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A Study on Association of Thyroid Stimulating Hormone with BMI, Insulin Resistance and Lipid Profile in Women with Polycystic Ovarian Syndrome

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Abstract

Polycystic ovary syndrome (PCOS) is one of the most common female metabolic endocrine disorder. It affects about 5-10% of women of reproductive age. It is thought to be one of the leading cause of female infertility**.** Women with PCOS demonstrate hormonal disturbances and serum lipid derangements. To determine and evaluate the association of thyroid stimulating hormone (TSH) with body mass index (BMI), insulin resistance (IR) and lipid profile parameters. To identify the cut-off value of TSH at which the association between TSH and IR exists. In this study we included 60 diagnosed cases of PCOD as per Rotterdam's criteria and 60 healthy age matched healthy controls from whom fasting blood sample was drawn to measure fasting insulin, free triiodothyronine (fT3), free thyroxine (fT4), thyroid stimulating hormone (TSH), follicle stimulating hormone (FSH), leutanizing hormone (LH) and prolactin levels by Chemiluminiscence immuno assay. Insulin resistance was calculated by employing homeostasis model assessment of insulin resistance (HOMA-IR). Lipid profile parameters (total cholesterol (TC), low density lipoproteins (LDL), high density lipoproteins (HDL) and triglycerides (TG)) were measured using automated clinical chemistry analyzer according to manufacturer's protocol. Women with high TSH (>2.5 mIU/L) levels were more insulin resistant as compared to women with low TSH (< 2.5 mIU/L). A significant association between increased TSH and IR was found in women with PCOS and the association was independent of body mass index (BMI).

Keywords: Polycystic ovarian disease, Thyroid stimulating hormone, Freetriiodothyronine, Free thyroxine & Insulin resistance.

Contents

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1. Introduction

Polycystic ovary syndrome (PCOS) is one of the most common female metabolic endocrine disorder affecting 5-10% of women of reproductive age. It is thought to be one of the leading cause of female infertility**.**PCOS consists of chronic anovulation, menstrual disturbances, hyperandrogenism, polycystic ovaries and metabolic syndrome[1]. Current definition of PCOS is based on Rotterdam consensus meeting in 2003 which defines the syndrome as presence of any two of following three criteria: Menstrual disturbances: oligomenorrhoea, clinical/biochemical signs of hyperandrogenism like acne & hirsutism and ultrasound appearance of polycystic ovary as polycystic adnexae. Women with PCOS demonstrate hormonal disturbances and serum lipid derangements.

One of the common hormonal disturbances that co-exist in PCOS patients is hypothyroidism. It is also reported that in women with PCOS approximately 50-70% has been reported to have hyperinsulinemic insulin resistance (IR) & metabolic syndrome (MS) which increases the risk for type 2 diabetes and cardiovascular disease[2, 3, 4, 5]. Insulin resistance (IR) is a state of hyperinsulinemia characterized by the decreased ability of insulin to act effectively on target tissues especially muscle, liver and adipose tissue is a prominent feature ofPCOS.More recently, investigators recognized insulin resistance, which characterizes 50 -90 % of PCOS women, as central componentsof PCOS, possibly playing an underlyingpathogenic role. Women with PCOS also show anincrease prevalence of abnormal β-cells function.[6, 7]

Insulin resistance is found in mostoverweight women with PCOS to greater extentthan can be expected from obesity.The gold standard method for quantifyinginsulin sensitivity had been the hyperinsulinemiceuglycemic clamp technique. However, thistechnique is expensive, labor intensive,uncomfortable for patient and time consuming. Many investigators have studied simple surrogateindices of insulin resistance in comparison with theindex assessed by euglycemic hyperinsulinemicclamp. One of these is Homeostasis modelassessment (HOMA) of insulin resistance (HOMA-IR) which provides a mathematical mean forestimating insulin resistance[8]. Hence the study was undertaken to evaluate the association of TSH with BMI, IR and lipid profile parameters.

2. Materials and Method

Source of data:

Hospital based "study on association of thyroid stimulating hormone with BMI, insulin resistance and lipid profile in women with polycystic ovarian syndrome" was conducted at S. S Hospital, Davangere (attached teaching hospital for S.S Institute of Medical Sciences & Research Centre, Davangere) between May 2012 - April 2013. We included 60 diagnosed cases of PCOS as per Rotterdam criteria and 60 healthy controls in the age group of 20-40 years. The study was approved by the ethical and research committee of S.S Institute of Medical Sciences and Research Centre, Davangere, to use human subjects in the research study. Written informed consent was taken from the study subjects. PCOS subjects and controls participated voluntarily in the study. Detailed medical history and relevant clinical examinations were carried out in both cases and controls. Based on inclusion and exclusion criteria, about 60 cases of polycystic ovarian syndrome 60age matched healthy controls were included.

Inclusion criteria:

We included 60 diagnosed cases of PCOS according to Current definition of PCOS which is based on Rotterdam consensus meeting in 2003. It defines the syndrome as presence of any two of following three criteria: Menstrual disturbances: oligomenorrhoea, clinical/biochemical signs of hyperandrogenism and ultrasound appearance of polycystic ovary as polycystic adnexae.

Exclusion criteria were:

Hyperandrogenism, IR, cushing's syndrome, known cases of thyroid disorders,h/o of thyroid surgery, women on thyroid hormone or iodine medication, women on oral contraceptive pills (OCP)&women on steroid treatment.

Procedures & definition of PCOS:

All the women underwent a complete screening panel, including physical examination, weight and height measurement.BMI was calculated as weight (kg) /height (mt^2).Hirsutism & hyperandrogenemia by the measurement of testosterone levels.IR was calculated by measuring fasting insulin & fasting serum glucose levels by employing HOMA-IR.

Sample collection: About 6 ml of fasting venous blood was drawn from subjects from antecubital vein under aseptic precautions, using a sterile disposable syringe. Serum was separated and stored at -80c for biochemical analysis.

Biochemical assays:

Serum levels of TSH, Prolactin were measured by eCLIA.Serum levels of Testosterone, fT3, fT4, FSH, LH & insulin were measured by CLIA.HOMA-IR was calculated by the formula HOMA-IR = fasting insulin X fasting glucose/22.5We also measured total cholesterol, LDL, HDL & TGs by using fully automated chemistry analyzeraccording to manufactures protocol.

Statistical analysis:

All of the data are presented as mean and SD. The data was analyzed using Studentunpaired't' test, ANACOVA, Youden index, and Chi-square test.p value <0.05 was considered statistically significant. The Youden index describes the performance of the analyses and is defined as Youden Index = sensitivity + specificity -1; and can vary from -1 to + 1. A test with a perfect accuracy would have a Youden Index of +1.

Table 1. Shows comparisons of BMI, fT3, fT4, TSH, LH, FSH, testosterone, prolactin & HOMA-IR between PCOS & healthy controls

Parameters	Healthy controls	PCOS	P value
BMI (kg/m^2)	20.56 ± 2.19	25.58 ± 4.18	< 0.001
fT3 (ng/m)	1.52 ± 0.7	1.58 ± 0.32	NS
fT4 (ng/mL)	1.4 ± 0.39	1.5 ± 0.41	NS
TSH (mIU/L)	1.29 ± 0.39	3.31 ± 1.17	< 0.001
LH (mIU/mL)	45 ± 0.89	53 ± 0.98	< 0.001
FSH (mIU/mL)	12.4 ± 3.2	19.8 ± 4.2	< 0.001
Testosterone (nmol/L)	0.7 ± 0.22	2 ± 0.8	< 0.001
Prolactin (mIU/mL)	17.88 ± 2.91	29.97 ± 2.91	< 0.001
HOMA-IR	1.31 ± 0.54	3.01 ± 0.94	< 0.001

Table 2. Diagnostic validity for cut-off value of TSH 3

TSH	Cases	Controls
≥ 3	32	2
≤ 3	28	58

Sensitivity: 53.33, Specificity: 96.66, PPV: 94.117, NPV: 67.44 and Youden Index: 0.5

Table 3. Diagnostic validity for cut-off value of TSH 2.5

TSH	Cases	Controls
≥ 2.5	46	2
≤ 2.5	14	58

Sensitivity: 76.66, Specificity: 96.66, PPV: 95.83, NPV: 80.00, and Youden Index: 0.73

Table 4. Comparisons of PCOS women with TSH < 2.5 mIU/L and with TSH ≥ 2.5 mIU/L

TSH < 2.5	TSH ≥ 2.5	p Value
22.7 ±1.09	29.7 ± 5.12	< 0.001
26.4 ± 4.34	29.5 ± 6.44	< 0.001
1.84 ± 0.30	3.37 ± 0.76	< 0.01
198 ± 6.2	199 ± 7.24	> 0.05
169 ± 3.42	170 ± 4.2	> 0.05
59 ± 5.4	50 ± 3.6	0.01
102 ± 2.34	110 ± 4.24	0.02

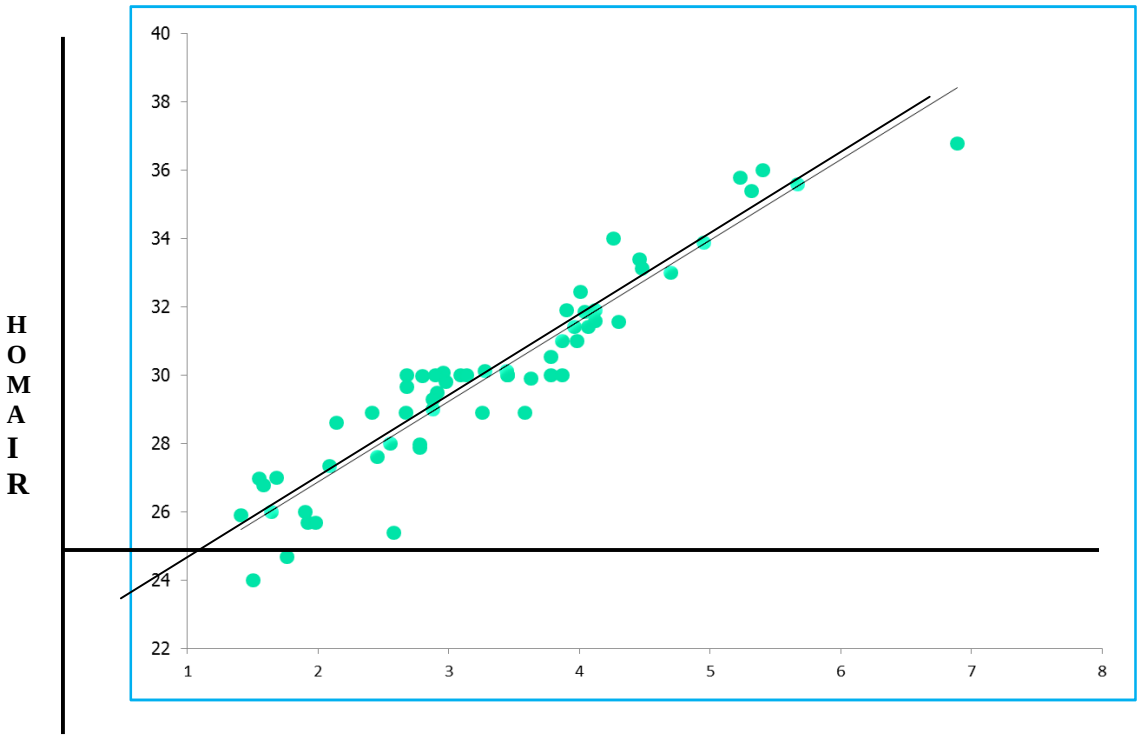

Figure1: Shows correlation of TSH with HOMA-IR (r = 0.924, p<0.001)

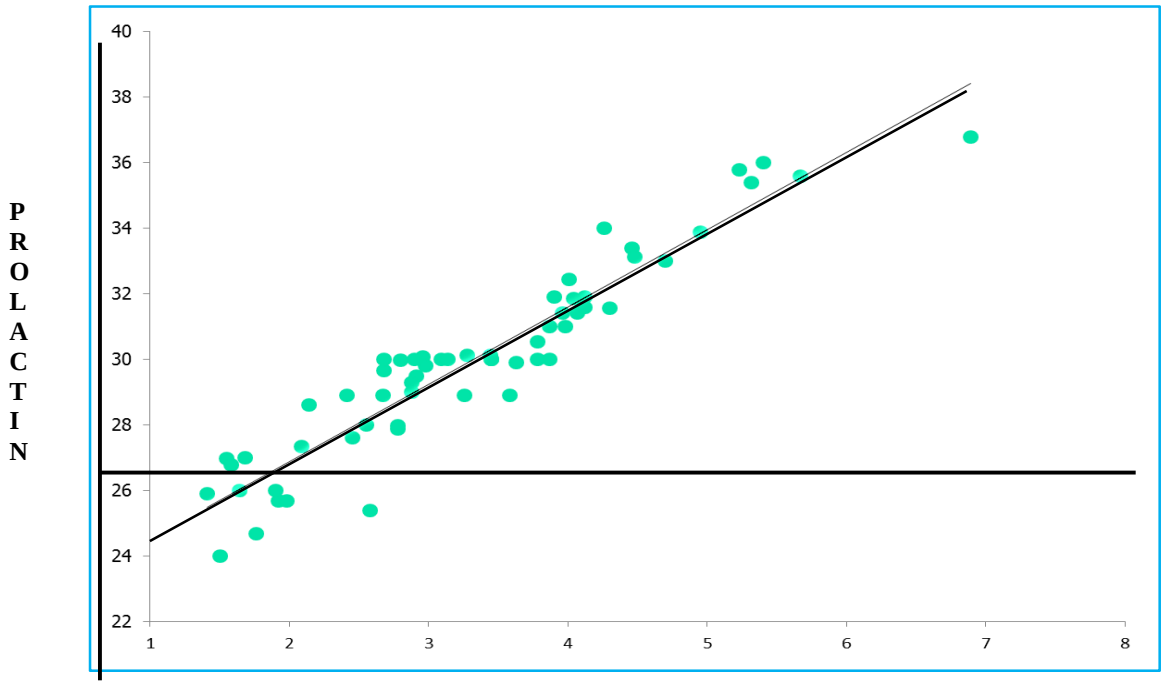

Figure 2. Shows correlation of TSH with prolactin (r=0.946, p<0.001)

3. Results and Discussion

A total of 60 cases and 60 controls in the age group of 20-40 were studied. As shown in **Table 1**:the mean ± SDs of BMI (kg/m)^2, fT3 (ng/mL), fT4 (ng/mL), TSH (mIU/L), LH (mIU/mL), FSH (mIU/mL) testosterone (nmol/L), Prolactin (mIU/mL) and HOMA-IR in controls are in the range of 20.56 ± 2.19, 1.52 ± 0.7, 1.4 ± 0.39, 1.29 ± 0.39, 45 ± 0.89, 12.4 ± 3.2, 0.7 ± 0.22, 17.88 ± 2.91,17.88 ± 2.91 and 1.31 ± 0.54, respectively. It is observed that the mean ± SDs of BMI (kg/m)^2, fT3 (ng/mL), fT4 (ng/mL), TSH (mIU/L), LH (mIU/mL), FSH (mIU/mL), testosterone (nmol/L), Prolactin (mIU/mL) and HOMA-IR in controls are in the range of 25.58 ± 4.18,1.58 ± 0.32, 1.5 ± 0.41, 3.31 ± 1.17, 53 ± 0.98, 19.8 ± 4.2 ,2 ± 0.8, 29.97 ± 2.91 and 3.01 ± 0.94respectively. It is evident that BMI, TSH, LH, FSH, Testosterone, Prolactin and HOMA-IR levels are increased in cases as compared to controls and the increase is statistically highly significant($p < 0001$). There was no statistically significant increase in FT3 and FT4 levels in cases as compared to controls.

Thyroid stimulating hormone (TSH) is more reliable indicator of hypothyroidism and is often associated with low levels of fT3 and fT4. Women with PCOS have a high prevalence of increased TSH levels as evidenced by a study conducted by Dahiya et al[9].Hypothyroidism itself can aggravate PCOS symptoms. Hypothyroidism can lead to low levels of sex hormone binding globulin (SHBG) which in turn can lead to higher concentrations of free testosterone and increased testosterone throughout the body and aromatization to estradiol and reducing the metabolic clearance rates of androstenedione and estrone. Since thyroidhormones are involved in the gonadotropin induced estradiol and progesterone secretion by human granulosa cells, hypothyroidism will interfere with ovarian function and fertility[10].A high level of testosterone is one of the factors which contribute to PCOS symptoms like infertility, polycystic ovaries, hirsutism, male pattern hair loss and acne. In addition our PCOS patients showed increased mean Prolactin levels and were more insulin resistant as compared to controls.

Table 2 and 3: Shows the diagnostic validity cut-off values of TSH at 3 mIU/L and 2.5 mIU/L. It is evident from the**Table 2**thatthe diagnostic validity of TSH at cut-off value of 3 the sensitivity, specificity, positive predictive value, negative predictive value and Youden Indexranges from 53.33, 96.66, 94.117, 67.44 and 0.5. It is observed from the **Table 3** that the diagnostic validity of TSH at cut-off value of 2.5 the sensitivity, specificity, positive predictive value, negative predictive value and Youden Index ranges from 76.66, 96.66, 95.83, 80.00 and 0.73 respectively. The diagnostic validity cut-off value of TSH 2.5 mIU/L showed high sensitivity, specificity and Youden Index compared to TSH cut-off value 3 mIU/L. We identified an association between TSH ≥ 2.5mIU/L and increasing IR in women with PCOS in our locality.

Table 4: Shows the mean ± SDs of age in years, BMI in kg/m^2, HOMA-IR and lipid total cholesterol (TC) in mg/dL, low density lipoproteins (LDL) in mg/dL, high density lipoprotein (HDL) in mg/dL and triglycerides (TG) in mg/dL are in the range of 22.7 ±1.09, 26.4 ± 4.34, 1.84 ± 0.30, 198 ± 6.2, 169 ±3.42, 59 ± 5.4 and 102 ± 2.34 in cases with TSH < 2.5 mIU/Lrespectively. It is observed that mean ± SDs of age in years, BMI in kg/m^2, HOMA-IR and lipid total cholesterol (TC) in mg/dL, low density lipoproteins (LDL) in mg/dL, high density lipoprotein (HDL) in mg/dL and triglycerides (TG) in mg/dL are in the range of 29.7 ± 5.12, 29.5 ± 6.44, 3.37 ± 0.76, 199 ± 7.24, 170 ± 4.2, 50 ± 3.6 and 110 ± 4.24 in cases with TSH ≥ 2.5 mIU/L. It is evident that BMI, HOMA-IR, HDL and TG are increased in cases with TSH ≥ 2.5 compared to cases with TSH < 2.5 mIU/L and the increase was statistically significant.

Table 5: Shows ANACOVA test to study the association of TSH with HOMA-IR independent of age and BMI in cases. It shows the mean ± SD of HOMA-IR is in the range of
1.84 ± 0.30 in cases with TSH < 2.5 and 3.37 ± 0.76 in cases with TSH ≥ 2.5.

Figure1*:* Shows correlation of TSH with HOMA-IR. TSH is highly significantly ($p < 0.001$) positively correlated ($r = 0.924$) with HOMA-IR.**Figure 2***:* Shows correlation of TSH with Prolactin. TSH is highly significantly ($p < 0.001$) positively correlated ($r = 0.946$) with Prolactin.

4. Conclusion

Thyroid function, as reflected by TSH levels, is associated with IR in women with PCOS independent of age and BMI.We found TSH cut-off value of 2.5 mIU/L which showed strong association with IR.

5. Implications of the Study

It is essential to screen for thyroid profile in diagnosed cases of PCOS.Since PCOS & hypothyroidism are coexisting it is also mandatory to screen for PCOS in hypothyroid women by measuring TSH.Knowing the proper cause in either condition treatment modalities could be improved in a much better way. Targeting at IR future development of diabetes & cardiovascular risk could be minimized.

6. Acknowledgement

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