

Interleukin-6 and insulin resistance in obese adolescents

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Abstract

Background Obesity has become a rapidly growing epidemic worldwide, increasing the risk of morbidity and mortality in adolescents. Obesity is due to an expansion of adipose tissue mass, which is an important source of cytokines and contributes to an increase in pro-inflammatory cytokines, such as interleukin-6 (IL-6). Interleukin-6 is significantly increased in obesity and may lead to a state of insulin resistance.

Objective To assess for a correlation between IL-6 levels and insulin resistance in obese adolescents

Methods We conducted a cross-sectional study from January to April 2012 in Manado, North Sulawesi. Subjects were either obese or normal body mass index (BMI) teens aged 13-18 years. Data collected were anthropometric status, BMI, and blood specimens for fasting plasma glucose levels, fasting insulin levels, and IL-6 levels. Insulin resistance was expressed as homeostatic model assessment of insulin resistance (HOMA-IR) level >2.77 . Data was analyzed by Pearson's correlation and linear regression tests to assess for a possible correlation between IL-6 levels and insulin resistance.

Results The mean BMI in the obese group was 31.21 (SD 3.61) kg/m² while the mean BMI in the normal group was 19.52 (SD 2.38) kg/m². There was no significant association between IL-6 and the occurrence of insulin resistance ($P=0.309$). The log regression coefficient value of IL-6 was negative ($b = -0.329$).

Conclusion There is no correlation between IL-6 levels and incidence of insulin resistance in obese adolescents.

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Keywords: interleukin-6, insulin resistance, obesity

Obesity has become a rapidly growing epidemic worldwide, increasing the risk of morbidity and mortality. Increasing prevalence of obesity in countries that are in the process of industrialization parallels the increasing incidence of type 2 diabetes in adults and children. The mechanism of insulin resistance in obese individuals remains under investigation.¹⁻⁴

Obesity is due to an expansion of adipose tissue mass, which is an important source of cytokines and contributes to an increase in pro-inflammatory cytokines. White adipose tissue appears to be functionally comparable to a dynamic endocrine organ, in that it produces and secretes various adipokines and pro-inflammatory factors, in particular interleukin-6 (IL-6), all of which play an important role in the chronic, low-grade, inflammatory state of obesity.⁵ Approximately 25% of circulating IL-6 has been estimated to be released by human subcutaneous adipose tissue in vivo. Numerous studies found that some humoral markers of inflammation are increased in obesity and type 2 diabetes mellitus. Based on this, the activation of the immune system in the long-term is assumed to play a role in the process of insulin resistance and diabetes mellitus.⁶ Insulin resistance

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causes blood glucose levels to remain high for longer times. This glucose induces oxidative stress, increased nuclear factor Kappa β and increased transcription of pro-inflammatory genes nuclear factor Kappa β - dependent binding to tumor necrosis factor- α (TNF- α) and IL-6.⁷⁻⁹

Interleukin-6 production has been shown to be significantly increased by adipose tissue in a state of obesity.¹⁰ The increased IL-6 levels in obese individuals may result in a state of insulin resistance and increased risk of cardiovascular complications. A positive correlation between IL-6 levels and insulin resistance in obese individuals has been observed in both adults and children.¹¹

There have been few studies in Indonesia investigating the relationship between IL-6 levels and insulin resistance in obese adolescents, hence, we aimed to assess for such a correlation.

Methods

We conducted a cross-sectional study between January to April 2012 in Manado, North Sulawesi. Subjects were obese or normal BMI teens aged 13-18 years. Thirty-two obese and 32 normal BMI teens were included in this study by consecutive sampling. The required sample size was determined by correlation coefficient equation with $Z\alpha = 5\%$, $Z\beta = 20\%$, and $r = 0.45$, yielding a minimum of 32 subjects per group.

Subjects were recruited from junior and senior high schools in Manado. We included children judged to be healthy by medical examinations and who were willing to be participated in the study. Parents provided the written informed consent and children assented to participate. We excluded teens with infections, those who had undergone treatment with any steroids, antibiotics, antipyretics, and diuretics, as well as those with a history of trauma, injury, or severe illness in the few months prior to the onset of the study.

Subjects in this study were comprised of middle adolescents (13-16 years old) and late adolescents (17-18 years old). Obesity was defined as a BMI $>95^{\text{th}}$ percentile for age and sex, while normal weight was defined as a BMI between 5^{th} - 84^{th} percentile, according to the US Centers for Disease Control and Prevention (CDC) 2000 curve. Insulin resistance was

defined as a clinical condition with potential decline of both endogenous and exogenous insulin to enhance glucose uptake and glucose utilization by the body's cells. Insulin resistance in this study is expressed in homeostatic model assessment of insulin resistance (HOMA-IR) levels (>2.77), as measured by ELISA technique using R&D Systems.¹²

Anthropometric status, physical examinations, and determination of health according to the operational definitions were performed. After an overnight fast, blood specimens for fasting plasma glucose levels and fasting insulin levels were taken. Serum IL-6 levels were measured by means of ELISA (R&D Systems). 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 levels and insulin resistance. We considered a P value of < 0.05 to be statistically significant.

This study was approved by Medical Ethics Committee of Sam Ratulangi University Medical School.

Results

In our study, there were 23 boys (35.9%) and 41 girls (64.1%). In the obese group, 9 out of 32 subjects were boys and 23 out of 32 were girls. In the normal BMI group, there were 14 boys and 18 girls. **Table 1** illustrates the characteristics of the obese and normal BMI subjects.

Higher mean of IL-6 level was found significantly in the obese group compared to normal BMI group ($P=0.004$). Linear regression analysis showed no significant association between IL-6 levels and

Table 1. Baseline characteristics of subjects

Characteristics	Obese group (n=32)	Normal BMI group (n=32)
Mean age (SD), years	15.04 (1.47)	15.89 (1.32)
Gender, n		
Female	23	18
Mean body weight (SD), kg	77.77 (12.31)	47.53 (9.41)
Mean body height (SD), cm	157.66 (8.44)	155.50 (9.50)
Mean BMI (SD), kg/m ²	31.21 (3.61)	19.52 (2.38)
Mean IL-6 level (SD), pg/mL	1.93 (1.71)	0.98 (0.33)
Insulin resistance, n (%)	15 (46.9)	0 (0)

HOMA-IR ($P=0.486$). Furthermore, logistic regression analysis also revealed no significant association between IL-6 levels and the incidence of insulin resistance in obese adolescents ($P=0.309$). Log regression coefficient value of IL-6 was negative ($b = -0.329$), showing an inverse relationship between the insulin resistance incidence and IL-6 levels in adolescents with obesity (Table 2 and Figure 1).

Table 2. Correlation between interleukin-6 with insulin resistance incidence in obese adolescents

Model	Regression coefficient	P value
Constant	-0.805	0.216
IL-6	-0.329	0.309

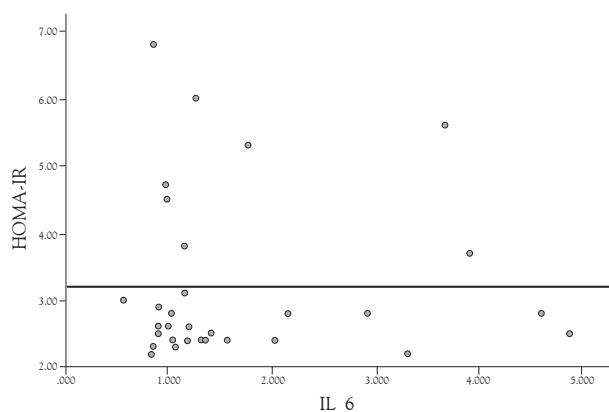


Figure 1. Correlation between IL-6 and HOMA-IR in obese adolescents

Discussion

We found obesity to be more common in girls, similar to findings by others studies which reported that obesity was more prevalent in girls (52%) than in boys (48%).¹³⁻¹⁵

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.¹⁶ In addition, Hendarto *et al.* reported that a chronic, low-grade, inflammatory state did not exist in subjects aged 5-9 years.¹⁷ It is possible that adipocytes in younger children have undergone hyperplasia, but not hypertrophy.

Obese individuals often suffer from impaired

glucose tolerance. Obese patients who lost weight showed an increase in metabolic aspects, especially glycemic control, blood pressure, and decreased plasma triglycerides. Obese individuals with abdominal fat accumulation have a higher risk of impaired glucose tolerance, non-insulin-dependent diabetes mellitus, and other metabolic disorders. Obesity may disrupt the ability of insulin to affect glucose uptake and metabolism in tissues sensitive to insulin (known as insulin resistance) and increase plasma insulin secretion. Reduction in insulin-stimulated glucose uptake in peripheral tissues and increased hepatic glucose production would interfere with the inhibition of glucose expenditure from the liver by fasting insulin.¹⁸

A study by Ricart *et al.* on obese patients' cells showed that they have reductions in insulin-binding relationships with a specific insulin-receptor tyrosine kinase activity, glucose transport activity, and in the level and activity of glycogen synthase.¹⁹ Insulin stimulates differentiation into adipocytes. In adipocytes, insulin promotes lipogenesis by stimulating the absorption of glucose and lipoprotein-derived fatty acids. Insulin also increases the absorption of fatty acids derived from circulating lipoproteins by stimulating lipoprotein lipase activity in adipose tissue. Insulin reduces damage through inhibition of triglyceride lipolysis. The initial molecular signal for insulin action involves the activation of insulin receptor tyrosine kinase, leading to phosphorylation of insulin receptor substrates (IRSs) on tyrosine residues.²⁰

The mean IL-6 level in our obese group was significantly higher compared to that of the normal BMI group ($P=0.004$). This result was consistent with study by Gallistl *et al.*²¹ who observed higher mean IL-6 levels in obese children [3.9 (SD 4.7) pg/mL] than in non-obese children [0.7 (SD 1.3) pg/mL]. Weiss *et al.* also discovered that IL-6 levels rose significantly with the degree of obesity, with the highest levels found in super-obese adolescents (mean 2.45 pg/mL).¹⁴ Interleukin-6 has been positively correlated with BMI in other studies.^{8,9} 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 be due to the increased adipose tissue.^{5,22}

In our study, linear regression analysis revealed no significant association between IL-6 and HOMA-IR ($P=0.486$) in obese adolescents. Furthermore,

logistic regression analysis revealed no significant association between IL-6 and the incidence of insulin resistance ($P=0.309$) in obese adolescents.

Increased IL-6 in obesity stimulates production of C-reactive protein (CRP) in the liver, indicating the occurrence of low-grade chronic inflammation. This inflammation may lead to endothelial dysfunction and subsequently to metabolic syndrome, atherosclerosis, and other complications.²³⁻²⁵

Weiss *et al.* reported that IL-6 was associated significantly with the degree of obesity and the level of CRP, but not significantly associated with the degree of insulin resistance.¹⁴ However, Agarwal *et al.* found no significant relationship between circulating IL-6 and a marker of insulin resistance (HOMA-IR).²⁶ In addition, Nemet *et al.* reported that there was no relationship between IL-6 and fasting insulin,²⁷ but a study by Kelly *et al.* suggested an increase in IL-6 tends to be a risk factor for metabolic syndrome in adolescents.²⁸

A limitation of this study was its cross-sectional design, as we could not determine the onset or length of mild chronic inflammatory states in these obese adolescents. Another limitation was not assessing our subjects' physical activity, diet, and lifestyle.

In conclusion, we find no association between IL-6 levels and the incidence of insulin resistance. However, this study may provide feedback to health workers about the existence of low-grade chronic inflammation in obese adolescents aged 13-18 years, a risk factor for cardiovascular abnormalities, metabolic syndrome, and future complications that may require early intervention. Understanding of these conditions for obese adolescents and their parents may raise awareness to improve lifestyles through healthy diets and increased physical activity.

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