MANAGEMENT OF ENDOCRINE DISEASE

The impact of subclinical hypothyroidism on anthropometric characteristics, lipid, glucose and hormonal profile of PCOS patients: a systematic review and meta-analysis

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Abstract

Objective: Subclinical hypothyroidism (SCH) is encountered in 10–25% of women with PCOS. To date, it remains unclear whether this coexistence influences the severity of metabolic and hormonal profile of these patients. The purpose of our systematic review is to investigate this potential relation.

Methods: We systematically searched Medline, Scopus, ClinicalTrials.gov, Cochrane Central Register of Controlled Trials (CENTRAL) and Google Scholar databases together with reference lists from included studies. All prospective and retrospective observational cohort studies that investigated the impact of subclinical hypothyroidism on hormonal and metabolic parameters of PCOS patients were included. The methodological quality of studies was assessed with the Ottawa–Newcastle criteria. Statistical meta-analysis was performed with the RevMan 5.3 software.

Results: Twelve studies were finally included in the present review, which enrolled 2341 PCOS patients. Among them, 577 had subclinical hypothyroidism, whereas the remaining 2077 were PCOS women with normal thyroid function. The presence of SCH significantly affected HDL (MD –3.92 mg/dL 95% CI: –6.56, –1.29) and triglycerides levels (26.91 mg/dL 95% CI: –3.79, 50.02). HOMA-IR was also affected (MD 0.82 95% CI: 0.15, 1.50). On the other hand, LDL, fasting glucose and 2-h OGTT were not influenced. Similarly, prolactin, FSH, LH, LH/FSH ratio and sex hormone-binding globulin remained unaffected.

Conclusion: Subclinical hypothyroidism does not influence the hormonal profile of women with PCOS. On the other hand, it results in mild metabolic abnormalities, which are not clinically important in a short-term setting.

Introduction

Polycystic ovary syndrome (PCOS) is an endocrine disorder that affects young women. Its prevalence ranges between 5% and 10% (1). It is frequently correlated with metabolic abnormalities such as dyslipidemia, insulin resistance, type 2 diabetes mellitus (DM) and the metabolic syndrome, thus contributing to the pathogenesis of cardiovascular disease (2, 3). Overt hypothyroidism has been linked to altered lipid profile and insulin insensitivity (4, 5, 6). Similarly, subclinical hypothyroidism (SCH) (which is described by elevated levels of thyroid-stimulating...
hormone (TSH) with normal free thyroxine levels) has been associated with decreased glucose disposal, increase of sex hormone-binding globulin (SHBG) levels, hyperlipidemia, increases in serum total cholesterol (TC), low-density lipoprotein cholesterol (LDL) and total triglyceride levels weight gain and insulin resistance in the general population (7, 8, 9, 10). The treatment of SCH in the general population remains controversial in our era as there is lack of substantial evidence to reach firm conclusions (11). Current recommendations, however, suggest that infertile women who wish to conceive should be treated if TSH values exceed 4 IU/L (12).

Besides metabolic alterations, PCOS is associated with distinctive alterations of reproductive hormones. Increases in luteinizing hormone-to-follicle-stimulating hormone ratio (LH/FSH) and circulating androgens contribute to the occurrence of the traditional phenotype of PCOS which includes acne, hirsutism and acanthosis nigricans. Insulin resistance is also apparent in the majority of the cases. Hypothyroidism, on the other hand, has not been linked to any of these disorders, apart from cases in which it coexists with PCOS. Subclinical hypothyroidism is frequently encountered among women with PCOS. It is estimated that its prevalence in this specific population ranges between 10% and 25% (13).

To date, it remains unclear whether SCH aggravates the severity of metabolic and hormonal alterations of women who suffer from PCOS. The aim of the present study is to investigate this hypothesis by summarizing the results of previous studies in the field. To accomplish this, we evaluated the phenotypic, hormonal and metabolic characteristics of PCOS women with and without SCH.

**Methods**

**Study design**

The present study was conducted according to the Preferred Reporting Items for Systematic Review and Meta-analyses (PRISMA) guidelines (14). The criteria of inclusion were determined in advance. We did not restrict our search in specific date range or languages. The search strategy was conducted in three stages. At the first stage (electronic search), we screened the titles and/or abstracts of all articles to determine whether they could be eligible for tabulation. At the second stage (evaluation of articles that were retrieved in full text from the previous stage), we kept all prospective and retrospective observational studies that reported the metabolic and hormonal profiles of PCOS patients with subclinical hypothyroidism. References of full-text articles were also screened to determine if they were eligible for inclusion in the present meta-analysis. Case reports and review articles were excluded from the tabulation and analysis of results. Animal studies were also excluded. Panagiotis Konstantopoulos and Venetia Florou tabulated the selected indices in structured forms. Any discrepancies in the methodology, retrieval of articles and statistical analysis were resolved by consensus.

**Literature search and data collection**

The electronic search was based on Medline (1966–2016), Scopus (2004–2016), Pople (1974–2016), ClinicalTrials.gov (2008–2016) and CENTRAL (1999–2016) databases. References of articles that were retrieved in full text were also screened to reduce the potential article losses. We also aimed to restrict the maximum number of keywords to avoid the possibility of losing articles that could contribute to our meta-analysis. Search strategies and results are shown in Figure 1.

Our search strategy included the MeSH terms ‘hypothyroidism’ [MeSH Terms] OR ‘hypothyroidism’ [All Fields] AND ‘polycystic ovary syndrome’ [MeSH Terms] OR ‘polycystic’ [All Fields] AND ‘ovary’ [All Fields] AND ‘syndrome’ [All Fields] OR ‘polycystic ovary syndrome’ [All Fields] OR ‘polycystic’ [All Fields] AND ‘ovary’ [All Fields] OR ‘polycystic ovary’ [All Fields]). The PRISMA flow diagram schematically presents our strategy (Fig. 1).

**Figure 1**

Search flow diagram.
**Table 1** Methodological characteristics of included studies that result in heterogeneity.

<table>
<thead>
<tr>
<th>Reference</th>
<th>Type of study</th>
<th>Ottawa–Newcastle</th>
<th>Exclusion criteria</th>
<th>SCH definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>(30)</td>
<td>Prospective</td>
<td>6</td>
<td>N/A</td>
<td>TSH &gt;4.2IU/mL</td>
</tr>
<tr>
<td>(29)</td>
<td>Prospective</td>
<td>6</td>
<td>21-hydroxylase-deficient non-classical adrenal hyperplasia; hyperandrogenism, insulin resistance and acanthosis nigricans syndrome; an androgen-secreting neoplasm; elevated levels of prolactin; Cushing syndrome; any history of manifest hypothyroidism or hyperthyroidism or any history of thyroid surgery; or use of thyroid hormone or iodine medication; hormonal therapy, (oral contraceptive pills or steroid medications) TSH ≥ 2.0IU/L</td>
<td></td>
</tr>
<tr>
<td>(32)</td>
<td>Prospective</td>
<td>6</td>
<td>21-hydroxylase-deficient non-classical adrenal hyperplasia; hyperandrogenism, insulin resistance and acanthosis nigricans (HAIRAN) syndrome; an androgen-secreting neoplasm; or any history of manifest thyroid dysfunction, surgery or thyroid hormone medication; thyroid autoimmunity; hormonal therapy, including oral contraceptive pills or steroid medications, within 6 months TSH ≥ 2.5IU/L</td>
<td></td>
</tr>
<tr>
<td>(22)</td>
<td>Prospective</td>
<td>7</td>
<td>Use of hormonal preparation, androgens or drugs affecting metabolic function+ glucose tolerance; diabetes mellitus; thyroid, renal, hepatic, cardiac dysfunction; non-classical adrenal hyperplasia; Cushing’s syndrome; hyperprolactinemia TSH 5.0–9.0IU/L</td>
<td></td>
</tr>
<tr>
<td>(23)</td>
<td>Prospective</td>
<td>7</td>
<td>DM; hyperprolactinemia; congenital adrenal Hyperplasia; hypothryroidism or hyperthyroidism; Cushing’s disease; hypertension; hypercholesterolemia; history of neoplasm; any medication intake (e.g., insulin-sensitizing drugs, oral contraceptives, antiandrogens, statins, aspirin, corticosteroids and GnRH agonists and antagonists) N/A</td>
<td></td>
</tr>
<tr>
<td>(24)</td>
<td>Prospective</td>
<td>7</td>
<td>Chronic diseases such as overt hypothyroidism and hyperthyroidism; kidney or liver failure; hyperprolactinemia; late-onset adrenal hyperplasia; diabetes TSH 4.5–10IU/L</td>
<td></td>
</tr>
<tr>
<td>(31)</td>
<td>Retrospective</td>
<td>N/A</td>
<td>N/A</td>
<td>TSH 5–10IU/L</td>
</tr>
<tr>
<td>(27)</td>
<td>Prospective</td>
<td>7</td>
<td>Clinical thyroid dysfunction; medication affecting carbohydrates, lipids, hormones TSH &gt;5.0 IU/L</td>
<td></td>
</tr>
<tr>
<td>(26)</td>
<td>Prospective</td>
<td>7</td>
<td>Hypertension; hypercholesterolemia; congenital adrenal hyperplasia; hypothryroidism or hyperthyroidism; Cushing’s disease; hyperprolactinemia; specific medications (e.g. oral contraceptives, corticosteroids, GnRH agonists and antagonists, insulin-sensitizing drugs, antiandrogens, aspirin) TSH &gt;4.0IU/L</td>
<td></td>
</tr>
<tr>
<td>(25)</td>
<td>Prospective</td>
<td>7</td>
<td>History of diabetes mellitus; hyperprolactinemia; congenital adrenal hyperplasia; hypothryroidism or hyperthyroidism; Cushing’s disease; renal; hepatic; or cardiac dysfunction; a history of ovarian or adrenal neoplasm+medication (e.g. oral contraceptives, insulin-sensitizing drugs, statins, radioactive Iodine, Levothyroxine, corticosteroids and GnRH agonists and antagonists) within 6 months of the enrolment TSH &gt;3.75 IU/L</td>
<td></td>
</tr>
<tr>
<td>(28)</td>
<td>Prospective</td>
<td>7</td>
<td>Different disorders with similar symptoms; subclinical/ overt hyperthyroidism; thyreostatic treatment TSH 4–20μU/mL</td>
<td></td>
</tr>
<tr>
<td>(33)</td>
<td>Prospective</td>
<td>7</td>
<td>Previously diagnosed thyroid disease; receiving hormonal therapy within 6 months of initial visit TSH ≥ 2.5 IU/L</td>
<td></td>
</tr>
</tbody>
</table>

N/A=data were not available.
Quality assessment

The quality assessment of individual studies included in the present systematic review was based on the Ottawa–Newcastle scale. This scale evaluates three separate domains that refer to 1) selection of study groups, 2) comparability of groups and 3) ascertainment of outcomes (15). The maximum score in the Ottawa–Newcastle Scale is 9, and in the present meta-analysis, we predetermined that studies with a score >7 had low risk of bias. On the other hand, studies with a score that was lower than 5 were highly suspicious of bias and studies with an intermediate score (between 5 and 7) were considered as moderate risk.

Statistical analysis

The meta-analysis was performed with the Review Manager (RevMan) 5.3 software (Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2011). Pooled mean differences (MD) and their 95% confidence intervals (CI) were calculated with the DerSimonian–Laird random effect model (REM). We did not take into account the evaluation of the $I^2$ test during the interpretation of study heterogeneity because the significant methodological differences depicted in Table 1 rendered necessary the calculation with the aforementioned model (REM) (16). The small number of enrolled studies in the present meta-analysis precluded assessment of publication bias (17).

Definitions

We investigated the alterations of metabolic parameters in patients with PCOS and SCH including serum total cholesterol (TC), triglycerides (TG), high-density lipoprotein (HDL), LDL, fasting glucose and homeostatic model assessment for insulin resistance (HOMA-IR). The anthropometric and hormonal alterations were also assessed including systolic and diastolic blood pressure, body mass index (BMI), waist circumference, waist-to-hip ratio, prolactin (PRL), FSH, LH, LH-to-FSH ratio and SHBG.

Results

Excluded studies

Four studies were excluded after reading the full text (18, 19, 20, 21). Two of them investigated the impact of subclinical hypothyroidism on the metabolic profile of PCOS; however, they also have a control group of healthy women without PCOS which does not meet the eligibility criteria (18, 20). One more study assessed the influence of different parameters on PCOS but did not investigate the outcomes assessed in the present meta-analysis (21). In addition, the last one was excluded as it presents outcomes related to the correlation between PCOS and autoimmune markers (19).

Included studies

Twelve studies were finally included in the present review, which enrolled 2654 PCOS patients (22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33). Among them, 577 women had PCOS and SCH and the remaining 2077 had PCOS only. The methodological characteristics of included studies are presented in Table 1.

Metabolic profile

The LDL values did not differ among the two groups (MD 5.75 mg/dL 95% CI: −2.41, 13.91). On the other hand, HDL

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Subclinical Hypothyroidism</th>
<th>Euthyroid</th>
<th>Mean Difference</th>
<th>Mean Difference</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Subgroup</td>
<td>Mean</td>
<td>SD</td>
<td>Total</td>
</tr>
<tr>
<td>2009; Dittrich</td>
<td></td>
<td>3.4</td>
<td>2.99</td>
<td>33</td>
</tr>
<tr>
<td>2011; Ganie</td>
<td></td>
<td>4.6</td>
<td>4.6</td>
<td>62</td>
</tr>
<tr>
<td>2012; Celik</td>
<td></td>
<td>2.92</td>
<td>2.34</td>
<td>20</td>
</tr>
<tr>
<td>2013; Benelli-Pinto</td>
<td></td>
<td>4.08</td>
<td>2.1</td>
<td>19</td>
</tr>
<tr>
<td>2014; Enzovaei</td>
<td></td>
<td>2.26</td>
<td>1.12</td>
<td>19</td>
</tr>
<tr>
<td>2014; Peri</td>
<td></td>
<td>4.78</td>
<td>2.53</td>
<td>29</td>
</tr>
<tr>
<td>2016; Lu</td>
<td></td>
<td>3.22</td>
<td>2.53</td>
<td>92</td>
</tr>
</tbody>
</table>

Heterogeneity: $I^2 = 56\%$, $P = 0.005$.

Test for overall effect: $z = 2.43 (P = 0.005)$.

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levels were significantly decreased in PCOS patients with subclinical hypothyroidism (MD -3.92 mg/dL, 95% CI: -6.56, -1.29). Triglycerides levels were elevated in the same group (26.91 mg/dL, 95% CI: -3.79, 50.02). HOMA-IR was also affected by SCH (MD 0.82, 95% CI: 0.15, 1.50 [Fig. 2]), whereas in the case of fasting glucose, there was no difference (MD 1.62 mg/dL, 95% CI: -0.71, 3.94 [Fig. 3]). Four studies reported the outcomes of oral glucose tolerance test. Three of them did not reveal significant differences. Specifically, Celik et al. reported that the 120-min oral glucose tolerance test (OGTT) was comparable among SCH and controls (108.76 mg/dL ±42.68 vs 98.32 mg/dL ±33.28, P=0.630) [23]. Pei et al. confirmed these findings (6.54 mmol/L ±2.57 vs 6.73 mmol/L ±2.22 P=0.98) as well as Trummer et al. (99.9 (83–111) vs 96.8 (81–117), P=0.562) [26, 28]. Lu et al., on the other hand, observed significant differences at 120 min (7.04 ±2.59 vs 6.25 ±1.80 mmol/L, P=0.015) [33].

**Anthropometric characteristics and blood pressure**

Neither systolic blood pressure nor diastolic blood pressure differed among the two groups (MD 0.11 mmHg 95% CI: -1.89, 2.11, P=0.91) and (MD 0.36 mmHg 95% CI: -1.20, 1.91, P=0.88) respectively. The same was also observed in the case of waist circumference (MD 1.39 cm 95% CI: -1.02, 3.81, P=0.26), waist/hip ratio (MD 0.01 95% CI: -0.01, 0.03, P=0.43) and BMI (MD 0.95 kg/m² 95% CI: -0.10, 2.00, P=0.08).

**Hormonal profile**

The hormonal profile of patients was underreported among the two groups among studies included in the present meta-analysis. An analysis of results was possible in the case of total testosterone levels, which did not significantly differ among PCOS women with subclinical hypothyroidism (MD 0.29 nmol/L, 95% CI: -0.09, 0.67, P=0.13). Three studies reported results for PRL. Among them, Benetti-Pinto et al. showed higher PRL levels in PCOS women with SCH when compared with women with normal thyroid function (17.74 ±7.74 vs 14.04 ±10.27 mg/mL, P=0.01) [24]. However, this observation was not confirmed by Dittrich et al. and Ganie et al. (10.76 ±7.70 vs 8.53 ±4.40 mg/mL, P=NS and 513.04 ±295.65 pmol/L vs 565.21 ±386.95 pmol/L, P=NS) [22, 32]. FSH and LH values were also similar among the two groups. Specifically, neither Ganie et al. (6.5 ±2.4 vs 5.3 ±2.2 IU/mL and 6.0 ±4.2 vs 5.7 ±4.4 IU/mL, P=NS) [22] nor Enzevaei et al. (8.03 ±2.70 vs 8.22 ±2.44 IU/mL, P=0.217 and 9.21 ±7.53 vs 10.11 ±8.46 IU/mL, P=0.805) [25], Dittrich et al. (6.43 ±1.97 vs 8.36 ±13.01 IU/mL, P=NS and 8.67 ±5.44 vs 8.34 ±5.72 IU/mL, P=NS) [32] or Lu et al. (4.96 ±1.41 vs 5.11 ±1.27 P=0.431 and 9.53 ±4.32 vs 10.55 ±4.82, P=0.122) observed any differences [33]. The LH/FSH ratio was reported by four studies. None of them reported significant differences [22, 25, 27, 33]. Finally, among the four studies that reported outcomes related to SHBG levels, only Dittrich reported that they were significantly reduced in the study group (33.65 ±17.21 vs 43.55 ±18.20 nmol/L, P=0.01) [27, 28, 29, 32].

**Sensitivity analysis**

After performing a sensitivity analysis by consecutively excluding studies included in the present meta-analysis, we observed that the study of Enzevaei et al. significantly influenced the level of statistical significance in the case of the metabolic profile parameters [25]. An e-mail has been sent to the corresponding author of this single study to confirm our findings; however, we did not receive a response.
Discussion

According to the findings of our study, the coexistence of SCH and PCOS results in mild alterations of serum lipids, which do not have clinical significance. Insulin resistance may also be slightly affected, as indicated by the HOMA-IR levels. However, current data in the field remain inconclusive because the remaining indices (such as OGTT, insulin levels, Matsuda index and QUICKI index) were underreported. In the case of the hormonal profile, PCOS women with SCH had minor alterations in total testosterone levels. On the other hand, FSH, LH and their ratio were not affected by the presence of SCH.

Our study supports the findings of recent studies concerning the additive effect of SCH on the metabolic profile of patients with conditions such as obesity (34, 35). The pathophysiological processes behind this observation have not been completely elucidated. To date, it is established that thyroid hormones promote the activity of 3-hydroxy-3methylglutaryl-coenzyme A (HMG-CoA) reductase. They also upregulate the LDL receptor gene (36). The reduction of HMG-CoA reductase activity that accompanies hypothyroidism results in altered total cholesterol and LDL levels. Substitution therapy with thyroxine improves these abnormalities, and it is estimated that within 4–6 weeks the lipid profile is significantly improved (4, 37). An inverse correlation of these two disorders has also been suggested by two study groups, which observed that the correction of insulin resistance with metformin resulted in TSH suppression (in patients with overt or subclinical hypothyroidism) (38, 39). Hence, a direct correlation of these two diseases seems to be present, which underlines the necessity for future research in the field.

Despite the fact that the observed alterations in serum levels are of minimal clinical significance, it remains unknown whether these have the potential to increase cardiovascular morbidity in a long-term basis. The current classification of hyperlipidemia is based on the adult treatment panel IV (ATP-IV) guidelines (40). According to these recommendations, lifetime risk assessment should be offered in 20–59-year-old patients and repeated every 4–6 years. The atherosclerotic cardiovascular disease (ASCVD) prevention tool stratifies patients in four separate stating groups. Among them, there is a group of individuals without clinical ASCVD or diabetes aged 40–75 years with an LDL of 70–189 mg/dL and an estimated 10-year ASCVD risk of 7.5% or higher.

To date, there is no consensus regarding the impact of PCOS on ASCVD. This is why it has not been introduced among the potential risk factors in these guidelines. The coexistence of SCH and PCOS and its impact on ASCVD is also not mentioned. It is our belief that future studies could elucidate this field.

Strengths and weaknesses of our study

The findings of our study are based on a systematic review of the literature. No language or date restriction was applied; therefore, the possibility of potential article losses is small. The majority of included studies were prospective, and given their methodological quality assessment, biases were limited. Patients with chronic diseases such as diabetes mellitus, metabolic disorders (e.g. hypercholesterolemia) and hormonal dysfunction (hyperprolactinemia etc) were also excluded from the majority of included studies, thereby reducing analytical and exclusion bias.

On the other hand, the definition of SCH differed between studies; however, we managed to overcome this barrier by introducing the DerSimonian–Laird random effects model, which takes into account potential differences between included studies. Publication bias has also been observed in the cases of several variables that were underreported, hence rendering impossible their meta-analysis and interpretation. Another potential of our study is the applicability of these results to women with PCOS in the general population. Previously, Luque-Ramirez et al. suggested that patients with PCOS studied in the clinical setting may significantly differ from those in the general population in terms of androgen excess, obese phenotype and so forth (41).

Conclusion

To date, there is no direct evidence to support that SCH exerts a detrimental impact on the metabolic and hormonal profile of PCOS patients. Therefore, supplementation with thyroid hormones is not justified until further evidence becomes available in the field. On the other hand, the mild metabolic alterations that are evident in patients with SCH and PCOS compared to PCOS patients without SCH might result in significant morbidity in a long-term setting. However, this hypothesis remains, to date, arguable, as there are no data relevant to this field.
Review

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Declaration of interest
The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of this review.

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Author contribution statement
V P conceived the idea, formed the tables and revised the MS. P K searched the literature, tabulated data and wrote the MS. A P searched the literature, tabulated data and wrote the MS. V P wrote the MS, reviewed the tables, provided consultation and revised the MS. N P wrote the MS, reviewed the tables, provided consultation and revised the MS.

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