Hypoadiponectinemia: A Risk Factor For Metabolic Syndrome

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ABSTRACT

Aim: *to find out correlation between plasma adiponectin levels, insulin resistance and IDF criteria of Mets Patients.*

Methods: *a case-control study was conducted on Native Javanese people from June 2006 to Januari 2007 in Outpatients Clinic of Dr Sardjito Hospital. The case group involved patients aged between 20 to 55 years old. The diagnosis of metabolic syndrome was confirmed according to IDF criteria. Patients without metabolic syndrome with matching age and sex,were taken as contro group.*

Results: *there were significant differences between case andh control group for BMI (body mass index) (30.2 ± 4.1 vs 26.9 ± 4.7 kg/m^2), waist circumference (93.5 ± 7.9 vs 84.4 ± 11.5 cm), triglyceride (207.4 ± 101.8 vs. 119.3 ± 71.5 mg/dL) , HDL cholesterol (48.6 ± 9.4 vs. 59.9 ± 11.8m g/dL), systolic blood pressure (132.8 ± 17.9mmHg vs 120.6 ± 13.5 mmHg) and and diastolic blood pressure (83.8 ± 8.5 mmHg vs. 79.4 ± 10.7), fasting blood glucose (128.3 ± 40.8 mg/dL vs. 100.7 ± 29.4 mg/dL), HOMA index (6.7 ± 17.4 vs. 2.0 ± 2.0) and adiponectin levels (3.8 ± 1.4 vs. 5.9 ± 2.5), respectively. For metabolic syndrome, hypoadiponectinemia showed the OR value of 6.0 (95% CI 2.13 to 16.98); insulin resistance showed the OR value of 5.7 (95% CI 1.3 to 25.02), after adjustment for waist circumference, TG, HLD, blood pressure, fasting blood glucose.*

Conclusion: *hypoadiponectinemia and insulin resistance represent independent risk factors for metabolic syndrome development.*

Key words**:** *hypoadiponectinemia, insulin resistance, metabolic syndrome, IDF criteria.*

INTRODUCTION

The Metabolic syndrome, a condition characterized by central obesity, hypertension, insulin resistance and atherogenic dyslipidemia, is a major and increasingly prevalent disorder in the developing world. The two primary risk factors for development of the metabolic syndrome apart from genetic factors are overweight/obesity and physical inactivity.[1]

Obesity is a major risk factor for insulin resistance, type 2 diabetes, heart disease, orthopedic problems, and many other chronic diseases. The incidence of obesity has dramatically increased and has become epidemic in the western world. The etiology is multifactorial, with genetic, environmental, socioeconomic, and behavioral or psychological influences, with an increase in the related morbidity and mortality. Obesity is the final consequence of a chronic positive energy balance, regulated by a complex network between endocrine tissues and the central nervous system. Fat tissue is increasingly viewed as an active endocrine organ with a high metabolic activity. Adipocytes produce and secrete several proteins that act as veritable hormones, responsible for the regulation of energy intake and expenditure. Many of these hormones, collectively called adipokines, play important roles in the inflammatory and atherosclerotic processes. Adiponectin is one of the most abundant adipose tissue-specific factors and appears to improve insulin sensitivity and inhibits vascular inflammation. Adiponectin is inversely correlated with leptin, its plasma levels are significantly reduced in obese subjects, in insulin-resistant subjects, and in type 2 diabetic patients and increased after weight reduction. Two independent case-control studies in healthy Caucasians and in Pima Indians indicate that low plasma adiponectin levels are associated with an increased risk of type 2 diabetes[2,3,4] and hypoadiponectine-

mia may contribute to insulin resistance and accelerated atherogenesis, and the reduction is believed to have a role in a pathogenesis of cardiovascular diseases associated with obesity and other components of metabolic syndrome.[2,5] Recent evidence has also suggested the role of adiponectin in the regulation of insulin action, energy homeostasis, obesity and insulin resistance. To further characterize the correlation between adiponectinemia and other components of metabolic syndrome, we measured plasma adiponectin.

This study was aimed to find out correlation between plasma adiponectin levels, insulin resistance and IDF criteria of Mets Patients

METHODS

A case-control study was conducted among Native Javanese people in June 2006 until Januari 2007 in Outpatients Clinic of Dr Sardjito Hospital. Case control study by matching of age and sex, age differences maximal 2 years. Inclusion criteria for cases group were age between 20 to 55 years old (males/females) and diagnosed as metabolic syndrome according to IDF criteria: abdominal obesity (waist circumference in males >90 cm & females >80 cm) and plus either 2 of the following factors:

1. Increased of triglyceride level: >150 mg/dl (1.7 mmol/l) or taking medication for lipid disorders.
2. Decreased of HDL cholesterol less than 40 mg (0.9 mmol/l) in males or less than 50 mg/dl (1.29 mmol/l) in females or taking medications for lipid disorders.
3. Increased of systolic blood pressure more than 130 mmHg or diastolic blood pressure more than 85 mmHg or taking antihypertension medications.
4. Increased of fasting blood glucose more than 100 mg/dl (5.6 mmol/l) or taking antidiabetic medication before if more than 5.6 mmol/l or 100 mg/dl.

Criteria for control group are age between 20 to 55 years old and they were matching by age and sex.

Patients taking drugs (glucocorticoid, isopreterenol, ß-adrenergik receptor agonist, androgens, estrogens, PPAR-g agonist) and smoking, were excluded from the study.

In all subjectsbody height and body weight were measured. Ten milliliters of venous blood were drawn after one night fasting. Adiponectin was measured with ELISA method. The fasting glucose concentration was measured by enzymatic colorimetric assay using a modified glucose oxidase-peroxidase method (Roche Diagnostics, Mannheim, Germany) and a Roche-Hitachi 917 analyzer. Commercial enzymatic tests were used for determining HDL-cholesterol and triglyceride (Roche Diagnostics) concentrations. The inter assay coefficient of variation was less than 5.0% for HDL-cholesterol, less than 2.5% for triglycerides. The degree of insulin resistance was calculated according to the homeostasis model assessment (HOMA) which is a good index for assessing insulin resistance in subjects with different degree of insulin resistance and has a good correlation with insulin mediated glucose uptake calculated by euglycemic hyperinsulinemic glucose clamp.[6] According to the homeostasis model assessment (HOMA),[13,14] insulin resistance (IR) was calculated as follows: IR = FI x g/22.5; where FI = fasting insulin (µu/ml) and g = fasting glucose (mmol/1).[6] Blood samples for insulin assay were collected in EDTA tubes and the plasma samples on the same day of collection was aliquoted in Eppendorf vials and stored at -80°C until thawed for insulin assay. Plasma insulin was measured by a commercial double-antibody, solid phase radioimmunoassay (Sorin Biomedica, Milan Italy, intra-assay c. v. 3.1 $\pm$ 0.3%).

All protocols were approved by the Institutional Review Board or Ethical Committee at Medical Faculty of Gadjah Mada University Yogyakarta, and all the subjects gave informed consent.

Statistical analyses were performed using SPSS 13.0 software. Unless otherwise stated, descriptive results of continuous variables are expressed as means ± SD for Gaussian distribution and as median (interquartile range) for non-Gaussian distribution. Mann Whitney U test was used to compare the differences between variables in the two groups for non parametric data and student t-test for parametric data, with the significance level of <0.05 and a confidence interval of 95%. The relation between variables was analyzed by simple correlation (Pearson's test or Spearman correlation) and logistic regression to know OR.

RESULTS

From June 2006 until January 2007, there were 80 patients include in this study (40 subjects in metabolic syndrome groups and 40 subjects without metabolic syndrome), with 35 (43.8%) male and 45 (56.2%) female. Clinical and biochemical variables of the study subjects are summarized in Table 1. The mean of the age was 46.11 $\pm$ 5.84 years old; mean of Body mass index 28.57 $\pm$ 4.67 kg/m^2 with the mean of Waist Circumference was 88.94 $\pm$ 10.82 cm; mean of HOMA IR, level of adiponectine, fasting glucose, HDL cholesterol and level of triglyceride were 4.35 $\pm$ 12.55;

Table 1.Clinical and biochemical variables

Varibles	Means ± Standard deviation (N=80)
Age (years)*	46.11 ± 5.84
Sex, n (%)	
Male	35 (43.8)
Female	45 (56.2)
Body mass index (kg/m^2)	28.57 ± 4.67
HOMA IR	4.35 ± 12.55
Adiponectine	4.86 ± 2.32
Waist Circumference (Asia, cm)	88.94 ± 10.82
Fasting glucose (mg/dl)	114.54 ± 37..95
HDL (mg/dL)	54.28 ± 12.05
Triglyceride (mg/dL)	163.34 ± 98.00
Blood Pressure Systolic (mmHg)	127.32 ± 17.09
Blood pressure Diastolic (mmHg)	81.83 ± 9.72

HDL = *high density lipoprotein*, HOMA IR: *homeostasis model assessment insulin resistance*

4.86 ± 2.32; 114.54 ± 37..95 mg/dL; 54.28 ± 12.05 mg/dL; 54.28 ± 12.05 mg/dL; and 163.34 ± 98.00 mg/dL, respectively. The mean of systolic and diastolic blood pressure were 127.32 ± 17.09 mmHg and 81.83 ± 9.72 mmHg.

There was no age difference between two groups, and there were significant difference between case group with control group for BMI (body mass index) (30.2 ± 4.1 vs 26.9 ± 4.7 kg/m^2), waist circumference (93.5 ± 7.9 vs 84.4 ± 11.5 cm), triglyceride (207.4 ± 101.8 vs. 119.3 ± 71.5 mg/dL) , HDL cholesterol (48.6 ± 9.4 vs. 59.9 ± 11.8 mg/dL), systolic blood pressure (132.8 ± 17.9mmHg vs. 120.6 ± 13.5 mmHg) and diastolic blood pressure (83.8 ± 8.5 mmHg vs. 79.4 ± 10.7 for diastolic blood pressure), fasting blood glucose 128.3 ± 40.8 mg/dL vs. 100.7 ± 29.4 mg/dL), HOMA index (6.7 ± 17.4 vs. 2.0 ± 2.0) and adiponectin levels (3.8 ± 1.4 vs. 5.9 ± 2.5), respectively. (Table 2)

Table 2. The difference physical and metabolic characteristics of the study population according IDF Mets Criteria (2005)

Variabel	Case (N=40)	Control (N=40)	*P*
Age (years)*	46.7 ± 5.7	45.91 ± 6	0.7
Body mass index (kg/m^2)*	30.2 ± 4.1	26.9 ± 4.7	0.02*
HOMA IR	6.7 ± 17.4	2.0 ± 2.0	0.1
Adiponectine	3.8 ± 1.4	5.9 ± 2.5	<0.001*
IDF Mets Criteria (2005)			
Waist Circumference (Asia, cm)	93.5 ± 7.9	84.4 ± 11.5	<0.001*
Plus 2 or more of the followings			
Fasting glucose (mg/dl)*	128.3 ± 40.8	100.7 ± 29.4	0.01*
HDL (mg/dL)*	48.6 ± 9.4	59.9 ± 11.8	<0.001*
Triglyceride (mg/dL)*	207.4 ± 101.8	119.3 ± 71.5	<0.001*
Blood pressure			
Systolic (mmHg)	132.8 ± 17.9	120.6 ± 13.5	0.02*
Diastolic (mmHg)	83.8 ± 8.5	79.4 ± 10.7	0.05*

HDL = high density lipoprotein, * si gnificance < 0.05

This data showed that hypoadiponectinemia has OR 6.0 (95% CI 2.13 – 16.98) and Insulin resistance OR 5.7 (95% CI 1.3 – 25.02) for metabolic syndrome development, after ajustment for waist circumference, TG, HLD, blood pressure, fasting blood glucose.

DISCUSSION

Multiple risk factor syndrome or metabolic syndrome is a growing medical problem in industrialized countries. Obesity is the central and causal component in this syndrome, but the mechanistic role of obesity has not been fully elucidated.[7] The incidence of obesity has dramatically increased and has become epidemic in the western world. The etiology is multi-factorial, with genetic, environmental, socioeconomic, and behavioral or psychological influences, with an increase in the related morbidity and mortality. Obesity is the final consequence of a chronic positive energy balance, regulated by a complex network between endocrine tissues and the central nervous system. Fat tissue is increasingly viewed as an active endocrine organ with a high metabolic activity. Adipocytes produce and secrete several proteins that act as veritable hormones, responsible for the regulation of energy intake and expenditure.[8] Adiponectin is one of the most abundant adipose tissue-specific factors and appears to improve insulin sensitivity and inhibit vascular inflammation. Serum adiponectin levels are low in obese subjects and increase after weight loss. Human adiponectin has 244 amino acids, and the molecular weight of the monomer is 26,413. However, it circulates in polymeric form. Adiponectin appears to be linked to glucose homeostasis since plasma adiponectin levels are lower in diabetic subjects and are positively correlated with glucose utilization. Adiponectin levels are lower in obese (defined by BMI) than in nonobese subjects. Furthermore, adiponectin levels increase after weight reduction. In addition, plasma adiponectin concentrations are negatively correlated with total body fat and waist-to-thigh ratio. Adiponectin was negatively correlated with weight and insulin in nonmorbidly obese subjects; interestingly, the basal levels of adiponectin were higher in morbidly obese patients. It is unknown whether adiponectin is related to direct measures of abdominal obesity (e.g., visceral fat and subcutaneous abdominal fat), which is known to be associated with insulin resistance. Adiponectin levels have a reported genetic heritability of 46%. Moreover, several quantitative trait loci have been identified that have significant evidence of linkage for obesity-related phenotypes with serum adiponectin levels. Genetic polymorphisms in the adiponectin gene have been identified and shown to be

associated with obesity and insulin resistance. Yet, the mechanism by which adiponectin influences insulin sensitivity in humans is unclear.[9]

In this study showed that hypoadiponectinemia and insulin resistance were risk factor for metabolic syndrome development with OR 6.0 and 5.7, respectively, after we did adjusted for waist circumference, TG, HLD, blood pressure, fasting blood glucose.

Asdie et al. in their study to determine the relationship of serum adiponectin to glucose intolerance in obese people, found that there was a significant correlation between log adiponectin with body mass index; fasting glucose; 2h-post prandial glucose; triglyceride; HDL; and HOMA IR.[10] Hotta et al., have reported a significant negative correlation between circulating adiponectin and triglyceride levels and a positive correlation between adiponectin and HDL cholesterol levels in type 2 diabetes.[11] Weyer et al., showed that serum adiponectin concentrations were more closely related to fasting insulinemia and to rate of insulin stimulated glucose disposal, a direct measurement of insulin sensitivity, than to percent body fat and the-2 hr glucose concentration suggesting that insulin resistance might be a major determinants of the hypoadiponectinemia in obesity and type-2 diabetes. One of possible mechanisms for is overproduction of TNF-a by adipose tissue.[12] Wasim et al., showed that serum log adiponectin concentration were positively correlated with 2-hr insulin values and history of hypertension and ischemic heart disease. They also found that adiponectin levels were correlated with or related to glucose tolerance.[13]

From previous study showed that AdipoR1/R2 appears to be inversely regulated by insulin in physiological and pathophysiological states such as fasting/refeeding, insulin deficiency and hyperinsulinemia models via the insulin/phosphoinositide 3-kinase / Foxo1 pathway and is correlated with adiponectin sensitivity. Adiponectin interferes with TNF-α signaling in endothelial cells. Adiponectin, a recently described adipocyte-derived hormone, has been postulated to have anti-inflammatory effects mediated, in part, by modulating TNFα activity. The suppressive effect of TNF on adiponectin gene expression in vitro and, conversely, the inhibition of the nuclear factor αβ induced by adiponectin have been reported. Likewise, human tissular studies showing that subjects with the highest levels of adiponectin mRNA expression secrete the lowest levels of TNF from their adipose tissue have corroborated these findings, linking this hormone with the TNF system. Decreased serum adiponectin may play a causative role in the development of insulin resistance. Development of hyperinsulinemia is one possible mechanism for the suppression of the adiponectin levels. However hyperinsulinemia per se seems unlikely as a mediator of low adiponectin levels, since adiponectin levels remain low in the later stage of type-2 diabetes in association with decreased insulin levels.[13] Hypoadiponectinemia may contribute to insulin resistance and accelerated atherogenesis associated with obesity.

Adipocyte insulin action or signal transduction rather than absolutely levels of insulin may regulate adiponectin concentration. Bogan and Lodish have shown that secretion adiponectin by 3T3-L1 adipocyte requires phosphatidylinositol 3 kinase (PI-3 kinase), a major intermediate of insulin signaling activity. Insulin stimulated insulin receptors substrate 1 (IRS 1) associated PI3K activity has been decreased in adipocytes of type-2 diabetes. Thus it is possible that the decreased adipocyte PI-3K activity in type 2 diabetes may contribute to the decrease of adiponectin levels.[14]

Some studies showed a relation between adiponectin and coronary heart disease risk factors. These results collectively indicate that plasma HDL-cholesterol levels and visceral fat masses independently are associated with plasma adiponectin concentrations. In another study a reduction in serum adiponectin level is associated with the prevalence and magnitude of systemic atherosclerosis including ischemic heart disease and ASO.[13,14]

CONCLUSION

Hypoadiponectinemia and Insulin resistance were risks factors for metabolic syndrome development.

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