

# A Comparative Study on Insulin Secretion, Insulin Resistance and Thyroid Function in Patients with Polycystic Ovary Syndrome with and without Hashimoto's Thyroiditis

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**Objective:** The incidence of Hashimoto's thyroiditis (HT) in patients with polycystic ovary syndrome (PCOS) is significantly higher than in normal controls, and there is a risk of more severe metabolic symptoms when the two diseases occur together. This study compares insulin secretion, insulin resistance (IR) and thyroid function in patients with PCOS with and without HT.

**Methods:** A total of 164 patients (52 patients with HT (HT+) and 112 patients without HT diagnosed PCOS at our hospital were enrolled for testing of oral glucose tolerance, insulin release, thyroid function, the presence of thyroglobulin and thyroid peroxidase antibodies, and blood lipid levels.

**Results:** Patients with PCOS and HT had higher insulin secretion and IR levels than those without HT, while free thyroxine and thyrotropin levels were significantly lower. The ratio of free thyroxine to thyrotropin was higher in patients with HT.

**Conclusion:** HT may related with IR and relatively low thyroid function in patients with PCOS. Thus, thyroid function and autoimmune status in patients with PCOS should be evaluated in clinical practice.

**Keywords:** polycystic ovary syndrome, Hashimoto's thyroiditis, insulin resistance, oral glucose tolerance test

## Introduction

Polycystic ovary syndrome (PCOS) is a highly prevalent disorder, representing the single most common endocrine-metabolic disorder in reproductive-aged women and is characterized by ovulatory dysfunction and/or androgen excess or polycystic ovaries.<sup>1</sup> PCOS is found in 6–10% of women of childbearing age.<sup>2,3</sup> Thyroid dysfunction can affect the female reproductive and endocrine systems.<sup>4,5</sup> Numerous studies have indicated that PCOS is often associated with autoimmune thyroiditis.<sup>6,7</sup> Young women with HT are most likely to present with normal thyroid function and elevated levels of thyroid peroxidase antibodies (TPOAb) and/or thyroglobulin antibodies (TGAb).<sup>8,9</sup> Patients with PCOS in combination with HT show more severe metabolic symptoms than those with PCOS or HT alone.<sup>6</sup>

This study aims to investigate insulin secretion, insulin resistance (IR), thyroid function and the metabolic characteristics of patients with PCOS, with and without HT.

## Subjects and Methods

### Subjects

This study was retrospective and a total of 164 patients aged 18–35 years were diagnosed with PCOS between June 2016 and December 2018 and attended the outpatient clinic of the Department of Endocrinology at the Second Guangdong Provincial General Hospital and did not receive specific treatment. None of the women had used hormones or drugs affecting glucose metabolism in the previous 3 months.

### Methods

#### Diagnostic Criteria

The diagnostic criteria for PCOS are those amended at the Rotterdam Conference in 2003. They are: chronic anovulation or incidental ovulation, clinical and/or biochemical signs of hyperandrogenism, and ovarian B ultrasound showing more than 12 follicles with a diameter of 2–9 mm in at least one ovary and/or an increase in ovarian volume of >10 mL. The presence of at least two of the three criteria above will confirm the diagnosis of PCOS, if other potential hyperandrogenism and ovulatory dysfunction diseases can be excluded. Patients with positive TGAbs and/or TPOAbs have been assumed to have Hashimoto's thyroiditis.<sup>9</sup>

#### Measurement of Anthropometric Data

The height and weight of the enrolled patients with PCOS were measured.

#### Oral Glucose Tolerance Test

After fasting for 10 hours, patients took 75 g of anhydrous glucose. Venous blood was drawn before (0 min) and at 30, 60, 120, and 180 min after sugar ingestion in order to measure blood glucose and insulin. Blood glucose was determined by the glucose oxidase method, using an Abbott AEROSET Automatic Biochemical Analyzer, and insulin level was determined by chemiluminescence, using an Abbott AEROSET i2000.

#### Determination of Thyroid Hormone and Thyroid Autoimmune Antibodies

Cubital vein blood was collected after overnight fasting, and serum free triiodothyronine (FT3), serum free thyroxine (FT4), and thyroid stimulating hormone (TSH) were measured using the chemiluminescence method (Roche E601). The reference ranges for FT3 and FT4 are 3.5–5.5 and 11.0–23.0 pmol/l respectively, while the reference range for TSH is 0.35–5.5 mIU/l.

#### Determination of Blood Lipids

Levels of total cholesterol (TCh), triglyceride (TG), high-density lipoprotein cholesterol (HDL-C) and low-density lipoprotein cholesterol (LDL-C) were also measured in cubital vein blood. Using an Abbott AREOSET O-ring Auto Biochemical Analyzer, TCh and TG were measured by enzymatic coupling colorimetry, while HDL-C and LDL-C were measured by the direct method. The reference ranges for TCh, TG, HDL-C and LDL-C were 3.0–6.0 mmol/l, 0.4–1.8 mmol/l, 1.0–1.8 mmol/l, and 2.0–3.1 mmol/l, respectively.

#### Statistical Analysis

Quantitative data were expressed as mean  $\pm$  SD, and the *t* test was used to make comparisons between the two groups. Covariance analysis was used to correct for body mass index (BMI) in order to further analyze the differences between the two groups ( $\alpha = 0.05$ ). All analyses were carried out using the SPSS20.0 statistical package.

## Results

Insulin levels in patients with PCOS and HT were significantly higher than in patients without HT at both 30 and 60 min, regardless of BMI correction. This difference was statistically significant. After BMI correction, there was a significant difference in fasting insulin levels between the two groups. Moreover, IR was significantly higher in the HT+ than in the HT- group after BMI correction. With respect to fat metabolism, the TCh level was significantly higher in the HT+ group after BMI correction. FT4 and FT4/TSH levels were significantly lower in the HT+ group, while the level of TSH was significantly higher, regardless of BMI correction (Tables 1 and 2).

## Discussion

Our results demonstrate that, compared with patients with PCOS but no HT, patients with HT have significantly higher levels of insulin, IR, TCh and TSH. However, FT4 and FT4/TSH levels are significantly lower in the HT+ group.

Patients with PCOS often present with elevated levels of thyroid autoantibodies. Many studies over the years have shown a higher presence of autoimmune thyroiditis (AIT) in specifically polycystic ovary syndrome patients. Thyroid disorders, especially Hashimoto's thyroiditis (HT), are observed significantly more often in patients with polycystic ovary syndrome (PCOS) than in the general population - approximately 27% and 8%, respectively. This is extremely important in young women, because both disorders are connected with

**Table 1** Comparison of Parameters Between Patients with Polycystic Ovary Syndrome with and without Hashimoto's Thyroiditis

	Hashimoto's Thyroiditis (n=52, Mean±SD)	Without Hashimoto's Thyroiditis (n=112, Mean±SD)	P
Age(years)	26.22±3.93	25.45±5.10	0.297
Height(cm)	158.18±4.95	155.86±22.01	0.464
Weight(kg)	57.05±9.65	61.97±16.23	0.048
BMI(kg/m <sup>2</sup> )	22.8±3.82	24.62±6.21	0.025
FINS(uIU/mL)	12.47±8.03	10.9±7.18	0.212
30INS(uIU/mL)	101.44±67.78	79.78±44.23	0.044
60INS(uIU/mL)	113.78±82.72	81.62±55.36	0.013
120INS(uIU/mL)	87.06±87.22	70.89±95.64	0.302
180INS(uIU/mL)	42.21±56.99	32.39±28.65	0.253
HOMA-IR	3.01±2.16	2.69±2.21	0.389
FT3(pmol/l)	4.82±0.81	4.94±0.56	0.372
FT4(pmol/l)	16.26±2.44	17.54±2.65	0.004
TSH(mIU/l).	2.82±1.23	2.16±1.15	0.001
FT4/TSH	7.25±4.01	11.05±6.87	<0.001
HDL(mmol/l)	1.28±0.25	1.23±0.27	0.298
TG(mmol/l)	1.31±0.89	1.4±1.01	0.582
TC(mmol/l)	4.69±0.98	4.44±1.05	0.160
LDL(mmol/l)	2.60±0.94	2.54±0.83	0.690

**Notes:** PCOS with HT compared to PCOS without HT, patients of PCOS with HT Insulin levels at 30 and 60 minutes were significantly higher, FT4 and FT4/TSH ratios were significantly lower and TSH was significantly higher (uncorrected for BMI) ( $p<0.05$ ).

**Table 2** Comparison of Parameters Between Patients with Polycystic Ovary Syndrome with and without Hashimoto's Thyroiditis (After Correction for Body Mass Index)

	Hashimoto's Thyroiditis (n=52, Mean(95% CI))	Without Hashimoto's Thyroiditis (n=112, Mean(95% CI))	P
FINS(uIU/mL)	13.64(11.92, 15.35)	10.59(9.43, 11.76)	0.005
30INS(uIU/mL)	103.45(88.6, 118.3)	78.51(67.85, 89.17)	0.008
60INS(uIU/mL)	120.51(103.05, 137.97)	79.66(67.83, 91.49)	<0.001
120INS(uIU/mL)	92.54(66.24, 118.84)	69.88(52.06, 87.7)	0.163
180INS(uIU/mL)	44.79(33.43, 56.14)	32.38(24.77, 40)	0.076
HOMA-IR	3.33(2.8, 3.85)	2.62(2.26, 2.97)	0.030
FT3 (pmol/l)	4.85(4.67, 5.04)	4.93(4.8, 5.05)	0.506
FT4 (pmol/l)	16.25(15.56, 16.94)	17.37(16.9, 17.84)	0.009
TSH (mIU/l)	2.79(2.46, 3.13)	2.16(1.94, 2.39)	0.002
FT4/TSH	7.3(5.56, 9.04)	11.02(9.84, 12.2)	0.001
HDL(mmol/l)	1.26(1.19, 1.33)	1.23(1.18, 1.28)	0.542
TG(mmol/l)	1.4(1.15, 1.66)	1.37(1.19, 1.55)	0.835
TC(mmol/l)	4.73(4.44, 5.02)	4.37(4.17, 4.58)	0.049
LDL(mmol/l)	2.68(2.44, 2.91)	2.49(2.32, 2.65)	0.191

**Notes:** Mean adjusted for BMI. PCOS with HT compared to PCOS without HT, patients of PCOS with HT Fasting insulin, 30-minute and 60-minute insulin levels were significantly higher ( $P<0.05$ ); HOMA-IR levels were significantly higher in PCOS with HT; FT4 and FT4/TSH ratios were significantly lower and TSH was significantly higher; TC was significantly higher (after correction for BMI) ( $P<0.05$ ).

fertility problems. As HT and PCOS occur together, fertility problems may become a serious clinical issue in these patients.<sup>7,10,11</sup> The first prospective study was completed by Janssen et al.<sup>11</sup> The results showed that levels of TPOAb and TGA, indicative of HT, were increased in the PCOS group

compared with the control group. Although all subjects had thyroid hormone levels in the normal range, the mean TSH level in the PCOS group was significantly higher than in the control group. In addition, a TSH level above the upper limit of normal was seen more often in the PCOS group. TPOAb

and TGAb were also significantly increased in the PCOS group.

An Iranian case-control study found that the level of TPOAb in patients with PCOS was significantly higher than that in controls. However, there was no difference in serum TSH and TGAb levels between the PCOS group and the control group.<sup>12</sup> A recent study in Italy suggests that the prevalence of HT in patients with PCOS is significantly higher than in controls.<sup>13</sup>

Furthermore, Arduc et al<sup>14</sup> confirm that HT occurs more frequently in patients with PCOS. In this study, TSH, TPOAb and TGAb levels of patients with PCOS were significantly higher than those of the control group. However, there were differences in FT3, FT4 and thyroid volume between the two groups. The slightly higher percentage of patients with HT in this study, compared with other studies, is likely due to different diagnostic criteria.

Mueller<sup>15</sup> reports that even when TSH concentration is in the normal range, BMI and IR are higher in women with PCOS whose TSH level is above 2 mIU/l compared with those with a TSH level below 2 mIU/l. Furthermore, IR is independent of BMI and age. This study suggests that a TSH value of about 2 mIU/l has optimum sensitivity and specificity to identify IR in women with PCOS.

Thyroid function appears to affect both the clinical and biochemical parameters of PCOS.<sup>6,16,17</sup> In cases of hypothyroidism, or when the TSH is in the upper limit of the normal reference range, PCOS combined with HT produces more significant metabolic changes compared with HT or PCOS alone. In fact, girls with HT and PCOS have a higher BMI, higher fasting glucose and IR, and higher cholesterol than those with HT alone or controls.<sup>18</sup> Similarly, women with PCOS with subclinical hypothyroidism also have higher TG and fasting insulin levels and higher IR than those with normal thyroid function. However, TC, HDL-C, and LDL-C show no differences.<sup>19,20</sup>

The findings of our study suggest that IR is more marked in PCOS with HT than in PCOS alone. While the TCh level was significantly higher in the HT+ group, blood glucose levels did not differ between the two groups at any time point during the oral glucose tolerance test. This suggests that patients with PCOS and HT have abnormal lipid metabolism compared with patients with PCOS alone. However, the weight of patients with PCOS and HT was significantly lower than that of patients with PCOS alone. The reason for this is unclear, although it may be due to the fact that almost all the HT patients enrolled in

this study had normal thyroid function (only 3 patients had subclinical hypothyroidism and TSH <10 mIU/l).

## Conclusion

This comparative study of patients with PCOS with and without HT found that insulin levels at 30 and 60 min are significantly higher in patients with PCOS and HT than in those without HT. This difference remained significant after correction for BMI. Furthermore, fasting insulin levels were also statistically different between the two groups. IR and TCh levels were also significantly higher in the HT+ group after BMI correction. Testing for thyroid function parameters revealed that FT4 and FT4/TSH levels in the HT+ group were significantly lower than in the HT− group, regardless of BMI correction, while the TSH level was significantly higher.

These differences suggest that HT may aggravate IR and result in relatively low thyroid function in patients with PCOS. Thus, thyroid function and autoimmune status in patients with PCOS should be evaluated in clinical practice.

## Ethics Approval and Consent to Participate

This study was conducted in accordance with the Declaration of Helsinki. This study was conducted with approval from the Ethics Committee of Guangdong Second Provincial General Hospital. Written informed consent was obtained from all participants.

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## Disclosure

The authors report no conflicts of interest in this work.

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