Subclinical Hypothyroidism Impact on the Characteristics of Patients with Polycystic Ovary Syndrome. A Meta-Analysis of Observational Studies

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Keywords

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Abstract

Background/Aims: Definitive polycystic ovary syndrome (PCOS) diagnosis should exclude thyroid dysfunctions. The purpose of the study is to examine the impact of subclinical hypothyroidism on the characteristics of PCOS patients.

Methods: A meta-analysis of the published observational studies was conducted. Medline, Scopus, and Cochrane database search was performed to identify the studies that compared euthyroid PCOS and subclinical hypothyroidism (SCH)-PCOS patients. A total of 9 studies were selected, totalizing the inclusion of 1,537 euthyroid PCOS and 301 SCH-PCOS. The data were expressed as raw mean difference and standard error, using the random-effects model. Heterogeneity among studies was examined using the Cochran's test (Q) and I^2 statistics. **Results:** Anthropometrical parameters were similar in both groups. Total cholesterol (TC) and triglyceride (TG) were higher in SCH-PCOS ($p = 0.036$ and $p = 0.012$). High-density lipoprotein cholesterol was lower in the SCH-PCOS group ($p = 0.018$). Fasting glucose was lower in

euthyroid PCOS ($p = 0.022$). All androgen levels were similar in both group ($p > 0.05$ for all). **Conclusion:** TC, TG and fasting glucose were higher in SCH-PCOS patients. Because of the heterogeneity among studies, some summarized results should be interpreted with caution. Consistent data for future studies addressing PCOS diagnosis are provided.

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Introduction

The most common clinical features of polycystic ovary syndrome (PCOS) include oligomenorrhea, amenorrhea, infertility, hirsutism, weight gain, central obesity, and acanthosis nigricans. Hormonally, it can present elevated luteinizing hormone (LH) levels with normal or slightly decreased levels of follicle-stimulating hormone, hyperandrogenemia, hyperinsulinemia, and normal levels of cortisol (F), prolactin (PRL), thyroid-stimulating hormone (TSH), thyroxine (T4), and free thyroxine (FT4) [1]. Low levels of sex hormone binding-globulin (SHBG) may represent a hyperinsulinemic status. Dyslipidemia, dysglycemia, and insulin resistance, frequent in PCOS patients, increase the

risks of type II diabetes mellitus and cardiovascular disease [2].

Primary overt hypothyroidism shares many of these signs and symptoms with PCOS. Clinically, patients with hypothyroidism may present menstrual disorders, infertility, hyperandrogenism signs, and weight gain [3]. Among the endocrine aspects, it can be characterized by mild increase in total testosterone (T) and free testosterone (fT) levels, increased total and free estradiol (E2), high PRL and LH, and decreased SHBG levels [3]. Dyslipidemia and insulin resistance are also common in hypothyroidism [4]. Moreover, ovaries with multicystic appearance are frequently found in patients with such thyroid dysfunction [5]. It must be noted that ovaries with multicystic appearance can be seen in other conditions including hypothalamic amenorrhea and women who used combined oral contraceptive.

Most subjects with subclinical hypothyroidism (SCH) have few symptoms of thyroid dysfunction, but it can lead to clinical, endocrine, or metabolic changes such as dyslipidemia, dysglycemia, insulin resistance, infertility, ovulatory dysfunction, obesity, and abnormal menstrual cycle [3, 6–8]. High levels of T, fT, LH, PRL, fasting and postprandial insulin, and glycated hemoglobin (HbA1C), increased homeostasis model assessment of insulin resistance index (HOMA-IR), and decreased levels of SHBG may be present in SCH [5, 9, 10]. Furthermore, SCH seems to be an independent risk factor for infarction and it is more frequent in women with metabolic syndrome [9, 11, 12]. Currently, well designed studies connecting or dissociating PCOS and SCH are still lacking [13].

Though definitive PCOS diagnosis should be confirmed only after exclusion of any other hyperandrogenic entity, including thyroid dysfunction [14], a number of studies have not described the criteria used to exclude hypothyroidism before confirming PCOS diagnosis [15–17] and many other studies have not measured, or reported TSH levels at all [18, 19]. Among the studies that clearly reported to have excluded thyroid dysfunction before the definitive diagnosis of PCOS, the used criteria were extremely different: manifested hypothyroidism [20], clinical suspicion of hypothyroidism [21], and different levels of TSH, ranging from 2.5 to 5.0 $\mu\text{UI/mL}$ to consider euthyroidism [4, 12, 22–28]. Given the lack of a specific guideline on this matter and the need for clearly defining which thyroid dysfunctions should be excluded from PCOS diagnosis, the present study aimed to examine the available literature comparing the characteristics of euthyroid PCOS and PCOS patients presenting SCH.

Material and Methods

The aim was to evaluate extant data regarding the characteristics of PCOS and SCH-PCOS patients. The electronic review of studies reporting on this matter was limited to English language. A combination of the terms PCOS and thyroid dysfunction, PCOS and SCH, hyperandrogenism and thyroid function, and oligomenorrhea and hypothyroidism were searched in Medline, Scopus, and Cochrane database. Additionally, references in reviews or original articles were hand-searched. A total of 154 potential articles were found and 135 were excluded after browsing the titles and abstracts. A total of 19 full papers and a complete abstract were assessed for eligibility. All included studies used the current established criteria to diagnose PCOS. Later, 11 publications were excluded because they did not compare PCOS with SCH-PCOS head to head or did not provide sufficient data for analysis [15–17, 23, 25, 28–33]. Attempts were made to contact the authors for further information but no answer was obtained. Finally, 9 full papers providing sufficient data for analysis were selected [4, 8, 11, 12, 22, 26, 27, 34, 35]. All inclusions were based on a clear description of PCOS with euthyroidism and PCOS with SCH. Study eligibility was verified independently by 2 authors (S.F.M. and M.M.W.Y.) and the study quality was assessed as recommended for meta-analysis of observational studies [36].

Statistical Analyses

Because the outcomes were reported on a meaningful same scale, the meta-analysis of enrolled studies was performed using the raw mean difference (RMD) [37]. Anthropometric, metabolic, and hormonal characteristics were compared between euthyroid PCOS and SCH-PCOS patients. The random-effects model was chosen because the included studies were not functionally identical when they have used different TSH cut-off levels to define SCH and may have different effect sizes [38]. Between-studies variance of the effect size (τ^2) was estimated using the method of moments [39]. In addition, heterogeneity among studies was examined using Cochran's Q test and quantified by the proportion of the observed variance as a measure of the degree of inconsistency in the studies using I^2 statistics [38, 39]. All analyses were performed using the Comprehensive Meta-Analysis software, version 2 (Biostat Inc., NJ, USA).

Results

Data comparing euthyroid PCOS and SCH-PCOS patients were extracted from 9 articles. All were already published in peer-reviewed journals between 2009 and 2017. All included studies were observational (Table 1): 6 were cross-sectional [4, 22, 26, 27, 34, 35] and 3 were case-control [8, 11, 12]. A total of 1,837 patients were enrolled, 1,537 euthyroid PCOS and 301 SCH-PCOS. In order to define PCOS, 1 study used National Institutes of Health (NIH) criteria [12], 1 used both NIH and Rotterdam criteria [4], and 7 used only Rotterdam criteria [8, 11, 22, 26, 27, 34, 35]. The TSH normal upper limit was set at 2.5 in

Table 1. Characteristics of observational studies comparing euthyroid PCOS patients and PCOS patients with subclinical hypothyroidism

Reference	year	Study design	PCOS diagnostic criteria	TSH cut-off	PCOS [N]	PCOS-like-SCH [N]	Country
Dittrich et al. [6]	2009	Cross-sectional	NIH or Rotterdam	<2.5	70	33	Germany
Ganie et al. [11]	2011	Case-control	NIH	<5.0	291	62	India
Celik et al. [7]	2012	Case-control	Rotterdam	Not given	39	61	Turkey
Benetti-Pinto et al. [34]	2013	Cross-sectional	Rotterdam	<4.5	149	19	Brazil
Enzevaei et al. [22]	2014	Cross-sectional	Rotterdam	<3.75	56	19	India
Huang et al. [26]	2014	Cross-sectional	Rotterdam	≤5.0	368	60	China
Pei et al. [35]	2014	Cross-sectional	Rotterdam	<4.0	39	29	China
Yu and Wang [11]	2016	Case-control	Rotterdam	<4.25	68	27	China
De Medeiros et al. [27]	2017	Cross-sectional	Rotterdam	<4.2	462	31	Brazil

1 study [4], 3.75 in 1 study [22], 4.0 in 1 study [35], 4.2 in 1 study [27], 4.25 in 1 study [11], 4.5 in 1 study [32], and 5.0 in 2 studies [12, 26]. One study did not provide a normal cut-off for TSH [8].

As a range of TSH cut-off levels was used in the included studies, the serum TSH concentrations were considerably different between euthyroid PCOS and SCH-PCOS patients. All the 9 studies reported on TSH, including 1,537 euthyroid PCOS and 301 SCH-PCOS patients, and the raw mean difference (RMD) was -4.193 , $SE = 0.404$ ($p < 0.001$). Due to the different cut-off used for TSH, these studies were highly heterogeneous regarding this aspect ($\tau^2 = 1.216$, $Q = 264.66$, $I^2 = 96.97\%$, $p < 0.001$). FT4 concentrations were similar in euthyroid PCOS and SCH-PCOS patients (1,113 PCOS and 221 SCH-PCOS, $RMD = 0.173$, $SE = 0.386$, $p = 0.654$) in 7 heterogeneous studies ($\tau^2 = 0.578$, $Q = 18.21$, $I^2 = 67.05\%$, $p = 0.006$).

The ages of euthyroid PCOS patients and SCH-PCOS patients were not different and the summarized effect size of 9 enrolled studies was $RMD = -0.467$, $SE = 0.550$ ($p = 0.396$). The studies showed moderate heterogeneity in their effect size ($\tau^2 = 1.519$, $Q = 19.17$, $I^2 = 58.27\%$, $p = 0.014$). A summary comparing anthropometric data between the 2 groups is shown in Figure 1. Waist circumferences were similar between euthyroid PCOS and SCH-PCOS patients (958 PCOS and 131 SCH-PCOS, $RMD = -0.517$, $p = 0.671$); the data were obtained from 4 homogeneous studies ($\tau^2 = 0.000$, $p = 0.633$). The waist to hip ratios (WHR) also were not different in euthyroid PCOS and SCH-PCOS patients (1,216 euthyroid PCOS and 192 SCH-PCOS patients, $RMD = -0.004$, $p = 0.597$) according 5 homogeneous studies ($\tau^2 = 0.000$, $p = 0.582$). Body mass indexes (BMIs) were similar in euthyroid PCOS and SCH-PCOS patients (1,573 PCOS and 300 SCH-PCOS, $RMD = -0.613$, $p = 0.237$); the 9 studies reporting on this

variable presented moderate homogeneity ($\tau^2 = 1.039$, $p = 0.051$).

Comparisons of the different lipid concentrations between euthyroid PCOS and SCH-PCOS women are given in Figure 2. Total cholesterol (TC) levels were lower in euthyroid PCOS when compared with SCH-PCOS patients in 9 studies (1,537 PCOS and 300 SCH-PCOS patients, $RMD = -0.395$, $p = 0.010$), but the studies were heterogeneous regarding this parameter ($\tau^2 = 0.164$, $p < 0.001$). High density lipoprotein cholesterol (HDL-C) levels were higher in euthyroid PCOS patients (1,285 PCOS and 271 SCH-PCOS patients, $RMD = 0.100$, $p = 0.004$), summary of 8 slightly heterogeneous in 8 studies ($\tau^2 = 0.004$, $p = 0.065$). Low density lipoprotein cholesterol (LDL-C) levels were not different in euthyroid PCOS and SCH-PCOS patients (1,285 PCOS and 271 SCH-PCOS patients, $RMD = -0.100$, $p = 0.384$) and the 8 studies had heterogeneous effect size ($\tau^2 = 0.086$, $p < 0.001$). Triglyceride (TG) levels were higher in SCH-PCOS patients (1,537 PCOS and 300 SCH-PCOS patients, $RMD = -0.281$, $p = 0.002$), according 9 heterogeneous studies ($\tau^2 = 0.048$, $p < 0.001$).

Comparisons of the carbohydrate metabolism mediators between euthyroid PCOS and SCH-PCOS patients are given in Figure 3. Fasting glucose concentrations were significantly higher in SCH-PCOS patients when compared with euthyroid PCOS patients (1,469 PCOS and 273 SCH-PCOS patients, $RMD = -0.109$, $p = 0.022$); the 8 included studies were highly homogeneous ($\tau^2 = 0.001$, $p = 0.022$). Fasting insulin levels were not different in SCH-PCOS and euthyroid PCOS patients (1,101 PCOS and 213 SCH-PCOS patients, $RMD = -0.180$, $p = 0.176$); the 7 studies presented moderate and significant heterogeneity ($\tau^2 = 0.071$, $p = 0.021$). HOMA-IR was not different in PCOS and SCH-PCOS patients (1,537 PCOS and

Fig. 1. Forest plot of the raw difference means of anthropometric parameters between euthyroid-PCOS and SCH-PCOS patients.

300 SCH-PCOS patients, RMD = -0.163 , $p = 0.616$) but the heterogeneity among studies was high ($\tau^2 = 0.758$, $p < 0.001$).

The summary of the differences in androgen concentrations between euthyroid PCOS and SCH-PCOS patients is shown in Figure 4. Total T concentrations were

similar in euthyroid PCOS and SCH-PCOS (1,379 PCOS and 266 SCH-PCOS patients, RMD = -0.114 , $p = 0.676$); the 6 studies presented high heterogeneity ($\tau^2 = 0.408$, $p < 0.001$). The levels of fT also were not different in euthyroid PCOS and SCH-PCOS patients (754 PCOS and 96 SCH-PCOS patients, RMD = 0.001 , $p = 0.916$) in 4 het-

Fig. 2. Forest plot of the lipids' raw difference means between euthyroid-PCOS and SCH-PCOS patients. (Figure 2 continued on next page.)

erogeneous studies ($\tau^2 = 0.000$, $p = 0.009$). SHBG concentrations also were not different when euthyroid PCOS patients were compared with SCH-PCOS patients (900 PCOS and 161 SCH-PCOS patients, $RMD = -8.877$, $p = 0.504$); the 3 studies were highly heterogeneous ($\tau^2 = 512.67$, $p < 0.001$). Free androgen index was similar in

PCOS and SCH-PCOS patients (968 PCOS and 151 SCH-PCOS patients, $RMD = -1.065$, $p = 0.550$); the 4 studies reporting on this parameter also were highly heterogeneous ($\tau^2 = 8.021$, $p = 0.001$). Dehydroepiandrosterone sulfate (DHEAS) levels were similar in euthyroid PCOS and SCH-PCOS patients (1,049 PCOS and 143 SCH-

PCOS, RMD = -0.571 , $p = 0.315$); the 4 studies also were highly heterogeneous regarding this parameter ($\tau^2 = 0.996$, $p = 0.003$).

Discussion

In view of the different criteria used to diagnose SCH from PCOS patients in the current literature, this meta-analysis was justified. The raw difference in mean ages of PCOS and SCH-PCOS patients verified in 9 studies with moderate heterogeneity was not statistically different. The meta-analysis also demonstrated that there were no difference between euthyroid PCOS and SCH-PCOS regarding some anthropometric parameters. However, 2 studies included in the meta-analysis showed higher BMI [4, 8] and another showed higher WHR [8] in SCH-PCOS patients when compared with euthyroid PCOS women. In previous studies, PCOS patients with TSH ≥ 2.5 $\mu\text{UI/mL}$ and non-PCOS patients with high-normal serum TSH levels have shown visceral obesity [8, 40]. A recent meta-analysis comparing SCH-PCOS with healthy control did not show any difference in anthropometric parameters between groups [41]. In general, the possible association between TSH levels and anthropometric parameters, mainly BMI, is still debatable and additional prospective studies should be undertaken to clarify the impact of elevated TSH levels on body shape. Comparisons of anthropometric parameters between SCH-PCOS and normal controls have already shown similar results [25].

The comparisons of serum lipids between euthyroid PCOS and SCH-PCOS may have not provided a defini-

tive conclusion in this meta-analysis because the heterogeneity among studies. However, the higher levels of TC in SCH-PCOS patients suggest that hypothyroidism may increase intestinal cholesterol absorption, overweighing the effects of decreased hepatic cholesterol synthesis [12, 15]. Increased TC level in non-PCOS women with SCH was already demonstrated in most, but not in all, studies [10, 42]. Equally higher levels of TC were reported in PCOS patients with TSH either >2.5 or <2.5 [40], but a positive correlation between TSH and TC levels was reported even in euthyroid non-PCOS subjects [43]. Clearly, the results of the current meta-analysis indicate that TC concentrations are higher in SCH-PCOS patients but because of the heterogeneity of the studies, this conclusion has to be taken with some cautions.

The finding of lower HDL-C levels in SCH-PCOS than in euthyroid PCOS patients in this meta-analysis supports the results of a previous study comparing euthyroid PCOS patients with TSH levels >2.5 or TSH <2.5 $\mu\text{UI/mL}$ [40]. In a non-PCOS population with SCH, the HDL-C level was found to be either similar or lower than the levels seen in normal controls. Further, no association between TSH and HDL-C concentrations was demonstrated in a recent study including non-PCOS individuals [44]. LDL-C levels were similar in euthyroid PCOS and SCH-PCOS patients in the present meta-analysis. Similar levels of LDL-C in euthyroid PCOS women when compared with healthy controls were also reported [40]. In non-PCOS patients with hypothyroidism, LDL-C concentrations have been found to be either similar to [45] or higher than [9, 44] controls. The TG levels were significantly higher in SCH-PCOS patients than in euthyroid

Fig. 3. Forest plot of the carbohydrates' raw difference means between euthyroid-PCOS and SCH-PCOS patients.

PCOS patients; previously higher levels of TG were reported in PCOS patients as a whole group [44]. In non-PCOS patients with SCH, TG levels were also found to be higher or not different from those found in healthy controls [10, 44, 46].

Thyroid hormones may also modulate the carbohydrate metabolism and a possible association between TSH and fasting glucose levels was previously reported [10]. It was also reported that metformin usage results in slight reduction of TSH levels [47]. The current meta-

Fig. 4. Forest plot of the androgens' raw difference means between euthyroid-PCOS and SCH-PCOS patients.

(Figure 4 continued on next page.)

analysis demonstrated higher levels of fasting glucose in SCH-PCOS. Similar results have been found in 2 previous studies including PCOS patients [4, 26]. In addition, PCOS patients as a whole group and healthy controls have shown similar fasting glucose levels in another study

[48]. Among non-PCOS patients, those with subclinical or overt hypothyroidism have presented similar [49] or higher [50] fasting glucose concentrations. The fasting insulin concentrations tended to be higher in SCH-PCOS in this meta-analysis. In 2 of the included studies [7, 21],

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SCH-PCOS patients showed significantly higher fasting insulin levels. It was previously shown that patients with SCH, either with or without PCOS, may present decreased insulin sensitivity in adipose and muscle tissues and higher levels of fasting insulin [4, 10, 23]. Some data have suggested that a decreased blood flow in peripheral tissues is the pathogenic mechanism behind increased insulin levels in women with hypothyroidism. The similar HOMA-IR in PCOS and SCH-PCOS patients demonstrated in the current meta-analysis was not consistent with the higher HOMA-IR previously reported in PCOS as a whole group when it was compared with healthy controls [40, 48] or non-PCOS patients with SCH [5]. A recent meta-analysis reported a significant decrease of HOMA-IR in SCH-PCOS and euthyroid PCOS as a whole group [41].

The current meta-analysis showed similar androgen concentrations in PCOS and SCH-PCOS patients. Only in 2, among 6 studies, total T levels were significantly higher in SCH-PCOS patients [4, 35]. Increased T levels were also found in patients with SCH who had only PCOS morphology on ultrasonography [6]. In non-PCOS women, overt hypothyroidism status has been associated with low T levels [3], but the presence of anti-thyroid antibodies seems not to influence T concentrations [29]. Levels of fT have also been reported not to be different between SCH-PCOS and PCOS women [22, 27, 34]. In other study, patients with hypothyroidism were reported to have high fT levels as a consequence of lower SHBG hepatic production [6], but this meta-analysis and other publications have shown that SHBG levels were similar in PCOS and SCH-PCOS patients [4, 26, 27]. Individually, only the study by Dittrich et al. [6] reported significant reduction in SHBG in SCH-PCOS patients [4]. Based on 4 heterogeneous studies that have reported on DHEAS concentrations,

DHEAS levels were similar in PCOS and SCH-PCOS patients [4, 26, 27, 34]. Only one study included in the meta-analysis reported significantly higher DHEAS concentrations in SCH-PCOS [34]. In other study, not included in this meta-analysis, DHEAS levels were not different in PCOS patients with or without hypothyroidism [51].

Although this meta-analysis tried to answer an interesting question, some limitations must be recognized: (a) instead of using a single cut-off, the enrolled and selected studies used a range from 2.5 to 5.0 $\mu\text{UI/mL}$ as upper normal limit for TSH to exclude the diagnosis of hypothyroidism. Even the knowledge that iodine diet may influence the baseline TSH levels [52], in clinical practice it is essential to define a single cut-off for an uniform and definitive diagnosis of SCH, (b) many of the included studies presented significant heterogeneity regarding the size effect of some biochemical and hormonal parameters, (c) the unequal sample size may have reduced the power of some findings. On the other hand, the current findings have scientific strength. One of the strengths of the study is the large number of patients included in the analysis. In addition, the meta-analysis highlights the need for establishing a single cut-off for TSH level in PCOS diagnosis and gives support for future studies regarding the impact of SCH on endocrine and metabolic changes in PCOS women.

Conclusion

In summary, though this meta-analysis showed that PCOS and SCH-PCOS share most endocrine and metabolic characteristics, a few differences must be considered. It was demonstrated that anthropometric parameters in PCOS and SCH-PCOS patients are similar.

Higher TC, TG, and fasting glucose concentrations in SCH-PCOS than in euthyroid PCOS patients suggest that SCH may worsen the lipid and carbohydrate metabolism in PCOS. HDL-C is much lower in SCH-PCOS than in euthyroid PCOS, attenuating the protective effect of HDL-C in the cardiovascular system of these patients. The differences in fasting glucose levels and some lipids need more long-term studies to establish their clinical implications. All summarized raw differences in the androgens mean levels showed no difference between PCOS and SCH-PCOS patients regarding these sex hormones. The clinical implications of the differences found between euthyroid PCOS and

SCH-PCOS are still unclear and more long-term studies with control of possible confounding covariates are yet required.

Ethical Approval

By this design (meta-analysis of published papers) an ethical approval is not necessary.

Disclosure Statement

The authors declare no conflict of interest.

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