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ORIGINAL PAPER/GYNECOLOGY

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Running title: Increased serum Hcy concentration in patients with PCOS

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ABSTRACT

Objectives: An increase in homocysteine (Hcy) concentration is closely related to polycystic ovary syndrome (PCOS). This study aimed to further explore serum homocysteine concentration and its influencing factors in clinically young (≤ 35 years) patients with PCOS and hyperandrogenism.

Material and methods: An electrochemical immunoassay was used to investigate the changes in serum homocysteine and related indexes in clinically young patients with PCOS and hyperandrogenism, and the results were statistically analyzed.

Results: Serum homocysteine concentration in clinically young patients with PCOS and hyperandrogenism (n = 208) was found to be significantly higher than in the control group (n = 663) (15.21 ± 9.99 vs. 12.56 ± 7.20 μmol/L, p < 0.0001), and the total testosterone concentration (1.65 ± 0.68 ng/mL) was higher in the PCOS group

than in the control group (1.52 ± 0.58 ng/mL), p = 0.007. The receiver operating characteristic curve showed that the area under the curve of homocysteine in predicting PCOS was 0.606, and the 95% confidence interval (CI) was 0.563–0.650 (p < 0.001). The homocysteine concentrations of the two groups were graded, and it was found that the percentage of patients with homocysteine levels > 15 μmol/L was 26.92% in the PCOS group and 19.15% in the control group; the difference between the two groups was statistically significant (p = 0.0143). The serum homocysteine levels of the two groups were higher in obese patients than in non-obese patients (normal weight vs. overweight), and the difference in the control group was statistically significant.

Conclusions: Serum homocysteine concentration in clinically young patients with PCOS and hyperandrogenism is elevated, so hyperhomocysteinemia can be used as one of the potential indicators of PCOS. In the process of the diagnosis and treatment of patients with PCOS, serum homocysteine concentration and body weight should both be considered.

Key words: polycystic ovary syndrome; hyperandrogenemia; homocysteine; hyperhomocysteinemia

INTRODUCTION

As polycystic ovary syndrome (PCOS) not only affects the reproductive system but also involves multiple systems and the metabolism of multiple substances, the presence of hyperandrogenemia and insulin resistance in these patients is an important factor affecting adverse outcomes [1].

Hyperandrogenemia in patients with PCOS may cause disorders of adipocyte morphology and function, resulting in the increase of inflammatory factors, such as serum interleukin-6, tumor necrosis factor α, lymphocyte/monocyte ratio and C-reactive protein; it also interferes with the insulin signaling pathway and causes a decrease in insulin sensitivity [2, 3]. However, the metabolism of high density lipoprotein and low density lipoprotein in the serum of obese PCOS patients is disorder, and the status of insulin resistance is more serious [4].

Recent studies found that homocysteine (Hcy) concentration increased in patients with PCOS. However, the correlation between elevated Hcy and biochemical characteristics like obesity, insulin resistance, and androgen levels in these patients has not yet been clarified, and the reported results vary. Furthermore, although many

studies have focused on the relationship between insulin resistance and Hcy, the results have been contradictory. Some studies found that an increase in Hcy concentration in patients with PCOS was related to obesity, hyperandrogenemia, and insulin resistance and that insulin increased the concentration of Hcy by regulating the transcription of cystathionine β-synthase (a key enzyme in Hcy metabolism), down-regulating the activity of methylenetetrahydrofolate reductase, or affecting glomerular filtration [5]. Other studies found that elevated Hcy was not related to obesity, androgen levels, or insulin resistance [6, 7] and that reducing insulin concentration in patients with PCOS did not reduce blood Hcy concentration. When metformin was used to treat insulin resistance in patients with PCOS in another study, insulin concentration decreased, the levels of Hcy and dehydroepiandrosterone increased, and the levels of cortisol, norepinephrine, and dehydroepiandrosterone sulfate did not change significantly [8], suggesting that there is no correlation between Hcy metabolism and insulin.

There are currently some works on the relationship between hyperhomocysteinemia and PCOS, and this paper is a contribution to clarifying the diagnostics of this problem.

MATERIAL AND METHODS
Subjects

Patients seeking fertility treatment in the Obstetrics and Gynecology Clinic of Yuncheng Central Hospital between October 1, 2017, and June 1, 2020, were enrolled in the present study. The age of the patients ranged from 21 to 35 years.

Subject confirmation and grouping

Each patient's detailed menstrual history, reproductive history, family history, and medication history from the previous three months was gathered. Tests of thyroid function, fasting blood glucose, fasting insulin, follicle-stimulating hormone (FSH), luteinizing hormone, prolactin, estradiol, and total testosterone (TES) were undertaken, and routine blood tests and a gynecological examination were performed. A total of 871 subjects were enrolled, including 208 patients with PCOS. The ages of the patients with PCOS ranged from 21–34 years, with an average age of 26.87 ± 2.66 years. The patients in the control group were between 21 and 35 years old, with an average age of 27.26 ± 3.03 years. The difference in age between the two groups was

not statistically significant (p = 0.098). This study was approved by the ethics committee of the hospital.

Diagnostic criteria

The diagnosis of PCOS was based on the 2003 Rotterdam diagnostic criteria, and all patients had clinical manifestations of oligo-ovulation or anovulation and hyperandrogenemia or hyperandrogenism, with or without polycystic ovaries. Patients in the PCOS group who had diseases that may affect ovulation (such as premature ovarian failure, primary ovarian dysfunction, hypothyroidism, fasting blood glucose > 6.1 mmol/L, endometriosis, hyperprolactinemia, ovarian tumors, or adrenal androgen-secreting tumors) were excluded. The control group consisted of women who needed a pregnancy aid because of male factors as well as tubal factors. Also, this subset of patients needs to be excluded for ovarian disease or comorbid conditions that may affect ovulation (same PCOS group). None of the patients had been treated with vitamins or hormones in the previous three months. Heavy smokers were also excluded.

Hyperandrogenemia

The androgen detected in this study was TES, with a reference range of 0.31–1.66 nmol/L.

Clinical manifestations of hyperandrogenism

Hyperandrogenism-induced alopecia, clinical manifestations of hirsutism with a Ferriman–Gallwey score ≥ 6, or acne.

Oligo-ovulation or anovulation

Patients who menstruate less than eight times a year or have a menstrual cycle of more than 35 days are considered oligo-ovulation or anovulation.

Obesity

Body mass index (BMI) = weight/height^2, BMI ≥ 28 kg/m^2.

Insulin resistance index

Insulin resistance index (HOMA-IR) = fasting blood glucose (FPG, mmol/L) ×

fasting insulin (fins, mIU/L)/22.5. HOMA-IR > 2.69 was considered indicative of insulin resistance [9].

Instruments and equipment

Main instruments

Automatic electrochemiluminescence immunoassay system, Cobas e601 (Roche, Germany); automatic biochemical analyzer, Cobas c701 (Roche, Germany); cryo-refrigerator (Sanyo, Japan).

Test reagents

Homocysteine test kit, 20162404810 [Roche Diagnostics (Shanghai) Co., Ltd., Germany]; gonad series test kit (electrochemiluminescence method), 20152403515 [Roche Diagnostics (Shanghai) Co., Ltd., Germany].

Research methods

Specimen acquisition

Elbow venous blood was collected after 8 hours of fasting on the morning of the 2nd–5th day of menstruation. This blood was tested in the Laboratory Department and Nuclear Medicine Department.

Determination of Hcy concentration

An enzymatic assay was used to determine Hcy concentration. This assay used the principles of an enzyme cycle assay to evaluate the conversion products of synergistic substrates. Free Hcy and S-adenosylmethionine were catalyzed by S-methyltransferase to produce methionine and S-adenosylhomocysteine (SAH). Subsequently, the amount of SAH was evaluated by coupled enzyme reaction. The SAH was catalyzed by SAH hydrolase to form adenosine (ADO) and Hcy. The Hcy entered the next cycle, so the detection signal was amplified. The ADO was immediately hydrolyzed to inosine and ammonia, which was further catalyzed by glutamate dehydrogenase, and NADH was converted to NAD+. The concentration of Hcy could then be inferred from the amount of NADH.

Determination of TES

An electrochemiluminescence method was adopted to determine TES levels. This test used sheep high-affinity monoclonal antibodies, which can specifically recognize

testosterone. This allowed the testosterone in a sample to be released from the dibromoestradiol and compete with testosterone derivatives (ruthenium-labeled) to bind the biotinylated antibodies.

Statistical analysis

The data were analyzed using Prism 6.0 software. Data were expressed as mean ± standard deviation ($x \pm$ SD). The quantitative data of the two groups were compared using Student's t-test, while the count data of the two groups were compared using a χ^2 test. The receiver operating characteristic (ROC) curve was drawn, and the area under the curve (AUC) was calculated to evaluate the predictive value of Hcy in patients with PCOS and hyperandrogenism. $p < 0.05$ was considered statistically significant.

RESULTS

Comparison of clinical data between the PCOS group and control group

The clinical indexes of the two groups are shown in Table 1. A total of 871 patients who met the criteria were enrolled, of which 208 had been diagnosed with PCOS. TES concentration (1.65 ± 0.68 ng/mL) was higher in the PCOS group than in the control group (1.52 ± 0.58 ng/mL), and the difference between the two groups was statistically significant $p = 0.007$. Serum Hcy concentration in the PCOS group (15.21 ± 9.99 µmol/L) was also higher than in the control group (12.56 ± 7.20 µmol/L), and the difference was statistically significant ($p < 0.001$). There were no significant differences between the two groups in age, BMI, FSH, prolactin, thyroid-stimulating hormone, and HOMA-IR scores ($p > 0.05$).

The predictive value of Hcy in clinically young patients with PCOS and hyperandrogenism

As shown in Figure 1, the AUC of Hcy in predicting PCOS was 0.606, and the 95% CI was 0.563–0.650 ($p < 0.001$), suggesting that Hcy has a certain predictive value for clinically young patients with PCOS and hyperandrogenism.

The percentage of patients with different concentrations of serum Hcy

Grading the Hcy concentrations of the two groups revealed that the percentage of patients with Hcy levels > 15 µmol/L was 26.92% in the PCOS group and 19.15% in the control group. The difference between the two groups was statistically significant

(p = 0.0143), suggesting that the incidence of hyperhomocysteinemia is higher in patients with PCOS and hyperandrogenism (Tab. 2).

Comparison of serum Hcy between non-obese and obese patients

The serum Hcy levels of the two groups were higher in obese patients than in non-obese patients (normal weight vs. overweight), and the difference in the control group was statistically significant (Tab. 3).

DISCUSSION

Hyperandrogenism is the core pathological feature of PCOS and is mainly caused by excessive synthesis of the ovaries or adrenal glands. PCOS may cause a variety of issues [10, 11].

Hcy [12] has several biological functions and participates in the metabolism of essential amino acid methionine. In healthy bodies, the production and metabolism of Hcy is maintained in balance. There are three forms of Hcy in the blood: 70–80% of it binds to serum protein (mainly albumin), almost 20% of it is in the form of disulfide (-S-S-), and the remaining 2% of it is in the reduced form (-SH) of Hcy. In cells, Hcy is mainly in the reduced form under the influence of enzymes and reducing agents. In the present study, the total blood Hcy level was detected in the enrolled patients. According to the standards of the American Heart Association, hyperhomocysteinemia can be divided into the following grades: normal (5–15 µmol/L), slightly elevated (15–30 µmol/L), moderately elevated (31–100 µmol/L), and severely elevated (> 100 µmol/L) [13].

A recent study found that PCOS is closely related to hyperhomocysteinemia. In the present study, the percentage of patients with hyperhomocysteinemia was higher in the PCOS group than in the control group. A previous study revealed that the probability of cardiovascular disease increased significantly when serum Hcy concentration was greater than 10 µmol/L [5].

As PCOS is a disease involving multiple systems and requiring long-term management, special attention should be paid to the impact of abnormal metabolites in the body, among which the concentration of Hcy is an important indicator to be monitored.

The treatment of hyperhomocysteinemia mainly refers to the treatment of cardiovascular and cerebrovascular diseases, and there is no unified standard for it. In

addition to a healthy diet of vegetables, fruits, and meat, it is recommended to supplement 400–1000 μg of folate, 50–100 mg of vitamin B6, and 100–900 ug of vitamin B12 every day [14].

Obesity may also affect serum Hcy concentration. In previous studies, the blood Hcy levels of obese patients with PCOS have been found to be significantly higher than those of patients without PCOS, and Hcy concentration has been identified as being directly proportional to BMI and waist circumference [15, 16]. Obese patients have reduced insulin sensitivity, which may cause the body to release too many inflammatory factors and promote the occurrence of insulin resistance; this, in turn, may induce hyperhomocysteinemia [17, 18]. In some obese patients with PCOS, the ovulation and menstrual cycle returns to normal when they lose 5–10% of their body weight [19]. In the present study, the average weight of patients in both groups was overweight (normal BMI: 18–22 kg/m^2), and the mean serum Hcy concentration in both groups was greater than 10 μmol/L. Considering that Hcy concentration may be related to obesity, analysis was conducted that indicating it was related to the increase of diet and rich food after infertility. In the control group, the serum Hcy concentration in obese patients was significantly higher than in non-obese patients, while in the PCOS group, although the serum Hcy concentration in obese patients was higher than in non-obese patients, the difference was not statistically significant. This may be due to the fact that hyperandrogenism is one of the causes of PCOS, and there were fewer obese patients (n = 27) in the PCOS group; however, these results need to be further studied based on the clinical data of larger samples.

The present study found that the concentrations of serum TES and Hcy in the PCOS group were significantly higher than those in the control group, and the difference was statistically significant. There were no significant differences in age, BMI, and HOMA-IR scores. The ROC results revealed that Hcy can be used as a good predictor of PCOS with hyperandrogenism, and it can be suggested that hyperhomocysteinemia is associated with hyperandrogenism. Free testosterone in serum can indirectly reflect the activity of androgens, but due to its complex detection methods, the most commonly used clinical detection index at present is total testosterone [20].

Many factors in the body can affect Hcy metabolism. Genetic defects or deficiency of folate (vitamin B9) and vitamin B12 can lead to an increase of Hcy in the cells [16]. The C677T polymorphism of methylenetetrahydrofolate reductase in

the general population can also lead to a decrease of enzyme activity, which, in turn, leads to an increase of Hcy concentration [21]. There are also differences in the serum Hcy levels of patients with PCOS who have different dietary habits in different regions.

CONCLUSIONS

In the present study, some of the factors that may affect the concentration of Hcy, including body weight, insulin resistance, and nationality, were excluded, and it was considered that androgens may be involved in the metabolism of Hcy. A previous study also reported that the concentration of serum Hcy decreased with a decrease in testosterone [22, 23]. Therefore, it can be suggested that the abnormal metabolism of Hcy in patients with PCOS and hyperandrogenism may be partly caused by the hyperandrogenism. In future studies, an animal model of PCOS with hyperandrogenism should be established in order to preliminarily explore the effect of androgens in ovarian tissue on Hcy metabolism and its mechanism.

Conflict of interest
All authors declare no conflict of interest.

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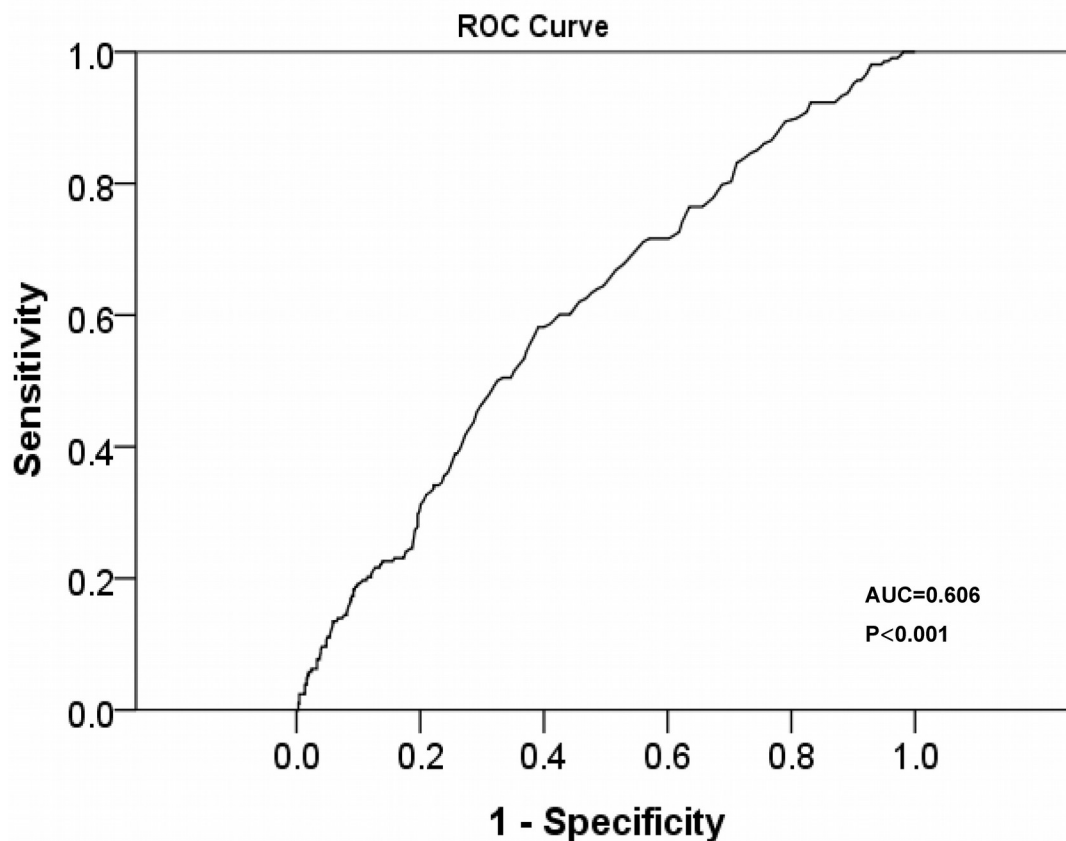
Figure 1. The receiver operating characteristic (ROC) for predictor Hcy changes in polycystic ovary syndrome with hyperandrogenism

Table 1. Comparison of clinical and BIOCHEMICAL data between the two groups

Characteristics	PCOS (n = 208)	Control (n = 663)	p-value
Age [year]	26.875 ± 2.658	27.262 ± 3.030	0.098
BMI [kg/m^2]	23.762 ± 3.613	23.208 ± 3.816	0.065
TES [nmol/L]	1.649 ± 0.676	1.519 ± 0.587	0.007
Hcy [μmol/L]	15.214 ± 9.993	12.563 ± 7.205	< 0.0001
FSH [IU/L]	6.164 ± 2.031	6.475 ± 3.515	0.225
FBG [mmol/L]	5.146 ± 0.452	5.072 ± 0.640	0.123
FINS [mIU/L]	10.21 ± 1.71	10.32 ± 1.63	0.431
HOMA-IR	2.33 ± 0.43	2.31 ± 0.42	0.621
TSH [uIU/mL]	2.648 ± 1.515	2.424 ± 1.673	0.085
PRL [μg/mL]	12.374 ± 7.470	13.453 ± 8.249	0.093
HHcy percentage	26.92	19.15	0.0143

PCOS — polycystic ovary syndrome; BMI — body mass index; TES — total testosterone; Hcy — homocysteine; FSH — follicle-stimulating hormone; HOMA-IR — insulin resistance index

Table 2. Analysis of percentage of serum Hcy in different concentrations of two roups

Groups/Grade (umol/L)	< 10	10–15	15–30 (Mild)	30–100 (Moderate)
Control (n, %)	284 (42.84)	252 (38.01)	105 (15.83)	22 (3.32)
PCOS (n, %)	60 (28.85)	91 (43.75)	41 (19.71)	16 (7.69)

PCOS — polycystic ovary syndrome

Table 3. Comparison of serum homocysteine concentration between obese and non-obese patients

Groups	BMI < 28 kg/m^2	BMI ≥ 28 kg/m^2	p-value
Control (n,%)	12.30 ± 6.794 (589, 88.83)	14.68 ± 9.68 (74, 11.17)	0.007
PCOS (n,%)	14.95 ± 14.93 (181, 87.01)	16.98 ± 11.55 (27, 12.99)	0.3268

BMI — body mass index; PCOS — polycystic ovary syndrome