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Subclinical hypothyroidism in patients with polycystic ovary syndrome: Distribution and its association with lipid profiles

Rong Huang [1], Jun Zheng [1], Shengxian Li, Tao Tao, Wei Liu *

Department of endocrinology and metabolism, Ren Ji Hospital, School of Medicine, Shanghai Jiao Tong University, Shanghai 200127, People's Republic of China

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ABSTRACT

Objective: The aim of this study was to examine the distribution of subclinical hypothyroidism (SCH) in patients with polycystic ovary syndrome (PCOS). We also aimed to investigate the associations between thyroid stimulating hormone (TSH) and lipid profiles and to determine the values at which TSH levels affected dyslipidemia risk in this population.
Study design: Women with PCOS ($n = 428$) from a Chinese Han population were recruited and stratified into five groups based on TSH levels. Multiple linear regression analysis was performed to investigate the associations between serum TSH and lipid profiles. Receiver operating characteristic (ROC) analysis was used to find the optimal TSH cut-off point for dyslipidemia risk.
Results: The SCH distribution was observed similarly in PCOS patients with different phenotypes (Chi-squares = 2.184, $P = 0.535$). There was a significant positive correlation between TSH and low density lipoprotein cholesterol (LDLc) ($P = 0.001$), even after adjustment for age, body mass index, waist to hip ratio, fasting plasma glucose, homeostatic model assessment-insulin resistance and free androgen index ($P < 0.001$). The optimal TSH cut-off point to indicate elevated LDLc risk was 4.07 mIU/L by ROC analysis.
Conclusion: Our data indicate that TSH is strongly associated with higher LDLc concentrations in PCOS patients. The optimal TSH cut-off point for elevated LDLc risk in this cohort was 4.07 mIU/L. These findings demonstrate that more attention might be paid to PCOS paients prior to overt clinical presentation.

Introduction

Polycystic ovary syndrome (PCOS) is one of the most common endocrine disorders in women of reproductive age, with a prevalence of 5–10% according to the Rotterdam criteria [1]. PCOS is characterized by well-recognized endocrine and metabolic disturbances including obesity, insulin resistance, dyslipidemia and infertility [2–5]. Dyslipidemia occurs with particularly high prevalence, being observed in up to 70% of women with PCOS [6]. Apart from known alterations in triglycerides (TG) and high-density lipoprotein cholesterol (HDLc), women with PCOS have higher low-density lipoprotein cholesterol (LDLc) concentrations [7]. Furthermore, PCOS patients exhibit an increased risk of type 2 diabetes and cardiovascular diseases [8].

Hypothyroidism is known to induce a clinical manifestation similar to PCOS [9–11], and therefore all existing criteria used for the diagnosis of PCOS aim to first exclude hypothyroidism [1,12,13]. Subclinical hypothyroidism (SCH) is defined as a mild elevation in thyroid stimulating hormone (TSH) levels, with normal serum free thyroxine levels [14,15]. It has been reported that SCH constitutes an independent risk factor for atherosclerosis and myocardial infarction, accompanied with increases in TG and LDLc [16,17]. However, others have reported no changes in lipid parameters in patients with SCH [18].

Both PCOS and hypothyroidism are associated with high prevalence of dyslipidemia, which is known to be one of the most common cardiovascular risk factors. Nevertheless, there are only a few studies concerning the alterations in lipid parameters in patients that present with both these syndromes (PCOS and SCH) and not surprisingly, the results are varied. A study conducted in India in 2011 revealed that patients with both PCOS and SCH had higher TG levels than euthyroid patients with PCOS, while other lipid profile parameters were unaffected [19]. In another study from a Brazilian PCOS population, SCH was found to be associated with higher LDLc levels [20]. The aim of the present study was to explore the variations of endocrine and metabolic characteristics of PCOS patients with SCH in a Chinese Han population. We also

* Corresponding author. Tel.: +86 2168383523.
E-mail address: sue_liuwei@163.com (W. Liu).
[1] These two authors contribute equally to this study.

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aimed to investigate the association between TSH and lipid profiles and to determine the cut-off value at which TSH became predictive for dyslipidemia risk in PCOS patients.

Materials and methods

Subjects

Four hundred and twenty-eight Chinese Han women with PCOS, between the ages of 18 and 45 years old met the Rotterdam (inclusion) criteria as well as the exclusion criteria of related disorders [1]. Patients with clinical thyroid dysfunction and taking medication known to affect carbohydrates, lipids or hormones were excluded from the study. The study was approved by the ethics committee of Shanghai Ren Ji Hospital and written informed consent was obtained from all the participants.

Blood collection, processing and analysis

We collected clinical data including age, height, weight, body mass index (BMI), waist circumference, hip circumference and waist to hip ratio (WHR). Fasting blood samples were taken at 08:00 hours during days 2–5 of the spontaneous menstrual cycle. If the patient had amenorrhoea for more than 3 months, the examination was performed during a bleeding episode after progestin withdrawal. Blood samples were centrifuged, aliquoted and immediately frozen at −70 °C for biochemical analysis. The concentrations of plasma total TG, total cholesterol (TC), HDLc and LDLc were measured by enzymatic assays (Cobas autoanalyzer, Roche diagnostic). The levels of serum hormones including follicle stimulating hormone (FSH), luteinizing hormone (LH), total testosterone (TT), sex hormone binding globulin (SHBG), sulfated dehydroepiandrosterone (DHEAS), free triiodothyronine, free thyroxine and TSH were detected by chemiluminescence (Elecsys autoanalyzer, Roche Diagnostics). The free androgen index (FAI) was calculated as TT × 100/SHBG [21]. Homeostatic model assessment-insulin resistance (HOMA-IR) was determined as fasting glucose × fasting insulin/22.5 [22].

Criteria for the diagnosis of different PCOS phenotypes, SCH and dyslipidemia

PCOS was diagnosed using the Rotterdam criteria, which includes the presence of at least two of the following elements [1]: oligo/anovulation (OA) (<8 spontaneous hemorrhagic episodes/year); biochemical hyperandrogenemia (HA) (serum TT was ≥2.08 nmol/L, DHEAS was ≥300 μg/L, or FAI was ≥4) [23]; polycystic ovaries (PCO) on ultrasound (at least 12 small follicles in at least one ovary and/or ovarian volume >10 mL). PCOS patients were classified into one of four phenotypes as follows: (1) HA, OA and PCO; (2) HA and OA; (3) HA and PCO; or (4) OA and PCO.

According to the normal reference range of the test (0.025 ≤ TSH < 5.0 mIU/L), SCH was defined as serum TSH levels above 5.0 mIU/L with normal free thyroxine levels. The enrolled patients were divided into two groups as PCOS with euthyroidism (normal thyroid function) and PCOS with SCH. The former group was further stratified by the quartile intervals of TSH levels as follows: Group 1 (0.025–1.01 mIU/L); Group 2 (1.01–1.57 mIU/L); Group 3 (1.57–2.32 mIU/L) and Group 4 (2.32–5.0 mIU/L). Those PCOS patients with SCH were assigned to Group 5 (TSH ≥ 5.0 mIU/L).

Dyslipidemia was defined by one or more of the following conditions based on the National Cholesterol Education Program (NCEP) Adult Treatment Panel III (ATP III) criteria: fasting TC ≥ 5.18 mmol/L; fasting TG ≥ 1.7 mmol/L; fasting HDLc < 1.04 mmol/L or fasting LDLc ≥ 3.34 mmol/L [24].

Statistical analysis

Data were presented as means ± standard deviation. The Kolmogorov–Smirnov test was used to examine the normal distribution and variables that were not normally distributed were log-transformed before analysis and then back-transformed to their original units for presentation in tables. Comparison of enumeration data was performed by Chi square test. Comparisons between different groups were performed using one-way analysis of variance with the Sidak method. Multiple linear regression analysis was performed to investigate the associations between TSH and lipid profiles with and without adjustment for age, BMI, WHR, FPG, HOMA-IR and FAI. To determine the optimal thresholds, the point on the receiver operating characteristic (ROC) curve with maximum Youden index [sensitivity-(1-specificity)] was calculated. Statistical analysis was performed using SPSS software (version 18.0), and a *P*-value of <0.05 was considered to be statistically significant.

Results

Baseline features of patients with PCOS in different groups

Given TSH values of 0.025–5.0 mIU/L as the diagnostic criteria for euthyroidism and ≥5.0 mIU/L as the cut-off point for SCH, 428 subjects were included, of which 368 subjects were PCOS with euthyroidism and 60 subjects were PCOS with SCH. We found that 14.0% (60/428) of the PCOS patients exhibited SCH (Table 1). In details, 33 (7.7%) presented phenotype 1 (HA + OA + PCO), 6 (1.4%) presented phenotype 2 (HA + OA), 15 (3.5%) presented phenotype 3 (HA + PCO) and 6 (1.4%) presented phenotype 4 (OA + PCO). Similar distribution of SCH was observed in PCOS patients with different phenotypes (Chi-squares = 2.184, *P* = 0.535) (Table 1).

A comparative description of the patients with different subcategories is shown in Tables 2 and 3. The five subgroups (Groups 1–5) consisted of 92 (21.5%), 95 (22.2%), 98 (22.9%), 83 (19.4%) and 60 (14.0%) patients with PCOS, respectively. Among clinical and endocrine parameters, age, BMI, WHR, FPG, HOMA-IR, FAI, DHEAS, FSH/LH and ovarian volumes were not different among the five subgroups (Table 2). The prevalence of dyslipidemia was significantly higher in patients with SCH when compared to their counterparts with euthyroidism (Chi-squares = 12.425, *P* = 0.014). With the elevation of TSH concentration, a trend to higher TC and LDLc was observed among the five subgroups (*P* = 0.049, 0.001,

Table 1
The SCH distribution in PCOS patients with different phenotypes.

	Phenotype				
	1 (HA + OA + PCO)	2 (HA + OA)	3 (HA + PCO)	4 (OA + PCO)	Total (*n*, %)
PCOS with euthyroidism (*n*, %)	165, 38.6	42, 9.8	113, 26.4	48, 11.2	368, 86.0
PCOS with SCH (*n*, %)	33, 7.7	6, 1.4	15, 3.5	6, 1.4	60, 14.0
Total (*n*, %)	198, 46.3	48, 11.2	128, 29.9	54, 12.6	428, 100

Data are presented as number or percentage.
Abbreviations: PCOS polycystic ovary syndrome; SCH subclinical hypothyroidism; HA hyperandrogenemia; OA oligo/anovulation; PCO polycystic ovaries.