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Original Research

Association of Serum Thyroid Hormone Levels with Androgen and Metabolic Parameters in Chinese Women with Polycystic Ovary Syndrome: A Retrospective Cross-Sectional Study

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Abstract

Background: We sought to explore the potential relationship between serum levels of thyroid hormones with those of androgen and metabolic parameters in women with polycystic ovary syndrome (PCOS). **Methods**: Data from 1059 Chinese women with PCOS and 1015 healthy women was retrospectively collected. This data including fasting glucose and insulin, thyroid-stimulating hormone (TSH), free triiodothyronine (FT3), free thyroxine (FT4), total triiodothyronine (TT3), total thyroxine (TT4), anti-thyroperoxidase antibody (ANTI-TPO), anti-thyroglobulin (ATG), dehydroepiandrosterone sulfate (DHEAS), total testosterone (TTE), follicle-stimulating hormone (FSH), luteinizing hormone (LH), estradiol (E2), prolactin (PRL), progesterone (PGN), triglyceride (TG), total cholesterol (TC), high-density lipoprotein cholesterol (HDL) and low-density lipoprotein cholesterol (LDL). Thyroid-related indicators were compared between PCOS and non-PCOS patients enrolled in this study. Independent variables of PCOS were compared among subgroups in accordance with the classification of TSH, homeostatic model assessment of insulin resistance (HOMA-IR), and TTE levels. To further explore the association between thyroid hormones levels and correlated metabolic parameters in PCOS, multiple regression analyses were conducted. **Results**: Our study found that PCOS patients had significantly higher serum TSH, FT3, TT3 and TT4 levels than non-PCOS patients. PCOS patients with TSH $\geq$2.5 mIU/L had significantly higher TG, fasting insulin, HOMA-IR and homeostatic model assessment of β-cell function (HOMA-B), however, these patients also displayed significantly lower DHEAS, HDL, and quantitative insulin sensitivity check index (QUICKI) when compared to patients with TSH levels $<$2.5 mIU/L. PCOS patients with HOMA-IR levels $\geq$2.5 mIU/L demonstrated significantly higher FT3 and TSH, but lower TT3 when compared to women with HOMA-IR levels $<$2.5 mIU/L. Four groups divided by TTE displayed significant differences in FT3 in PCOS patients. Multiple linear regression analysis showed that TSH was significantly negatively associated with DHEAS and QUICKI. **Conclusions**: TSH levels are closely correlated to the metabolic and endocrine characteristics of PCOS, especially dyslipidemia and insulin resistance.

Keywords: polycystic ovary syndrome; thyroid function; androgen; insulin resistance; lipid metabolism

1. Introduction

Polycystic ovary syndrome (PCOS) is one of the most common endocrine and metabolic disorders, affecting approximately 6 to 21% women of reproductive age based on Rotterdam (ESHRE/ASRM) criteria [1]. PCOS is characterized by clinical and/or biochemical signs of hyperandrogenism, oligomenorrhoea or chronic anovulation, and polycystic ovaries on ultrasonography [2]. Hyperandrogenism, insulin resistance and lipid metabolism disorders have been proven important in the development of PCOS [3–5].

As thyroid dysfunction has been proposed as a possible cause for female infertility and menstrual disorders [6,7], many studies have shown that thyroid functions significantly influence both clinical and biochemical characteristics of PCOS [8–12]. A meta-analysis involving 6 studies concluded that the prevalence of autoimmune thyroiditis, serum thyroid stimulating hormone (TSH), anti-thyroperoxidase antibody (ANTI-TPO), and anti-thyroglobulin (ATG) positive rates in PCOS patients were all significantly higher than those in control groups [12]. Subclinical hypothyroidism (SCH), caused primarily by autoimmune thyroiditis, is present in 5%–10% of patients with PCOS [13]. Hence, it is advised to consider screening for thyroid function and thyroid-specific autoantibodies in patients with PCOS [14]. Serum TSH levels, the most reliable indicator reflective of thyroid function, is closely related to insulin resistance, serum lipids levels, and hormonal disorders in both healthy euthyroid subjects and PCOS individuals [8–11].

In the present study, we conducted a comprehensive retrospective analysis of the relationship between serum thyroid hormones with androgen and metabolic parameters in women with PCOS using a population-based cohort.

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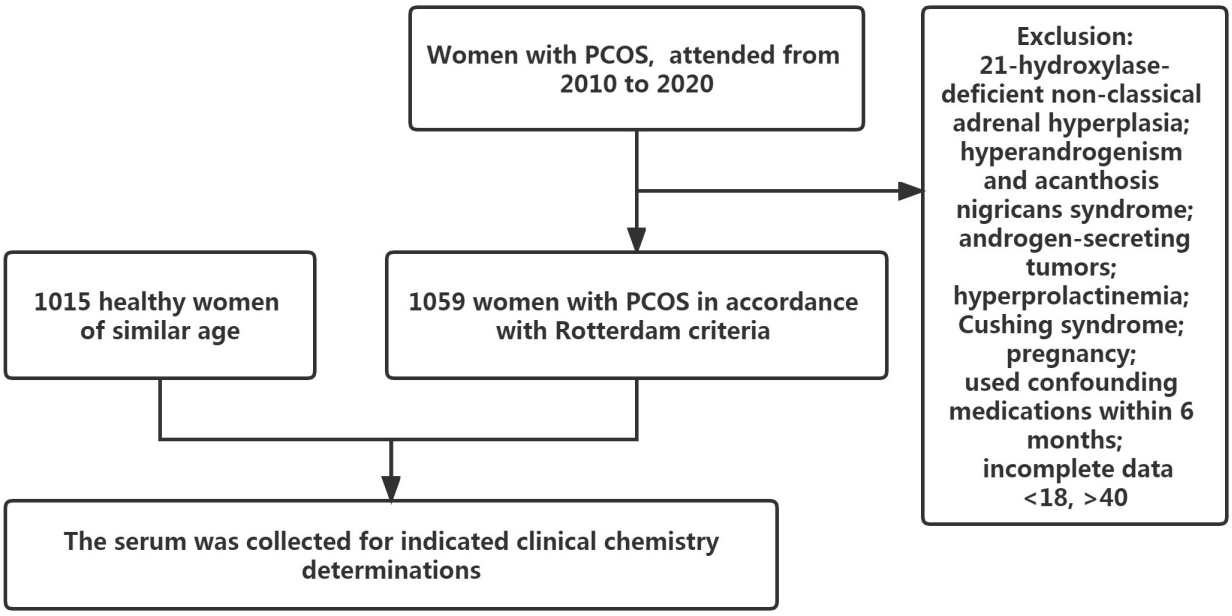

Fig. 1. Flow of the participants. PCOS, polycystic ovary syndrome.

2. Material and Methods

2.1 Study Subjects

This study followed a retrospective cross-sectional design and was conducted in Women's Hospital, School of Medicine, Zhejiang University. All data was collected from the hospital's electronic medical records system. This study was approved by the Ethics Committee of the Women's Hospital, School of Medicine, Zhejiang University.

All women included in this study with PCOS attended our Outpatient Department between January 2010 and May 2020. These women met the definition of PCOS in accordance with the Rotterdam criteria (ESHRE/ASRM) [2]. The exclusion criteria were: 21-hydroxylase-deficient non-classical adrenal hyperplasia; hyperandrogenism and acanthosis nigricans syndrome; androgen-secreting tumors; hyperprolactinemia; cushing syndrome; pregnancy. Participants under the age of 18 years old or over the age of 40 years old were also excluded from the study. Women who had used confounding medications, including oral contraceptive pills, antilipidemic drugs, steroid medications, and insulin-sensitizing drugs within 6 months of their initial visit were also excluded from this study as was incomplete data.

The final PCOS cohort was 1059 after subject exclusion was conducted or incomplete data was determined. We pre-defined inclusion and exclusion criteria to reduce selection bias. Our study sought to obtain a dataset that was as complete as possible, and eliminated any case with indicators missing. Considering the importance of androgen and insulin parameters to this study, we collected the available data of dehydroepiandrosterone sulfate (DHEAS) and fasting insulin although there were missing data on some cases included in the study. As a result of these efforts there were 698 individuals with complete case data for DHEAS, and 731 individuals with complete case data for fasting insulin included in this analysis.

A total of 1015 healthy women of similar age who came to our hospital for physical examination during the same period were included in the study as the non-PCOS group. Due to the limitation of physical examination items, we only extracted data on those patients with complete thyroid function data. The flow of participants is displayed in the Fig. 1. Informed consent was obtained from all participants.

2.2 Biochemical Measurements

All assays were carried out in a diagnostic endocrine laboratory using established commercial assays that are routinely monitored through participation in external quality-control programs. Blood samples were obtained from peripheral veins during the 3rd to 5th days of the menstrual cycle, or taken at random times in cases of an irregular menstrual cycle.

Blood samples were collected and after allowing to clot, the serum was collected for indicated clinical chemistry determinations. Glucose and insulin levels were measured after an overnight fasting period of 12 hours. TSH, free triiodothyronine (FT3), free thyroxine (FT4), total triiodothyronine (TT3), total thyroxine (TT4), fasting insulin, ANTI-TPO, and ATG were measured with the use of a chemiluminescent immunoassay method (Abbott I-2000 analyzer, Abbott Park II, Chicago, IL, USA). Hormonal assays conducted included DHEAS, total testosterone (TTE), follicle stimulating hormone (FSH), luteinizing hormone (LH), estradiol (E2), prolactin (PRL) and progesterone (PGN). Analysis of these hormones were conducted by electrochemiluminescence immunoassay method

Table 1. Comparison of the levels of thyroid function parameters between PCOS and non-PCOS women.

Items	PCOS (N = 1059)	non-PCOS (N = 1015)	*p*-value
Age (years)	28 (26–30)	28 (26–31)	0.901
FT3 (pmol/L)	4.46 (4.13–4.86)	4.20 (3.84–4.62)	<0.001
FT4 (pmol/L)	13.62 (12.63–14.74)	13.50 (12.33–14.80)	0.088
TSH (mIU/L)	1.65 (1.22–2.30)	1.58 (1.15–2.21)	0.015
TT3 (nmol/L)	1.67 (1.50–1.87)	1.54 (1.37–1.70)	<0.001
TT4 (nmol/L)	90.47 (78.92–105.24)	83.64 (73.82–95.54)	<0.001

Note: Data were presented as medians with 25% and 75% quartiles or number with percentage. Comparisons were made using Mann-Whitney test. FT3, free triiodothyronine, FT4, free thyroxine; TSH, thyroid-stimulating hormone; TT3, total triiodothyronine, TT4, total thyroxine; PCOS, polycystic ovary syndrome.

on a Cobas 8000 e-602 analyzer (Roche Diagnostics Ltd, Mannheim, Germany). Fasting glucose, triglyceride (TG), total cholesterol (TC), high-density lipoprotein cholesterol (HDL) and low-density lipoprotein cholesterol (LDL) were analyzed on an Abbott c16000 analyzer (Abbott Park II, Chicago, IL, USA) using standard methods per manufacturer's instructions.

2.3 Definitions and Calculations

Subclinical hypothyroidism was defined as TSH levels $\geq$2.5 mIU/L in association with normal thyroid hormones, and TSH $\leq$2.5 mIU/L was defined the euthyroid patient group [10].

Insulin resistance (IR) could be predicted using multiple indices, including HOMA-IR (homeostatic model assessment of insulin resistance), HOMA-B (homeostatic model assessment of β-cell function) and QUICKI (quantitative insulin sensitivity check index). The following formulas were used for calculations: HOMA-IR = fasting insulin (μIU/mL) $\times$ fasting glucose (mmol/L) / 22.5 [15]; HOMA-B = 20 $\times$ fasting insulin (μIU/mL) / (fasting glucose (mmol/L) – 3.5) [15]; QUICKI = 1 / (Log fasting insulin (μIU/mL) + Log (fasting glucose (mmol/L) $\times$ 18)) [16]. In the present study, a HOMA-IR value $\geq$2.5 was considered suggestive of IR.

2.4 Statistical Analysis

The software used for statistical analyses was SPSS statistical software package, version 26.0 (IBM, Armonk, NY, USA). Kolmogorov-Smirnov analysis was conducted to assess the normality of continuously variable data. We found that all variables were generally not normally distributed, thus the data was expressed as medians with 25% and 75% quartiles. Categorical variables are expressed as number with percentage. The Mann-Whitney U test was performed to compare variables between subgroups divided by TSH and HOMA-IR. The Kruskal-Wallis H test was used among four groups divided by the quartiles of TTE. The Chi-squared test was used for comparison of categorical variables. Multiple regression analyses were further performed considering TSH, FT3 and FT4 as dependent variables and statistically significant correlated metabolic parameters as independent variables. All of the tests were two-sided, and a p value < 0.05 was considered statistically significant.

3. Results

3.1 Comparison of the Levels of Thyroid Function Parameters between PCOS and Non-PCOS Women

Parameters of thyroid function were compared between PCOS and non-PCOS women, results of these analyses are shown in Table 1. FT3, TSH, TT3 and TT4 levels were found to be significantly higher in the PCOS group when compared to the non-PCOS group ($p < 0.001$, $p = 0.015$, $p < 0.001$ and $p < 0.001$, respectively).

3.2 Comparison of the Levels of Endocrine and Metabolic Parameters between PCOS Women Displaying Different TSH Concentrations

A total of 211 women included in this study had TSH levels $\geq$2.5 mIU/L and 848 women had TSH levels <2.5 mIU/L. Anthropometric and endocrine characteristics of these women were compared, and data gathered is presented in Table 2. TG, fasting insulin, HOMA-IR, and HOMA-B levels were found to be significantly higher in women with TSH levels $\geq$2.5 mIU/L compared to those with TSH levels <2.5 mIU/L ($p = 0.001$, $p = 0.003$ and $p = 0.001$, respectively). Conversely, women with TSH levels $\geq$2.5 mIU/L were younger and showed significantly lower DHEAS, HDL and QUICKI levels ($p < 0.001$, $p = 0.001$ and $p = 0.003$, respectively). The positive ratios of ANTI-TPO and ATG in women with TSH levels $\geq$2.5 mIU/L were significantly higher when compared to women with TSH <2.5 mIU/L.

3.3 Comparison of the Levels of Endocrine and Metabolic Parameters between PCOS Women with and without IR

The thyroid function and endocrine features of women with fasting insulin tests are shown in Table 3. A total of 332 women with HOMA-IR values of $\geq$2.5 were classified as having IR, while 399 women had HOMA-IR values of <2.5. Women with IR showed significantly higher FT3, TSH, TTE, TC, LDL and TG concentrations in comparison

Table 2. Comparison of the levels of endocrine and metabolic parameters between PCOS women with different TSH concentrations.

Items	TSH <2.5 mIU/L (N = 848)	TSH ≥2.5 mIU/L (N = 211)	*p*-value
Age (years)	28 (26–31)	27 (26–30)	0.018[a]
FSH (IU/L)	5.89 (5.06–6.79)	5.83 (4.82–6.58)	0.184[a]
LH (IU/L)	10.51 (6.72–15.54)	10.61 (7.13–14.67)	0.889[a]
LH/FSH	1.81 (1.173–2.65)	1.89 (1.35–2.68)	0.392[a]
E2 (pmol/L)	142.20 (104.43–182.60)	131.00 (106.40–169.50)	0.098[a]
PRL (ng/mL)	14.30 (10.50–19.50)	14.50 (11.10–20.10)	0.425[a]
PGN (nmol/L)	1.59 (1.02–2.40)	1.42 (0.96–2.20)	0.094[a]
TTE (nmol/L)	1.40 (1.00–1.80)	1.40 (0.90–1.80)	0.873[a]
DHEAS (μmol/L)	N = 565	N = 135	
	7.80 (6.00–10.20)	6.70 (5.00–8.70)	<0.001[a]
TC (mmol/L)	4.70 (4.22–5.32)	4.70 (4.05–5.30)	0.416[a]
LDL (mmol/L)	2.64 (2.19–3.19)	2.62 (2.10–3.18)	0.439[a]
HDL (mmol/L)	1.30 (1.09–1.54)	1.22 (1.03–1.50)	0.001[a]
TG (mmol/L)	1.17 (0.83–1.62)	1.32 (0.92–1.87)	0.002[a]
Fasting glucose (mmol/L)	5.17 (4.89–5.46)	5.19 (4.96–5.49)	0.328[a]
Insulin resistance parameters	N = 571	N = 160	
Fasting insulin (μIU/mL)	9.25 (6.40–14.48)	11.90 (7.60–16.70)	0.001[a]
HOMA–IR	2.11 (1.47–3.50)	2.76 (1.71–4.11)	0.003[a]
HOMA–B	109.87 (79.28–164.77)	142.28 (93.05–191.01)	0.001[a]
QUICKI	0.34 (0.32–0.36)	0.33 (0.31–0.35)	0.003[a]
ANTI-TPO			
Positive	60 (7.9%)	34 (17.6%)	<0.001[b]
Negative	695 (92.1%)	159 (82.4%)	
ATG			
Positive	142 (16.8%)	53 (25.4%)	0.004[b]
Negative	702 (83.2%)	156 (74.6%)	

Note: Data were presented as medians with 25% and 75% quartiles or number with percentage. PCOS, polycystic ovary syndrome; TSH, thyroid stimulating hormone; FSH, follicle stimulating hormone; LH, luteinizing hormone, E2, estradiol, PRL, prolactin; PGN, progesterone; TTE, total testosterone; DHEAS, dehydroepiandrosterone sulfate; TC, total cholesterol; HDL, high-density lipoprotein cholesterol; LDL, low-density lipoprotein cholesterol; TG, triglyceride; HOMA–IR, homeostatic model assessment of insulin resistance; HOMA-B, homeostatic model assessment of β-cell function; QUICKI, quantitative insulin sensitivity check index; ANTI-TPO, anti-thyroperoxidase antibody; ATG, anti-thyroglobulin. [a]Mann-Whitney test; [b]Chi-squared test.

with women with HOMA-IR values of <2.5 ($p < 0.001$, $p = 0.001$, $p = 0.001$, $p < 0.001$, $p < 0.001$ and $p < 0.001$, respectively). In addition, TT3, FSH, LH, LH/FSH, and E2 concentrations were significantly lower in women with IR compared to women with HOMA-IR values <2.5 ($p < 0.001$, $p = 0.013$, $p < 0.001$, $p < 0.001$, $p = 0.025$ and $p < 0.001$, respectively).

3.4 Comparison of Endocrine and Metabolic Variables among PCOS Women with Differing TTE Levels

All study participants were divided into four subgroups according to TTE quartiles. As shown in Table 4, age, FT3, LH, LH/FSH, E2, DHEAS, PGN, fasting insulin, HOMA-IR, and QUICKI levels demonstrated significant differences among the subgroups ($p = 0.001$, $p = 0.005$, $p < 0.001$, $p < 0.001$, $p < 0.001$, $p < 0.001$, $p < 0.001$, $p = 0.014$, $p = 0.022$ and $p = 0.022$, respectively).

3.5 Association of TSH, FT3 and FT4 Levels with Androgen and Metabolic Characteristics

Multiple linear regression analyses were performed with TSH, FT3, and FT4 serving as response variables and metabolic parameters listed in Table 5 as predictor variables. The model showed that TSH was significantly negatively associated with DHEAS and QUICKI ($p < 0.001$ and $p = 0.003$, respectively). In contrast, FT4 was significantly positively associated with DHEAS ($p = 0.014$). FT3 was significantly positively associated with LH/FSH, LDL, HDL and TG ($p = 0.047$, $p < 0.001$, $p = 0.001$ and $p < 0.001$, respectively) and significantly negatively associated with TC and QUICKI ($p < 0.001$ and $p = 0.003$, respectively).

4. Discussion

To our knowledge, this work represents is the most comprehensive study describing the association be-

Table 3. Comparison of the levels of endocrine and metabolic variables between PCOS women withand without IR.

Items	HOMA-IR <2.5 (N = 399)	HOMA-IR ≥2.5 (N = 332)	*p*-value
Age (years)	28 (26–30)	28 (26–30)	0.840[a]
FT3 (pmol/L)	4.44 (4.12–4.87)	4.58 (4.24–4.95)	<0.001[a]
FT4 (pmol/L)	14.05 (12.9–15.01)	13.31 (12.39–14.49)	0.061[a]
TSH (mIU/L)	1.59 (1.13–2.14)	1.86 (1.3–2.55)	0.001[a]
TT3 (nmol/L)	1.78 (1.56–1.98)	1.69 (1.53–1.87)	<0.001[a]
TT4 (nmol/L)	88.39 (76.70–108.02)	89.35 (78.97–103.99)	0.171[a]
FSH (IU/L)	6.00 (5.16–6.82)	5.76 (4.83–6.55)	0.013[a]
LH (IU/L)	12.00 (7.58–17.24)	9.93 (6.47–13.34)	<0.001[a]
LH/FSH	2.05 (1.30–2.90)	1.75 (1.19–2.23)	<0.001[a]
E2 (pmol/L)	146.10 (107.30–191.56)	139.6 (108.93–168.78)	0.025[a]
PRL (ng/mL)	14.40 (10.60–20.00)	14.20 (10.93–19.48)	0.961[a]
PGN (nmol/L)	1.36 (0.86–2.14)	1.43 (0.95–2.24)	0.399[a]
TTE (nmol/L)	1.30 (1.00–1.80)	1.50 (1.10–2.00)	0.001[a]
DHEAS (μmol/L)	N = 249	N = 219	
	7.44 (5.55–9.90)	8.10 (6.10–10.30)	0.100[a]
TC (mmol/L)	4.61 (4.08–5.16)	4.81 (4.36–5.55)	<0.001[a]
LDL (mmol/L)	2.57 (2.06–3.02)	2.83 (2.37–3.41)	<0.001[a]
HDL (mmol/L)	1.36 (1.16–1.59)	1.15 (0.97–1.32)	<0.001[a]
TG (mmol/L)	0.99 (0.73–1.37)	1.50 (1.09–2.11)	<0.001[a]
ANTI-TPO			
Positive	33 (9.0%)	33 (10.8%)	0.436[b]
Negative	334 (91.0%)	273 (89.2%)	
ATG			
Positive	69 (17.3%)	62 (18.8%)	0.598[b]
Negative	329 (82.7%)	267 (81.2%)	

Note: Data were presented as medians with 25% and 75% quartiles or number with percentage. IR, insulin resistance; FT3, free triiodothyronine, FT4, free thyroxine; TSH, thyroid-stimulating hormone; TT3, total triiodothyronine, TT4, total thyroxine; PCOS, polycystic ovary syndrome; TSH, thyroid stimulating hormone; FSH, follicle stimulating hormone; LH, luteinizing hormone; E2, estradiol; PRL, prolactin; PGN, progesterone; TTE, total testosterone; DHEAS, dehydroepiandrosterone sulfate; TC, total cholesterol; LDL, low-density lipoprotein cholesterol; HDL, high-density lipoprotein cholesterol; TG, triglyceride; ANTI-TPO, anti-thyroperoxidase antibody; ATG, anti-thyroglobulin; HOMA–IR, homeostatic model assessment of insulin resistance. [a]Mann-Whitney test; [b]Chi-squared test.

tween variables measuring thyroid hormones, glycolipid metabolism, and androgen levels in a cohort of patients with PCOS. Compared with non-PCOS women, thyroid-related indicators were generally increased in women with PCOS. An alteration in lipid metabolism and insulin resistance parameters was observed in PCOS patients with SCH compared with PCOS with euthyroidism. PCOS patients with IR had significantly higher FT3 and TSH levels and this was accompanied with alterations in serum lipids and sex hormone levels. The regression model used further confirmed the association between thyroid hormones with serum lipid levels and insulin resistance in women with PCOS. Moreover, a correlation between serum thyroid hormones and androgen level in women with PCOS was also observed.

In the current study, elevated FT3, TSH, TT3 and TT4 levels were found in women with PCOS compared with non-PCOS patients, a finding that was previously reported [17]. TSH levels were subsequently used to stratify PCOS patients into 2 subgroups: SCH and euthyroid women. Compared with the commonly employed cutoff of 4.0–5.0 mIU/L used to diagnose SCH, previous studies have proposed that the upper limit for TSH should be 2.0–2.5 mIU/L [18,19]. The upper limit used for TSH in this study was 2.5 mIU/L as used in previous literature [10]. Under such conditions, SCH was diagnosed with an incidence rate of 19.92% in PCOS patients. Many studies have demonstrated metabolic alterations and IR in patients with SCH; however, overall results are mixed [20–22]. In our study, a significant trend to higher IR indices was observed in PCOS patients with TSH levels ≥2.5 mIU/L compared with TSH <2.5 mIU/L. In accordance, QUICKI was found to be positively correlated with both TSH and FT3 levels. Consistent with our results, Yu *et al.* [22] reported significantly higher HOMA-IR in SCH-PCOS Chinese patients, but they utilized TSH >4.25 mIU/L as the cutoff for SCH, and their groups were matched for body mass index (BMI). Celik *et al.* [20] also found HOMA-IR was higher in SCH-PCOS but after adjusting for related predic-

Table 4. Comparison of the levels of endocrine and metabolic variables among PCOS women with different TTE levels.

Items	TTE ≤0.9 (N = 266)	0.9 < TTE ≤ 1.4 (N = 307)	1.4 < TTE ≤ 1.8 (N = 235)	TTE >1.8 (N = 251)	*p*-value
Age (years)	29 (26–31)	28 (26–31)	28 (26–30)	27 (25–30)	0.001[a]
FT3 (pmol/L)	4.43 (4.04–4.80)	4.42 (4.10–4.84)	4.46 (4.10–4.89)	4.57 (4.27–4.93)	0.005[a]
FT4 (pmol/L)	13.61 (12.53–14.83)	13.73 (12.84–14.60)	13.44 (12.57–14.89)	13.61 (12.59–14.66)	0.871[a]
TSH (mIU/L)	1.70 (1.30–2.31)	1.60 (1.22–2.28)	1.61 (1.20–2.42)	1.69 (1.19–2.25)	0.719[a]
TT3 (nmol/L)	1.67 (1.48–1.93)	1.67 (1.49–1.85)	1.65 (1.50–1.83)	1.68 (1.52–1.86)	0.737[a]
TT4 (nmol/L)	91.50 (77.37–108.43)	93.38 (80.13–107.07)	89.38 (77.07–102.52)	87.49 (79.01–104.79)	0.130[a]
FSH (IU/L)	5.87 (4.83–6.81)	5.90 (5.04–6.78)	5.90 (5.25–6.76)	5.72 (4.87–6.68)	0.268[a]
LH (IU/L)	7.43 (4.65–11.29)	10.60 (6.70–14.84)	12.27 (8.56–16.94)	12.87 (8.93–17.15)	0.000[a]
LH/FSH	1.30 (0.87–1.90)	1.79 (1.19–2.44)	2.04 (1.37–2.90)	2.23 (1.63–3.03)	0.000[a]
E2 (pmol/L)	119.65 (81.71–166.63)	135.50 (99.52–175.50)	143.60 (111.70–178.20)	158.40 (122.00–191.20)	0.000[a]
DHEAS (μmol/L)	N = 175	N = 199	N = 156	N = 170	
	5.90 (4.70–7.50)	7.40 (5.80–9.33)	8.25 (6.53–10.25)	10.00 (7.50–12.42)	0.000[a]
PRL (ng/mL)	14.15 (10.68–20.88)	14.50 (10.60–19.40)	14.20 (10.60–19.60)	14.50 (10.10–19.30)	0.947[a]
PGN (nmol/L)	1.30 (0.84–1.84)	1.61 (1.00–2.26)	1.69 (1.06–2.40)	1.93 (1.13–3.05)	0.000[a]
TC (mmol/L)	4.64 (4.16–5.21)	4.70 (4.26–5.32)	4.74 (4.21–5.37)	4.70 (4.15–5.35)	0.407[a]
LDL (mmol/L)	2.54 (2.08–3.04)	2.63 (2.23–3.16)	2.69 (2.19–3.24)	2.70 (2.18–3.28)	0.059[a]
HDL (mmol/L)	1.29 (1.08–1.52)	1.29 (1.08–1.53)	1.31 (1.13–1.59)	1.25 (1.06–1.48)	0.092[a]
TG (mmol/L)	1.21 (0.88–1.67)	1.16 (0.86–1.65)	1.15 (0.80–1.70)	1.27 (0.84–1.72)	0.543[a]
Fasting glucose (mmol/L)	5.15 (4.87–5.41)	5.14 (4.91–5.39)	5.18 (4.94–5.51)	5.24 (4.90–5.55)	0.207[a]
Insulin resistance parameters	N = 159	N = 214	N = 179	N = 179	
Fasting insulin (μIU/mL)	8.70 (6.80–13.50)	9.15 (6.28–13.18)	10.70 (6.90–16.53)	11.60 (7.00–17.60)	0.014[a]
HOMA–IR	2.08 (1.52–3.29)	2.08 (1.47–3.18)	2.48 (1.51–4.06)	2.76 (1.58–4.14)	0.022[a]
HOMA–B	109.88 (78.57–154.93)	109.02 (79.19–156.37)	121.94 (82.13–194.38)	124.86 (80.92–192.11)	0.081[a]
QUICKI	0.34 (0.32–0.36)	0.34 (0.32–0.36)	0.33 (0.32–0.36)	0.33 (0.31–0.36)	0.022[a]
ANTI-TPO					
Positive	23 (9.7%)	23 (8.5%)	24 (11.4%)	24 (10.6%)	0.732[b]
Negative	215 (90.3%)	249 (91.5%)	187 (88.6%)	203 (89.4%)	
ATG					
Positive	50 (18.9%)	57 (18.6%)	41 (17.5%)	47 (18.9%)	0.976[b]
Negative	214 (81.1%)	249 (81.4%)	193 (82.5%)	202 (81.1%)	

Note: Data were presented as median with 25% and 75% quartiles, or number with percentage. PCOS, polycystic ovary syndrome; TTE, total testosterone; FT3, free triiodothyronine; FT4, free thyroxine; TSH, thyroid stimulating hormone; TT3, total triiodothyronine; TT4, total thyroxine; FSH, follicle stimulating hormone; LH, luteinizing hormone; E2, estradiol; DHEAS, dehydroepiandrosterone sulfate; PRL, prolactin; PGN, progesterone; TC, total cholesterol; LDL, low-density lipoprotein cholesterol; HDL, high-density lipoprotein cholesterol; TG, triglyceride; HOMA-IR, homeostatic model assessment of insulin resistance; HOMA-B, homeostatic model assessment of β-cell function; QUICKI, quantitative insulin sensitivity check index; ANTI-TPO, anti-thyroperoxidase antibody; ATG, anti-thyroglobulin. [a] Kruskal-Wallis H test; [b] Chi-squared test.

tors, such as BMI and waist-to-hip ratio, no significant difference was observed. However, Mueller *et al.* [21] concluded that women with TSH ≥2.0 mIU/L tended to display higher HOMA-IR regardless of their BMI. We also observed higher TG and lower HDL in the subgroup with higher TSH without observing any changes in either TC or LDL. In addition, significantly positive correlations were found between TC, TG, LDL, HDL and FT3. Similar results were observed among euthyroid PCOS subjects in the study by Mueller *et al.* [21] based on a TSH cutoff of 2 mIU/L independent of BMI and age.

Insulin resistance plays an important role in the development of PCOS through various proposed mechanisms [4]. Incidence of IR in PCOS was nearly half in our study as HOMA-IR ≥2.5 was used to define IR. The occurrence of dyslipidemia in the PCOS population has been noted, and there is strong correlation with IR [23]. Our findings confirmed this relationship as results showed that TC, TG, and LDL were all significantly higher, and HDL was lower in IR-PCOS women. In addition, IR-PCOS patients displayed significantly higher TSH and FT3 and, as mentioned above, SCH-PCOS patients displayed higher IR indices. Thus, our results support a close association among thyroid function, IR, and lipid metabolism in PCOS women. To further elucidate the correlation between lipid metabolism and thyroid function among women with PCOS, a comprehensive analysis in conjunction with lipidomics could potentially unveil intriguing discoveries. In addition, LH/FSH was found to be lower in IR-PCOS patients and this result was in agreement with a previous study [24]. An increased LH/FSH

Table 5. Association of TSH, FT3 and FT4 levels with androgen and metabolic characteristics.

Items	TSH		FT3		FT4	
	β (95% CI)	*p*-value	β (95% CI)	*p*-value	β (95% CI)	*p*-value
Age (years)	–0.092 (–0.05–0.000)	0.054	–0.082 (–0.025–0.001)	0.076	0.069 (–0.010–0.068)	0.151
LH/FSH	–0.017 (–0.106–0.074)	0.722	0.094 (0.001–0.095)	0.047	0.051 (–0.067–0.212)	0.307
TTE (nmol/L)	0.008 (–0.152–0.177)	0.885	0.074 (–0.023–0.150)	0.152	0.012 (–0.226–0.285)	0.820
DHEAS (µmol/L)	–0.184 (–0.085–0.025)	0.000	–0.010 (–0.017–0.014)	0.849	0.130 (0.012–0.105)	0.014
TC (mmol/L)	0.155 (–0.137–0.490)	0.269	–0.537 (–0.496–0.166)	0.000	–0.031 (–0.540–0.432)	0.828
LDL (mmol/L)	–0.199 (–0.541–0.064)	0.123	0.612 (0.237–0.556)	0.000	0.023 (–0.427–0.511)	0.861
HDL (mmol/L)	–0.022 (–0.504–0.366)	0.755	0.234 (0.165–0.623)	0.001	0.123 (–0.092–1.257)	0.090
TG (mmol/L)	0.078 (–0.056–0.234)	0.226	0.225 (0.064–0.217)	0.000	0.031 (–0.171–0.278)	0.639
QUICKI	–0.156 (–7.587–1.541)	0.003	–0.155 (–4.043–0.862)	0.003	0.027 (–3.487–5.885)	0.615

Note: β, effect size; CI, confidence interval. TSH, thyroid stimulating hormone; FT3, free triiodothyronine; FT4, free thyroxine; LH, luteinizing hormone; FSH, follicle stimulating hormone; TTE, total testosterone; DHEAS, dehydroepiandrosterone sulfate; TC, total cholesterol; LDL, low-density lipoprotein cholesterol; HDL, high-density lipoprotein cholesterol; TG, triglyceride; QUICKI, quantitative insulin sensitivity check index. Comparisons were made using multiple regression analyses.

ratio, as a marker of inappropriate gonadotropin secretion, which is one of the most characteristic hormonal features in PCOS, proved not to be the consequence of IR based on findings from a clinical trial [25,26]. Further studies are required to determine the relationship between gonadotropin secretion and IR, as well as compensatory hyperinsulinemia.

Comparing SCH-PCOS and euthyroid-PCOS patients, this study found significant differences in DHEAS. Among the various androgens analyzed, testosterone is deemed to have significant biological activity [27]. PCOS patients typically display testosterone levels of approximately 1.5–2 times higher than the general population [27]. Thus, according to the TTE levels, patients were further divided into four categories: TTE $\leq$0.9, 0.9 $<$ TTE $\leq$ 1.4, 1.4 $<$ TTE $\leq$ 1.8 and TTE $>$1.8 nmol/L. Among the indicators of thyroid function, FT3 was higher in the subgroup with highest level of TTE. In the linear regression model used, a weak negative correlation was observed between DHEAS and TSH levels. Consistently, PCOS patients with a TSH level of $\geq$2.5 mIU/L showed lower DHEAS. The results of previous studies that reported on thyroid function and androgen levels in PCOS patients were inconsistent [28–30]. For example, TTE and DHEAS were similar in PCOS and SCH-PCOS patients in the study authored by Huang *et al.* [30]. Benetti-Pinto *et al.* [28] also reported that TTE was similar in PCOS and SCH-PCOS patients, but DHEAS was higher in SCH-PCOS patients. Based on these findings, the conclusions are viewed as inconsistent and merit further study with greater sample sizes and inclusion of subjects with various ethnicities.

The current study also found that the subgroup with higher TTE showed greater HOMA-IR. Similarly, Bil *et al.* [29] reported higher HOMA-IR in patients with PCOS phenotype and androgen excess when compared to non-hyperandrogenemia PCOS patients. It bears consideration that compensatory hyperinsulinemia has been reported to promote androgen production through multiple mechanisms [31–34].

The present retrospective study was limited in several ways. First, our diagnosis of IR was based on a homeostatic test rather than by the gold standard method of euglycemic-hyperinsulinemic clamp. Similarly, total testosterone was detected through an electrochemiluminescent immunoassay, rather than using the gold standard method of liquid chromatography-mass spectrometry (LC-MS)/MS. Second, we recognize that confounding factors exist, for example, BMI is an important influencing factor of endocrine and metabolic disorders, but this value could not be obtained, as well as the absence of free androgen index among androgen estimations. A key strength of the present study was the large sample size of the study and this large dataset can compensate for the above outlined shortcomings, at least to some extent. However, patients were principally located in Zhejiang, China and this fact geographically and demographically limited our findings. Notwithstanding these limitations, this study contributes to our understanding of the relationship between thyroid function, lipid metabolism, and insulin resistance in Chinese women with PCOS.

5. Conclusions

The serum level of thyroid-related indicators is significantly increased and significantly correlated with dyslipidemia and insulin resistance in PCOS patients compared with non-PCOS women. In addition, PCOS patients with higher TSH levels tend to have greater dyslipidemia and IR. Similarly, severe dyslipidemia as well as higher TSH and TTE was found in PCOS patients with higher HOMA-IR.

Abbreviations

PCOS, Polycystic ovary syndrome; SCH, Subclinical hypothyroidism; IR, Insulin resistance; HOMA-IR, Home-

ostatic model assessment of insulin resistance; HOMA-B, Homeostatic model assessment of β-cell function; QUICKI, Quantitative insulin sensitivity check index; TSH, Thyroid stimulating hormone; FT3, Free triiodothyronine; FT4, Free thyroxine; TT3, Total triiodothyronine; TT4, Total thyroxine; ANTI-TPO, Anti-thyroperoxidase antibody; ATG, Anti-thyroglobulin; DHEAS, Dehydroepiandrosterone sulfate; TTE, Total testosterone; FSH, Follicle stimulating hormone; LH, Luteinizing hormone; E2, Estradiol; PRL, Prolactin; PGN, Progesterone; TG, Triglyceride; TC, Total cholesterol; HDL, High-density lipoprotein cholesterol; LDL, Low-density lipoprotein cholesterol; BMI, body mass index.

Availability of Data and Materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Author Contributions

MMP and FQ designed the research protocol. JHZ and MMP conducted the study. JHZ collected data and MMP performed the data analysis. MMP and QZ explained data and wrote the manuscript. FFW and MJ developed the methods and provided help and advice on writing review. MJ revised the manuscript. All authors contributed to editorial changes in the manuscript. All authors read and approved the final manuscript. All authors have participated sufficiently in the work to take public responsibility for appropriate portions of the content and agreed to be accountable for all aspects of the work in ensuring that questions related to its accuracy or integrity.

Ethics Approval and Consent to Participate

All subjects gave their informed consent for inclusion before they participated in the study. The study was conducted in accordance with the Declaration of Helsinki, and the protocol was approved by the Ethics Committee of Women's Hospital, School of Medicine, Zhejiang University (approval number: IRB-20210101-R).

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Conflict of Interest

The authors declare no conflict of interest. Fan Qu is serving as one of the Guest editors of this journal. We declare that Fan Qu had no involvement in the peer review of this article and has no access to information regarding its peer review. Full responsibility for the editorial process for this article was delegated to Shigeki Matsubara.

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