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A STUDY OF THYROID-STIMULATING HORMONE, PROLACTIN, INSULIN RESISTANCE IN POLYCYSTIC OVARIAN SYNDROME AND THEIR CORRELATION WITH BODY MASS INDEX

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ABSTRACT

Background: Polycystic ovarian syndrome (PCOS) is a diverse and complicated female endocrine condition that affects one in every 15 women globally and is a substantial economic health burden that is expected to increase as obesity becomes more prevalent. Despite the fact that the pathogenesis of PCOS is not completely known, obesity and IR (Insulin Resistance) seem to have a critical part in the development of PCOS. Our study attempts to analyze the Thyroid-stimulating hormone (TSH), Prolactin (PRL), Fasting Insulin, and IR in the form of the HOMA-IR index and their correlation with BMI in PCOS controls. **Materials and methods:** A comparative cross-sectional research were carried out with 50 women having PCOS and 50 healthy women of similar age and BMI as controls. Fasting samples were examined for TSH, PRL, and Fasting Insulin levels by chemiluminescence immune assays and IR in the form of the HOMA-IR index. The results were then correlated with BMI. Statistical analysis was carried out using SAS 9.2, and SPSS 15.0 software. **Results:** A significant increase in PRL (22.49 ± 17.21 ng/ml vs 12.87±4.31ng/ml), Fasting insulin (13.51±6.12 vs 6.77±2.13µU/L), and HOMA-IR (2.76±1.21 vs 1.38±0.44), in PCOS patients in comparison to controls (P<0.001) was seen. Subclinical hypothyroidism, TSH >5 mIU/ml was observed in 22% of the PCOS patients. There was a strong relationship between HOMA-IR (P=0.001), and Fasting Insulin (P=0.004) with BMI in the PCOS group. **Conclusion:** The analysis revealed a higher incidence of mild hyerprolactinemia and mildly elevated TSH levels in PCOS. This implies the assessment of thyroid function and PRL levels in all PCOS patients. This work also showed increased Insulin Levels and marked IR in the PCOS group. Further IR showed a positive correlation to BMI indicating the need for lifestyle modification to improve fertility and prevent dysglycemic disease in the long run.

KEYWORDS: Polycystic ovarian syndrome (PCOS), Prolactin (PRL), Body Mass Index (BMI), Insulin resistance (IR), Thyroid-stimulating hormone (TSH).

INTRODUCTION

PCOS is a diverse and complicated female endocrine condition that affects one in every 15 women globally and is a substantial economic health burden that is expected to increase as obesity becomes more prevalent. Hypertension, lipid disease, abnormal glucose metabolism, IR, Obesity, and other cardiovascular diseases are common in PCOS patients. It is usually recognized that reproductive activity in women with PCOS is substantially influenced by their body weight and metabolic condition. Although the PCOS etiology is unknown, IR and, obesity seems to play a crucial role. IR is important in the aetiology of PCOS, and Indians are recognized to have a high incidence of IR, hence PCOS could be prevalent in our population as well.[2]

Despite the enormous number of studies in the area of PCOS research, long-term impact and therapy are still a difficulty. The majority of current treatments are focused on menstrual regularity and infertility. PCOS women are at significant risk of developing IR, endometrial cancer, premature arteriosclerosis, dyslipidemia, and type II diabetes, hence correcting the underlying endocrinological pathology and biochemical abnormalities at the earliest are required. Hormonal profiling forms an essential technique in the investigation of the root causes of PCOS. Furthermore, it could aid in the selection of treatment options that will lead to a better result, and it may also be used as a tool for determining a diagnosis. Changes in hormonal profile, in addition to clinical prognosis, could aid in determining treatment effectiveness.

IR could have a significant role in the development of polycystic ovaries in women having PCOS, whereas obesity appears to be the primary factor. As a result, IR and β-cell dysfunction are pathogenic PCOS determinants.

However, hypothyroidism and hyperprolactinemia are positively linked and the relation between hypothyroidism is widely known to be a trigger for hyperprolactinemia. In contrast, there is no indication that PCOS and hyperprolactinemia have a pathophysiological link which indicates that the latter's presence in a person with PCOS should be owing to other pathology as well as etiological studies. The goal of this research was to investigate the relationship between PRL, PCOS, IR, and thyroid hormones, as well as their relationship to BMI. Hence this study will aim to explain this multidirectional link in PCOS, incorporating their complex relationships, and present a unified pathological basis for the same and help in better management.

OBJECTIVES OF THE STUDY

1. Assessment of TSH, PRL, Fasting Insulin, Insulin resistance in the form of HOMA-IR index, and BMI in PCOS and healthy controls
2. To determine if there is any statistically significant difference in these parameters between the PCOS cases and healthy controls.
3. The results will be analyzed for a possible correlation with various BMI categories i.e., lean, normal weight, overweight and obese.

MATERIAL AND METHODS

The research was conducted in Anugrahaa Hospital, a secondary care center in the suburbs of Bangalore, India. It was an observational cross-sectional analysis. A total of 100 women of the age group 18 to 35 who attended the outpatient OBG department were examined of which 50 were cases as well as 50 controls. The research protocol was accepted by the institutional ethical committee. An informed consent form was signed by all of the participants.

Selection criteria

a) CASES

The Rotterdam criteria[3] were used to identify 50 newly diagnosed PCOS patients who fulfilled two of the following criteria; anovulation or oligomenorrhea, biochemical or/and clinical symptoms of hyperandrogenism, and ultrasound diagnosis of polycystic ovaries. Any major co-morbid disease suspected CAH, or an ovarian or adrenal tumor were all considered exclusion criteria.

b) CONTROLS

50 healthy age-matched women with normal menstrual cycles were selected as controls.

Sample collection and Analysis

Samples of venous blood were obtained from the women following a fast of 12hours.

Serum TSH and serum Prolactin were assayed by chemiluminiscent immunoassay using Vitros 3600 and 5600 respectively. Serum fasting Insulin was analyzed on Cobas 6000, Roche diagnostics. Serum FBS was estimated using the GOD-POD method.

BMI was determined using the formula BMI=Wt (kg)/Ht $(m)^2$

BMI was categorized as follows: 30 and above – obese, 29.9 to 25– overweight, 24.9 to18.5 –normal weight, <18.5–underweight

HOMA –IR was assessed with the formula: HOMA = (FBS in mmol/L x Fasting Insulin in µU/mL)/22.5

Normal ranges of Serum TSH = 0.4 - 4.2 mcIU/ml, Serum Prolactin = 3 -18.6 ng/ml, HOMA – IR > 2.5 as Insulin resistance in the Indian population[4], Fasting Insulin =2.6-24.9 mIU/L

Statistical Analyses

Statistical software: The ANOVA ("Analysis of Variance") was applied to assess the significance of research variables between 3 or more patients' groups, and the student t-test ("two-tailed, independent") was employed to assess the significance of research variables on a continuous scale in 2 groups on measured variables using Systat 12.0, MedCalc 9.0.1, Stata 10.1, SPSS 15.0, SAS 9.2 as well as R environment version 2.11.1. Fisher Exact/ Chi-square test was applied to assess the significance of research variables on a categorical scale between 2 or more groups.

RESULTS

A significant increase in PRL (22.49 ± 17.21 ng/ml vs 12.87±4.31ng/ml), Fasting insulin (13.51±6.12 vs 6.77±2.13µU/L), and HOMA-IR (2.76±1.21 vs 1.38±0.44), in PCOS patients in comparison to controls (P< 0.001) was seen. Subclinical hypothyroidism, TSH >5 mIU/ml was observed in 22% of the PCOS patients. There was a strong relationship between HOMA-IR (P= 0.001) & Fasting Insulin (P= 0.004), with BMI in the PCOS group. (Fig 1)

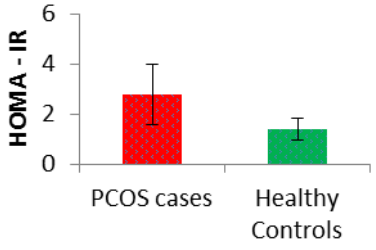

Fig. 1: HOMA –IR distribution in the 2 groups analyzed.

Table 1: Comparison of study & clinical variables in two groups examined.

Variables	PCOS cases	Healthy Controls	Total	P-value
Age in years	24.46±3.43	25.16±3.41	24.81±3.42	0.309
BMI (kg/m^2)	25.05±4.23	23.05±3.17	24.05±3.86	0.009**
TSH	3.29±2.21	2.74±1.29	3.02±1.82	0.136
Prolactin Hormones	22.49±17.21	12.87±4.31	17.68±13.39	<0.001**
Fasting Insulin	13.51±6.12	6.77±2.13	10.14±5.68	<0.001**
FBS (mg/dl)	83.62±10.57	82.70±10.06	83.16±10.27	0.657
HOMA-IR	2.76±1.21	1.38±0.44	2.07±1.14	<0.001**

Table II: Comparison of Study variables according to BMI in PCOS cases.

In PCOS cases	BMI (kg/m^2)				Total	P value
	<18.5	18.5-24.9	25-29.9	30 & above		
TSH	4.50±2.96	3.08±2.50	3.46±2.05	3.45±0.99	3.29±2.21	0.820
Fasting insulin	8.35±1.12	11.44±6.03	15.79±4.91	19.07±4.24	13.51±6.12	0.004**
Prolactin Hormones	20.25±12.8	27.40±21.02	14.52±4.58	18.29±9.42	22.49±17.21	0.136
HOMA-IR	1.73±0.03	2.32±1.20	3.21±0.87	4.00±0.70	2.76±1.21	0.001**

ANOVA test

Fasting Insulin and HOMA-IR showed a strong correlation with BMI and showed an increasing trend with an increase in BMI.

Table III: Comparison of Study variables according to BMI in healthy controls.

In healthy controls	BMI (kg/m^2)				Total	P value
	<18.5	18.5-24.9	25-29.9	30 & above		
TSH	2.02±1.09	2.72±1.33	2.84±0.93	5.02±0.00	2.74±1.29	0.253
Fasting insulin	6.21±3.67	6.40±1.63	8.71±3.06	9.36±0.00	6.77±2.13	0.030*
PRL	8.06±3.57	12.93±4.04	13.11±3.89	23.10±0.00	12.87±4.31	0.020*
HOMA-IR	1.16±0.55	1.28±0.33	1.91±0.54	2.19±0.00	1.38±0.44	<0.001**

ANOVA test

- HOMA –IR indicated a strong positive relationship with BMI in the control group. Serum Insulin and PRL showed moderate significance in correlation to BMI. This indicates Insulin resistance increases as BMI increases and more so in the case of polycystic ovarian disease.
- TSH and PRL had no significant correlation with the BMI in the PCOS group (P=0.290)
- Both the means of TSH and PRL were higher in the PCOS than in the control group (TSH 3.29 ± 2.21 vs 2.74±1.29 mIU/L) and (PRL 22.49±17 vs 12.87±4.31 ng/ml) respectively.
- Fasting Insulin levels showed a strong correlation with BMI (r=0.467 & P=0.001).in PCOS and control groups (r= 0.454 & P= 0.001)
- ANOVA test was significant between the various groups of BMI (lean, normal, overweight, obese) in relation to Fasting Insulin (P= 0.004) in PCOS and moderately significant in controls P=0.030
- HOMA-IR also indicated a strong relationship with BMI (r=0.502 & P<0.001) and control group (r= 0.604 & P< 0.001).
- ANOVA test was significant between the various groups of BMI (lean, overweight, obese) in relation to HOMA-IR in both PCOS (P= 0.001) and control groups (P<0.001)

DISCUSSION

In the present research, the PCOS group had 4%, 56%, 26 %, and 14%, and the control group had 6%, 78%, 14%, and 2% in the lean, normal weight, overweight and obese category respectively. The mean BMI was 25.05±4.23 in cases and 23.05±3.17 in controls indicating that the average weight was greater in the PCOS group and was significant (P=0.009). This was in accordance with the studies of Lim et al[5] which showed an enlarged occurrence of overweight in PCOS women. Women who are overweight or obese who have PCOS are more likely to be detected because they have a poorer reproductive clinical presentation, which might lead to an exaggeration of the obesity-PCOS link.

The current research showed elevated TSH levels in PCOS patients in comparison to controls. 22% of PCOS women had TSH >5 mcIU/L in comparison to 8% in controls. This result was consistent with Yasmin et al[6], who found a high mean TSH level in PCOS patients. Muderris et al[7] found that severe long-term hypothyroidism causes ovarian enlargement and/or cyst development. Additionally, restoring blood hormone levels to euthyroidism causes ovarian shrinkage, ovarian cyst resolution, and reversal of PCOS-like symptoms. Simultaneously, the findings were in line with those of Ghosh et al[8], who proposed that hypothyroidism caused

a drop in levels of SHBG and a rise in levels of testosterone in order to investigate the role of hypothyroidism in the PCOS development.

The additional finding in this study was there was no correlation between TSH with BMI. Our study was in line with the findings of Benitti-pinto et al[9] who showed PCOS women had a higher prevalence of subclinical hypothyroidism but had no correlation to BMI.

We also found no correlation between PRL and TSH in the PCOS group. These findings were in line with those of Robin et al[10], who found that hyperprolactinemia in conjunction with clinical, hormonal ultrasound characteristics of PCOS is not uncommon in clinical practice. Moreover, there is currently no evidence of a pathophysiological link between the 2 entities.

There was no significant connection between PRL and BMI (P=0.136) in our research. Ernst B et al. observed neither any substantial relationship between PRL levels of basal serum and the obesity level or associated metabolic problems nor any systematic variations in basal blood contents after significant weight reduction, they also demonstrated that extra energy is directed directly to the visceral fat depot by PRL.[11] This is contrary to Shibli-Rahhal and Schlechte[12] who described an association between prolactin and obesity.

There was no correlation between PRL and Fasting Insulin, PRL, and HOMA –IR in the analysis. The effect of PRL on IR and glucose metabolism is based on its circulating concentration. Prolactin levels that are physiologically raised cause typical adaptive rises in "glucose-stimulated insulin" production by increasing β-cell mass and enhancing hepatic insulin sensitivity, as well as an indirect effect on energy and glucose balance by boosting hypothalamic dopamine synthesis. In diabetic mice, pathologically high degrees of PRL increase whole-body and hepatic IR and decrease insulin secretory ability.[13]

Hyperinsulinemia and IR are aspects that have a significant role in PCOS pathogenesis. 36% of PCOS women in our research had fasting insulin >18 µU/ml and none of the healthy controls had >18 µU/ml. The incidence of IR is similar to that noted by Kalra A et al.[10] The instigators of their research, have shown a link between IR and obesity with dyslipidemia in Indian PCOS women and have noted a 76.9 percent incidence of IR. Insulin levels in overweight/obese persons are substantially greater than in normal-weight patients. There are a number of processes that contribute to the condition of IR: Hepatic clearance was reduced or pancreatic sensitivity was elevated due to peripheral target tissue resistance. IR is frequent in non-obese PCOS women, and IR in obese PCOS women is made up of two distinct contributions, one distinct to PCOS as well as another particular to obesity.[13] PCOS is characterized by hyperinsulinemia, which occurs in the absence of obesity. Numerous findings have revealed substantial decreases in insulin sensitivity and maximum rates of insulin-stimulated glucose transfer as a result of a decline in the number of GLUT4 glucose transporters. IR seems to be linked to increased "serine phosphorylation" of the insulin receptor is at least 50 percent of PCOS women, resulting in signaling suppression. Insulin alone causes IR; when a cell is subjected to insulin, the synthesis of "Type 4 Glucose Transporters" (GLUT4) on the cell membrane declines somewhat in the context of hyperinsulinemia. This downregulation operates as a positive feedback loop, boosting insulin demand. Excess circulating insulin seems to contribute to insulin resistance through down-regulating insulin receptors at the cellular level. Long-term and repetitive increases of circulating insulin cause this down-regulation.[14]

Obesity is a significant component, and it seems that it has a greater impact on insulin action in women having PCOS than in women without the condition. In order to represent the spectrum of body weight from lean to obese both PCOS women and controls were grouped and studied separately. HOMA IR and greater fasting insulin in the PCOS group led us to compare the incidence of IR in normal weight, lean, and obese/overweight patients (Table II). Taking a cut of the value of 3, only the overweight and obese PCOS group had marked IR in comparison to lean and normal weight. but the HOMA IR index in controls was all less than 2.5. Thus, in our study, the Fasting Insulin and Insulin resistance increased as body weight increased from lean to obese in both PCOD and controls and was more pronounced in PCOS as shown by their higher values. Our results were in line with the analyses of Cresswell et al[15], where PCOS patients with BMI>25 was more Insulin resistant than those with BMI<25. Hormonal irregularities could be linked to carbohydrate imbalance, resulting in hyperinsulinemia and IR, which may progress to type 2 diabetes. IR related to hyperinsulinemia impacts around 50% percent of PCOS patients, both slim and obese. This resulted from peripheral tissue resistance to insulin and reduced hepatic insulin degradation. Insulin resistance is most likely induced by defects in tissue insulin receptors.[16]

The percentage of patients with IR is similar in normal weight and obese/overweight persons. Furthermore, the difference in mean HOMA between obese/overweight as well as normal-weight individuals is statistically negligible. However, greater insulin levels in overweight/obese people, as mentioned above, suggest that PCOS issues are exacerbated or hastened by excess body weight.

CONCLUSION

Our studies were carried out to indicate the precise correlation between BMI, Insulin resistance, hyperprolactinemia, and hypothyroidism in the occurrence of PCOS. We report from our study, that

women with PCOS had a higher frequency of obesity and overweight. Obesity is still a mystery as to whether it is a consequence or a cause of the condition. The role of Obesity in the development of PCOS has to be examined further in long-term investigations.

There was a high frequency of thyroid abnormalities, mostly subclinical hypothyroidism, in PCOS patients, indicating the necessity of correcting hypothyroidism early in the therapy of PCOS-related infertility. Thyroid health has a significant influence on PCOS pathology, influencing all facets of the condition. Correction of subclinical hypothyroidism will improve hormonal and metabolic health overall.

The current study also showed mild hyperprolactinemia in the PCOS which could be due to elevated TSH levels.

We cannot detect any significant association between serum PRL, TSH, and BMI. Further multicentric investigations with a greater number of PCOS subjects in each of the BMI categories will help in determining the risk of endocrine and metabolic diseases.

Obesity increases IR, and the incidence of polycystic ovaries rises IR. Obesity seems to have a bigger impact on IR than the existence of polycystic ovaries. In PCOS, the degree of overweight and obesity is closely associated with IR. In comparison to lean PCOS and controls, PCOS subgroups showed higher fasting insulin, fasting glucose along with HOMA score (IR) values. Insulin resistance indicated a significant correlation to BMI in the PCOS cases indicating IR was a combined effect of obesity and polycystic ovaries.

We like to conclude PCOS treatment should be a multidirectional approach and include a balance of the metabolic, endocrine, and anthropometric parameters and that Insulin resistance has a major role.

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