

Association of Hypoadiponectinemia with Metabolic Syndrome in Patients with Polycystic Ovary Syndrome

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Patients with polycystic ovary syndrome (PCOS) have an increased prevalence of metabolic syndrome (MBS). Hypoadiponectinemia is closely associated with MBS. The aim of our study was to evaluate the association of adiponectin levels with MBS in patients with PCOS. We studied 60 patients with PCOS and 60 age-matched control subjects. Serum adiponectin, fasting glucose, triglycerides, high-density lipoprotein (HDL) levels, blood pressure and waist circumference were measured for each subject. The results showed that 33% of patients with PCOS were diagnosed with MBS; this was 11.7% in the control group ($p < 0.01$). Adiponectin levels were significantly lower in PCOS patients with MBS than PCOS patients without MBS ($p < 0.001$). After adjustment for body mass index (BMI), adiponectin levels were correlated negatively with waist circumference, triglycerides, diastolic blood pressure, homeostasis model assessment (HOMA) and positively with HDL. PCOS patients with adiponectin levels lower than median value had 10.5-fold higher risk of having MBS. Logistic regression analysis revealed that adiponectin levels were independently associated with the risk of having MBS, and the significance did not change after adjusting for each component of MBS. We concluded that patients with PCOS had an increased prevalence of MBS and thus an increased risk of cardiovascular disease. Hypoadiponectinemia was independently associated with MBS in these patients. Adiponectin as an endogenous biologically relevant modulator of vascular remodeling may have a role in the development of MBS in PCOS patients.

Key words: metabolic syndrome ■ obstetrics/gynecology ■ cardiovascular

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INTRODUCTION

Polycystic ovary syndrome (PCOS) is among the most common endocrine diseases of women of reproductive age and is a common cause of anovu-

latory infertility, menstrual dysfunction and hirsutism.^{1,2} The consequences of PCOS extend beyond the reproductive axis and are now recognized as having a major effect throughout life on the metabolic and cardiovascular health of affected women.³ Insulin resistance is postulated to contribute the metabolic abnormalities of the syndrome.^{3,4} Women with PCOS are at substantial risk for the development of metabolic and cardiovascular abnormalities similar to those that make up metabolic syndrome (MBS).⁵ Recently, some studies assessed the prevalence of MBS in PCOS women and found it higher in PCOS women than normal women.^{6,7} This finding is not surprising, since both PCOS and MBS share insulin resistance as a central pathogenetic feature.³

Adiponectin is an adipocytokine mainly expressed by adipose tissue. In contrast to other adipocytokines, adiponectin is reduced in obese and diabetic individuals.⁸ Plasma adiponectin concentrations correlate inversely with obesity,⁸ cardiovascular disease,⁹ dyslipidemia¹⁰ and insulin resistance.^{8,11} Adiponectin is inversely associated with the expression of the MBS and its individual traits in obese patients, but a lack of change in adiponectin levels by weight loss may reflect persistent adipocyte dysregulation.¹² Hypoadiponectinemia is demonstrated to be an important background for both insulin resistance and atherosclerotic vascular diseases, which may correspond to MBS,¹³ suggesting that adiponectin levels may be useful in identifying MBS.^{12,14–18} Plasma adiponectin levels are associated with insulin resistance in lean and obese PCOS patients.^{19–22} In this study, we investigated the relationship between adiponectin levels and MBS and its components in PCOS patients.

MATERIALS AND METHODS

Sixty patients with PCOS (mean age 24.6 ± 4.6 years) and 60 age-matched control subjects (mean age 26.1 ± 4.9 years) were enrolled in the study. The patients were recruited from patients referred to Endocrine Clinic of Ankara Training Hospital, Ankara, Turkey. The diagnosis of PCOS was made according to criteria by Rotterdam ESHRE/ASRM-sponsored PCOS consensus workshop group (2004) and was based on the presence of: 1) oligo- and/or anovulation

(≤ 8 menstrual periods annually); 2) clinical signs and laboratory findings of hyperandrogenism; 3) polycystic ovaries; and 4) the exclusion of other disorders such as Cushing syndrome, late-onset congenital adrenal hyperplasia, thyroid dysfunction, hyperprolactinemia or androgen-secreting tumors.²³ Clinical hyperandrogenism was defined by a Ferriman-Gallwey score of >8 , whereas biochemical hyperandrogenism was documented with an elevated total testosterone ($T > 2$ nmol/L). Pelvic ultrasound was performed for each subject and defined as polycystic ovaries if there were ≥ 10 cysts 2–8 mm diameter, arranged around a stroma. All patients were free of other diseases and were taking no medication for ≥ 3 months. Female subjects with no known medication, no signs of anovulation and hyperandrogenism were taken as control subjects. The study was approved by the local ethical committee, and informed consent was obtained from each subject.

Each subject had height and weight recorded at the initial visit. Waist circumference was measured at the level of the umbilicus. Blood pressure was measured three times in the same arm after the patient was seated and at rest for a minimum of 15 minutes and the mean of the systolic and diastolic measurements was reported. Body mass index (BMI) was calculated as body weight (kg) divided by body height squared (m^2).

The subjects were classified as having MBS if they met ≥ 3 of the National Cholesterol Education Program ATP III (NCEP ATP III) criteria: waist circumference >88 cm, triglycerides ≥ 1.69 mmol/L, high-density lipoprotein (HDL) cholesterol <1.29 mmol/L, blood pressure $\geq 130/85$ mmHg or treated hypertension, and fasting glucose ≥ 6.1 mmol/L or greater.²⁴

All women were studied between days 2–5 of a spontaneous or progesterone-induced menstrual cycle. Blood samples were collected in the morning after an overnight fast. Total cholesterol, triglycerides and HDL cholesterol were measured by enzymatic methods. LDL cholesterol was calculated using the Friedewald formula. Fasting plasma glucose was determined by the glucose oxidase

method. Insulin levels were measured by microparticulate enzyme immunoassay. All of the above were done with Roche reagents (Hitachi D 2400, E 170). Serum adiponectin levels were measured by ELISA (B-Bridge Human Adiponectin ELISA kit). Homeostasis model assessment (HOMA) score was calculated in all subjects as fasting plasma insulin ($\mu\text{u/ml}$) \times fasting glucose (mmol/L) / 22.5.²⁵ Log versions of HOMA were calculated.

The statistical analysis was performed using the SPSS® 11.5 (SPSS Inc., Chicago, IL) package. For continuous variables, data were presented as mean \pm standard deviation (SD) or median (minimum, maximum), and categorical variables were expressed by frequency counts. Normality of the distribution was assessed by Shapiro-Wilks test. Results that were not normally distributed were log transformed before analysis. A p value <0.05 was considered statistically significant. Comparisons of categorical variables of the two groups were analyzed by Chi-squared test. Differences between groups were calculated using a Student's t test for independent samples. The Pearson's correlation coefficients were calculated. Independent relationships between adiponectin and other variables were assessed by partial correlation analyses. Logistic regression analysis was used to analyze the association between the MBS and adiponectin levels and other variables. The receiver operating characteristic (ROC) analysis of the criteria for MBS by serum adiponectin level was performed.

RESULTS

The anthropometric and metabolic characteristics of PCOS patients and control subjects are shown in Table 1. According to NCEP criteria, 33.3% (20/60) of our PCOS patients were diagnosed with MBS, while this was 11.7% (7/60) in the control group ($p < 0.01$). Of the patients with PCOS, 20% (12/60) had three criteria, 8.3% (5/60) had four criteria and 5% (3/60) had five criteria of MBS. Adiponectin levels were significantly lower in PCOS patients with MBS than patients without MBS (6136.2 ± 244.3

Table 1. Anthropometric and metabolic variables of polycystic ovary syndrome (PCOS) and control groups

Variables	PCOS (n=60)	Control (n=60)	P
Age (years)	24.6 \pm 4.6	26.1 \pm 4.9	NS
Waist circumference (cm)	83.1 \pm 9.2	80.2 \pm 8.7	NS
BMI (kg/m ²)	28.0 \pm 5.5	26.7 \pm 4.5	NS
Systolic blood pressure (mmHg)	122.3 \pm 7.9	115.3 \pm 2.0	<0.05
Diastolic blood pressure (mmHg)	77.6 \pm 8.6	75.3 \pm 3.3	NS
Fasting glucose (mmol/L)	5.0 \pm 1.5	4.9 \pm 0.4	NS
Total cholesterol (mmol/L)	4.6 \pm 0.1	4.2 \pm 0.1	<0.05
LDL cholesterol (mmol/L)	2.9 \pm 0.6	2.5 \pm 0.6	<0.05
HDL cholesterol (mmol/L)	1.2 \pm 0.2	1.3 \pm 0.2	NS
Triglyceride (mmol/L)	1.2 \pm 0.6	1.1 \pm 0.7	NS
Homeostasis model assessment	3.16 (0.59–9.68)	1.14 (0.17–4.90)	<0.001
Adiponectin (ng/ml)	8182.5 \pm 305.5	9291.0 \pm 244.3	NS

NS: Not significant

ng/ml vs. $9,205.3 \pm 305.5$ ng/ml, $p < 0.001$). Insulin resistance assessed by HOMA was significantly higher in PCOS patients with MBS than patients without MBS [3.48 (1.97 – 9.68) vs. 1.60 (0.59 – 7.20), $p < 0.001$].

We investigated the relationship between adiponectin levels and components of MBS. After adjustment for BMI, adiponectin levels were correlated negatively with waist circumference ($r = -0.51$, $p < 0.001$), triglycerides ($r = -0.32$, $p < 0.05$), diastolic blood pressure ($r = -0.26$, $p < 0.05$), HOMA ($r = -0.573$, $p < 0.001$); and positively with HDL cholesterol ($r = 0.37$, $p < 0.01$). There was no correlation between adiponectin levels and fasting glucose or systolic blood pressure ($p > 0.05$).

Adiponectin levels were compared in PCOS patients with or without each MBS component (Table 2). Patients with abdominal obesity had lower adiponectin levels than patients without abdominal obesity ($7,360.8 \pm 289.9$ ng/ml vs. $9,654.2 \pm 304.9$ ng/ml, $p = 0.03$). Adiponectin levels were significantly lower in patients with hypertriglyceridemia and in patients with low HDL cholesterol levels ($7,345.4 \pm 228.4$ ng/ml vs. $9,084.8 \pm 335.2$ ng/ml, $p = 0.024$ and $.6 \pm 306.3$ ng/ml vs. $10,030.0 \pm 315.7$ ng/ml, $p = 0.024$, respectively). There was no significant difference in adiponectin levels between hypertensive and normotensive patients, and between patients with high and normal fasting glucose levels. In PCOS patients with insulin resistance, adiponectin levels were significantly lower than PCOS patients without insulin resistance ($5,827.3 \pm 218.3$ ng/ml vs. $9,864.8 \pm 278.1$ ng/ml, $p < 0.05$).

The area under the ROC curve for adiponectin levels was 0.793 ± 0.059 . The best cut-off value of adiponectin to identify the presence of MBS was $8,160$ ng/ml with a sensitivity of 85% [95% confidence interval (CI): 62.1–96.6%] and a specificity of 65% (95% CI: 48.3–79.4%). In PCOS patients with adiponectin levels $< 8,160$ ng/ml, 54.8% (17/31) had MBS, and in patients with adiponectin

levels $> 8,160$ ng/ml, 10.3% (3/29) had MBS ($p < 0.001$), and the estimated risk odds ratio (OR) was 10.524.

Using logistic regression analysis, we calculated the OR of the MBS as predicted by adiponectin was 0.81 (95% CI: 0.71–0.94; $P = 0.005$). The OR did not change after adjustment for BMI (OR=0.82, 95% CI: 0.75–0.95; $P = 0.02$). Furthermore, the ORs were not substantially different when adjusted for HDL cholesterol (OR=0.80, 95% CI: 0.68–0.90; $P = 0.009$), blood pressure (OR=0.78, 95% CI: 0.65–0.88; $P = 0.006$), fasting glucose (OR=0.81, 95% CI: 0.69–0.95; $P = 0.006$), triglycerides (OR=0.91, 95% CI: 0.79–0.96; $P = 0.017$) and waist circumference (OR=0.82, 95% CI: 0.70–0.92; $P = 0.03$).

DISCUSSION

Metabolic syndrome, representing a cluster of insulin resistance, hypertension and dyslipidemia, identifies individuals at increased risk for atherogenic cardiovascular diseases.²⁶ PCOS is associated with insulin resistance, and metabolic and anthropometric abnormalities of this syndrome overlap with the components of MBS. Recent studies reported an increased prevalence of MBS in PCOS patients.^{5–7} In our study, 33.3% of PCOS patients had MBS, which is nearly three-fold higher prevalence than the age-adjusted control women. This finding is consistent with those from previous reports of Ehrmann et al. (33.4%),⁷ Apridonidze et al. (43%)⁶ and Glueck et al. (46%).⁵ As the presence of MBS correlates with cardiovascular disease risk, this finding of a markedly high prevalence of MBS in women with PCOS suggests that these women are at increased risk for atherosclerotic cardiovascular diseases.

Adiponectin has potential inhibitory activities of atherogenic process. Physiological concentration of adiponectin was demonstrated to strongly inhibit the expression of adhesion molecules, intracellular adhesion molecule-

Table 2. Relationship between adiponectin levels and metabolic syndrome components in PCOS patients

MBS component	n	Adiponectin (ng/ml)	p
Raised blood pressure			
Present	6	$7,591.9 \pm 284.8$	NS
Absent	54	$9,208.7 \pm 340.7$	
Abdominal obesity			
Present	21	$7,360.8 \pm 289.9$	0.003
Absent	39	$9,654.2 \pm 304.9$	
High glucose			
Present	2	$4,080.0 \pm 721.2$	NS
Absent	58	$8,323.9 \pm 315.6$	
High triglycerides			
Present	17	$7,345.4 \pm 228.4$	0.024
Absent	43	$9,084.8 \pm 335.2$	
Low HDL			
Present	48	$7,720.6 \pm 306.3$	0.024
Absent	12	$10,030.0 \pm 315.7$	

NS: Not significant

1, vascular cellular adhesion molecule-1 and e-selectin.²⁷ Adiponectin was shown to inhibit the tumor necrosis factor (TNF- α), a major molecular mechanism for the inhibition of monocyte adhesion to endothelial cells.²⁸ Adiponectin also inhibits the expression of the scavenger receptor class A-1 of macrophages, resulting in an inhibition of foam cell formation.²⁹ In addition, adiponectin inhibits the proliferation and migration of smooth-muscle cells.³⁰ These vascular cellular functions may be responsible from the antiatherogenicity of adiponectin. Adiponectin is reported to correlate negatively with BMI, waist circumference, plasma glucose, insulin and triglycerides; but positively with HDL cholesterol.^{9-11,31} Lower adiponectin levels are associated with increased intima media thickness in diabetic men independently of HOMA.³² Recent population-based studies regarding the association of adiponectin with MBS revealed a close association of hypo adiponectinemia with MBS, suggesting that adiponectin can be a marker of MBS.^{14,16} Matsuzawa et al. suggested that genetic hypo adiponectinemia may be part of the genetic background of MBS.¹³ Adiponectin levels were reported to be associated with insulin resistance per se or other metabolic abnormalities in women with PCOS.^{20,21,33} In the present study, PCOS women with MBS had lower adiponectin levels than women without MBS, indicating the association of hypo adiponectinemia with MBS in PCOS women.

In our study, adiponectin levels were associated negatively with waist circumference, abdominal obesity and hypertriglyceridemia; and positively with HDL cholesterol levels. These findings are similar to the findings reported by Mohan et al. and confirmed the association between adiponectin and dyslipidemia and abdominal obesity.¹⁶ Blood pressure was not associated with adiponectin levels, as described previously.^{15,16} Fasting glucose levels were not correlated with adiponectin. Only two patients had high fasting glucose levels, which may be the reason why we could not find a statistically significant association between adiponectin levels and fasting glucose.

PCOS women with MBS were more insulin resistant than women without MBS, confirming the role of insulin resistance in the pathogenesis of MBS. Adiponectin levels were negatively correlated with HOMA, supporting the insulin-sensitizing effect of adiponectin levels. Insulin resistance plays a major role in the pathogenesis of MBS and PCOS and is closely associated with hypo adiponectinemia. Thus, hypo adiponectinemia, along with insulin resistance, appears to be a critical link between PCOS and MBS.

We found a serum adiponectin level of 8,160 ng/ml was the best cut-off value with a sensitivity of 85% and specificity of 65%. This cut-off value is similar to the value that Gilardini et al. reported (8.3 μ g/ml, sensitivity 77% and specificity 79% for boys and 8.1 μ g/ml, sensitivity 82% and specificity 57% for girls) in obese children and adolescents with an 11-fold increase in the risk of having MBS.³⁴ A lower cut-off value for adiponectin

(4 μ g/ml) was reported in Japanese adults by Kumada et al.³⁵ Ogawa et al. found that cut-off value for adiponectin was 6.65 μ g/ml (sensitivity 63.9% and specificity 66.7%) in Japanese obese children.¹⁷ Ethnic differences might account for the differences in the cut-off value of adiponectin levels, as reported by Gilardini et al.³⁴ Further large-scale surveys are necessary to propose such a cut-off value in clinical practice in PCOS women. However, in our study population, 54.8% of PCOS patients with adiponectin levels <8,160 ng/ml had MBS, while 10.3% of patients with adiponectin levels >8,160 ng/ml had MBS. The estimated risk OR for MBS was 10.524, indicating that PCOS women with adiponectin levels <8,160 ng/ml had 10.5 times higher risk for MBS. This finding supports that adiponectin levels <8,160 ng/ml may identify patients at risk for cardiovascular diseases.

In our cohort, logistic regression analysis revealed an association between adiponectin and MBS. The predictive ability of adiponectin to distinguish the PCOS women with or without MBS remained significant after adjusting for BMI. When each component of MBS was introduced separately as a covariate, the predictive ability of adiponectin to distinguish the PCOS patients with MBS from patients without MBS did not change substantially after adjusting for each variable. These results indicate that adiponectin is an independent determinant of MBS in patients with PCOS. Adiponectin as an endogenous biologically relevant modulator of vascular remodeling may have a role in the development of MBS in PCOS patients. Further evaluation and treatment strategies can be instituted to increase adiponectin levels in these patients. Lifestyle modifications and therapeutic agents, such as adiponectin promoters, reported to elevate adiponectin levels.³⁶⁻⁴⁰ Whether an increase in adiponectin levels of the PCOS women participates in the reduction of the cardiovascular diseases needs to be further evaluated.

In conclusion, patients with PCOS have an increased prevalence of MBS and thus an increased risk for atherogenic cardiovascular diseases. Given that hypo adiponectinemia is associated independently with MBS in PCOS patients, it may have a role in the development of MBS, and determination of adiponectin levels may be useful in the work up of cardiovascular diseases in these patients.

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