

# Thyroid Hormones and Cardiometabolic Risk Factors in Saudi Women with Polycystic Ovary Syndrome: A Cross-Sectional Study

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**Objective:** The PCOS-thyroid nexus has recently drawn the focus of various investigations due to the prevalence of thyroid problems in PCOS. Additionally, risk factors for cardiovascular disease (CVD) are more prevalent in PCOS women. Therefore, we aim to assess the levels of thyroid hormones in Saudi females with polycystic ovary syndrome (PCOS) and to examine the correlation between cardiometabolic risk factors (CMRFs) and thyroid hormones in PCOS patients.

**Methods:** A cross-sectional research with 200 PCOS-diagnosed female patients was conducted from April 2018 to April 2020. In addition to other anthropometric and serum biochemical markers, glycemic status, thyroid function test, lipid profiles, homocysteine, and C-reactive protein levels were detected in patients.

**Results:** In PCOS, hypothyroidism is more common than hyperthyroidism (55 vs 27.5%,  $p = 0.05$ ). While women with raised TSH (hypothyroidism) had a higher BMI, WC, FBG, and poorer HDL-C ( $p < 0.05$ ). Significant differences were found in LDL-C, TG, Homocysteine, and CRP levels (all  $p < 0.001$  and  $< 0.05$ ). PCOS women with hypothyroidism at increased risk of CVD, as indicated by AIP (Atherogenic Index of plasma) ( $0.57 \pm 0.42$ ) was found. The elevated TSH levels were favorably linked with TG, Homocysteine, CRP, BMI, AIP, and WC (all  $p < 0.001$ ,  $0.05$ ) but negatively connected with HDL-C and FT4.

**Conclusion:** A strong relationship between PCOS and thyroid dysfunction was detected since PCOS hypothyroid groups had higher TSH levels and CMRFs. This group's CVD risk was elevated due to CRP, homocysteine, triglycerides, and obesity.

**Keywords:** thyroid disorder, insulin resistance, obesity, polycystic ovary syndrome, atherogenic index of plasma

## Introduction

PCOS (polycystic ovary syndrome), which involves about one in 15% of women worldwide, is a heterogeneous endocrine disorder that is defined by oligo- or anovulation, clinical and/or biochemical signs of hyperandrogenism, and polycystic ovaries.<sup>1</sup> The prevalence of PCOS represents 5–10% of women worldwide.<sup>1</sup> The latest studies on Madinah females stated that 32.5% have PCOS with an average age of  $21 \pm 2$  years. PCOS is a condition that affects a woman's reproductive system, but it is also an endocrinopathy that may have serious consequences for her overall health. It has been established that PCOS and thyroid problems may impact fertility and reproductive biology.

What's more noteworthy is that hypothyroidism may initiate, maintain, or exacerbate this disease.<sup>2</sup> Due to the frequency of thyroid disorders in PCOS, the PCOS-thyroid nexus has been the recent interest of several studies.<sup>2,3</sup> The bulk of the data indicated that PCOS patients were four times more likely to develop autoimmune thyroiditis and excessively elevated TSH levels.<sup>2,3</sup> Many reproductive-aged women with PCOS also suffer from hypothyroidism. Ramanand et al found that 3–4% of women of reproductive age had hypothyroidism.<sup>4</sup> It has been shown that the prevalence of hypothyroidism is above average (18% vs 6%).<sup>3</sup> Numerous recent studies, however, have shown that women with PCOS have a greater chance of having thyroid disorders. Hyperthyroidism may contribute to some PCOS symptoms, including infertility, hypertension, irregular menstrual cycles, mental illnesses, and a low body mass index.<sup>5,6</sup>

Similarly, data indicates that 65% of women with hyperthyroidism had menstrual irregularities, compared to only 17% of women with normal thyroid function.<sup>7</sup> According to another study, menstrual abnormalities caused by hyperthyroidism are 2.5 times more prevalent than the control group.<sup>8</sup>

Several studies have also shown that women with PCOS are more likely to have cardiovascular disease (CVD) risk factors such as hypertension, dyslipidemia, diabetes, and obesity, as well as raised C-reactive protein (CRP) or homocysteine levels.<sup>9–11</sup> In addition, both clinical and subclinical, hyperthyroidism and hypothyroidism may contribute to the progression of CVD. Even modest changes in thyroid hormone levels elevate CVD mortality by 20% to 80%.<sup>12</sup>

Thyroid problems often substantially affect the CVD system through numerous mechanisms, such as dyslipidemia or hypertension. Further study of this kind is required to characterize the correlation between thyroid hormone levels and PCOS complications such as CVD, especially in Saudi Arabian females. Therefore, the study aims to assess the levels of thyroid hormones in Saudi females with PCOS and the relationship between thyroid hormones and PCOS comorbidities such as CVD.

## Methods

A cross-sectional study included female patients already diagnosed with PCOS but not yet received treatments. Their age ranged from 20–35 years and was recruited from different hospitals in the Madinah region during the period of April 2018 to April 2020. Generally women between the ages of 20 and 40 were diagnosed with PCOS using the ROTTERDAM criterion were selected for study.<sup>13</sup> 200 healthy females as controls range age 18–33 years without a history of irregularly menstruating or cardiovascular disease (CVD), diabetes or thyroid disorders, without clinically apparent of hyperandrogenism or pregnant, or menopause was included in the study. While, patients with congenital hypothyroidism or hyperthyroidism, CVD, diabetes, thyroidectomy patients, and a history of radiation to the neck and head in cancer patients were excluded from study. Before enrollment in the trial, each participant's informed written permission was obtained.

## Analysis of Blood Samples

Blood tests were conducted at Madinah hospital labs for thyroid-stimulating hormone (TSH), fasting blood glucose (FBG), homocysteine levels, triglyceride (TG), total cholesterol, high-density lipoprotein cholesterol (HDL-C), free tetraiodothyronine (FT4), low-density lipoprotein-cholesterol (LDL-C) and C-reactive protein (CRP). Meanwhile, 2 mL of the leftover blood sample was centrifuged (1000-x g, 5 minutes), then, the hormone levels in serums were evaluated by a completely quantitative ELISA-based chemiluminescent assay (CUSABIO Technology LLC, Houston, USA). All operations were done according to the manufacturer's instructions provided by the lab in Madinah Hospitals. The normal values of homocysteine vary between 5 and 15  $\mu\text{mol/L}$  and  $\text{CRP} < 10 \text{ mg/L}$ .<sup>14</sup> The reference ranges for TSH, and FT4 were set as 0.35 to 4.94 IU/mL and 0.70 to 1.48 ng/dL, respectively. Participants with thyroid dysfunction were divided into four groups: Primary hypothyroidism (a) is defined by a serum TSH level  $> 4.94 \text{ IU/mL}$  and a low FT4 level ( $0.7 \text{ ng/dL}$ ); primary hyperthyroidism (b) is defined by a serum TSH level  $0.35 \text{ IU/mL}$  and a high FT4 level ( $> 1.48 \text{ ng/dL}$ ); and subclinical hypothyroidism (c) is defined by elevated TSH values with normal FT4 levels.<sup>15</sup> In particular, the Atherogenic Index of plasma =  $\log (\text{TG}/\text{HDL-C})$  was also determined. AIP levels less than 0.11 suggest a low risk for CVD, whereas values between 0.11 and 0.21 indicate a moderate risk and values above 0.21 indicate a high risk.<sup>16</sup>

## Anthropometric Measurements

Measurements of height and weight were performed. All measures were averaged after being assessed three times to compute the mean. The weight was calculated using an electronic scale. The height of a vertical wall was measured using a measuring tape. The body mass index was calculated using the subjects' height and weight. Obesity ( $> 30.0 \text{ kg/m}^2$ ), overweight ( $25.0\text{--}29.9 \text{ kg/m}^2$ ), and normal weight ( $18.5\text{--}25.0 \text{ kg/m}^2$ ) were determined based on the BMI.<sup>14</sup> Three measurements of each participant's waist were taken using a flexible but non-elastic measuring tape within half a centimetre. While waist circumference was taken at the level of the natural waist (the narrowest part of the torso) or one finger width under the umbilicus. Women who measured 88 centimeters or more around their waist were classified as

being obese in their abdominal region, while those who measured less than 88 centimeters were classified as being normal in this area.<sup>14</sup>

## Ethical Consideration

This study was authorized by Taibah University in Al Madinah Al Munawarah's ethical committee (CLN201704) in the field of applied medical sciences.

## Data Analysis

For statistical analysis, GraphPad Prism 7 (GraphPad Software, CA, USA) was utilized. In the quantitative statistics, percentages mean, and standard deviations all showed. Using a one-way analysis of variance (ANOVA), several continuous variables were compared across categories. Using Pearson's correlation, thyroid hormone levels were associated with glucose, CRP, homocysteine, BMI, atherogenic index of plasma (AIP), and lipid profile. At the 5% significance level ( $p \leq 0.05$ ), all changes were determined to be statistically significant.

## Results

### PCOS Patients and Controls' Clinical and Biochemical Features

Table 1 summarizes the clinical and biochemical features of PCOS and control women. It was found that PCOS participants had substantially higher BMI, waist circumference (WC), homocysteine, and CRP levels than control subjects (all  $p < 0.001$ ). The value of AIP differs significantly between PCOS and control participants ( $0.5 \pm 0.16$  vs  $0.10 \pm 0.11$ ,  $p = 0.002$ ). In addition, TSH, TG, and total cholesterol (TC) levels were higher in PCOS than in controls (all  $p < 0.05$ ); although FT4 and HDL-c levels were lower (all  $p < 0.05$ ).

### Clinical and Biochemical Characteristics of PCOS Women Categorized by Thyroid Disorders Categories

Further subdivision of PCOS patients is done by types of thyroid disorders; hypothyroidism, subclinical hypothyroidism, hyperthyroidism, and subclinical hyperthyroidism. Besides, higher ubiquity of hypothyroidism was observed in PCOS compared to the ubiquity of hyperthyroidism (55% vs 27.5%,  $p = 0.05$ ). Whereas a lower ubiquity of subclinical hypothyroidism and subclinical hyperthyroidism (15% vs 2.5%) were observed. As demonstrated in Table 2, women with relatively elevated TSH levels (hypothyroidism) had significantly higher WC, FBG, BMI, and lower HDL-C compared

**Table 1** Clinical and Biochemical Characteristics in PCOS Patients and Controls

Parameter	PCOS Patients n=200	Control n=200	p-value
Age (years)	33.5±10.13	37.5±11.21	—
FBG (mmol/L)	5.3±0.27	4.8±0.37	>0.05
LDL-C (mmol/L)	2.47±0.45	2.25±0.23	>0.05
HDL-C (mmol/L)	0.85±0.60	1.5±0.72	0.02*
Total cholesterol (TC)(mmol/L)	6.89±0.99	5.12±0.27	0.03*
Triglycerides (TG) (mmol/L)	2.95±1.94	1.89±1.24	0.04*
AIP= log (TG/ HDL-C)	0.5±0.16	0.1±0.11	0.002**
BMI (kg/m <sup>2</sup> )	33.57±9.56	24.37±8.56	0.03*
Waist circumference (WC) cm	138±22.36	87±15.19	0.03*
Homocysteine (μmol/L)	110.59±21.54	15.5±7.12	0.001**
CRP (mg/l)	29.9±11.21	9.2±7.11	0.002*
TSH μIU/mL	6.8±3.21	1.2±0.51	0.001**
FT4 ng/dL	0.5±0.31	1.2±0.31	0.002**

**Notes:** Data were obtained as the mean ± (SD) for continuous variables; p-value was obtained from one-way ANOVA. \* $p \leq 0.05$ , \*\* $p \leq 0.001$ .

**Table 2** Characteristics of PCOS Women According to Categories of Thyroid Disorders

Parameter	Hypothyroidism	Subclinical Hypothyroidism	Hyperthyroidism	Subclinical Hyperthyroidism	P-value
	n=110 (55%)	n=30 (15%)	n=55 (27.5%)	n=5 (2.5%)	
FBG (mmol/L)	6.8±0.77	4.6±0.87	5.1±0.64	4.8±0.67	0.05*
LDL-C (mmol/L)	2.85±0.73	2.5±0.74	2.70±0.97	2.3±0.75	0.05*
HDL-C (mmol/L)	0.80±0.52	1.0±0.30	1.2±0.30	1.3±0.30	0.03*
Total cholesterol (mmol/L)	5.82±1.89	4.82±0.87	5.80±1.85	4.83±1.35	>0.05
Triglycerides (TG) (mmol/L)	2.99±2.64	1.77±1.14	1.79±2.51	1.75±1.12	0.04*
AIP	0.6±0.42	0.24±0.22	0.17±0.11	0.12±0.10	0.05*
BMI (kg/m <sup>2</sup> )	33.5±15.85	25.5±10.23	21.5±11.24	20.5±11.24	0.04*
Waist circumference (WC) cm	125±42.12	100±33.10	88.5±20.11	87±21.10	0.03*
Homocysteine (μmol/L)	89.5±21.12	60.5±28.12	50.5±21.11	20.5±10.13	0.003*
CRP (mg/l)	27.8±15.11	20.8±11.10	15.6±12.13	10.0±5.2	0.04*
TSH μIU/mL	5.9±3.14	5.2±3.11	0.32±0.10	0.31±0.15	0.001**
FT4 ng/dL	0.4±0.31	0.88±0.74	1.89±0.81	0.87±0.41	0.002**

**Notes:** Data were obtained as the mean ± (SD) for continuous variables, P-value was obtained from one-way ANOVA. \*P≤0.05, \*\*P≤0.001. Primary Hypothyroidism: serum high TSH > 4.94 μIU/mL and low FT4 < 0.7 ng/dL. Primary Hyperthyroidism: serum low TSH < 0.35 μIU/mL and high FT4 > 1.48 ng/dL. Subclinical Hypothyroidism: increased TSH values with normal FT4 levels. Subclinical Hyperthyroidism: decreased TSH values with normal FT4 levels.

with the hyperthyroidism group (all  $p < 0.05$ ). Also, substantial differences between the hypothyroidism and hyperthyroidism groups in the levels of LDL-C, TG, Homocysteine, and CRP (all  $p < 0.001$  and  $< 0.05$ , Table 2) were detected. Furthermore, observed PCOS women with hypothyroidism were at high risk of CVD as indicated by AIP value ( $0.6 \pm 0.42$ ) compared with other groups.

## Analysis of PCOS and Hypothyroidism in Females and the Risk of CMRFs

Cardiometabolic risk factors (CMRFs) includes high LDL-C, high triglycerides, low HDL-C, hyperglycemia (high blood glucose levels), obesity, increased waist circumference, and high CRP levels.<sup>16</sup> Therefore, the associations of high levels of TSH, CRP, and Homocysteine with CMRFs in women with PCOS and Hypothyroidism were analyzed. The participants with hypothyroidism have a significant positive association between CRP levels and cardiometabolic variables evaluated such as FBG, TG, AIP, and BMI, except FT4 ( $r = -0.52$ ;  $p = 0.04$ ). Also, it is positively correlated with high levels of TSH (all  $p < 0.05$ , Table 3).

In the same group, FBG ( $r = 0.72$ ;  $p = 0.03$ ), LDL-C ( $r = 0.60$ ;  $p = 0.02$ ), TG ( $r = 0.82$ ;  $p = 0.01$ ), AIP ( $r = 0.53$ ;  $p = 0.02$ ), TSH ( $r = 0.52$ ;  $p = 0.05$ ), and CRP ( $r = 0.61$ ;  $p = 0.04$ ) correlated positively, while HDL-C ( $r = -0.56$ ;  $p = 0.03$ ) were negatively correlated with Homocysteine levels (Table 3). In addition, the high TSH levels positively correlated with CMRFs variables such as TG ( $r = 0.57$ ;  $p = 0.02$ ), BMI ( $r = 0.56$ ;  $p = 0.04$ ), AIP ( $r = 0.54$ ;  $p = 0.02$ ), and WC ( $r = 0.54$ ;  $p = 0.05$ ) but negatively correlated with HDL-C and FT4 ( $r = -0.54$ ;  $p = 0.05$ ,  $r = -0.82$ ;  $p = 0.003$ , respectively).

## Discussion

This analysis of PCOS patients with hypothyroidism is the first to examine the correlation between TSH and CMRFs. In our cohort, the higher ubiquity of hypothyroidism was detected in PCOS compared to the prevalence of hyperthyroidism (55% vs 27.5%). While a lower prevalence of subclinical hypothyroidism and subclinical hyperthyroidism (15% vs 2.5%) were revealed. This is in agreement with earlier studies. For example, Nanda et al study report that out of 196 cases of PCOS, 1.02% had hyperthyroidism, and 13.26% had hypothyroidism.<sup>17</sup> Also, Ozdemir et al identified that there were 107 women with PCOS, 15.9% of patients had hypothyroidism and 1.8% had hyperthyroidism.<sup>18</sup>

In this study, researchers discovered evidence that PCOS patients with moderately elevated TSH levels and had a higher risk of CVD development. It was discovered that the PCOS women with hypothyroidism had high levels of TSH, CRP, and Homocysteine, which were considered previously as important independent predictors of high CVD

**Table 3** Pearson's Correlation Coefficients Between Key Variables in Women with PCOS and Hypothyroidism

Parameter	CRP		Homocysteine		TSH	
	<i>r</i>	<i>P</i>	<i>r</i>	<i>P</i>	<i>r</i>	<i>P</i>
<b>FBG (mmol/L)</b>	<b>0.531</b>	<b>0.03*</b>	<b>0.721</b>	<b>0.03*</b>	0.242	>0.05
<b>LDL-C (mmol/L)</b>	0.221	>0.05	<b>0.601</b>	<b>0.02*</b>	0.212	>0.05
<b>HDL-C (mmol/L)</b>	0.121	>0.05	−0.562 <sup>#</sup>	0.03*	−0.542 <sup>#</sup>	0.05*
<b>Total cholesterol (mmol/L)</b>	0.213	>0.05	0.221	>0.05	0.311	>0.05
<b>Triglycerides (TG) (mmol/L)</b>	<b>0.541</b>	<b>0.01*</b>	<b>0.821</b>	<b>0.01*</b>	<b>0.572</b>	<b>0.02*</b>
<b>AIP</b>	<b>0.534</b>	<b>0.02*</b>	<b>0.532</b>	<b>0.02*</b>	<b>0.541</b>	<b>0.02*</b>
<b>BMI (kg/m<sup>2</sup>)</b>	0.131	>0.05	0.311	>0.05	<b>0.564</b>	<b>0.04*</b>
<b>Waist circumference (WC) cm</b>	0.141	>0.05	0.110	>0.05	<b>0.546</b>	<b>0.05*</b>
<b>Homocysteine (μmol/L)</b>	<b>0.612</b>	<b>0.04*</b>	1	–	<b>0.521</b>	<b>0.05*</b>
<b>CRP (mg/l)</b>	1	–	<b>0.612</b>	<b>0.04*</b>	<b>0.537</b>	<b>0.05*</b>
<b>TSH μIU/mL</b>	<b>0.537</b>	<b>0.05*</b>	<b>0.521</b>	<b>0.05*</b>	1	–
<b>FT4 ng/dL</b>	−0.521 <sup>#</sup>	0.04*	0.212	>0.05	−0.823 <sup>#</sup>	0.003**

**Notes:** P-values were obtained from Pearson's correlation; Starred values point to a significant level. Bold positive correlation; <sup>#</sup>Negative correlation.

\*P≤0.05, \*\*P≤0.001.

risk. In addition, the study revealed significant strong associations between them and traditional CMRFs such as fasting blood glucose levels, BMI (obesity indicators), triglycerides, and waist circumferences (central obesity indicator).

The first evidence that supported the study's hypotheses is that serum TSH level was substantially higher in the PCOS population with an increase in the BMI, WC, and triglycerides levels associated with a high value of AIP, which is an essential indicator for CVD. Some studies in adults who have hypothyroidism (high levels of TSH) showed that there was an association with adverse cardiovascular outcomes, for example, carotid intima thickness,<sup>19,20</sup> coronary heart disease,<sup>21</sup> heart failure<sup>22</sup> and stroke.<sup>23</sup>

Evidence suggests that CRP may greatly indicate CVD and chronic vessel inflammation.<sup>24,25</sup> This is because a growing CRP level may serve as a signal of circulating inflammatory markers before acute events occur. There is a correlation between elevated levels of CRP and the development of CVD.<sup>26</sup> Previous studies were used to determine how PCOS and hypothyroidism affected CRP levels in Saudi women. CRP, thyroid stimulating hormone, and triglyceride levels were considerably higher in patients with PCOS who had a high cardiovascular risk, as defined by AIP (0.21); although HDL-C were lower. Patients with elevated CRP levels also tended to be overweight, as measured by their BMI and WC, suggesting that CRP may indirectly impair cardiovascular health by influencing cardiometabolic factors. CRP levels were inversely related to WC, BMI, and AIP. CRP is correlated with measures of obesity such as BMI, adiposity, and, WC, according to previous cross-sectional studies.<sup>27,28</sup>

In addition, recent studies have shown that elevated homocysteine levels are associated with an increased risk of CVD.<sup>29</sup> Researchers believe that homocysteine causes endothelial dysfunction, which in turn causes vascular damage and CVD.<sup>30</sup> Several other studies have shown a correlation between homocysteine and CVD, although most of these studies failed to consider the impact of other traditional CVD risk factors. Even after accounting for established CVD risk variables such as fasting blood glucose, triglyceride levels, HDL-C, BMI, and adiposity index, a high homocysteine level may be an independent predictor of increased CVD risk in PCOS women with hypothyroidism. Homocysteine's effect on cardiometabolic variables may have a knock-on effect on cardiovascular health. From the results of our research, we conclude that PCOS patients with hypothyroidism and an elevated AIP value are more likely to have high levels of homocysteine, which is associated with elevated glucose, low-density lipoprotein (LDL), and triglyceride levels.

Based on the findings, it was evaluated that women with PCOS are at high risk of hypothyroidism as indicated by high levels of TSH, which was positively correlated with increasing the risk of CVD through its influencing on raising the levels of CRP, Homocysteine, triglycerides, and BMI. The research is the first to evaluate in-depth the connection between TSH levels and CMRFs in PCOS patients. Therefore, the link between thyroid profile and CMRFs in PCOS

patients may be better detected. A limited sample size, however, is one of the study's drawbacks. Prospectively, this research may be conducted with a bigger sample size.

## Conclusion

There was an association between the PCOS and thyroid dysfunction as the TSH levels of the PCOS hypothyroid groups were significantly higher than the control groups, and the CMRFs were significantly high in the PCOS hypothyroid groups. This group was at high risk of CVD due to high levels of CRP, Homocysteine, triglycerides, and obesity. Therefore, physicians need to monitor the thyroid profile, CRP, and homocysteine levels of PCOS patients and treat the thyroid dysfunction that may assist in managing menstrual irregularities and infertility and reduce the risk of CVD.

## Data Sharing Statement

The dataset produced for this study is accessible on request to the corresponding author.

## Ethics Approval Statement

Ethical authorization to carry out the study was obtained from the Ethical Committee at the College of Applied Medical Sciences (CLN201704), Taibah University, and Madinah.

## Consent

Written informed consent was obtained according to the Helsinki guidelines.

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## Author Contributions

All authors made a significant contribution to the work reported, whether in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

## Disclosure

There is no conflict of interest.

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