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Original Article

Relationship of thyroid stimulating hormone with sex hormones in patients with polycystic ovary syndrome: a single-center, retrospective observational study

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Abstract: Objective: The purpose of this study is to study the relationship between thyroid stimulating hormone (TSH) and sex hormones in patients with polycystic ovary syndrome (PCOS). Methods: The study population comprised 2440 PCOS patients who were divided into three groups on the basis of TSH levels. TSH, free thyroid hormone (FT4), free thyroid hormone (FT3), follicle stimulating hormone (FSH), luteinizing hormone (LH), estradiol (E_2), progesterone (P), testosterone (T) and prolactin (PRL) were measured by electrochemiluminescence immunoassay. Moreover, the ratio of LH to FSH was also calculated. Furthermore, the relationship between TSH and sex hormones was performed by spearman rank correlation analysis. Results: No differences found among groups regarding to demographic parameters. The sex hormones, including FSH, LH, LH/FSH and P, had no obvious different in these three groups. The level of E_2 in group C was markedly decreased compared with group B ($P < 0.05$). The highest T and PRL levels were found in group C. A significant and positive relation was also observed between the TSH and T ($r = 0.317$, $P = 0.015$) and PRL ($r = 0.365$, $P = 0.007$) in PCOS patients. Conclusions: The levels of T and PRL were significantly increased when TSH ≥ 4.0 μIU/mL, and TSH was significantly and positively correlated with T and PRL in patients with PCOS.

Keywords: Sex hormones, thyroid stimulating hormone, polycystic ovary syndrome

Introduction

The polycystic ovary syndrome (PCOS) is recognized as one of the most common endocrine abnormalities of women with a prevalence ranging from 5% to 15% [1, 2]. Moreover, it has affected up to one in five reproductive-aged women and is associated with metabolic diseases, including type 2 diabetes mellitus, high incidence of obesity, insulin resistance and hyperlipidemia, cardiovascular diseases and psychological features [2, 3]. Emerging evidence suggests that long-term metabolic effects are linked to a low-grade chronic inflammatory state with the triad of hyperinsulinemia (HIR), hyperandrogenism (HA), and low-grade inflammation acting together in a vicious cycle in the pathophysiology of PCOS [4].

There is a relationship between thyroid function and insulin sensitivity and alterations in lipids and metabolic parameters [5]. Recent studies have also shown that thyroid function is associated with the occurrence of PCOS [6, 7]. Autoimmune thyroiditis (AIT) and subclinical hypothyroidism (SCH) are more prevalent among women with PCOS [8]. The presence of SCH is associated with endocrine and metabolic imbalances in PCOS patients, and the excessive body weight seems to promote this interplay [9]. Intriguingly, thyroid-stimulating hormone (TSH), total triiodothyronine (TT3) and total thyroxine (TT4) are significantly increased in PCOS patients and may be related with metabolic changes, including insulin resistance and high-density lipoprotein (HDL) and apolipoprotein A (ApoA) secretion [10]. A retrospective study indicates that non-obese women with insulin resistance PCOS has significantly higher serum TSH levels than non-obese women without insulin resistance PCOS [11].

Table 1. Demographic and clinical characteristics of PCOS women with different levels of TSH

Characteristics	Group A (n = 1589)	Group B (n = 627)	Group C (n = 224)	*P* for trend
Age (Years)	33.07 ± 2.05	32.53 ± 3.28	32.85 ± 5.48	0.381
BMI (kg/m^2)	23.41 ± 3.16	24.53 ± 4.22	22.94 ± 3.52	0.472
Systolic BP (mmHg)	118.8 ± 12.4	120.4 ± 10.7	125.2 ± 13.1	0.925
Diastolic BP (mmHg)	84.2 ± 10.2	83.5 ± 9.3	78.9.2 ± 8.7	0.733
FBG (mmol/L)	4.79 ± 1.02	5.05 ± 0.78	4.93 ± 0.94	0.705
HbA1c (%)	5.13 ± 0.58	5.35 ± 0.72	4.83 ± 0.81	0.637
Triglyceride (mmol/L)	1.25 ± 0.81	1.15 ± 0.68	1.21 ± 0.74	0.571
TC (mmol/L)	4.95 ± 0.95	4.67 ± 1.05	4.84 ± 0.98	0.617
TSH (μIU/mL)	1.08 ± 0.46	3.36 ± 0.67①	5.08 ± 0.86②	< 0.001
FT4 (pmol/L)	17.1 ± 2.58	16.2 ± 2.25	15.93 ± 2.96	0.373
FT3 (pmol/L)	4.76 ± 0.57	5.08 ± 0.49	5.15 ± 0.66	0.142

PCOS, polycystic ovary syndrome; TSH, thyroid stimulating hormone; BMI, body mass index; FBG, fasting blood glucose; TC, Total cholesterol; FT4, free thyroid hormone; FT3, free triiodothyronine. Values are expressed as mean ± SD. ①compared with group A, $P < 0.001$; ②compared with group B, $P < 0.001$.

PCOS affects reproduction by regulating various mechanisms, especially HA and increased luteinizing hormone (LH) [12]. Androgens, follicle stimulating hormone (FSH), anti-Müllerian hormone (AMH) and estradiol (E_2) are essential in human ovarian folliculogenesis [13]. During the pre-antral follicle growth, FSH is already active and promotes follicle growth in synergy with theca cell-derived androgens [13]. Androgen excess is a key feature of PCOS and results in, or contributes to, the clinical phenotype of these patients and will contribute to the ovulatory and menstrual dysfunction of these patients; the most recognizable sign of androgen excess includes hirsutism, acne, and androgenic alopecia or female pattern hair loss (FPHL) [14]. Another study shows that women with PCOS have an increased risk of preterm delivery compared with the background population. The increased risk is confined to HA women with PCOS [15]. While the study found that PCOS leading to HA be likely present in both adrenal and ovarian tissues [16]. These findings suggest that PCOS is closely related to sex hormones disorder. However, little information is available regarding this relationship between TSH and sex hormones in women with PCOS. Therefore, this study was done by analytical determination TSH, FT4, FT3, FSH, LH, E_2, P, T and PRL, and calculated the ratio of LH/FSH in 2440 patients with PCOS, to explore the relationship between TSH and various indexes of sex hormones in patients with PCOS.

Materials and methods

Participants

A total of 2440 participants were collected from 2010/01/01 to 2016/12/14 in Changzhou Hospital of Traditional Chinese Medicine of Jiangsu Province (Jiangsu, China). All subjects met the following requirements: (1) 2003 Rotterdam PCOS diagnostic criteria [17]; (2) 18~50 years old, and FSH < 40 IU/L; (3) Before the sex hormone test, all participants were not using any drugs 3 months ago (e.g. hormone drugs, contraceptives and so on); (4) The value of FT3 and FT4 were in the normal reference value in our hospital (FT3: 2.3~7.7 pmol/L, FT4: 12.2~28.0 pmol/L). 2003 Rotterdam PCOS diagnostic consensus [17]: (1) rare ovulation or no ovulation; (2) clinical and/or biochemical manifestation hyperandrogenism; (3) polycystic ovary (PCO): Each ovary contains at least 12 follicles with diameters ranging from 2 to 9 mm, and/or ovarian volume > 10 ml (Calculation of ovarian volume: 0.5 × ovarian length × ovarian width × ovarian thickness). This could be diagnosed as PCOS if the above 3 have 2. At the same time, it needs to exclude congenital adrenal hyperplasia, androgen secreting tumors, Cushing syndrome and other diseases. This study was approved by the ethics committee of Changzhou Hospital of Traditional Chinese Medicine of Jiangsu Province. The subjects fully understood the research contents and signed informed consent. The PCOS patients were divided into three groups according to the value of TSH: Group A (n = 1589) TSH < 2.5 μIU/mL; Group B (n = 627) 2.5 ≤ TSH < 4.0 μIU/mL; Group C (n = 224) TSH ≥ 4.0 μIU/mL.

Research methods

All patients who were in 2~5 day of the menstrual cycle and were examined FSH, LH, E_2, P, T, PRL with venous blood after sitting quietly 30 minutes in the early morning fasting state. We used electrochemical immunoassay instrument and reagent of Abbott Trading Company

Table 2. Comparison of sex hormones levels in the three groups of PCOS women

Index	Group A (n = 1589)	Group B (n = 627)	Group C (n = 224)	*P* for trend
FSH (mIU/mL)	6.207 ± 0.125	6.140 ± 0.177	5.858 ± 0.311	0.592
LH (mIU/mL)	7.444 ± 0.198	7.235 ± 0.255	7.262 ± 0.478	0.816
LH/FSH	1.344 ± 0.029	1.339 ± 0.051	1.345 ± 0.071	0.996
E_2 (pg/mL)	72.625 ± 2.034	75.332 ± 3.501	62.817 ± 4.132①	0.139
P (ng/mL)	0.276 ± 0.006	0.289 ± 0.011	0.284 ± 0.015	0.538
T (ng/mL)	0.418 ± 0.012	0.437 ± 0.012	0.561 ± 0.088②,③	0.002
PRL (ng/mL)	18.817 ± 0.394	20.695 ± 0.697⑥	24.758 ± 1.233④,⑤	0.000

①compared with group B, *P* = 0.048; ②compared with group B, *P* = 0.005; ③compared with group A, *P* = 0.000; ④compared with group B, *P* = 0.002; ⑤compared with group A, *P* < 0.001; ⑥compared with group A, *P* = 0.016. PCOS, polycystic ovary syndrome; FSH, follicle stimulating hormone; LH, luteinizing hormone; E_2, estradiol; P, progesterone; T, testosterone; PRL, prolactin. Values are expressed as mean ± SD.

Table 3. Correlation coefficients between sex hormones levels and TSH in PCOS women

Variables	r	*P*
FSH (mIU/mL)	-0.148	0.327
LH (mIU/mL)	0.092	0.539
LH/FSH	0.117	0.212
E_2 (pg/mL)	-0.203	0.148
P (ng/mL)	0.084	0.683
T (ng/mL)	0.317	0.015
PRL (ng/mL)	0.365	0.007

TSH, thyroid stimulating hormone; PCOS, polycystic ovary syndrome; FSH, follicle stimulating hormone; LH, luteinizing hormone; E_2, estradiol; P, progesterone; T, testosterone; PRL, prolactin. Values are expressed as mean ± SD.

Limited (Shanghai, China). Moreover, we determined and observed the results according to the specification. All patients were also examined TSH, FT3 and FT4 with venous blood in the early morning fasting state. We used Cobas 6000 electrochemical immunoassay instrument and reagent of Roche. And we also determined and observed the results according to the specification.

Statistical methods

Statistical analysis was performed by SPSS 21.0 software (SPSS Inc., Chicago, IL, USA). The measurement data were expressed by mean ± standard deviation (SD). We used the trend P test for comparing continuous variables. The variable of each group was tested for normality. The abnormal data were transformed in order to further analyze. Sample mean of each group was compared by single factor variance analysis. Pairwise comparison used LSD method. Spearman correlation coefficient was used to analyze the correlation between different indexes TSH. The difference was statistically significant when P < 0.05.

Results

The demographic and clinical characteristics of PCOS women were recapitulated as shown in **Table 1**. No differences were observed of age, BMI, Systolic BP, Diastolic BP, FBG, HbA1c, Triglyceride and TC in the three groups. The differences of TSH in the three groups were statistically significant (*P* < 0.001). However, no statistical differences were noted in FT3 and FT4 among the three groups.

The sex hormones levels in the three groups of PCOS women were shown in **Table 2**. The levels of FSH, LH, E_2, P and LH/FSH ratio had no obvious different among the three groups. However, our result demonstrated that E_2 was significantly decreased in group C as compared to Group B (*P* < 0.05). Intriguingly, our findings also found that the differences of T and PRL in the three group patients were statistically significant (*P* < 0.05). T and PRL in group C were higher than group B, and the differences were statistically significant (*P* < 0.05). PRL in group B was higher than group A, and the difference was statistically significant (*P* < 0.05). Subsequently, the correlation coefficients between the sex hormones and TSH were performed in the PCOS women. The results demonstrated that the correlations of TSH and sex hormones (including FSH, LH, E_2, P and LH/FSH ratio) had no statistical significance in the PCOS women (**Table 3**). Interestingly, the T (r = 0.317, *P* = 0.015) and PRL (r = 0.365, *P* < 0.007) were significantly and positively correlated with TSH in the PCOS women (**Table 3**).

Discussion

Our results indicate that PCOS patients with TSH ≥ 4.0 μIU/mL show an increase in T and PRL levels and have a decrease in E_2 levels.

More importantly, in correlation analysis between TSH and sex hormones in PCOS women, only T and PRL are proven to be significantly and positively correlated with TSH. These findings suggest that the increase of TSH may be a risk factor for the development and progression of PCOS in women.

PCOS women show a high prevalence of metabolic disturbances including insulin resistance, dyslipidemia, chronic low-grade inflammation and HA [18]. The characteristics of HA in women with PCOS include elevated total and free testosterone levels and low sex hormone-binding globulin (SHBG) levels [19]. Moreover, women with PCOS have significantly increased risk of pregnancy-related complications including gestational diabetes, hypertensive disorders, premature delivery and delivery by cesarean section [3]. This study found that TSH was associated with T and PRL in patients with PCOS, and the levels of T and PRL were significantly increased when TSH > 4.0 μIU/ml. In women with PCOS, TSH ≥ 2.0 μIU/mL is associated with insulin resistance independently of body mass index and age, and hypothyroid disturbances and elevated TSH levels are common findings among women with PCOS [20]. Moreover, Recent research has shown that both TSH and total testosterone are significantly higher in PCOS patients compared with the healthy controls [10]. At present, the American endocrine Association's diagnostic criteria for SCH is that TSH > 4.0 mIU/L when FT3 and FT4 are normal [21]. Based on these findings, we can conclude that this study has more clinical significance on account of refining TSH group, which may help early prevention and treatment of endocrine and metabolic disorders.

At present, the classification of Rotterdam is the most used of PCOS diagnosis [17]; however, this classification has been used for more than 10 years. Although its fundamental principle is still valid, each of its three items needs to be updated. Furthermore, the definition of PCOS proposed in 2003 is now obsolete when using the latest generation of ultrasound machines [22]. Our study demonstrated that three group patients with PCOS of different TSH had different sex hormones levels. Especially, when TSH > 4.0 μIU/mL, hormone levels, including T and PRL, were significantly different among the three groups. Therefore, our findings suggest that every woman with diagnosed PCOS should be screened for TSH levels to prevent thyroid dysfunction induced metabolic disturbances.

This study found that the levels of T and PRL were significantly increased when TSH > 4.0 μIU/mL in patients with PCOS. Albu et al has been shown that 322 PCOS patients with normal serum PRL levels can independently predict the extent of metabolic abnormalities [23]. Yilmaz et al has been found that elevated PRL levels may increase the risk of developing atherothrombotic events via the activation of platelets in women with PCOS [24]. Therefore, it may play an important role in reducing the levels of androgen and PRL if the PCOS patients with TSH > 4.0 μIU/L were given moderate thyroxine treatment. It could reduce the risk of atherosclerosis in PCOS patients, at the same time, it may improve the metabolic function of PCOS patients and various clinical symptoms (e.g. hirsutism, acne, ovulation disorders and menstrual disorders) caused by AE or HA [25]. Moreover, it may even be helpful for PCOS pregnancy which is the purpose of most PCOS patients.

In conclusion, the classification analysis conducted in this study showed that a TSH threshold of 4.0 μIU/L was associated with the disorder of sex hormones in PCOS patients. Our study also offers the possibility that, the potential use of TSH as a relevant feature that can be involved in PCOS-related metabolic disturbances.

Disclosure of conflict of interest

None.

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