CLINICAL STUDY

Evidence for altered adipocyte function in polycystic ovary syndrome

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Abstract

Background: Adipocytokines are produced by adipose tissue and have been thought to be related to insulin resistance and other health consequences. We measured leptin, adiponectin, and resistin simultaneously in women with polycystic ovary syndrome (PCOS) and age- and weight-matched controls. Our hypothesis was that these simultaneous measurements would help determine whether adipocytokine secretion is abnormal in PCOS independent of body mass and whether these levels are related to insulin resistance as well as other hormonal changes.

Methods: Fifty-two women with PCOS and 45 normal ovulatory women who were age- and weight-matched were studied. Blood was obtained for adipocytokines (leptin, adiponectin, and resistin) as well as hormonal parameters and markers of insulin resistance as assessed by the quantitative insulin-sensitivity check index. Body mass index (BMI) was stratified into obese, overweight, and normal subgroups for comparisons between PCOS and controls.

Results: Adiponectin was lower ($P < 0.05$) and resistin was higher ($P < 0.05$) while leptin was similar to matched controls. Breakdown of the groups into subgroups showed a strong body mass relationship for leptin with no changes in resistin although adiponectin was lower in PCOS, even controlling for BMI. In controls, leptin and adiponectin and leptin and resistin correlated ($P < 0.05$) but not in PCOS. In controls, all adipocytokines correlated with markers of insulin resistance but not in PCOS.

Conclusions: When matched for BMI status, decreased adiponectin in PCOS represent the most marked change. This alteration may be the result of altered adipose tissue distribution and function in PCOS but no correlation with insulin resistance was found.

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Introduction

In recent years it has been shown that adipocytes are secretory cells that produce a variety of proteins with hormonal-type functions, which collectively have been called adipocytokines. The first adipose hormone discovered was leptin (1), a 146 amino acid protein which acts mostly as a signaling factor from adipose tissue to the central nervous system thus regulating food intake and energy expenditure (2). Leptin is not produced exclusively by adipocytes but its circulating levels are strictly correlated to adipose mass and are higher in obese humans (3). A few years later, a novel protein produced in large quantities by adipocytes, adiponectin, was synthesized (4). Adiponectin is a 244 amino acid protein that is produced exclusively by adipose cells and may have a role in preventing or counteracting the development of insulin resistance (5–7). In contrast to leptin, the production of adiponectin is decreased in

obese subjects (6, 8). Finally, a third protein produced by adipocytes, resistin, was synthesized (9) and was thought to be related to the development of insulin resistance (9). It has been reported that circulating levels of resistin are increased in obesity (10, 11). However, in other studies (12), resistin was found not to be associated with obesity or insulin resistance. Differences in results may be due to assay differences where different epitopes on resistin were targeted leading to differences in specificity (13).

Alterations in circulating levels of the adipocytokines have been considered to be useful in evaluating adipose tissue function and/or distribution (14). In the general population there is an inverse relationship between leptin and adiponectin (15, 16), but their diurnal rhythms are out of phase, suggesting a different regulatory mechanism for these two adipocytokines (17). On the other hand, different areas of fat may have a different capacity to produce these proteins. It has

been reported that leptin is mostly produced by subcutaneous adipose tissue while adiponectin correlates with visceral fat production but not with subcutaneous fat (18). It has also been reported that the administration of adiponectin reduces visceral fat (19).

Discordant results regarding relationships of resistin with the other adipocytokines have been reported. While in some studies no correlation between resistin and adiponectin or leptin was found (12), other authors have reported a positive correlation between levels of resistin and leptin (16).

Polycystic ovary syndrome (PCOS) is a disorder characterized by hyperandrogenism and insulin resistance (20). At least 50% of women affected by PCOS are obese (20, 21), and because of the importance of insulin resistance and obesity in this disorder several studies have measured circulating levels of leptin and adiponectin (22–26). In most studies, leptin levels were similar to those of controls of similar body weight, while adiponectin levels have been found to be either lower or similar. A recent study has reported that resistin levels are normal (when adjusted for body mass index (BMI)) in women with PCOS (27). However, to our knowledge, no study in women with PCOS has measured the secretion of all three adipocytokines at the same time. This approach may be useful to understand whether adipocytokine function is perturbed and if changes may relate to the insulin resistance and other endocrine characteristics of PCOS.

Accordingly, in this study we measured these three adipocytokines simultaneously in 52 women with PCOS and matched controls and evaluated their interrelationships, as well as their correlations with insulin resistance, gonadotropins, and androgen secretion. Our hypothesis was that adipocytokine secretion is altered in women with PCOS, and is independent of body mass, and that this may relate to insulin resistance in PCOS as it has been shown to be in normal women. Our data suggested that while levels of adiponectin and resistin, but not leptin, are abnormal when compared with matched controls, by carefully stratifying by BMI, only adiponectin is abnormal in PCOS. These changes were independent of BMI, suggesting altered adipose function/distribution. There was no correlation of these changes with insulin resistance or other hormone factors in PCOS.

Materials and methods

Subjects

Fifty-two women with PCOS were studied. The diagnosis of PCOS was based on the classic criteria of hyperandrogenism and chronic anovulation. The women with PCOS had a mean age of 25.2 ± 1 years and a mean BMI of 28.7 ± 0.8 . Their waist/hip ratio (WHR) was 0.86 ± 0.02 .

Forty-five normal ovulatory women aged (25.1 ± 0.7 years) and weight matched (mean BMI 28.5 ± 0.5) to women with PCOS were also studied. Their WHR was also similar to that of women with PCOS (0.87 ± 0.01). The normal women were selected on the basis of not having hirsutism or signs of androgenization and all had normal ovulatory menstrual cycles. The presence of normal ovulation was assessed by measurements of serum progesterone (> 20 nM/l) on days 22–23 of the menstrual cycle.

BMI stratification

For the purposes of determining the influence of obesity on the three adipocytokines, and their relationships with other hormonal parameters, we subdivided both PCOS and controls into three separate groups. Women with PCOS were subdivided into groups of normal weight (BMI < 25) $n = 15$; overweight (BMI 25–30) $n = 19$, and obese (BMI > 30) $n = 18$. In the control group, there were 14 women with BMI < 25 , 16 women with BMI 25–30, and 15 women with BMI > 30 .

In all women with PCOS and in normal controls, during the follicular phase (days 5–8), a fasting blood sample was obtained between 0800 and 0900 h for measurements of luteinizing hormone (LH), follicle-stimulating hormone (FSH), estradiol, testosterone, androstenedione ($\Delta 4$), dehydroepiandrosterone sulfate (DHEAS), insulin, glucose, leptin, adiponectin, and resistin. Insulin resistance was calculated by the quantitative insulin-sensitivity check index (QUICKI) (28).

Assays

Serum gonadotropin and androgen levels were measured by well-established RIAs (29–31). Serum levels of testosterone and $\Delta 4$ were measured after extraction with diethyl ether and separation by celite column partition chromatography. Plasma glucose levels were determined by the glucose oxidase technique. Insulin was determined with a double antibody method using reagents obtained from Linco Research, Inc. (St Charles, MO, USA). Leptin was measured by an ELISA method using materials provided by DSL (Webster, Texas, USA). Adiponectin was measured by an ELISA method using materials provided by B-Bridge Int. Inc. (Sunnyvale, CA, USA). Resistin was measured by an ELISA method using materials provided by BioVendor (Brno, Czech Republic).

In all hormonal assays, the intra-assay coefficient of variation was $< 6\%$, and the interassay coefficient of variation was $< 15\%$.

Institutional review board approval was obtained, and all patients and controls gave written consent. All subjects were considered to be sedentary, and were not dieting or receiving any medications. No subject received hormonal medications for at least 3 months before the study.

Statistical analyses

Analysis of variance was used for comparisons. Post hoc testing was carried out by Student's *t*-test with log transformation. Analysis of covariance was used to evaluate the role of body weight on differences in metabolic parameters. Pearson product moment correlation and stepwise multivariate linear regression analysis with forward selection were used to analyze correlations. $P < 0.05$ was considered statistically significant. All data are expressed as means $\pm$ s.e.

Results

Compared with normal controls, women with PCOS had increased ($P < 0.01$) levels of LH, testosterone, Δ_4 , DHEAS and insulin (Table 1). Patients with PCOS also had lower QUICKI values than controls ($P < 0.01$) (Table 1).

In evaluating the entire group of normal controls, and women with PCOS, the PCOS group had lower ($P < 0.05$) levels of adiponectin and higher ($P < 0.05$) levels of resistin while leptin levels were not significantly different (Table 1).

Table 2 provides data evaluating all subjects based on BMI stratification. The obese controls had higher insulin and lower QUICKI than normal weight controls, although LH and LH/FSH were similar. All PCOS subjects had higher insulin and lower QUICKI values, but obese women had a greater degree of insulin resistance. Obese PCOS subjects had higher LH but similar LH/FSH ratios.

In controls, increasing BMI resulted in higher leptin and lower adiponectin but similar levels of resistin (Table 3). Leptin was only significantly higher in the obese (BMI > 30) group compared with the normal group, while the overweight group (BMI 25–30) had significantly lower levels than the obese group.

In PCOS, leptin was higher in the obese versus normoweight patients; there were no differences in leptin between PCOS and controls when compared on the basis of BMI stratification. Adiponectin was lower in obese PCOS compared with normoweight PCOS ($P < 0.05$) but normoweight PCOS also had lower adiponectin levels than both normoweight and overweight controls ($P < 0.05$). There were no differences in resistin levels (Table 3).

Correlations

In normal subjects, there was a negative correlation between leptin and adiponectin ($r = -0.45$, $P < 0.01$) and a positive correlation between leptin and resistin ($r = 0.31$, $P < 0.05$). A negative correlation between adiponectin and resistin was also found ($r = -0.30$, $P < 0.05$). In PCOS these correlations were not found.

In normal subjects, all adipocytokines correlated significantly with BMI (leptin $r = 0.55$, $P < 0.01$; adiponectin $r = -0.36$, $P < 0.05$; resistin $r = 0.40$, $P < 0.01$), with serum insulin (leptin $r = 0.41$, $P < 0.01$; adiponectin $r = -0.36$, $P < 0.05$; resistin $r = 0.36$, $P < 0.05$), and with QUICKI (leptin $r = -0.39$, $P < 0.01$; adiponectin $r = 0.32$, $P < 0.05$; resistin $r = -0.41$, $P < 0.01$). The analysis of the regression curves indicated a strong BMI dependency of all adipocytokines and the correlations of adipocytokines with insulin and QUICKI were lost if the values were corrected for BMI. Leptin and resistin but not adiponectin also correlated negatively with WHR (leptin $r = -0.39$, $P < 0.01$; resistin $r = -0.34$, $P < 0.05$).

In PCOS, leptin maintained its correlations with BMI ($r = 0.61$, $P < 0.01$), with insulin ($r = 0.34$,

Table 1 Hormonal parameters, insulin resistance (calculated by QUICKI) and adipocytokine values in 52 women with PCOS and in 45 normal weight- and age-matched controls. Values are means $\pm$ s.e.

	LH (mU/ml)	FSH (mU/ml)	Testosterone (ng/dl)	Δ_4 (ng/ml)	DHEAS (μ mol/l)	Insulin (μ U/ml)	QUICKI	Leptin (pg/ml)	Adiponectin (μ g/ml)	Resistin (ng/ml)
PCOS	13.5 $\pm$ 1**	7.9 $\pm$ 0.4	109 $\pm$ 5**	3.5 $\pm$ 0.2**	5.2 $\pm$ 0.3**	19.2 $\pm$ 1.1**	0.315 $\pm$ 0.003**	30.4 $\pm$ 2.5	8.2 $\pm$ 0.6*	6.1 $\pm$ 0.4*
Controls	9.1 $\pm$ 0.2	9.1 $\pm$ 0.2	41 $\pm$ 3	1.5 $\pm$ 0.1	2.9 $\pm$ 0.2	9 $\pm$ 0.5	0.353 $\pm$ 0.002	26.2 $\pm$ 2.8	10.5 $\pm$ 0.7	5.1 $\pm$ 0.2

* $P < 0.05$, ** $P < 0.01$ vs controls.

Table 2 Hormonal parameters and insulin resistance in control and PCOS women subcategorized by BMI. Values are means $\pm$ s.e.

	<i>n</i>	Insulin	QUICKI	LH	LH/FSH
Normoweight controls	14	6.9 $\pm$ 0.6*	0.368 $\pm$ 0.007*	8.6 $\pm$ 0.2	0.9 $\pm$ 0.1
Overweight controls	16	8.7 $\pm$ 1.6	0.365 $\pm$ 0.004	9.1 $\pm$ 0.4	1 $\pm$ 0.2
Obese controls	15	9.3 $\pm$ 0.9	0.353 $\pm$ 0.005	9.5 $\pm$ 0.5	1 $\pm$ 0.3
Normoweight PCOS	15	15.2 $\pm$ 1.1**	0.326 $\pm$ 0.003**	8.1 $\pm$ 1.3	2.1 $\pm$ 0.6
Overweight PCOS	19	17.4 $\pm$ 1.89	0.319 $\pm$ 0.004	12.6 $\pm$ 1.6	2.3 $\pm$ 0.4
Obese PCOS	18	24 $\pm$ 2.2	0.303 $\pm$ 0.005	16.3 $\pm$ 2	2.4 $\pm$ 0.4

* $P < 0.05$ vs obese controls; ** $P < 0.01$ vs obese PCOS.

Table 3 Serum adipocytokine levels in control and PCOS women subcategorized by BMI. Values are means $\pm$ S.E.

	BMI	Leptin (pg/ml)	Adiponectin (μ g/ml)	Resistin (ng/ml)
Normoweight controls	23 $\pm$ 0.22††	15.3 $\pm$ 1.44††	13 $\pm$ 1.5*††	5 $\pm$ 0.4
Overweight controls	27.3 $\pm$ 0.4	23.4 $\pm$ 2	11.4 $\pm$ 1.3*†	5.3 $\pm$ 0.4
Obese controls	34.6 $\pm$ 0.9	31.2 $\pm$ 0.9	7.1 $\pm$ 0.6	6 $\pm$ 0.4
Normoweight PCOS	22.7 $\pm$ 0.4**	18.1 $\pm$ 2**	9.2 $\pm$ 1.1*‡	6 $\pm$ 0.9
Overweight PCOS	27.1 $\pm$ 0.4	27 $\pm$ 2.5	9.1 $\pm$ 0.9	6.1 $\pm$ 0.5
Obese PCOS	35.1 $\pm$ 1.2	34.6 $\pm$ 2.1	6.9 $\pm$ 0.7	6.3 $\pm$ 0.9

* $P < 0.05$; ** $P < 0.01$ vs obese PCOS; † $P < 0.05$; †† $P < 0.01$ vs obese controls; ‡ $P < 0.05$ vs normoweight controls; || $P < 0.05$ vs overweight controls.

$P < 0.05$), and with QUICKI ($r = -0.40$, $P < 0.01$). However, adiponectin correlated only with BMI ($r = -0.28$, $P < 0.05$) but not with insulin ($r = 0.03$), or with QUICKI ($r = -0.02$), and resistin did not correlate with any of these parameters (with BMI $r = 0.10$; with insulin $r = 0.04$; with QUICKI $r = 0.04$). No correlations between adipocytokines and WHR were found. Also in these patients, the analysis of regression curves indicated a strong correlation between leptin (but not adiponectin or resistin) and BMI and the correlations of leptin with insulin and QUICKI were lost if the values were corrected for BMI.

In both normal women and patients with PCOS, no correlations between adipocytokines and gonadotropins or LH/FSH ratios were found.

Discussion

PCOS is a heterogeneous syndrome characterized by hyperandrogenism and insulin resistance (20, 32). The mechanism that is responsible for insulin resistance is unclear and several hypotheses have been suggested (33). Because obesity is linked to insulin resistance and many women with PCOS are obese, it is possible that, at least in a subgroup of patients, insulin resistance is worsened by excessive adipose mass. Recently, it has been shown that adipose tissue produces several polypeptides (adipocytokines) that may control food intake or regulate insulin sensitivity (14).

In this study, in a group of women with PCOS and in a group of controls, matched for BMI, age and WHR, we evaluated three of these adipocytokines simultaneously: leptin, adiponectin, and resistin. It is conjectured that in evaluating the relationships between the various hormones secreted by adipose tissue, some insight might be gained into the function of this tissue in women with PCOS.

Our data showed that in PCOS leptin levels were similar to those of matched controls and in general were strongly correlated with body weight (expressed as BMI) and less well with insulin and insulin sensitivity (expressed as QUICKI). There was little difference between controls and women with PCOS and the correlations of leptin with insulin and insulin resistance were strictly dependent on changes in body weight.

However, the other two adipocytokines were different in PCOS compared with controls. Adiponectin was clearly lower in PCOS. For the entire group, resistin levels were also higher in PCOS, although this difference was less obvious with BMI stratification.

A decrease of adiponectin and an increase of resistin have been linked to the development of insulin resistance (5–7, 9) and therefore our findings may help explain the insulin resistance of women with PCOS although we could not demonstrate this directly. While in normal women both adiponectin and resistin, although in opposite ways, correlated with insulin and QUICKI, which is consistent with data in the literature (5–7, 9, 34), these correlations were not found in PCOS. Similarly, while in normal women the three adipocytokines correlated with each other, in PCOS these correlations were not evident. These data may suggest that the mechanisms that determine insulin resistance in PCOS are not linked to the changes of adiponectin and resistin. Alternatively, the correlations may be lost because insulin resistance in PCOS is determined by several mechanisms, which may or may not be linked to alterations in the secretion of these two adipocytokines.

The normality of leptin and the altered levels of adiponectin and resistin may be the consequence of altered adipose tissue function but also may be due to a difference in fat distribution in that women with PCOS have proportionally more visceral adipose tissue (5). In fact, it has been suggested that differences in adipose tissue distribution may influence the secretion of the different adipocytokines (18, 19). While the WHR was similar in PCOS and controls, the WHR may be a relatively insensitive index of the distribution of adipose mass. Consistent with this hypothesis, by dividing the studied subjects into obese and normoweight groups, it was found that obese patients and controls did not have differences in adipocytokine levels while normoweight women with PCOS had significantly lower levels of adiponectin compared with normoweight and overweight controls. This may suggest that normoweight women with PCOS may have an increase of visceral fat even if body weight is normal.

Therefore, it is possible that women with PCOS who are considered to be normoweight have, in reality, an

increase in total visceral adipose tissue that may contribute to the development of cardiovascular risk in these patients. This alteration in body composition and adipocytokine secretion may also be reflected in lipid levels, which was not a subject of this report.

In conclusion, our data have shown that compared with controls of similar body weight, women with PCOS have altered adipocyte secretion. Circulating adipocytokine levels were different with lower levels of adiponectin being the most marked change while resistin was slightly increased. Only leptin was similar in PCOS and controls and was strictly related to BMI. These alterations may be the result of altered adipose tissue function, most probably that of increased visceral fat in women with PCOS, which occurs even with a normal BMI. While altered adiponectin secretion may still be involved in the characteristic insulin resistance of PCOS, our data do not support the hypothesis that this is the main pathogenetic mechanism.

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