Paediatrica Indonesiana

VOLUME 51 January • 2011 NUMBER 1

Original Article

Adiponectin and highly sensitive C-reactive protein levels in obese children aged 9 to 15 years

Frecillia Regina, Kristellina Tirtamulia, Sarah Maria Warouw

Abstract

Background Childhood obesity is a widespread and growing problem associated with health problems such as metabolic syndrome, diabetes mellitus and cardiovascular disease. A low-grade chronic inflammatory state, reflected by decreased adiponectin and increased highly sensitive C-reactive protein (hsCRP) levels, may play a role in metabolic syndrome associated with obesity.

Objective To assess and compare adiponectin and hsCRP levels in obese and normal weight children.

Methods We conducted a cross-sectional, case-controlled study in Manado from May to July 2010. Subjects were selected from obese, but otherwise healthy children aged 9-15 years. Control subjects were schoolmates with normal body mass index (BMI). We performed physical examinations, measured blood pressure, weight and height, and calculated BMI for all subjects. After an overnight fast, all subjects were tested for fasting blood glucose, adiponectin and hsCRP levels.

Results The mean adiponectin level in the obese group was 3.6 μg/mL (SD 1.43), lower than that of the normoweight group, 4.8 μg/mL (SD 1.67) ($P < 0.0001$). The mean hsCRP level in the obese group was 3.3 mg/L (SD 3.62) while that of the normoweight group was 0.8 mg/L (SD 1.39) ($P < 0.0001$). There was no inverse correlation between adiponectin and hsCRP levels in obese group ($r = 0.048$, $P = 0.362$).

Conclusions Lower adiponectin and higher hsCRP levels in the obese group is consistent with a low-grade chronic inflammatory state. Other factors that influence adiponectin and hsCRP production or inflammatory pathways of other adipokines need further evaluation. Early intervention is needed to reduce body weight in obese children. **[Paediatr Indones. 2011;51:7-11]**.

Keywords: *adiponectin, C-reactive protein, obese*

The prevalence of childhood obesity has been rising greatly worldwide.[1] Obesity is an exaggeration of normal adiposity.[2] Adipose tissue expansion is a two-step process. Initially, increased levels of triglycerides in adipocytes increase the average adipocyte size (hypertrophy). Later, this increased storage capacity in adipose tissue requires the recruitment and differentiation of preadipocytes from the stromal vascular compartment of adipose tissue (hyperplasia). Adipocytes in white adipose tissue have traditionally been viewed as cells involved primarily in energy storage, however, it is now clear that adipocytes also secrete mediator substances, called adipokines.[3] Adiponectin is one such adipokine exclusively secreted by adipose tissue and exhibits anti-inflammatory properties. Tumor necrosis factor (TNF)-α, whose production is increased in obese people, dose-dependently reduces the expression of the adiponectin gene in adipocytes by suppressing its promoter activity. Adiponectin gene expression is also reversibly downregulated by interleukin (IL)-6, a cytokine whose expression in fat cells increases

From the Department of Child Health, Medical School of Sam Ratulangi University, Manado, Indonesia.

Reprint request to: Frecillia Regina, MD, Department of Child Health, Medical School, Sam Ratulangi University, Prof. Dr. R. D. Kandou Hospital, Jalan Raya Tanawangko no 56, Manado 95115, Indonesia. Tel +62-431-821652, fax. +62-431-859091, e-mail: cil_23@yahoo.com

with cell size.[4] Previous studies have reported lower adiponectin levels in obese children and adolescents than in their normoweight counterparts.[5,6]

Highly sensitive C-reactive protein (hsCRP) is a highly sensitive assay to measure CRP levels.[7] CRP has proatherogenic and proinflammatory effects and is an acute-phase reactant synthesized by the liver in response to IL-6. Levels of hsCRP have been observed to be higher in obese children than in children of normal weight.[8,9] A previous study found a significant inverse correlation between hsCRP and adiponectin levels that reflects a low-grade chronic inflammatory state in obese children. This state of inflammation is associated with metabolic syndrome, type 2 diabetes mellitus and cardiovascular disease.[10]

In Indonesia, the prevalence of childhood obesity is increasing.[11] There has been limited reporting on adiponectin and hsCRP levels and the correlation of the two levels in obese Indonesian children. Therefore, the objective of this study is to assess and compare adiponectin and hsCRP levels in obese and normal weight children.

Methods

We performed a cross-sectional study in Manado, Indonesia from May to July 2010. We randomly selected 20/44 elementary schools and 10/17 junior high schools. A sample size of 50 children per group was necessary for a level of confidence of 95% and statistical power of 80%. To account for a possible 20% dropout rate, we selected 60 obese children and a similar number for the normal weight control group. The inclusion criteria for the obese group were children aged 9-15 years with a BMI ≥ 95 percentile for age and sex according to CDC 2000 Growth Reference Charts or ≥ 30 kg/m^2. For the control group, we recruited schoolmates of similar age and normal weight (5-84 percentiles for age and sex according to CDC 2000 Growth Reference Charts) by simple randomization. We excluded children with acute inflammation, type 2 diabetes mellitus, hypertension or heart disease. Acute inflammation was defined as having infection or trauma, along with consumption of antipyretic, analgesic or antibiotics within 3 weeks. Type 2 diabetes mellitus was defined as having symptoms of polyuria, polydipsia, or polyphagia with fasting blood glucose level ≥ 126 mg/dL. Hypertension was defined as a mean systolic and/or diastolic blood pressure ≥ 95th percentiles according to age and sex after triplicate measurements with an appropriate cuff. Heart disease was defined as having symptoms of dyspnea, edema, palpitations, chest pain, cyanosis, heart murmur, or signs of heart failure. We obtained informed consent from all parents and assent from all children after the nature of the procedures was explained and before testing commenced.

We performed history taking and physical examinations, measured blood pressure, weight, height, and calculated BMI (weight/height^2) on all subjects. After an overnight fast, all subjects were tested for fasting blood glucose, adiponectin and hsCRP levels in Prodia laboratory. Fasting blood glucose was measured in order to exclude subjects with type 2 diabetes mellitus. Serum adiponectin levels were measured by the enzyme-linked immunosorbent assay (ELISA) kit from Phoenix Pharmaceuticals Inc, Belmont, CA, USA (EK-ADI-01). The sensitivity of the adiponectin assay was 0.40 μg/ml. The intra- and interassay coefficients of variation (CVs) were <10 and <15%, respectively. Levels of hsCRP were measured by a high-sensitivity assay for CRP using a Dade Behring kit that detected levels above 0.20 mg/L by nephelometry.

Statistical analysis

We used Student's t test for independent samples to compare adiponectin and hsCRP levels in the two groups. If they were not well distributed, we used the Mann-Whitney U test. We used Pearson's correlation coefficient to examine the relationship between adiponectin and hsCRP levels. All analyses were conducted by SPSS 17 version with a P value < 0.05 considered statistically significant.

Results

Ninety-eight of 186 obese children met the inclusion criteria. We randomly selected 60 of the 98 obese children for this study. Three patients were later excluded due to common cold at the time we performed laboratory examination. Fifty-seven obese children and 58 normoweight children comprised the final groups. The subjects' characteristics are shown

in **Table 1**. We found that obese children had higher mean systolic and diastolic blood pressure.

In obese children, the mean adiponectin levels were significantly lower and the mean hsCRP levels were significantly higher than those in normoweight children (**Table 2**). There were no statistical differences in adiponectin and hsCRP levels between boys and girls (**Table 3**). The adiponectin and hsCRP correlation in obese children is shown in **Figure 1**. There was no significant inverse correlation between adiponectin and hsCRP levels.

Table 1. Characteristics of study subjects

Characteristic	Group	
	Obese N=57	Normoweight N=58
Age, mean (SD) yr	12.3 (1.50)	12.4 (0.97)
Male gender, n	35	30
Blood pressure		
• Systolic, mean (SD) mmHg	113.3 (8.47)	107.3 (8.99)
• Diastolic mean (SD) mmHg	74.1 (6.89)	68.4 (8.39)

Table 2. Comparison of adiponectin and hsCRP levels

	Group				
	Obese		Normoweight		
	n = 58	95% CI	n = 57	95% CI	P
Adiponectin, mean (SD) µg/mL	3.6 (1.43)	3.20 to 3.97	4.8 (1.67)	4.35 to 5.23	< 0.0001
hsCRP, mean (SD) mg/L	3.3 (3.62)	2.36 to 4.28	0.8 (1.39)	0.43 to 1.16	< 0.0001

Table 3. Comparison of adiponectin and hsCRP level according to gender

	Group									
	Obese					Normoweight				
	Boys n = 58	95% CI	Girls n = 58	95% CI	P	Boys n= 57	95% CI	Girls n= 57	95% CI	P
Adiponectin, mean (SD) µg/mL	3.5 (1.44)	3.02 to 4.01	3.7 (1.45)	3.06 to 4.34	0.380	4.8 (1.81)	4.14 to 5.50	4.8 (1.53)	4.17 to 5.36	0.898
hsCRP, mean (SD) mg/L	3.2 (3.27)	2.10 to 4.36	3.4 (4.18)	1.60 to 5.30	0.527	0.8 (1.28)	0.29 to 1.25	0.8 (1.52)	0.23 to 1.40	0.579

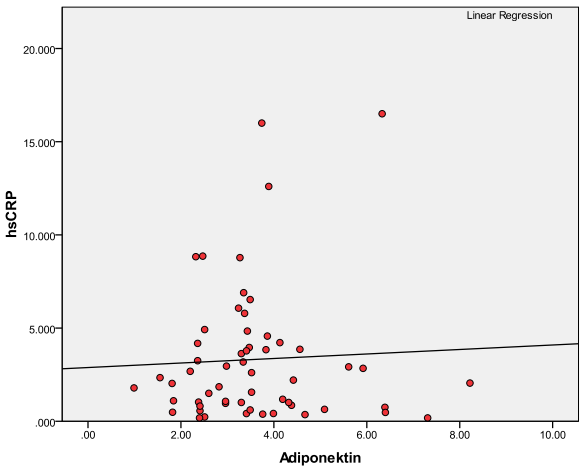

Figure 1. Adiponectin and hsCRP correlation in obese children.

Discussion

We chose children aged 9-15 years for our study because a previous study of superobese boys aged 5-9 years showed no correlation between leptin, adiponectin, TNF-α, CRP levels and insulin resistance, indicating that these subjects were not in a low-grade chronic inflammatory state.[16] Another study also confirmed that increased hsCRP and decreased adiponectin levels started at the age of 9 years.[17]

Our results show significantly lower adiponectin levels in obese children than in normoweight children. However, we found that mean adiponectin levels in obese (3.6 μg/mL) and normoweight children (4.8 μg/mL) in our study were lower than those of previous studies.[5,6] Further study should be conducted to determine if these differences in adiponectin levels are due to genetic influences, dietary intake or lifestyle or other causes.[4] We found no statistical differences in adiponectin levels between boys and girls in our study, consistent with the work of Stern et al. who observed no gender influence on adiponectin levels.[4]

We found mean hsCRP levels of 3.3 mg/L in obese children and 0.8 mg/L in normoweight children, a statistically significant difference and consistent with a previous report that showed hsCRP level to increase with higher BMI measurements.[8] These hsCRP concentrations are consistent with the finding of Kapiotis et al, who reported mean hsCRP levels of 4.1 mg/L in obese children and 0.9 mg/L in normoweight children.[9] We found no statistical difference in hsCRP levels between boys and girls, consistent with the results of a previous study where hsCRP levels were not influenced by gender.[9]

In our study, no significant inverse correlation was found between adiponectin and hsCRP concentrations, consistent with the results of Nagel et al who performed a cross-sectional study among 450 children aged 10 years ($r=-0.05$; $P=0.30$).[12] However, Winer et al found a significant inverse correlation between hsCRP and adiponectin levels in their study.[10] Several possible reasons may explain this discrepancy. First, Winer et al had 589 subjects comprised of white, black and Hispanic children,[10] while our study subjects were all Indonesian. Second, people in Manado consume fish, which contains high omega 3 levels, as the main source of protein. A diet high in omega 3 can influence adiponectin levels.[4] Other possible factors include an adiponectin gene mutation[13] or polymorphism[14] or other inflammatory pathways that correlate to hsCRP such as leptin, apolipoprotein, or fibrinogen.[12] Further study should be conducted to evaluate which factors are related to adiponectin and hsCRP.

Although we had excluded subjects with hypertension in this study, we found that systolic and diastolic blood pressures were significantly higher in obese children than normoweight children. This finding serves to highlight that childhood obesity is a risk factor for hypertension and obese children need blood pressure monitoring.[15]

Some limitations of our study were a lack of evaluating dietary intake, lifestyle, pubertal status, genetic influence, and other adipokine inflammatory pathways.[4,12-14] Another limitation was that we measured the concentration of total adiponectin instead of high molecular weight adiponectin.[18] In addition, cohort retrospective studies are needed to assess the starting time of obesity and chronic inflammation in obese children.

In conclusion, we found lower adiponectin and higher hsCRP levels in obese children than in normoweight children aged 9-15 years. These adiponectin and hsCRP levels in obese children are a sign of a low-grade chronic inflammatory state. Early intervention is needed to reduce body weight in obese children to help prevent low-grade chronic inflammation, and its subsequent complications, such as metabolic syndrome.

References

1. Wang Y, Monteiro C, Popkin BM. Trends of obesity and underweight in older children and adolescents in the United States, Brazil, China and Russia. Am J Clin Nutr. 2001;75:971-7.
2. Redinger RN. The pathophysiology of obesity and its clinical manifestations. Gastroenterol Hepatol. 2007;3:856-63.
3. Trujillo ME, Scherer PE. Adipose tissue-derived factors: impact on health and disease. Endocr Rev. 2006;27:762-78.
4. Stern N, Osher E, Greenman Y. Hypoadiponectinemia as a marker of adipocyte dysfunction part I: the biology of adiponectin. J Cardiometab Syndr. 2007;2:174-82.
5. Valle M, Martos R, Gascón F, Cañete R, Zafra MA, Morales R. Low-grade systemic inflammation, hypoadinopectinemia and a high concentration of leptin are present in very young obese children, and correlate with metabolic syndrome. Diabetes Metab. 2005;31:55-62.
6. Weiss R, Dziura J, Burgert TS, Tamborlane WV, Taksali SE, Yeckel CW, et al. Obesity and the Metabolic Syndrome in Children and Adolescents. N Engl J Med. 2004;350:2362-74.
7. Abraham J, Campbell CY, Cheema A, Gluckman TJ, Blumenthal RS. C-reactive protein in cardiovascular risk

assessment: a review of the evidence. J Cardiometab Syndr. 2007;2:119-23.

8. Wu DM, Chu NF, Shen MH, Wang SC. Obesity, plasma high sensitivity C-reactive protein levels and insulin resistance status among school children in Taiwan. Clin Biochem. 2006;39:810-5.
9. Kapiotis S, Holzer G, Schaller G, Haumer M, Widhalm H, Weghuber D, et al. A proinflammatory state is detectable in obese children and is accompanied by functional and morphological vascular change. Arterioscler Thromb Vasc Biol. 2006;26:2541-6.
10. Winer JC, Zern TL, Taksali SE, Dziura J, Cali AMG, Wollschlager M, et al. Adiponectin in childhood and adolescent obesity and its association with inflammatory markers and components of the metabolic syndrome. J Clin Endocrinol Metab. 2006;91:4415-23.
11. Mexitalia M. Nutrisi pencegahan: prudent diet. In: Gunawan G, editor. Tumbuh kembang, nutrisi dan endokrin. 5th Continuing Professional Development; Banjarmasin 2006 Februari 18-19. Banjarmasin: Indonesian Pediatric Society - South Borneo Branch; 2006: p. 29-42.
12. Nagel G, Rapp K, Wabitsch M, Büchele G, Kroke A, Zöllner I, et al. Prevalence and cluster of cardiometabolic biomarkers in overweight and obese schoolchildren: results from a large survey in southwest Germany. Clin Chem. 2008;54:317-25.
13. Ohashi K, Ouchi N, Kihara S. Adiponectin I164T mutation is associated with the metabolic syndrome and coronary artery disease. J Am Coll Cardiol. 2004;43:1195-1200.
14. Stumvoll M, Tschritter O, Fritsche A. Association of the T-G polymorphism in adiponectin (exon 2) with obesity and insulin sensitivity: interaction with family history of type 2 diabetes. Diabetes. 2002;51:37-41.
15. Schiel R, Beltschikow W, Kramer G, Stein G. Overweight, obesity and elevated blood pressure in children and adolescents. *Eur J Med Res.* 2006;11:97-101.
16. Hendarto A. Telaah peran leptin, adiponektin, tumor necrosis factor-α, C reactive protein, asupan karbohidrat dan lemak terhadap resistensi insulin pada anak lelaki superobes usia 5-9 tahun [dissertation]. Jakarta: University of Indonesia, 2009.
17. Punthakee Z, Delvin EE, O'Loughlin J, Paradis G, Levy E, Platt RW, et al. Adiponectin, adiposity, and insulin resistance in children and adolescents. J Clin Endocrinol Metab. 2006;91:2119-25.
18. Araki S, Dobashi K, Kubo K, Asayama K, Shirahata A. High molecular weight, rather than total, adiponectin levels better reflect metabolic abnormalities associated with childhood obesity. J Clin Endocrinol Metab. 2006;91:5113-6.