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Original Research Article

Association of Thyroid Stimulating Hormone with Insulin Resistance in Polycystic Ovarian Syndrome

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Abstract

Background*:** Polycystic Ovarian Syndrome (PCOS) is a major endocrine disorder in reproductive age women. PCOS is associated with insulin resistance. Some of the PCOS women also have thyroid dysfunction. There are variable and controversial findings regarding the association of thyroid stimulating hormone with insulin resistance. The objective of our study was to analyze the relation between thyroid stimulation hormone with insulin resistance in patients with PCOS. ***Methods*:** The case control study was carried out on 216 reproductive age women with PCOS. Insulin resistance was measured by Homeostatic model assessment of insulin resistance (HOMA-IR) and those with HOMA-IR more than 1.9 were defined as having insulin resistance. PCOS women with insulin resistance were cases (n=108) and those without insulin resistance were controls (n=108). Thyroid stimulating hormone (TSH) levels was assessed in both groups.Association of thyroid stimulating hormone with insulin resistance was analyzed. ***Result: The mean serum TSH level was significantly more in insulin resistant PCOS women (3.87±3.44 mIU/L) than those without insulin resistance (2.29±1.66 mIU/L). Hypothyroidism (TSH >2.5 mIU/L) were present in 63.9% of insulin resistant PCOS women compared to 31.3% of those without insulin resistance. The odds of hypothyroidism (TSH level >2.5 mIU/L) was 4.19 times more in insulin resistant PCOS women. ***Conclusion*:** There is significant positive association of hypothyroidism with insulin resistance in PCOS.

Keywords: Polycystic ovarian syndrome; insulin resistance; thyroid stimulating hormone; hypothyroidism.

INTRODUCTION

Polycystic ovarian syndrome (PCOS) is an endocrine and metabolic disorder that affects 5-10% of women of reproductive age [1]. The Rotterdam revised diagnostic criteria define PCOS by the presence of at least two out of three: oligo or anovulation, hyperandrogenism and enlarged polycystic ovaries on ultrasound. Women with PCOS have a marked increase in the prevalence of central obesity associated with higher risk of insulin resistance (IR) and a higher prevalence of diabetes [2]. Approximately 50% to 75% of patients with PCOS are insulin resistant [3]. In women with PCOS, IR has been associated with an increased risk of the metabolic syndrome (MS), type 2 diabetes mellitus (DM), and cardiovascular disease, and has been reported to cause subfertility [4]. In women

with PCOS, hyperinsulinemia and insulin resistance is believed to be a key link in generation of symptoms like menstrual irregularity, anovulatory infertility and hyperandrogenism as well as hirsutism. Regression of these symptoms may be achieved by reducing the hyperinsulinemia [5]. A hyper pigmented skin lesion or acanthosis nigricans with its severity directly correlated to the degree of insulin resistance is frequently noted in obese women as well as in some lean affected women of PCOS [6]. Abnormal (atherogenic) serum lipid profile in PCOS may be attributed to the impaired insulin action or the insulin resistance and lipid changes in PCOS women may affected by obesity and hyperandrogenism [7].

Thyroid dysfunction is common in women of reproductive age, with a prevalence of elevated TSH ranging from 4-9% in this population [6]. Dittrich *et al*., [8] found that women with polycystic ovary syndrome and thyroid-stimulating hormone ≥2.5 mIU/l had significantly higher body mass index, higher fasting insulin concentrations and altered insulin resistance indices. Mueller *et al*., [9] found that PCOS women with TSH levels at or more than 2 mIU/l were younger, had a higher body mass index (BMI) and were more insulin-resistant. Liu *et al*., [10] found that TSH levels in patients with polycystic ovary syndrome was positively correlated with body mass index and insulin resistance index. Ramanand *et al*., [11] revealed that HOMA-IR (Homeostatic model assessment of insulin resistance) values were significantly more in hypothyroid PCOS women. Presence of hypothyroidism significantly increased severity of insulin resistance as well as obesity in PCOS. So in women with PCOS, a significant association between thyroid function and IR was found and the association appeared to be independent of age and body mass index (BMI).

However there are controversial findings as well. Ganie *et al*., [12] assessed that subclinical hypothyroidism was not associated with alteration in phenotypic expression and insulin resistance in young women with PCOS. Naher *et al*., [13] revealed that there was no significant association between IR and TSH in the PCOS subjects. Ravi and Gokaldaset *et al*., [14] also could not find any significant correlation between serum TSH, serum insulin and BMI.

Women with PCOS have a high prevalence of increased TSH level with frequent prevalence of concomitant insulin resistance (IR) and metabolic syndrome (MS). Subclinical hypothyroidism developing these women may aggravate IR and other risk factors. In the above context this study was under taken to find the association of TSH with insulin resistance in PCOS women.

METHODS

The case control study was carried out in the Department of Reproductive Endocrinology and Infertility, Bangabandhu Sheikh Mujib Medical University (BSMMU), Dhaka from January 2019 to December 2019.The study population consisted of the diagnosed PCOS patients of reproductive age (20-40 years) attending PCOS clinic of the Department of Reproductive Endocrinology & Infertility of BSMMU during the study period. Exclusion criteria were overt or clinical hypothyroidism, congenital adrenal hyperplasia, androgen- secreting tumors, diabetes mellitus, Cushing's syndrome and other endocrinopathies like hyperprolactinemia. Sample size was calculated at 108 for each group with 80% power and alpha 0.05. Institutional Review Board approved the study and all participants gave informed consent.

Insulin resistance was measured by HOMA-IR (Homeostatic model assessment of insulin resistance). Fasting insulin was measured by ARCHITECT insulin assay kits, a Chemiluminescent Micro particleImmunoassay (CMIA) for the quantitative determination of human insulin in human serum or plasma. Study population was divided into two groups. Fasting plasma glucose was estimated by Glucose-Oxidase method (GOD-PAP). The following equation was used to calculate the homeostasis model assessment (HOMA-) IR index. The HOMA-IR is calculated by dividing the product of the fasting glucose (mmol/L) and fasting insulin (mU/mL) concentrations by a constant: [glucose (mmol/L)] [insulin (mU/mL)]/22.5. PCOS women having HOMA-IR greater than 1.6 was determined to be insulin resistant. PCOS patients with insulin resistance (IR) were grouped as case and PCOS Patients without insulin resistance (IR) was grouped as control. Serum TSH was measured by Micro particle Enzyme immunoassay (MEIA). TSH reading above 2.5 mIU/L was considered high (elevated).

Statistical analysis was done by unpaired t-test and Chi-square test. A p value of <0.05 was considered statistically significant. Correlation between serum TSH and insulin resistance index was analyzed by Pearson's correlation test. Statistical analyses were carried out by using the Statistical Package for Social Sciences version 22.0 for Windows (SPSS Inc., Chicago, Illinois, USA).

RESULTS

Table 1 summarizes the demographic variables of study patients. Table 2 describes the clinical variables of the study patients. The difference was statistically not significant (p>0.05) between the two groups, except for body mass index. The BMI was significantly more in insulin resistant group.

Table 1: Distribution of the study patients by demographic data (n=216)

Demographic data	Insulin resistant (n=108)		Insulin sensitive (n=108)		p value
	n	%	n	%	
Age (in years)					
≤20	7	6.5	4	3.7	
21-30	86	79.6	90	83.3	
31-40	15	13.9	14	13.0	
Mean±SD	26.03±4.12		26.6±4.07		[a]0.307[ns]
Range (min-max)	18-36		18-38		
Socioeconomic Status					
≤6821.14	3	2.8	2	1.9	
6827.791-26851.99	81	75.0	77	71.3	
26858.64-83018.22	24	22.2	29	26.9	
Mean±SD	23463±15617		22528±10557		[a]0.606[ns]
Range (min-max)	2000-80000		8000-60000		
Occupation					
Housewife	75	69.4	75	69.4	[b]1.000[ns]
Others	33	30.6	33	30.6	
Education					
Primary	57	52.8	59	54.6	[b]0.875[ns]
Secondary	28	25.9	29	26.9	
Graduate	16	14.8	12	11.1	
Post graduate	7	6.5	8	7.4	

ns= not significant

Note: New country classification by income level submitted by World Bank Data Team On FRI, 07/01/2016

Table 2: Distribution of the study patients clinical, endocrine and sonographic variables (n=216)

Parameters	Insulin resistant (n=108)		Insulin sensitive (n=108)		p value
	n	%	n	%	
Menstrual History					[a]0.189[s]
Oligomenorrhea	101	93.5	98	90.7	
Amenorrhea	5	4.6	3	2.8	
Normal cycle	2	1.9	7	6.5	
	Mean±SD		**Mean±SD**		
Testosterone (ng/dl)	36.25±25.67		30.01±22.39		0.058[ns]
Range (min-max)	1.01-114.26		1.26-90.6		
	n	**%**	**n**	**%**	
USG Findings					
Normal study	13	12.0	17	15.7	0.431[ns]
Bilateral Polycystic Ovaries	95	88.0	91	84.3	
BMI (kg/m^2)					
Under weight (<19 kg/m^2)	2	1.9	0	0.0	
Normal weight (19-24.9 kg/m^2)	19	17.6	22	20.4	
Overweight (25-29.9 kg/m^2)	60	55.6	65	60.2	
Obese (30-34.9 kg/m^2)	22	20.4	21	19.4	
Morbid obesity (>35 kg/m^2)	5	4.6	0	0.0	
Mean±SD	27.58±3.77		26.65±3.01		0.046[s]
Range (min-max)	17.0-38		19.6-34.2		
Waist/Hip ratio					
Mean±SD	0.94±0.06		0.93±0.05		0.184[ns]
Range (min-max)	0.83-1.31		0.78-1.05		

s= significant

ns= not significant

Table 3: Distribution of the study patients by serum TSH level (n=216)

Serum TSH level	Insulin resistant (n=108)		Insulin sensitive (n=108)		p value
	n	%	n	%	
≤2.5 (mIU/liter)	39	36.1	75	69.4	0.001[s]
>2.5-5 (mIU/liter)	45	41.7	27	25.0	
>5-10 (mIU/liter)	19	17.6	5	4.6	
>10 (mIU/liter)	5	4.6	1	0.9	

s= significant

Table 3 shows the distribution of the study patients by serum TSH level. It was observed that more than one third (41.7%) patients belonged to serum TSH level >2.5-5 (mIU/liter) in insulin resistant group and 27(25.0%) in insulin sensitive group. The difference was statistically significant (p<0.05) between two groups.

Table 4: Distribution of the study patients by mean serum TSH level (n=216)

Mean serum TSH level	Insulin resistant (n=108)	Insulin sensitive (n=108)	p value
Mean±SD	3.87±3.44	2.29±1.66	0.001[s]
Range (min-max)	0.6-24.3	0.04-11	

s= significant
p value reached from unpaired t-test

The mean serum TSH level was more in insulin resistance group (3.87±3.44 mIU/L) then in insulin sensitive group (2.29±1.66 mIU/L). The difference was statistically significant (p<0.05) between the two groups.

Table 5: Distribution of the study patients by serum TSH level (n=216)

Serum TSH level	Insulin resistant (n=108)		Insulin sensitive (n=108)		Odds Ratio (95% Confidence Interval)	p value
	n	%	n	%		
Hypothyroidism (>2.5 mIU/L)	69	63.9	33	31.3	4.19(2.28-7.71)	0.001[s]
Euthyroidism (≤2.5 mIU/L)	39	36.1	75	68.7		

s= significant

Table 5 shows the distribution of the study patients by serum TSH level. It was observed that almost two third (63.9%) patients had hypothyroidism (serum TSH level >2.5 mIU/L) in insulin resistant group and 33(31.3%) in insulin sensitive group. The odds of hypothyroidism (serum TSH level >2.5 mIU/L) was 4.19 times more in insulin resistant PCOS women.

Figure 1 and 2 show correlation of insulin resistance (HOMA-IR) with serum TSH levels above and below the threshold of 2.5mIU/L. There is significant positive correlation of insulin resistance with serum TSH levels above 2.5 mIU/L.

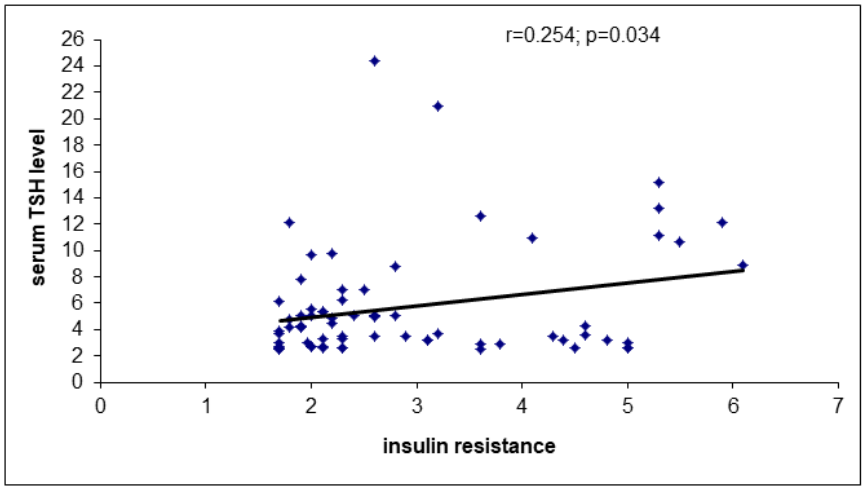

Figure 1: Scatter diagram showing positive significant Pearson's correlation (r=0.254; p=0.034) between insulin resistance and serum TSH levels >2.5mIU/L

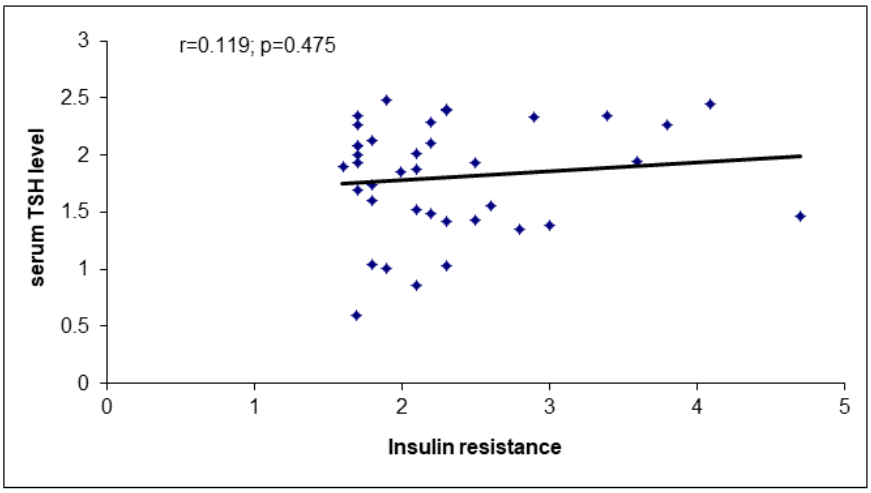

Figure 2: Scatter diagram showing positive but non-significant Pearson's correlation (r=0.119; p=0.475) between insulin resistance and serum TSH levels <2.5mIU/L

DISCUSSION

Polycystic ovarian syndrome is considered to be a disorder of the metabolic syndrome, which increases the risk of Type-2 diabetes mellitus and cardiovascular diseases substantially [15]. Like many other disorders of metabolic syndrome, insulin resistance is thought to be a central phenomenon where many of the other abnormalities converge.

The objective of our study was to see the association between serum TSH levels with insulin resistance in patients with polycystic ovarian syndrome. It was observed that the mean serum TSH level was 3.87±3.44 (mIU/L) in insulin resistant PCOS women, significantly higher than 2.29±1.66 (mIU/L) in those without insulin resistance.

Similar result was found in the study of Liu *et a*l., [10] where serum TSH level in insulin resistance group was higher than in non-insulin resistance group (3.1±1.1 mU/L vs. 2.3±0.8 mU/L). Other studies [8, 9, 11, 16] as well found an association of subclinical hypothyroidism with insulin resistance in women with polycystic ovarian syndrome (PCOS). Mueller et al [10] observed that insulin resistance (IR) was more common in PCOS women with TSH > 2 mIU/L than those with TSH < 2 mIU/L. Dittrich *et a*l., [8] showed that insulin resistance (IR) indexes were higher in women with PCOS and TSH levels > 2.5 mIU/L compared with those with lower TSH levels. Benetti-Pinto *et al*., [16] reported that the thyroid stimulating hormone (TSH) ≥ 2.77mIU/L was associated with a diagnosis of insulin resistance. In hypothyroidism, glucose uptake in muscle and adipose tissue is resistant to insulin, resulting in higher concentrations of insulin in these patients [17].

In contrast some studies [12-14] found no significant difference of TSH level between insulin resistant and non-resistant groups. Naher *et al*., [13] found that the median serum TSH level in the insulin resistance group was 2.25 µIU/ml (range 0.89-5.71 µIU/ml) and in non-insulin resistance group 2.58 µIU/ml (range 0.74-20.86 µIU/ml). They measured the insulin sensitivity by HOMA % S. Forty seven (47.0%) percent subjects were in the range of 50 to 100 of insulin sensitivity whereas, 26.5% were lower insulin sensitivity (<50). Similarly in another study Ganie *et al*., [12] found no association of insulin sensitivity as measured by HOMA-IR with subclinical hypothyroidism. However they used the threshold HOMA IR value 2.29 for detection of insulin resistance which is much higher than our threshold of 1.6. The above variations could be due to disparity on sample size, difference in subject selection, differences in study designs & methods, as well as in the methods used to measured serum TSH, serum glucose, fasting insulin and quality of laboratory kits and different threshold levels.

In our study there was a positive significant Pearson's correlation (r=0.254; p=0.034) between insulin resistance and serum TSH level (>2.5mIU/L) in PCOS patients with insulin resistance. Similarly Dittrich *et al*., [8] found that there was a significant positive correlation (r=0.387, p<0.05) between TSH with HOMA-IR in women with TSH ≥2.5 mIU/l. Similar correlation between insulin resistance with serum TSH level were also observed by Liu *et al*., [10].

Limitations of the study include population selected from one selected center which is not favorable to generalization of the findings.The study was conducted over a very short period of time with relatively small sample size. Further studies with large number of patients can be undertaken.

Thyroid hormones exert profound effects in the regulation of glucose homeostasis. These effects may be due to modifications of circulating insulin levels, counter regulatory hormones, intestinal absorption, hepatic production and uptake of glucose by

peripheral tissue (fat and muscle). Hypothyroidism can break this equilibrium and alter glucose metabolism leading to insulin resistance. Insulin resistance is the central pathophysiological phenomenon underlying the metabolic syndrome which is a major cardiovascular risk factor.

Hence it will be good practice to screen PCOS women for presence of subclinical hypothyroidism (SCH) and insulin resistance. Early detection and prompt intervention can prevent or delay the appearance of various metabolic and cardiovascular consequences associated with insulin resistance. Along with diabetes treatment, if we check and treat hypothyroidism even in subclinical stage, it will take care of its contribution to total insulin resistance. Modulating serum TSH level earlier may reverse the progress to NIDDM and its health hazards in PCOS patients.

CONCLUSION

Serum TSH level is significantly elevated in PCOS patients with insulin resistance compared to PCOS patients without insulin resistance. Statistical significant positive correlation exists between insulin resistance and serum TSH levels more than 2.5 mIU/L. The outcome of the PCOS women is likely to improve if the hypothyroidism, subclinical or clinical and insulin resistance are diagnosed and treated earlier.

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