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Altered leptin, adiponectin, resistin and ghrelin secretion may represent an intrinsic polycystic ovary syndrome abnormality

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Abstract

The aim of the study was to investigate whether altered adipose tissue secretion of various adipokines is secondary to obesity, hyperandrogenism, and hyperinsulinemia or intrinsic to polycystic ovary syndrome (PCOS). This cross-sectional study included 151 women diagnosed with PCOS by the Rotterdam criteria and 95 healthy women matched by age, body mass index (BMI), and waist-to-hip ratio (WHR). Clinical, biochemical, and hormonal characteristics were assessed. Serum concentrations of ghrelin and adiponectin were found to be significantly lower and concentrations of leptin and resistin significantly higher in women with PCOS than in healthy women matched by age, BMI, and WHR. A PCOS diagnosis made the largest contribution to predicting serum levels of leptin, adiponectin, resistin, and ghrelin in all stepwise multiple regression models, which included PCOS diagnosis, BMI, WHR, luteinizing hormone, total testosterone, free testosterone and homeostatic model assessment of insulin resistance as independent predictors. Leptin, adiponectin, ghrelin and resistin levels may serve as independent biomarkers for the diagnosis of PCOS.

Introduction

Polycystic ovary syndrome (PCOS) is a multisystem, endocrinological, reproductive and metabolic disorder characterized by oligo-/anovulation, hyperandrogenism and polycystic ovaries [1,2]. Many of the metabolic

abnormalities that manifest in PCOS, mainly including insulin resistance (IR), impaired glucose tolerance, type 2 diabetes mellitus (DM2), and dyslipidemia, are worsened by concurrent obesity [3]. However, some of these metabolic perturbations occur even in lean women with PCOS and therefore are rightfully recognized as intrinsic to PCOS [4–6]. Although many of these findings can be largely explained by the increased prevalence of abdominal obesity, even in normal-weight PCOS patients [7], some data suggest that disrupted secretion of adipose tissue-derived hormones (adipokines) and the gut hormone ghrelin precede the signs of metabolic syndrome observed in PCOS patients [6]. Whether adipokine and ghrelin dysfunction is a consequence of the interaction among obesity, visceral fat distribution, hyperandrogenemia, and hyperinsulinemia or is an intrinsic feature of PCOS is yet to be determined.

Therefore, the aim of this study was to investigate whether altered adipose tissue secretion of various adipokines is secondary to obesity, hyperandrogenism, and hyperinsulinemia or intrinsic to PCOS.

Study population

A portion of the data from this cohort was published previously [8]. The patients were recruited from the University of Zagreb Clinical Hospital Center Zagreb, Croatia, from 2009 to 2011. A total of 151 PCOS patients and 95 healthy control subjects were enrolled. The diagnosis of PCOS was confirmed according to the Rotterdam consensus criteria [1,2].

The control group consisted 95 healthy volunteers before entering an *in vitro* fertilization (IVF) program due to male-factor infertility. For all women included in the control group, ovulation was confirmed by a progesterone level ≥22 nmol/L obtained during the luteal phase of two consecutive menstrual cycles. All patients in the control group had no clinical or biochemical signs of hyperandrogenism and had normal ultrasound imaging results of the ovaries. The control group and the PCOS group were matched by age, body mass index (BMI), and waist-to-hip ratio (WHR).

No participants used any medication that could influence androgen, glucose, insulin or lipid levels for at least six months prior entering to study. All participants were recruited during the early follicular phase of a spontaneous or progesterone-induced menstrual cycle (day 3–5). After overnight fasting (>12 h), blood

samples for biochemical and hormonal analysis were drawn, transvaginal ultrasound was performed, and the BMI and WHR were calculated.

Biochemical measurements

Fasting blood samples were obtained for measurements of luteinizing hormone (LH), follicle-stimulating hormone (FSH), thyrotrophic hormone (TSH), prolactin (PRL), total testosterone (TT), sex hormone-binding globulin (SHBG), free testosterone (FT), dehydroepiandrosterone sulfate (DHEAS), androstenedione (A), 17-OH-progesterone (17-OHP), glucose, insulin, leptin, adiponectin, resistin and ghrelin. Serum LH, FSH, TSH, PRL and TT concentrations were determined by chemiluminescent immunometric assays (Ortho-Clinical Diagnostics, Johnson & Johnson, Rochester, NY). Serum SHBG, DHEAS, and A levels were measured using chemiluminescent immunometric assays (Siemens Healthcare Diagnostics Inc., Deerfield, IL). The concentration of 17-OHP was determined by a solid-phase enzyme-linked immunosorbent assay (ELISA) based on the principle of the competitive binding (DRG-diagnostics, Marburg, Germany). FT was calculated from the TT and SHBG levels as previously described [9] using a web-based calculator (http://www.issam.ch/freetesto.htm). Plasma glucose levels were measured by the UV-photometric hexokinase method, and serum insulin levels were measured by chemiluminescent immunometric assay (Siemens Healthcare Diagnostics Inc., Deerfield, IL). IR was quantified using the homeostatic model assessment of IR (HOMA-IR) (fasting insulin (mU/L)×fasting glucose (mmol/L))/22.5) [10]. Serum leptin levels were measured by radioimmunoassay (RIA, DRG International, NJ). Serum adiponectin levels were measured by an ELISA (Bio Vendor, Czech Republic). Serum resistin levels were measured by an enzyme immunoassay (DRG International, NJ). Serum ghrelin levels were measured with an RIA (DRG International, NJ).

Statistical analysis

Values are expressed in means ± standard deviations. An independent Student's *t*-test was used to compare the mean values between patients and controls. Pearson's correlation coefficient (*r*) was used to assess the linear associations of different clinical, biochemical and hormonal parameters with serum leptin, adiponectin,

resistin and ghrelin levels in both patients and controls. To explore the effects of PCOS, BMI, WHR, HOMA-IR, LH, TT and FT on serum leptin, adiponectin, resistin, and ghrelin levels, stepwise multiple regression models were constructed with leptin, adiponectin, resistin and ghrelin as dependent variables and all others as independent variables. All statistical analyses were performed using SPSS for Windows (version 15.0; SPSS, Inc., Chicago, IL). A value of $p < .05$ was considered to indicate a statistically significant difference.

The Ethics Committee of the Medical School, University of Zagreb, approved the study (protocol No. 04–1116-2006). Informed written consent was obtained from all participants enrolled in the study.

Results

The baseline characteristics of PCOS patients and control subjects are presented in Table 1. Associations of different clinical, hormonal and metabolic parameters with serum leptin, adiponectin, resistin, and ghrelin levels in PCOS patients and controls are presented in Table 2.

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Table 1. Clinical, hormonal and metabolic characteristics of women with PCOS and the healthy control group.

	Total			Normal weight			Overweight		
	PCOS (*N* = 151)	**Control (*N* = 95)**	***p***	**PCOS (*N* = 97)**	**Control (*N* = 77)**	***p***	**PCOS (*N* = 54)**	**Control (*N* = 18)**	***p***
Age (years)	26.5 ± 6.0	26.4 ± 2.7	.849	26.4 ± 5.9	26.4 ± 2.7	.969	26.7 ± 6.1	26.3 ± 2.6	.689
BMI (kg/m_2)	24.8 ± 4.8	23.3 ± 4.1	.013	22.4 ± 1.7	21.8 ± 1.8	.042	29.1 ± 5.4	29.6 ± 5.3	.755
WHR	0.79 ± 0.08	0.79 ± 0.07	.880	0.77±.07	0.78 ± 0.08	.200	0.83 ± 0.09	0.83 ± 0.08	.912
FSH (IU/L)	3.64 ± 1.24	5.5 ± 1.6	<.001	3.7 ± 1.2	5.5 ± 1.6	<.001	3.5 ± 1.3	5.5 ± 1.9	<.001
LH (IU/L)	8.5 ± 4.1	3.9 ± 1.1	<.001	9.2 ± 4.7	4.0 ± 1.1	<.001	7.2 ± 2.5	3.6 ± 1.0	<.001
TT (nmol/L)	2.3 ± 1.0	1.2 ± 0.4	<.001	2.3 ± 0.9	1.2 ± 0.4	<.001	2.3 ± 1.2	1.3 ± 0.5	<.001
FT (pmol/L)	42.7 ± 25.1	14.3 ± 6.8	<.001	40.7 ± 22.5	14.2 ± 6.9	<.001	46.2 ± 29.0	14.8 ± 6.5	<.001
Androstenedione (nmol/L)	10.9 ± 4.5	n/a	n/a	11.1 ± 4.9	n/a	n/a	10.4 ± 3.6	n/a	n/a

	Total			**Normal weight**			**Overweight**		
	PCOS (*N* = 151)	**Control (*N* = 95)**	***p***	**PCOS (*N* = 97)**	**Control (*N* = 77)**	***p***	**PCOS (*N* = 54)**	**Control (*N* = 18)**	***p***
DHEAS (nmol/L)	6.6 ± 2.5	n/a	n/a	6.6 ± 2.5	n/a	n/a	6.7 ± 2.6	n/a	n/a
SHBG (nmol/L)	43.4 ± 31.1	71.1 ± 21.7	<.001	47.7 ± 33.8	71.4 ± 22.0	<.001	35.9 ± 4.4	69.9 ± 21.0	<.001
HOMA-IR	2.7 ± 3.0	1.3 ± 0.5	<.001	2.2 ± 2.2	1.3 ± 0.6	<.001	3.4 ± 4.0	1.4 ± 0.4	.001
HOMA-IR >2.5 (%)	29.1	4.2	<.001	21.6	5.2	.002	42.6	0	<.001
Total cholesterol (nmol/L)	4.5 ± 0.4	4.3 ± 0.4	<.001	4.4 ± 0.4	4.2 ± 0.3	<.001	4.7 ± 0.3	4.6 ± 0.3	.179
Triglycerides (nmol/L)	1.7 ± 0.2	1.4 ± 0.4	<.001	1.3 ± 0.4	1.7 ± 0.2	<.001	1.7 ± 0.3	1.6 ± 0.2	.171
HDL-C (nmol/L)	1.5 ± 0.3	2.1 ± 0.3	<.001	1.5 ± 0.2	2.0 ± 0.3	<.001	1.4 ± 0.2	2.3 ± 0.3	<.001

	Total			Normal weight			Overweight		
	PCOS (*N* = 151)	**Control (*N* = 95)**	***p***	**PCOS (*N* = 97)**	**Control (*N* = 77)**	***p***	**PCOS (*N* = 54)**	**Control (*N* = 18)**	***p***
LDL-C (nmol/L)	2.4 ± 0.5	1.4 ± 0.2	<.001	2.3 ± 0.5	1.4 ± 0.1	<.001	2.6 ± 0.4	1.6 ± 0.4	<.001
CRP (mg/L)	2.1 ± 0.5	1.5 ± 0.6	<.001	2.1 ± 0.5	1.4 ± 0.6	<.001	2.2 ± 0.5	1.8 ± 0.6	.002
Leptin (ng/mL)	10.5 ± 1.3	7.7 ± 1.3	<.001	10.5 ± 1.3	7.7 ± 1.3	<.001	12.5 ± 1.4	11.5 ± 1.0	.007
Adiponectin (ng/mL)	9.5 ± 1.3	13.9 ± 1.3	<.001	9.5 ± 1.3	13.9 ± 1.3	<.001	8.4 ± 1.9	12.1 ± 1.5	<.001
Resistin (ng/mL)	11.4 ± 1.9	8.5 ± 1.2	<.001	11.4 ± 1.9	8.5 ± 1.2	<.001	13.3 ± 2.5	11.3 ± 1.7	.002
Ghrelin (pg/mL)	1279.1 ± 151.5	1775 ± 174.1	<.001	1279.1 ± 151.5	1775.8 ± 174.1	<.001	971.5 ± 167.4	1325.4 ± 79.2	<.001

Values are expressed as means ± SD.

BMI: body mass index; WHR: waist-to-hip ratio; FSH: follicle-stimulating hormone; LH: luteinizing hormone; TT: total testosterone; FT: free testosterone; DHEAS: dehydroepiandrosterone sulfate; HOMA-IR: homeostatic model assessment of insulin resistance; HDL-C: high-density lipoprotein cholesterol; LDL-C: low-density lipoprotein cholesterol; CRP: C-reactive protein.

Table 2. Associations of different clinical, hormonal and metabolic parameters with serum leptin, adiponectin, resistin, and ghrelin levels in PCOS patients and controls.

	PCOS				**Control**			
	Leptin	**Adiponectin**	**Ghrelin**	**Resistin**	**Leptin**	**Adiponectin**	**Ghrelin**	**Resistin**
BMI (kg/m$_2$)	0.614**	–0.560**	–0.674**	0.486**	0.877**	–0.756**	–0.809**	0.901**
WHR	0.305**	–0.123	–0.307**	0.135	0.350**	–0.327**	–0.369**	0.362**
FSH (IU/L)	–0.052	0.054	0.111	–0.048	–0.090	0.078	0.113	–0.060
LH (IU/L)	–0.223**	0.051	0.188*	–0.055	–0.114	0.097	0.150	–0.108
TT (nmol/L)	–0.092	–0.036	0.013	–0.020	–0.039	–0.005	–0.062	0.023
FT (pmol/L)	–0.007	–0.053	–0.038	–0.045	–0.041	0.001	–0.062	–0.022
Androstenedione (nmol/L)	–0.110	0.030	0.002	–0.002	N/A	N/A	N/A	N/A
DHEAS (nmol/L)	0.143	–0.166*	–0.099	0.157	N/A	N/A	N/A	N/A
SHBG (nmol/L)	–0.136	0.075	0.136	0.006	0.060	–0.056	0.004	0.058

	PCOS				Control			
	Leptin	**Adiponectin**	**Ghrelin**	**Resistin**	**Leptin**	**Adiponectin**	**Ghrelin**	**Resistin**
HOMA-IR	0.207*	–0.034	–0.199*	0.136	0.010	0.109	–0.086	–0.029
Total cholesterol (nmol/L)	0.325**	–0.225**	–0.342**	0.363**	0.427**	–0.266**	–0.371**	0.416**
Triglycerides (nmol/L)	0.380**	–0.311**	–0.504**	0.252**	–0.275**	0.284**	–0.332**	–0.211*
HDL-C (nmol/L)	–0.182*	0.132	0.311**	–0.175*	0.368**	–0.213*	0.350**	0.258*
LDL-C (nmol/L)	0.206*	–0.128	–0.243**	0.278**	0.249*	–0.217*	–0.201	0.374**
CRP (mg/L)	–0.036	0.026	–0.107	0.145	0.230*	–0.177	–0.226*	0.269**

BMI: body mass index; WHR: waist-to-hip ratio; FSH: follicle-stimulating hormone; LH: luteinizing hormone; TT: total testosterone; FT: free testosterone; DHEAS: dehydroepiandrosterone sulfate; HOMA-IR: homeostatic model assessment of insulin resistance; HDL-C: high-density lipoprotein cholesterol; LDL-C: low-density lipoprotein cholesterol; CRP: C-reactive protein.

**$p < .001$; *$p < .05$.

To determine whether adipokine secretion is possibly disrupted due to the interactions among obesity, abdominal fat distribution, LH, hyperandrogenism and IR or is an intrinsic feature of PCOS, we tested the predictive values of a PCOS diagnosis and the BMI, WHR, LH, TT, FT and HOMA-IR values for the serum concentrations of adipokines in all subjects included in the study (Table 3). All variables were entered into

stepwise regression models with leptin, adiponectin, ghrelin, and resistin as dependent variables. A model using PCOS, BMI, WHR, and TT as predictors explained 70.5% (adjusted $R2$) of the variability in serum leptin levels, whereas 77.9% (adjusted $R2$) of the variability of serum adiponectin could be explained by PCOS and BMI. A model using BMI, PCOS, WHR, and HOMA-IR as predictors explained 79.6% (adjusted $R2$) of the variability of serum ghrelin levels, while 59% (adjusted $R2$) of the variability of serum resistin levels could be explained using PCOS, BMI, and FT as predictors. In all stepwise multiple regression models, a PCOS diagnosis was the most significant predictor for each adipokine tested (Table 3).

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Table 3. Stepwise multiple regression models with leptin, adiponectin, ghrelin, and resistin as dependent variables.

	B-coefficient	***p***
Leptin (R_2=0.705)		
BMI	0.552	<.001
PCOS	–0.581	<.001
TT	–0.105	.012
WHR	0.092	.013
Adiponectin (R_2=0.779)		
BMI	–0.382	<.001
PCOS	0.738	<.001
Ghrelin (R_2=0.796)		
BMI	–0.453	<.001
PCOS	0.660	<.001

	B-coefficient	*p*
WHR	–0.083	.007
HOMA-IR	–0.069	.024
Resistin (R_2=0.590)		
BMI	0.513	<.001
PCOS	–0.571	<.001
FT	–0.120	.019

Only variables that contributed to the model are presented here.

BMI: body mass index; PCOS: polycystic ovary syndrome; WHR: waist-to-hip ratio; FSH: follicle-stimulating hormone; TT: total testosterone; FT: free testosterone; HOMA-IR: homeostatic model assessment of insulin resistance; PCOS: polycystic ovary syndrome.

Discussion

Although adipokine dysregulation is common in PCOS, it is still unknown whether these changes are secondary to obesity, hyperandrogenism, and hyperinsulinemia or intrinsic to PCOS. This study aimed to clarify the inconsistent results reported by previous studies.

Leptin

We found significantly increased serum leptin levels in PCOS patients compared to control subjects, even when stratified by BMI, suggesting that the elevated serum leptin level in PCOS patients is not only a result of increased body mass but is also due to specific factors related to PCOS. Our results, however, showed no association of serum leptin levels with TT or FT serum levels in women with PCOS, which is consistent with

previously published studies [11,12]. In contrast, when these associations were controlled for BMI and WHR, a significant negative association between serum leptin and TT levels was observed. TT was retained as a significant negative predictor of the serum leptin level when it was included as an independent variable in our stepwise regression model, further confirming the association.

The HOMA-IR value was not independently associated with serum leptin levels. We probably failed to detect this association because 2/3 of our PCOS patients were of normal weight. We speculate that if a higher number of overweight PCOS patients had been included in the study, the more pronounced role of IR associated with a higher BMI on serum leptin levels would have been identified.

When we constructed a stepwise regression model employing the serum leptin level as an objective variable and adjusted for various confounding factors as explanatory variables, a PCOS diagnosis had the greatest predictive value for serum leptin levels, followed by BMI. It is therefore, obvious that the serum leptin level is nearly equally affected by obesity and the diagnosis of PCOS *per se* and that among all examined adipokines in our study, leptin is perhaps the least specific for the diagnosis of PCOS.

Adiponectin

Many studies, including ours, have demonstrated hypoadiponectinemia in PCOS patients irrespective of obesity; however, these studies highlighted the importance of abdominal fat distribution. We failed to establish a link between serum levels of adiponectin and WHR, contrary to the results of other studies [13–16]. The lack of association between WHR and adiponectin in our population may be partly explained by the higher proportion of normal-weight PCOS patients included in our study, as well as possible differences in body fat distribution among Croatian women compared to women of other European countries.

We found no association between serum adiponectin levels and serum concentrations of TT or FT in PCOS patients, which is consistent with the work of several other authors [17]. We observed a significant negative association between DHEAS and adiponectin levels in our PCOS group, but this was lost after controlling for BMI and WHR.

Several reports have described associations of adiponectin levels with indicators of IR [17–19] which were further supported by a meta-analysis published in 2009 [17]. We were unable to demonstrate any association

between serum adiponectin levels and IR measured by the HOMA-IR in our population, similar to studies by Sarray et al. and O'Connor et al. [20] and the meta-analysis published by Li et al. [21]. These conflicting results are likely attributable to the differences in genetic predisposition for obesity and IR in distinct populations.

We demonstrated that a PCOS diagnosis served as the strongest independent predictor of serum adiponectin levels in stepwise multiple regression models. Adiponectin was the most specific factor for a diagnosis of PCOS among all adipokines examined.

Resistin

In our study, serum resistin levels were significantly elevated in PCOS patients compared to controls, irrespective of BMI, which is consistent with the results of Yilmaz et al. [22]. We found significant inverse correlations between serum resistin level and BMI as well as WHR in both the PCOS and control group, suggesting that obesity parameters negatively influence serum resistin levels.

We did not establish a link between resistin levels and HOMA-IR values or between resistin and the levels of androgen hormones in women with PCOS. Surprisingly, FT remained a significant independent predictor of serum resistin levels when we controlled for PCOS, BMI, WHR, HOMA-IR, LH, and TT in a stepwise regression model.

In stepwise multiple regression analysis, when a diagnosis of PCOS, BMI, WHR, HOMA-IR, LH, TT, and FT were included as independent explanatory variables of the concentration of serum resistin, a PCOS diagnosis was the strongest predictor among them.

Ghrelin

We found significantly lower serum ghrelin levels in PCOS patients than in healthy women, irrespective of BMI, which is consistent with data published by Barber et al. [23]. We found a significant negative association between serum ghrelin levels and HOMA-IR in the PCOS group, but this association was lost after adjustment for BMI and WHR. Furthermore, we did not establish a link between the concentrations of serum ghrelin and TT or FT in women with PCOS, in contrast with previously published studies [14,24].

The stepwise multiple regression model demonstrated that the variability of serum ghrelin could be explained by a PCOS diagnosis, BMI and HOMA-IR as confounding factors. A PCOS diagnosis made the largest unique contribution to predicting serum ghrelin levels.

Conclusion

The results of our study clearly demonstrate significantly altered secretion of leptin, adiponectin, resistin, and ghrelin in PCOS patients compared to healthy subjects irrespective of obesity parameters. In all stepwise multiple regression models, a PCOS diagnosis made the largest unique contribution to predicting serum leptin, adiponectin, resistin, and ghrelin levels. Therefore, it is likely that other factors independent of obesity, IR and increased production of androgens, yet unique to the diagnosis of PCOS, affect serum levels of adipokines and ghrelin in women with PCOS.

Disclosure statement

No potential conflict of interest was reported by the authors.

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