

# Association of Serum Leptin with Anthropometric Indices of Obesity, Blood Lipids, Steroidal Hormones, and Insulin Resistance in Polycystic Ovarian Syndrome

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ABSTRACT

**Background:** Polycystic ovarian syndrome (PCOS) is a major form of anovulatory infertility in women. It is often associated with obesity and insulin resistance (IR), both of which are linked to leptin and its receptors. **Aim:** The aim of this study was to evaluate the interrelationship between serum leptin level with anthropometric indices of obesity, lipid profile, IR, and with circulating steroidal hormones in PCOS women. **Settings and Design:** An observational case-control study was conducted in a medical college and hospital setting. **Methods:** Ninety diagnosed cases of PCOS along with ninety age-matched normal women were enrolled. Serum insulin, lipid profile, steroidal hormones, and serum leptin were estimated. IR was calculated using the Homeostatic Model Assessment-IR. Anthropometric measurements were also taken of each study participant. **Statistical Analysis:** Descriptive statistics along with independent sample *t*-test and Pearson (*r*) correlation coefficients were used. **Results:** Women with PCOS had high mean value of waist circumference ( $P = 0.00$ ), hip circumference ( $P = 0.00$ ), and hormonal levels than the control group (luteinizing hormone [LH] [ $P = 0.00$ ], testosterone [ $P = 0.00$ ], LH/follicle-stimulating hormone ratio [ $P = 0.00$ ], leptin [ $P = 0.00$ ], and IR [ $P = 0.00$ ]). Serum insulin levels ( $P = 0.02$ ), IR ( $P = 0.01$ ), body mass index (BMI) ( $P = 0.03$ ), and fasting blood sugar ( $P = 0.01$ ) had a positive correlation with leptin. Insulin ( $P = 0.01$ ), IR ( $P = 0.02$ ), fasting blood sugar ( $P = 0.001$ ), and leptin ( $P = 0.00$ ) were more in the obese control group. **Conclusion:** Serum leptin level is raised in PCOS patients, and it is correlated positively with BMI, fasting blood sugar, insulin metabolism, and IR.

**KEYWORDS:** *Insulin resistance, obesity, polycystic ovarian syndrome, serum leptin, steroidal hormones*

## INTRODUCTION

Polycystic ovarian syndrome (PCOS) is a common endocrine disorder to affect women in their reproductive years and has an estimated prevalence of 4%–10% based on National Institute of Health (NIH) diagnostic criteria.<sup>[1]</sup> It is the most common cause of hirsutism and infertility due to anovulation.<sup>[1]</sup> The exact etiology of PCOS is still unknown, however, endocrinological dysregulation is manifested as hyperandrogenism and anovulation. In PCOS women,

increased insulin levels (50-70%) and insulin resistance have been identified as significant contributor to the metabolic and reproductive abnormalities.<sup>[2]</sup>

A critical body mass of adipose tissue is essential for the normal development of female reproductive functions.<sup>[3]</sup> Obesity, on the other hand, has been shown to produce

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derangement of female reproductive functions and infertility.<sup>[4]</sup> Leptin is an anorexigenic peptide hormone which is secreted by adipocytes and circulates in the plasma as a free or protein-bound adipokine.<sup>[5]</sup> Leptin decreases appetite, increases energy expenditure, and reduces the production of neuropeptide Y from the hypothalamus. Neuropeptide Y increases food intake and after a long-term administration leads to obesity.<sup>[6]</sup> Leptin may also have a role in reproductive function, acting at many levels of the hypothalamic–pituitary–ovarian axis.<sup>[7]</sup> Circulating leptin concentration is regulated by insulin.<sup>[8]</sup>

PCOS is a major form of anovulatory infertility in women. It is often associated with obesity and IR, both of which are features that are linked to leptin and its receptors. Thus, the objective of the present study was to evaluate the interrelationship between serum leptin level with anthropometric indices of obesity, lipid profile, IR, and with circulating steroidal hormones in PCOS women from a sample population.

## METHODS

This observational case–control study was conducted in the department of biochemistry in collaboration with the endocrinology clinic of the department of medicine in a medical college and hospital setting. The study was conducted for the period of 8 months from April 2017 to November 2017. PCOS women in the reproductive age (18–40 years), diagnosed as per Rotterdam criteria<sup>[9]</sup> and not on any treatment for PCOS, attending the endocrinology clinic of the department of medicine for treatment were included in the study. Age-matched healthy female volunteers with no problem of PCOS, attending medicine outpatient department (not endocrinology clinic), and willing to participate in the study were enrolled as controls. A detailed history was taken and clinical examination was done in all subjects in the study groups.

### Inclusion criteria for selection of cases

The Rotterdam European Society for Human Reproduction and Embryology/American Society for Reproductive Medicine-sponsored PCOS consensus criteria were used to diagnose PCOS. Women with presence of any two of the following three features were included in the study:<sup>[9]</sup>

1. Oligomenorrhea and/or amenorrhea (oligomenorrhea >45 days or <8 cycles per year and amenorrhea >3 months in women with previous periodic menses) for a period of 6 months
2. Clinical and/or biochemical hyperandrogenemia, presence of acne, hirsutism (Ferriman and Gallwey [FG] score >8), and alopecia

3. Polycystic ovaries on sonography (>12 follicles in one or both ovaries, 2–9 mm in diameter, and/or increased ovarian volume >10 mL).

### Inclusion criteria for selection of controls

- Regular menstrual cycle
- No menstrual abnormalities
- Absence of hirsutism, alopecia, and acne
- Age-matched one control for each case.

### Exclusion criteria

Patients with any other potential causes of hyperandrogenism such as congenital adrenal hyperplasia and androgen-secreting tumor, hypothyroidism, Cushing's syndrome, hyperprolactinemia, and other IR conditions like acromegaly were excluded from the study. None of the subjects were alcoholic or smoker.

### Sample size

Taking the reference of one study done by Thathapudi *et al.*<sup>[10]</sup> at Hyderabad (India), the insulin level in the obese PCOS patient group was  $14.20 \pm 13.50$   $\mu\text{U/mL}$  and insulin level in the control group was  $6.60 \pm 3.19$   $\mu\text{U/mL}$ . Taking 95% confidence interval and 85% power of the study, the sample size came out to be 60 in each group. Hence, for the purpose of the study, ninety subjects in each group (case and control) were included.

### Anthropometric measurements

Anthropometric measurements taken included weight, height, waist circumference (WC), and hip circumference (HC). Weight was measured using a digital weighing machine (calibrated up to 0.1 kg) with subjects using light clothes and no shoes, and height was measured by a clinic stadiometer. WC was taken at midpoint between the lower margin of the last palpable rib and the top of the iliac crest in standing position, and HC was taken in centimeter around the widest portion of buttocks, with tape parallel to floor.<sup>[11]</sup> Body mass index (BMI) was calculated by dividing weight in kilograms by square of height in meters. They were further classified as per Asia-pacific guidelines for the Asian population. Underweight is  $<18.5$   $\text{kg/m}^2$ ,  $18.5$ – $22.9$   $\text{kg/m}^2$  is normal,  $23$ – $24.9$   $\text{kg/m}^2$  is considered overweight, and  $\geq 25$   $\text{kg/m}^2$  is considered obese.<sup>[12]</sup> However, individuals can be subdivided into obese and lean, based on BMI  $\geq 25$  and  $<25$ , respectively.<sup>[10]</sup>

### Biochemical and hormonal analysis

5 milliliters of venous blood sample was taken from the antecubital vein aseptically in plain red vacutainer for follicle-stimulating hormone (FSH), LH, testosterone, dehydroepiandrosterone sulfate (DHEAS), and insulin level. Serum was separated by centrifugation at 2000 rpm for 10 min after clotting. Separated serum

was stored at  $-20^{\circ}\text{C}$  till further analysis. Serum LH, FSH, testosterone, and DHEAS were estimated by chemiluminescence method. Hormonal samples were taken on the 3<sup>rd</sup> day of menstrual cycle if the periods were regular and random sample was taken in oligomenorrheic women.

Blood glucose, serum triglyceride (TG), serum cholesterol, serum high-density lipoprotein (HDL), and low-density lipoprotein (LDL) were performed as per standard methods by RANDOX autoanalyzer using standard reagent kits.

Insulin estimation was done by immunoassay. IR was calculated using the Homeostatic Model Assessment-IR (HOMA-IR).<sup>[13]</sup> HOMA-IR was calculated as the product of the insulin value ( $\mu\text{U}/\text{ml}$ ) and the fasting plasma glucose value ( $\text{mg}/\text{dl}$ ), divided by 405.

Serum leptin was analyzed by enzyme-linked immunosorbent assay. The assay utilizes the sandwich technique with the antibodies that bind to leptin.

Ultrasound was done by USG machine Siemens ACUSON X300 with transabdominal probe with 2–6 Mz frequency and transvaginal probe with 4–9 Mz frequency with the help of the department of radiology of the institute.

### Statistics

The result of the study was expressed as mean  $\pm$  standard error of mean. Independent sample *t*-test was used for quantitative analysis between the groups. The relationship between leptin and independent variables was evaluated by Pearson (*r*) correlation coefficients.  $P < 0.05$  was considered statistically significant. Statistical analysis was performed using the Statistical package for the Social Sciences trial version 20.0 software (SPSS Inc., released in 2011, IBM Corporation, Armonk, New York, United States) and MS Excel 2010 spreadsheet.

### Ethics

Institutional ethical approval was obtained with institutional ethics committee number IEC/Th/16/Biochem 1 dated December 02, 2016. The written informed consent from all the patients participating in the study was obtained according to Helsinki Declaration 2013 (revised version), and refusal to participate in the study did not interfere with the treatment provided to them.

### Definitions

1. Regular menstrual cycle: Menstrual cycle with an intermenstrual interval of 21–35 days and the variation of cycle length from one period to another was  $\leq 7$  days
2. Oligomenorrhea: Menstrual cycle with an intermenstrual interval of  $\geq 36$  days ( $< 9$  cycles per year)

3. Hirsutism was graded using a modified FG scoring system (assess hair growth on nine body areas, namely upper lip, chin, chest, upper back, lower back, upper abdomen, lower abdomen, upper arms, and thighs). Hair growth is rated from 0 (no growth of terminal hair) to 4 (extensive hair growth) in each of the nine locations. A patient's score may therefore range from a minimum score of 0 to a maximum score of 36. A score of 8 or higher is regarded as indicative of androgen excess
4. IR is defined as decreased sensitivity or responsiveness to the metabolic actions of insulin, such as insulin-mediated glucose disposal and inhibition of hepatic glucose production
5. Acne vulgaris is the formation of comedones, papules, pustules, nodules, and/or cysts as a result of obstruction and inflammation of pilosebaceous units (hair follicles and their accompanying sebaceous gland). Acne develops on the face and upper trunk.

## RESULTS

A total of ninety subjects with PCOS (cases) and ninety subjects without PCOS were selected for the present study. The mean age of cases and controls was  $24.45 \pm 6.16$  and  $23.18 \pm 2.26$  years, respectively. The most common clinical signs of increased androgen levels among the cases were hirsutism and acne. Out of 90 cases, 71 (78%) had hirsutism (FG score  $> 8$ ) and acne. The mean value of WC and HC was significantly high in the PCOS group, though for BMI, a significant difference between the groups was not observed. Women with PCOS had significantly high hormonal levels such as LH, testosterone, DHEAS, LH/FSH ratio, insulin, leptin, and IR than the control group which is shown in Table 1.

Table 2 depicts the correlation of serum leptin with biochemical markers and anthropometric measurements in PCOS patients and its controls. Serum insulin levels, IR, BMI, and fasting blood sugar had a significant positive correlation with leptin. Hormones such as LH, FSH, testosterone, and DHEAS had a negative correlation with leptin levels though it was nonsignificant in cases.

As shown in Table 3, BMI was significantly high in obese in both the groups. Insulin, IR, fasting blood sugar, and leptin were significantly more in obese in the control group. The mean level of leptin, cholesterol, LDL, FSH, and testosterone was high in obese in both the groups, but it was nonsignificant.

## DISCUSSION

PCOS is a common anovulatory infertility problem, characterized by chronic anovulation and

hyperandrogenemia.<sup>[14]</sup> These features manifest with gradual increase of adipose tissue,<sup>[15]</sup> which is often linked to leptin and its receptor.<sup>[16]</sup> Leptin seems to

**Table 1: Comparison between polycystic ovarian syndrome and control groups regarding anthropometric indices of obesity, leptin levels, fasting blood sugar levels, and hormonal characteristics (statistical method used: independent *t*-test)**

	PCOS group (n=90)	Control group (n=90)	P
BMI (kg/m <sup>2</sup> )	23.62±3.92	23.06±1.02	0.19
WC	78.38±9.94	70.32±8.07	0.00
HC	97.92±9.74	92±7.77	0.00
WHR	0.7998±0.05646	0.7670±0.08739	0.003
Cholesterol (mg/dl)	163.80±36.33	143.80±33.091	0.00
HDL-C (mg/dl)	49.68±8.97	45.32±7.73	0.001
LDL-C (mg/dl)	95.28±29.81	85.39±26.24	0.019
TGs (mg/dl)	34.34±28.99	28.23±29.12	0.16
FSH (mIU/ml)	6.67±2.91	6.30±3.22	0.42
LH (mIU/ml)	12.73±8.86	5.88±4.28	0.00
LH/FSH	2.27±2.41	1±0.73	0.00
Total testosterone (ng/ml)	63.32±15.05	14.17±2.82	0.00
Serum DHEAS (µg/dl)	205.60±50.56	187.21±37.61	0.01
Insulin (U/L)	32.11±19.17	23±4.79	0.00
IR	7.27±4.49	4.86±1.07	0.00
Leptin (mIU/ml)	34.16±21.18	23.38±7.69	0.00
FBS (mg/dl)	91.78±8.14	84.57±3.56	0.00

PCOS=Polycystic ovarian syndrome, BMI=Body mass index, WC=Waist circumference, HC=Hip circumference, WHR=Waist-hip ratio, HDL-C=High-density lipoprotein cholesterol, LDL-C=Low-density lipoprotein cholesterol, FSH=Follicle-stimulating hormone, FBS=Fasting blood sugar, IR=Insulin resistance, LH=Luteinizing hormone, DHEAs=Dehydroepiandrosterone sulfate, TGs=Triglycerides

be directly associated with obesity by preserving homeostasis of energy with reduced food intake and increased energy spending.<sup>[17]</sup> The results of this study show that the PCOS group had significantly higher levels of insulin, IR, fasting blood sugar, and all plasma lipids compared to age-matched controls. The findings were similar to Daghestani *et al.*<sup>[18]</sup> study except that HDL was high in the PCOS group in our study. In the present study, mean levels of LH, LH/FSH ratio, testosterone, and DHEAS were significantly higher in the PCOS group than the control group, but association with FSH was nonsignificant. The findings were similar to a study done by Chakrabarti<sup>[16]</sup> in India where the mean LH, LH/FSH ratio, androgen levels, and fasting levels of insulin were high in the PCOS group compared to the control group. The result was not in coherence with Jahromi *et al.*<sup>[19]</sup> where LH, FSH, and testosterone were low in PCOS patients. Jalilian *et al.*<sup>[20]</sup> study depicted that the mean level of FBS, LH, FSH, and fasting insulin did not differ significantly between the study groups.

In the present study, anthropometric variables such as WC, HC, and waist-hip ratio (WHR) were significantly high in women with PCOS, but BMI was very similar between the two groups. Daghestani *et al.*<sup>[18]</sup> study found that the anthropometric variables were very similar in the two groups except for WHR which was significantly higher in the PCOS patients. The mean BMI was significantly higher in the PCOS group in some studies.<sup>[16,19-21]</sup>

The leptin level was significantly high in the PCOS group which was very similar to other studies.<sup>[16,19-21]</sup> This is because leptin is predominantly synthesised by

**Table 2: Pearson correlation coefficient of leptin with anthropometric indices and hormonal levels in polycystic ovarian syndrome patients**

	Pearson's correlation coefficient (r) of leptin in PCOS group	P	Pearson's correlation coefficient (r) of leptin in control group	P
BMI (kg/m <sup>2</sup> )	0.219	0.038	0.315	0.003
Insulin (U/L)	0.237	0.025	0.706	0.000
IR	0.264	0.012	0.655	0.000
FBS (mg/dl)	0.267	0.011	0.228	0.031
WC	-0.027	0.803	-0.053	0.623
HC	-0.060	0.574	-0.135	0.206
Total cholesterol (mg/dl)	0.063	0.558	0.124	0.245
TGs (mg/dl)	-0.086	0.420	0.234	0.027
HDL (mg/dl)	0.064	0.549	0.033	0.755
LDL (mg/dl)	0.075	0.480	0.016	0.884
FSH (mIU/ml)	-0.005	0.964	0.230	0.029
LH (mIU/ml)	-0.059	0.582	-0.064	0.549
Testosterone (ng/ml)	-0.020	0.851	-0.085	0.424
DHEAS (µg/dl)	-0.025	0.814	-0.061	0.567

BMI=Body mass index, IR=Insulin resistance, FBS=Fasting blood sugar, WC=Waist circumference, HC=Hip circumference, HDL=High-density lipoprotein, LDL=Low-density lipoprotein, FSH=Follicle-stimulating hormone, LH=Luteinizing hormone, TGs=Triglycerides, PCOS=Polycystic ovarian syndrome, DHEAs=Dehydroepiandrosterone sulfate

**Table 3: Association of body mass index with lipid profile, leptin level, insulin resistance, steroidal hormone level, and waist/hip circumference (statistical method used: independent t-test)**

	Patient group (n=90)	Mean±SD	P
BMI (kg/m <sup>2</sup> )	Lean (n=73)	22.12±1.93	0.000
	Obese (n=17)	30.06±3.76	
Cholesterol (mg/dl)	Lean	161.53±36.87	0.201
	Obese	173.53±33.18	
HDL-C (mg/dl)	Lean	50.48±8.73	0.104
	Obese	46.24±9.451	
LDL-C (mg/dl)	Lean	94.14±30.06	0.45
	Obese	100.18±29.03	
TGs (mg/dl)	Lean	36.82±30.16	0.04
	Obese	23.71±20.82	
Insulin (U/L)	Lean	33.48±18.82	0.18
	Obese	26.24±20.12	
FBS (mg/dl)	Lean	91.62±7.76	0.74
	Obese	92.47±9.85	
Leptin (mIU/ml)	Lean	32.29±20.80	0.09
	Obese	42.18±21.48	
IR	Lean	7.58±4.43	0.201
	Obese	5.94±4.65	
FSH (mIU/ml)	Lean	6.58±2.82	0.58
	Obese	7.06±3.30	
LH (mIU/ml)	Lean	13.19±9.29	0.21
	Obese	10.76±6.55	
Testosterone (ng/ml)	Lean	63.03±16.19	0.58
	Obese	64.59±8.77	
DHEAS (µg/dl)	Lean	209.60±51.21	0.10
	Obese	188.41±45.05	
WC	Lean	78.55±10.08	0.73
	Obese	77.65±9.53	
HC	Lean	97.97±9.37	0.93
	Obese	97.71±11.52	

BMI=Body mass index, HDL-C=High-density lipoprotein cholesterol, LDL-C=Low-density lipoprotein cholesterol, FBS=Fasting blood sugar, IR=Insulin resistance, FSH=Follicle-stimulating hormone, LH=Luteinizing hormone, WC=Waist circumference, HC=Hip circumference, SD=Standard deviation, DHEAS=Dehydroepiandrosterone sulfate, TGs=Triglycerides

adipocytes, and higher BMI is distributed with high frequency in the PCOS group than in control women. In the present study, the difference in the leptin levels reached greater magnitude of significance when PCOS women were categorized under obese (BMI >25) and nonobese (BMI ≤25) subgroups. However, Daghestani *et al.* study showed that there was no significant difference in leptin levels between the PCOS and control groups, but leptin levels were significantly higher in obese PCOS patients in comparison to lean patients.<sup>[18]</sup>

In both the groups, a significant positive correlation of leptin was found with BMI which was in coherence with few studies.<sup>[16,18-24]</sup> Logically increase in fat cells

and BMI is accompanied by increase in leptin secretion. It had been shown that insulin directly induces leptin mRNA in adipocytes *in vitro*, suggesting that insulin may stimulate leptin secretion. The results of our study show higher leptin levels among the cases, most of whom were in the lean body weight BMI range. This shows that most of the PCOS patients with lean BMI had fat cells in the abdomen with increased abdominal obesity depicted by significantly increased WC in cases. In the present study, a significant positive correlation of leptin was found with insulin, IR, and fasting blood sugar and nonsignificant negative correlation of serum leptin was found with WC, HC, FSH, LH, testosterone, and DHEAS. Many studies showed a significant correlation of leptin with insulin<sup>[16,18,24]</sup> IR,<sup>[19,24,25]</sup> FBS,<sup>[19]</sup> cholesterol, LDL,<sup>[18,24]</sup> TG, HDL, WHR,<sup>[18]</sup> and WC.<sup>[24]</sup> A positive relationship of serum leptin was found with LH.<sup>[25]</sup> No significant correlation of leptin was found with insulin, FBS, and FSH in a study conducted by Jalilian *et al.*<sup>[20]</sup> Few studies found no significant relationship of leptin with testosterone.<sup>[16,23]</sup>

Insulin, IR, fasting blood sugar, and leptin were significantly more in obese in the control group. Most of our cases were of lean weight and had BMI in the normal range, but high insulin and IR were detected in them showing impaired glucose metabolism. The mean level of leptin, cholesterol, LDL, FSH, and testosterone was high in obese in both the groups, but it was nonsignificant. These findings were different from few studies where serum leptin level was significantly high in obese PCOS compared to lean PCOS.<sup>[20]</sup>

The limitation of our study was that it was a cross-sectional study design which may limit causality formation of the hypotheses, so longitudinal study may be planned in future. The second limitation is that we did not evaluate the molecular mechanisms (polymorphism studies and proteomics) for further validation of our observations.

## CONCLUSION

Thus, it may be concluded that serum leptin level is raised in PCOS patients and it is correlated positively with BMI, fasting blood sugar, insulin metabolism, and IR. The anthropometric measurements (HC, WC, and WHR), lipid profile (cholesterol, LDL, TGs, and HDL), LH level, LH/FSH ratio, testosterone level, serum DHEAS insulin level, and IR are high in patients with PCOS. The study shows a weak correlation of leptin with reproductive hormones. To establish the correlation between leptin and reproductive hormones, further studies may be done with large sample size.

### Data availability statement

The data that support the findings of the study are available from the corresponding author, upon reasonable request.

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Nil.

### Conflicts of interest

There are no conflicts of interest.

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