Paediatrica Indonesiana

VOLUME 56 March • 2016 NUMBER 2

Original Article

High sensitivity C-reactive protein, left ventricular mass, and systolic function in obese adolescents

Erling David Kaunang[1], Suryani As'ad[2], Sarah M. Warouw[1], Peter Kabo[2]

Abstract

Background Obesity has been associated with structural and functional cardiac muscle defects. High sensitivity C-reactive protein (hs-CRP) has been utilized as an independent predictor of future cardiovascular disease.

Objective To assess for correlations between hs-CRP, left ventricular mass, and systolic function in obese adolescents.

Methods This cross-sectional study was conducted from August 2013 to February 2014. Subjects were obese adolescents aged 13-18 years with a body mass index (BMI) >95th percentile, according to the 2000 Centers for Disease Control and Prevention Growth Chart. Subjects underwent laboratory testing of serum hs-CRP levels, as well as left ventricular mass and function measurements by echocardiography. Descriptive analysis was performed on patients' characteristics and correlation analysis was done by Pearson's test with a significance level of $P<0.05$.

Results Subjects were 40 obese adolescents. There was no statistically significant correlation between hs-CRP and left ventricular mass ($r=0.083$; $P=0.305$). There was a moderate correlation between hs-CRP with ejection fraction (EF) ($r=0.372$ and $P=0.009$) and fractional shortening (FS) of the left ventricle ($r=0.420$ and $P=0.003$).

Conclusion In obese adolescents, we find no correlation between hs-CRP and left ventricular mass. However, hs-CRP is moderately correlated with left ventricular EF and FS. **[Paediatr Indones. 2016;56:124-8.]**.

Keywords: *hs-CRP, left ventricular mass, left ventricular function, obesity*

Obesity has been associated with abnormalities in the structure and function of cardiac muscle. Previous studies have shown that obese children have larger left ventricular mass, thicker wall, and wider ventricular space compared to non-obese children. Increases in left ventricular mass can lead to left ventricle hypertrophy, which is a cause of morbidity and mortality in cardiovascular disease.[1-3] Obesity has also been associated with left ventricular systolic and diastolic dysfunction, which may eventually lead to cardiomyopathy.[4,5] M-mode echocardiography is considered to be essential to approximate left ventricular mass in obese children. Echocardiography can be a trustworthy, non-invasive indicator of left ventricular hypertrophy.[6,7]

C-reactive protein is an acute phase, serum protein. Increases in hs-CRP indicate the presence of inflammation. The relationships between inflammation, obesity, and insulin resistance has been previously described.[8] C-reactive protein has been utilized as a predictor of cardiovascular disease, as it can be

From the Department of Child Health, Sam Ratulangi University Medical School, Manado[1], and Hasanuddin University Medical School, Makassar[2], Indonesia.

Reprint requests to: Erling David Kaunang, Department of Child Health, Sam Ratulangi University Medical School, Manado. Tel. 081356176111; Fax. 0431-859091; E-mail: drdavidkaunang@yahoo.com.

detected in the initial phase of the atherosclerosis development. The hs-CRP can be used to evaluate cardiovascular disease, as increased hs-CRP without any infection may independently predict future metabolic disease.[8,9] This study was conducted to assess for the correlations between hs-CRP and left ventricular mass and systolic function in obese adolescents.

Methods

We conducted a cross-sectional study in obese adolescents aged 13-18 years from junior high and high schools in Manado, from August 2013 to February 2014. Study subjects were obese adolescents who were enrolled consecutively. We excluded chidren with congenital heart disease, acquired heart disease, or metabolic disorders. Parental informed consent was obtained for every subject. Subjects underwent physical examinations and data collection comprising of identity, measurement of body weight (BW) and height, and calculation of BMI. Body mass index (kg/m^2) was calculated as body weight (kg) divided by body height squared (m^2) and categorized as obese for BMI >95th percentile, based on the *CDC 2000 Growth Chart* for age and sex.[10] Serum hs-CRP levels were measured on all subjects. Left ventricular mass and systolic function (ejection fraction/EF and fractional shortening/FS) was measured by echocardiography (*E. SaoteMylab 4.0*).

Data were reported in the form of distributive tables. Parametric data was analyzed by mean, standard deviation (SD) and 95% confidence interval (CI), while non-parametric data was analyzed by median, minimum and maximum values. Correlations between hs-CRP levels and left ventricular mass and function were done by Pearson's test and simple linear regression, with a P value of <0.05 was considered statistically significant. Data analysis were done by using the *Statistical Product and Service Solutions (SPSS) for Windows version 22* software. The study was approved by Ethics Committees of the Sam Ratulangi University Medical School, Manado.

Results

Of the 40 obese adolescent subjects, 15 (38%) were boys and 25 (63%) were girls. Subjects' characterisitics are shown in **Table 1**. Mean body weight was 83.11kg, ranging from 58kg to 131 kg. Mean body height was 158.3cm, ranging from135.0 to179.0 cm. Subjects' mean BMI was32.99 kg/m^2, ranging from 25.80 to 43.00 kg/m^2.

The lowest levels of hs-CRP was 0.40 mg/dL and the highest was 19.80 mg/dL with a mean of 3.60 mg/dL. Mean and range of cardiac parameters can be seen in **Table 1**. There was no statistically significant correlation between hs-CRP with left ventricular mass (r=0.083,P=0.305). However, hs-CRP was moderately correlated with left ventricular EF (r=0.372, P=0.009, **Figure 1**) and FS (r=0.420 and P=0.003, **Figure 2**).

Discussion

Obesity is known to be a major risk factor for high rates of morbidity and mortality in cardiovascular disease. In obese children, ventricular wall thickening may occur, accompanied by large ventricular chambers, compared to those of normal weight children. The ratio between the ventricular wall width and the radius of the chamber, which identifies relative wall thickening, is greater in obese than in normal weight children.[2]

Table 1. Subjects' characteristics

Characteristics		95% CI
Mean height (SD), cm	158.3 (9.94)	155.12 to 161.48
Mean weight (SD), kg	83.11 (15.44)	78.17 to 88.05
Mean BMI (SD), kg/m^2	32.99 (3.54)	31.86 to 34.13
Mean hs-CRP (SD), mg/dL	3.60 (4.0)	2.31 to 4.87
Mean left ventricular mass (SD), g	381.2 (184.38)	322.23 to 440.17
Mean EF (SD), %	65.55 (13.68)	61.18 to 69.92
Mean FS (SD), %	36.98 (10.53)	33.61 to 40.34

EF=ejection fraction; FS= fractional shortening

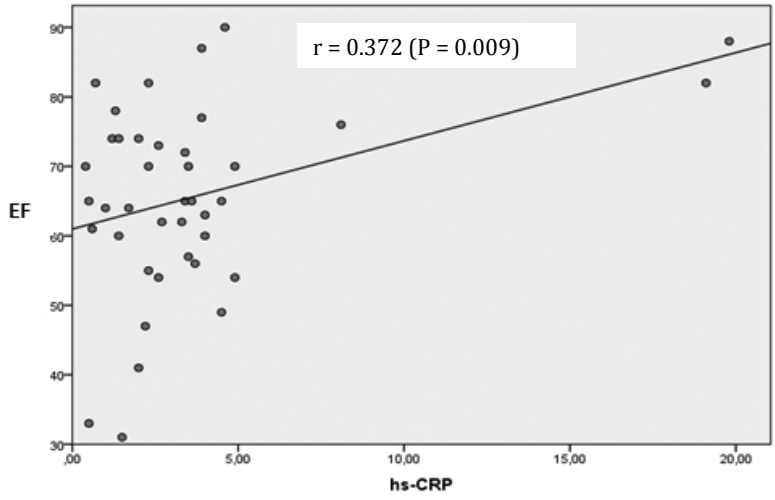

Figure 1. Scatterplot of the relationship between hs-CRP and left ventricular EF

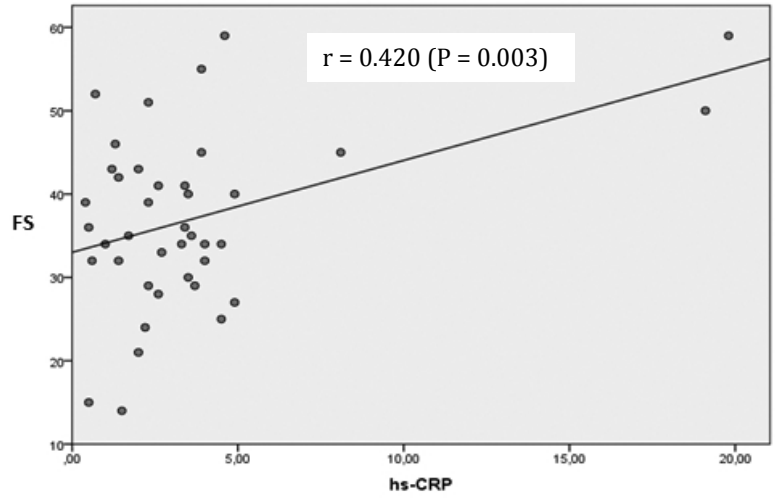

Figure 2. Scatterplot of the relationship between hs-CRP and left ventricular FS

This study was carried out in obese adolescents aged 13-18 years in junior high and high schools in Manado. A total of 40 adolescents each underwent history-taking, physical examination, hs-CRP measurement, and echocardiography. We chose adolescents aged 13-18 years as our sample population, because previous study found that the prevalence of obesity was increased in that age group. A study in Saudi Arabia reported one obese child in every 6 children aged 6-18 years.[11] In Indonesia, the results of a survey on favorites elementary school children and junior high schools in large cities found that the prevalence of obesity ranged from 15-30%. A Jakarta study reported that the highest prevalence of obesity was at the age of 17-18 years (11.4%), followed by 12-18 years (6.2%), and 6-12 years (4%).[10,12] Of the 40 obese adolescents in our study, there were fewer boys (15 or37.5%) than girls (25 or 62.5%). However, Simsek *et al.* reported more boys than girls (52% *vs.* 36%, respectively) among 75 obese children with a mean age of 10.79 years.[13] Another study also found more obese boys than girls,[14] but neither of these

studies found significant associations between the incidence of obesity and gender.

In our study, the mean left ventricular mass in obese adolescents was 381.20 g. A previous study reported that the left ventricular mass in obese adolescents was 126 (SD 27) g, while that of non-obese subjects was 90 (SD 20) g (P<0.001).[15] Another study found that30 obese children aged 11.2 (SD 2.9) years had a mean left ventricular mass of 98.5 (36.4) g.[16] Left ventricular hypertrophy detected by echocardiography is a risk factor for morbidity and mortality in cardiovascular disease. Obesity in children and adolescents is the main factor that determines left ventricular mass.[17,18] In obese children, increased plasma volume also increases cardiac output, which enhances the work of the left ventricle, causing an increase in left ventricular mass.[19,20]

In our study, the mean hs-CRP of obese adolescents was 3.60 mg/dL. Pearson's correlation analysis showed that there was no significant correlation between hs-CRP and left ventricular mass (r=0.083;P=0.305). The CRP levels are influenced by several factors, such as smoking, obesity, and level of physical activity. A study from the *National Heart, Lung, and Blood Institute* (NHLBI) stated that socioeconomic factors (age, level of education, and place of residence), obesity, sedentary lifestyle, hormone replacement therapy (HRT), alcohol consumption, and diabetes mellitus had a 30% impact on CRP variability in men and a 22% impact in women.[8] Genetic factors also play an important role. Because of the racial and ethnic variations in CRP levels, the value limit of 3 mg/L, according to the CDC/AHA guidelines, cannot be applied to all individuals.[8]

The relationship between inflammation, obesity, and insulin resistance has been studied.[21] In susceptible individuals, the release of adipokines, such as tumor necrosis factor α and interleukin-6 (IL-6) produced by macrophages and adipocytes, can directly stimulate production of CRP in the liver.[20] A cross-sectional study showed that CRP levels correlated with atherogenic dyslipidemia, obesity, hypertension, and insulin resistance.[21] The continuous production of CRP can aggravate chronic inflammation by means of endothelial cell activation. The importance of measuring CRP was heightened when a more sensitive measurement method for CRP, called high sensitivity-CRP (hs-CRP) was discovered. C-reactive protein is the most sensitive acute phase protein and is, therefore, called the golden marker for inflammation.[9,21] High sensitivity C-reactive protein is used as a predictor of vascular disease because it has the ability to stimulate the early stages of the formation of atherosclerosis, including increased expression of endothelial cell adhesion molecules, chemokines, and chemoattractants, as well as uptake of low-density lipoprotein(LDL) by macrophages.[9] In addition, CRP can modulate the production of vasoactive endothelial cells, such as lowering the (NOS) mRNA vasoconstriction and increase the production of endothelin-1. The NOS (*nanos*) itself is subject to translation regulation that is reminiscent of the requirement for localization of mRNA for its translation.[9] Another negative influence of CRP is its stimulation of nuclear factor kappa β (NF-kβ), which activates programmed cell death (apoptosis) of endothelial cells and reduces the formation of blood vessels (angiogenesis).[8,9]

C-reactive protein can lead to the thickening of the neo-intima through angiotensin as well as inhibiting endothelial progenitor cell differentiation and function. C-reactive protein is not only a marker of inflammation in atherosclerosis, but it is also a mediator of the disease, due to its contribution to the pathogenesis of lesion and plaque formation, as well asthrombosis, through interactions of C-reactive protein with neo-intima and their effects on endothelial cells.[9] Pearson's correlation analysis revealed a statistically significant moderate correlation between hs-CRP and left ventricular EF(r=0.372;P=0.009) or FS (r=0.420;P=0.003) in obese adolescents, indicating that hs-CRP level is associated with systolic function.

The limitations of this study were its cross-sectional research design, as it cannot accurately be used to evaluate other risk factors that may have led to increased left ventricular mass. Also, we did not evaluate the timespan of obesity in our subjects. Long exposure to obesity can effect increases in left ventricular mass. Although we asked subjects from when they first experienced obesity, the answers given were unclear, as they may have been based on the onset of weight gain. As such,we could not distinguish between overweight and obese nutritional status. Further study needs to be done with prospective cohort design to assess the increase in left ventricular massof obese children.

In conclusion, hs-CRP level is not significantly correlated with left ventricular mass, however it has some moderate correlations with left ventricular systolic function. Further study should be conducted to assess whether long-term childhood obesity is associated with increased left ventricular mass and left ventricular function.

Conflict of interest

None declared.

References

1. Fox E, Taylor H, Andrew M, Han H, Mohamed E, Garrison R, *et al*. Body mass index and blood pressure influences on left ventricular mass and geometry in African Americans: The Atherosclerotic Risk in Communities (ARIC) Study. Hypertension. 2004;44:55-60.
2. Marinov L. Changes in the left ventricular muscle mass in adolescents. J IMAB. 2009.16-8.
3. Eraky AZE. Assessment of carotid intima-media thickness and LV structure and function in obese adolescents [thesis]. [Arabia]: Suez Canal University. 2011.
4. Hanevold C, Waller J, Daniels S, Portman R, Sorof J. The effects of obesity, gender and ethnic group on left ventricular hypertrophy and geometry in hypertensive children: a collaborative study of the International Pediatric Hypertension Association. Pediatrics. 2004;113:328-32.
5. Halenka M. Noninvasive measurement of early atherosclerosis by high resolution B-mode ultrasonography. Acta Univ Palacki Olomuc Fac Med.1999;142:7-11.
6. Sastroasmoro S. Ekokardiografi. In: Sastroasmoro S, Mardiyono B. editors. Buku ajar kardiologianak. Jakarta: BinarupaAksara; 1994.p.103-26.
7. Levy D, Garrison RJ, Savage DD, Kannel WB, Castelli WP. Prognostic implications of echocardiographically determined left ventricular mass in the Framingham Heart Study. N Engl J Med. 1990;322:1561-6.
8. Verma S, Buchanan MR, Anderson TJ. Endothelial function testing as a biomarker of vascular disease. Circulation. 2003;108:2054-9.
9. Abraham J, Campbell CY, Cheema A, Gluckman TJ, Blumenthal RS, Danyi P. C-reactive protein in cardiovascular risk assessment: a review of the evidence. J Cardiometab Syndr. 2007;2:119-23.
10. al-Nuaim AR, Bamgboye EA, al-Herbish A. The pattern of growth and obesity in Saudi Arabian male school children. Int J ObesRelatMetabDisord. 1996;20:1000-5.
11. Sjarif DR. 2011. Obesitas anak dan remaja. In: Sjarif DR, Lestari ED, Mexitalia M, Nasar SS. editors. Nutrisi pediatrik dan penyakit metabolik. 1st ed. Jakarta: Ikatan Dokter Anak Indonesia. p.230-43.
12. Sjarif DR, Nasar SS. Obesitas. In: Pudjiadi AH, Hegar B, Handyastuti S, Idris NS, Gandaputra EP, Harmoniati ED,editors. Pedoman pelayanan medis. Jakarta: Ikatan Dokter Anak Indonesia; 2010.p.197-204.
13. Simsek E, Balta H, Balta Z, Dallar Y. Childhood obesity-related cardiovascular risk factors and carotid intima-media thickness. Turk J Pediatr. 2010;52:602-11.
14. Stabouli S, Kotsis V, Karagianni C, Zakopoulos N, Konstantopoulos A. Blood pressure and carotid artery intima-media thickness in children and adolescents: the role of obesity. Hellenic J Cardiol. 2012;53:41- 7.
15. Rider OJ, Francis JM, Ali MK, Byrne J, Clarke K, Neubauer S, *et al*.Determinants of left ventricular mass in obesity: a cardiovascular magneticresonance study. JCardiovascMagnRes. 2009;11:1-14.
16. Ghanem S, Mostafa M, Ayad S. Early echocardiography abnormalities in obese children and adolescent and reversibility of these abnormalities after significant weight reduction. J Saudi Heart Assoc. 2010;22:13-8.
17. Hariyanto D, Madiyono B, Sjarif DR, Sastroasmoro S. Hubunganketebalantunika intima media artericarotisdenganobesitaspadaremaja. Sari Pediatri. 2009;113:159-67.
18. Reinehr T, Wunsch R.Intima media thickness-related risk factors in childhood obesity. Int J Pediatr Obes. 2011;6Suppl 1:46-52.
19. Steinberger J, Daniels SR. Obesity, insulin resistance, diabetes, and cardiovascular risk in children: an American Heart Association scientific statement from the Atherosclerosis, Hypertension, and Obesity in the Young Committee (Council on Cardiovascular Disease in the Young) and the Diabetes Committee (Council on Nutrition, Physical Activity, and Metabolism). Circulation. 2003;107:1448-53.
20. Guardamagna O, Abello F, Saracco P, Baracco V, Rolfo E, Pirro M. Endothelial activation, inflammation and premature atherosclerosis in children with familial dyslipidemia. Atherosclerosis. 2009;207:471-5.
21. Ridker PM. High-sensitivity C-reactive protein: potential adjunct for global risk assessment in the primary prevention of cardiovascular disease. Circulation. 2001;103:1813-8.