Study on Chronic Low-Grade Inflammation and Influential Factors of Polycystic Ovary Syndrome

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Key Words

Polycystic ovarian syndrome · Inflammation, low-grade chronic · Insulin resistance · Triglycerides

Abstract

Objective: To determine whether or not there is an increased level of serum C-reactive protein (CRP), of peripheral white cell count and of associated factors in Chinese patients with polycystic ovary syndrome (PCOS). **Subjects and Methods:** Seventy-four patients with PCOS were recruited for the study. The control group consisted of 51 normal healthy women of a similar age and body mass index (BMI). The basic physical parameters, white cell count, CRP, sex hormone and fasting insulin were measured. The glycolipid metabolic index and the insulin sensitivity index were calculated. **Results:** The serum CRP level (2.13 vs. 0.86 mg/l, $p < 0.001$) and total leukocyte count (7.50 ± 1.83 vs. $6.55 \pm 1.66 \times 10^9$ /l, $p < 0.01$) were significantly higher in PCOS patients than in normal healthy women. Even PCOS patients with normal BMI had an increase in CRP and leukocyte count. The serum CRP level of PCOS patients was positively correlated with BMI ($R = 0.57$, $p < 0.001$) and triglycerides ($R = 0.47$, $p < 0.001$) and negatively correlated with the insulin sensitivity index ($R = -0.60$, $p < 0.001$). **Conclusion:** The data showed that chronic nonspecific inflammation exists among Chinese patients with PCOS and that this kind of inflammation was related to insulin resistance, BMI, and triglycerides.

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Introduction

Polycystic ovary syndrome (PCOS) can cause infertility in reproductive-aged women. It is usually complicated by the manifestation of metabolic disorders such as central obesity, insulin resistance (IR), and abnormal blood fat [1]. Recently, it has been shown that PCOS can cause a systemic chronic low-grade inflammation mainly marked by a mild increase in C-reactive protein (CRP) [2]. There is a disagreement about the connection between neuroendocrine dysfunction, especially hyperandrogenism of PCOS patients, and chronic nonspecific inflammation [3, 4] based on studies done with Caucasians with PCOS. It has also been shown that there is an ethnic difference in the correlation between androgen and insulin levels [5], glycolipid metabolism [6], and body fat distribution. Li et al. [7] showed that the prevalence of hyperandrogenism, obesity, and IR was lower in Chinese women with PCOS than in women from other ethnic groups. Therefore, it is necessary to find out whether or not chronic low-grade inflammation exists among Chinese patients with PCOS and its influential factors.

Miller et al. [8] reported that chronic low-grade inflammation played an important role during the onset and progression of diabetes and cardiovascular disease. The serum inflammatory factor level can reflect the incidence of these diseases. Blood CRP <1 , 1 – 3 , and >3 mg/l represent a low, middle, and high risk of cardiovascular disease in the future, respectively.

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The purpose of this study is (1) to discuss whether or not chronic low-grade inflammation exists among Chinese PCOS patients mainly based on the analysis of CRP and peripheral white cell count and (2) to study the correlation between CRP and BMI, central obesity anthropometrical index, testosterone, glycolipid metabolic index, insulin sensitivity index, etc., and determine the factors related to chronic low-grade inflammation of Chinese PCOS patients. This study for the first time evaluated the chronic low-grade inflammation of PCOS patients on the Chinese mainland to provide an experimental foundation for the clinical treatment of PCOS patients and the prevention of long-term complications. The aim of this study was to examine the difference of CRP and peripheral white cell count in women with and without PCOS.

Subjects and Methods

Subjects

All PCOS patients attending the Department of Gynecologic Endocrinology, Beijing Obstetrics and Gynecology Hospital, Capital Medical University from July to December 2005 were asked to participate. According to the Rotterdam criteria [9], the diagnosis of PCOS was based on the association of at least two of the three following criteria: (1) oligoovulation or anovulation, (2) clinical or biochemical signs of hyperandrogenism, and (3) polycystic ovaries. Congenital adrenal hyperplasia, androgen-secreting tumors, Cushing's syndrome, thyroid disease and prolactinoma were excluded. The controls were simultaneously recruited from patients seen for an annual exam during the same period. All controls had regular menstrual cycles (at least 12/year) and no history of hirsutism or infertility. The exclusion criteria were women taking drugs such as metformin and oral contraceptives in the 3 months before selection, severe disease of important organs such as heart, liver, lung, kidney, spleen and the hematological system, acute/chronic infectious diseases, trauma, or a history of surgery 1 month before selection; women known to have cardiovascular diseases and/or diabetes; women with blood pressure >130/85 mm Hg or hypertension on maintenance medication, severe or multiple thrombosis risk factors, prodrome, or relevant histories, thyroid dysfunction and nicotine and alcohol addiction. All patients gave informed consent before their inclusion in the study. The study was approved by the Human Ethics Committee of the Beijing Obstetrics and Gynecology Hospital, Capital Medical University. A total of 74 PCOS patients and 51 controls were recruited. The control group was similar in age and BMI to the PCOS group.

Design

Basic Physical Parameters and Blood Index

On the day of the study, subjects reported in the morning in a fasting state to the Department of Endocrinology for Gynecology. Body weight and height were measured to the nearest 0.1 kg with the patient wearing light clothes and no shoes. The BMI was cal-

culated as kilograms per square meter. Waist circumferences (WC) and hip circumferences (HC) were measured in duplicate at the level of the umbilicus (waist) and greater trochanter (hip). Mean systolic and diastolic blood pressure was assessed with two readings after 5 min of rest sitting down. Ultrasound tests were performed on all the PCOS patients and controls.

The following blood indices of the PCOS patients and the controls group were measured: TSH, prolactin, progesterone, total testosterone, luteinizing hormone (LH), and follicle-stimulating hormone (FSH), estradiol (E_2), insulin (immunochemiluminescent method, reagents produced by Bayer, Germany), total cholesterol, triglycerides, HDL cholesterol (immunochemistry colorimetry method, reagents produced by Beijing Laibang Company, China), low-density cholesterol, apolipoprotein A1, apolipoprotein B (immunoturbidimetry method, reagents produced by Beijing Laibang Company, China) and CRP (latex agglutination turbidimetry method, reagents produced by Deling Company, China). Oral glucose intolerance was performed in all subjects with a fasting glucose level followed by a 2-hour glucose level (glucose oxidase oxygen electrode method, reagents produced by Shanghai Fenghui Medical Science and Technology Company, China) obtained after a 75-gram glucose load. White cell count in end-capillary blood, namely finger blood, was determined with the blood analyzer. All subjects had regular diets on the 3 days before drawing blood. Blood samples were taken from those with regular menses ($n = 54$) during the 3rd to 5th day of the menstrual cycle and from those with irregular menses ($n = 71$) after a transvaginal ultrasound that revealed no follicles of a diameter >10 mm.

The homeostatic model assessment-insulin resistance (HOMA-IR) was used as a surrogate measure of insulin sensitivity, calculated as: fasting insulin (mU/l) $\times$ fasting glucose (mmol/l)/22.5 [10].

Statistical Analysis

The SPSS 12.0 (SPSS Institute, Chicago, Ill., USA) statistical software for data management and analysis was used. First, we performed a normality test of data. Data in normal distribution were presented as means $\pm$ SD, while the nonnormal distribution was described with the median. Wilcoxon rank-sum test was used to evaluate differences between PCOS and control groups. The χ^2 test was performed for categorical variables. The natural logarithm was used to linearize the insulin sensitivity index and CRP of the group before statistical analysis. The correlation between CRP of the PCOS group and BMI, central obesity anthropometric index, testosterone, glycolipid metabolic index, insulin sensitivity index, FSH and LH indices was analyzed through multiple regression. In all analyses, a two-tailed α level of 0.05 was used.

Results

Physical and blood indices were measured in all the subjects. Baseline characteristics are shown in table 1. There were no differences between subjects with and without PCOS for age and BMI; however, WC and WC/HC ratio were significantly higher in the PCOS group than in the control group ($p < 0.01$ and $p < 0.05$, respec-

Table 1. Comparison of body measurement indices, blood fat, blood glucose, insulin sensitivity index and inflammation markers in the PCOS group and the control group

	PCOS group (n = 74)	Control group (n = 51)	p
Age, years	28 ± 4	29 ± 4	0.115
BMI	26.49 ± 4.83	25.33 ± 3.65	0.130
Waist circumference, cm	86.6 ± 11.3	79.9 ± 9.4	<0.01
Waist-hip ratio	0.92 ± 0.50	0.90 ± 0.05	<0.05
Waist circumference/ body height	0.54 ± 0.07	0.50 ± 0.06	<0.001
Testosterone, ng/dl	70.95 ± 23.29	38.95 ± 10.69	<0.001
LH, mIU/ml	10.09 ± 5.10	4.07 ± 4.34	<0.001
FSH, mIU/ml	5.13 ± 1.58	4.74 ± 1.51	0.174
Total cholesterol, mmol/l	4.80 ± 1.01	4.87 ± 1.18	0.716
Triglycerides, mmol/l	1.36 ± 0.84	1.00 ± 0.58	<0.05
HDL, mmol/l	1.25 ± 0.37	1.45 ± 0.35	<0.05
LDL, mmol/l	3.00 ± 0.93	2.99 ± 1.11	0.982
Apolipoprotein A1, g/l	0.98 ± 0.27	1.29 ± 0.40	<0.001
Apolipoprotein B, g/l	0.86 ± 0.23	0.89 ± 0.25	0.449
Fasting insulin, mU/l	20.44 ± 6.83	11.85 ± 4.46	<0.001
Fasting glucose, mmol/l	5.35 ± 0.60	5.18 ± 0.49	0.103
2-hour glucose, mmol/l	6.99 ± 2.09	6.03 ± 2.14	<0.05
HOMA-IR	4.67	2.51	<0.001
CRP, mg/l	2.13	0.86	<0.001
White cell count, × 10 ⁹ /l	7.50 ± 1.83	6.55 ± 1.66	<0.01

Table 2. Percentage of the PCOS group and the control group in the different CRP ranges

CRP, mg/l	PCOS (n = 74)	Control (n = 51)
<1	40.8% (29)	68.7% (35)*
1–3	32.5% (23)	27% (14)*
>3	27% (19)	4.3% (2)*

* p < 0.05.

tively). The following blood indices were higher in the PCOS than the control group: testosterone, LH (p < 0.001), triglycerides (p < 0.05), fasting insulin (p < 0.001), HOMA-IR (p < 0.001) and 2-hour glucose after a 75-gram glucose load (p < 0.05). However, the high-density lipoprotein (p < 0.05) and apolipoprotein A1 (p < 0.001) were lower in the PCOS group than in the control group. There was no statistical difference between the PCOS and the control group in FSH, LDL and apolipoprotein B. The inflammation marker CRP (p < 0.001) and total leuko-

cyte count (p < 0.01) were significantly higher in the PCOS group.

The percentage of cases with CRP 1–3 mg/l and CRP >3 mg/l was higher in the PCOS group than in the control group (table 2). Twenty-seven percent (19/74) of PCOS patients had CRP >3 mg/l. BMI, triglycerides, and insulin sensitivity index were the determinants of the CRP increase in PCOS patients. The CRP were positively correlated with BMI (r = 0.57, p < 0.001) and triglycerides (r = 0.47, p < 0.001). The insulin sensitivity index was highly and negatively correlated with CRP (r = -0.60, p < 0.001). Total R² of BMI, insulin sensitivity index, triglycerides = 0.437. Standard coefficients of insulin sensitivity index, BMI, and triglycerides were -0.310, 0.268 and 0.208, respectively. The above three indices accounted for 43.7% of the cause of CRP increase in the following order: insulin sensitivity index > BMI > triglycerides. Indices such as WC, WC/HC, and WC/body height for central obesity evaluation were not determining factors of the CRP increase in PCOS patients. Fasting insulin, blood glucose, total cholesterol, high-density lipoprotein, low-density lipoprotein, apolipoprotein A1, and apolipoprotein B also had no direct relationship with CRP increase in this study.

Discussion

We have shown for the first time that chronic low-grade inflammation exists in Chinese PCOS patients from the Chinese mainland. The increase in low-grade chronic inflammation in women with PCOS is associated with IR, BMI and triglycerides rather than PCOS status per se. The 27.0% of PCOS patients with CRP >3 mg/l and a higher total leukocyte count than the controls indicate that the PCOS patients were at a high risk of cardiovascular diseases and diabetes.

This study also demonstrated that total testosterone and LH were higher in PCOS patients with neuroendocrine dysfunction than in the control group. Although there was no difference in BMI in the two groups, WC and waist-hip ratio were higher in the PCOS group than in the control group, indicating that PCOS patients are more prone to central obesity. Triglycerides increased significantly while high-density lipoprotein and apolipoprotein A protecting against cardiovascular diseases dropped in the PCOS group, indicating that PCOS patients are more prone to abnormal blood fat than healthy women of a similar age and BMI. The higher fasting insulin level, the higher 2-hour glucose after a 75-gram glu-

cose load and the higher HOMA-IR in the PCOS demonstrated that PCOS patients with abnormal glucose metabolism were more prone to IR than the control group. Therefore, abnormal glycolipid metabolism is a risk factor for cardiovascular diseases and diabetes in PCOS patients.

In this study, the insulin sensitivity index and BMI were two determining factors of serum CRP level in PCOS patients. CRP was positively correlated with BMI and negatively correlated with the insulin sensitivity index. This conclusion is similar to that of other studies [11, 12], indicating that chronic low-grade inflammation in PCOS patients is mainly caused by abnormal metabolism. Obesity, chronic low-grade inflammation, and IR are closely related to each other [13]. Higher BMI usually means higher total body fat content. Both lipocytes and macrophages in fatty tissue can secrete a proinflammatory factor. Excessive fatty tissue will lead to excessive secretion of proinflammatory factor, resulting in chronic low-grade inflammation, and promoting onset and progression of IR [14]. Triglycerides are another determining factor of the serum CRP level in PCOS patients; CRP increases with increasing triglyceride concentrations. It might be a factor distinguishing Chinese PCOS patients from Caucasians with chronic low-grade inflammation in PCOS. Ahmad et al. [15] reported that in a healthy population with normal BMI, triglycerides between 100 and 150 mg/dl (1.13–1.70 mmol/l) were positively correlated with CRP (>2.1 mg/l). On one hand, triglycerides can cause stress to the endoplasmic reticulum of fatty tissue to generate more inflammatory factor; on the other hand, triglycerides can also cause chronic inflammation of vascular endothelial cells. In human blood circulation, triglyceride-rich lipoproteins are chylomicron and very-low-density lipoprotein. Kawakami et al. [16] reported that very-low-density lipoprotein could activate blood vessel endothelium nuclear factor kappa B. Nuclear factor kappa B is the key nuclear factor for priming and regulating inflammation. We still need more basic and clinical research to prove the correlation between triglycerides and CRP in PCOS patients.

There is still a dispute over whether or not chronic low-grade inflammation is closely related to central obesity [2, 17, 18]. The study of Diamanti-Kandarakis et al. [2] on 25 young Greek women with PCOS and 25 controls of a similar age and body mass index demonstrated that the presence of increased serum levels of inflammation in young women with PCOS appeared to be interrelated with hyperandrogenemia in this insulin-resistant population. The study of Puder et al. [17] on 20 Swiss patients

with PCOS and 15 controls, matched for body mass index and age, showed that the increase in low-grade chronic inflammation in women with PCOS was primarily associated with increased central fat excess rather than the PCOS status per se. Our study found no correlation between CRP and WC, waist-hip ratio, and WC/body height of PCOS patients. The sample size or race might be the cause of these differences. Our study using linear regression to simultaneously analyze the linear correlation between a dependent variable and multiple independent variables demonstrated that only BMI, triglycerides, and insulin sensitivity index were related to CRP, indicating that the influence of WC on CRP was not significant compared with the three indices. It has been shown that waist-hip ratio, WC/body height, and especially WC were positively correlated with abdominal fat accumulation and can accurately reflect the level of central obesity [19]. Most PCOS patients have central obesity. Therefore, measuring WC alone may fail to accurately reflect the total fat in Chinese PCOS patients. At present, mainly western countries conduct CRP and central obesity studies on Caucasian women. Because fat is distributed in various parts of the body, ethnic differences may exist [20]; hence, more research data are needed on other ethnic groups including Chinese to establish the relationship between various body compositions and chronic low-grade inflammation in patients with PCOS.

Similar to Möhlig et al. [3], we did not find any correlation between serum total testosterone and CRP, BMI, or WC. Although hyperandrogenism is one feature of PCOS, only free testosterone can enter cells and tissue via blood to exert biological functions [21]. Free androgen index (FAI), called total testosterone/sex hormone-binding globulin, is also a common index for evaluating free testosterone. Diamanti-Kandarakis et al. [2] reported that FAI was highly correlated with serum CRP of PCOS patients, which was also found in healthy middle-aged women [22] and postmenopausal women very susceptible to cardiovascular disease [23].

BMI, triglycerides, and IR accounted for a CRP increase of only 43.7% in PCOS patients. There still remain influential factors of over 50% not listed in this study. Among these possible factors are IL-6, FAI, CRP, gonovariation [24], and exercise habits [25].

Limitations of this Study

In this study we did not measure the level of sex hormone, haptoglobin and body fat and could not evaluate the influence of body composition and free testosterone on chronic low-grade inflammation of PCOS patients.

Conclusion

The data showed that CRP, total leukocyte count and HOMA-IR were highly significant in PCOS patients compared to healthy control women. Therefore, chronic low-grade inflammation exists among Chinese PCOS patients. This kind of inflammation is related with IR, BMI, and triglycerides; PCOS patients are a high-risk group for cardiovascular diseases and diabetes. Further-

more, according to this study, CRP may be a better marker of inflammation in women with PCOS because its evaluation is simple and economical.

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