Original article

Does the thyroid hormonal levels alter in polycystic ovarian disease? A comparative cross sectional study

Archana Shirsath[1], Neela Aundhakar[2] , Prathmesh Kamble[3]

[1] Assistant Professor, Physiology, RCSM Government Medical college, Kolhapur

[2] Professor & Head, Department of Physiology, RCSM Government Medical college, Kolhapur

[3] Assistant Professor, Physiology, B.J. Medical College and Sassoon General Hospitals, Pune

Correspondence to: Dr. Archana Shirsath

Abstract

Background: Polycystic ovarian disease (PCOD) is an intense problem which manifests later as infertility, obesity, insulin resistance, dyslipidemia, endothelial dysfunction and overt diabetes mellitus. PCOD is often associated with abnormalities of other endocrine glands. Women with PCOD may be four times more likely to suffer from hypothyroidism.1 Hypothyroidism can aggravate PCOD symptoms. It can lead to low levels of sex hormone binding globulin (SHBG) which in turn can lead to higher concentrations of free testosterone throughout the body. High level of testosterone is one of the factors which contributes to PCOD symptoms like infertility, polycystic ovaries, hirsutism, male pattern hair loss and acne.The study was undertaken to assess thyroid hormonal levels (Triiodothyronine, Thyroxine and Thyroid stimulating hormone) in polycystic ovarian disease patients and compare it with age and gender matched healthy females.

Study methodology: Thyroid hormone level were measured in 60 Subjects within the age group of 20 to 30 years were selected and divided into two groups. Group I consisted of 30 diagnosed female patients of PCOD and Group II comprised of 30 age matched control group with normal menstrual cycles. We measured Thyroid stimulating hormone (TSH) ,Total T3 (Tri-iodothyronine),Total T4 (Thyroxine) In the present study, Thyroid function test (TFT) was done by using Enzyme linked immumosorbant assay (ELISA) method. The T3 ELISA Kit, T4 ELISA Kit and TSH ELISA Kit used in the study, were intended for the quantitative measurement of total T3, total T4 and TSH in human serum by a microplate immunoenzymatic assay. These kits are manufactured by LDN, Labor Diagnostika Nord GmBH and Co.KG, Am Eichenhain 1, Nordhorn. Serum T3, T4 and TSH levels were estimated on Erba Mannheim Company's ELISA washer and reader machine named Erba Lisa Wash and Erba Lisa II. Thyroid hormonal levels were compared by applying unpaired t test

Results: The TSH levels were significantly increased in PCOD patients compared with the healthy controls, while Total T3 and Total T4 levels were normal in both group.

Conclusion: In present study, polycystic ovarian disease patients had subclinical hypothyroidism and probable reason for this is unopposed estrogen which stimulates autoimmune reaction like generation of Thyroid Peroxidase (TPO) antibodies and it may lead to subclinical hypothyroidism in polycystic ovarian disease. Mild hypothyroidism can be difficult to diagnose and is often overlooked. Therefore all patients having polycystic ovarian disease should be subjected to analysis of thyroid hormonal profile so that this common treatable disorder is not missed and is treated in time.

Key word: Polycystic ovarian disease, Thyroid stimulating hormone

Introduction

According to some researchers, a number of women with PCOD may also have an underactive thyroid gland. It has been suggested that undiagnosed mild hypothyroidism complicates PCOD problems, especially if women are obese in spite of regular diet and exercise. Thyroid hormones set the metabolic "thermostat" and if this metabolic thermostat is set at low level, it is difficult to lose weight and avoid cellular

sluggishness. If hypothyroidism is diagnosed and treated early, some of PCOD symptoms may diminish. [1,2] The most common cause of hypothyroidism is autoimmune thyroiditis (AIT) and it also shares the same genetic background with PCOD as both are clustered in families. So it can be assumed that there might be some common genetic defect in both disorders because it seems to have an oligo-genetic background.[3, 4] Autoimmune thyroiditis is supposed to be related to variants in the HLA gene. In contrast PCOD is related to genetic predispositions for insulin resistance, especially defects in insulin signaling pathways, genetic variants in LH, follistatin and to CYP11a, a gene coding for P450 cholesterol side chain cleavage.[5] Other autoimmune reactions are also common in PCOD [6] like production of antiphospholipids antibodies, thyroglobuline antibodies or thyroid peroxidase antibodies.[7] Role of stimulatory antibodies was also speculated as a pathogenetic mechanism of PCOD.[8] Sex hormone binding globulin (SHBG) is a glycoprotein produced in the liver acting as a carrier for different sexual steroid hormones. SHBG displays a higher binding affinity for testosterone and dihydrotestosterone. Hypothyroidism can lead to a reduction of SHBG and increase in free testosterone.[9] In PCOD, plasma binding activity of sex hormone binding globulin is decreased, which results in decreased plasma concentrations of total testosterone but their unbound fractions are increased. Hypothyroid women have decreased rate of metabolic clearance of androstenedione and estrone exhibit an increase in peripheral aromatization. Free testosterone is one of the factors contributing to PCOD symptoms i.e. infertility, polycystic ovaries, hirsutism, male pattern hair loss, and acne. [9]

It has also been proved that adequate levels of circulating thyroid hormone are of primary importance for normal reproductive function. Triiodothyronine modulates follicular stimulating hormone and luteinizing hormone action on steroid biosynthesis, and multiple triiodothyronine binding sites have been identified in mammalian granulosa and stromal cells, and more recently in human oocytes. Any impairment of triiodothyronine concentrations available locally may therefore represent a cause of disruption of the normal female reproductive function.[9] Studies show a threefold higher prevalence of hypothyroidism in PCOD patients hence it has been suggested that all patients with PCOD should be screened for thyroid function and thyroid-specific auto antibodies even without evidence of overt thyroid dysfunction. [1] Common cause is Hashimoto's thyroiditis, an autoimmune disease of the thyroid gland. Other possible causes are thyroid surgery or radiation, some drugs, hormone therapy, dietary deficiencies, and exposure to toxic environmental chemicals and metals. Symptoms of hypothyroidism are fatigue or weakness, weight gain, menstrual problems, lower body temperature, cold extremities, inability to focus, constipation, depression, muscle aches, brittle nails, dry skin, and hair loss. Women with hypothyroidism also are more likely to have velvety, hyper pigmented skin folds called acanthosis nigrans.[2]

Thyroid function test.: Most commonly recommended are [10] Thyroid stimulating hormone (TSH) screening test, Total T3 (Tri-iodothyronine) and Total T4 (Thyroxine). Advanced investigation for further management Free T3, Free T4, TPO antibody – Thyroid peroxidase (TPO) antibody, Thyroglobuline (TG) antibodies, TSH receptor stimulating antibodies, Radioiodine scanning and uptake, Biopsy, Ultrasonography of thyroid gland.

The study aims to assess thyroid hormonal status (Triiodothyronine, Thyroxine and Thyroid

www.ijbamr.com P ISSN: 2250-284X , E ISSN : 2250-2858

stimulating hormone) in polycystic ovarian disease patients and compare it with age matched healthy females.

Materials and Method:

The study was carried out in collaboration with Department of Obstetrics and Gynaecology, Sassoon general hospital and private hospital, Pune. The Institutional Ethics Committee approved the study protocol. Subjects within the age group of 20 to 30 years were selected and divided into two groups. Group I consisted of 30 diagnosed female patients of PCOD. Group II comprised of 30 age matched control group with normal menstrual cycles.

INCLUSION CRITERIA: Patients diagnosed as PCOD by using revised diagnostic criteria (Rotterdam criteria) 11 if 2 out of 3 from the following were present: Oligo and or anovulation , Clinical and biochemical signs of hyperandrogenism , Polycystic ovaries, Female patients in the age group: 20-30 years.

EXCLUSION CRITERIA: Diagnosed cases of diabetes mellitus, thyroid dysfunction, Cushing's syndrome, congenital andrenal hyperplasia, hyperproloctinemia, androgen secreting tumor, renal and liver disorders.

Subjects taking medicines like ovulation induction agents, antiandrogens, antidiabetic, antiobesity, hormonal drugs and current or previous use of oral contraceptives within last 6 months, smoking and alcohol addiction.

Selected patients were thoroughly interviewed in Obstetrics and gynecology department of the institute. Based on inclusion and exclusion criteria, a total of 60 subjects were selected for the present study.

The study protocol was explained in detail to all the subjects and informed written consent regarding participation in the study was obtained from them. Then 5 ml blood sample was obtained from the participants under all aseptic precautions. Then assessment of Thyroid stimulating hormone (TSH) ,Total T3 (Tri-iodothyronine),Total T4 (Thyroxine) was carried out. In the present study, Thyroid function test (TFT) was done by using Enzyme linked immumosorbant assay (ELISA) method. The T3 ELISA Kit, T4 ELISA Kit and TSH ELISA Kit used in the study by a microplate immune-oenzymatic assay. These kits are manufactured by LDN, Labor Diagnostika Nord GmBH and Co.KG, Am Eichenhain 1, Nordhorn. Serum T3, T4 and TSH levels were estimated on Erba Mannheim Company's ELISA washer and reader machine named Erba Lisa Wash and Erba Lisa II. Thyroid hormonal levels were compared by applying unpaired t test.

Results:

Table 1 depicts the physical characteristics of the normal controls as well as the patients of PCOD. Age, height of both the groups was comparable as statistically there was no difference between them ($P>0.05$). Difference in mean values of age between control group (25.60±2.88 yrs) and PCOD group (25.50±2.53 yrs) was not statistically significant. ($p>0.05$) Also the difference in mean values of height between control group (159.80±7.90 cm) and PCOD group (157.80±5.54 cm) was not statistically significant. ($p>0.05$) But weight of the PCOD females was higher than control and the difference was statistically highly significant. ($p<0.001$). Mean value of weight was higher in PCOD group (62.23±5.47 kg) as compared to control group (53.90±7.94 kg) and difference was statistically highly significant. ($p<0.001$)

Table 2 Our study showed that serum levels of T3 of PCOD group (1.30±0.16), when compared with control group (1.26±0.21) was statistically non significant (>0.05). Similarly difference in mean values of T4 of PCOD group (7.87±1.38) and

control group (7.52±1.82) was found to be statistically non significant. (>0.05)

Table 2 and Graph 1,2 show that difference in mean values of levels of TSH of PCOD group (7.13±1.60) was statistically significantly higher ($p < 0.001$) when compared with control group (1.26±0.45).

Discussion:

Our study showed no statistical difference in serum level of T3 ($p>0.05$) and T4 ($p>0.05$). in both group. Thus in our study the thyroid hormone levels i.e. serum levels of T3 and T4 were within normal range in PCOD group (Table 2, Graph 2) The serum TSH levels were higher in PCOD group when compared with control group. The difference was found to be statistically significant ($p < 0.001$) (Table 2 and Graph 1). The present study shows mild increase in serum TSH level with normal serum T3 and serum T4 levels in PCOD group which suggest presence of subclinical hypothyroidism in that group.

Similar result was obtained by Janssen OE et al [12] in his study, which demonstrated a threefold higher prevalence of hypothyroidism in patients with PCOD. This is in accordance with previous studies [13,14,15,16]

Ghosh et al [2] studied the underlying pathophysiological mechanisms of ovarian cyst formation in patients with subclinical and overt hypothyroidism, and observed that the formation of ovarian cysts, similar to those occurring in PCOD may be restricted only to individuals with subclinical hypothyroidism and the patients with severe and long standing hypothyroidism may not show ovarian cyst formation.

The probable cause of this subclinical hypothyroidism found in the present study is not clear. Immune system is finely balanced by interaction of various factors one of which is estrogen-progesterone balance. Normally estrogen has immune stimulatory action and progesterone seems to counteract this action.[12] Thus normally immune stimulatory action is kept in check. However, in PCOD patients, progesterone is absent or nearly absent because of anovulatory cycles.[12] Thus the imbalance of normal to high estrogen levels and low progesterone levels, so called 'unopposed estrogen', causes over stimulation of immune system leading to production of autoimmune antibodies.[12] It has been found that autoimmune reactions are common in PCOD [6] and also it has been demonstrated that in PCOD there is high titer of thyroglobuline(TG) antibodies and thyroid peroxidase (TPO) antibodies which lead to autoimmune thyroiditis.[7] There is high incidence of autoimmune thyroiditis in PCOD subjects and it has been observed that autoimmune thyroiditis and PCOD share same genetic background as both are clustered in same families.[3,4] The most common cause of subclinical hypothyroidism is autoimmune thyroiditis (AIT).[2] This might explain the subclinical hypothyroidism in PCOD patients in the present study.

Conclusion:

In present study, polycystic ovarian disease patients had subclinical hypothyroidism and probable reason for this is unopposed estrogen which stimulates autoimmune reaction like generation of Thyroid Peroxidase (TPO) antibodies and it may lead to subclinical hypothyroidism in polycystic ovarian disease. Therefore all patients having polycystic ovarian disease should be subjected to analysis of thyroid hormonal profile so that this common treatable disorder is not missed and is treated in time.

Table1: Descriptive characteristics of baseline parameters in control group and PCOD group:

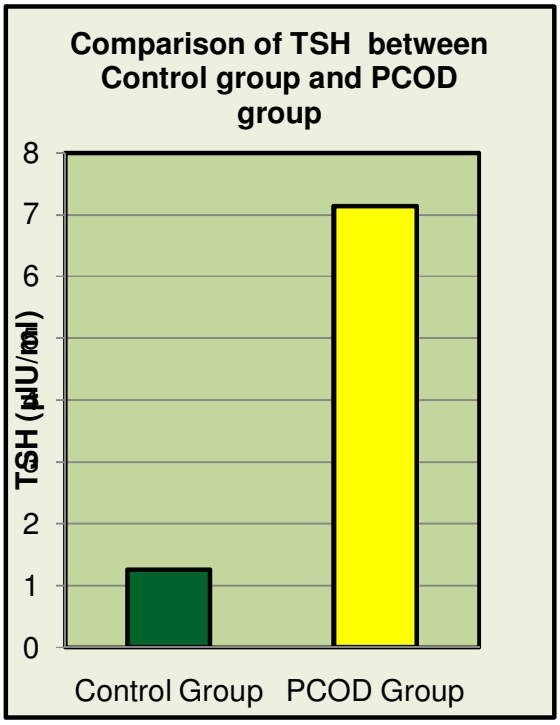
Parameter	Control group (n=30) (Mean±SD)	PCOD group (n=30) (Mean±SD)	p value
Age (years)	25.60±2.88	25.50 ±2.53	>0.05
Height (cm)	159.80±7.90	157.80±5.54	>0.05
Weight (kg)	53.90±7.94	62.23±5.47	<0.001**

* p<0.05 statistically significant ** p<0.001 statistical highly significant

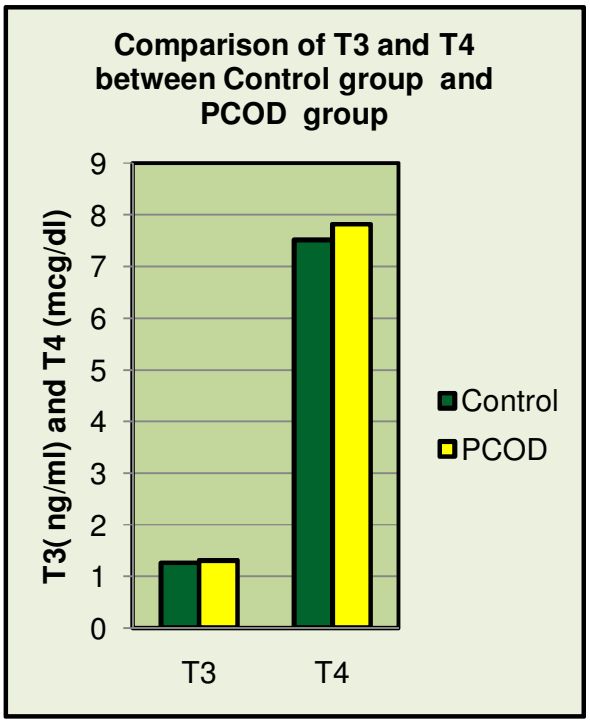
Table 2 : Comparison of Thyroid hormone levels (T3, T4) in control group and PCOD group:

Parameter	Control group (n=30) (Mean±SD)	PCOD group (n=30) (Mean±SD)	p value
T3 (ng/ml)	1.26±0.21	1.30±0.16	>0.05
T4 (mcg/dl)	7.52±1.82	7.87±1.38	>0.05
TSH(µIU/ml)	1.26 ±0.45	7.13±1.60	<0.001**

Graph 1 Comparison of TSH in control group and PCOD group:



Graph 2: Comparison of Thyroid hormone levels (T3, T4) in control group and PCOD group:



References

1. Bussen S, Steck T, Dietl J. Increased prevalence of thyroid antibodies in euthyroid women with a history of recurrent in-vitro fertilization failure. Hum Reprod 2000; 15(3): 545-8.

2. Ghosh S, Kabir SN, Pakrashi A, Chatterjee S, Chakravarty B. Subclinical hypothyroidism: a determinant of polycystic ovary syndrome. Horm Res 1993; 39: 61–66.

3. Dunaif A, Thomsas A. Current concepts in the polycystic ovary syndrome. Annu Rev Med 2001; 52: 401-19.

4. Franks S, Gharani N, McCarthy M. Candidate genes in polycystic ovary syndrome. Hum Reprod Update 2001; 7(4): 405-10.

5. Urbanek M, Legro RS, Driscoll DA, Azziz R, Ehrmann DA, Norman RJ. Thirty-seven candidate genes for polycystic ovary syndrome: strongest evidence for linkage is with follistatin. Proc Natl Acad Sci U S A 1999; 96(15): 8573-8.

6. Fenichel P, Gobert B, Carre Y, Barbarino–Monnier P, Hieronimus S. Polycystic ovary syndrome in autoimmune disease. Lancet 1999; 353: 2210.

7. Roussev RG, Kaider BD, Price DE, Coulam CB. Laboratory evaluation of women experiencing reproductive failure. Am J Reprod Immunol 1996; 35(4): 415-20.

8. van Gelderen CJ, Gomes dos Santos ML. Polycystic ovary syndrome. evidence for an autoimmune mechanism in some cases. J Reprod Med 1993; 38(5): 381-6.

9. Krassas GE, Poppe K, Glinoer D. Thyroid function and Human Reproductive Health. Endocr Rev 2010; 31(5): 702-55.

10. Giannini AJ, Malone DA, Loiselle RH, Price WA. Blunting of TSH response to TRH in chronic cocaine and phencyclidine abusers. J Clin Psychiatry 1987; 48 (1): 25-6.

11. The Rotterdam ESHRE/ARSM-sponsored PCOS Consensus Workshop Group. Revised 2003 consensus on diagnostic criteria and long-term health risks related to polycystic ovary syndrome. Hum Reprod 2004; 19: 41–7.

12. Janssen OE, Mehlmauer N, Hahn S, Offner AH, Gartner R. High prevalence of autoimmune thyroiditis in patients with polycystic ovary syndrome. Eur J Endocrinol 2004; 150(3): 363-6.

13. Wu X, Zhang Z, Su Y. functional status of pituitary –ovary, adrenal and thyroid axes in women with polycystic ovarian syndrome. Zhonghua Fu Chan ke Za Zhi 1998; 33(3): 153-6.

14. Abalovich M, Mitelberg L, Allami C, Gutierrez S, Alcaraz G, Otero P, et al. Subclinical hypothyroidism and thyroid autoimmunity in women with infertility. Gynecol Endocrinol 2007; 23(5): 279-83.

15. Zelija VA. The effects of subclinical hypothyroidism treatment in PCOD women with metabolic syndrome. Eur Society Endocrinol 2009; 20: 663.

16. Ganie MA, Laway BA, Wani TA, Zargar MA, Nisar S, Ahamed F et al. Association of subclinical hypothyroidism and phenotype, insulin resistance, and lipid parameters in young women with polycystic ovary syndrome. Fertil Steril 2011; 95(6): 2039-43.