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Association Between Lipid Profiles, Frequency of Thyroid Hormone and Insulin Resistance in Poly Cystic Ovarian Syndrome

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Abstract

The Polycystic ovarian syndrome is a feature of the various menstrual cycles, infertility, hormonal irregularities, and hyperandrogenism. Insulin resistance, lipedema and hyperandrogenism are the most widespread endocrine disorder in PCOS. Most half of women with PCOS suffer from hirsutism, weight gain, metabolic syndrome, insulin resistance, hypothyroidism, and dyslipidemia. The Aim of the Study is to measure thyroid function, especially hypothyroidism in women with the polycystic ovarian syndrome and its association with insulin resistance. It also aims to estimate the effect of hypothyroidism on the level of each of the following biochemical parameters: lipid profile, glucose, insulin, anti mullerain hormones, sex hormone and thyroid disorders frequency (hypothyroidism) in PCOS.

Subjects, Materials and Methods: This study was performed on patients in the outpatient clinics of the Obstetrics, Gynecology and Infertility Clinic *and* at the al-Yarmouk Teaching Hospital in 2020, and it included 30 (control group) and 70 patients, including 35 euthyroid PCOS and 35 hypothyroidism PCOS (PCOS group), in the age group 15-45 years. Thyroid hormone levels Thyroxine (FT3, FT4) and Thyroid Stimulating Hormone (TSH), Luteinizing Hormone (LH), Follicle Stimulating Hormone (FSH), Prolactin (PRL), Testosterone, Progestogen, Estradiol (E2), Anti Mullerian Hormones (AMH), Thyroperoxidase Anti Bodies (anti TPO), Insulin were measured by using a device cobas e411, and Lipid profile and Glucose by using a device cobas c311.

Results: There was an increase in TSH levels, a decrease in thyroxine, an increase in lipid profile levels, an increase in the sex hormones levels, increase glucose and insulin resistance which is a sign of diabetes type 2. However, the reverse is noticed in the relation of hypothyroidism on PCOS with weight gain, lipids, insulin resistance, androgynism and hirsutism. The most frequent thyroid disorders affecting PCOS in this study were found to be autoimmune thyroiditis and hypothyroidism.

Conclusions: More than half of the women with PCOS suffer from hypothyroidism, compared to the normal women. As it was observed that dyslipidemia, weight gain, hirsutism, insulin resistance and sex hormones were more in hypothyroidism PCOS women compared to normal control subjects. We also concluded that PCOS and hypothyroidism are interrelated, as the presence of either is a cause of the other and that means the PCOS is more than just oligomenorrhea, amenorrhea, or infertility.

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1. Introduction

Polycystic ovary syndrome is the most usual endocrine disorder in adult women between (15 to 44) years [1]. When women are infertile because the absence of ovulation, the most likely source is PCOS. The first discovery of this syndrome was in 1721 in Italy [2]. Polycystic ovary syndrome (PCOS) is a collection of symptoms in women like variation in sex hormones, elevated androgens (male hormones) (hyperandrogenemia), increase in luteinizing hormone levels (LH) with normal or moderately increased levels of follicle-stimulating hormone (FSH), thyroid-stimulating hormone (TSH) and prolactin (PRL), [3]. Low concentration of free thyroxin (FT4, FT3) with an increase in the sex hormone binding-globulin (SHBG), insulin, and glucose, Irregular or absent menstrual periods, heavy periods, excess weight, acne, pelvic pain, facial hair, and difficulty pregnancy are the most prevalent symptoms of PCOS. PCOS linked cases include weight gain, mood disorders, heart disease and appear cancer of endometrial, and type 2 diabetes [4].

PCOS produce from a mixture of inherited and environmental factors [5]. Risk factors of late effects include obesity, absence of exercise, cardiovascular disease and a family history of this case. Diagnosis is usually used are Rotterdam criteria that refer to presence of the PCOS to be found in any 2 from 3 criteria, in the absence of other diseases that may cause these results.[6]: 1-No ovulation, 2-High androgen levels, 3- Ovarian cysts (Figure 1).

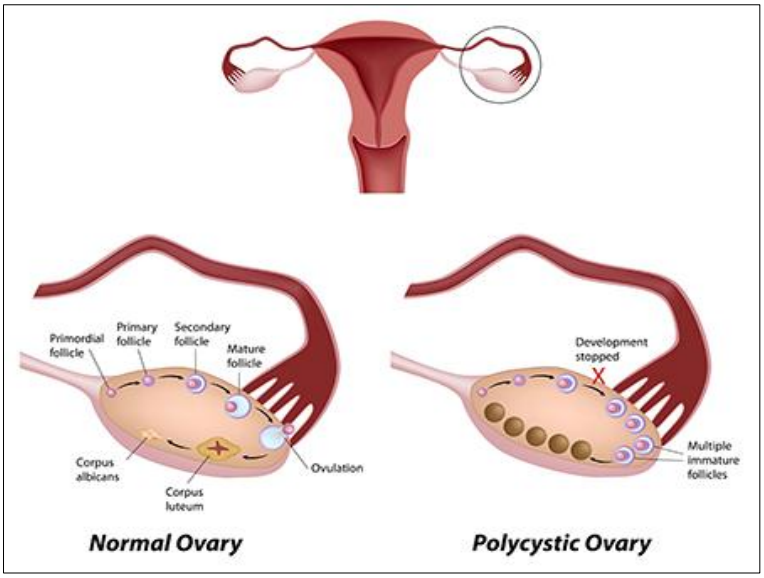

Figure 1. Polycystic ovarian [14].

It occurs in a normal menstrual cycle, is released one ova from a dominant follicle when the ova size reaches to 16 mm the ovulation occurs after approximately 12–14 days when the follicle remnant is converted into corpus luteum, which contracts and produces progesterone-. In PCOS this process does not occurs because the ova size reaches to 5-7 mm there is something -called "follicular arrest" No single follicle reaches to size (16 mm or more), [3].

The follicles may be directed along the periphery of the ovary, and appear as a string of pearls on an ultrasound scan. These "cysts" are truly unripe follicles not cysts. The follicles have initiated to grow but the growth has pause ("arrested") at an early stage due to ovarian function disorder.

Polycystic ovary syndrome (PCOS) and Thyroid disorders are two of the most common endocrine disorders in the general woman. Despite the etiopathogenesis of hypothyroidism and PCOS being completely different, these two diseases have many features in common. The development in ovarian volume and cystic increase in ovaries in primary hypothyroidism. Additionally, a thyroid defect has been noticed to be more common in women with PCOS than in normal women. [8] (Figure 2) with hypothyroidism may present menstrual cycle defect, weight gain, hyperandrogenism signs, and infertility may appear, which can be recognized by slight increase in estradiol (E2), increased total and free testosterone (FT) levels, rise luteinizing hormone (LH), high prolactin (PRL) and low concentration of sex hormone binding-globulin (SHBG) levels, [9]. Dyslipidemia and insulin resistance (hyperglycaemia) are also found in hypothyroidism.

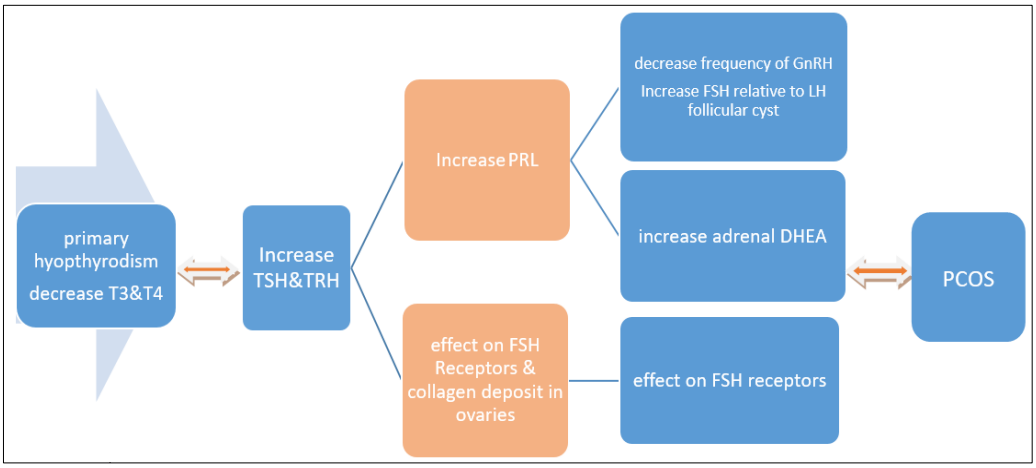

Figure 2. The inverse relationship between a PCOS and hypothyroidism, [8].

Cholesterol synthesis occurs in the liver. Also, a rate-limiting enzyme in cholesterol synthesis is 3-Hydroxy-3-Methyl-Glutaryl Coenzyme Reductase (HMGCR), which is controlled by some hormones, like insulin, glucocorticoid, glucagon, estrogen and thyroid hormone [10]. In hypothyroid status, HMGCR mRNA levels are decreased and therapy with thyroid hormone returns it to the normal level. Thyroid hormone induces HMGCR transcription. [11]. Thyroid hormone plays an essential role in lipolysis and lipogenesis, thyroid hormone maintains Lipoprotein Lipase (LPL) an enzyme that controls for removing Triglycerides (TG) from circulating chylomicrons and Very Low Density Lipoproteins (VLDL). LPL catalyzes TG breakdown into non-esterified fatty acid and transporting it to adipose tissue where it is re-esterified and storage as TG (Figure 3). In hypothyroidism are slightly elevated triglyceride levels and increase serum levels of total cholesterol, LDL, while HDL-are low, that's lead to atherosclerosis, [12].

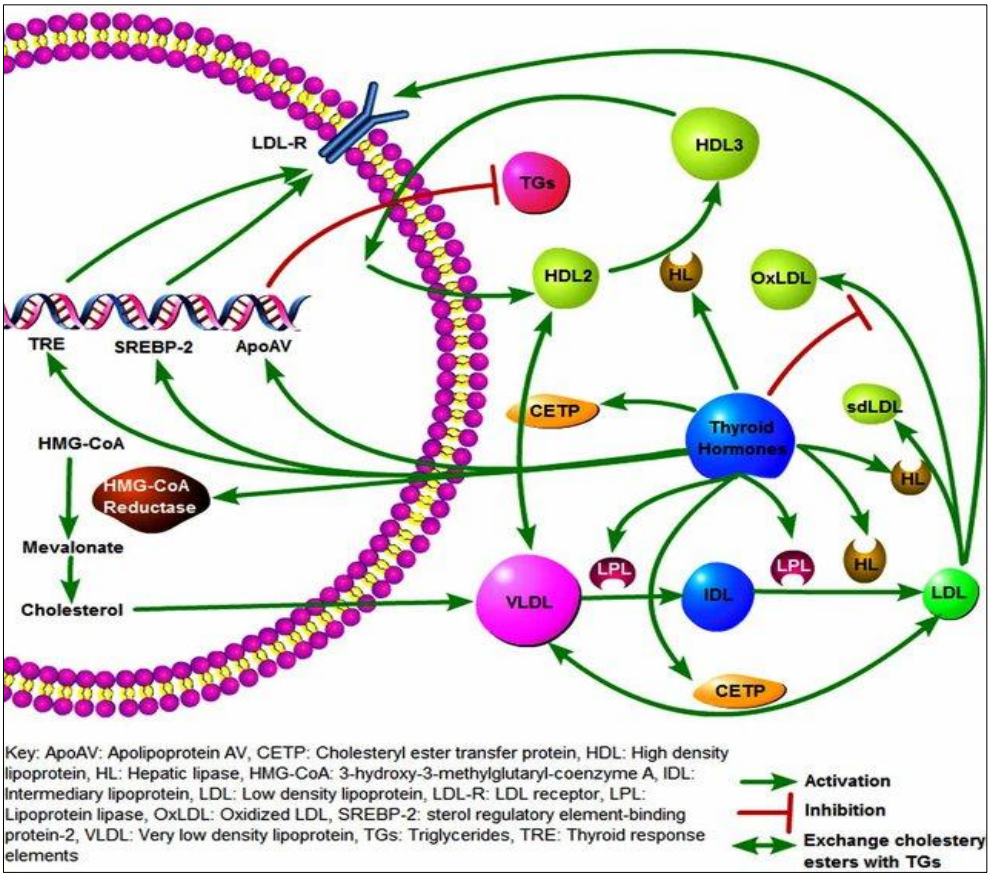

Figure 3. Effect of thyroid gland on lipid metabolism, [11].

Insulin resistance means that the body is less able to send glucose to the body cells as a source of energy, in other words, it cannot use insulin well. It leads to the production of larger quantities of the pancreas to maintain sugar levels which leads to the accumulation of insulin levels in the body and may lead to negative effects such as high levels of androgens, the male hormone, especially testosterone, which in turn increases the symptoms of acne, hirsutism and Obesity, which worsens the symptoms of PCOS, can also worsen the emergence of type 2 diabetes [13]. Increased insulin also leads to changes in the skin, such as skin tags and dark areas [14] (Figure 4).

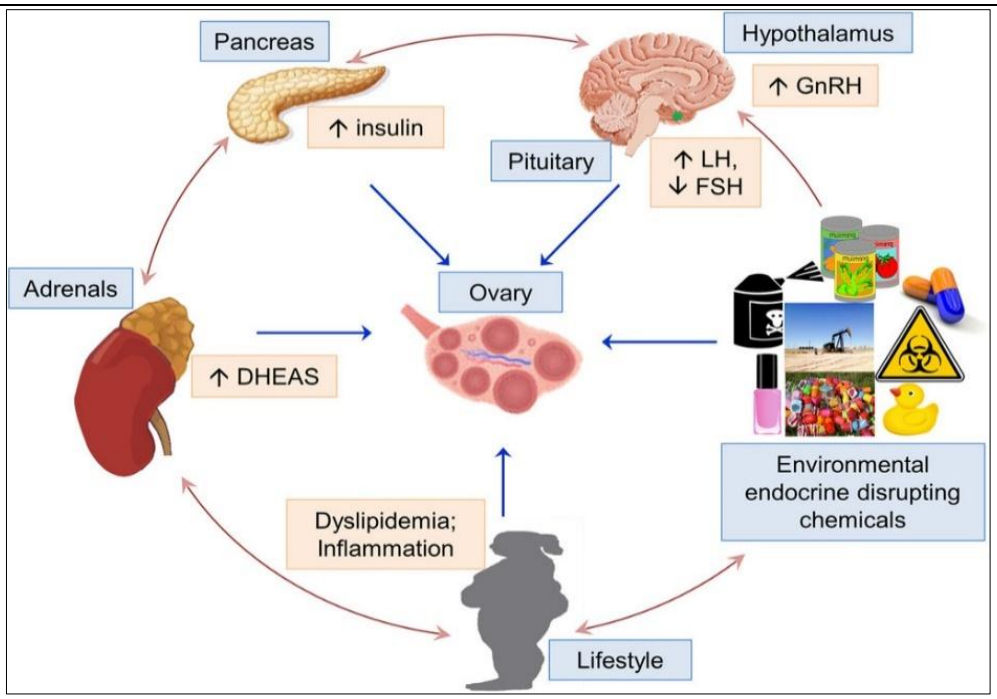

Figure 4. Relationship between BMI with PCO& its complications [8], where LH: Luteinizing Hormone, FSH: Follicle-Stimulating Hormone, where DHEA-S: Dehydroepiandrosterone sulfate, GnRH: Gonadotropin-releasing hormone.

2. Subject, Materials and Methods

This research was conducted on patients coming to the Department of obstetrics, gynecology and infertility clinic at an al-Yarmouk teaching hospital and Outpatient Clinics in 2020.This study included 100 patients, including 30 (control group), 35 Euthyroid PCOS and 35 hypothyroidism PCOS (PCOS group), in the age group 15-45 years. Hormones were measured TSH, FT3, FT4, FSH, LH, PRL, Testosterone, Progestogen, Estradiol, AMH, Anti TPO and Insulin. Using a device Cobas e411, likewise lipid profile and glucose were measured by using a device Cobas c311.Calculation Cobas C systems automatically calculate the analytic concentration of each sample.

- **Control inclusion criteria**
  1. Healthy.
  2. Mental.
  3. Not using any form of medication.
- **Control exclusion criteria**
  1. Positive past-medical history (cardiovascular diseases, hypertension, renal diseases, etc.).
  2. Positive past-surgical history (any surgical like nephrectomy, thyroidectomy, hysterectomy etc.).
  3. Diabetic.
- **The control hasn't operations in past history or any diseases**

Statistical Analysis: Data was expressed as mean ± SD and percentage. The mean ($\bar{X}$) and the standard deviation (SD) was calculated by using the following equation:

$$SD = \sqrt{\frac{\sum(X-\bar{X})^2}{N-1}}$$

where:

SD = standard deviation.

X = each value in the data set.

$\bar{X}$ = mean of all values in the data set (mean of X).

N = number of values in the data set.

Adopting p value < 0.05 of statistically significant level by Student's t-test, Microsoft Excel (2007) was used to complete statistical calculations, the following equations were also used

BMI = weight (Kg)/square high (m^2)

HOMA-IR = fasting insulin (μU/L)×fasting glucose (mg/dl)/405.

3. Results

Biochemical parameters and Clinical were estimated and compared amongst euthyroid controls (n = 30), hypothyroidism PCOS (n = 35), and euthyroid PCOS (n = 35) (Table 1).

Table 1. Clarifies the comparison in clinical and biochemical tests for hypothyroidism PCOS, euthyroid PCOS, and euthyroid control.

	hypothyroidism PCOS (= 35)(mean ± SD)	**Euthyroid PCOS (= 35)(mean ± SD)**	**Euthyroid control (=30) (mean ± SD)**	***p* value**
Age (years)	28.21 ± 5.9	25.37 ± 4.5	27.1 ± 3.9	NS
BMI (Kg/m^2)	31.70 ± 4.9	29.91 ± 5.1	26.3 ± 4.7	0.01**
Hypertension (%)	8 (25.9)	12 (16.17)	6 (5.5)	0.001*
Hirsutism (%)	26 (92%)	53 (75%)	5 (5%)	0.01**
Ferriman and Gallwey score	21.91 ± 5.3	19.37 ± 4.9	9.21 ± 4.3	0.01**
LH (mIU/ml)	14.12 ± 7.6	11.7 ± 6.8	5.21 ± 3.7	0.01**
FSH (mIU/ml)	4.6 ± 1.9	4.9 ± 1.8	4.31 ± 1.9	NS
LH/FSH ratio	2.7 ± 0.5	2.6 ± 0.7	1.3 ± 0.29	NS
Free T3 (pg/ml)	2.32 ± 1.3	2.92 ± 1.3	3.92 ± 0.7	NS
Free T4 (ng/dl)	1.1 ± 1.0	1.33 ± 1.1	1.42 ± 1.6	NS
TSH (mIU/ml)	7.7 ± 3.5	3.1 ± 1.5	3.3 ± 1.2	< 0.01**
Anti-TPO ab (IU/ml)	137.54 ± 51.8	31.59 ± 5.1	19.73 ± 10.3	< 0.001*
Free testosterone (pg/ml)	25.09 ± 6.3	19.34 ± 7.9	11.2 ± 5.7	< 0.01**
Estradiol (pg/ml)	76.24 ± 29.26	61.83 ± 26.7	57.31 ± 18.6	NS
Progesterone (ng/ml)	2.3 ± 0.6	2.8 ± 1.2	7.6 ± 4.3	NS
SHBG (nmol/L)	33.7 ± 12.8	35.9 ± 14.9	41.5 ± 21.6	0.02*
PRL(µg/L)	19.8 ± 14.9	17.47 ± 7.2	15.5 ± 5.8	0.03*
Glucose (mmol/L)	4.99 ± 0.5	4.59 ± 0.5	4.4 ± 0.5	0.01**
Insulin(mu/L)	14.7 ± 3.2	13.0 ± 3.2	8.3 ± 2.2	0.03*
HOMA-IR	4.3 ± 1.1	2.9 ± 1.4	1.7 ± 0.7	0.01**
Total cholesterol (mg/dl)	240 ± 29.6	200 ± 23.1	149 ± 24.8	0.01**
Triglycerides (mg/dl)	146 ± 21.3	110 ± 16.7	94.3 ± 10.6	0.001**
LDL Chol. (mg/dl)	161 ± 17.3	139 ± 12.6	110 ± 20.4	0.02*
HDL Chol. (mg/dl)	36.4 ± 15.4	44.9 ± 9.6	60.9 ± 5.2	0.04*

NS between hypothyroidism PCOS and Euthyroid PCOS, $*p < 0.05$; statistically significant; $**p < 0.01$; statistically high significant.

3.1 Age and BMI of hypothyroidism PCOS, PCOS for Euthyroid, and Euthyroid control group:

PCOS for hypothyroidism, PCOS for Euthyroid, and Euthyroid thyroid control groups were all compared with age and BMI. The average age of participants was (28.21 ± 5.9) years for the hypothyroidism PCOS group and (25.37 ± 4.5) for the euthyroid PCOS and (27.1 ± 3.9) for the control group years. The hypothyroidism PCOS group displayed significantly higher average body mass index (BMI; 31.70 ± 4.9kg/m^2) compared to euthyroid PCOS (29.91 ± 5.1) and the euthyroid control group mass index (BMI; 26.3 ± 4.7 kg/m^2).

3.2 Sex hormonal parameters of PCOS for hypothyroidism, PCOS for Euthyroid and Euthyroid control group:

It was found that The hypothyroidism PCOS were having significantly increase LH (14.12 ± 7.6) compared to euthyroid PCOS (11.7 ± 6.8) and the euthyroid control group (5.21 ± 3.7) ($p < 0.01$), LH/FSH ratio (2.7 ± 0.5) in The hypothyroidism PCOS and Euthyroid PCOS (2.6 ± 0.7) were having significantly higher compared to the euthyroid control group (1.3 ± 0.29), and HOMA-IR (4.3 ± 1.1) higher in The hypothyroidism PCOS compared to euthyroid PCOS(2.9 ± 1.4) and the euthyroid control group (1.7 ± 0.7). On estimation of thyroid function significantly in The hypothyroidism PCOS higher TSH (7.7 ± 3.5) compared to PCOS for euthyroid and the control group for euthyroid ($p < 0.01$),and anti-TPO ab in PCOS for The hypothyroidism (137.54 ± 51.8) very higher compared to PCOS for euthyroid and the control group for euthyroid ($p < 0.001$), levels and significantly in The hypothyroidism PCOS lower T3 (2.32 ± 1.3) compared to euthyroid PCOS (2.92 ± 1.3) and the euthyroid control group (3.92 ± 0.7), Thyroxine levels were found to be partially lower in The hypothyroidism PCOS and Euthyroid PCOS compared to the euthyroid control group. Free Testosterone levels were higher in the hypothyroidism PCOS (25.09 ± 6.3) compared to euthyroid PCOS (19.34 ± 7.9) and the latter was higher than the euthyroid control group (11.2 ± 5.7), while levels of estradiol increase and progesterone were lower in the hypothyroidism PCOS compared with euthyroid PCOS and less than the euthyroid control group.

PCOS and control groups were matched with E2, AMH, AMH for the PCOS group was two to three times higher (3.3±1.4) pmol/L than the control group, and the group of PCOS showed estradiol (67.34 ± 45.21) Pg/ml much more

than the control group, therefore the fertility period was less in PCOS Compared with the control group (Table 2).

Table 2. Describes the effect of E2 and AMH in the PCOS group on fertility.

Variable	Min-Max	Mean± SD
Estradiol Pg/ml	11.0-185.3	67.34 ± 45.21
AMH pmol/L	0.6-6.7	3.3 ± 1.4

E2, Estradiol; AMH, Anti-Mullerain Hormone.

3.3 Frequency of thyroid disorders:

It was observed that the frequency of thyroid disorders was significantly higher in PCOS, it was found that the percentage of the PCOS group was 24% of overt hypothyroidism, 28% of patients with autoimmune thyroiditis (AIT), 5% with subclinical hypothyroidism, and 18% of those with goitre, the control group was found to have subclinical hypothyroidism 2% (0.01), only 4% AIT (< 0.001), overt hypothyroidism 10% (= 0.0002), and 9% goitre (< 0.02) (Table 3).

By the presence of anti-TPO antibody, autoimmune thyroiditis (AIT) with a radiographic ultrasound examination (USG) was diagnosis. And subclinical hypothyroidism was diagnosed with high TSH levels > (4.0 mIU / mL) with thyroxin hormones (T4, T3) levels within the normal range, and overt hypothyroidism was diagnosed when levels of TSH > (4.0 mIU / mL) and levels of T3 and T4 were below normal. goiter by clinical examination and ultrasound.

Table 3. Frequency of thyroid disorders (hypothyroidism) between PCOS and control groups.

Thyroid disorder	PCOS n (%)	Control n (%)	p value
Subclinical Hypothyroidism	5	2	0.01∗
Autoimmune thyroiditis	28	4	<0.001**
Overt hypothyroid	24	10	0.0002**
Goitre	18	9	0.02∗

∗p < 0.05; statistically significant; **p < 0.001 statistically high significant

3-4 Lipid Parameters and glucose of hypothyroidism PCOS, Euthyroid PCOS, and Euthyroid Control Subjects.

Lipid parameters, total cholesterol in the hypothyroidism PCOS (240 ± 29.6) and euthyroid PCOS (200 ± 23.1) higher subjects compared to the euthyroid control group (149 ± 24.8). The TG in hypothyroidism PCOS (146 ± 21.3) and euthyroid PCOS (110 ± 16.7) higher subjects compared to the euthyroid control group (94.3 ± 10.6) and LDL in The hypothyroidism PCOS (161 ± 17.3) and euthyroid PCOS (139 ± 12.6) higher subjects compared to the euthyroid control group (110 ± 20.4), while HDL in the hypothyroidism PCOS (36.4 ± 15.4) and euthyroid PCOS (44.9 ± 9.6) was found to be significantly decrease compared to control group of the euthyroid (60.9 ± 5.2). Glucose in the hypothyroidism PCOS (4.99 ± 0.5) and euthyroid PCOS (4.59 ± 0.5) higher subjects compared to the euthyroid control group (4.4 ± 0.5) (Table 1).

4. Discussion

The possible mechanism of hypothyroidism in PCOS is associated obesity (high body mass index). Insulin resistance may lead to decrease deiodinase-2 activity, resulting in relatively low levels of T3 and higher levels of TSH. A mechanism has also been proposed indicating obesity that leads to increase levels of leptin (Figure 5), which stimulates the hypothalamus, leading to increased secretion of TRH. both of these pathways may work simultaneously explaining the higher incidence of hypothyroidism in PCOS. [15]. Based on the results of our study, PCOS is associated with hypothyroidism compared to normal women, through increased TSH levels, decreased levels of FT3 and FT4, and increased hirsutism closely with increased testosterone and a significant increase in LH, with little or no change in FSH Increased levels of the hormone estradiol and decreased progesterone, leading to decreased ovulation and infertility and in the long term to endometrial accumulation which is a major risk factor for uterine cancer. [16]. The action of hypothyroidism on HOMA-IR was also evaluated (Table 1). It was found that HOMA-IR in thyroid PCOS is significantly increased compared to thyroid controls. [9]. In their study they found an association between elevated levels of TSH and insulin resistance, increased insulin resistance in hypothyroidism due to failure transport of GLUT-4 insulin receptors found in fat and muscle cells. [17]. We also found an elevated lipidemic in the thyroid PCOS group compared to the normal lipidemic group of PCOS, In similar studies Tuzcu et al. and Al-Sayed et al. It reported significantly elevated total cholesterol and LDL cholesterol in hypothyroidism compared to controls. AMH is an important measure of ovarian function, and it is beneficial in evaluating cases such as PCOS and premature failure of ovarian. AMH levels were found to be about two or three times elevated in women with PCOS compared to normal women. The increase in AMH levels is due to an increase in the number of follicles, and the amount of AMH produced per follicle. The increase amount of androgens that are characteristic of PCOS also stimulate an increase in AMH production [18] (Table 2). Also, the most frequency thyroid disorders affecting PCOS in this study were found to be autoimmune thyroiditis and hypothyroidism (Table 3), [19].

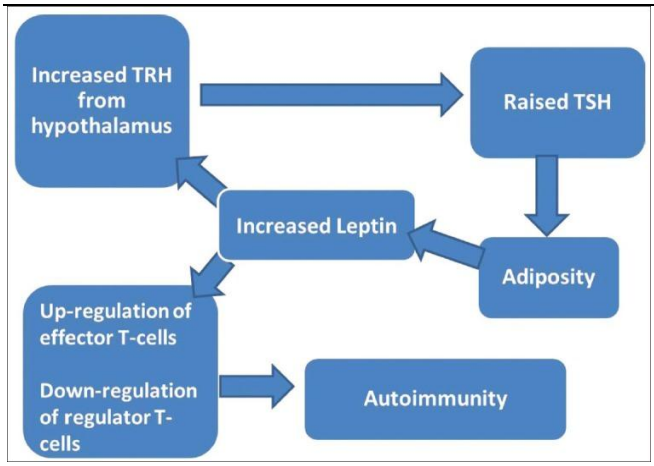

Figure 5. Relationship between increase leptin with secretion of TRH and TSH, where TRH: Thyroid Releasing Hormone, TSH: Thyroid Stimulating Hormone

5. Conclusion

Through our study, we conclude that: PCOS is associated with hypothyroidism a higher rate of compared to normal women. A change in the sex hormones, lipid profile and insulin resistance that leads to type 2 diabetes may also play a role in increasing the body's production of androgen and feeling that women with PCOS are producing the hormone estrogen which in the long term can lead to the accumulation of endometriosis which is a major risk factor for uterine cancer. It was also noted that the AMH hormone increased, which may be a cause of delayed pregnancy or infertility in women with PCOS, and accordingly, PCOS is much more than just oligomenorrhea, menopause, or infertility.

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Conflicts of Interest

The authors declare that there is no conflict of interest.

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