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Interleukin-6 and highly sensitive C-reactive protein in obese adolescents

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Abstract

Background Childhood obesity is a major health concern. Obesity is due to an expansion of adipose tissue mass. This tissue produces pro-inflammatory cytokines, such as interleukin-6 (IL-6). IL-6 is considered to be the chief stimulator of the production of highly sensitive C-reactive protein (hsCRP) in the liver. Both molecules are responsible for the chronic low-grade inflammatory state in obese individuals.

Objective To assess a correlation between IL-6 and hsCRP in obese adolescents.

Methods This cross-sectional study was conducted from March to June 2011 in Manado. Subjects were obese and normal body mass index (BMI) teens aged 13-18 years. Serum glutamic oxaloacetic transaminase (SGOT) and serum glutamic pyruvic transaminase (SGPT) levels were measured to rule out liver impairment. IL-6 and hsCRP levels were also measured. Data was analyzed by Pearson's correlation and linear regression to test for correlation between IL-6 and hsCRP levels.

Results There was a strongly positive correlation between IL-6 and hsCRP levels in obese adolescents ($r=0.79$ with $P<0.001$). IL-6 and hsCRP levels were not significantly associated in subjects with normal BMI.

Conclusions There was a strongly positive correlation between IL-6 and hsCRP levels in obese adolescents, suggestive of an ongoing, chronic, low-grade inflammatory state. **[Paediatr Indones. 2012;52:219-22]**.

Keywords: *interleukin-6, hsCRP, obesity, adolescents*

Obesity represents an expansion of adipose tissue mass, which is an important source of cytokines and contributes to a proinflammatory milieu. White adipose tissue appears to be functionally comparable to a dynamic endocrine organ, in that they produce and secrete various adipokines and proinflammatory factors, particularly interleukin-6 (IL-6), all of which play an important role in the chronic low-grade inflammatory state of obesity.[1,2] Approximately 25% of circulating IL-6 has been estimated to be released by human subcutaneous adipose tissue in vivo. In addition, IL-6 stimulates the production of acute phase proteins in the liver, possibly explaining the observed associations between body mass index (BMI) and highly sensitive C-reactive protein (hsCRP).[3]

Chase et al. showed that elevated hsCRP levels were positively associated with elevated serum levels of IL-6.[4] IL-6 derived from visceral adipose tissue drains directly into the portal system causing the obesity-associated rise in liver hsCRP production. This observation suggests ongoing chronic low-grade inflammatory processes, that in time may

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lead to endothelial dysfunction or the development of metabolic syndrome, atherosclerosis, and a constellation of other complications.[5] In contrast to other studies, Chaikate et al. found no correlation between IL-6 and hsCRP.[6] To date, there have been few studies in Indonesia investigating the correlation between IL-6 and hsCRP in obese teens, hence, we aimed to assess the association between the molecules.

Methods

Thirty-two obese and 32 normal BMI teens aged 13-18 years were included in this study by consecutive sampling. Required sample size was determined by correlation coefficient equation with $Z\alpha$ set at 5%, $Z\beta$ set at 20%, and r set at 0.45, yielding $\geq$ 32 children per group. Subjects were recruited from junior and senior high schools in Manado. We included adolescents judged to be healthy by medical examination and who did not take any medications including steroids and analgesics in the 3 weeks prior to study enrollment. Parents provided written informed consent and adolescents assented to participation. Exclusion criteria were history of liver impairment and low birth weight. Obesity was defined as a BMI $>95^{th}$ percentile for age and sex, while normal BMI was defined as a BMI between 5^{th}-84^{th} percentile, according to the US Centers for Disease Control and Prevention (CDC) criteria. Low birth weight was defined as a birth weight of less than 2500 grams. Liver impairment was defined as having abnormal liver function tests.

After an overnight fast, blood specimens were taken from all subjects. Serum IL-6 concentrations were measured by means of ELISA (R&D Systems). HsCRP concentrations were measured by nephelometry. SGOT and SGPT levels were measured by standard clinical chemistry analyses. All measurements were performed at a reference laboratory.

Pearson's correlation and regression analyses were used to evaluate the degree of association between IL-6 and hsCRP levels. We considered a P value of < 0.05 to be statistically significant. Statistical analysis was performed with the Statistical Product and Services Solutions (SPSS) version 17.0.

Results

Characteristics of the obese and normal BMI subjects are shown in **Table 1**. Thirty-five children were initially included in the obese group, but 3 were excluded due to liver impairment. Of the 32 remaining subjects, 9 were male and 23 were female. Of the 32 subjects in the normal BMI group, there were 14 males and 18 females. The oldest subjects in both groups were 18.2 years old, while the youngest subject in the obese group was 13 years old and in the normal BMI group was 13.5 years old. In normal BMI children, mean body weight was 47.5 (SD 9.41) kg, mean body height was 155.5 (SD 9.50) cm, and mean BMI was 19.5 (SD 2.38) kg/m^2. All measurements were lower than those of the obese group, where the mean body weight was 77.8 (SD 12.31) kg, mean body height was 157.7 (SD 8.44) cm, and mean BMI was 31.2 (SD 3.61) kg/m^2.

Table 1. Characteristics of obese and normal BMI adolescents

Characteristics	Group	
	Obese n=32	Normal BMI n=32
Mean age, years (SD)	15.0 (1.47)	15.9 (1.32)
Male gender, n	9	14
Female gender, n	23	18
Mean body weight, kg (SD)	77.8 (12.31)	47.5 (9.41)
Mean body height, cm (SD)	157.7 (8.44)	155.5 (9.50)
Mean BMI, kg/m^2 (SD)	31.2 (3.61)	19.5 (2.38)
Mean IL-6, pg/mL (SD)	1.9 (1.71)	1.0 (0.33)
Mean hsCRP, mg/L (SD)	2.4 (3.64)	0.4 (0.31)

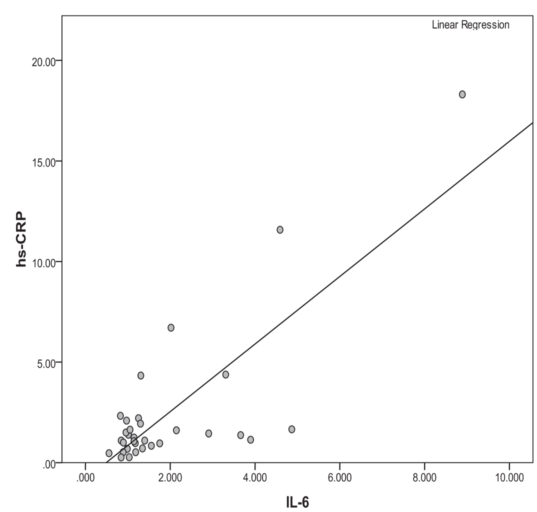

Figure 1. Correlation between IL-6 and hsCRP levels in the obese group

Similar to the anthropometric measurements, IL-6 and hsCRP levels in the normal BMI group were lower than those of the obese group.

Pearson's correlation test revealed a highly significant positive correlation between IL-6 and hsCRP levels in the obese group (r=0.79, P<0.001) as shown in **Figure 1**. However, the correlation between IL-6 and hsCRP levels in the normal BMI group showed only a weak positive correlation (r=0.31, P=0.045) as shown in **Figure 2**.

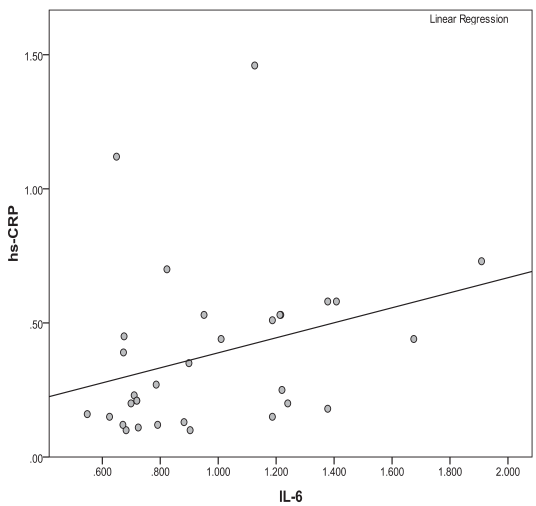

Figure 2. Correlation between IL-6 and hsCRP levels in the normal BMI group

Discussion

This study was conducted in Manado, where subjects were recruited by consecutive sampling from junior and senior high schools. There were 23 boys (35.9%) and 41 girls (64.1%) enrolled. Of the 32 obese subjects, there were 9 boys and 23 girls, similar to findings by Weiss *et al.* who reported that obesity was more prevalent in girls (52%) than in boys (48%).[7] Likewise, Pedrosa *et al.* found that of 82 obese subjects, 51.2% were girls and the rest were boys.[8]

Our subjects were 13-18 years of age. The reason for choosing this age group was that by the age of 13 years, lean body mass percentage is thought to be similar to that of adults. A constant rate between lean body mass and body fat should be observed in this age group, compared to that of pre-pubertal aged children.[9] In addition, Hendarto reported that the chronic, low-grade inflammatory state did not exist in 5-9 years old subjects. It is possible that in the younger children the adipocytes underwent hyperplasia, but not hypertrophy.[10] Furthermore, Warouw *et al.* found that the chronic low-grade inflammatory state was present in 9-15 year-old obese children.[11]

The mean IL-6 level in the obese group was significantly higher compared to that of the normal BMI group (P=0.004). This result was consistent with a study by Gallistl *et al.* who observed higher mean IL-6 levels in obese children (3.9 pg/mL, SD 4.7) than in non-obese children (0.7 pg/mL, SD 1.3).[12] Weiss *et al.* also discovered that IL-6 levels rose significantly with the degree of obesity, with highest levels found in super-obese adolescents (mean 2.45 pg/mL).[13] IL-6 has been positively correlated with BMI.[14-16] Adipose tissue is known to be the main source of serum IL-6, at approximately 25% of total serum IL-6. Thus, higher IL-6 levels may have been due to the increased adipose tissue.[3,17]

Mean hsCRP level in the obese group was significantly higher than that of the normal BMI group (P=0.004). Similarly, Ford *et al.* also observed higher hsCRP levels in children with higher BMI. They concluded that BMI was the most consistent and strongest predictor of hsCRP levels in children.[18] Qureshi *et al.* also indicated that excess adiposity was associated with significantly higher levels of hsCRP.[19] In addition, Pedrosa *et al.* found high levels of hsCRP (3.8 mg/L, SD 8.1) in obese children, with a positive linear association to BMI.[8] Our results were also consistent with a study by Denney-Wilson *et al.* who reported a positive correlation between hsCRP levels and obesity (P<0.001).[20]

Linear regression analysis revealed a weakly positive correlation between IL-6 and hsCRP levels in the normal BMI group (r=0.31, P=0.045). However, in the obese group there was a significant and stronger positive correlation between IL-6 and hsCRP levels (r=0.79, P<0.001). This result was consistent with a study by Browning *et al.* who showed that IL-6 and hsCRP levels were correlated (r=0.33, P<0.05).[21] Pradhan *et al.* also observed a positive correlation between IL-6 and hsCRP levels (r=0.39, P<0.001).[14] Furthermore, Bastard *et al.* found a highly significant relationship between IL-6 and hsCRP levels (r=0.68, P<0.001), consistent with our study.[22]

The observed elevation of IL-6 levels in obese teens leads to further production of hsCRP in the liver, indicating an ongoing chronic low-grade inflammatory state. This state may cause endothelial dysfunction, and in turn, metabolic syndrome, atherosclerosis, and a constellation of other complications.[22,23]

In conclusion, we observed increased IL-6 and hsCRP levels in obese adolescents, with a strong positive correlation between these molecules. Early intervention to reduce body weight is needed and may be achieved through dietary management and increased physical activity.

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