Plasma adiponectin and insulin resistance in women with polycystic ovary syndrome

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Objective: To determine plasma adiponectin concentration in women with and without polycystic ovary syndrome (PCOS) and to assess possible correlations of adiponectin to the hormonal and metabolic parameters, including measures of insulin resistance (IR).

Design: Case–control study.

Setting: Tertiary-referral university hospital.

Patient(s): One hundred eighty selected women were classified as follows: 45 obese (body mass index [BMI] >30 kg/m²) with PCOS; 45 lean (BMI <25 kg/m²) with PCOS; 45 obese (BMI >30 kg/m²) without PCOS, and 45 lean (BMI <25 kg/m²) without PCOS.

Intervention(s): Blood samples were collected from all women with or without PCOS between 8 and 11 AM, after an overnight fast.

Main Outcome Measure(s): Serum levels of luteinizing hormone (LH), follicle-stimulating hormone (FSH), thyroid-stimulating hormone (TSH), free T₄, testosterone (T), 17α-hydroxyprogesterone, Δ4-androstenedione (Δ4-A), dehydroepiandrosterone (DHEA), dehydroepiandrosterone sulfate (DHEAS), sex hormone-binding globulin (SHBG), insulin, and plasma levels of adiponectin and glucose. Measures of IR included fasting serum insulin, glucose-to-insulin ratio, and homeostasis model assessment (HOMA).

Result(s): Adiponectin concentrations were found to be significantly decreased in women with PCOS and in obese women without PCOS as compared with lean women without PCOS. Adiponectin concentrations correlated inversely with body weight, BMI, fasting plasma glucose, serum insulin, Δ4-A, DHEA, DHEAS, and HOMA but correlated positively with serum T, SHBG, FAI, and glucose-to-insulin ratio. Multiple regression analysis showed that BMI, HOMA, Δ4-A, and insulin were independent determinants of adiponectin concentrations.

Conclusion(s): Hypoadiponectinemia is evident in obese and lean women with PCOS with variable degree of IR; and it is suggested that IR per se or other metabolic abnormalities of PCOS are involved in the regulation of adiponectin concentration in women with PCOS. (Fertil Steril 2005;83:1708–16. ©2005 by American Society for Reproductive Medicine.)

Key Words: Adiponectin, PCOS, insulin resistance

Polycystic ovary syndrome (PCOS) is a common complex and heterogenous endocrine disorder that is characterized by oligomenorrhea or amenorrhea, hyperandrogenism, and multiple small subcapsular cystic follicles in the ovary on ultrasonography (1). It affects ≤10% of women of reproductive age (2), with approximately 16%–80% of the affected women being obese (3). Polycystic ovary syndrome frequently is associated with insulin resistance (IR) accompanied by compensatory hyperinsulinemia (4), and IR is enhanced by the interaction between obesity and the syndrome (5). Whether hyperinsulinemia in PCOS is related to a defect in insulin action (6), to increased insulin secretion (7), to decreased hepatic clearance of the hormone (8), and/or to a combination of these mechanisms is, however, under investigation. Moreover, the contribution of body mass and/or body fat distribution to IR of PCOS remains controversial (6, 7, 9–11). In addition, women with PCOS with IR and the resultant hyperinsulinemia are at an increased risk of developing diabetes, hypertension, dyslipidemia, and atherosclerosis (12).

The adipose tissue not only stores triglycerides as a source of energy (13) but also is considered to be an endocrine organ that supervises energy metabolism through the expression of a variety of genes of secretory proteins (14–18). The human apM1 gene recently has been discovered, and it is expressed exclusively in white adipose tissue (19). The prod-
The diagnosis of PCOS was based on the established guidelines by the consensus group for diagnosis of PCOS (29). Polycystic ovary syndrome was defined on the basis of the following criteria: [1] infertility with oligomenorrhea (interval between periods was ≥35 days) or amenorrhea (absence of vaginal bleeding for 6 months) or hirsutism, [2] presence of multiple cysts (≥10 small [2–8 mm in diameter]) arranged peripherally and scattered throughout the dense core of stroma (the necklace appearance of follicular cysts) on transvaginal ultrasonography performed by two experienced technicians at the Department of Radiology at KAUH, [3] increased (LH–FSH) concentration ratio, and [4] elevated serum testosterone (T) concentration. All of the above criteria were present in all women with PCOS studied, which may make the PCOS patients studied a subset of the PCOS group.

In addition, the diagnosis of PCOS also was based on the exclusion of other PCOS-like syndromes, including adrenal dysfunction, Cushing’s syndrome, congenital adrenal hyperplasia, androgen-producing tumors, hyperprolactinemia, and thyroid dysfunction. In a total of 90 normo-ovulatory women who were matched for age, BMI, and ethnicity, randomly recruited from the general gynecology clinics at KAUH to serve as controls without PCOS (hereafter referred to as the control group), the mean (±SD) duration of the menstrual cycle was 28.6 ± 1.03 days. Ovulatory cycles were confirmed previously by midultral serum progesterone (P) values of ≥8.0 ng/mL for three consecutive cycles with no signs of hyperandrogenism.

All women examined agreed to participate in the present study, and a written informed consent was obtained from each woman. The study protocol was in agreement with KAUH ethical standards and the Helsinki Declaration of 1975, as revised in 1989. The study was approved by the Ethics Committee of KAUH.

**Study Protocol**

Venous blood was collected between 8 and 11 AM, with the subject in a fasting state. The following hormones were measured: follicle-stimulating hormone (FSH), luteinizing hormone (LH), prolactin (PRL), thyroid-stimulating hormone (TSH), free thyroxine (FT4), total T, dehydroepiandrosterone (DHEA), dehydroepiandrosterone sulfate (DHEAS), and 17α-hydroxyprogesterone (17-OHP) and Δ4-androstenedione (Δ4-A). Serum levels of sex hormone-binding globulin (SHBG) and insulin, together with plasma glucose and adiponectin, also were measured.

The BMI was calculated as weight/(height)^2 in kilograms per square meter, and women were considered lean at BMI <25 kg/m^2; women were considered obese at BMI >30 kg/m^2. Waist-to-hip ratio was calculated as waist circumference in centimeters divided by hip circumference in centimeters. None of the women studied had taken medications known to affect plasma sex steroids for ≥3 months before the study.

Studies were performed in regularly cycling control groups during the early follicular phase (days 2–5) of the menstrual cycle and in women with PCOS on days 2–5 of spontaneous cycle or after withdrawal of bleeding.

**Laboratory Measurements**

Plasma adiponectin was determined by using a commercially available ELISA kit (Linco Research, St. Charles, MO;
intra-assay and interassay coefficients of variance (CVs): 4.9% and 6.3%, respectively). All hormones were measured by methods based on electrochemiluminescence immunoassay by using the Elecsys 2010 Autoanalyzer System (Boehringer Mannheim, Mannheim, Germany) with dedicated reagents obtained from Boehringer Mannheim. The intra-assay and interassay CVs for the hormones measured were as follows: FSH (1.7% and 4.7%), LH (1.1% and 3.1%), PRL (2.9% and 4.1%), TSH (4.2% and 5.2%), FT₄ (2.1% and 4.5%), T (2.4% and 3.8%), insulin (3.0% and 4.7%), and DHEAS (4.1% and 5.2%), respectively. DHEA (intra-assay and interassay CV: 7.5% and 5.5%, respectively) and DHEAS (4.1% and 5.2%), respectively. DHEA (intra-assay and interassay CV: 7.5% and 5.5%, respectively) and DHEAS (4.1% and 5.2%), respectively. DHEA (intra-assay and interassay CV: 7.5% and 5.5%, respectively) and DHEAS (4.1% and 5.2%), respectively. DHEA (intra-assay and interassay CV: 7.5% and 5.5%, respectively) and DHEAS (4.1% and 5.2%), respectively. DHEA (intra-assay and interassay CV: 7.5% and 5.5%, respectively) and DHEAS (4.1% and 5.2%), respectively. DHEA (intra-assay and interassay CV: 7.5% and 5.5%, respectively) and DHEAS (4.1% and 5.2%), respectively. DHEA (intra-assay and interassay CV: 7.5% and 5.5%, respectively) and DHEAS (4.1% and 5.2%), respectively. DHEA (intra-assay and interassay CV: 7.5% and 5.5%, respectively) and DHEAS (4.1% and 5.2%), respectively. DHEA (intra-assay and interassay CV: 7.5% and 5.5%, respectively) and DHEAS (4.1% and 5.2%), respectively. DHEA (intra-assay and interassay CV: 7.5% and 5.5%, respectively) and DHEAS (4.1% and 5.2%), respectively. DHEA (intra-assay and interassay CV: 7.5% and 5.5%, respectively) and DHEAS (4.1% and 5.2%), respectively.

Glucose levels were measured by enzymatic method. Measurements were performed by using an Autoanalyzer (Hitachi 912; Boehringer Mannheim), with dedicated reagents obtained from Boehringer Mannheim. The free androgen index (FAI) was calculated according to the following formula: T (nmol/L) × 100/SHBG (nmol/L). Insulin resistance in the fasting state was assessed by using homeostasis model assessment (HOMA) and was calculated with the following formula: fasting plasma glucose (mmol/L) × fasting serum insulin (μU/mL) divided by 22.5, as described by Matthews et al. (30). High HOMA scores denote IR. The glucose (mmol/L) to insulin (pmol/L) ratio, proposed as an index of peripheral insulin sensitivity (31), was also calculated.

There is an ongoing discussion concerning the best marker of insulin sensitivity in various populations. The American Diabetes Association (32) recommends the fasting insulin level itself, whereas other investigators consider the use of the mathematical combinations of the fasting glucose and insulin levels that were found to correlate best with formal measures of insulin sensitivity (9). Indeed, glucose-to-insulin ratio was found to be a good measure of insulin sensitivity in obese women with PCOS and exhibited high sensitivity for detecting IR, as reported elsewhere by Legros et al. (31) and confirmed recently by Ducluzeau et al. (33). Accordingly, in the present study, both glucose-to-insulin ratio and HOMA values were used in part of the analysis to stratify women according to IR.

In the present study, IR was defined as an abnormal result in fasting serum insulin, glucose-to-insulin ratio, or HOMA values, as determined by the threshold values being more than the 95th percentile of the healthy normo-ovulatory lean control women group. These values were as follows: fasting serum insulin, >64.4 pmol/L; glucose-to-insulin ratio, <9.53; and HOMA, >3.82; respectively. Hence, IR was found in 76.0% and 27.8% of women with PCOS and of the control women, respectively, by fasting serum insulin; in 78.9% and 34.4% of women with PCOS and of the control women, respectively, by HOMA; and in 74.0% and 31.1% of women with PCOS and of the control women, respectively, by glucose-to-insulin ratio values. All differences were statistically significant as compared with the corresponding control group ($P<.001$; $\chi^2 = 6.9$, all groups).

**Statistical Analysis**

Results are presented as means ± SD, and data were analyzed by using SPSS statistical package, version 11.0 for Windows (SPSS Inc., Chicago, IL). Results that were not normally distributed were log-transformed before analysis. Bivariate correlation analysis (calculation of Spearman’s coefficient) was used to assess the correlation between fasting plasma adiponectin and other variables. Analysis of variance was used to examine differences among the groups for different variables, and the Bonferroni criterion was used when significance tests were performed. Independent relationships between fasting plasma adiponectin and other variables were assessed by multiple regression and partial correlation analysis. The threshold for statistical significance was set at $P<.05$.

Fasting plasma adiponectin values in all women studied ($n = 180$) were divided into tertiles. The percentage distribution of adiponectin in women with or without PCOS in relation to IR in the tertiles was calculated. In addition, to study the influence of IR on fasting plasma adiponectin, all women were grouped together ($n = 180$) and were divided into tertiles of IR measures: fasting serum insulin, glucose-to-insulin ratio, and HOMA. Chi-square analysis was performed to assess the differences in the proportions between the subgroups.

**RESULTS**

The basic anthropometric characteristics of the women studied are presented in Table 1. The study groups were of similar age, although obese women of the control group were slightly older than those of the corresponding lean control group ($P<.021$). However, as expected, the obese women with or without PCOS exhibited higher values for BMI and WHR as compared with lean control groups. Endocrine and metabolic parameters are summarized in Table 2. Women with PCOS (both lean and obese) showed significantly increased levels of LH as compared with corresponding control groups ($P<.001$ in each case). Levels of LH did not differ significantly between lean or obese control women without PCOS.

Compared with corresponding controls, women with PCOS showed significantly increased levels of the following hormones (change is indicated after the name of each hormone, comparing lean vs. obese women, respectively): T (by...
TABLE 1

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Controls (n = 90)</th>
<th>Obese (n = 90)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (y)</td>
<td></td>
<td>25.9 ± 5.8</td>
<td>22.7 ± 2.4</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>28.3 ± 5.2</td>
<td>26.3 ± 5.2</td>
<td>.000</td>
</tr>
<tr>
<td>WHR</td>
<td>0.82 ± 0.164</td>
<td>0.82 ± 0.164</td>
<td>.998</td>
</tr>
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</table>

Note: All data except confidence intervals are given as mean ± SD.

Fertility and Sterility

Insulin resistance that was significantly greater in women with PCOS was found to be enhanced by obesity. Obese women with PCOS showed moderately higher fasting levels of plasma glucose (by 17.9%; P < .05) and serum insulin (by 53.1%; P < .05), as compared with corresponding lean control groups, respectively. Obese control women showed increased fasting levels of plasma glucose and serum insulin, as compared with the corresponding lean control group (by 14.1%; P < .01 and by 31.1%; P < .000), respectively. Obese women with PCOS showed significantly lower glucose-to-insulin ratio and higher HOMA values (both are measures of IR) as compared with other groups studied, indicating more IR in obese women with PCOS than in other groups.

The fasting plasma adiponectin concentrations were significantly decreased in obese women with PCOS (by 23.4%; P < .005) or without PCOS (by 34.7%; P < .000) as compared with the case in corresponding lean control groups, respectively; and consequently, plasma adiponectin concentrations were comparable among obese women examined. In addition, plasma adiponectin decreased by 21.3% (P < .05) in lean women with PCOS as compared with in the lean control group. The percentage distribution of women with or without PCOS in tertiles of fasting plasma adiponectin is presented in Figure 1. The tertile values of adiponectin (µg/mL) were as follows: tertile 1 = 7.1–13.5; tertile 2 = 13.6–16.7; tertile 3 = 16.8–26.0, respectively. A significantly higher percentage of women with IR were in tertile 1 (range: 60.9%–69.6%) when various measures of IR were used, compared with the percentage of women with IR in tertile 3 of adiponectin (range: 4.3%–8.7%), respectively (P < .000).

To examine the influence of IR, as indicated in the present study, on fasting plasma concentrations of adiponectin, all women were grouped together, and the whole cohort was divided into tertiles of measures of IR: fasting serum insulin, glucose-to-insulin ratio, and HOMA. As seen in Table 3, significant hypoadiponectinemia was evident in women with IR (P < .000).

In women with PCOS (n = 90), without PCOS (n = 90), or in the two groups combined (n = 180), calculations of Spearman’s coefficients showed that fasting plasma adiponectin concentrations were inversely correlated with body weight (P < .000), BMI (P < .000), fasting plasma glucose (P < .000), fasting serum insulin (P < .000), serum Δ4-A (P < .01), serum DHEA (P < .000), serum DHEAS (P < .000), and HOMA (P < .000). Adiponectin showed significant positive correlation with serum T (P < .01), serum SHBG
<table>
<thead>
<tr>
<th>Parameter</th>
<th>PCOS (n = 90)</th>
<th>Controls (n = 90)</th>
<th>95% Confidence intervals</th>
<th>P value</th>
<th>95% Confidence intervals</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Lean (n = 45)</td>
<td>Obese (n = 45)</td>
<td></td>
<td></td>
<td>Lean (n = 45)</td>
<td>Obese (n = 45)</td>
</tr>
<tr>
<td>FSH (mIU/L)</td>
<td>6.13 ± 0.87</td>
<td>6.31 ± 0.98</td>
<td>5.17, 7.25</td>
<td>.866</td>
<td>6.75 ± 0.39</td>
<td>6.48 ± 0.75</td>
</tr>
<tr>
<td>LH (mIU/L)</td>
<td>17.09 ± 1.65</td>
<td>19.27 ± 3.19</td>
<td>7.61, 19.76</td>
<td>.193</td>
<td>8.72 ± 1.02^a</td>
<td>8.55 ± 1.16^b</td>
</tr>
<tr>
<td>TSH (mIU/L)</td>
<td>2.79 ± 0.72</td>
<td>2.89 ± 0.61</td>
<td>1.64, 3.01</td>
<td>.132</td>
<td>2.69 ± 0.42</td>
<td>3.06 ± 0.79^b</td>
</tr>
<tr>
<td>FT4 (nmol/L)</td>
<td>15.4 ± 1.86</td>
<td>16.01 ± 2.35</td>
<td>14.78, 16.56</td>
<td>.500</td>
<td>15.24 ± 1.55</td>
<td>15.69 ± 2.62</td>
</tr>
<tr>
<td>T (nmol/L)</td>
<td>3.78 ± 2.41</td>
<td>4.54 ± 0.99</td>
<td>3.38, 5.11</td>
<td>.142</td>
<td>0.66 ± 0.17^a</td>
<td>0.71 ± 0.15^b</td>
</tr>
<tr>
<td>17-OHP (nmol/L)</td>
<td>3.39 ± 1.15</td>
<td>3.30 ± 1.21</td>
<td>2.85, 3.85</td>
<td>.864</td>
<td>0.79 ± 0.19^a</td>
<td>0.85 ± 0.34^b</td>
</tr>
<tr>
<td>Δ4-A (nmol/L)</td>
<td>4.07 ± 0.26</td>
<td>5.10 ± 9.24</td>
<td>4.27, 4.77</td>
<td>.000</td>
<td>0.959 ± 0.63</td>
<td>1.19 ± 0.69^b</td>
</tr>
<tr>
<td>DHEA (umol/L)</td>
<td>27.48 ± 1.87</td>
<td>31.72 ± 2.21</td>
<td>28.06, 4.07</td>
<td>.000</td>
<td>17.07 ± 1.58^a</td>
<td>19.24 ± 1.50^b</td>
</tr>
<tr>
<td>DHEAS (umol/L)</td>
<td>3.42 ± 0.22</td>
<td>4.38 ± 0.30</td>
<td>3.60, 4.07</td>
<td>.000</td>
<td>2.89 ± 0.26^a</td>
<td>3.85 ± 0.39^b</td>
</tr>
<tr>
<td>SHBG (nmol/L)</td>
<td>33.52 ± 2.21</td>
<td>31.65 ± 1.78</td>
<td>31.75, 33.66</td>
<td>.040</td>
<td>56.13 ± 4.92^a</td>
<td>48.58 ± 2.99^b</td>
</tr>
<tr>
<td>FAI</td>
<td>11.13 ± 3.38</td>
<td>14.11 ± 2.99</td>
<td>10.42, 14.99</td>
<td>.051</td>
<td>1.41 ± 0.58^a</td>
<td>1.56 ± 0.35^b</td>
</tr>
<tr>
<td>Glucose (mmol/L)</td>
<td>5.46 ± 0.17</td>
<td>6.44 ± 0.72</td>
<td>5.58, 6.18</td>
<td>.000</td>
<td>5.04 ± 0.40^a</td>
<td>5.71 ± 0.41^b</td>
</tr>
<tr>
<td>Insulin (pmol/L)</td>
<td>70.38 ± 14.78</td>
<td>135.50 ± 23.82</td>
<td>62.41, 116.11</td>
<td>.000</td>
<td>51.36 ± 14.78^a</td>
<td>70.67 ± 19.08^b</td>
</tr>
<tr>
<td>GIR × 100</td>
<td>8.07 ± 1.68</td>
<td>4.83 ± 0.60</td>
<td>5.76, 7.57</td>
<td>.000</td>
<td>10.44 ± 2.90^a</td>
<td>8.61 ± 2.34^b</td>
</tr>
<tr>
<td>HOMA</td>
<td>3.80 ± 0.83</td>
<td>8.73 ± 2.44</td>
<td>4.67, 7.22</td>
<td>.000</td>
<td>1.41 ± 0.74^a</td>
<td>3.91 ± 1.32^b</td>
</tr>
<tr>
<td>Adiponectin (µg/mL)</td>
<td>15.94 ± 3.08</td>
<td>12.21 ± 2.48</td>
<td>12.86, 15.77</td>
<td>.005</td>
<td>20.26 ± 2.48^a</td>
<td>13.23 ± 1.46^b</td>
</tr>
</tbody>
</table>

Note: All data except confidence intervals and P values are mean ± SD; GIR = glucose-to-insulin ratio.
^a Statistically different from corresponding lean women with PCOS.
^b Statistically different from obese women with PCOS.
However, no significant correlation was observed between plasma adiponectin concentrations and the concentrations of FSH, LH, 17-OHP, PRL, TSH, and FT₄. By using stepwise multiple regression analysis (n = 180), in model 1 (including fasting serum insulin only as an index of IR with other variables), the BMI and contributions from other variables, namely Δ4-A and fasting serum insulin, were significant independent determinants of fasting plasma adiponectin concentrations (adjusted $r^2 = 0.647; P<.000$); and in model 2 (including HOMA only as an index of IR with other variables), BMI, Δ4-A, HOMA, and fasting plasma glucose were significant independent determinants of fasting plasma adiponectin concentrations (adjusted $r^2 = 0.680; P<.000$; Table 4).

**DISCUSSION**

It has been established that adiponectin is almost exclusively produced in adipose tissue, and previous studies have shown that obesity, IR, and type 2 diabetes were associated with low plasma adiponectin concentrations (18, 21–24). In the present study, obese women (BMI $>30$ kg/m²) showed significantly decreased fasting plasma concentrations of adiponectin as compared with that of matched lean women (BMI $<25$ kg/m²) with or without PCOS. These findings are consistent with those from previous reports, in which significant hypoadiponectinemia was evident, in both control (24, 25, 34) and PCOS obese (29, 30) women, respectively. Moreover, lean women with PCOS showed significantly moderate decreases in the concentrations of plasma adiponectin as compared with the corresponding lean control group. These results contrast with those reported by Orio et al. (27), who showed no significant differences in plasma adiponectin levels among lean women with or without PCOS.

**TABLE 3**

<table>
<thead>
<tr>
<th>Measures of insulin resistance by IR tertiles</th>
<th>Plasma adiponectin in µg/mL (mean ± SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fasting serum insulin</td>
<td></td>
</tr>
<tr>
<td>High</td>
<td>95</td>
</tr>
<tr>
<td>Intermediate</td>
<td>35</td>
</tr>
<tr>
<td>Low</td>
<td>50</td>
</tr>
<tr>
<td>GIR</td>
<td></td>
</tr>
<tr>
<td>High</td>
<td>98</td>
</tr>
<tr>
<td>Intermediate</td>
<td>30</td>
</tr>
<tr>
<td>Low</td>
<td>52</td>
</tr>
<tr>
<td>HOMA</td>
<td></td>
</tr>
<tr>
<td>High</td>
<td>102</td>
</tr>
<tr>
<td>Intermediate</td>
<td>32</td>
</tr>
<tr>
<td>Low</td>
<td>46</td>
</tr>
</tbody>
</table>

Note: All $P$ values = .0000.

and more recently criticized the study of Panidis et al. (28) in relation to the study design (35). Such disagreement could be related to the relatively small sample size examined previously and/or to the differences in the extent of metabolic abnormalities, including the degree of IR and/or the extent and location of obesity among women of the present study, as compared with that described by Orio et al. (27). Additionally, the molecular mechanisms modulating IR may vary among individuals, and thus the levels of adiponectin also may vary.

A significant negative correlation between plasma adiponectin concentrations and body weight together with BMI was evident in women with or without PCOS. The latter results are in accordance with those previously reported (24, 25, 29, 30, 35), which demonstrated that adiponectin is the only adipocytokine that, despite its exclusive production in the white adipose tissue, is inversely regulated by obesity. However, plasma adiponectin concentrations were found to correlate negatively with adiposity and with WHR (25), diabetic dyslipidemia (22), cardiovascular disease (21), and IR (25, 36). In addition, plasma adiponectin concentrations correlated more with hyperinsulinemia and IR than with obesity or body fat (25), and hypoadiponectinemia was found to be an independent risk factor for future development of type 2 diabetes (37–39) but not for obesity (40).

Polycystic ovary syndrome frequently is associated with IR with compensatory hyperinsulinemia and obesity (4). Insulin resistance is considered to play a major role in the etiology of PCOS (41) and recently, Seow et al. (42) demonstrated that IR in PCOS involves both receptor and post-receptor defects, including defects in phosphatidylinositol 3-kinase and the GLUT-4 glucose transporter. In addition, women with PCOS frequently exhibit impaired peripheral insulin-stimulated glucose utilization and higher basal insulin levels, probably caused by increased insulin secretion and/or decreased hepatic clearance of the hormone; such abnormalities were independent of obesity (9).

In the present study, fasting hyperinsulinemia (a surrogate measure of IR) with higher frequency of IR were more prevalent in obese women with PCOS as compared with those in lean PCOS and control groups. Bivariate correlation analysis showed significant negative correlation between the plasma concentrations of adiponectin and body weight, BMI, fasting plasma glucose, serum T, Δ4-A, and FAI; model 2 included WHR, BMI, HOMA, fasting plasma glucose, serum T, Δ4-T, Δ4-A, DHEA, DHEAS, SHBG, and FAI.

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Polycystic ovary syndrome frequently is associated with IR with compensatory hyperinsulinemia and obesity (4). Insulin resistance is considered to play a major role in the etiology of PCOS (41) and recently, Seow et al. (42) demonstrated that IR in PCOS involves both receptor and post-receptor defects, including defects in phosphatidylinositol 3-kinase and the GLUT-4 glucose transporter. In addition,
In women with PCOS, it was suggested that IR and hyperinsulinemia may represent two distinct features of the insulin disorders of the syndrome: the former appears to be more dependent on obesity, whereas the latter appears to be a primary feature of PCOS (45). It is possible, therefore, that the observed hypo-adiponectinemia in the examined women could be partly related to obesity per se and/or to its metabolic consequences and/or to the metabolic abnormalities characteristic of PCOS itself. Recently, it was demonstrated that androgens suppressed the expression of adiponectin by decreasing its secretion (46), and previous studies in humans indicated that androgens decreased insulin sensitivity (47), and because hyperandrogenemia is considered to be part of the metabolic abnormalities of PCOS (1–4), it is possible therefore that the observed hypo-adiponectinemia in women with PCOS or obese women without PCOS might be related directly or indirectly to changes in the levels of androgens.

The mechanisms underlying the close association between fasting adiponectinemia and that of IR are currently unknown. A direct effect of hyperinsulinemia to down-regulate apM1 gene expression in adipose tissue is an unlikely possibility because insulin was found to up-regulate apM1 in experimental animal studies (18, 48) and also because of the fact that adiponectin levels do not decrease postprandially in humans (49). However, a 21% decrease in BMI accompanied by a 46% increase in circulating adiponectin was reported by Yang et al. (49), suggesting a long-term regulation of adiponectin levels by changes in insulin sensitivity.

Moreover, it is possible that adiponectin itself may directly influence the degree of IR and/or the extent of hyperinsulinemia. Evidence to support the latter suggestion includes, first, increased levels of TNF-α (50) that interfere with insulin receptor signaling, and thus, suppressing adiponectin expression in adipose tissue (51). Indeed, recently, Giugliano et al. (52) described an inverse relationship between adiponectin and TNF-α in obese women after liposuction, and Kern et al. (53) found a significant inverse correlation between plasma adiponectin and TNF-α mRNA expression, and subjects with the highest levels of adiponectin mRNA expression secreted the lowest levels of TNF-α from their adipose tissue in vitro. Second, the evidence includes increased levels of an as-yet-unidentified protein released by the increasing fat mass of obesity that destabilizes adiponectin mRNA (54) and thus suppresses adiponectin expression by adipose tissue. Third, the evidence includes increased formation by adiponectin of matrixes in the interstitium of different tissues, thus affecting intermediary metabolism in a similar fashion to that described for collagens VII and X, which are known to be matrix-forming proteins (17). Fourth, the evidence includes the fact that insulin stimulates adiponectin secretion in rodents (18); it is therefore possible that adiponectin concentrations are decreased in obesity because of IR in the adipocyte itself. Further studies are required to determine to what extent the above possible mechanisms contribute to the hypo-adiponectinemia that is observed in women with PCOS.

In conclusion, the results of the present study showed that hypo-adiponectinemia is evident in obese and lean women with PCOS with variable degree of IR. They also suggest that IR per se and/or other metabolic abnormalities of PCOS (e.g., hyperandrogenemia) are involved in the control of adiponectin concentrations in women with PCOS.

REFERENCES

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43. Vionnet N, Han I, E included the following markers: BMI, waist circumference, and estimated percentage of body fat. The results showed a significant correlation between BMI and waist circumference and plasma adiponectin levels. The correlation coefficient was 0.56 (p<0.001). This suggests that adiponectin levels are positively correlated with body fat. However, the correlation between adiponectin levels and the estimated percentage of body fat was not significant (r=0.12, p=0.36).