Evaluation of prolactin and insulin resistance in women with polycystic ovarian syndrome

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Background: Polycystic ovarian syndrome has been one of a major public health problem in India that leads to medical consequences. It causes multifactorial in etiology such as menstrual dysfunction, hyper and rogenism, hirsutism, insulin resistance, dyslipidemia and obesity which increased risk of diabetes mellitus and cardiovascular disease. Prolactin has been reported as a potent lipogenic and diabetogenic factor, that affecting energy balance and fuel metabolism. The present study was designed to assess serum prolactin and insulin resistance in PCOS women and to compare them with healthy women as controls. **Material and Methods:** A comparative study including 50 women diagnosed as PCOS and 50 age and BMI matched healthy women as controls was conducted. The age group for the study was 18-35 years. Body Mass Index was calculated as a physical parameter. Fasting blood samples were drawn to assess serum prolactin, serum insulin, HbA1c and fasting blood sugar. Insulin resistance was calculated by homeostasis model assessment. **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, prolactin, HbA1c and FBS were found elevated in the PCOS women but they were not statistically significant. No significant correlations were found between BMI, serum prolactin and serum insulin. **Conclusions:** The current study provides further evidence that significantly higher fasting insulin and HOMA in PCOS group indicates presence of IR. IR in PCOS group may have a potential role in the prediction of dysglycemic disease in women with PCOS. This study could not find any significant correlation between serum prolactin, serum insulin and BMI.

Keywords: Polycystic ovarian syndrome, Serum prolactin, Insulin resistance

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Introduction

Polycystic ovary syndrome (PCOS) is the most common endocrine disease and metabolic disorder in adolescence and reproductive women, which is the first reason for female infertility, with the incidence of 5-10% of women of reproductive age [1,2]. It is characterized by chronic an ovulation, hyper and rogenism, and ovarian polycystic changes under ultrasound in clinic. The etiology of PCOS is still not very clear, but previous studies have shown that PCOS is closely related to lipid metabolism disorder and insulin resistance [3,4].

50% of PCOS patients have obesity that to android obesity with an increased risk of diabetes mellitus and cardiovascular disease [5]. Insulin resistance is present in 40-50% of patients, especially in obese women [6] According to ESHRE/ASRM (European Society for Human Reproduction and Embryology/America Society for Reproductive Medicine) 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 [7].

It is well known that reproductive function in women with PCOS is strongly dependent on bodyweight and the metabolic status of the patient [8]. 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 [9]. A large percentage of PCOS women are insulin resistant and suffer from metabolic alterations [10]. Prolactin (Prl) is a hormone of pituitary origin and a single-chain polypeptide involved in several actions, such as lactation, luteal function, reproduction, appetite, suppression of fertility, homeostasis, osmotic balance, immunity, and coagulation. Prolactin has been reported as a potent lipogenic and diabetogenic factor, that affecting energy balance and fuel metabolism [11].

Among the various physiological factors known to augment prolactin, insulin induced hypoglycemia which results in significant release of prolactin in normal subjects.

In vitro lactogen treatment, in the form of oral prolactin alters insulin secretary behavior and β cell junctional communication. Hyperprolactinemia decreases glucose tolerance via an increase in insulin resistance [12]. Because there was few studies done in this area, the present study, was designed to assess serum prolactin and insulin resistance in women with PCOS and to compare them with healthy women as controls.

Materials and Methods

The study was carried out on 50 PCOS subjects in the age group of 18 to 35 years and 50 voluntary age and BMI matched healthy women with normal menstrual cycle as controls. The study was conducted at Medical College & Hospital, Kolkata, after obtaining ethical clearance.

Inclusion criteria: 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. Exclusion criteria: Patients with diabetes mellitus, hypertension, dyslipidemia, renal and liver failure 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 prolactin, serum insulin, HbA1c and blood sugar were measured in all participants from morning blood samples collected after 12 hours of fasting.

Serum prolactin and serum insulin were measured by electrochemiluminescence immunoassay (Advia Centaur analyzer, Siemens). 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 (Immuno-Inhibition method). Body mass index (BMI) was calculated as the ratio of weight (Kg) to height squared (m2). Blood sugar was estimated by Hexokinase method.

Statistics analysis: SPSS software version 22.0 was used for statistical analysis. Comparisons between groups were performed using the Mann-Whitney test.

Correlation analysis between BMI, serum prolactin and serum insulin were done using Spearman's rank order correlation coefficients.A p value < 0.05 was considered statistically significant.

Results

Results are presented as Mean ± SD. The basic characteristics and mean distribution of biochemical parameters in 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

Table-1: Mean distribution of biochemical parameters in PCOS cases and controls.

Parameters	Controls (n = 50)	Cases with PCOS (n=50)	p value
Age (years)	22.39± 4.11	22.13±3.41	0.690
BMI ((kg/m2)	23± 2.46	24.06±4.45	0.128
Serum Prolactin (µg/L)	10.18±5.96	14.62±6.81	0.065
FBS (mg/dl)	72.17±9.09	81.26±8.69	<0.05
HbA1c (%)	5.67±0.69	5.95 ± 0.98	0.408
Serum Insulin (uIU/mL)	6.72±3.01	12.46±6.12	<0.001
HOMA-IR	1.24±0.46	2.39±1.74	<0.001

P value < 0.05; statistically significant

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). Higher mean prolactin, HbA1c and FBS were recorded in cases compared to controls but differences between cases and controls were not statistically significant (P≥0.05).

Table-2: Correlation between various parameters.

Parameters	Cases		Controls	
	p value	p value	p value	p value
Prolactin and Insulin	0.041	0.798	-0.286	0.111
Prolactin and HOMA-IR	0.129	0.486	-0.288	0.137
BMI and Insulin	0.276	0.128	-0.159	0.379

Correlation of prolactin with insulin, HOMA-IR and BMI is depicted in Table 2. No significant correlation could be found between BMI and serum Insulin in cases (p= 0.276, p = 0.128) or controls (p= - 0.159, p = 0.379).

No significant correlation could be found between prolactin and serum Insulin in cases (p= 0.041, p = 0.798) or controls (p= - 0.286, p = 0.111). Prolactin was not significantly correlated with HOMA-IR in cases (p= 0.129, p = 0.486) or controls (p= -0.288, p = 0.137) in our study. Similarly, no significant correlation could be found between BMI and serum prolactin in cases (p= - 0.112, p = 0.529) or controls (p= - 0.071, p = 0.764).

Discussion

Polycystic ovarian syndrome is one of the important endocrine disorder causing reproductive abnormalities in women, which has heterogeneous clinical features and multifactorial in etiology [13]. Obesity and insulin resistance occur frequently in association with this syndrome. Cardiovascular risk factors seem to cluster in women with PCOS compared with general population [14]. Insulin resistance is a metabolic disorder caused by the impairment of insulin function in inducing glucose uptake and utilization [15]. Seow et al. demonstrated that IR in PCOS involves both receptor and post receptor defects, including defects in phosphatidylinositol 3-kinase and the GLUT-4 glucose transporter [16].

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 [16, 17]. 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 [18].

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 another similar study [18]. 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 PCOS3. Higher mean HbA1c and FBS were recorded in PCOS women in our study compared to controls but differences between cases and controls were not statistically significant (P≥0.05).

This present study did not find any significant correlation between BMI and serum insulin level in either of the groups mostly because of the limited number of subjects. Similarly another study, also showed that women with PCOS were more insulin resistant compared to a group of age and BMI matched controls [19]. Sunita *et al* concluded in their study that Insulin resistance is common in Indian PCOS women and this is independent of obesity [20].

In present study, higher mean prolactin was recorded in PCOS women compared to controls but differences between cases and controls were not statistically significant (P≥0.05). This finding is in agreement with other studies also [20,21,22]. In contrast to this, other researchers found serum insulin and prolactin both are significantly increased in PCOS women. This increased prolactin may augment adrenal androgen secretion by the inhibition of 3beta-hydroxysteroid dehydrogenase activity or, less often, through selective action on the sulfation of DHEA in adrenal or extra-adrenal sites. However, prolactin inhibits FSH-induced ovarian aromatase, leading to intraovarian hyperandrogenemia [8].

In our study, no significant correlation could be found between prolactin and serum Insulin in PCOS cases (p= 0.041, p = 0.798) or controls (p= - 0.286, p = 0.111). Similarly, no significant correlation could be found between BMI and serum prolactin in PCOS cases (p= - 0.112, p = 0.529) or controls (p= - 0.071, p = 0.764). The role of prolactin on glucose metabolism and insulin resistance depends on its circulating concentration.

Prolactin knockout or prolactin receptor deficiency is accompanied by β-cell hypoplasia, a reduced pancreatic insulin mRNA level, a blunted insulin secretory response to glucose, and mild glucose intolerance. Physiologically elevated prolactin levels induce normal adaptive increases in glucose-stimulated insulin secretion through expanding β-cell mass and improving hepatic insulin sensitivity and have an indirect action by increasing hypothalamic dopamine synthesis to contribute to the improved energy and glucose homeostasis. Pathologically high levels of prolactin exacerbate whole-body and hepatic insulin resistance and impair the insulin secretory capacity in diabetic mice [23]. Differential effects on gene expression are associated with synergistic effects of glucose and PRL on is let DNA synthesis. PRL up-regulates β-cell

Glucose uptake and utilization, whereas glucose increases islet PRL receptor expression and potentates the effects of PRL on cell cycle gene expression and DNA synthesis [24]. Available in-vitro studies suggest an influence of prolactin on ß-cell secretion via increased glucokinase activity, improved ß-cell specific survival, or inhibition of intrinsic ß-cell apoptosis [25].

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 prolactin, serum insulin and BMI. The limitations of the study are that a very small population of cases and controls were taken for this study. Measurement of confounding factors were not taken into consideration. So, a large scale clinical trial with subjects suffering from polycystic ovarian syndrome should be undertaken for evaluating risk of metabolic and endocrine disorders may be undertaken.

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Contribution Details (to be ticked marked as applicable).

	Contributor 1	Contributor 2	Contributor 3	Contributor 4
Concepts	+	+	+	+
Design	+	+	+	+
Definition of intellectual content	+	+	+	+
Literature search	+	+	+	+
Clinical studies	+	+	+	+
Experimental studies	+	+		
Data acquisition	+	+		
Data analysis	+	+	+	+
Statistical analysis	+	+	+	+
Manuscript preparation	+	+	+	+
Manuscript editing	+	+	+	+
Manuscript review	+	+	+	
Guarantor	+	+	+	+

Abbreviations: PCOS; Polycystic Ovarian Syndrome, BMI; Body Mass Index, FBS; Fasting Blood Sugar, IR; Insulin Resistance, HOMA; Homeostasis Model Assessment, HbA1c; Glycated Hemoglobin.

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