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Original Article

Correlations Between Lipid Profile, High-Sensitivity C-Reactive Protein, Matrix Metalloproteinase, and Left Ventricular Mass and Function Among Adolescents With Obesity

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ABSTRACT

Background: The prevalence of obesity among adolescents is steadily increasing. Obese adolescents are thought to have impaired lipid profile, high-sensitivity C-reactive protein (hs-CRP), matrix metalloproteinase 9 (MMP-9), and left ventricular mass and function, which are potential for further research. This study aimed to compare total cholesterol, low-density lipoprotein (LDL), high-density lipoprotein (HDL), triglycerides, hs-CRP, MMP-9, and left ventricular mass and function between obese and nonobese adolescents.

Methods: A cohort study was conducted in Manado from August 2013 to February 2014. This study enrolled adolescents aged between 13 and 18 years whose body mass index (BMI) was greater than 95th percentile according to CDC 2000 recommendation.

Results: A total of 80 subjects, consisting of 40 subjects in both obese and nonobese arms, were included in this study. The results from the comparative analysis were as follows: total cholesterol: 194.25/160.88 mg/dL, LDL: 136.63/104.65 mg/dL, HDL: 46.13/48.60 mg/dL, triglycerides: 113.10/69.68 mg/dL, hs-CRP: 3.60/0.64 mg/dL, and MMP-9: 620.50/391.64 mg/dL. There were significant differences in total cholesterol, LDL, hs-CRP, and MMP-9 levels ($P < 0.001$) between the obese and nonobese groups. The univariate analysis showed a significant relationship between BMI and left ventricular mass ($P < 0.01$), HDL and left ventricular mass ($P = 0.036$), triglycerides and left ventricular mass ($P = 0.01$), MMP-9 and left ventricular mass ($P < 0.01$), and hs-CRP and left ventricular mass ($P = 0.001$).

Conclusions: Among the obese adolescents in the age group of 13 to 18 years old, there was an alteration in lipid profile, hs-CRP levels, MMP-9 levels, and left ventricular mass and function. ***(Iranian Heart Journal 2021; 22(1): 57-65)***

KEYWORDS: Obese adolescents, Lipid profile, hs-CRP, MMP-9, Left ventricular mass, Left ventricular function

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Recently, obesity has become a worldwide epidemic with an increasing prevalence among children and adolescents. In Indonesia, according to the Basic Health Research (Riskesdas) data in 2010, obese adolescents aged between 13 and 15 years in North Sulawesi Province accounted for 3.4% and

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those aged between 16 and 18 years represented 2.1% of the population.[1-5]

High-sensitivity C-reactive protein (hs-CRP) can assist in the early identification of patients at high risk for cardiovascular diseases.[5-10] Matrix metalloproteinase 9 (MMP-9) possesses gelatinase activity, which exerts a wide influence on ventricular remodeling, ventricular dilatation, and heart failure.[11, 12] Existing studies have demonstrated a strong association between obesity and increased left ventricular mass and hypertrophy.[13-19]

This study aimed to determine whether lipid profile, hs-CRP, and MMP-9 can detect an increase in left ventricular mass and impaired left ventricular function earlier among obese adolescents so that the risk of cardiomyopathy later in adulthood could be prevented.

METHODS

Study Design

The current cohort study was designed to address the hypothesis regarding the presence or absence of a relationship between lipid profile, hs-CRP, MMP-9, and left ventricular mass and function among obese adolescents.

The fractional flow reserve (FFR) measurement was performed in accordance with the latest recommendations, and an FFR value of less than 0.80 was considered the cutoff point for an ischemic lesion.

Ethical Clearance

This study was approved and reviewed by the Health Research Ethics Advisory Team at the Prof. Dr. R. D. Kandou General Hospital Manado (reference No. PP.028 / XI / DIK / 2013).

Study Settings

The study was conducted in Manado from August 2013 to February 2014. The study population comprised all adolescents aged between 13 and 18 years who attended junior high and high schools in the city of Manado. The subjects consisted of individuals in the study population who met the inclusion criteria and were grouped according to their body mass index (BMI) into obese and nonobese groups.

Study Subjects and Sample Size

The study subjects consisted of obese and nonobese individuals aged between 13 and 18 years attending junior and senior high schools in the city of Manado who fulfilled the inclusion criteria and whose parents agreed to participate and were willing to sign an informed consent form. Subjects who suffered 1 or more of the following conditions such as congenital heart diseases, acquired heart diseases, and metabolic disorders were excluded from the study.

The number of subjects required to validate the research hypothesis was estimated based on the value of each variable in the hypothesis.

a. The sample size for the comparison of total cholesterol was calculated using the formula for the numerical data comparison of 2 independent groups (Sastroasmoro, 2014):

   $n = n_2 = 2\,[(Z\alpha + Z\beta)\ X\ s / x_1 - x_2]^2$

   With the provision of:

   $Z\alpha = 1.96$ ($\alpha = 0.05$)

   $Z\beta = 0.842$ ($\beta = 0.20$ or power = 80%)

   $x_1 - x_2$ = clinically important mean difference = 20 mg/dL

   standard deviation (s) = 30 mg/dL

   $Nn = 2\,[(1.96 + 0.842) \times 30 / 20]^2$

   n = 36

   Via the same equation, the sample size was calculated for each variable being compared, which resulted in a number of approximately 20 to 40 subjects per group.

b. The sample size for the left ventricular mass ratio was determined using the same formula with the provision of:

   $Z\alpha = 1.96$ ($\alpha = 0.05$)

$Z\beta = 0.842$ ($\beta = 0.20$ or power 80%)
x_1-x_2 = clinically important mean difference = 25 g
standard deviation (s) = 40 g
$Nn = 2[(1.96 + 0.842) \times 40/25]^2 = 40$

c. The sample size for the correlation between hs-CRP and left ventricular mass was estimated using the formula for correlation testing:
$Nn = [(z\alpha+z\beta)/0.5 \ln [(1+r)/(1-r)]^2+3$
$= [(1.96 + 0.842) / 0.5 \ln [1+0.6) / (1-0.6)]^2 + 3 = 14$
Thus, as many as 40 individuals in each study group were needed; this number was considered adequate for performing a multivariate analysis with 8 independent variables.

Data Collection

The stages of data collection methods were as follows:

- Writing an application letter for approval as well as explaining the objectives and benefits of the study to the Head of the National Education Office of Manado and the Headmasters of the respective Middle and High Schools.
- All parents/guardians of the assigned adolescents, aged between 13 and 18 years, received detailed information and explanations in advance, which described the research process and its benefits. The parents/guardians were asked to provide their written consent for participation.
- The children whose parents provided their consent for participation were interviewed, and they underwent physical examinations in order to obtain their general health status and to rule out conditions or diseases that would affect the study results. Clinical interviews and physical examinations were carried out by the researchers.
- Body weight and height measurements were carried out by the researchers to obtain anthropometric status.
- Finally, an echocardiographic assessment was performed by experienced consultant cardiologists.

- Collected Data:
  - History: name, gender, age, address, parent/guardian identity, and history of recent or prior diseases (questionnaire attached).
  - Physical examinations: weight and height measurements in all adolescents with obesity.
  - Laboratory tests: total cholesterol, low-density lipoprotein (LDL), high-density lipoprotein (HDL), triglycerides, hs-CRP, and MMP-9 levels.
- The parents were informed about the preparation that should be done a day prior to blood sample collection, including 8-hour fasting, starting at 00.00 AM. The subjects were not allowed to have food or drink until the time of blood sampling at 08.00 AM.
- Furthermore, 10 mL of blood was taken by the investigators, assisted by laboratory staff. The puncture area was kept sterile through disinfection using moistened cotton that contained 70% alcohol solution. The collected samples were examined at the clinical laboratory, and the results were sent directly to the investigator and were recorded in the prepared form.
- Echocardiographic assessments: Cooperative subjects did not require any preparation other than the provision of information to both subjects and parents about the examination procedure to be performed and reassurances that the procedure is not painful and dangerous. The subjects were instructed to lie down in a bed, and echocardiography was

performed to determine the mass and function of the left ventricle.

Data regarding clinical history, physical examinations, anthropometric measurements, and echocardiographic examinations were recorded in the prepared form. All the recorded data were included in the statistical analyses.

Statistical Analysis

The data analyses were performed using a 2-tailed independent *t*-test if the data of the 2 groups were normally distributed, while for the abnormally distributed data, the Mann–Whitney *U* test was performed. The Pearson correlation test/linear regression test was performed to investigate the correlation between 2 continuous variables. The effects of various variables on left ventricular mass and function were determined via a multivariate analysis using multiple regressions. All the analyses were performed with SPSS software, version 22. A *P* value of less than 0.05 was considered statistically significant.

RESULTS

Between August 2013 and February 2014, the current investigation recruited 80 adolescents. Of this total, 40 subjects were obese with the lowest body weight of 58 kg and the highest of 131 kg. The shortest of these obese subjects was 135 cm tall, while the height of the tallest one was 179 cm. In the obese group, the lowest and highest BMI was 25.80 kg/m^2 and 43.00 kg/m^2, respectively. The remaining 40 subjects were included in the nonobese group, with the lowest body weight of 35 kg and the highest body weight of 66 kg. The shortest subject in the nonobese group was 146 cm tall, whereas the height of the tallest subject was 177.50 cm. Additionally, in the nonobese group, the lowest and highest BMI was 14.20 kg/m^2 and 24.80 kg/m^2, correspondingly (Table 1).

Table 1 shows that the levels of total cholesterol, LDL, and triglycerides among obese adolescents were high compared with the normal children; the difference was statistically significant. Similar results were noted in the median levels of hs-CRP, MMP-9, and left ventricular mass since the values were higher in the obese group than in the nonobese adolescents ($P \leq 0.05$). A significant difference ($P < 0.05$) was also found in regard to left ventricular diastolic function, while no such difference ($P > 0.05$) was found with regard to left ventricular systolic function. The mean E/A value did not differ significantly between the 2 groups.

The univariate analysis revealed a significant relationship between BMI, HDL, triglycerides, MMP-9, and hs-CRP and left ventricular mass (Table 2). Nonetheless, in the multivariate analysis, a significant relationship was found only between BMI and left ventricular mass. All the multivariate analyses thereafter showed the same results, where the only variable related to left ventricular mass was BMI (Table 3).

There was no significant relationship between the independent variables and left ventricular function (ejection fraction) according to the univariate analyses (Table 4). In the multivariate analyses, however, a significant relationship was found between BMI and hs-CRP and left ventricular function (ejection fraction). All the subsequent multivariate analyses yielded similar results (Table 5).

Tabel 1: Characteristics and comparisons of lipid profile, hs-CRP, MMP-9, and left ventricular mass and function between the obese and nonobese adolescents

Variables	Obese (n = 40)	Nonobese (n = 40)	*P* value
Gender			
- Male, n (%)	15 (37.5)	14 (35)	
- Female, n (%)	25(62.5)	26 (65)	
Height, mean (SD) cm	158.30 (9.94)	160.67 (8.18)	0.124
Weight, median (IQR) kg	79.5 (20.75)	48.0 (9.25)	< 0.001
BMI, mean (SD) kg/m^2	32.99 (3.54)	18.52 (2.30)	< 0.001
Total cholesterol, median (IQR) mg/dL	183.50 (47.50)	155.50 (33.75)	< 0.001
LDL, median (IQR) mg/dL	126.50 (43.5)	100.50 (34.0)	< 0.001
HDL, mean (SD) mg/dL	46.13 (9.73)	48.40 (7.91)	0.127
Triglycerides, median (IQR) mg/dL	110.0 (56.25)	61.50 (36.0)	< 0.001
hs-CRP, median (IQR) mg/dL	2.65 (2.55)	0.30 (0.5)	< 0.001
MMP-9, median (IQR) mg/dL	580.25 (359.85)	375.95 (142.6)	< 0.001
Left ventricular mass, median (IQR) g	334.50 (269.0)	136.50 (32.5)	0.001
Left ventricular systolic function			
- EF , mean (SD) %	65.55 (13.68)	69.03 (10.62)	0.104
- FS , mean (SD) %	36.98 (10.53)	39.15 (8.45)	0.151
Left ventricular diastolic function			
- E , mean (SD) cm/s	51.94 (42.31)	38.40 (37.47)	0.005
- A , mean (SD) cm/s	32.94 (28.92)	15.97 (21.07)	0.002
- E/A	1.75 (0.61)	1.77 (0.41)	0.407

hs-CRP, High-sensitivity C-reactive protein; MMP-9, Matrix metalloproteinase 9; BMI, Body mass index; LDL, Low-density lipoprotein; HDL, High-density lipoprotein; EF, Ejection fraction; FS, Fractional shortening; E, Mean peak diastolic flow velocity of the left ventricle; A, Mean peak velocity of the left ventricle during atrial contraction

Table 2: Results from the univariate analysis regarding the relationship between BMI and laboratory examinations as independent variables and left ventricular mass as the dependent variable

Variables	Coefficient B	Standard Error	Coefficient Beta	*t*	*P* value
Total cholesterol	0.799	0.534	0.167	1.497	0.139
BMI	16.573	1.811	0.720	9.152	0.000
LDL	0.886	0.531	0.186	1.668	0.099
HDL	-4.775	2.242	-0.234	-2.130	0.036
Triglycerides	1.238	0.467	0.288	2.652	0.010
MMP-9	0.243	0.067	0.381	3.640	0.000
hS-CRP	20.267	5.816	0.367	3.485	0.001

BMI, Body mass index; MMP-9, Matrix metalloproteinase 9; LDL, Low-density lipoprotein; HDL, High-density lipoprotein; hs-CRP, High-sensitivity C-reactive protein

Table 3: Results from the multivariate analysis concerning the relationship between BMI and laboratory examinations as independent variables and left ventricular mass as the dependent variable

Variables	*Coefficient B*	*Standard Error*	*Coefficient Beta*	*t*	*P value*
(Constant)	*7.510*	*113.484*		*0.066*	*0.947*
Total cholesterol	*1.535*	*3.021*	*0.321*	*0.508*	*0.613*
BMI	*15.911*	*2.372*	*0.691*	*6.707*	*0.000*
Triglycerides	*-0.484*	*0.548*	*-0.112*	*-0.883*	*0.380*
LDL	*-1.732*	*2.846*	*-0.363*	*-0.609*	*0.545*
HDL	*-4.569*	*3.293*	*-0.224*	*-1.388*	*0.170*
hS-CRP	*3.461*	*5.067*	*0.063*	*0.683*	*0.497*
MMP-9	*0.057*	*0.056*	*0.089*	*1.020*	*0.311*

BMI, Body mass index; MMP-9, Matrix metalloproteinase 9; LDL, Low-density lipoprotein; HDL, High-density lipoprotein; hs-CRP, High-sensitivity C-reactive protein

Table 4: Results of the univariate analysis vis-à-vis the relationship between BMI and laboratory results as independent variables and left ventricular function as the dependent variable

Variables	Coefficient B	Standard Error	Coefficient Beta	*t*	*P* value
Total cholesterol	0.025	0.037	0.078	0.689	0.493
BMI	-0.274	0.174	-0.175	-1.573	0.120
LDL	0.023	0.037	0.070	0.624	0.534
HDL	-0.007	0.157	-0.005	-0.044	0.965
Triglycerides	0.015	0.033	0.052	0.463	0.645
MMP-9	-0.007	0.005	-0.171	-1.530	0.130
hS-CRP	0.662	0.418	0.177	1.585	0.117

Dependent variable: ejection fraction

BMI, Body mass index; MMP-9, Matrix metalloproteinase 9; LDL, Low-density lipoprotein; HDL, High-density lipoprotein; hs-CRP, High-sensitivity C-reactive protein

Table 5: Results of the multivariate analysis as regards the relationship between BMI and laboratory results as independent variables and left ventricular function as the dependent variable

Variable	Coefficient B	Standard Error	Coefficient Beta	*t*	*P* value
(Constant)	75.955	10.662		7.124	0.000
Total cholesterol	0.134	0.284	0.414	0.474	0.637
BMI	-0.563	0.223	-0.360	-2.528	0.014
Triglycerides	0.035	0.052	0.120	0.678	0.500
LDL	-0.117	2.846	-0.361	-0.437	0.664
HDL	-0.142	3.293	-0.102	-0.458	0.648
hS-CRP	1.234	5.067	0.329	2.593	0.012
MMP-9	-0.006	0.056	-0.139	-1.145	0.256

Dependent variable: ejection fraction
BMI, Body mass index; MMP-9, Matrix metalloproteinase 9; LDL, Low-density lipoprotein; HDL, High-density lipoprotein; hs-CRP, High-sensitivity C-reactive protein

DISCUSSION

The present study was conducted on adolescents between 13 and 18 years of age since previous studies have suggested that the prevalence of obesity begins to increase at around this age range. Simsek et al[20] conducted a study on 75 obese children at a mean age of 10.79 ± 2.03 years and found that most of the subjects were males (52% vs 36%). A similar result was found in a study by Stabouli et al.[21] Still, neither of these studies demonstrated a significant relationship between sex and obesity.

Among obese children and adolescents, the monitoring of lipid profile should always be performed because, according to previous studies, overweight and obese children tend to have abnormal changes in cholesterol levels (dyslipidemia) and several other cardiovascular risk factors such as the levels of insulin and CRP and blood pressure.[22, 23] We found a very significant difference in the levels of total cholesterol, LDL cholesterol, and triglycerides between our obese and nonobese groups.

Among obese individuals, echocardiographic studies have found ventricular wall thickening and large heart chambers in obese children compared with normal children. The ratio between ventricular wall thickening and cubicle radius (relative wall thickening) was reported to be greater in obese children than in normal children.[14] In the current investigation, the mean left ventricular mass in obese adolescents was higher than that in their nonobese counterparts (381.20 g vs132 g; *P* < 0.01). Ghanem et al[24] examined 30 obese children at a mean age of 11.2 ± 2.9 years and reported a left ventricular mass value of 98.5 g ± 36.4 g.

In the present study, the mean peak diastolic flow velocity of the left ventricle (E) in the obese group was higher than that of the nonobese group (51.49 cm/s vs 28.40 cm/s; *P* = 0.005). Also, the mean peak velocity of the left ventricle during atrial contraction (A) among the obese adolescents was higher than that among the nonobese adolescents (32.94 cm/s vs 15.97 cm/s; *P* = 0.002). These results indicated an alteration in left ventricular diastolic function among obese adolescents. Among obese children and adolescents, cardiac output increases due to an increased plasma volume, thereby increasing the work of the left ventricle and causing an increase in left ventricular mass.[18, 25]

Our univariate analysis suggested that BMI (*P* < 0.01), HDL (*P* = 0.036), triglycerides (*P* < 0.01), MMP-9 (*P* < 0.01), and hs-CRP (*P* = 0.001) were associated with left ventricular mass. Our multivariate analysis showed that only BMI was associated with left ventricular mass (*P* < 0.01). Excessive body weight increases metabolic requirements and, hence, increases the total blood volume and cardiac output. The heart in obese adolescents is forced to work harder to supply blood to tissues; this is followed by an increase in left ventricular volume and subsequently left ventricular dilatation and left ventricular mass enlargement (hypertrophy).[8, 9, 26]

In our multivariate, BMI (*P* = 0.014) and hs-CRP (*P* = 0.012) showed a significant relationship with left ventricular function, whereas such a relationship was not evidenced in the univariate analysis. It is worth noting that hs-CRP can aid in the early identification of patients at high risk for cardiovascular diseases, which may not be detected through only lipid screening.[5-10] Moreover, hs-CRP can be used as an independent predictor of cardiovascular diseases where an elevation in CRP levels among obese individuals without other comorbidities possesses a good prognostic value for the occurrence of metabolic syndrome later in life.[7, 27]

Further large well-constructed prospective studies on children are needed to assess the duration of obesity associated with an increase in left ventricular mass and decreased left ventricular function.

CONCLUSIONS

The results of the present study on obese adolescents aged between 13 and 18 years demonstrated an alteration in lipid profile, hs-CRP, MMP-9, and left ventricular mass and function. Higher BMI and hs-CRP levels among obese adolescents are significantly associated with an increase in left ventricular mass and a decrease in left ventricular function.

Ethical Compliance

Source of Funding: This study was funded by the authors. Informed consent was obtained from each individual participant involved in this study.

This study was conducted in accordance with the 1964 Declaration of Helsinki and its subsequent amendments.

Conflict of Interest: None declared.

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