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Obesity and inflammatory biomarkers in women with polycystic ovary syndrome

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ABSTRACT

Objective: To evaluate the roles of obesity and inflammatory biomarkers associated with medical complications in women with PCOS.
Study design: Retrospective, BMI-matched study. A total of 330 patients, including 165 women with PCOS and 165 women without PCOS, were evaluated. The insulin resistance (homeostasis model assessment insulin resistance index – HOMA) and lipid profiles were assessed. The adiponectin, leptin, ghrelin, resistin, anti-müllerian hormone (AMH), sex hormone-binding globulin (SHBG), high sensitivity C-reactive protein (hs-CRP), and interleukin-6 (IL-6) levels were also measured.
Results: Women with PCOS had significantly higher AMH, fasting insulin, total cholesterol, and low-density lipoprotein levels and lower SHBG levels compared with the controls. There was no difference in the serum obesity and inflammatory biomarkers between the PCOS cases and the controls. After adjusting for BMI and age, IL-6 was positively correlated with HOMA, and SHBG was negatively correlated with HOMA, triglyceride, and LDL.
Conclusions: The serum adipokines levels are not good markers for PCOS. PCOS patients were characterized by their high AMH and low SHBG levels. A low level of SHBG should play an important role in the pathogenesis of the medical complications observed in women with PCOS.
Clinical trial registration number NCT01989039.

Introduction

Polycystic ovary syndrome (PCOS) is associated with an adverse cardiometabolic profile consisting of increased total or central adiposity, increased insulin resistance and abnormal glucose metabolism [1]. However, obesity [2] and inflammation [3] might be associated with the pathogenesis of medical complications in women with PCOS.

PCOS induces an increase in serum inflammatory cardiovascular risk markers [4]. Low-grade chronic inflammation in PCOS patients is indicated by the presence of elevated C-reactive protein (CRP) levels and inflammatory cytokines. CRP has been proven to be one of the strongest predictors of the risk of cardiovascular events in patients with or without cardiovascular disease [5]. Furthermore, PCOS is associated with higher anti-Müllerian hormone (AMH) [6] and lower sex hormone-binding globulin (SHBG) [7].

Obesity, characterized by adipocyte hypertrophy, was the major determinant factor for medical and cardiovascular complications among women with PCOS [2]. Adipose tissue can be considered a key endocrine organ because it releases multiple bioactive substances, known as adipose-derived secreted factors or adipokines, with pro-inflammatory or anti-inflammatory activities [8]. Products of adipocytes, such as leptin, adiponectin and resistin, and gut peptides, such as ghrelin, are considered crucial in the interactions between energy balance and reproduction [9]. All of these molecules may lead to local and generalized inflammation,

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mediating obesity-associated vascular disorders, including hypertension, diabetes, atherosclerosis, and insulin resistance [10]. Dysregulated production or secretion of these adipokines due to adipose tissue dysfunction can contribute to the pathogenesis of obesity-linked complications [8].

Both PCOS and obesity are reported to induce an increase in serum inflammatory cardiovascular risk markers. The precise mechanisms underlying these associations require additional studies to clarify the state of the cardiovascular system in women with PCOS to determine the relative contributions of different factors, including insulin resistance, androgen status and BMI [8]. To understand the insulin resistance and metabolic complications in women of reproductive age, adipokines and inflammatory markers should be treated as important predictors. Therefore, we conducted this study to evaluate the correlation of adipokines and inflammatory markers with insulin resistance in women with PCOS.

Materials and methods

This study was approved by the Institutional Review Board of Taipei Medical University – Wan Fang Hospital, Taipei, Taiwan and was registered at ClinicalTrials.gov with the identifier NCT01989039. We retrospectively reviewed the medical records of female patients who visited our Reproductive Endocrinology Clinic from January 1, 2009, to December 31, 2012.

The study population

Women who had a complete set of anthropometric measurements as well as clinical and biochemical data regarding insulin resistance parameters, inflammatory and obesity biomarkers were initially included in the study. The following data were collected and calculated: (1) obesity hormone levels: adiponectin, leptin, ghrelin, and resistin; (2) inflammatory markers: interleukin (IL)-6 and high-sensitivity C-reactive protein (hs-CRP); (3) anti-müllerian hormone (AMH); (4) serum androgen levels, including total testosterone, androstenedione, dehydroepiandrosterone sulfate (DHEA-S), and the free androgen index (FAI), which was calculated as follows: FAI = total testosterone (nmol/l) × 100/sex hormone binding globulin (SHBG) (nmol/l); (5) insulin sensitivity and glucose tolerance assessments, and (6) lipid profiles, including total cholesterol, triglyceride, high-density lipoprotein (HDL), and low-density lipoprotein (LDL) levels. The body mass index (BMI) was defined as the body weight in kilograms divided by the body height in meters squared (kg/m^2). The insulin sensitivity index was evaluated by the homeostasis model assessment insulin resistance index (HOMA) using the following formula:

$$\text{HOMA} = \frac{\text{fasting insulin}\ (\mu\text{U}/\mu\text{L}) \times \text{fasting glucose}\ (\text{mg/dL})}{405}$$

The cut-off value for normal insulin sensitivity in this study was HOMA < 2.14 which based on a previous study of the Chinese population [11].

The following subjects were excluded from the study populations: (1) women who had been diagnosed with malignant tumors, Asherman's syndrome, Mullerian agenesis, or chromosomal anomalies; (2) females younger than 14 or older than 45 years; (3) women who received hormones/drugs for major medical diseases within the previous three months; and (4) women with hyperprolactinemia and premature ovarian failure.

A total of 455 women were initially included for evaluation in the study (Table 1). To make a comparative control group, participants were separated into five subgroups according to their BMI (<20, between 20 and 25, between 25 and 30, between 30 and 35, BMI >35), and women with PCOS and non-PCOS were matched by the values of each BMI subgroup. Ninety cases of PCOS and 35 non-PCOS controls were excluded, and 165 cases of PCOS and 165 non-PCOS controls were finally included (Fig. 1).

Adiponectin, leptin and ghrelin were measured by RIA (LINCO Research, Inc. St. Charles, Missouri, MO, USA), and resistin was measured by enzyme immunoassay (R&D Systems, Inc. Minneapolis, MN, USA).

PCOS was diagnosed according to the Androgen Excess and PCOS Society criteria [12], which requires hyperandrogenism and ovarian dysfunction. Hyperandrogenism (HA) was defined as hirsutism and/or biochemical hyperandrogenaemia (BioHA). The definitions of oligo-anovulation, hyperandrogenism and polycystic ovaries have been described in detail previously [2].

Statistical analysis

The statistical analysis was performed using SPSS 13.0 for Windows (SPSS, Inc., Chicago, IL, USA). We evaluated the correlation between serum HOMA, total testosterone and inflammatory markers using Pearson's correlation coefficients with the two-tailed method (Table 1). Partial correlations adjusted by age and BMI in the above parameters were also performed. The data are represented as the means ± standard deviation in Tables 1 and 3. We used chi-square and Fisher's exact test to compare categorical variables and ANOVA to compare continuous variables in Tables 1 and 3. Differences

Table 1
Clinical and biomarkers in studied women classified by 5 subgroups of BMI.

	Total	BMI < 25	BMI 20–25	BMI 25–30	BMI 30–35	BMI >35	*p*-value
Case number	455	117	139	94	56	49	<0.001*
PCOS %	56% (255/455)	35% (41/117)	54% (75/139)	64% (60/94)	70% (39/56)	82% (40/49)	<0.001*
Insulin resistance %	52% (236/455)	21% (25/117)	42% (58/139)	65% (61/94)	88% (49/56)	88% (43/49)	
Age (y/o)	27.4 ± 6.5	26.5 ± 6.3	27.3 ± 6.4	27.4 ± 6.5	29.1 ± 6.8	27.6 ± 6.6	0.151
BMI (kg/m^2)	25.3 ± 6.5	18.6 ± 0.9	22.1 ± 1.4	27.3 ± 1.4	32.2 ± 1.2	38.5 ± 3.2	<0.001*
HOMA[a]	3.47 ± 3.71	1.79 ± 2.32	2.08 ± 1.22	4.01 ± 3.80	6.20 ± 3.94	7.27 ± 5.52	<0.001*
SHBG (ng/dL)	42.2 ± 29.6	65.6 ± 33.0	46.7 ± 27.2	30.2 ± 17.2	21.4 ± 8.5	20.5 ± 14.3	<0.001*
hs-CRP (mg/L)	0.25 ± 0.38	0.12 ± 0.38	0.14 ± 0.24	0.24 ± 0.29	0.42 ± 0.34	0.67 ± 0.54	<0.001*
IL-6 (pg/mL)	2.63 ± 4.15	2.35 ± 3.97	2.21 ± 3.26	2.65 ± 3.88	2.47 ± 3.60	4.57 ± 6.77	<0.001*
Adipose tissue components							
Resistin (ng/mL)	10.32 ± 10.46	10.99 ± 9.23	10.41 ± 13.49	10.65 ± 8.18	10.13 ± 10.75	8.06 ± 6.17	0.557
Ghrelin (ng/mL)	598.2 ± 693.3	634.9 ± 568.4	726.6 ± 1091.1	523.1 ± 237.6	455.1 ± 227.7	451.2 ± 241.4	0.029*
Adiponectin (ng/mL)	9181 ± 6090	13,403 ± 6911	9618 ± 6274	7253 ± 3915	5590 ± 2470	5661 ± 2554	<0.001*
Leptin (ng/mL)	15.13 ± 11.99	6.96 ± 4.77	10.41 ± 5.16	18.18 ± 8.60	24.31 ± 11.80	31.70 ± 17.37	<0.001*

Note: Data are either mean ± SD or are percentage; *$p < 0.05$.

[a] Insulin resistance (HOMA > 2.14); The homeostasis model assessment insulin resistance index (HOMA), interleukin (IL)-6, high sensitivity C-reactive protein (hs-CRP), sex hormone-binding globulin (SHBG).