Original Research Paper

Volume - 11 | Issue - 10 | October - 2021 | PRINT ISSN No. 2249 - 555X | DOI : 10.36106/ijar

Biochemistry

CAN PROLACTIN BE A MARKER FOR DEVELOPMENT AND PROGRESSION OF PCOS?

Dr. Satyaki Basu	Resident, Department of Biochemistry, Medical College, Kolkata.
Dr. Dipankar Kundu	Associate Professor, Department of Biochemistry, Medical College, Kolkata.
Dr. Santu Mondal	Resident, Department of Biochemistry, Medical College, Kolkata.
Dr. Sourish Ghosh*	Resident, Department of Biochemistry, Medical College Kolkata. *Corresponding Author

ABSTRACT **Background:** Polycystic ovarian syndrome has been one of a major public health problem. It causes multifactorial in etiology such as menstrual dysfunction, hyperandrogenism, 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 newly diagnosed as PCOS and 50 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 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. Prolactin and FPG were found elevated in the PCOS women and were statistically significant.

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 found significant correlation between serum prolactin and serum insulin.

KEYWORDS : Polycystic ovarian syndrome, Serum prolactin, Insulin resistance

INTRODUCTION

Polycystic ovarian syndrome (PCOS) is one of a major public health problem in India and is the most common endocrine disease and metabolic disorder in adolescent and reproductive age group women, which is the first reason for female infertility, with the incidence of 5-10% of women of reproductive age group[1]. During the reproductive years, PCOS is associated with important reproductive morbidity, including infertility, irregular uterine bleeding, and increased pregnancy loss[2]. The syndrome is characterized by Hyperandrogenism, Ovulatory dysfunction and Polycystic-appearing ovaries[3].

Women with PCOS are also at higher risk for Insulin resistance, Type 2 diabetes mellitus, Obesity, Dyslipidemia, Hypertension, atherosclerotic cardiovascular disease, Endometrial, hyperplasia and endometrial cancer, Obstructive sleep apnoea and mood disorders. 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[4,5]. PCOS is associated with increased metabolic and cardiovascular risk factors[6]. These risks are linked to Insulin resistance (IR) and are compounded by the common occurrence of obesity, although insulin resistance also occurs in nonobese women with PCOS[7].

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. Hyperprolactinemia and polycystic ovary syndrome (PCOS) are on the list of the most frequent causes of female infertility[8].

This study will enable us to establish a loop between alterations in levels of prolactin and Insulin resistance with the development and progression of PCOS in women. Because there were 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 newly diagnosed PCOS subjects in the age group of 18 to 35 years and 50 healthy women with normal menstrual cycle as controls. The study was conducted at Medical College Kolkata, after obtaining ethical clearance. 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. Informed consent was obtained from all the participants.

Baseline data including age, detailed medical history, clinical examinations and relevant investigations were included as part of the methodology. Serum prolactin, serum insulin (electrochemiluminescence immunoassay) and blood sugar (Hexokinase method) were measured in all participants from morning blood samples collected after 12 hours of fasting. 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.

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

RESULTS

Table 1: Table Showing Age Distribution Between Cases And Controls

Age in years	Cases	Controls	Total
<20	9(18%)	10(20%)	19(19%)
20-30	38(76%)	37(74%)	75(75%)
31-40	3(6%)	3(6%)	6(6%)
Total	50(100%)	50(100%)	100(100%)
Mean ± SD	23.38±3.85	23.66±4.03	23.52±3.93

Samples are age matched with P=0.723, student t test

Table 2: Table Showing Distribution Of FPG/PRL Values In Cases And Controls

	Cases (n=50)	Controls (n=50)	Total (n=100)	
FPG (mg/dl)				
<70	2(4%)	14(28%)	16(16%)	<0.001**
70-90	32(64%)	34(68%)	66(66%)	
>90	16(32%)	2(4%)	18(18%)	
PRL (µg/L)				
<6	4(8%)	9(18%)	13(13%)	0.140
6-9	8(16%)	12(24%)	20(20%)	
>9	38(76%)	29(58%)	67(67%)	

Chi square test

Table 3: Table showing distribution of Fasting Insulin (µIU/ml) values in Cases and Controls

Fasting Insulin (µIU/ml)	Cases	Controls	Total
<10	16(32%)	44(88%)	60(60%)
10-20	28(56%)	6(12%)	34(34%)
>20	6(12%)	0(0%)	6(6%)
Total	50(100%)	50(100%)	100(100%)

P<0.001**, Significant, chi square test

Table 4: Table Showing Distribution Of HOMA-IR Values In Cases And Controls

HOMA IR	Cases	Controls	Total
<1.1	6(12%)	21(42%)	27(27%)
>1.1	44(88%)	29(58%)	73(73%)
Total	50(100%)	50(100%)	100(100%)

P=0.001**, Significant, chi square test

Table 5: Comparison Of Study Variables In Cases And Controls

variables	Cases	Controls	Total	P value
FPG (mg/dl)	87.81±15.54	74.62±9.54	81.21±14.44	<0.001**
PRL (µg/L)	14.68±6.86	10.21±4.41	12.44±6.16	<0.001**
Fasting Insulin (µIU/ml)	14.01±6.30	6.98±2.43	10.50±5.92	<0.001**
HOMA IR	3.11±1.77	1.18±0.54	2.15±1.62	<0.001**

Table 6: Pearson Correlation

Pair	Cases		Controls	
	r value	p value	r value	p value
PRL vs FASTING INSULIN	0.455	0.001**	-0.061	0.678
PRL vs HOMA IR	0.622	<0.001**	-0.021	0.885
PRL VS FPG	0.624	<0.001**	-0.073	0.617

Mean values of FPG were found to be higher in cases compared with controls(Table 5) and were statistically significant(p value: <0.001).

Serum Insulin and HOMA-IR were found to be significantly higher (p values: <0.001 and <0.001 respectively) in PCOS cases compared with controls in the present study (Table 5).

Higher mean prolactin was recorded in PCOS women compared to controls (Table 5) and differences between cases and controls were statistically significant (p value ≤ 0.05).

Correlation could be found between prolactin and serum Insulin in PCOS cases (Table 6)

DISCUSSION

Polycystic ovarian syndrome is one of the important endocrine disorders causing reproductive abnormalities in women, which has heterogeneous clinical features and multifactorial in etiology[7]. 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[9]. Insulin resistance is a metabolic disorder caused by the impairment of insulin function in inducing glucose uptake and utilization[10]. 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[11]. 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[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[12].

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[12]. 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.

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[13,14]. 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.

In our study, correlation could be found between prolactin and serum Insulin in PCOS cases.

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. Differential effects on gene expression are associated with synergistic effects of glucose and PRL on islet 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[15]. 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[16].

In the present study, measurement of IR for every PCOS woman were done. Confirming our results previous studies showed that FBS was not a good indicator for IR. Some studies have also shown that FBS concentration was not different between PCOS and control groups[17]. Prior investigations showed higher levels of fasting insulin and HOMA-IR in PCOS cases compared to the controls[17,18]. The overall prevalence of IR in PCOS has been reported to be between 50-75% in the previous studies. In our study, FBS >90 was detected in only 32% of the PCOS women in favour of its low sensitivity confirming a previous study[19]. In addition, glucose/ insulin ratio and MacAuley index has lower sensitivities. Considering the fact that improving lifestyle and weight reduction play important roles in prevention and management of PCOS consequences, we decided to choose HOMA-IR with the most sensitivity as was suggested before[20].

Higher mean FPG was recorded in PCOS women in our study compared to controls and differences between cases and controls was found to be statistically significant (P= <0.001). This result agrees with a study done by Burghen et al[21] who reported that the elevation of fasting plasma glucose was associated with hyperinsulinemia.

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[12].

The limitations in the present study is firstly the number of cases and

controls were very small so the linearity and correlations among the variables could not be clearly established. Secondly, measurement of confounding factors were not taken into consideration.

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 find significant correlation between serum prolactin and serum insulin.

REFERENCES

[1] J. Adams, D. W. Polson, and S. Franks, "Prevalence of polycystic ovaries in women with anovulation and idiopathic hirsutism," British Medical Journal, vol. 293, no. 6543, pp. 355–359, 1986.

[2] Shlomo M., Ronald J. K., Richard J. A., Clifford J. R., Allison B. G., Williams Textbook of Endocrinology. 14th ed. Canada, Elsevier, Inc., 2020; 612-622.

[3] ACOG Committee on Practice Bulletins—Gynecology. ACOG practice bulletin no. 108: Polycystic ovary syndrome. Obstet Gynecol 2009;114:936–949.

[4] A. Galluzzo, M. C. Amato, and C. Giordano, "Insulin resistance and polycystic ovary syndrome,"Nutrition, Metabolism and Cardiovascular Diseases, vol. 18, no. 7, pp. 511–518, 2008.

[5] H. J. Teede, S. Hutchison, S. Zoungas, and C. Meyer, "Insulin resistance, the metabolic syndrome, diabetes, and cardiovascular disease risk in women with PCOS," Endocrine, vol. 30, no. 1, pp. 45–53, 2006.

[6] Legro RS, Kunselman AR, Dodson WC, Dunaif A. Prevalence and predictors of risk for type 2 diabetes mellitus and impaired glucose tolerance in polycystic ovary syndrome: a prospective, controlled study in 254 affected women. J Clin Endocrinol Metab. 1999;84:165–169.

[7] Dunaif A. Insulin resistance and the polycystic ovary syndrome: mechanism and implications for pathogenesis. Endocr Rev. 1997;18:774–800.

[8] Szosland K, Pawlowicz P, Lewiński A. Prolactin secretion in polycystic ovary syndrome (PCOS). Neuro Endocrinol Lett. 2015;36(1) 53-58. PMID: 25789595.

[9] Aral SD, Cates WJr. The increasing consent with infertility: Why now. J.A.M.A. 1983; 250:2327-2331.

[10] Jonathan S. B., Deborah L. B., Berek & Novak's gynecology. 16th ed. Philadelphia, Wolters Kluwer, 2020, Chapter 34.

[11] Rotterdam ESHRE/ASRM-Sponsored PCOS Consensus Workshop Group.Revised 2003 consensus on diagnostic criteria and long-term health risks related to polycystic ovary syndrome. Fertil Steril 2004;81:19–25.

[12] 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.

[13] 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.

[14] 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.

[15]` 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.

[16] 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.

[17] Ludwig A, Weiss J, Tauchert S, Dietze T, Rudolf S, Diedrich K, et al. Influence of hypo- and hyperglycaemia on plasma leptin concentrations in healthy women and in women with polycystic ovary syndrome. *Hum Reprod* 2007; 22: 1555-1561.

[18] Layegh P, Mousavi Z, Farrokh Tehrani D, Parizadeh SM, Khajedaluee M. Insulin resistance and endocrine-metabolic abnormalities in polycystic ovarian syndrome: Comparison between obese and non-obese PCOS patients. Int J Reprod Biomed 2016; 14: 263-270.

[19] Koiou E, Dinas K, Tziomalos K, Toulis K, Kandaraki EA, Kalaitzakis E, et al. The phenotypes of polycystic ovary syndrome defined by the 1990 diagnostic criteria are associated with higher serum vaspin levels than the phenotypes introduced by the 2003 criteria. Obes Facts 2011; 4: 145-1450.

[20] Fritz MA, Sreroff L. Chronic anovulation and the polycystic ovary syndrome. In: Baltimore MD. Clinical Gynecologic Endocrinology and Infertility. 8th Ed. Philadelphia, Lippincott Williams & Wilkins; 2011: 495-532.

[21] Mohiti-Ardekani J, Tarof N, Aflatonian A. Relationships between free leptin and insulin resistance in women with polycystic ovary syndrome. Int J Reprod Med 2009; 7: 53-58.