

Retinol binding protein 4, obesity, and insulin resistance in adolescents

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Abstract

Background Obesity is a global problem. Even in poor and developing countries, obesity has reached alarming levels. In childhood, obesity may lead to insulin resistance. Retinol binding protein (RBP4), secreted primarily by liver and adipose tissues, was recently proposed as a link between obesity and insulin resistance. The role of RBP4 in pediatric obesity and its relationship with insulin resistance have not been well elucidated.

Objective To compare RBP4 levels in obese and lean adolescents and to assess for a relationship between RBP4 levels and insulin resistance.

Method This cross-sectional study was conducted in three senior high schools in Padang, West Sumatera, Indonesia. Subjects were adolescents aged 14-18 years, who were obese or normal weight (n=56). We measured subjects' body mass index (BMI) and serum RBP4 concentrations. Insulin resistance was assessed using the homeostasis model assessment of insulin resistance (HOMA-IR) index.

Results Similar RBP4 levels were found in the obese and normoweight groups ($P > 0.05$). Higher RBP4 levels were found in the insulin resistant compared to the non-insulin resistant group, but the difference was not significant ($P > 0.05$).

Conclusion There is no significant difference in mean RBP4 levels in obese adolescents compared to normoweight adolescents. Nor are mean RBP4 levels

significantly different between obese adolescents with and without insulin resistance. [Paediatr Indones. 2017;57:1-7. doi: 10.14238/pi57.1.2017.1-7].

Keywords: obesity; retinol binding protein 4 (RBP4); insulin resistance

Obesity in children is one of the most serious challenges of the 21st century. Childhood obesity has reached alarming levels, with prevalences increased from 4.2% in 1990 to 6.7% in 2010.^{1,2} In Indonesia, the prevalence of obesity, according to the National Socioeconomic Survey (SUSENAS), has increased in both urban and rural areas.³ Children who are overweight or obese have an 80% risk of becoming obese as adults.^{4,5} Obesity in children can lead to insulin resistance,

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which is a key component of metabolic syndrome.⁶ Insulin resistance is responsible for 46.8% of coronary heart disease in type 2 diabetes, 6.2% of non-type 2 diabetes, and 12.5% of the total population in the United States.³

Adipose tissue is metabolically active organ secreting a number of signal peptides with various biological functions. These adipokines play an important role in the regulation of adipocyte differentiation, metabolism, and local inflammatory response. Adipokines are also involved in the regulation of systemic fat and glucose metabolism in the brain, liver, and muscle. Secreted adipokines include leptin, tumor necrosis factor- α (TNF- α), interleukin-6 (IL-6), and chemokine (CC-motif) ligand 2 (CCL2), adiponectin, resistin, omentin, vaspin, visfatin, chemerin and retinol binding protein 4 (RBP4).^{4,5} The RBP4 is a lipocalin protein produced in the liver and mature adipose tissues that carry retinol in the circulation.^{7,8} Serum RBP4 levels were found to be increased and positively correlated with BMI in obese non-diabetics and diabetics. The RBP4 levels were elevated in subjects with impaired glucose tolerance and diabetes mellitus type 2, but inversely related to insulin sensitivity. It is not clear if a retinol-dependent mechanism is associated with obesity or insulin resistance.⁶ The aim of this study was to compare serum RBP4 levels in obese to lean adolescents and to assess for a relationship between RBP4 levels and insulin resistance.

Methods

The subjects for this study were 14 to 18-year-old adolescents (n=56) from three senior high schools in Padang. The children were recruited through direct observation and anthropometric data. Our intent was to enroll 28 normoweight and 28 obese children for the study. Written informed consent was obtained from parents and oral informed assent from the children. The study was approved by the Ethics Committee of the Andalas University Medical School. We took anthropometric data by measuring body weight and heights. Height was measured to the nearest 0.5 cm and weight to the nearest 100 g using a digital balance. After measuring BMI, resting blood pressure was measured by auscultation. Subjects

filled questionnaires on family history, diet, and behavior. Subjects provided 8-mL blood specimens by venipuncture in the morning after a 12-h overnight fast. The HOMA-IR index was used to assess subjects for insulin resistance. The present HOMA cut off point for diagnosis of insulin resistance is 3.16. The HOMA cut off point of >2.5 is valid for adults but not for adolescents.⁹

Body mass index (BMI) of the children was calculated as weight (kilograms)/height (meters-squared). Age and gender-specific criteria from the Centers for Disease Control (CDC) 2000 were used to classify children as normal weight, or obese (above the 95th percentile). Statistical analysis was performed using SPSS 17.0 for Windows software. Non-normally distributed variables were expressed as median (range) and normally distributed data by mean (SD). We used descriptive analysis, T-test, and regression correlation for data analysis. Descriptive analysis was used to describe the mean (SD) for ratio scale data, such as age, body weight, height, BMI, insulin levels, fasting blood glucose levels, HOMA-IR, and RBP4 levels. Analysis T-test was used to assess for differences in the obese and normoweight groups. Results with P values <0.05 were considered to be statistically significant.

Results

Anthropometric and metabolic data of the subjects, by weight classification, are shown in **Table 1**. The mean BMIs were 32.36 (4.00) kg/m² in the obese group and 21.85 (2.49) kg/m² in the normoweight group. Median systolic/diastolic blood pressures were significantly higher in the obese group than in the normoweight group (P <0.05).

Mean insulin level was significantly higher in the obese group than in the normoweight group (P <0.05). Also, the mean HOMA-IR value was significantly higher in the obese group than in the normoweight group (P <0.05). The mean RBP4 level was 24.27 (5.32) pg/mL in the obese group and 24.68 (8.10) mg/mL in the normoweight group (P > 0.05).

Obese subjects' anthropometric, metabolic, and insulin resistance data are shown in **Table 2**. Insulin resistance was found in 10/28 adolescents in the obese group, and in none of the normoweight subjects. Median HOMA-IR in the insulin-resistant group was

significantly higher than in the non-insulin resistant group ($P < 0.05$). However, mean RBP4 levels were not significantly different in the insulin resistant and non-insulin resistant groups [26.42 (5.02) $\mu\text{g/mL}$ vs. 23.08 (5.23) $\mu\text{g/mL}$, respectively]. There was also no statistically significant difference in median RBP4 levels between the two groups ($P > 0.05$).

and adolescents. Weight loss was associated with a decrease in insulin concentration and improved insulin sensitivity in adolescents. In a study of 122 adolescents, obese adolescents had more insulin resistance and abnormal lipid profiles compared to lean adolescents.¹⁰ A population-based study conducted in the United States in 4,902 children aged 12-19 years

Table 1. Anthropometric and metabolic data of subjects by weight classification

Characteristics	Obese group (n=28)	Normoweight group (n=28)	P value
Gender, n(%)			
Male	4 (14.28)	13 (46.42)	0.020*
Female	24 (85.72)	15 (53.58)	
Median age (range), years	16 (15-18)	16 (15-18)	0.392**
Family history of obesity, n(%)			
Yes	15 (53.57)	8 (28.57)	0.103**
No	13 (46.43)	20 (71.43)	
Median systolic BP (range), mmHg	120 (100-150)	110 (90-120)	0.004**
Median diastolic BP (range), mmHg	80 (60-100)	70 (60-80)	0.002*
Median random blood glucose (range), mg/dL	78.00 (69-99)	77.5 (68-95)	0.465**
Mean insulin (SD), $\mu\text{IU/mL}$	12.73 (7.13)	5.65 (3.59)	0.001*
Mean HOMA-IR (SD)	2.63 (1.58)	1.06 (0.61)	0.001*
Mean RBP4 (SD), $\mu\text{g/mL}$	24.27 (5.32)	24.68 (8.10)	0.827*

*T-test; **Mann-Whitney test

Table 2. Anthropometric and metabolic data of obese subjects by insulin resistance classification

Characteristics	Insulin resistant group (n=10)	Non-insulin resistant group (n=10)	P value
Gender, n			
Male	2	2	0.452*
Female	8	16	
Median age (range), years	16.5 (15-18)	16 (15-18)	0.710**
Family history of obesity, n(%)			
Yes	7	8	0.184*
No	3	10	
Median BMI (SD), kg/m^2	34.26 (4.49)	31.10 (3.39)	0.061*
Mean systolic BP (SD), mmHg	127 (14.18)	119.44 (15.13)	0.207*
Mean diastolic BP (SD), mmHg	85 (10.80)	79.44 (11.61)	0.225 ⁿ
Median random blood glucose (range), mg/dL	85 (71-94)	77 (69-99)	0.064*
Mean insulin (SD), $\mu\text{IU/mL}$	20.38 (5.61)	8.45 (3.26)	0.001*
Mean RBP4 (SD), $\mu\text{g/mL}$	26.42 (5.02)	23.08 (5.23)	0.114*

*T-test; **Mann-Whitney test

Discussion

Insulin resistance, as described by the HOMA-IR index, was significantly increased in the obese group compared to the normoweight group. The incidence of insulin resistance in obese adolescent subjects was 35.71%. The relationship between adiposity and insulin resistance has been reported in adults

reported that the incidence of insulin resistance in obese adolescents was 52.1%.¹¹ Similarly, Gatenbein et al. reported a significant increase in HOMA-IR in obese adolescents compared to controls.¹²

Insulin resistance causes hyperinsulinemia which can lead to glucose intolerance, atherogenic dyslipidemia, hypertriglyceridemia, and increased blood pressure. Systolic and diastolic blood pressures were significantly higher in the obese group compared

to the normoweight group ($P < 0.05$). Graham *et al.* also reported an increase in systolic blood pressure in obese adolescents with increased HOMA-IR values, compared to the control group. Insulin acts to increase renal sodium retention and free water clearance. Insulin resistance also increases the activity of the sympathetic nervous system and stimulates the growth of vascular smooth muscle. Insulin levels were found to be significantly higher in patients with essential hypertension compared with normotensive controls.¹³

We found no statistically significant differences in the RBP4 levels in obese and normoweight adolescents. In the obese group, RBP4 levels were higher in adolescents with insulin resistance compared to obese adolescents without insulin resistance, although this difference was not statistically significant ($P > 0.05$). Several factors play a role in the pathogenesis of obesity-related insulin resistance including increased levels of free fatty acids, hormones, and cytokines released by the adipose network.¹² The relationship between RBP4 and insulin resistance in cross-sectional studies is still unclear. However, several studies in adults showed a significant association between RBP4, obesity and metabolic syndrome.¹⁴

A study conducted on 42 adolescents aged 14-18 years in Canada found that RBP4 levels were higher in obese children than in thin children. Furthermore, higher RBP4 levels were associated with insulin resistance, but also by the inflammation factor, C-reactive protein (CRP).¹⁵ Reinehr *et al.* conducted a longitudinal study over one year by examining RBP4 levels in obese children before and after weight loss due to exercise intervention, behavior, and nutrition. They found that RBP4 levels were higher in the obese group, but decreased after weight loss. In addition, RBP4 levels at puberty were higher than at the age of puberty.^{13,15}

A previous study examined RBP4 and its relationship to insulin resistance in 49 American children at puberty. This study showed that there were no significant differences in mean RBP4 levels in the age of puberty between the sample and the control groups. RBP4 was correlated with levels of triglycerides, but not related to IMT.¹⁶

Graham *et al.* conducted a study to measure RBP4 levels, insulin resistance, and metabolic components in three groups: lean, obese, and diabetic.

They found that RBP4 levels correlated with obesity, impaired glucose tolerance, and diabetes mellitus type 2, however, RBP4 levels were also elevated in non-obese and non-diabetic subjects who had a family history of obesity and type 2 diabetes. There were 15 non-obese adolescents in the group who had higher RBP4 levels above the mean value of 24.68 (8.10) ug/dl, eight (53.33%) of whom had a family history of obesity.¹³

Several other studies also reported that RBP4 levels were not significantly different in obese and non-obese children.¹⁵⁻¹⁷ A previous study conducted on 80 obese girls aged 9-15 years who were divided into a control group, nutrition, obesity and severe obesity year in Greece. They examined levels of RBP4 and lipocalin-2 and their relationships to high-sensitivity C-reactive protein (hs-CRP), leptin, and adiponectin. Mean RBP4 level was 24.8 (1.3) mg/dL in the control group and 24.9 mg/dL in the obese group.¹⁶ Similarly, we found that mean RBP4 levels were 24.68 (8.10) mg/dL in the non-obese group and 24.27 (5.32) mg/dL in the obese group. In addition, Kanaka-Gatenbein *et al.* reported that levels of RBP4 and lipocalin-2 inversely correlated with BMI and hs-CRP, while leptin positively correlated with IMT.¹⁵ Janke *et al.* conducted a study of 74 obese, overweight, and underweight subjects and found that RBP4 mRNA was downregulated in the subcutaneous adipose network, and circulating RBP4 levels did not differ among the three groups.¹⁷

The correlation of serum RBP4 levels and plasma insulin levels indicates that the expression of RBP4 in adipose tissue may be a direct consequence of hyperinsulinemia. However, subjects with type 2 diabetes had lower fasting insulin levels than subjects with impaired glucose tolerance with the same degree of insulin resistance, but with the same levels of RBP4. In addition, RBP4 and insulin levels were not related in subjects who did not experience an increase in insulin sensitivity after exercise. Therefore, the primary reduction of plasma insulin levels alone does not determine serum RBP4 levels. However, there may be a threshold at which plasma insulin is permissive for increased expression of RBP4 in adipocytes, because RBP4 levels decreased in subjects with newly onset type 1 diabetes and returned to normal after insulin treatment.¹³

In several pediatric studies, the major biological

Obese subjects' anthropometric, metabolic, and insulin resistance data are shown in **Table 2**. Insulin resistance was found in 10/28 adolescents in the obese group, and in none of the normoweight subjects. Median HOMA-IR in the insulin-resistant group was significantly higher than in the non-insulin resistant group ($P < 0.05$). However, mean RBP4 levels were not significantly different in the insulin resistant and non-insulin resistant groups [26.42 (5.02) pg/mL vs. 23.08 (5.23) mg/mL, respectively]. There was also no statistically significant difference in median RBP4 levels between the two groups ($P > 0.05$).

Discussion

Insulin resistance, as described by the HOMA-IR index, was significantly increased in the obese group compared to the normoweight group. The incidence of insulin resistance in obese adolescent subjects was 35.71%. The relationship between adiposity and insulin resistance has been reported in adults and adolescents. Weight loss was associated with a decrease in insulin concentration and improved insulin sensitivity in adolescents. In a study of 122 adolescents, obese adolescents had more insulin resistance and abnormal lipid profiles compared to lean adolescents.¹⁰ A population-based study conducted in the United States in 4,902 children aged 12-19 years reported that the incidence of insulin resistance in obese adolescents was 52.1%.¹¹ Similarly, Gatenbein et al. reported a significant increase in HOMA-IR in obese adolescents compared to controls.¹²

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determinant of serum RBP4, namely vitamin A status, was not measured.¹⁴ The RBP4 is specific to the transport protein for blood retinol. Retinol intake disorders and vitamin A status affect the release of RBP4 by the liver and circulating RBP4 in the blood. It remains unclear whether the relationship between RBP4 and insulin sensitivity depends on retinol.¹⁴ Aeberli *et al.* examined the levels of serum RBP4 and retinol, as well as the ratio of RBP4 to retinol and vitamin A intake in 79 Swiss children. Subject groups were normoweight, overweight, and obese. They examined the relationship of these variables to insulin resistance, sub-clinical inflammation, and metabolic syndrome. They found that only 3% of children had low vitamin A status. RBP4 and RBP4/SR significantly correlated with serum triglycerides and RBP4/SR correlated with fasting insulin. The ratio of RBP4/SR was more strongly correlated with obesity, central obesity, and metabolic syndrome components compared to serum RBP4.¹⁴

Many confounding factors accompany studies of this kind, ranging from methodology to sampling. Retinol status, iron status, and renal function also affect RBP4 levels, but not many studies have linked these factors. The ratio of retinol to RBP4 is influenced by the state of deficiency and obesity. But in the case of obesity, synthesized RBP4 released by adipose tissue into circulation does not bind to retinol.¹⁸ Vitamin A deficiency can interfere with iron metabolism and aggravate anemia. In recent years, increased iron intake and increased iron reserves have been recognized to be significant contributors to insulin resistance in the general population and in patients with type 2 diabetes.¹⁹ In contrast, iron supplementation significantly increases plasma retinol and RBP4.¹⁹ Fernandez-Real *et al.* conducted a study on 132 non-diabetic, middle-aged men, by checking their iron status and RBP4. They found that RBP4 levels positively correlated with serum ferritin and RBP4 levels decreased after iron depletion. They concluded that RBP4 plays an important role in relation to the resistance RBP4 insulin.¹⁹ However, studies in children and adolescents have been limited. The relationship of RBP4 with some metabolic parameters has been studied in detail, but little is known about the relationship of this adipokine with kidney function, especially in patients with decreased (mild-moderate) glomerular filtration rate (GFR).

Ziegelmeier *et al.* determined serum RBP4 levels in 58 adult patients on chronic hemodialysis (32 diabetic and 26 non-diabetic) and 59 control subjects (29 diabetic and 30 non-diabetic). A GFR of 50 mL/min and RBP4 correlated with clinical and biochemical kidney function, glucose and lipid metabolism, as well as inflammation in both groups. They found that RBP4 was negatively correlated with GFR, and RBP4 levels were higher in patients with decreased kidney function.¹⁰ In our study, we did not check the statuses of retinol, iron, and kidney function due to cost and the limited number of blood specimens taken.

The adipokine, RBP4, is promising in humans as a link between adiposity, insulin resistance, type 2 diabetes mellitus, and metabolic syndrome components. However, many studies on the relationship and/or causality due to RBP4 expression in the above circumstances have not been fully explained.⁸

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