

## Inflammatory markers and lipid profiles in obese children

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### Abstract

**Background** Over 340 million children and adolescents aged 5-19 were overweight or obese in the year 2016. Individuals with obesity are at risk for metabolic disorders and lipid abnormalities. Adipose tissue is a major source of pro-inflammatory cytokines.

**Objective** To evaluate possible correlations between inflammatory markers IL-6, TNF $\alpha$ , and hs-CRP with lipid profiles between obese and non obese children.

**Methods** Eighty children, aged 13 to 15 years, were enrolled in this study (40 normoweight and 40 obese). All participants's (obese and normoweight children) total plasma cholesterol, HDL cholesterol, triglycerides, as well as circulating levels of inflammatory factors, such as TNF $\alpha$ , IL-6, and high sensitivity-C-reactive protein (hs-CRP) level were measured.

**Results** Obese children had significantly higher triglycerides (TG) and cholesterol, as well as lower HDL than normoweight subjects. Mean LDL levels were not significantly different between groups. The IL-6, TNF $\alpha$ , hs-CRP levels were significantly positively correlated with waist circumference. Analysis of the 4 blood lipid parameters and 3 inflammatory markers revealed significant positive correlations of triglycerides to TNF $\alpha$  and hs-CRP. In addition, HDL had significant negative correlations to both TNF $\alpha$  and hs-CRP. No correlations were found between IL-6 and the 4 lipid parameters, nor between TNF $\alpha$  or hs-CRP to LDL and cholesterol. Multivariate regression analysis revealed a significant association between weight-height ratio with hs-CRP ( $R^2$  0.118; 95%CI 1.65 to 191;  $P=0.046$ ). Obesity is associated with adverse lipid and inflammation markers in children.

**Conclusion** Obesity is associated with higher TG, cholesterol, TNF $\alpha$ , and hs-CRP levels, as well as lower HDL. [Paediatr Indones. 2021;61:271-6 ; DOI: 10.14238/pi61.5.2021.271-6 ].

**Keywords:** inflammatory marker; lipid abnormality; obese; children

Obesity is defined as a disorder or disease characterized by excessive accumulation of body fat tissue that may impair health. Obesity in children is a complex problem, as its cause is multifactorial, making management difficult.<sup>1</sup>

The worldwide prevalence of obesity nearly tripled between 1975 and 2016. In 2016, 41 million children under the age of 5 and over 340 million children and adolescents aged 5-19 were overweight or obese. Childhood obesity is associated with premature death and disability in adulthood. In addition, obese children might experience breathing difficulties, increased risk of fractures, hypertension, early markers of cardiovascular disease, insulin resistance, and psychological effects.<sup>2</sup>

In Indonesia, the prevalence of obesity in children under five increased both in urban and rural areas, according to *Survei Sosial Ekonomi Nasional (SUSENAS/ National Socioeconomic Survey)*. In a 2013 Indonesian national survey, the prevalence of combined overweight

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and obesity was 11.9%. The prevalence of 'at-risk'/overweight/obesity increased significantly from 10.3% to 16.5%. Childhood obesity requires special early attention because insulin resistance, inflammation, and dyslipidemia increase the risk of cardiovascular disease in adulthood.<sup>3</sup>

Obesity is associated with low-grade inflammatory processes characterized by increased circulating levels of pro-inflammatory cytokines such as IL-6, TNF $\alpha$ , and acute-phase proteins like CRP. Although this finding was observed in obese and normoweight children, results were higher in obese children. Some studies have reported that weight loss, through diet, was associated with reduction in circulating levels of IL-6, TNF $\alpha$ , CRP, and other markers of inflammation, regardless age, sex, and BMI.<sup>4,5</sup>

Because adipose tissue is a major source of pro-inflammatory cytokines, such as IL-6 and TNF $\alpha$ , both cytokines increase hepatic lipogenesis and trigger a systemic acute-phase response.<sup>5</sup> Individuals with obesity are at increased risk for metabolic disorders. Thus, we aimed to evaluate for correlations between inflammatory markers, IL-6, TNF $\alpha$ , and hs-CRP, and lipid profiles in obesity.

## Methods

Our target population was obese and normoweight school-aged children (6-18 years) living in Makassar District, South Sulawesi, Indonesia. The population accessible as subjects was junior high school students aged 13-15 years from private schools with middle and upper socioeconomic status based on the criteria determined by the Makassar City Education Office.

This cross-sectional study enrolled 40 normoweight and 40 obese children (48 males and 32 females). Students underwent anthropometric assessments. Those with BMI > 95<sup>th</sup> percentile for age and sex (*CDC Growth Chart*) were assigned to the obese group. This study was conducted from January to September 2018. Children with obesity due to organic causes such as hormonal medication or corticosteroids, endocrine disorders, hereditary or genetic syndromes associated with obesity, obstructive sleep apnea, or any chronic disease, were excluded due to the influence of possible co-morbidities of obesity.

This study was approved by the Ethics and

Research Committee of Hasanuddin University. Written informed consent was obtained from subjects' parents or legal guardians following a full and detailed explanation of the study protocol.

Anthropometric measurements included body weight, height, and BMI. Weight was measured to the nearest 0.1 kg using a digital floor scale placed on a hard, level uncarpeted floor. Subjects were barefooted and asked to remove jackets and pullovers during weight and height measurements. For height measurements, subjects faced directly forward and stretched to their fullest height. Using a vertical microtoise on the wall, subjects were instructed to adhere tightly to the wall at the shoulders, buttocks, back of knees, and heels. Height was measured to the nearest 0.1 centimeter. Waist circumference was measured to the nearest cm at the level of umbilicus, with the subject standing and breathing normally. Body mass index (BMI) [weight in kg divided by height squared in meters; kg/m<sup>2</sup>] was compared with appropriate age/sex reference standards (*CDC Growth Chart*).<sup>7</sup>

Biochemical measurements were done with 5 mL morning blood specimens (without anticoagulant) collected after a minimum of eight hours fasting by colorimetric enzyme methods, including total cholesterol, high-density lipoprotein (HDL) cholesterol, low density lipoprotein (LDL) cholesterol, and triglycerides (TG). Commercially available ELISA kits (*Bioassay Technology*, China) were used for quantitative measurement of human serum IL-6 and TNF $\alpha$ , C-reactive protein (CRP).

The significance threshold was considered to be  $P > 0.05$ . Statistical analyses were performed using the *Statistical Package for Social Sciences, version 21.0* software. Quantitative data were expressed as mean with standard deviation (SD). Qualitative data were expressed as frequency and percentage. Mann-Whitney U test was used when comparing between two means. Chi-square ( $X^2$ ) test was used to compare proportions between two qualitative parameters. Spearman's correlation was used to analyze different quantitative variables.

## Results

**Table 1** shows that there was no significant difference in mean age between the control group [13.5 (SD 0.85)

years] and obese group [13.2 (SD 1.01) years] ( $P > 0.05$ ), or sex ( $P > 0.05$ ). The mean BMI was 21.7 (SD 1.73)  $\text{kg}/\text{m}^2$  in the control group and 30.1 (SD 3.06)  $\text{kg}/\text{m}^2$  in the obese group. The mean waist circumference (WC) was 77.5 (4.90) cm in the control group and 92.5 (6.02) cm in the obese group, which was significantly different ( $P < 0.01$ ). The WtHR was also significantly higher in the obese group than in the control group ( $P < 0.01$ ). The obese group had significantly higher TNF $\alpha$  ( $P < 0.01$ ) and hs-CRP ( $P < 0.01$ ) than the control group, but IL-6 was not significantly different between the two groups ( $P > 0.05$ ).

The obese group had significantly higher TG and cholesterol, and lower HDL compared to the normoweight group, but LDL was not significantly different (Table 1).

The analyses of IL-6, TNF $\alpha$ , and hs-CRP levels to other continuous variables of anthropometric

parameters and blood lipids are presented in Table 2. The IL-6, TNF $\alpha$ , hs-CRP levels were significantly correlated with WC. The IL-6 was the only inflammatory marker with no significant correlation to BMI and WtHR. In addition, no significant correlations were found for IL-6 with the four blood lipid parameters. However, TNF $\alpha$  significantly correlated with triglyceride and HDL, and also hs-CRP correlated with triglyceride and HDL. The TNF $\alpha$  and hs-CRP had significant positive correlations to TG levels and significant negative correlations to HDL.

Table 3 shows the multiple linear regression analysis of hs-CRP concentration as the dependent variable among obese group. Only WtHR was significantly associated with hs-CRP (95%CI 1.65 to 191;  $P = 0.046$ ).

**Table 1.** Comparison of obese and normoweight subject characteristics

Characteristics	Normoweight (n = 40)	Obese (n = 40)	P value
Sex M/F, n	23/17	25/15	0.648
Mean age (SD), years	13.5 (0.85)	13.2 (1.01)	0.146
Mean BMI (SD), $\text{kg}/\text{m}^2$	21.7 (1.73)	30.1 (3.06)	0.000
Mean WC (SD), cm	77.5 (4.90)	92.5 (6.02)	0.000
Mean WtHR (SD)	0.49 (0.003)	0.58 (0.003)	0.000
Mean TG (SD), mg/dL	101.4 (84.81)	124.6 (42.56)	0.000
Mean HDL (SD), mg/dL	52.7 (13.56)	47.1 (8.07)	0.007
Mean Cholesterol (SD), mg/dL	164.1 (24.13)	184.4 (32.77)	0.003
Mean LDL (SD), mg/dL	109.8 (26.91)	120.55 (33.36)	0.175
Mean TNF- $\alpha$ (SD), mg/dL	8.8 (10.89)	23.7 (15.73)	0.000
Mean IL-6 (SD), mg/dL	6.3 (3.59)	7.2 (4.19)	0.366
Mean hs-CRP (SD), mg/dL	1.08 (2.15)	4.6 (10.28)	0.000

WtHR=weight to height ratio

**Table 2.** Analyses of IL-6, TNF $\alpha$ , and hs-CRP to anthropometric and lipid profiles among all subjects

Parameters	IL-6		TNF $\alpha$		hs-CRP	
	r	P value	r	P value	r	P value
BMI	0.178	0.114	0.452	0.000	0.618	0.000
WC	0.292	0.009	0.471	0.000	0.616	0.000
WtHR	0.165	0.144	0.429	0.000	0.632	0.000
Triglyceride	-0.036	0.749	0.278	0.012	0.271	0.015
Cholesterol	-0.213	0.058	0.048	0.674	0.142	0.210
LDL	-0.190	0.091	0.91	0.420	0.034	0.765
HDL	-0.046	0.688	-0.337	0.002	-0.221	0.049

**Table 3.** Multiple linear regression analysis of hs-CRP level with anthropometric and biochemical variables in the obese group

Parameters	Hs-CRP		Model R2
	B	P value	
Constant	-51.92		
BMI	-0.142	0.477	
WC	0.002	0.992	
TG	0.092	0.559	0.152
HDL	0.054	0.730	
TNF	-0.143	0.363	
IL-6	0.036	0.820	
WtHR	96.345	0.04	0.118

## Discussion

The escalating global obesity epidemic has been described by the WHO, which noted that children are suffering chronic complications that were once seen only in adults.<sup>7</sup> In our subjects, no significant difference in age and sex was observed between normoweight and obese children. A previous study also found no significant difference between the sexes and obesity.<sup>8</sup>

Overweight and obese adolescents have an increased risk of high blood lipid levels. High levels of LDL and TG, combined with low HDL levels, have been found in children with central obesity. These changes are dangerous and have been correlated with cardiovascular disease in the general population.<sup>9</sup> We found that TG levels and cholesterol of obese children was increased and plasma HDL were decreased compared to normoweight children. However, LDL levels of normoweight and obese children were not significantly different. This result may have been influenced by the type of fat intake (type of milk usually consumed, frequency of trimming fat from meat, and type of spread usually used on bread), but we did not evaluate subjects' diets. Nor did we evaluate pubertal state, which can interfere with lipid metabolism. According to Zoair *et al.*,<sup>7</sup> obese children had significantly higher total TG and lower HDL compare with healthy children. However, Elnashar *et al.*<sup>10</sup> found that all types of lipids were significantly associated with obesity.

In our study, serum TNF $\alpha$  and hs-CRP were significantly higher in obese children than in

normoweight children, while the IL-6 was not significantly different. These marker elevations indicate the presence of inflammation in obese children. Similarly, a study found increasing level of cytokines TNF $\alpha$ , hs-CRP, fibrinogen, and other biological markers of inflammation in obese children.<sup>11</sup> Hyperplastic and hypertrophic adipocytes in obese children enhance synthesis of pro-inflammatory adipokines, and macrophages migrate to adipose tissue.<sup>12</sup> Pro-inflammatory status is a risk factor for chronic disease. In addition, hs-CRP has been associated with vascular inflammation.<sup>13</sup>

Elevated TG concentration in the obese group was positively correlated with inflammatory markers, including hs-CRP and TNF $\alpha$ . The HDL levels had negative correlations to hs-CRP and TNF $\alpha$ . This result indicates a cardio-metabolic risk for obese children, similar to a previous study.<sup>5</sup> All inflammatory markers, except IL-6, were positively correlated with WC and BMI. In a previous systematic review and meta-analysis obesity was strongly associated with increased CRP level.<sup>14</sup> A variety of hormones and cytokines are released by adipose tissue, an active endocrine organ. Accumulation of free fatty acids in obesity activates the pro-inflammatory serine kinase cascade, which boosts the secretion of cytokines leading to an inflammatory milieu.<sup>15</sup> A study in severely obese patients noted that genetic polymorphisms may explain the inter-individual variability in CRP.<sup>16</sup>

In contrast to our findings, a study reported that IL-6 in obese adolescents was higher than in healthy controls,<sup>17</sup> which was in agreement with another study which reported that IL-6 production is significantly enhanced by adipose tissue in obesity.<sup>18</sup> The IL-6 is a circulating cytokine with various functions such as inflammation, host defense, and tissue injury. It is produced by many cell types and tissues, including immune cells, fibroblasts, endothelial cells, skeletal muscles, and adipose tissue. Adipose cells contribute 15-30% of circulating IL-6 levels in the absence of acute inflammation.<sup>17,19</sup>

Our analysis revealed significant positive relationships between WC and all inflammatory markers (hs-CRP, IL-6, and TNF $\alpha$ ) in obese children. The results showed that young obese children experience increased levels of CRP that related with central obesity. However, multiple regression analysis revealed that only WtHR was significantly

correlated with hs-CRP in obese children. The WtHR is an excellent tool for measuring central obesity and cardiovascular risk from obesity. Our results were in agreement with Da Silva *et al.*<sup>20</sup>

Obesity, as measured by BMI, WC, and WtHR, in childhood was found to be a major predictor of CRP in young adulthood. There is growing interest in interventions that can decrease CRP levels in overweight and obese children. In a systematic review, every 1 kg of weight loss in adults obtained through surgical, lifestyle, dietary, or exercise interventions, led to a mean change in CRP level of -0.13 mg/L. Weight loss could directly lead to reduced CRP levels by reducing excess lipids stored in adipocytes, which are hypertrophied in obesity.<sup>21,22</sup>

In conclusion, obesity is associated with higher TG, cholesterol, TNF, and hs-CRP levels, as well as lower HDL. The TNF and hs-CRP have significant positive correlations with triglycerides negative correlations with HDL. Chronic inflammation and dyslipidemia increase the risk of cardiovascular disease in adults, so nutritional states in childhood require special early attention.

## Conflict of Interest

None declared.

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