

Serum adiponectin levels in women with polycystic ovary syndrome

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BACKGROUND: Adiponectin is regarded as a possible link between adiposity and insulin resistance. The study aim was to measure serum adiponectin levels in women with polycystic ovary syndrome (PCOS) and to assess possible correlations between adiponectin and the hormonal or metabolic parameters of the syndrome. **METHODS:** Eighty-five selected women were classified as: Group I ($n = 35$) with PCOS + body mass index (BMI) >25 kg/m²; group II ($n = 35$) with PCOS + BMI <25 kg/m²; and group III (controls; $n = 15$) ovulating without hyperandrogenaemia and BMI <25 kg/m². Blood samples were collected between the days 3 and 6 of a spontaneous menstrual cycle, at 09:00, after an overnight fast. Serum levels of FSH, LH, prolactin, 17 α -OH-progesterone, sex hormone-binding globulin (SHBG), androgens, insulin, adiponectin and glucose were measured. **RESULTS:** Adiponectin levels were significantly decreased in group I compared with groups II and III. No significant difference in adiponectin levels was found between groups II and III, despite significant differences in insulin levels and glucose:insulin ratio. Multiple regression analysis showed that Δ_4 -androstenedione levels and BMI values were the only significant determinants of serum adiponectin levels. **CONCLUSIONS:** Serum adiponectin levels are reduced in obese women with PCOS. Although adiponectin does not seem to be actively involved in the pathogenesis of PCOS, there seems to be an interaction between adiponectin and steroid synthesis or action.

Key words: adiponectin/adiposity/body mass index/insulin resistance/PCOS

Introduction

Since the discovery of leptin (Zhang *et al.*, 1994), it has become clear that adipose tissue is not merely an inert reserve of triglycerides, but rather an active endocrine organ that oversees energy metabolism. This seems to be accomplished among other means by the action of so-called 'adipo(cyto)kines'—biological molecules which are secreted and most likely contribute to peripheral insulin sensitivity (Ahima and Flier, 2000; Vernon *et al.*, 2001). One relatively well-studied molecule of this type is adiponectin. This is a 224-amino acid protein which was first identified in 1995 (Scherer *et al.*, 1995), has a molecular weight of 30 kDa, and is also referred to as Adipocyte Complement-Related Protein 30 kDa (ACRP30). *In vitro*, adiponectin has been shown to have anti-atherogenic effects (Ouchi *et al.*, 1999; 2001; Okamoto *et al.*, 2000), and a number of cell culture experiments and studies in animal models (Berg *et al.*, 2001; Hotta *et al.*, 2001; Yamamuchi *et al.*, 2001) have suggested that adiponectin has a potent insulin-sensitizing action.

In humans, adiponectin levels were found paradoxically to be decreased in obese, compared with normal individuals (Arita *et al.*, 1999), making it the only known adipocyte-specific hormone that is down-regulated in obesity. Moreover, decreased adiponectin levels are associated with coronary artery disease and increase significantly after weight reduction (Hotta *et al.*, 2000), whereas high adiponectin levels are independently associated with increased insulin sensitivity (Weyer *et al.*, 2001; Philips *et al.*, 2003) and reduced risk of type 2 diabetes in Pima Indians (Lindsay *et al.*, 2002). Recently, beneficial effects of adiponectin on both glucose and lipid metabolism in white, non-diabetic individuals have been reported. Specifically, plasma adiponectin levels were negatively correlated with 2-h triglycerides and the free fatty acid (FFA) concentrations during the oral glucose tolerance test (OGTT), and correlated positively with high-density lipoprotein (HDL) levels and insulin sensitivity, measured using an euglycaemic clamp and estimated from the OGTT. Those relationships remained significant after adjustments for sex and

percentage of body fat (Tschritter *et al.*, 2003). Furthermore, in another recently published study, adiponectin concentrations in plasma were found to be independently associated with a reduced risk of type 2 diabetes in apparently healthy individuals (Spranger *et al.*, 2003).

With regard to human reproduction, women were found to have significantly higher adiponectin levels than men (Arita *et al.*, 1999). A similar sexual dimorphism was also demonstrated in mice (Combs *et al.*, 2003), wherein tissue adiponectin levels were found to rise early in puberty, and to increase further after neonatal castration in males or adult ovariectomy in females. Furthermore, adiponectin expression was found to be suppressed by estrogens *in vitro*, and stimulated by bromocryptine while being suppressed by prolactin.

All of the above findings favour a pleiotropic insulin-sensitizing action of adiponectin, which seems to antagonize the inflammatory and other humoral factors that promote insulin resistance, and is subject to complex hormonal control. The adiponectin receptor and downstream signalling pathway have been identified (Steppan and Lazar, 2002).

Polycystic ovary syndrome (PCOS) is characterized by chronic anovulation and hyperandrogenism (Zawadski and Dunaif, 1992; Panidis *et al.*, 2000; Costello and Eden, 2003). PCOS affects 5–10% of women of reproductive age (Franks, 1995), and is responsible for 50–70% of cases with anovulatory infertility (Adams *et al.*, 1986; Hull, 1987). It is, therefore, the most frequent cause of anovulation and probably the most common endocrine disorder among women (Homburg, 1996).

Insulin resistance with compensatory hyperinsulinaemia are prominent features of PCOS. Both lean and obese women with PCOS show reduced insulin sensitivity and hyperinsulinaemia to some extent (Dunaif *et al.*, 1989), but insulin resistance is exacerbated by the interaction between obesity and the syndrome (Dunaif, 1994; 1997). Hyperinsulinaemia is thought to result in increased androgen biosynthesis (Adashi *et al.*, 1985) and decreased levels of sex hormone-binding globulin (SHBG) (Nestler *et al.*, 1991), playing a major role in the pathogenesis of hyperandrogenism. In addition to reproductive morbidity, insulin resistance and the resultant hyperinsulinism place patients at risk of long-term metabolic disorders, such as impaired glucose tolerance (up to 35%) and type 2 diabetes (up to 10%) (Ehrmann *et al.*, 1999), as well as cardiovascular disease (Futterweit, 1999).

The aim of the present study was to: (i) measure serum adiponectin levels in women with PCOS and with a body mass index (BMI) either less than or more than 25 kg/m²; and (ii) assess possible correlations between adiponectin and the hormonal or metabolic parameters of the syndrome. The study was conducted in order to investigate the possible involvement of adiponectin in the pathogenesis of PCOS, since it has been stated that adiponectin might be a possible link between obesity and insulin resistance; moreover, adiponectin seems to interact with the gonadal axis. Finally, PCOS is associated with impaired glucose tolerance, diabetes mellitus and obesity. It should be noted that no previously published studies on circulating adiponectin levels in women with PCOS were identified.

Materials and methods

Subjects

A total of 85 women, aged between 14 and 39 years, all of whom were outpatients at the Endocrine Unit of the 2nd Department of Obstetrics and Gynecology of the Aristotle University of Thessaloniki at the Hippocrattion Hospital of Thessaloniki, were selected for the study. The women had presented with at least one of the following signs: oligomenorrhoea, fertility problem, hirsutism, acne, or male-pattern alopecia. None of the women had either galactorrhoea or any systemic disease that might affect their reproductive physiology. In addition, none of the women reported the use of any medication that might interfere with the normal function of the hypothalamic–pituitary–gonadal axis.

The women were allocated to three groups on the basis of BMI value and a diagnosis of PCOS. Hence, group I ($n = 35$) women had PCOS + BMI >25 kg/m²; group II ($n = 35$) had PCOS + BMI <25 kg/m²; and group III (controls; $n = 15$) were ovulating without hyperandrogenaemia + BMI <25 kg/m². A diagnosis of PCOS in groups I and II was based on the presence of chronic anovulation (fewer than six cycles in 12 months) and hyperandrogenaemia. Furthermore, other common causes of hyperandrogenism (prolactinoma, congenital adrenal hyperplasia, Cushing syndrome and virilizing ovarian or adrenal tumours) were excluded, in accordance with National Institutes of Health criteria (Zawadski and Dunaif, 1992). All women in group III had normal ovulating cycles (blood progesterone levels >10 ng/ml in two consecutive cycles), and no signs of hyperandrogenism. In all women, the basal serum levels of FSH, LH, testosterone, Δ_4 -androstenedione and dehydroepiandrosterone sulphate (DHEA-S) were measured. Serum levels of prolactin, 17 α -OH-progesterone, SHBG, glucose, insulin and adiponectin were also measured. The free androgen index (FAI) was calculated according to the equation: testosterone (nmol/l) \times 100/SHBG (nmol/l). The glucose:insulin ratio was also calculated.

Blood samples were collected between days 3 and 6 of a spontaneous menstrual cycle, at 09:00, after an overnight fast. Informed consent was obtained from all 85 women, and the study was approved by the Institutional Review Board.

Assay methods

All assays of hormonal levels and plasma glucose were carried out at the Department of Biochemistry of the Aristotle University of Thessaloniki School of Medicine.

Plasma glucose concentrations were measured using a glucose oxidase technique with an auto analyser (Roche/Hitachi 902; Roche Diagnostics GmbH, Mannheim, Germany). LH, FSH and prolactin levels were measured with an enzyme-linked immunoassay (EIA), using commercial kits (Nichols Institute Diagnostics, CA, USA). Testosterone was measured with a Direct RIA kit (Sorin, Biomedica); Δ_4 -androstenedione with a Gamma Coat [¹²⁵I] RIA kit (Inestar Corp.); DHEA-S with direct RIA solid-phase coated tubes (Zer Science Based Industries Ltd); 17 α -OH-progesterone with an ImmChem Double Antibody [¹²⁵I] RIA kit (ICN Pharmaceuticals, Inc.); insulin with a Coat-A-count Insulin kit (Diagnostic Products Corp.); and SHBG with an immunoradiometric assay (IRMA) kit (SHBG: [¹²⁵I] IRMA Kit, Orion Diagnostica). Adiponectin levels were measured with a commercial radiometric immunoassay kit (Linco Research Inc., St Charles, MO, USA).

The intra-assay coefficients of variation (CV) were 1.5% for FSH, 0.7% for LH, 2.7% for prolactin, 3.8% for insulin, 4.1% for 17 α -OH-progesterone, 1.3% for testosterone, 5.9% for androstenedione, 9.4% for DHEA-S, 5.8% for SHBG and 3.6% for adiponectin. The average inter-assay CV were 3.2% for FSH, 1.7% for LH, 3.4% for prolactin,

4.4% for insulin, 6.3% for 17 α -OH-progesterone, 2.2% for testosterone, 9.2% for androstenedione, 12.1% for DHEA-S, 7.8% for SHBG and 5.2% for adiponectin.

Statistical analysis

Statistical analyses were performed using SPSS software (v. 11.5 SPSS, Inc., Chicago, IL, USA). All values were log-transformed to achieve a more normal distribution. Means were compared with the unpaired *t*-test. Bivariate correlation analysis (calculation of the Pearson coefficient) was used to assess the correlation of serum adiponectin levels to each parameter. Independent relationships between serum adiponectin levels and those parameters to which they were found to correlate significantly were assessed using multiple regression and partial correlation analysis (controlling for those parameters that were found to be independent determinants of serum adiponectin levels in multiple regression analysis). A *P*-value < 0.05 was considered statistically significant.

Results

The clinical features of the women studied are summarized in Table I. There was no significant inter-group difference in age, but the mean BMI was significantly higher in group I compared with group II (*P* < 0.001) and group III (*P* < 0.001). There was no significant difference in BMI between groups II and III.

Biochemical parameters are summarized in Table II. Women with PCOS (groups I and II) had lower FSH levels compared with controls, but this difference was not significant. LH levels were significantly higher in women with PCOS and normal BMI (group II) compared with women having PCOS + BMI >25 kg/m² (group I, *P* < 0.005) and controls (group III, *P* < 0.05). LH levels did not differ significantly between groups I and III. No significant differences in prolactin levels were observed, although five women in group I (14.3%) and two in group II (5.7%) had serum prolactin levels above normal.

Compared with controls, women with PCOS had significantly higher serum levels of testosterone, Δ_4 -androstenedione, 17 α -OH-progesterone and DHEA-S (group I versus III, *P* < 0.001; group II versus III, *P* < 0.001 in all comparisons). Serum levels of the above hormones did not differ significantly between groups I and II. However, the FAI was significantly greater in group I than in group II (*P* < 0.05) and group III (*P* < 0.001), and also in group II compared with group III (*P* < 0.001). SHBG levels were significantly lower in group I than in groups II and III (*P* < 0.005 and *P* < 0.001 respectively), and lower in group II compared with group III (*P* < 0.001). Serum concentrations of gonadotrophins, androgens, 17 α -OH-progesterone and SHBG are summarized in Figure 1A and B.

Blood glucose levels were significantly higher in women with BMI >25 kg/m² (group I versus III, *P* < 0.05; group I versus II, *P* < 0.001), whereas no significant difference was observed between women with a BMI <25 kg/m² (groups II and III). However, insulin resistance, which was significantly greater in women with PCOS, was found to be exacerbated by obesity. In the present study, insulin resistance was assessed by measuring serum insulin levels (group I versus III, *P* < 0.001; group II versus III, *P* < 0.05; group I versus II, *P* < 0.001) and calculating the glucose:insulin ratio (group I versus III,

P < 0.001; group II versus III, *P* < 0.05; group I versus II, *P* < 0.001).

Serum adiponectin levels in group I were significantly lower than those of groups III and II (*P* < 0.05), whereas no significant difference existed between women with PCOS and normal BMI and women without PCOS. Serum concentrations of insulin and adiponectin, as well as blood glucose levels and the value of the glucose:insulin ratio and FAI in all three groups are summarized in Figure 1C.

Calculation of the Pearson coefficient showed that adiponectin levels were positively correlated with SHBG levels (*r* = +0.224, *P* < 0.05). Serum adiponectin levels were found to be negatively correlated with BMI (*r* = -0.322, *P* < 0.005) (Figure 2), and with Δ_4 -androstenedione levels (*r* = -0.327, *P* < 0.005) (Figure 3), FAI (*r* = -0.23, *P* < 0.05) and plasma glucose level (*r* = -0.242, *P* < 0.05). In women with PCOS as a group, serum adiponectin levels were also negatively correlated with BMI (*r* = -0.316, *P* < 0.01), Δ_4 -androstenedione levels (*r* = -0.335, *P* < 0.01) and plasma glucose levels (*r* = -0.277, *P* < 0.05), whereas in controls adiponectin was not correlated with any parameter. No significant correlation was observed between serum adiponectin levels and the concentration of FSH, LH, testosterone, DHEA-S, 17 α -OH-progesterone, insulin or the glucose:insulin ratio. In multiple regression analysis (*n* = 85), the BMI and Δ_4 -androstenedione level were found to be significant independent determinants of adiponectin levels (*r*² = +0.1, *P* < 0.005 and *r*² = +0.11, *P* < 0.005 respectively) (Figures 2 and 3). Partial correlation analysis showed that SHBG levels and FAI did not correlate with circulating adiponectin independently of either BMI or Δ_4 -androstenedione level. However, the correlation of serum adiponectin levels with glucose concentration remained significant (*P* < 0.05) after adjustment for Δ_4 -androstenedione levels, but not for BMI.

Discussion

It has been established that adiponectin is almost exclusively produced in adipose tissue (Berg *et al.*, 2002; Tsao *et al.*, 2002). In the present study, serum adiponectin levels were significantly lower in women with PCOS + BMI >25 kg/m² compared with women with BMI <25 kg/m², with or without PCOS. No difference was found in adiponectin levels between groups II and III (BMI <25 kg/m²). A significant negative correlation between adiponectin concentration in the serum and BMI was also observed (Figure 2). These findings are in accord with those of others (Arita *et al.*, 1999; Weyer *et al.*, 2001; Tschritter *et al.*, 2003), who established adiponectin as the only 'adipokine' that is suppressed by increased body fat.

The present study is the first in which serum adiponectin levels in women with PCOS were measured. It is difficult to draw any firm conclusions from these data; nevertheless, adiponectin levels did not differ significantly between women in groups II and III, though women with PCOS and normal BMI had significantly higher levels of insulin, and a smaller glucose:insulin ratio—in other words, they were more resistant to insulin. This finding might lead to the conclusion that, in

Table I. Clinical features of women with polycystic ovary syndrome (PCOS) and healthy controls

Clinical feature	Group I (n = 35)	Group II (n = 35)	Group III (n = 15)
Diagnosis	PCOS + BMI >25 kg/m ²	PCOS + BMI < 25 kg/m ²	Controls (BMI <25 kg/m ²)
Age (years)	26.8 ± 5.2	25.7 ± 4.0	27.8 ± 4.9
BMI (kg/m ²)	32.5 ± 6.1 (25.3–44.9)	21.6 ± 1.6 (18.6–24.8)	20.5 ± 2.0 (18.3–24.4)
	I vs. II, <i>P</i> < 0.001; I vs. III, <i>P</i> < 0.001; II vs. III, NS		

Values expressed as mean ± SD; values in parentheses are ranges.

BMI = body mass index; NS = not significant.

Table II. Hormonal and metabolic parameters of women with PCOS and healthy controls

Circulating level	Group I	Group II	Group III	Reference value
FSH (mIU/ml)	5.6 ± 2.0 I vs. II, NS; I vs. III, NS; II vs. III, NS	5.7 ± 1.4	6.6 ± 2.2	3.6–13.7
LH (mIU/ml)	6.1 ± 3.2 I vs. II, <i>P</i> < 0.005; I vs. III, NS; II vs. III, <i>P</i> < 0.05	9.1 ± 5.3	6.0 ± 2.1	1.9–11.9
Prolactin (ng/ml)	13.9 ± 8.4 I vs. II, NS; I vs. III, NS; II vs. III, NS	14.5 ± 6.1	11.6 ± 5.6	3.0–23.2
Testosterone (ng/dl)	92.6 ± 23.9 I vs. II, NS; I vs. III, <i>P</i> < 0.001; II vs. III, <i>P</i> < 0.001	93.8 ± 24.9	32.6 ± 11.2	10–80
Δ ₄ -Androstenedione (ng/ml)	3.0 ± 1.1 I vs. II, NS; I vs. III, <i>P</i> < 0.001; II vs. III, <i>P</i> < 0.001	2.9 ± 1.0	1.5 ± 0.4	0.6–2.7
DHEA-S (ng/ml)	2954.6 ± 896.6 I vs. II, NS; I vs. III, <i>P</i> < 0.001; II vs. III, <i>P</i> < 0.001	2807.5 ± 1106.0	1402.5 ± 301.0	400–3800
17α-OH-progesterone (ng/ml)	1.1 ± 0.4 I vs. II, NS; I vs. III, <i>P</i> < 0.001; II vs. III, <i>P</i> < 0.001	1.1 ± 0.4	0.6 ± 0.2	0.2–1.0
SHBG (nmol/l)	28.5 ± 14.6 I vs. II, <i>P</i> < 0.005; I vs. III, <i>P</i> < 0.001; II vs. III, <i>P</i> < 0.001	38.9 ± 17.0	72.6 ± 25.8	20.0–120.0
Insulin (μIU/ml)	14.7 ± 9.7 I vs. II, <i>P</i> < 0.001; I vs. III, <i>P</i> < 0.001; II vs. III, <i>P</i> < 0.05	7.9 ± 3.8	5.7 ± 2.0	4.0–25.0
Glucose (mg/dl)	91.1 ± 13.0 I vs. II: <i>P</i> < 0.001, I vs. III: <i>P</i> < 0.05, II vs. III: NS	84.2 ± 10.2	82.7 ± 7.1	70–110
FAI ^a	14.6 ± 8.3 I vs. II, <i>P</i> < 0.05; I vs. III, <i>P</i> < 0.001; II vs. III, <i>P</i> < 0.001	10.6 ± 7.0	1.9 ± 1.2	< 5
Glucose:insulin ratio ^b	8.9 ± 5.1 I vs. II, <i>P</i> < 0.001; I vs. III, <i>P</i> < 0.001; II vs. III, <i>P</i> < 0.05	12.6 ± 5.2	15.9 ± 4.6	>4.5
Adiponectin (ng/ml)	10 563.0 ± 10 326.7 I vs. II, <i>P</i> < 0.05; I vs. III, <i>P</i> < 0.05; II vs. III, NS	15 106.6 ± 10 862.6	13 879.7 ± 7059.2	–

Values are mean ± SD.

^aFree androgen index; calculated as: [testosterone (nmol/l) × 100/SHBG (nmol/l)].

^bCalculated as: [Glucose (mg/dl)/Insulin (μIU/ml)].

DHEA-S = dehydroepiandrosterone sulphate; SHBG = sex hormone-binding globulin; NS = not significant.

PCOS, adiponectin is not associated with insulin resistance that is not induced by obesity.

Nonetheless, insulin resistance of PCOS and its compensatory hyperinsulinaemia are most marked when there is interaction between the syndrome and obesity (Dunaif, 1994; 1997). Adiponectin levels were significantly lower in women with a BMI >25 kg/m² than in women with a normal BMI, along with higher insulin levels. The glucose:insulin ratio was significantly smaller in women with a BMI >25 kg/m², compared with the ratio in women with a normal BMI. Bivariate correlation analysis, however, showed that adiponectin levels did not correlate with either insulin levels or the glucose:insulin ratio, which is an index of insulin resistance (Legro *et al.*, 1998); rather, they were negatively correlated with BMI, glucose levels and FAI, and positively correlated with SHBG levels. The latter is reduced in PCOS (Figure 1C), and the reduction is further induced by obesity (Nestler *et al.*, 1991). This relationship also explains the higher levels of

circulating androgens (FAI) in women with PCOS and BMI >25 kg/m², compared with women with PCOS and a BMI <25 kg/m².

In other words, adiponectin levels were found to correlate significantly with certain obesity-associated parameters. This finding might indicate the involvement of adiponectin in the dysregulated metabolic state of PCOS. Therefore, a stepwise multiple regression analysis and subsequent partial correlation adjusting for independent determinants was performed, in order to assess independent relationships. Notably, adiponectin levels were found not to correlate with any of the above parameters, independently of BMI. These findings do not appear to favour a direct link between adiponectin and PCOS-associated insulin resistance, independently of increased adiposity.

The present results seem to be inconsistent with substantial evidence suggesting that adiponectin plays an important, beneficial role in insulin sensitivity in rodents (Berg *et al.*,

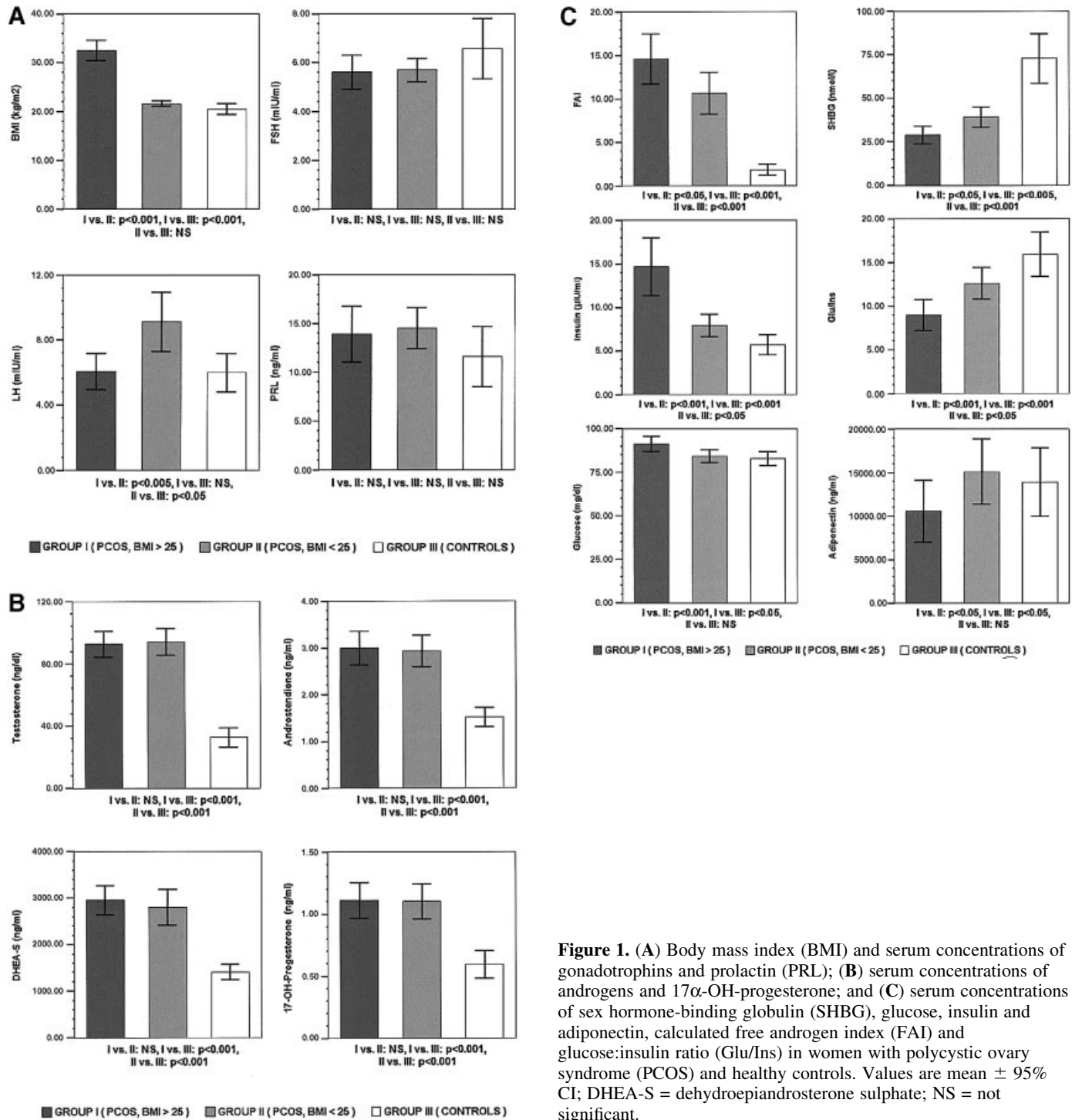


Figure 1. (A) Body mass index (BMI) and serum concentrations of gonadotrophins and prolactin (PRL); (B) serum concentrations of androgens and 17 α -OH-progesterone; and (C) serum concentrations of sex hormone-binding globulin (SHBG), glucose, insulin and adiponectin, calculated free androgen index (FAI) and glucose:insulin ratio (Glu/Ins) in women with polycystic ovary syndrome (PCOS) and healthy controls. Values are mean \pm 95% CI; DHEA-S = dehydroepiandrosterone sulphate; NS = not significant.

2001; Yamamuchi *et al.*, 2001), non-human primates (Hotta *et al.*, 2001) and humans (Hotta *et al.*, 2000; Weyer *et al.*, 2001; Philips *et al.*, 2003; Spranger *et al.*, 2003; Tschritter *et al.*, 2003). Based on the present findings alone, it cannot be excluded with certainty that adiponectin is involved in PCOS-associated resistance to insulin. The negative results obtained might be due to the small number of women studied, in addition to the fact that insulin resistance was estimated using the glucose:insulin ratio. Although this ratio has been suggested as a simple and valuable measure of insulin sensitivity

in women with PCOS (Legro *et al.*, 1998), more sensitive (Radziuck, 2000) and dynamic methods (namely the hyper-insulinaemic isoglycaemic glucose clamp and OGTT) have been implemented in most studies demonstrating the insulin-sensitizing effects of adiponectin *in vivo*. Notably, however, none of these reports included women with PCOS.

Existent, yet paradoxical, interactions between adiponectin and gonadal function and development in mice have been reported recently (Combs *et al.*, 2003). In the present study, no correlation between serum adiponectin levels and testoster-

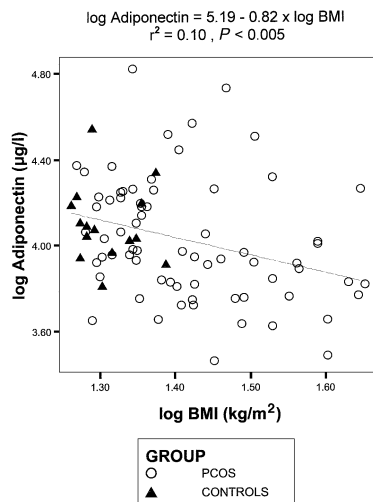


Figure 2. Correlation of BMI to serum adiponectin levels. Scatter-plot diagram (logarithmic scale). $r(\log) = -0.322$, $n = 85$ ($P < 0.005$).

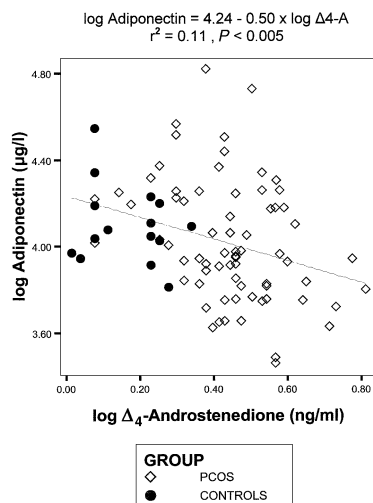


Figure 3. Correlation of circulating Δ_4 -androstenedione to serum adiponectin levels. Scatter-plot diagram (logarithmic scale). $r(\log) = -0.327$, $n = 85$ ($P < 0.005$).

one—the hormone mainly responsible for PCOS-associated clinical hyperandrogenism—was found, and there was no BMI-independent correlation with FAI. However, a significant and independent correlation with Δ_4 -androstenedione levels was observed (Figure 3), and this was suggestive of an interaction between adiponectin and steroid synthesis or action. Intriguingly, a strong negative correlation between another hormone (ghrelin) and Δ_4 -androstenedione—but not with testosterone and other androgens—has been recently reported (Pagotto *et al.*, 2002). The correlation with glucose, though BMI-dependent, remained significant after adjustment for Δ_4 -androstenedione levels—unlike SHBG levels and FAI, which were not correlated with circulating adiponectin independently of either BMI or Δ_4 -androstenedione levels.

In conclusion, the negative correlation between serum adiponectin and BMI may be confirmed for the first time in

women with PCOS. It is also evident that women with PCOS and a normal BMI do not have significantly higher serum adiponectin levels than ovulating women with normal BMI and without hyperandrogenism, and that circulating adiponectin levels are independently correlated with Δ_4 -androstenedione levels. No correlation between adiponectin levels and the glucose:insulin ratio, insulin, gonadotrophin, testosterone or 17α -OH-progesterone levels was found. Finally, the observed correlation between adiponectin levels and glucose, SHBG and FAI was seen to be BMI-dependent. The above findings suggest that adiponectin is most likely not actively involved in the pathogenesis of PCOS, though it might play a role in the complicated metabolic abnormalities of the syndrome.

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Submitted on March 11, 2003; accepted on May 7, 2003