sensitivity. Homa-IR is one of

the most commonly used tests and is thought to represent mainly hepatic IR.[37] IR in peripheral organs such as skeletal muscle and adipose tissue also plays an important role in systemic IR. Yeckel et al.[38] showed that WBISI can be used to predict insulin sensitivity in obese young people and can be a good tool to assess insulin sensitivity. In our study, the severity of obesity and EAT thickness showed negative significant correlations with WBISI. In addition, WBISI was found to be significantly lower as the MetS component increased. Studies have shown that WBISI has a significant negative correlation with visceral fat, hepatic fat fraction, and pancreatic fat fraction.[39] There has been no study on its relationship with EAT thickness. While many cardiometabolic parameters do not change, the WBISI changes according to the severity of obesity and MetS risk, and its negative correlation with EAT thickness suggests that it may be a suitable parameter in the early detection and evaluation of cardiometabolic risk in obese patients.

In our study, SUA was higher in patients with increased MetS components. It is thought that high SUA levels regulate oxidative stress, inflammation, and enzymes related to glucose and lipid metabolism and constitute a mechanism for the deterioration of metabolic homeostasis.[40] In studies conducted in adults, high SUA levels have been found to be associated with MetS.[14] Similarly, in a study conducted in children, SUA levels were found to be increased in obese/overweight children, regardless of age, puberty, gender, and BMI, as well as the frequency of MetS, IR, and dyslipidemia.[41] These results suggest that the relationship between SUA and metabolic and cardiovascular risk factors begins in early childhood. In another adult study, no correlation was observed between EAT and glycemia, total serum cholesterol, HDL, or TG, while a significant positive correlation was found between EAT and SUA.[42] Studies conducted in childhood are rare, and a positive correlation has been reported between EAT thickness and SUA.[43] We also found a positive correlation between EAT thickness and SUA.

Studies have shown that liver function tests, including AST, ALT, and GGT, can be valuable parameters in evaluating the metabolic status of adults.[44] The association between MetS and liver function tests has also been demonstrated in children.[45] In our study, it was determined that as the number of MetS components increased, there was an increase in the values of liver enzymes, and a statistical difference was found between the groups in the AST levels. GGT was also investigated as a marker of MetS, and GGT levels were found to be strongly associated with cardiovascular risk factors.[46] Studies between GGT and EAT thickness are rare, and there is no study from the childhood period. A positive correlation was found between EAT thickness and GGT in adult studies.[47] A positive correlation was found between EAT and GGT also in our study.

Our study has a few limitations. Most importantly, we could not measure waist circumference or clearly distinguish patients with and without MetS. Second, the population size is small.

In conclusion, no other research has been found in the literature like our study. All parameters, such as MetS components, SUA, EAT thickness, and insulin resistance, were evaluated together according to the severity of obesity in children. Especially after class 2 obesity, the increase in EAT thickness, further decrease in insulin sensitivity, and the decrease in the number of people without the MetS component suggest that obese people should be followed closely and necessary interventions should be made to prevent obesity from progressing to further dimensions. The increase in the liver function tests, SUA and EAT thickness, and decrease in the WBISI as the number of MetS components increase show that these can be easily measurable parameters used at follow-up. Expanded case-control studies on this subject will further contribute to the literature.

Ethical approval

The study was approved by the Clinical Research Ethics Committee of Ankara Bilkent City Hospital with decision no 23-4512 dated July 12, 2023.

Author contribution

The authors confirm contribution to the paper as follows: SStudy conception and design: GB, YOS; data collection: GB, YOS; analysis and interpretation of results: GB; draft manuscript preparation: GB, YOS. All authors reviewed the results and approved the final version of the manuscript.

Source of funding

The authors declare the study received no funding.

Conflict of interest

The authors declare that there is no conflict of interest.

REFERENCES

1. Kumar S, Kelly AS. Review of childhood obesity: from epidemiology, etiology, and comorbidities to clinical assessment and treatment. Mayo Clin Proc 2017; 92: 251-265. https://doi.org/10.1016/j.mayocp.2016.09.017
2. Molnár D. The prevalence of the metabolic syndrome and type 2 diabetes mellitus in children and adolescents. Int J Obes Relat Metab Disord 2004; 28(Suppl 3): S70-S74. https://doi.org/10.1038/sj.ijo.0802811
3. Carbone S, Lavie CJ, Arena R. Obesity and heart failure: focus on the obesity paradox. Mayo Clin Proc 2017; 92: 266-279. https://doi.org/10.1016/j.mayocp.2016.11.001
4. Ortega FB, Sui X, Lavie CJ, Blair SN. Body mass index, the most widely used but also widely criticized index: would a criterion standard measure of total body fat be a better predictor of cardiovascular disease mortality? Mayo Clin Proc 2016; 91: 443-455. https://doi.org/10.1016/j.mayocp.2016.01.008
5. Iacobellis G. Epicardial fat links obesity to cardiovascular diseases. Prog Cardiovasc Dis 2023; 78: 27-33. https://doi.org/10.1016/j.pcad.2023.04.006
6. Sironi AM, Petz R, De Marchi D, et al. Impact of increased visceral and cardiac fat on cardiometabolic risk and disease. Diabet Med 2012; 29: 622-627. https://doi.org/10.1111/j.1464-5491.2011.03503.x
7. Gastaldelli A, Morales MA, Marraccini P, Sicari R. The role of cardiac fat in insulin resistance. Curr Opin Clin Nutr Metab Care 2012; 15: 523-528. https://doi.org/10.1097/MCO.0b013e328358be7b
8. Ansaldo AM, Montecucco F, Sahebkar A, Dallegri F, Carbone F. Epicardial adipose tissue and cardiovascular diseases. Int J Cardiol 2019; 278: 254-260. https://doi.org/10.1016/j.ijcard.2018.09.089
9. Rabkin SW. Epicardial fat: properties, function and relationship to obesity. Obes Rev 2007; 8: 253-261. https://doi.org/10.1111/j.1467-789X.2006.00293.x
10. Iacobellis G, Assael F, Ribaudo MC, et al. Epicardial fat from echocardiography: a new method for visceral adipose tissue prediction. Obes Res 2003; 11: 304-310. https://doi.org/10.1038/oby.2003.45
11. Iacobellis G, Ribaudo MC, Assael F, et al. Echocardiographic epicardial adipose tissue is related to anthropometric and clinical parameters of metabolic syndrome: a new indicator of cardiovascular risk. J Clin Endocrinol Metab 2003; 88: 5163-5168. https://doi.org/10.1210/jc.2003-030698
12. Xu Y, Cheng X, Hong K, Huang C, Wan L. How to interpret epicardial adipose tissue as a cause of coronary artery disease: a meta-analysis. Coron Artery Dis 2012; 23: 227-233. https://doi.org/10.1097/MCA.0b013e328351ab2c
13. Pierdomenico SD, Pierdomenico AM, Cuccurullo F, Iacobellis G. Meta-analysis of the relation of echocardiographic epicardial adipose tissue thickness and the metabolic syndrome. Am J Cardiol 2013; 111: 73-78. https://doi.org/10.1016/j.amjcard.2012.08.044
14. Jeong J, Suh YJ. Association between serum uric acid and metabolic syndrome in Koreans. J Korean Med Sci 2019; 34: e307. https://doi.org/10.3346/jkms.2019.34.e307
15. Shah AS, Zeitler PS, Wong J, et al. ISPAD Clinical Practice Consensus Guidelines 2022: type 2 diabetes in children and adolescents. Pediatr Diabetes 2022; 23: 872-902. https://doi.org/10.1111/pedi.13409
16. Bianchi C, Miccoli R, Trombetta M, et al. Elevated 1-hour postload plasma glucose levels identify subjects with normal glucose tolerance but impaired β-cell function, insulin resistance, and worse cardiovascular risk profile: the GENFIEV study. J Clin Endocrinol Metab 2013; 98: 2100-2105. https://doi.org/10.1210/jc.2012-3971

17. Kelly LA, Lane CJ, Weigensberg MJ, Toledo-Corral CM, Goran MI. Pubertal changes of insulin sensitivity, acute insulin response, and β-cell function in overweight Latino youth. J Pediatr 2011; 158: 442-446. https://doi.org/10.1016/j.jpeds.2010.08.046

18. Hampl SE, Hassink SG, Skinner AC, et al. Clinical practice guideline for the evaluation and treatment of children and adolescents with obesity. Pediatrics 2023; 151: e2022060640. https://doi.org/10.1542/peds.2022-060640

19. Skinner AC, Perrin EM, Moss LA, Skelton JA. Cardiometabolic risks and severity of obesity in children and young adults. N Engl J Med 2015; 373: 1307-1317. https://doi.org/10.1056/NEJMoa1502821

20. National High Blood Pressure Education Program Working Group on High Blood Pressure in Children and Adolescents. The fourth report on the diagnosis, evaluation, and treatment of high blood pressure in children and adolescents. Pediatrics 2004; 114(2 Suppl 4th Report): 555-576. https://doi.org/10.1542/peds.114.2.S2.555

21. Zimmet P, Alberti KG, Kaufman F, et al. The metabolic syndrome in children and adolescents - an IDF consensus report. Pediatr Diabetes 2007; 8: 299-306. https://doi.org/10.1111/j.1399-5448.2007.00271.x

22. American Diabetes Association. 2. classification and diagnosis of diabetes. Diabetes Care 2017; 40: S11-S24. https://doi.org/10.2337/dc17-S005

23. Matsuda M, DeFronzo RA. Insulin sensitivity indices obtained from oral glucose tolerance testing: comparison with the euglycemic insulin clamp. Diabetes Care 1999; 22: 1462-1470. https://doi.org/10.2337/diacare.22.9.1462

24. Powell-Wiley TM, Poirier P, Burke LE, et al. Obesity and cardiovascular disease: a scientific statement from the American Heart Association. Circulation 2021; 143: e984-e1010. https://doi.org/10.1161/CIR.0000000000000973

25. Tskhvedadze N, Giorgadze E, Janjgava S. The impact of the degree of obesity on metabolic parameters in children and adolescents. Georgian Med News 2018; (285): 51-56.

26. Toemen L, Santos S, Roest AAW, et al. Pericardial adipose tissue, cardiac structures, and cardiovascular risk factors in school-age children. Eur Heart J Cardiovasc Imaging 2021; 22: 307-313. https://doi.org/10.1093/ehjci/jeaa031

27. Blancas Sánchez IM, Aristizábal-Duque CH, Fernández Cabeza J, et al. Role of obesity and blood pressure in epicardial adipose tissue thickness in children. Pediatr Res 2022; 92: 1681-1688. https://doi.org/10.1038/s41390-022-02022-x

28. Ozdemir O, Hizli S, Abaci A, Agladioglu K, Aksoy S. Echocardiographic measurement of epicardial adipose tissue in obese children. Pediatr Cardiol 2010; 31: 853-860. https://doi.org/10.1007/s00246-010-9720-y

29. Barbaro G, Piedimonte A, Podagrosi M, et al. Epicardial adipose tissue and signs of metabolic syndrome in children. Eat Weight Disord 2016; 21: 269-276. https://doi.org/10.1007/s40519-015-0221-0

30. Blüher M. Metabolically healthy obesity. Endocr Rev 2020; 41: bnaa004. https://doi.org/10.1210/endrev/bnaa004

31. Okyay K, Balcioglu AS, Tavil Y, Tacoy G, Turkoglu S, Abaci A. A relationship between echocardiographic subepicardial adipose tissue and metabolic syndrome. Int J Cardiovasc Imaging 2008; 24: 577-583. https://doi.org/10.1007/s10554-008-9295-3

32. Mazur A, Ostański M, Telega G, Malecka-Tendera E. Is epicardial fat tissue a marker of metabolic syndrome in obese children? Atherosclerosis 2010; 211: 596-600. https://doi.org/10.1016/j.atherosclerosis.2010.02.036

33. Eren E, Koca B, Ture M, Guzel B. Epicardial adiposity in children with obesity and metabolic syndrome. Iran J Pediatr 2014; 24: 411-417.

34. Abacı A, Tascılar ME, Sarıtas T, et al. Threshold value of subepicardial adipose tissue to detect insulin resistance in obese children. Int J Obes (Lond) 2009; 33: 440-446. https://doi.org/10.1038/ijo.2009.1

35. Akyol B, Boyraz M, Aysoy C. Relationship of epicardial adipose tissue thickness with early indicators of atherosclerosis and cardiac functional changes in obese adolescents with metabolic syndrome. J Clin Res Pediatr Endocrinol 2013; 5: 156-163. https://doi.org/10.4274/Jcrpe.1064

36. Kim JK. Hyperinsulinemic-euglycemic clamp to assess insulin sensitivity in vivo. Methods Mol Biol 2009; 560: 221-238. https://doi.org/10.1007/978-1-59745-448-3_15

37. Tagi VM, Giannini C, Chiarelli F. Insulin resistance in children. Front Endocrinol (Lausanne) 2019; 10: 342. https://doi.org/10.3389/fendo.2019.00342

38. Yeckel CW, Weiss R, Dziura J, et al. Validation of insulin sensitivity indices from oral glucose tolerance test parameters in obese children and adolescents. J Clin Endocrinol Metab 2004; 89: 1096-1101. https://doi.org/10.1210/jc.2003-031503

39. Cohen M, Syme C, Deforest M, et al. Ectopic fat in youth: the contribution of hepatic and pancreatic fat to metabolic disturbances. Obesity (Silver Spring) 2014; 22: 1280-1286. https://doi.org/10.1002/oby.20674

40. Lima WG, Martins-Santos ME, Chaves VE. Uric acid as a modulator of glucose and lipid metabolism. Biochimie 2015; 116: 17-23. https://doi.org/10.1016/j.biochi.2015.06.025

41. Özalp Kızılay D, Şen S, Ersoy B. Associations between serum uric acid concentrations and cardiometabolic risk and renal injury in obese and overweight children. J Clin Res Pediatr Endocrinol 2019; 11: 262-269. https://doi.org/10.4274/jcrpe.galenos.2018.2019.0241

42. Rubio-Guerra AF, Benítez-Maldonado DR, Lozano-Nuevo JJ, Arana-Pazos KC, Huerta-Ramirez S, Narváez-Rivera JL. Correlation between epicardial fat thickness and biochemical markers of metabolic risk. Med Clin (Barc) 2018; 151: 236-238. https://doi.org/10.1016/j.medcli.2018.01.019

43. Schusterova I, Leenen FH, Jurko A, Sabol F, Takacova J. Epicardial adipose tissue and cardiometabolic risk factors in overweight and obese children and adolescents. Pediatr Obes 2014; 9: 63-70. https://doi.org/10.1111/j.2047-6310.2012.00134.x

44. Kim HR, Han MA. Association between serum liver enzymes and metabolic syndrome in Korean adults. Int J Environ Res Public Health 2018; 15: 1658. https://doi.org/10.3390/ijerph15081658

45. Wang J, Qu HQ, Huang K, et al. High prevalence of elevated serum liver enzymes in Chinese children suggests metabolic syndrome as a common risk factor. J Paediatr Child Health 2020; 56: 1590-1596. https://doi.org/10.1111/jpc.15038

46. Lee DH, Jacobs DR, Gross M, et al. Gamma-glutamyltransferase is a predictor of incident diabetes and hypertension: the Coronary Artery Risk Development in Young Adults (CARDIA) Study. Clin Chem 2003; 49: 1358-1366. https://doi.org/10.1373/49.8.1358

47. Ege MR, Guray U, Guray Y, Demirkan B, Kisacik H. Serum γ-glutamyltransferase levels correlate with epicardial adipose tissue thickness in patients with coronary artery disease. Angiology 2013; 64: 21-25. https://doi.org/10.1177/0003319711433197