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Original Article

Biochemistry Section

Correlation of Serum Leptin with Body Mass Index and Insulin Resistance in Polycystic Ovarian Syndrome in a Tertiary Care Centre of Southern Odisha, India

PRACHI JENA[1], RASMITA KUMARI PADHY[2], DEVI PRASAD PRADHAN[3], NIRUPAMA DEVI[4]

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ABSTRACT

Introduction: Leptin is an adipocyte derived hormone encoded by *ob* gene which serves as a relay link between metabolic signals and brain that regulate the hypothalamic pituitary ovarian axis. Leptin is related with obesity, which is a most important cause of Polycystic Ovarian Syndrome (PCOS) in women of reproductive age group.

Aim: To evaluate leptin concentration and to analyse its correlation with Body Mass Index (BMI) and insulin resistance in PCOS.

Materials and Methods: This case-control study was conducted from December 2018 to December 2019 at Department of Biochemistry in collaboration with Department of Obstetrics and Gynaecology, MKCG Medical College and Hospital, Berhampur, Odisha, India. A total of 60 PCOS subjects, aged between 15-30 years (30 obese PCOS and 30 lean PCOS) and 30 age-matched, normal ovulatory healthy controls were included in the study. Parameters such as serum leptin, fasting plasma insulin, Homeostatic Model Assessment-Insulin Resistance (HOMA-IR), Fasting Plasma Glucose (PPG), Postprandial Plasma Glucose (PPPG) were estimated using commercial kits. One-way Analysis of Variance (ANOVA) test was used for data analysis and the Pearson's correlation method was used to find the correlation between the parameters.

Results: The mean age of women in all the three PCOS groups was found to be 22.4±3.13 years. The BMI of obese PCOS patients (31.9±4.7 kg/m^2) and lean PCOS patients (21.4±2.2 kg/m^2) were higher than that of healthy controls (20.7±1.8 kg/m^2) which was statistically significant (p-value <0.001). The serum leptin in obese PCOS were significantly higher (28.0±17.8 ng/mL) than lean PCOS (5.8±2.2 ng/mL) and fasting plasma insulin in lean PCOS were (10.9±2.4 µIU/mL) significantly lower than obese PCOS (30.2±14.8 µIU/mL). Mean serum leptin levels had significant positive correlation with BMI in lean and obese PCOS and insulin resistance in obese PCOS.

Conclusion: In the present study, high leptin concentration was observed in PCOS patients and there was positive correlation of leptin with BMI in both lean and obese PCOS groups and leptin was positively correlated with insulin resistance in obese PCOS.

Keywords: Adipocyte, Basal metabolic index, Obesity, Plasma glucose

INTRODUCTION

The PCOS is characterised by irregular or absence of menstruation, acne, hirsutism and obesity. In developed countries, approximately 5-10% of the female population are affected with PCOS which is a complex metabolic, endocrine and reproductive disorder [1]. The PCOS is commonly seen in countries having higher prevalence rate of obesity and type 2 diabetes [2]. The women with PCOS vary in degrees of weight, out of total PCOS cases 30-75% of cases are mostly overweight or obese associated with central obesity [3]. The central obesity is associated with insulin resistance, hyperinsulinaemia, type 2 diabetes, hyperandrogenaemia, metabolic syndrome and infertility [4]. There appears to be a link between symptoms associated with PCOS with either high androgen or insulin hormone levels [5,6]. However, it cannot be concluded that, not all women with polycystic ovaries have PCOS and not all women with PCOS have polycystic ovaries [7]. Presently, PCOS is diagnosed using Rotterdam criteria (2003): two out of the three following features i.e., Ovulatory dysfunction (<21 or >35 days), Hyperandrogenism (clinically or biochemically), Polycystic ovaries in ultrasound with exclusion of thyroid disease (TSH), hyperprolactinemia (prolactin) and Non classical Congenital Adrenal Hyperplasia [NCCAH (17-hydroxy progesterone)] [8].

Adipose tissue produces Leptin which is a product of *ob* gene of chromosome 7, which is not only responsible for causing obesity, but also has a long list of endocrine functions [9]. Higher and lower levels of leptin are also related with infertility though the mechanism of involvement is still undiscovered [10,11]. There is association of leptin and its receptors in PCOS associated with obesity and insulin resistance [12,13]. High serum level of leptin was found in obese women [14]. If the inter-relationship between leptin, obesity, and insulin action is taken into consideration then there might be a role of Leptin in the pathophysiology of PCOS. Hence, PCOS patients may serve as a reliable study population for the assessing the relationship between hyperinsulinaemia with leptin concentrations besides its association with obesity [15]. No relevant documentation about the role of leptin and its association with insulin in pathophysiology in PCOS was found in Southern Odisha. Thus, the present study sought to evaluate leptin concentration and its correlation with insulin resistance and BMI in patients with PCOS. This study is a part of authors previous research thesis titled "Evaluation of leptin concentration, insulin resistance and its correlation with reproductive hormones" which was done to assess role of leptin with reproductive hormones in PCOS by the same authors with same sample size, study duration and demographic data [16].

MATERIALS AND METHODS

This case-control study was conducted from December 2018 to December 2019 at Department of Biochemistry in collaboration with Department of Obstetrics and Gynaecology, MKCG Medical College and Hospital, Berhampur, Odisha, India after obtaining Institutional ethical clearance [IEC 673/2018]. Both case and control groups gave informed consent for participation in the study.

Inclusion criteria: Newly diagnosed PCOS cases aged between 15-30 years as per Rotterdam Criteria who came to Gynaecology Outpatient Department (OPD) [8] were included. Healthy age-matched normal ovulatory females were randomly chosen from attendants of patients, nursing and MBBS students and from general populations with BMI <25 kg/m^2.

Exclusion criteria: Subjects with family history of any chronic illness such as diabetes, hypothyroidism, women using oral contraceptive pills or insulin sensitising drugs atleast three months prior to study period were excluded from the study. Women with dysmenorrhoea, infertility due to tubal blockage and other pelvic abnormality were also excluded from the study.

Sample size calculation: From the previous data records it was observed that on an average 25 to 30 cases of PCOS had visited the Gynaecology OPD of MKCG MC, Berhampur per month. So on an average 15 newly diagnosed PCOS cases as per the Rotterdam criteria [8] and considering the exclusion criteria with attrition of 5%, data collection was done for four months dedicated to sample collection as a convenient purposeful sampling comprised of 60 patients.

According to the BMI, the cases were divided into two groups as lean PCOS group with BMI <25 kg/m^2 and obese PCOS group with BMI ≥25 kg/m^2. Thirty healthy age-matched normal ovulatory females with BMI <25 kg/m^2, were included as controls. The menstrual history of last menstrual period, amenorrhoea, dysmenorrhoea, oligomenorrhoea, infertility due to tubal blockage and other pelvic abnormality were taken according to a predesigned data collection proforma. The anthropometric measurements like height, weight and BMI were collected.

Study Procedure

A total of 5 mL of blood sample was collected on day 2-3 of menstrual cycle of all controls and blood of PCOS cases were collected independently of menstrual cycle due to irregular menses and were labelled properly and serum was stored at -20ºC.

The routine biochemical parameters were assayed using commercially available kits (AGAPPE Diagnostics Ltd.) by TOSHIBA 120 FR auto analyser. Thyroid profile, serum Luteinising Hormone (LH), FSH and Prolactin (assessed for diagnostic purpose only), fasting plasma insulin, FPG and PPPG were assayed by Roche Cobas e411 electrochemiluminescence and both the internal and external quality control were maintained. All the normal ranges of parameters are mentioned in [Table/Fig-1] [17-20].

Parameters	Normal range
Triiodothyronine (T3)	1.3-3.1 nmol/l
Tetraiodothyronine (T4)	66-181 nmol/l
Thyroid Stimulating Hormone (TSH)	0.27-4.2 µIU/mL
Prolactin	5-25 ng/mL
Follicle Stimulating Hormone (FSH)	3-18 µIU/mL
Luteinising Hormone (LH)	4-18 µIU/mL
Insulin	2.6-24.9 µIU/mL
Leptin	3.7-11.1 ng/mL
Fasting Plasma Glucose (FPG)	70-110 mg/dL
Postprandial Plasma Glucose (PPPG)	<140 mg/dL

[Table/Fig-1]: Normal range of different parameters [17-20].

Estimation of Serum Leptin

The serum leptin level was assayed by using commercial kit of Diagnostic Biochem Canada Inc, in a sandwich type of enzyme immunoassay. This enzyme immunoassay technique uses two highly specific monoclonal antibodies. One of them is a monoclonal antibody specific for leptin and another is monoclonal antibody specific for different epitope of leptin which is conjugated to biotin [17,18].

Estimation of HOMA-IR

Insulin resistance was calculated using the HOMA-IR using the following formula:

HOMA-IR=[fasting glucose (mg/dL)×fasting plasma insulin (mU/mL)/405]

or

HOMA-IR=[fasting glucose (nmol/L)×fasting insulin (µU/mL)/22.5]

HOMA-IR value <3 is categorised as normal, 3-5 as moderate and >5 as severe insulin resistance [21,22].

STATISTICAL ANALYSIS

The statistical analysis of the data was done using International Business Machines (IBM) Statistical Package for the Social Sciences (SPSS) version 25.0. Data analysis was done using one-way Analysis of Variance (ANOVA) test and represented as represented as mean±standard deviation, correlation was calculated by using the Pearson's correlation method and their relationship between variables was shown by scatter plot. A 'p-value of <0.05 was taken as significant.

RESULTS

Both the study population were age-matched. The control group did not have any gynaecological abnormality. Out of the 60 PCOS cases, 65% presented with history of amenorrhoea and 35% with oligomenorrhoea of more than two months duration.

The mean age in PCOS women in all the three groups were found to be (22.5±2.8 years) in controls, (22.0±2.8 years) in lean PCOS and (22.8±3.7 years) in obese PCOS which were statistically not significant (p=0.602). The mean BMI of lean and obese PCOS patients were (21.4±2.2 years) and (31.9±4.7 years) respectively which was higher than that of healthy controls and was statistically significant (p<0.001) [Table/Fig-2].

Parameters	Control (n=30) (BMI <25)	Lean PCOS (n=30) (BMI <25)	Obese PCOS (n=30) (BMI >25)	Total (N=90)	p-value (ANOVA)
Age (years)	22.5±2.8	22.0±2.8	22.8±3.7	22.4±3.13	0.602
Height (cm)	152±5.4	148.7±4.5	157.8±6.6	152.9±6.7	<0.001
Weight (kg)	48.9±5.0	48.7±4.8	79.8±13.5	59.2±17.09	<0.001
BMI (kg/m^2)	20.7±1.8	21.4±2.2	31.9±4.7	24.8±6.0	<0.001

[Table/Fig-2]: Anthropometric parameters of the research subjects.
Values presented as mean±SD

The mean PPPG of lean and obese PCOS patients were (118.2±15.5 mg/dL) and (120.9±19.6 mg/dL) respectively which was higher than that of healthy controls (110.03±8.9 mg/dL) and was statistically significant (p=0.020). There was no statistically significant difference observed in case of FPG level in all groups (p=0.076). The mean values in lean and obese PCOS of HOMA-IR (2.15±0.7, 6.9±3.7) and serum leptin (5.8±2.2, 28.0±17.8) were respectively, which were higher among both the case groups than the healthy controls and was found to be statistically significant (p<0.001) [Table/Fig-3].

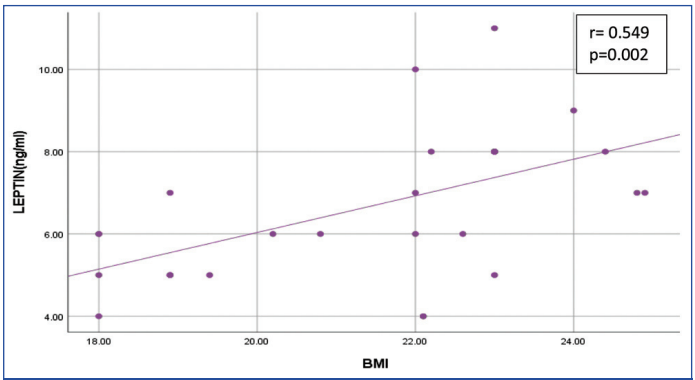
Parameters	Control (BMI <25)	Lean PCOS (BMI <25)	Obese PCOS (BMI >25)	Total (N=90)	p-value (ANOVA)
FPG (mg/dL)	87.4±10.3	93.3±10.6	91.5±9.4	90.7±10.3	0.076
PPPG (mg/dL)	110.03±8.9	118.2±15.5	120.9±19.6	116.4±15.8	0.020
Fasting insulin (µIU/mL)	10.5±1.6	10.9±2.4	30.2±14.8	17.2±12.6	<0.001
Leptin (ng/mL)	5.2±2.1	5.8±2.2	28.0±17.8	13.3±14.6	<0.001
HOMA-IR	2.07±0.5	2.15±0.7	6.9±3.7	3.6±3.2	<0.001

[Table/Fig-3]: Comparison of glucose, insulin, leptin and HOMA-IR values of the research subjects.
Values presented as mean±SD

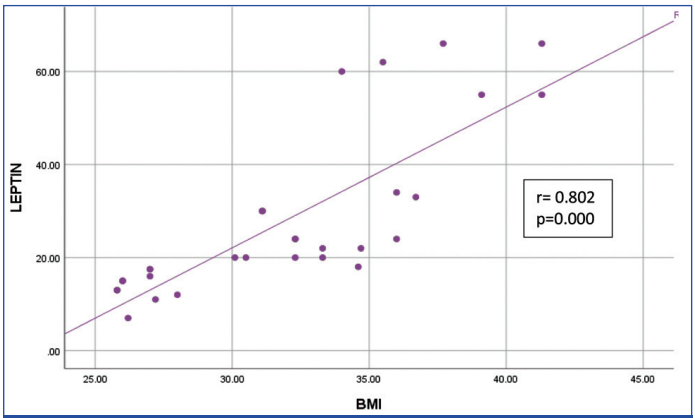
There was significant positive correlation of serum leptin with BMI in lean PCOS (r=0.549, p=0.002) and obese PCOS (r=0.802, p<0.001). There was significant positive correlation of serum leptin with PPPG in obese PCOS (r=0.361, p=0.016) but fasting plasma glucose did not correlate with leptin in any study population. Fasting plasma insulin level in lean PCOS (r=0.384, p=0.036) and obese PCOS (r=0.556, p<0.001) groups had positive correlation with leptin which was statistically significant. HOMA-IR positively correlated with serum leptin only in obese PCOS (r=0.517, p=0.003) which was statistically significant [Table/Fig-4-9].

Parameters	Lean PCOS		Obese PCOS	
	'r' value	p-value	'r' value	p-value
BMI (kg/m^2)	0.549	0.002**	0.802	<0.001**
FPS (mg/dL)	0.372	0.063	0.263	0.084
PPPG (mg/dL)	0.130	0.490	0.361	0.016*
Fasting plasma insulin (µIU/mL)	0.384	0.036*	0.556	<0.001**
HOMA-IR	0.474	0.531	0.517	0.003**

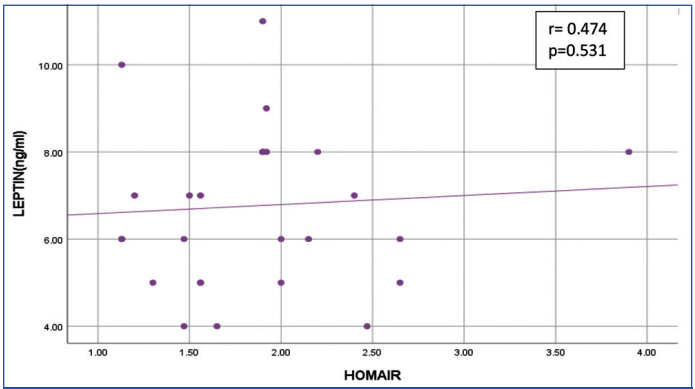
[Table/Fig-4]: Correlation of BMI, plasma insulin and HOMA-IR with leptin in the research subjects.
Pearsons's correlation test
*Correlation is significant at the 0.05 level (2-tailed); **Correlation is significant at the 0.01 level (2-tailed)



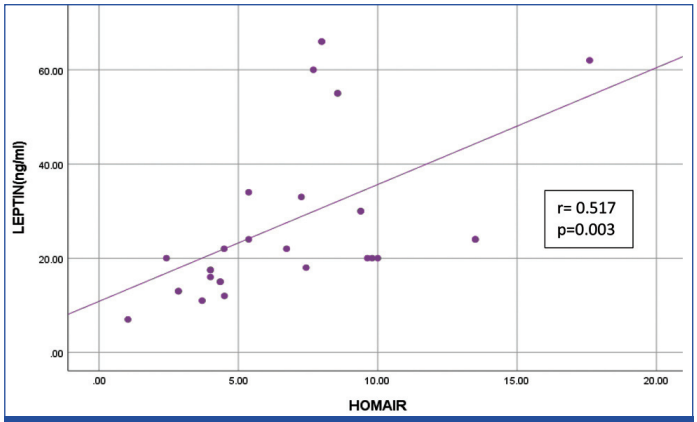
[Table/Fig-5]: Scatter diagram showing correlation Leptin with BMI in lean PCOS.



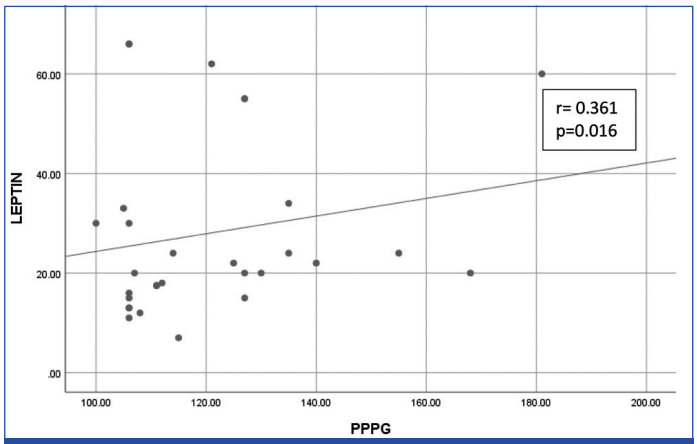
[Table/Fig-6]: Scatter diagram showing correlation Leptin with BMI in obese PCOS.



[Table/Fig-7]: Scatter diagram showing correlation of serum leptin with HOMA-IR in lean PCOS.



[Table/Fig-8]: Scatter diagram showing correlation of serum leptin with HOMA-IR in obese PCOS.



[Table/Fig-9]: Scatter diagram showing correlation of serum leptin with PPPG in obese PCOS.

DISCUSSION

In the present study, it was observed that FPG was in normal range and no statistical difference in FPG levels between cases and controls. However, the PPPG values were significantly higher in obese PCOS cases than lean category of PCOS and controls with significant statistical difference between cases and controls. So, it may be concluded that obese PCOS having impaired glucose tolerance are more prone to develop type 2 diabetes mellitus. Similar study done by Bala M et al., found no statistical difference in FPG level, however HbA1c levels in cases were increased which were statistically significant showing that PCOS cases are prone to develop diabetes [23].

In the present study, the serum leptin level was significantly raised in obese PCOS cases as compared to lean PCOS and healthy controls which had significant positive correlation with body weight and BMI. Erturk E et al., and Jalilian N et al., had found positive association of serum leptin with BMI [24,25]. Chakrabarti J and Sadaria RG and Ravi BV study findings corroborate this study findings which has significant positive correlation between serum leptin and BMI in PCOS (p-value <0.001) [9,26]. Thus, leptin is secreted from adipocytes into circulation, acting as a sensing hormone to hypothalamus to inform the brain about excess amount of fat present in the body [27].

The fasting plasma insulin level was significantly increased in obese PCOS cases than lean and controls (p<0.001). The HOMA-IR value was greater in obese PCOS than lean and controls indicating that insulin resistance was significantly higher in obese PCOS. In this study, positive correlation was observed between serum leptin levels with HOMA-IR which was similar to the study conducted by Jahromi BN et al., their study found out positive correlation of leptin and insulin with BMI in obese PCOS which explains that adipose tissue plays a dynamic role in overall energy homeostasis of the body and reproductive system (HPO axis) by acting as an endocrine organ [28].

The present study was similar with Hahn S et al., and Mohiti-Ardekani J et al., they have shown that serum leptin values higher in obese patients who also have higher insulin resistance confirming the association between them and suggesting that hyperinsulinaemia leading to insulin resistance causes hyperleptinaemia. So, insulin resistance and hyperinsulinaemia may also be the factors that affect serum leptin levels [29,30]. Mendonca HC et al., also found the correlation between leptin, insulinaemia and BMI and observed that serum insulin levels were increased in PCOS patients, who were normal weight PCOS and obese PCOS [31]. This result suggests that insulin resistance does not only depend on obesity but also presence of PCOS.

Erturk E et al., stated that serum leptin level correlate with obesity but not with insulin level in PCOS [24]. However, in the same year Moschos S et al., in their study on leptin gene expression in PCOS showed that that insulin causes hyperleptinaemia which leads to leptin resistance [32]. Chakrabarti J and Athrey M et al., suggested that hyperleptinaemia in PCOS may have a masking effect in hyperinsulinaemia. Insulin could increase leptin mRNA in adipocytes and has a possible role in stimulating leptin secretion. Increased serum leptin level leading to leptin resistance will further increase obesity leading to development of metabolic syndrome and cardiovascular disease [9,33].

Leptin is satiety hormone that sends signal to hypothalamus in brain about the energy homeostasis. In case of obesity, the signalling pathway is hampered i.e., despite having abundant body fat stores the body continue to secrete increased level of serum leptin that stimulate brain to increase food intake, thus leads to leptin resistance. While copious amount of leptin may be present, the brain doesn't get appropriate signals, so it erroneously thinks body is starving even though it has more than enough energy stored. Hyperleptinaemia in obese PCOS is due to leptin resistance [28].

Ovary is a dynamic multicompartmental organ with ever-changing tissue which is under the chief regulatory control of hypothalamic-pituitary axis. In many reproductive functions such as gametogenic and steroidogenic activities of ovary, leptin has emerged as potential peripheral signal and regulator [9]. Leptin is now considered as a possible link between nutrition and reproduction and may be directly associated with obesity by preserving homeostasis of energy which is associated with reduced food intake and increased energy spending [10]. It is observed that high leptin levels are presumed to exert a negative influence on the normal ovarian function and fertilisation which is required for the development of the embryo and decreased leptin levels disrupt the neuroendocrine regulation of reproduction [15]. The concept of leptin resensitisation has evolved as a new hypothesis, that refers to the reversal of leptin-resistant states which is linked to reduction of body adiposity and leptinaemia [34].

Limitation(s)

Present study did not evaluate the other reproductive parameters like testosterone and estradiol hormones which may have association with leptin in PCOS due to unavailability of test parameters. The sample size of the present study was less and were enrolled using convenient sampling.

CONCLUSION(S)

Mean serum leptin levels were increased in obese PCOS group than lean PCOS group and healthy controls which had significant positive correlation with BMI and insulin resistance. PCOS patient of insulin resistance and leptin resistance can be treated with insulin sensitising agents, such as metformin, to improve endocrine and metabolic disturbances to reduce long-term health risks. Large sample size with estimation of other hormones like oestrogen, testosterone and HbA1c can be done for further assessment which were not feasible in the present study. Genetic polymorphism on leptin gene and fat mass and obesity associated (FTO) gene can be done to find out their influence on pathophysiology of PCOS.

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PARTICULARS OF CONTRIBUTORS:
1. Senior Resident, Department of Biochemistry, MKCG Medical College, Berhampur, Odisha, India.
2. Associate Professor, Department of Biochemistry, MKCG Medical College, Berhampur, Odisha, India.
3. Assistant Professor, Department of Biochemistry, MKCG Medical College, Berhampur, Odisha, India.
4. Professor, Department of Biochemistry, MKCG Medical College, Berhampur, Odisha, India.

NAME, ADDRESS, E-MAIL ID OF THE CORRESPONDING AUTHOR:
Dr. Prachi Jena,
Senior Resident, Department of Biochemistry, MKCG Medical College,
Berhampur-760004, Odisha, India.
E-mail: jenaprachi@gmail.com

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