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A Study on Assessment of Thyroid Stimulating Hormone and Insulin Resistance in Women with Polycystic Ovarian Syndrome

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Running Title: TSH and Insulin Resistance in PCOS

Abstract: ***Objective: Polycystic ovarian syndrome(PCOS), the most common cause of infertility, is a disorder characterized by chronic anovulation, hyperandrogenism, hyperinsulinemia, and often presence of obesity. Obesity has been linked to endocrine disorders especially thyroid dysfunction. The present study was designed to assess thyroid stimulating hormone and insulin resistance in women with PCOS and to compare them with healthy women as controls. Material and Methods: A comparative study including 30 women diagnosed as PCOS and 30 age and BMI matched healthy women as controls was conducted. The age group for the study was 18-35 years. Fasting blood samples were drawn to assess serum Insulin, HbA1c, triiodothyroxine(T_3), thyroxine(T_4), thyroid stimulating hormone(TSH) and fasting blood sugar(FBS). Insulin resistance(IR) was calculated by homeostasis model assessment(HOMA). Body Mass Index(BMI) was also calculated. Results: A significant increase in fasting serum insulin ($p<0.001$) and HOMA – IR ($p<0.001$) were found in patients with PCOS in comparison with controls. Mean BMI, T_3, T_4, TSH, FBS and HbA1c were found elevated in the PCOS women but they were not statistically significant. No significant correlations were found between BMI, TSH and serum insulin. Conclusions: Serum Insulin and HOMA-IR were found to be significantly higher in PCOS subjects compared to controls. All the above derangements confirm that PCOS is associated with insulin resistance and places the subject at a higher risk of metabolic syndrome. We could not find any significant correlation between serum TSH, serum insulin and BMI because our study consisted of a limited number of PCOS subjects and controls.***

Keywords: PCOS, TSH, Insulin resistance.

1. Introduction

Polycystic ovary syndrome (PCOS) is one of the common endocrine disorders affecting 5 to 10 % women [1]. According to ESHRE/ASRM consensus workshop at Rotterdam in 2003, the diagnosis of PCOS is based on the presence of any two of (1) chronic anovulation, (2) clinical/ biochemical parameters for hyperandrogenism, and (3) polycystic ovaries on ultrasonography [2]. PCOS subjects are often accompanied by obesity, insulin resistance, abnormal glucose metabolism, lipid disorder, hypertension, and other risk factors of cardiovascular disease [3]. Although the pathophysiology of PCOS is not fully understood, insulin resistance and obesity, central obesity in particular, seem to play a key role in the development of PCOS [4]. A large percentage of PCOS women are insulin resistant and suffer from metabolic alterations [5]. The hyperinsulinemia may cause hyperandrogenism by inhibiting hepatic synthesis of SHBG and by binding insulin like growth factor -1 (IGF -1) receptors in the ovary leading to increased androgen production by thecal cells [6].

Hypothyroidism has been shown to cause many metabolic derangements, such as decrease in glucose disposal or its uptake by muscles or adipose tissues in response to insulin, increase in the level of sex hormone-binding globulin, weight gain, and hyperlipidemia, all of which can lead to insulin resistance. In particular it has been extensively demonstrated that thyroid hormones, and specifically T3, have insulin antagonistic effects at the liver level that lead to an increased glucose hepatic output, via an enhanced rate of gluconeogenesis and glycogenolysis [7]. Hemoglobin A1c (HbA1c) is a commonly used marker of chronic glycemia, and it reveals the average blood glucose levels over a 2- to 3-month period. The problem of the day-to-day variability of glucose values and the need for fasting and preceding dietary preparations can be avoided most of the time using HbA1c [8]. The purpose of the study was to assess thyroid profile, insulin resistance and HbA1c levels in PCOS women and to compare them with healthy women as controls.

2. Materials and Methods

The study was carried out on 30 PCOS subjects in the age group of 18 to 35 years and 30 voluntary age and BMI matched healthy women with normal menstrual cycle as controls. The study was conducted at Kempegowda Institute of Medical Sciences & Hospital. The diagnosis of PCOS was fulfilled as per Rotterdam criteria. Presence of at least two criteria from clinical, hormonal and abdominal USG category was considered diagnostic of PCOS. Patients with diabetes mellitus, hypertension, dyslipidemia, renal and liver failure, thyroid disorders and other endocrine disorders and patients receiving hormonal / non-hormonal treatment for PCOS were excluded from the study. The institutional ethical committee approved the study protocol. Informed consent was obtained from all the participants.

A pre-structured and pre-tested proforma was used to collect the data. Baseline data including age, BMI, detailed medical history, clinical examinations and relevant investigations were included as part of the methodology. Serum insulin, T3, T4, TSH, HbA1c, blood sugar, blood urea and serum creatinine were measured in all participants from morning blood samples collected after 12 hours of fasting. Serum insulin, T3, T4 and TSH were measured by electrochemiluminescence immunoassay (Elecsys 2010 analyzer, Roche Diagnostics). Insulin Resistance (IR) was estimated via the homeostasis model assessment insulin resistance index (HOMA-IR), as follows: HOMA-IR = fasting insulin (mU/L) × fasting glucose (mmol/L)/22.5. HbA1c was measured by boronate affinity method (NycoCard HbA1c Glycated Hemoglobin Assay k993131). Body mass index (BMI) was calculated as the ratio of weight (Kg) to height squared (m^2). Blood sugar was estimated by GOD/POD method.

Statistics analysis:
SPSS software version 13.0 was used for statistical analysis. Comparisons between groups were performed using the Mann-Whitney test. Correlation analysis between BMI, TSH and serum insulin were done using Spearman's rank order correlation coefficients. A P value < 0.05 was considered statistically significant.

3. Results

Results on continuous measurements are presented as Mean ± SD. The basic characteristics of the cases and controls are depicted in Table 1. There was no significant difference in age between two groups. Slightly higher mean BMI was recorded in cases than in controls but the difference in mean BMI between the two groups was not statistically significant (P>0.05). Higher mean fasting serum Insulin and higher mean HOMA-IR were recorded in cases compared to controls and the difference between them were found to be statistically significant (P<0.001). No significant correlation could be found between BMI and serum Insulin in cases (ρ= 0.283, p = 0.130) or controls (ρ= - 0.163, p = 0.388). Higher mean T3, T4, TSH, HbA1c and FBS were recorded in cases compared to controls but differences between cases and controls were not statistically significant (P≥0.05). Correlations are depicted in Table 2. No significant correlation could be found between TSH and fasting serum Insulin in cases (ρ= 0.261, p = 0.164) or controls (ρ= 0.040, p = 0.834). Similarly, No significant correlation could be found between BMI and serum TSH in cases (ρ= 0.244, p = 0.193) or controls (ρ= - 0.094, p = 0.621).

4. Discussion

The consequences of the polycystic ovary syndrome extend beyond the reproductive axis; women with the disorder are at substantial risk for the development of metabolic, endocrine and cardiovascular abnormalities. Insulin resistance is a metabolic disorder caused by the impairment of insulin function in inducing glucose uptake and utilization [9]. Seow et al. demonstrated that IR in PCOS involves both receptor and postreceptor defects, including defects in phosphatidylinositol 3-kinase and the GLUT-4 glucose transporter. In addition, women with PCOS frequently exhibit impaired peripheral insulin-stimulated glucose utilization and higher basal insulin levels, probably caused by increased insulin secretion and/or decreased hepatic clearance of the hormone; such abnormalities were independent of obesity [10,11]. Insulin resistance is defined clinically as the inability of a known quantity of exogenous or endogenous insulin to increase glucose uptake and utilization in an individual as much as it does in a normal population [3]. In present study, Higher mean fasting serum Insulin and higher mean HOMA-IR were recorded in PCOS subjects compared to controls and the difference between them were found to be statistically significant (P<0.001). This was consistent with Shou-Kul Xiang et al. They found in their study that the HOMA-IR of the PCOS women was significantly higher than that of the age-matched healthy women, which suggested that insulin resistance had a crucial role in pathogenesis of PCOS [3]. We could not find any significant correlation between BMI and serum insulin level in either of the groups mostly because of the limited number of subjects. Puder JJ et al also showed in their study that women with PCOS were more insulin resistant compared to a group of age and BMI matched controls [12]. Sunita J R et al concluded in their study that Insulin resistance is common in Indian PCOS women and this is independent of obesity [13].

Thyroid gland dysfunction leading to hypothyroidism is a common disorder affecting women more often than men. The clinical features of hypothyroidism also include weight gain, menstrual irregularities and infertility. An association has been reported between PCOS and hypothyroidism. Most of the time hypothyroidism is subclinical and diagnosed first time during evaluation of PCOS. TSH is the most sensitive indicator of hypothyroidism. [14]. The prevalence of hypothyroidism in women in the reproductive age (20–40 years) varies between 2% and 4%. In this age group, autoimmune thyroid disease (AITD) is the most common cause of hypothyroidism. Hypothyroidism is associated with a broad spectrum of reproductive disorders ranging from abnormal sexual development through menstrual irregularities to infertility. Thyroid responsivity by the ovaries could be explained by the presence of the thyroid hormone receptors on human oocytes. TSH also affects estrogen metabolism and decreases production of sex hormone binding globulin [15]. Since thyroid hormones are involved in the gonadotropin induced estradiol and progesterone secretion by human granulosa cells, hypothyroidism will interfere with ovarian function and fertility [16].

In women with PCOS, who frequently have insulin resistance and metabolic syndrome, the additional development of subclinical hypothyroidism (SCH) may aggravate insulin resistance and other risk factors. In particular, women with insulin resistance and higher serum TSH values are described as having a higher risk for dyslipidaemia and severe cardiovascular risk factors. Experimental studies have shown that in normal conditions, thyroid hormones may influence the expression or activation of uncoupling protein, β-adrenergic receptor and peroxisome proliferator–activated receptor-γ, all of which are involved in regulating insulin sensitivity [17]. Thyroid hormones also co-operate with catecholamines to enhance lipolysis and

reduce visceral fat mass, with resultant improvement in insulin resistance [18]. The thyroid hormone deficiency or mutation of deiodinase, which is the regulator of thyroid hormone metabolism, has also been shown to induce obesity and insulin resistance [19].

Women with PCOS have a high prevalence of increased thyroid-stimulating hormone levels as evidenced by a study conducted by Dahiya et al [14]. In present study, there was no statistically significant increase in T3, T4, TSH, HbA1c and FBS levels in cases as compared to controls. Kanagavalli P et al also concluded in their study that when the PCOD was provisionally diagnosed in the patients of mean age 20.8yrs, the gynaecological profile was abnormal with normal thyroid profile [20]. No significant correlation could be found between TSH and fasting serum Insulin in cases or controls in our study. This finding was consistent with study done by Bakker SJ et al [21]. These findings are mostly due to small sample size. Sushma B J et al found in their study that TSH and HOMA-IR levels were significantly higher in PCOS cases compared to controls and TSH is highly significantly ($p < 0.001$) positively correlated with HOMA-IR [22].

Our study implicates the utility of BMI, serum insulin and TSH in PCOS subjects for evaluating risk of metabolic and endocrine disorders which would be helpful for an early medical intervention.

5. Conclusion

Fasting Serum Insulin and HOMA-IR were found to be significantly higher in PCOS subjects compared to controls in our study. All the above derangements confirm that PCOS is associated with insulin resistance and places the subject at a higher risk of metabolic syndrome. We could not find any significant correlation between serum TSH, serum insulin and BMI. Because our study consisted of a limited number of PCOS subjects and controls from a single population, further studies with larger number of PCOS subjects will be beneficial in elucidating the relationship between TSH, serum insulin and BMI in polycystic ovarian syndrome for evaluating risk of metabolic and endocrine disorders.

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Tables are given below:

Table 1: Mean distribution of biochemical parameters in PCOS cases and controls. Values are expressed as means ±SD.

Parameters	Cases with PCOS (n=30)	Controls (n = 30)	P value
Age (years)	23.37 ± 4.09	23.73 ± 3.81	0.744
BMI ((kg/m2)	24.00 ± 4.41	22.51 ± 2.31	0.126
Serum Insulin	12.01 ± 6.74	6.80 ± 3.10	<0.001*
HOMA-IR	2.35 ± 1.40	1.27 ± 0.58	<0.001*
HbA1c	5.91 ± 0.97	5.63 ± 0.36	0.432
T3	118.31 ± 14.11	113.06 ± 20.14	0.245
T4	8.80 ± 2.95	8.11 ± 1.47	0.728
TSH	2.76 ± 1.14	2.53 ± 1.54	0.311
FBS	80.33 ± 10.53	74.67 ± 9.59	0.050

*denotes significant difference

Table 2: Correlation between various parameters

Parameters	Cases		Controls	
	ρ value	P value	ρ value	P value
TSH and Insulin	0.261	0.164	0.040	0.834
BMI and Insulin	0.283	0.130	-0.163	0.388
BMI and TSH	0.244	0.193	-0.094	0.621