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## The Connections Between Androgens and Adipose Tissue Function in Polycystic Ovary Syndrome Patients

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### Abstract

Few studies reported that androgens levels could be among the regulators of adipose tissue hormones. Polycystic ovary syndrome (PCOS) is characterized by both increased adiposity and hyperandrogenism, but the relationship between androgens levels and adipokines in PCOS has not been well characterized. Our aim was to study the relationship between leptin, adiponectin, total testosterone, sex hormone binding globulin (SHBG) and free androgen index (FAI) in PCOS patients. We conducted a cross-sectional study on 131 PCOS patients (mean age 24 [6] yrs, mean body mass index (BMI) 25.8 [10.44] kg/m<sup>2</sup>) diagnosed based on Rotterdam Consensus criteria. All the patients were evaluated by clinical, paraclinical and hormonal exam. HOMA-IR was calculated for all the patients. Leptin was positively associated with age ( $p < 0.05$ ), BMI ( $p < 0.0001$ ), waist-hip ratio (WHR) ( $p < 0.0001$ ), waist circumference (WC) ( $p < 0.0001$ ), HOMA-IR ( $p < 0.0001$ ), insulinemia ( $p < 0.0001$ ) and FAI ( $p < 0.0001$ ) and negatively with SHBG ( $p < 0.0001$ ). Adiponectin was negatively associated with age ( $p < 0.05$ ), BMI ( $p < 0.0001$ ), WC ( $p < 0.0001$ ), WHR ( $p < 0.0001$ ), HOMA-IR ( $p < 0.0001$ ), insulinemia ( $p < 0.0001$ ) and FAI ( $p < 0.005$ ) and positively associated with SHBG ( $p < 0.0001$ ). Both adipokines were not correlated with total testosterone. The association between serum leptin and FAI/SHBG was lost after adjustment for age and body mass index.

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In turn the relationship between leptin and FAI, but not SHBG was independent of HOMA-IR. Circulating adiponectin was associated with SHBG independently of adiposity and HOMA-IR, but the association with FAI was lost after adjustment for HOMA-IR. In conclusion, circulating adipokines are correlated with FAI and SHBG serum levels. This association seems to be mediated by adiposity for leptin. Although the link between adiponectin and FAI is probably due to insulin resistance, SHBG seems to directly modulate adiponectin production.

**Keywords:** polycystic ovary syndrome; adiponectin; leptin.

## **1. Introduction**

Adipokines are proteic products of the adipose tissue with complex actions on the glucose and fat metabolism, energy balance, inflammatory response and reproductive function [1, 2]. Among the adipokines, leptin and adiponectin are the most extensively studied and their circulating levels were associated with the risk of diabetes melitus, ischemic stroke and myocardial infarction. Therefore it is believed that adipokines are potential mediators of the cardiometabolic complications associated with obesity. Regulators of adipose tissue hormones production remain incompletely understood, although few studies addressed this aspect and identified some possible modulators of adipocytes function, among them being sex hormones [3, 4]. A recent study in midlife women reported an inverse association between total testosterone level and circulating adiponectin independent of adiposity suggesting an independent effect of androgens on adiponectin production [5].

Polycystic ovary syndrome (PCOS) is the most frequent endocrinopathy of reproductive age women, affecting 5-10 % of them and being characterized by hyperandrogenism and chronic oligoovulation. PCOS is not only a reproductive disorder, but also a disease which carries an increased risk for metabolic complications due to the insulin resistance found in most of these patients. Although insulin resistance is an intrinsic characteristic of the disease, the metabolic and reproductive phenotype could be aggravated by the presence of obesity especially with central distribution, frequently found in these patients. Moreover PCOS patients seem to present also a dysfunction of the adipose tissue independently of adiposity distribution [6] the determinants of this dysfunction are not yet clarified. Although the androgens were previously suggested as possible regulators of adiposity function and hyperandrogenism is a central feature of PCOS, the relationship between circulating androgens and adipose tissue function was not well characterized in PCOS patients. Both adiponectin and leptin serum levels were demonstrated to accurately reflect the production in adipose tissue in PCOS patients, being an adequate marker of adiposity function [7]. Therefore the aim of our study was to analyze the relationship between leptin, adiponectin and serum androgens levels in PCOS patients.

## **2. Materials and Methods**

We performed a cross-sectional study which included 131 PCOS patients admitted in a tertiary care department between January 2007 and September 2011. All the patients gave the written informed consent before evaluation. The study was approved by the local Ethic Committee. Inclusion criteria were: no significant associated health condition, age between 18 and 40 yr. Exclusion criteria were: pregnancy in the last three months, lactating

women, current or recent treatment (in the last three months) with insulin sensitizing or combined oral contraceptives, postmenopausal status. PCOS diagnosis was based on the Rotterdam Consensus criteria [8] (the presence of two out of the following): oligo- or anovulation, clinical and/or biochemical hyperandrogenism and polycystic ovary appearance on transvaginal ultrasound, after exclusion of androgen producing tumours, 21-hydroxylase deficiency, hypercorticism, thyroid dysfunction, hypogonadism and hyperprolactinemia.

All the patients included in the study underwent a complete physical examination including weight, height, waist (WC) and hip circumferences (HC) measurements, determined to the nearest 0.1 kg and 0.1 cm, respectively. BMI was calculated by dividing the weight to the height squared (Kg/m<sup>2</sup>). Waist-hip ratio (WHR) was obtained as WC divided by HC. Clinical hyperandrogenism, chronic ovulatory dysfunction were evaluated as previously described [9].

Blood samples were obtained at baseline and 2 hours after a standard oral glucose tolerance test (OGTT) in days 3-5 of a spontaneous or progesterone-induced menstrual cycle, between 08:00 AM and 10:00 AM after a 12-h overnight fast. A pelvic ultrasonography was performed in the same day by an experienced operator in order to evaluate ovarian morphology.

Total testosterone (TT), sex hormone binding globulin (SHBG), thyroid stimulating hormone (TSH), luteinizing hormone (LH), follicle stimulating hormone (FSH), estradiol, prolactin, adiponectin, leptin, glucose, insulin were measured from baseline serum samples in all subjects. Measurements of glucose and insulin fasting and 2h during oral glucose tolerance test (OGTT) were also performed in all patients not previously diagnosed with diabetes mellitus. Morning serum 17-hydroxiprogesterone and cortisol after an overnight suppression test were evaluated only in selected patients with a high clinical suspicion index.

For the measurement of TT, SHBG, TSH, LH, FSH, estradiol, prolactin, cortisol, insulin, 17-hydroxiprogesterone a chemiluminescent immunometric assay (Immulite 2000, Siemens Healthcare Diagnostics Products Ltd.) was used. Serum adiponectin and leptin levels were measured with an ELISA kit (DRG Instruments, Germany).

The homeostasis model assessment of insulin resistance (HOMA-IR) and free androgen index (FAI) were calculated as already described [9]. Biochemical hyperandrogenism was defined as an elevation of total testosterone  $\geq 0.73$  ng/mL and / or of FAI  $\geq 4.5$  [9].

Statistical analysis was performed using SPSS version 20.0 (SPSS Inc., Chicago, IL, USA). Data are expressed as median and interquartile range. Variables non-normally distributed were logtransformed before submission to multiple regression analysis. In all performed statistical procedures, *P* values  $< 0.05$  were considered statistically significant.

### **3. Results**

A total number of 131 PCOS patients were included in the study with a median age of 24 years and median BMI of 25.8 kg/m<sup>2</sup> (table 1).

Table 1. Clinical and paraclinical parameters of the study group

Parameter	Median [interquartile range]
Age (yrs)	24 [6]
BMI (kg/m <sup>2</sup> )	25.8 [10.44]
WHR	0.82 [0.11]
WC (cm)	82 [25.31]
HOMA-IR	2.42 [2.98]
Fasting insulin (μUI/mL)	11.45 [14.2]
2h insulin (μUI/mL)	61.2 [76.45]
Total testosterone (ng/ml)	0.75 [0.45]
SHBG (nmol/L)	36.6 [31.1]
FAI	6.91 [8.17]
Adiponectin (mg/L)	8.81 [6.38]
Leptin (ng/ml)	20 [25.9]

Table 2. Correlation between serum adiponectin levels and clinical and paraclinical parameters (Spearman analysis was applied. r: correlation coefficient between serum adiponectin and variate parameters found in the first column; NS: not-significant).

Parameter	r	p
Age (yrs)	-0.191	0.029
BMI (kg/m <sup>2</sup> )	-0.526	<0.0001
WHR	-0.551	<0.0001
WC (cm)	-0.566	<0.0001
HOMA-IR	-0.452	<0.0001
Fasting insulin (μUI/mL)	-0.451	<0.0001
2h insulin (μUI/mL)	-0.321	<0.0001
Total testosterone (ng/ml)	0.040	NS
SHBG (nmol/L)	0.363	<0.0001
FAI	-0.285	0.002
leptin(ng/ml)	-0.329	<0.0001

Using Spearman correlation test we found that serum adiponectin level was significantly and negatively correlated with age, anthropometrical indices of adiposity (BMI, WC and WHR), fasting and 2h insulinemia, HOMA-IR index and FAI and positively with SHBG (table 2). Serum leptin level was positively correlated with age, BMI, WC, WHR, HOMA-IR, fasting and 2h insulinemia, FAI and negatively with SHBG (table 3). We also found a negativ correlation between serum levels of leptin and adiponectin (table 3). On the other hand

neither circulating leptin or adiponectin were correlated with total testosterone (table 2 and table 3). From the clinical and biochemical parameters analyzed, serum leptin level was strongest correlated with BMI ( $r = -0.779$ ,  $p < 0.0001$ ) and serum adiponectin level was strongest correlated with WC ( $r = -0.566$ ,  $p < 0.0001$ ).

Table 3. Correlation between serum leptin levels and clinical and paraclinical parameters (Spearman analysis was applied. r: correlation coefficient between serum leptin and variate parameters found in the first column; NS: not-significant).

Parameter	r	p
Age (yrs)	0.218	0.014
BMI ( $\text{kg}/\text{m}^2$ )	0.779	<0.0001
WHR	0.461	<0.0001
WC (cm)	0.736	<0.0001
HOMA-IR	0.658	<0.0001
Fasting insulin ( $\mu\text{UI}/\text{mL}$ )	0.618	<0.0001
2h insulin ( $\mu\text{UI}/\text{mL}$ )	0.524	<0.0001
Total testosterone (ng/ml)	0.161	NS
SHBG (nmol/L)	0.400	<0.0001
FAI	-0.391	<0.0001
Adiponectin (mg/L)	-0.329	<0.0001

Standard multivariate linear regression analysis showed that, after adjustment for BMI and age, FAI and SHBG were no longer significantly associated with serum leptin levels. In these models BMI was the only independent predictor of serum leptin level ( $\beta = 0.699$ ,  $p < 0.0001$  in the model including FAI;  $\beta = 0.700$ ,  $p < 0.0001$  in the model with SHBG). In two models of multiple linear regression including leptin as dependent variable and age, HOMA-IR and FAI or SHBG as independent variables, age ( $\beta = 0.183$ ,  $p = 0.019$  in the model with FAI,  $\beta = 0.181$ ,  $p = 0.023$  in the model with SHBG), HOMA-IR ( $\beta = 0.522$ ,  $p < 0.0001$  in the model with FAI,  $\beta = 0.561$ ,  $p < 0.0001$  in the model with SHBG) and FAI ( $\beta = 0.187$ ,  $p = 0.023$ , but not SHBG) were independent predictors of serum leptin.

Serum adiponectin were independently associated with both FAI ( $\beta = -0.206$ ,  $p = 0.026$ ) and SHBG ( $\beta = 0.260$ ,  $p = 0.006$ ) after adjustment for age and WHR. In these models WHR was the strongest independent predictor of circulating adiponectin ( $\beta = -0.423$ ,  $p < 0.0001$  in the model with FAI,  $\beta = -0.393$ ,  $p < 0.0001$  in the model with SHBG), but age was no longer independently associated with adiponectin after adjustment for confounders. On the other hand, analyzing the influence of FAI / SHBG on adiponectin serum level taking into account the insulin resistance we observed that age ( $\beta = -0.195$ ,  $p < 0.032$  in the model with FAI,  $\beta = -0.215$ ,  $p < 0.016$  in the model with SHBG), HOMA-IR ( $\beta = -0.356$ ,  $p < 0.001$  in the model with FAI,  $\beta = -0.321$ ,  $p < 0.001$  in the model with SHBG) and SHBG ( $\beta = 0.250$ ,  $p < 0.01$ ) were independently associated

with circulating adiponectin. Instead FAI was not significantly associated with adiponectin in this model containing HOMA-IR.

#### **4. Discussions**

Our study showed that in PCOS patients there is an association between the serum levels of adipokines (leptin and adiponectin) and androgenic status (reflected by circulating FAI and SHBG). Although our data suggest a link between both FAI and SHBG and adipose tissue function (reflected by circulating adipokines levels), it is difficult to demonstrate a causal relationship due to the cross-sectional design of our study. Moreover the data available from the literature support a bidirectional relationship, probably closing a vicious circle. Thus circulating adipokines are closely related to the adiposity quantity and increase in adiposity, in particular the abdominal type, is associated with insulin resistance and hyperinsulinemia which determine the suppression of hepatic SHBG production and increases the ovarian androgen synthesis through enhancement of LH-mediated steroidogenesis in the theca cells [10], providing a possible explanation for the association between adiposity function and FAI/SHBG. Thus a first hypothesis which would explain the association between circulating adipokines and FAI/SHBG is that the relationship is due to the capacity of adiposity to modulate androgens production and bioavailability. Therefore the two parameters are associated because both similarly reflect the adiposity quantity and function.

Conversely, androgens are generally viewed as able to significantly influence the adipocyte function and the distribution of body fat in women [11], favoring visceral adiposity [12]. However, most of the evidences come from the clinical studies showing a positive association between serum testosterone values and abdominal adiposity in patients with or without hyperandrogenism [13, 14]. Actually, the results of the clinical studies are heterogeneous, not all of them confirming this association. Even more confusing, experimental studies showed an inhibitory effect of the androgens on the differentiation of subcutaneous preadipocytes in mature adipocytes [15]. However in visceral adipose tissue testosterone exerts a proliferative effect on preadipocytes [16]. Therefore testosterone seems to increase visceral adiposity without a major influence on subcutaneous adiposity. Thus this capacity of testosterone to modulate adiposity distribution could be another explanation for the relationship between adipokines and androgenic status. However the possibility that androgens to influence the adipose tissue function without influencing the adiposity quantity should not be neglected as few studies demonstrated the capacity of androgens to modulate some aspects of adipose tissue function [17].

A third hypothesis for the mechanisms underlying the association between circulating adipokines and FAI is the capacity of adipokines to modulate the androgen production since the receptors of both leptin and adiponectin were identified in the ovary. However, experimental studies showed that leptin inhibited the androstendione production by internal theca cells and adiponectin had synergistic effect with insulin and IGF-I in theca cells [10]. These effects are opposite to the observed association in our study, suggesting that the direct action of adipokines on the ovary is not a pivotal mechanism.

In order to shed some light on the relationship between androgens and adipokines serum levels in our PCOS patients we analyzed the association taking into account adiposity and insulin resistance. Although in bivariate

analysis serum leptin levels were correlated with FAI and SHBG, after adjustment for BMI and age this relationship was no longer significant, suggesting that the association is rather due to the effect of adiposity on FAI and SHBG. However a modulator effect of androgens or SHBG on adipose tissue function could not be excluded since the receptors for both SHBG and androgens were found on adipocytes [18]. Moreover the testosterone administration was shown to influence adipokines production in hypogonadal men [19, 20], although similar data are not available for women.

The strong relationship between global adiposity reflected by BMI and leptin serum level suggested by the bivariate analysis was also supported by the fact that BMI was the only independent predictor of serum leptin level in multivariate regression model including also age and FAI/SHBG. This finding suggests that global adiposity is the most significant regulator of circulating leptin in our patients. Indeed this association is in accord with the physiological role of leptin to regulate the fat mass and body weight, therefore its production reflecting the fat stores of the body. This aspect is confirmed by the results of few experimental studies, most of them on normal ovulatory women, showing that leptin expression is increased in overweight and obese women predominantly by increased production in subcutaneous adipose tissue [21]. Subcutaneous adiposity is quantitatively the most important compartment of the total adipose tissue being best reflected by BMI, therefore explaining the close correlation between BMI and serum leptin.

Although the mechanism is not completely clarified, leptin seems to be associated with insulin resistance as showned by the data from the *ob/ob* mice and from the patients with human immunodeficiency virus infection and lipoatrophy secondary to antiretroviral therapy. On the other hand, the results of the clinical studies are heterogeneous, some [22], but not all studies confirming this association [23]. In our patients circulating leptin was significantly correlated with both HOMA-IR and insulinemia (fasting and 2h during oral glucose tolerance test). This association was independent of age and androgenic status. In turn, after adjustment for adiposity (BMI) the relationship between serum leptin and insulin resistance was no longer statistically significant (data not shown), suggesting that adiposity is an important mediator of this connection, probably by strongly influencing both parameters.

Insulin resistance is one of the factors contributing to hyperandrogenism in PCOS, therefore being a possible confounder when analyzing the relationship between leptin and androgens. However, the link between leptin and FAI seems to be independent of insulin resistance as showned in multiple regression analysis. On the other hand SHBG was not associated with leptin serum levels independently of insulin resistance, suggesting a stronger influence of insulin resistance on serum SHBG in comparison to FAI.

In our study group serum adiponectin level was negatively correlated with FAI and their relationship was independent of adiposity. Therefore, although the adiposity could influence both adiponectin and bioavailable testosterone, this is not entirely responsible for the association of the two parameters. Probably our results are due to the androgens capacity to influence the adipose tissue function reflected by adiponectin independently of adipose tissue quantity. Although the effect of androgens to modulate leptin production by the adipose tissue was reported in men, the same aspect in women was less addressed in previous studies. One experimental report suggested that the adiponectin secretion is not influenced by sex hormones [24], although the effect could

variate according to gender, adipocytes type and hormonal interactions [25]. However few studies evaluated this aspect and future research is necessary to clarify this aspect.

Adiponectin is strongly and negatively associated with insulin resistance in many previous studies, probably due to the insulin sensitzing effect of adiponectin, but also to the fact that the most insulin resistant adipocytes are those secreting less adiponectin [26]. Insulin resistance and the resulting hyperinsulinemia is also one of the main regulator of hyperandrogenism in PCOS. The relationship between insulin resistance and both adiponectin and FAI seems to be responsible for the observed link between adiponectin and hyperandrogenism in our study group.

On the other hand serum level of SHBG was associated with circulating adiponectin independent of age, adiposity and insulin resistance, suggesting a direct effect of SHBG on adipose tissue function in PCOS patients. Strong evidences regarding this aspect are lacking, but the SHBG receptors are present on the adipocytes and SHBG is an independent risk factor for metabolic syndrome and diabetes mellitus [27, 28], supporting our hypothesis.

However in these models WHR was the most significant independent predictor of circulating adiponectin level, demonstrating the major role of central adiposity in regulation of serum adiponectin level. Indeed in vitro studies suggest that adiponectin production is inversely proportional to visceral adiposity and may be determined primarily by adipocyte size and insulin sensitivity, with larger, insulin-resistant adipocytes producing less adiponectin [26].

Plasma levels of both adiponectin and leptin were previously showed to be correlated with age [26] and this was true in our patients as well. However the association was lost after adjustment for adiposity parameters, suggesting that probably increase in adiposity with age is the responsible mechanism.

Our study has limitations, one of them being the cross-sectional design which does not allow us to confirm a causal relationship between adipose tissue dysfunction and androgenic status in our patients. Another limitation is the lack of a complete profile of circulating androgens in the present study since they may have a different relationship with the adiposity.

## **5. Conclusions**

Our study showed that both adipokines were related to FAI and serum levels of SHBG, although the relationship seems to be differently modulated by adiposity and insulin resistance. Thus, the link between leptin and FAI/SHBG appears to be modulated by global adiposity. In turn the relationship between adiponectin and FAI are rather due to insulin resistance with a minor contribution of the central adiposity. However the link between adiponectin and SHBG seems to be independent of confounders like adiposity, insulin resistance and age. In order to gain further knowledge regarding the link between adiposity dysfunction and androgens in PCOS patients future interventional studies are necessary.



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