# IMPACT OF SUBCLINICAL HYPOTHYROIDISM ON METABOLIC PARAMETERS IN POLYCYSTIC OVARIAN SYNDROME

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## ABSTRACT

**Objective:** To determine the frequency of Subclinical hypothyroidism (SCH) in women diagnosed with PCOS and to analyze its effect on various hormonal and biochemical markers, compared to healthy individuals.

**Materials and Methods:** The study was conducted at Rahman Medical Institute, Peshawar, from March 2023 to August 2023. This was a case-control study in which 200 participants were selected using a non-probability convenient sampling technique. It included 100 female patients who were diagnosed with PCOS based on the Rotterdam criteria and 100 Healthy age-matched controls were included with an age range of 13-45 years . Each individual's clinical, biochemical, and ultrasound assessments including TSH, LH, FSH, prolactin, and testosterone, via electrochemiluminescence immunoassay, lipid profiles, and HbA1c levels were measured.

**Results:** The study showed that a total of 200 participants (100 women diagnosed with PCOS and 100 controls) were compared. The frequency of subclinical hypothyroidism was significantly higher in women with PCOS compared to the control group (29% vs. 6%, p = 0.001). PCOS women had significantly higher BMI (Mean=30.4 ± 4.4 vs 25.1 ± 3.0), and waist circumference (Mean=88.1±6.3 vs 74.4±4.8), however, no significant difference was found in the mean age of both groups (Mean= 27.9±4.7 vs 27.1± 4.5 yrs. P value= 0.1). In PCOS, the mean TSH value was 3.81±1,95 and 2.7±0.2 in the control group**.** Upon comparing the metabolic parameters between the SCH and Euthyroid subgroups, the results showed that the SCH group had significantly higher levels of HbA1c (7.304 ± 0.832 vs. 5.214 ± 0.19, p = 0.001), LDL (159.63 ± 15.57 vs. 79.04 ± 22.3, p = 0.001), Total cholesterol (335.00 ± 94.64 vs. 91.87 ± 33.15, p = 0.001), and Triglycerides (368.92 ± 100.63 vs. 160.28 ± 21.78, p = 0.001). In contrast, the Euthyroid group exhibited higher HDL levels (46.56 ± 4.27 vs. 41.97 ± 8.94, p = 0.001). The Risk estimation of subclinical hypothyroidism is significant in the PCOS group compared to the Control group, (Odds Ratio = 2.95 with 95% confidence interval).

**Conclusion**: The frequency of subclinical hypothyroidism (SCH) was significantly higher in women with PCOS compared to the control group (29% vs. 6%, p = 0.001) and was associated with more severe metabolic disturbances.

**Keywords**: Subclinical hypothyroidism, polycystic ovarian syndrome, TSH, LH, FSH.

## INTRODUCTION

The endocrine disorder that is polycystic ovarian syndrome (PCOS) has many significant metabolic and reproductive challenges, affecting women of reproductive age, categorized by symptoms, like menstrual irregularities, anovulation, hyperandrogenism, and metabolic disturbances.

In PCOS patients insulin resistance (IR) and hyperandrogenism are common and contribute to the development of metabolic syndrome and related conditions, such as obesity, dyslipidemia, and hyperglycemia. [1] The metabolic problem along with reproductive dysfunctions in PCOS also increases the risk of cardiovascular diseases and diabetes. [2]

The clinical and biochemical features of this syndrome are associated with thyroid function. PCOS has many metabolic disorders, including IR, dyslipidemia, and weight gain. [3] The function of the thyroid gland is metabolism regulation, and if there are slight alterations in thyroid function, it will affect various metabolic pathways. SCH is well-defined by increased serum thyroid-stimulating hormone (TSH) levels with normal free thyroxin (T4) levels and is associated with an increased risk of developing obvious hypothyroidism and metabolic problems. [4]

Research suggests that SCH is mostly prevalent in women with PCOS compared to the overall public. [5, 6] The mechanisms linking

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SCH with PCOS are complex and multifaceted. One proposed mechanism involves the effect of elevated TSH on ovarian function, which may alter 'follicle-stimulating hormone (FSH) and luteinizing hormone (LH) levels, potentially exacerbating the hyperandrogenism state in PCOS. Additionally, the chronic low-grade inflammation and IR present in PCOS may contribute to the development of SCH, creating a vicious cycle that further worsens metabolic and reproductive health. [7, 8]

The coexistence of SCH and PCOS presents significant clinical implications, as SCH may worsen metabolic and reproductive abnormalities in PCOS, leading to poorer outcomes. Women with both PCOS and SCH may face a higher risk of developing dyslipidemia, prediabetes, and cardiovascular diseases compared to those with PCOS only. SCH may affect treatment response in PCOS, requiring a more personalized management approach. [9]

Given the shared metabolic disturbances and the potential for SCH to aggravate the clinical course of PCOS, this study aims to evaluate thyroid function and the prevalence of SCH in women with PCOS'. Additionally, the study seeks to determine the impact of SCH on hormonal and biochemical parameters, including those indicative of dyslipidemia and prediabetes.

## MATERIALS AND METHODS

This study was conducted over six-month period from March 2023 to August 2023, in the Outpatient Department of Endocrinology and the Chemical Pathology section of the Pathology Department at Rahman Medical Institute (RMI), Peshawar, Pakistan. The study involved female patients aged 13-45 years presented with symptoms such as 'hirsutism, oligomenorrhea, or infertility' and were diagnosed with PCOS based on the Rotterdam criteria. [10] Healthy 'age-matched individuals without any signs of PCOS were added as controls. 200 participants (100 women diagnosed with PCOS and 100 controls) were selected using a non-probability convenient sampling technique. The sample size was determined using the online software Open Epi, assuming a confidence interval of 95%. The women who were menopausal, pregnant, lactating women, smokers, or having overt thyroid dysfunction were excluded. The study protocol was reviewed and approved by the Institutional Ethics Committee of RMI (NO: RMI-REC/Ethical Approvals/CPSP Synopsis/32). Written Informed consent was obtained from all participants before enrollment. Standard clinical procedures were followed for sampling. Demographic data and clinical records of all participants were thoroughly reviewed. All participants underwent a comprehensive clinical examination and anthropometric measurements. Blood samples (5 mL) were gathered from participants on day two or three of their menstrual cycle.

Serum TSH, LH, FSH, prolactin, and testosterone levels were measured using the Cobas 6000 analyzer via electrochemiluminescence immunoassay, with intra-assay and inter-assay coefficients of variation (CV) below 5%. Following standard protocols the lipid profile and HBA1c were measured using the Cobas c-511 clinical chemistry analyzer (Roche Diagnostics Ltd., Mannheim, Germany) following standard protocols.

Dyslipidemia is defined as LDL cholesterol >150 mg/dl, triglycerides >200 mg/dl, or HDL cholesterol <40 mg/dl. HbA1c levels between 5.7% and 6.4% were classified as prediabetes, while levels ≥6.5% were considered diagnostic of diabetes.[4] Subclinical Hypothyroidism (SCH) is defined as TSH levels >4.25 mIU/mL, with further classification of overt hypothyroidism or hyperthyroidism based on American Thyroid Association guidelines[5]. All laboratory instruments were calibrated when required to ensure accuracy and precision, and samples were run in duplicates when necessary. Any discrepancies were addressed through repeat testing.

All statistical analyses were performed using SPSS version 26, for the continuous variables, (BMI, waist circumference, LH, FSH, prolactin, testosterone, TSH, T3, free T4, HbA1c, LDL, HDL, cholesterol, and triglycerides), means and standard deviations were calculated. To compare these parameters between the PCOS group and control groups, between the subclinical hypothyroidism SCH and Euthyroid subgroups within the group of PCOS, 'the Independent t-test was used'. For the categorical variables oligomenorrhea, infertility, hyperandrogenism, and thyroid status (SCH vs. Euthyroid), the Chi-square test was performed to estimate differences in proportions between the groups. In addition, the comparison of metabolic parameters (HbA1c, LDL, HDL, cholesterol, and triglycerides) between the SCH and Euthyroid subgroups within the PCOS group was analyzed by Independent t-test. The Chi-square test assessed the frequency of diabetes and dyslipidemia between these subgroups. For risk estimation of SCH in PCOS

and Control group Odds Ratio was calculated. A p-value of less than 0.05 was taken as statistically significant.

## RESULTS

Results showed that the PCOS group had significantly raised BMI and waist circumference compared to controls (p = 0.001). The prevalence of oligomenorrhea, infertility, and signs of hyperandrogenism was noticeably higher in the PCOS group with a (p value=0.001). PCOS patients had significantly elevated levels of Prolactin, Testosterone, and TSH compared to controls (p = 0.001). In addition, metabolic markers HbA1c, LDL, cholesterol, and triglycerides were significantly higher in the PCOS group, as shown in Table 1

**Table 1: Demographic and Clinical Characteristics of PCOS and Control Group.**

| Variable | PCOS Group (n=100) Mean ± SD | Control Group (n=100) Mean ± SD | p-value |
|---|---|---|---|
| **Age (years)** | 27.9 ± 4.7 | 27.1 ± 4.57 | 0.1 |
| **BMI (kg/m²)** | 30.4 ± 4.4 | 25.1 ± 3. | 0.001 |
| **Waist Circumference (cm)** | 88.1 ± 6.3 | 74.4 ± 4.8 | 0.001 |
| **Oligo menorrhea** | 69 (93.2%) | 5 (6.8%) | 0.001 |
| **Infertility** | 31 (81.6%) | 7 (18.4%) | 0.001 |
| **Signs of Hyperandrogenism** | 54 (91.5%) | 5 (8.5%) | 0.001 |
| **LH mIU/ml** | 12.89 ± 3.98 | 5.9 ± 2.12 | 0.02 |
| **FSH mIU/ml** | 5.68 ± 0.46 | 5.03 ± 0.6 | 0.2 |
| **Prolactin mIU/ml** | 258.3 ± 157.2 | 24.01 + 5.01 | 0.001 |
| **Testosterone ng/ml** | 1062.7 ± 258.2 | 12.03 ± 3.08 | 0.001 |
| **TSH uIU/ml** | 3.819 ± 1.95 | 2.7 ± 1.27 | 0.001 |
| **$T_3$ nmol/L** | 1.94 ± 0.38 | 2.12 ± 0.51 | 0.007 |
| **Free $T_4$ pmol/L** | 15.46 ± 2.18 | 16.92 ± 2.72 | 0.001 |
| **HbA1c** | 5.82 ± 1.06 | 5.137 ± 0.34 | 0.001 |
| **LDL mg/dl** | 101.71 ± 41.31 | 84.90 ± 22.33 | 0.001 |
| **HDL mg/dl** | 30.23 ± 6.31 | 45.39 ± 3.29 | 0.8 |
| **Triglyceride mg/dl** | 220.79 ± 110.9 | 159.68 ± 22.10 | 0.001 |
| **Cholesterol mg/dl** | 162.38 ± 124.92 | 97.34 ± 31.63 | 0.001 |

The frequency of subclinical hypothyroidism (SCH) was significantly higher in women with PCOS compared to the control group (p = 0.001) as shown in Table 2.

**Table 2: Frequency of SCH and Euthyroidism in PCOS and Control Group**

| Variable | PCOS n=100 | Control n=100 | P value |
|---|---|---|---|
| **SCH** | 29 (29%) | 6(6%) | 0.001 |
| **Euthyroid** | 71(71%) | 94 (94%) | |

In the comparison of the metabolic parameters in SCH and Euthyroids subgroups within the PCOS population, metabolic dysregulation is more common in the PCOS group, as shown in Table 3

**Table 3: Comparison of Metabolic Parameters in both SCH and Euthyroids in PCOS**

| Metabolic parameters | SCH (PCOS) n=29 | Euthyroid (PCOS) n=71 | p-value |
|---|---|---|---|
| **HbA1c** | 7.304 ± 0.832 | 5.214 ± 0.19 | 0.001 |
| **LDL** | 159.63 ± 15.57 | 79.04 ± 22.3 | 0.001 |
| **HDL** | 41.97 ± 8.94 | 46.56 ± 4.27 | 0.001 |
| **Cholesterol** | 335.00 ± 94.64 | 91.87 ± 33.15 | 0.001 |
| **Triglyceride** | 368.92 ± 100.63 | 160.28 ± 21.78 | 0.001 |

Table 4 shows, that the odds of having SCH are **nearly 3 times higher** in the **PCOS group** than in the **control group**. This suggests that **women with PCOS are more likely to develop subclinical hypothyroidism** compared to women in the control group.

**Table 4: Risk Estimation of SCH in PCOS and Control Group**

| Groups | SCH | Euthyroids | Odds Ratio |
|---|---|---|---|
| PCOS | 29 | 71 | 2.95 |
| Control | 6 | 94 | |
| Total | 35 | 165 | |

## DISCUSSION

The prevalence of subclinical hypothyroidism (SCH) in women with polycystic ovarian syndrome (PCOS) observed in this study aligns with existing literature that highlights an elevated risk of thyroid dysfunction in PCOS patients. H. fan et al. identified a similarly high prevalence of SCH among women with PCOS, indicating that thyroid abnormalities[7] were common comorbidity in this population increased TSH levels noted in PCOS patients with SCH, as seen in our study, corroborating findings from Bai H et al. which underscore SCH's role in exacerbating PCOS symptoms through its influence on reproductive hormones, notably LH and FSH, impact on metabolic markers. [11] More observed metabolic disturbances, heightened HbA1c, and unfavorable lipid profiles, reflect findings from Ding H, et al. who reported a correlation between PCOS and increased metabolic risks, including dyslipidemia and elevated blood glucose levels. [12] Our study found higher levels of HbA1c in the SCH subgroup, indicating impaired glucose control, which aligns with other studies linking SCH to worsened insulin resistance (IR) in PCOS. Palomba et al. also highlighted similar patterns of increased metabolic risk among PCOS patients with SCH, suggesting that thyroid dysfunction may contribute to impaired glucose metabolism and predispose patients to prediabetes and diabetes. [13]

The dyslipidemic SCH subgroup, marked by elevated LDL, total cholesterol, and triglycerides, supports findings from Liu et al. who documented a similar association between thyroid dysfunction and lipid abnormalities in PCOS patients. [14] Lower HDL levels in the SCH group finding with Luo et al highlight the heightened 'cardiovascular risk in women with both PCOS and SCH', emphasizing the importance of lipid management in this subgroup. [15] HDL, often considered protective against diseases, was found to be significantly lower in SCH-affected individuals, underscoring the compounded metabolic risks associated with both PCOS and thyroid dysfunction. The study's association of higher diabetes prevalence in the SCH group was also consistent with Zhong et al who observed that SCH contributes to insulin resistance and, consequently, a higher risk of diabetes in women with PCOS. Elevated TSH levels in SCH may contribute to chronic inflammation, a factor linked to insulin resistance and frequently observed in PCOS. [16] This link between inflammation and insulin resistance has been noted in the literature, suggesting that inflammation may play a role in perpetuating the metabolic challenges seen in SCH and PCOS. [17]

The current study's findings on the need for personalized management plans for PCOS patients with SCH align with previous research advocating individualized treatment approaches. Literature highlights 'the importance of regular thyroid function monitoring in PCOS patients to address the unique metabolic challenges' posed by SCH. As suggested by Rani and Chandna multi-omics approaches could be beneficial in allowing for tailored therapeutic strategies that mitigate the metabolic implications of SCH. [18] This study showed that women with PCOS had 2.87 times the odds of having SCH than controls, suggesting PCOS might be a risk factor for SCH. [19] The limitation of the study is that it is a single-center study, large multi-centered studies are required to further explore the role of SCH in causing metabolic dysfunctions in PCOS patients.

Our research reflects the complex relationship between SCH and PCOS, emphasizing the need for integrated care approaches. Future research should explore intervention strategies to manage SCH in PCOS patients, as current studies suggest that treating SCH may reduce metabolic derangements.

## CONCLUSION

A significant prevalence of SCH in women with PCOS and its aggravating effect on metabolic and reproductive health. SCH in PCOS patients was 'associated' with dyslipidemia and altered glycemic control, underlining the need for regular thyroid function screening.

## AUTHORS CONTRIBUTIONS

1. Safia Rahman: Conceived and designed the analysis, data collection, statistical analysis, literature search.
2. Zakia Rehman: Study design, data collection, statistical analysis, literature search.
3. Ambreen gul: Data Collection
4. Naumana Rehman: literature search
5. Momina Haq: Data analysis
6. Maryum Farooq: Conceived and designed the study.

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**ETHICAL CONSIDERATION:** The study was approved by the Ethical board of Rehman Medical Institute.

## REFERENCES

1. Сюсюка В, Сергієнко М, Макуріна Г, et al. Characteristics of phenotypes (clinical variants) of polycystic ovary syndrome in women of reproductive age. *Репродуктивне здоров'я жінки* 2021(2):27-31. DOI: https://doi.org/10.30841// doi.org/10.30841/2708-8731.2.2022.261816
2. Zhu T, Cui J, Goodarzi MO. Polycystic ovary syndrome and risk of type 2 diabetes, coronary heart disease, and stroke. *Diabetes* 2021; 70 (2):627-37. DOI: 10.2337/db20-0800
3. Rani S, Chandna P. Multiomics analysis–based biomarkers in diagnosis of polycystic ovary syndrome. *Reproductive Sciences* 2023; 30 (1):1-27.DOI https://doi.org/10.1007/s43032-022-00863-9
4. Kamrul-Hasan A, Aalpona FTZ, Selim S. Impact of Subclinical Hypothyroidism on Reproductive and Metabolic Parameters in Polycystic Ovary Syndrome–A Cross-sectional Study from Bangladesh. *European Endocrinology* 2020;16(2):156. DOI: 10.17925/EE.2020.16.2.156
5. Raj D, Pooja F, Chhabria P, et al. Frequency of subclinical hypothyroidism in women with polycystic ovary syndrome. *Cureus* 2021;13(9) DOI: 10.7759/cureus.17722
6. Wu Q, Gao J, Bai D, et al. The prevalence of polycystic ovarian syndrome in Chinese women: a meta-analysis. *Annals of palliative medicine* 2021;10(1):747-87. DOI: 10.21037/apm-20-1893
7. Fan H, Ren Q, Sheng Z, et al. The role of the thyroid in polycystic ovary syndrome. *Frontiers in Endocrinology* 2023;14:1242050. doi: 10.3389/fendo.2023.1242050
8. Zia B, Nisar S, Ansari SZ. PCOS and Obesity: The Role of TSH on Fat Metabolism and Its Dysfunctional Repercussions. *Obstetrics and Gynecology Advances* 2023:81.
9. Ho C-W, Chen H-H, Hsieh M-C, et al. Increased risk of polycystic ovary syndrome and it's comorbidities in women with autoimmune thyroid disease. *International journal of environmental research and public health* 2020;17(7):2422. DOI: 10.3390/ijerph17072422
10. The Rotterdam ESHRE/ASRM---Sponsered PCOS Consensus Workshop

Group. Revised 2003 consensus on diagnostic criteria and long-term health risks related to polycystic ovary syndrome (PCOS)*human reproduction*. 2004;19(1):14-47. DOI: 10.1016/j.fertnstert.2003.10.004

11. Bai H, Ding H, Wang M. Polycystic Ovary Syndrome (PCOS): Symptoms, Causes, and Treatment. *Clinical and Experimental Obstetrics & Gynecology* 2024;51(5):126. DOI: 10.31083/j.ceog5105126
12. Ding H, Zhang J, Zhang F, et al. Resistance to insulin and elevated level of androgen: A major cause of polycystic ovary syndrome. *Frontiers in endocrinology* 2021;12:741764. DOI: 10.3389/fendo.2021.741764
13. Palomba S, Colombo C, Busnelli A, et al. Polycystic ovary syndrome and thyroid disorder: a comprehensive narrative review of the literature. *Frontiers in Endocrinology* 2023;14:1251866. doi.org/10.3389/fendo.2023.1251866
14. Liu J, Chen Y, Ren B, et al. Alteration of lipid profile between subclinical hypothyroidism and well-matched controls: a meta-analysis. *Hormone and Metabolic Research* 2023;55(07):479-86. DOI: 10.1055/a-2081-4599
15. Luo X, Cai W-Y, Wu X-K. Prevalence, pattern and predictors for dyslipidemia of Chinese women with polycystic ovary syndrome. *Frontiers in cardiovascular medicine* 2021;8:790454.
16. Zhong P, Guan B, Lin Y, et al. Changes in inflammatory factors, oxidative stress, glucose and lipid metabolism, and insulin resistance in patients with polycystic ovary syndrome. *Cellular and Molecular Biology* 2021;67(5):45-50. DOI: 10.14715/cmb/2021.67.5.6
17. Sheikh A. Polycystic ovary syndrome and metabolic syndrome: Risks in later life. Polycystic Ovary Syndrome: Elsevier 2024:75-86. https://doi.org/10.1016/B978-0-323-87932-3.00019-0
18. Zhao X, Feng X, Zhao X, et al. How to screen and prevent metabolic syndrome in patients of PCOS early: implications from metabolomics. *Frontiers in Endocrinology* 2021;12:659268. DOI: 10.3389/fendo.2021.659268
19. Ding X, Yang L, Wang J, Tang R, Chen Q, Pan J, Yang H, Chen X, Chen Z, Mu L. Subclinical Hypothyroidism in Polycystic Ovary Syndrome: A Systematic Review and Meta-Analysis. Front Endocrinol (Lausanne). 2018 Nov 27;9:700. doi: 10.3389/fendo.2018.00700. PMID: 30542323; PMCID: PMC6277795.