

Research Article

## Assessment of prolactin and insulin resistance in women with polycystic ovarian syndrome

B.V. Ravi<sup>\*1</sup>, Sadaria Roshni Gokaldas<sup>1</sup> and D.R. Savithri<sup>2</sup>

<sup>1</sup>Department of Biochemistry, Kempegowda Institute of Medical Sciences, Banashankari 2<sup>nd</sup> stage, Bangalore – 560070, India.

<sup>2</sup>Department of Obstetrics and Gynaecology, Kempegowda Institute of Medical Sciences, Bangalore – 560070, India.

**\*Correspondence Info:**

Dr. B.V. Ravi,  
Professor and Head,  
Department of Biochemistry,  
Kempegowda Institute of Medical Sciences,  
Banashankari 2<sup>nd</sup> stage, Bangalore – 560070, India.  
E-mail: [drbv ravi@gmail.com](mailto:drbv ravi@gmail.com)

### Abstract

**Background:** Polycystic ovarian syndrome (PCOS), the most common cause of infertility, is a disorder characterized by chronic anovulation, hyperandrogenism, hyperinsulinemia, and often presence of obesity. 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 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 prolactin, serum insulin, HbA1c 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, 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. We could not find any significant correlation between serum prolactin, serum insulin and BMI because our study consisted of a limited number of PCOS subjects.

**Keywords:** Polycystic ovarian syndrome, Serum prolactin, Insulin resistance

### 1. Introduction

Polycystic ovary syndrome (PCOS) is one of the common endocrine disorders affecting 5 to 10 % of reproductive age women<sup>1</sup>. 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<sup>2</sup>. PCOS subjects are often accompanied by obesity, insulin resistance, abnormal glucose metabolism, lipid disorder, hypertension, and other risk factors of cardiovascular disease<sup>3</sup>. It is well known that reproductive function in women with PCOS is strongly dependent on bodyweight and the metabolic status of the patient<sup>4</sup>. 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<sup>5</sup>. A large percentage of PCOS women are insulin resistant and suffer from metabolic alterations<sup>6</sup>.

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<sup>7</sup>. 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 secretory behavior and  $\beta$  cell junctional communication. Hyperprolactinemia decreases glucose tolerance via an increase in insulin resistance<sup>8</sup>. 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.

### 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 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 (Elecsys 2010 analyzer, Roche Diagnostics). IR was estimated via the homeostasis model assessment insulin resistance index (HOMA-IR), as follows:  $HOMA-IR = \text{fasting insulin (mU/L)} \times \text{fasting glucose (mmol/L)} / 22.5$ . 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.

### 2.1 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, serum prolactin 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  $\pm$  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 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 ( $P \geq 0.05$ ). 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 ( $\rho = 0.283$ ,  $p = 0.130$ ) or controls ( $\rho = -0.163$ ,  $p = 0.388$ ). No significant correlation could be found between prolactin and serum Insulin in cases ( $\rho = 0.042$ ,  $p = 0.825$ ) or controls ( $\rho = -0.295$ ,  $p = 0.113$ ). Prolactin was not significantly correlated with HOMA-IR in cases ( $\rho = 0.131$ ,  $p = 0.492$ ) or controls ( $\rho = -0.281$ ,  $p = 0.133$ ) in our study. Similarly, no significant correlation could be found between BMI and serum prolactin in cases ( $\rho = -0.117$ ,  $p = 0.537$ ) or controls ( $\rho = -0.075$ ,  $p = 0.694$ ).

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

Parameters	Cases with PCOS (n=30)	Controls (n = 30)	P value
Age (years)	23.37 $\pm$ 4.09	23.73 $\pm$ 3.81	0.744
BMI ((kg/m <sup>2</sup> )	24.00 $\pm$ 4.41	22.51 $\pm$ 2.31	0.126
Serum Prolactin	14.08 $\pm$ 6.87	10.78 $\pm$ 6.72	0.065
Serum Insulin	12.01 $\pm$ 6.74	6.80 $\pm$ 3.10	$< 0.001^*$
HOMA-IR	2.35 $\pm$ 1.40	1.27 $\pm$ 0.58	$< 0.001^*$
HbA1c	5.91 $\pm$ 0.97	5.63 $\pm$ 0.36	0.432
FBS	80.33 $\pm$ 10.53	74.67 $\pm$ 9.59	0.050

\*denotes significant difference; Values are expressed as means  $\pm$  SD

**Table 2: Correlation between various parameters**

Parameters	Cases		Controls	
	$\rho$ value	P value	$\rho$ value	P value
Prolactin and Insulin	0.042	0.825	-0.295	0.113
Prolactin and HOMA-IR	0.131	0.492	-0.281	0.133
BMI and Insulin	0.283	0.130	-0.163	0.388
BMI and Prolactin	-0.117	0.537	-0.075	0.694

## 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<sup>9</sup>. 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<sup>10,11</sup>. 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<sup>3</sup>. 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 *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<sup>3</sup>. 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 ( $P \geq 0.05$ ). 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 *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<sup>12</sup>. Sunita *et al* concluded in their study that Insulin resistance is common in Indian PCOS women and this is independent of obesity<sup>13</sup>.

Studies showed mild hyperprolactinemia has been reported in 5% to 30% of patients with PCOS<sup>14</sup>. In present study, higher mean prolactin was recorded in PCOS women compared to controls but differences between cases and controls were not statistically significant ( $P \geq 0.05$ ). This finding was consistent with Ansam<sup>15</sup>, Soodabeh *et al*<sup>16</sup> and Sunita *et al*<sup>13</sup>. In contrast to this, Roy *et al* found in their study that 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<sup>4</sup>. Cristianne *et al* also found prolactin is significantly higher in PCOS women<sup>17</sup>.

In our study, no significant correlation could be found between prolactin and serum Insulin in PCOS cases ( $\rho = 0.042$ ,  $p = 0.825$ ) or controls ( $\rho = -0.295$ ,  $p = 0.113$ ). Similarly, no significant correlation could be found between BMI and serum prolactin in PCOS cases ( $\rho = -0.117$ ,  $p = 0.537$ ) or controls ( $\rho = -0.075$ ,  $p = 0.694$ ). The role of prolactin on glucose metabolism and insulin resistance depends on its circulating concentration. Prolactin knockout or prolactin receptor deficiency is accompanied by  $\beta$ -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  $\beta$ -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<sup>18</sup>. Differential effects on gene expression are associated with synergistic effects of glucose and PRL on islet DNA synthesis. PRL up-regulates  $\beta$ -cell glucose uptake and utilization, whereas glucose increases islet PRL receptor expression and potentiates the effects of PRL on cell cycle gene expression and DNA

synthesis<sup>19</sup>. Available in-vitro studies suggest an influence of prolactin on  $\beta$ -cell secretion via increased glucokinase activity, improved  $\beta$ -cell specific survival, or inhibition of intrinsic  $\beta$ -cell apoptosis<sup>20</sup>.

## 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 prolactin, 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 polycystic ovarian syndrome for evaluating risk of metabolic and endocrine disorders.

## References

1. Ramanand SJ, Ramanand JB, Jain SS, Raparti GT, Ghanghas RR, Halasawadekar NR, Patil PT, Pawar MP. Leptin in non PCOS and PCOS women: a comparative study. *Int J Basic Clin Pharmacol* 2014; 3:186-93.
2. Pikee Saxena, Anupam Prakash, Aruna Nigam, Archana Mishra. Polycystic ovary syndrome: Is obesity a sine qua non? A clinical, hormonal, and metabolic assessment in relation to body mass index. *Indian Journal of Endocrinology and Metabolism*. 2012 Nov-Dec; 16(6):996-9.
3. Shou-Kul Xiang, Fei Hua, Ying Tang, Xiao-Hong Jiang, Qi Zhuang, Feng-Juan Qian. Relationship between serum lipoprotein ratios and insulin resistance in polycystic ovary syndrome. *International Journal of Endocrinology*. 2012 April; 2012(2012), 173281:1-4.
4. Roy George K., Malini N. A. The prevalence and etiology of polycystic ovarian syndrome (PCOS) as a cause of female infertility in central Travancore. *The bioscan* 2014; 9(1):01-06.
5. Lerchbaum E., Schwetz V., Giuliani A., Obermayer-Pietsch B. Assessment of glucose metabolism in polycystic ovary syndrome: HbA1c or fasting glucose compared with the oral glucose tolerance test as a screening method. *Human Reproduction* 2013 June: 1–8.
6. Matthias Mohlig, Annette Jurgens, Joachim Spranger, Kurt Hoffmann, Martin O Weickert, Hans W Schlosser, et al. The androgen receptor CAG repeat modifies the impact of testosterone on insulin resistance in women with polycystic ovary syndrome. *European Journal of Endocrinology* 2006; 155:127–30.
7. Zadeh-Vakili A, Tehrani FR, Hashemi S, Amouzegar A, Azizi F. Relationship between Sex Hormone Binding Globulin, Thyroid Stimulating Hormone, Prolactin and Serum Androgens with Metabolic Syndrome Parameters in Iranian Women of Reproductive Age. *J Diabetes Metab* 2012; S2:008.
8. Tahia H. Saleem, Howaida A. Nafady, Housny A. Hassan. Serum Prolactin and Blood Glucose Levels Before and After an Oral Glucose-load in Patients with Diabetes Mellitus and Liver Cirrhosis. *Asian Journal of Medical Sciences* 2013; 5(1): 09-18.
9. Thanyarat Wongwananuruk, Manee Rattanachaiyanont, Suchada Indhavivadhana, Pichai Leerasiri, Kitirat Techatraisak, Prasong Tanmahasamut. Prevalence and Clinical Predictors of Insulin Resistance in Reproductive-Aged Thai Women with Polycystic Ovary Syndrome. *International Journal of Endocrinology* 2012:1-6.
10. Seow K-M, Juan C-C, Wu L-Y, Hsu Y-P, Yang W-M, Tsai Y-L, et al. Serum and adipocyte resistin in polycystic ovary syndrome with insulin resistance. *Hum Reprod* 2004; 19:48–53.
11. Ovalle F, Aziz R. Insulin resistance, polycystic ovary syndrome and diabetes mellitus. *Fertil Steril* 2002; 77:1095–105.
12. Puder JJ, Varga S, Kraenzlin M, et al. Central fat excess in polycystic ovarian syndrome: relation to low-grade inflammation and insulin resistance. *J Clin Endocrinol Metab* 2005; 90:6014-21.
13. Sunita J Ramanand, Balasaheb B Ghongane, Jaiprakash B Ramanand, Milind H Patwardhan, Varsha M Patwardhan, Ravi Ghanghas et al. Hormonal Profile of Polycystic Ovary Syndrome (PCOS) In Indian Women. *Research Journal of Pharmaceutical, Biological and Chemical Sciences* Oct-Dec 2012; 3(4):1159-72.
14. Michael T. Sheehan. Polycystic Ovarian Syndrome: Diagnosis and Management. *Clinical Medicine & Research* 2004; 2(1):13-27.
15. Ansam A. Al-Bayatti. Insulin resistance and upper-body obesity in polycystic ovary syndrome. *Middle East Fertility Society Journal* 2006; 11(3):202-9.
16. Soodabeh Zandi, Saeideh Farajzadeh, Hamideh Safari. Prevalence of polycystic ovary syndrome in women with acne: hormone profiles and clinical findings. *Journal of Pakistan Association of Dermatologists* 2010; 20: 194-198.
17. Cristianne Serafim da Silva Feuser, Jacklyne Silva Barbosa, Evelyn Barzotto da Silva, Sebastiao Freitas de Medeiros. Current insights into gonadotropic pituitary function in the polycystic ovary syndrome. *Asian Pacific Journal of Reproduction* 2014; 3(1): 64-70.
18. Guang Ning et al. Circulating Prolactin Associates with Diabetes and Impaired Glucose Regulation. *Diabetes Care* 2013; 36:1974-80.
19. Arumugam R., D. Fleenor, D. Lu, M. Freemark. Differential and complementary effects of glucose and prolactin on Islet DNA synthesis and gene expression. *Endocrinology* 2011; 152(3):856-68.
20. Lisa Balbach, Henri Wallaschofski, Henry Völzke, Matthias Nauck, Marcus Dörr, Robin Haring. Serum prolactin concentrations as risk factor of metabolic syndrome or type 2 diabetes? *BMC Endocrine Disorders* 2013; 13(12):1-8.