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Serum leptin level-insulin resistance-based correlation in polycystic ovary syndrome obese and non-obese sufferer female

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ABSTRACT

Background: Polycystic ovary syndrome (PCOS) is a common heterogeneous endocrine disorder, affecting 5–10% of females with hyperandrogenism and prolonged anovulation.

Objective: This study was done to understand the serum leptin role in women with PCOS and its link with the body mass index (BMI) and insulin resistance (IR).

Patients and methods: This 1-year study was conducted in the Departments of Obstetrics and Gynecology as well as Infertility Unite in AL-Diwaniyah Maternity and Pediatrics Teaching Hospital, Iraq, in which 40 patients with PCOS (study group) and 40 healthy (non-PCOS) patients (control group) participated. After BMI assessment, both the study and control groups were further stratified into subgroups as normal weight and overweight patients. Blood samples were obtained for all patients for the serum leptin level (SLL), fasting blood glucose (FBG), and serum insulin level. The HOMA-IR equation was used to estimate insulin resistance for all patients.

Results: SLL of the PCOS women (mean ± SD, 22.29 ± 10.96 ng/ml) was significantly ($P < 0.05$) higher (17.89 ± 8.29 ng/ml) when compared to that of the control group. Insulin level was significantly elevated in the obese control and PCOS women (16.87 ± 3.52) μ UI/L and (15.09 ± 5.27) μUI, respectively, compared to normal BMI control and PCOS patients ($P \leq 0.01$). Insulin resistance was significantly higher in obese (control and PCOS) patients (2.47 ± 0.40 and 2.30 ± 0.43, respectively), compared to normal BMI (control and PCOS) patients ($P \leq 0.01$).

Conclusions: In obese patients, serum leptin significantly correlated with BMI in the presence of hyperinsulinemia and elevated insulin resistance.

Keywords: *body mass index; insulin resistance; leptin; polycystic ovary syndrome*

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INTRODUCTION

As many as 15% of females throughout the globe are affected by polycystic ovary syndrome (PCOS), a heterogeneous endocrine condition. PCOS may be caused by different factors, and it may appear in many ways, including hirsutism, acne, hyperandrogenemia, polycystic ovaries, anovulation, and infertility. Insulin resistance (IR), hyperinsulinemia, dyslipidemia, and obesity are all common complications of PCOS.[1] As a prominent infertility factor, PCOS is often connected to obesity and IR, both of which are influenced by leptin and its receptors.[2]

Fat cells and small intestinal enterocytes produce leptin, a hormone that assists in managing energy balance by impairing hunger. This reduces adipose tissue fat storage. Leptin acts on cell receptors in the hypothalamus arcuate nucleus, and obese people have a decreased sensitivity to leptin, making it difficult to identify satiety despite high energy presence.

Hyperinsulinemia may be a source of leptin resistance, which in turn can contribute to obesity and metabolic syndrome in those who have it, and more fat cells create greater blood leptin levels, which are linked to higher IR in PCOS women with high BM levels.[3]

Indirect impacts such as elevated blood sugar levels, is first developed because of IR, with no apparent signs of IR. The fundamental mechanism of IR is still to some extent a mystery, despite a wide range of possible reasons.[4] Obesity and family history of diabetes are both influential factors for IR. IR may be estimated using HOMA equations. HOMA-IR measures IR, whereas HOMA-B measures pancreatic beta-cell activity using fasting blood values. The two equations are as follows:

HOMA-IR = glucose × insulin/22.5
HOMA-B = 20 × insulin/glucose-3.5%

IR: Insulin resistance.
β: β-cell activity.
Insulin unit: μIU/mL. Tis equation is during fasting.
IR normal range: (0.5–1.4). Early IR: if >1.9.
Strong IR: if >2.9[3]

PATIENTS AND METHODS

The exploring work was done in the Departments of Obstetrics and Gynecology as well as Infertility Unit in AL-Diwaniyah Maternity and Pediatrics Teaching Hospital, Iraq, from the period of February 2018 to February 2019. Forty patients with PCOS, aged 20–40 years, were considered as study group, and 40 healthy non-PCOS patients, who have a regular cycle with no clinical features of hyperandrogenism or ultrasound evidence of PCOS were considered as the control group.

PCOS patient-based selection criteria

Rotterdam criteria were employed to identify PCOS women to participate in the study. Those showing discontinuity or irregularity in menses, oligomenorrhea (six or fewer menses per year), amenorrhea, hirsutism, and high levels of serum testosterone, no less than 12 follicles (2–9 mm per diameter) via ultrasonographic detection (around a dense core of the stroma of the ovary) were selected.

Exclusion criteria

Systemic disorders, such as thyroid illnesses, Cushing's syndrome, systemic inflammatory disorder, hyperprolactinemia, and diabetes mellitus, and those who are on oral contraceptive medicines, hormonal therapy, carbohydrate-altering drugs, sex hormones, and lactating patients were excluded from the current study. Consent forms were collected from the participants, and the study protocol was approved by the Iraqi Ethical Committee.

Height, weight, and BMI were measured and:

BMI = Body weight (kg)/height (m)². After BMI assessment, both the study and control groups were further stratified into subgroups, as normal weight,

if BMI 19–25 kg/m², and overweight patients, if BMI more than 25–30 kg/m², respectively.

Laboratory measurement

Follicular phase–based blood collection of samples was performed for all participants. The serum was separated and stored at −20°C the next laboratory tests. The serum levels of luteinizing hormone (LH), follicular stimulating hormone (FSH), free testosterone (pg/l), and thyroid stimulating hormone (TSH) were measured using standard radioimmunoassay (RIA [Roche Hitachi, Japan]). During the period of 8:00 AM–10:00 AM (12 hour–based fasting), FBG (mmol/l) was reported via the use of a glucose oxidase method, and serum insulin level (μIU/l) was determined by RIA (Roche Hitachi, Japan), and SLL (ng/l) by an enzyme-linked immunosorbent assay (ELISA) technique (Human LEP-USA) and BioTek EPSON, USA machine.

HOMA-IR equation has been utilized in the study to estimate IR for all participants as follows: fasting glucose level (mmol/l) × fasting insulin level (μU/l)/22.5.

Statistical analysis

SPSS v23 and Microsoft Office Excel 2010 were employed in the analysis and presenting of data. Categorical (converted to numbers) and numerical (mean ± standard deviation [SD]) data were used. Chi-square test (correlation), t-test, one-way ANOVA, and LSD tests were utilized. $P \leq 0.05$ and $P \leq 0.01$ were used.

RESULTS

Table 1 shows the comparison of the demographic characteristics of the control and PCOS patients which was not significant ($P > 0.05$).

BMI of the control group was 24.83 ± 3.38 kg/m² with 42.5% being of normal BMI, and 57.5% being overweight. In the PCOS group, the mean ± SD of the BMI was 25.05 ± 3.85 with 45.0% being of normal BMI, and 55.0% being overweight.

Table 2 shows the hormonal level of the control and PCOS groups in which SLL (mean ± SD) was significantly elevated in PCOS females, which was 22.29 ± 10.96 ng/ml, if read against the (control) non-PCOS group (17.89 ± 8.29; $P < 0.05$).

Table 2 also shows that serum level of LH was significantly higher among the PCOS group ($P \leq 0.01$), and the level of FSH was higher among the non-PCOS compared with the PCOS group ($P \leq 0.05$).

No significant ($P > 0.05$) alteration regarding the free testosterone and TSH levels was recognized between the control and PCOS groups.

TABLE 1. Demographic Characteristic of Controls and PCOS Patients.

Characteristic	Control group n = 40	PCOS group n = 40	P
Age (years)			
Mean ± SD	27.98 ± 5.19	28.85 ± 5.29	0.458* NS
Range	19–39	20–40	
BMI (kg/m²)			
Mean ± SD	24.83 ± 3.38	25.05 ± 3.85	0.782* NS
Range	19–30	19–29	
Normal, n (%)	17 (42.5 %)	18 (45.0 %)	0.822** NS
Overweight and obese, n (%)	23 (57.5 %)	22 (55.0 %)	

BMI, body mass index; n, number of cases; PCOS, polycystic ovary syndrome; SD, standard deviation.
**Independent samples t-test; **Chi-square test; NS, not significant at P > 0.05.*

TABLE 2. Hormonal Levels of Control Participants and PCOS Women.

Characteristic	Control group n = 40	PCOS group n = 40	P
Leptin ng/ml			
Mean ± SD	17.89 ± 8.29	22.29 ± 10.96	0.047* S
Range	5–30	8–38	
FSH			
Mean ± SD	6.25 ± 0.88	5.32 ± 1.08	0.031* S
Range	4–7	4–8	
LH			
Mean ± SD	5.4 ± 0.96	6.0 ± 1.03	0.009* HS
Range	4–8	4–8	
Free testosterone pg/ml			
Mean ± SD	1.24 ± 0.43	1.20 ± 0.31	0.577* NS
Range	0.6–2	0.6–2	
TSH			
Mean ± SD	4.13 ± 0.81	3.79 ± 0.60	0.136* NS
Range	3–6	3–5.2	

FSH, follicular stimulating hormone; LH, luteinizing hormone; n, number of cases; PCOS, polycystic ovary syndrome; SD, standard deviation; TSH, thyroid stimulating hormone.
**Independent samples t-test; S, significant at P ≤ 0.05; NS, not significant at P > 0.05; HS, highly significant at P ≤ 0.01.*

Table 3 shows that in PCOS, FBS level was significantly ($P < 0.01$) elevated compared to that from the control group.

The PCOS-based insulin level was significantly ($P \leq 0.05$) higher (15.25 ± 5.89) μ UI/l compared with that in the control women (12.51 ± 5.85) μ UI/l.

PCOS-based IR was significantly higher ($P \leq 0.05$) than that from the control group (2.34 ± 0.04) and (1.73 ± 0.52), with $P \leq 0.05$. PCOS-based IR incidence was 40.0%, while in the control participants it was 27.5%

Table 4 shows the control- and PCOS-based hormonal levels according to the BMI, as SLL was significantly higher in the control obese and PCOS obese patients than normal BMI (control + PCOS) group ($P \leq 0.01$).

LH level was higher with obese (control and PCOS) participants than normal BMI in the control and PCOS group ($P \leq 0.05$).

The control-based FSH level was higher than that from the PCOS participants ($P \leq 0.05$).

The levels of free testosterone and TSH were not statistically different between obese and non-obese control and PCOS group ($P < 0.05$).

Table 5 shows that FBS level was significantly higher in obese PCOS patients than normal BMI PCOS patients ($P \leq 0.01$), and insulin level was significantly higher in obese control and PCOS patients, 16.87 ± 3.52 μ UI/L and 15.09 ± 5.27 μUI, respectively, compared to normal BMI control and PCOS patients ($P \leq 0.01$). Insulin resistance was significantly higher in obese control and PCOS patients, 2.47 ± 0.40 and 2.30 ± 0.43, respectively, compared to normal BMI (control and PCOS patients), and 47.8% of the obese control patients had higher insulin resistance than normal BMI (PCOS and control) patients (5.6% and 0.0%, respectively [$P \leq 0.01$]).

TABLE 3. Fasting Blood Glucose, Insulin Level, and Insulin Resistance in Controls and PCOS Patients.

Characteristic	Control group n = 40	PCOS group n = 40	P
FBS mmol/l			
Mean ± SD	5.53 ± 0.74	6.11 ± 0.93	0.002* HS
Range	4–7	4–8	
Insulin level µUI/l			
Mean ± SD	12.51 ± 5.85	15.25 ± 5.89	0.040* S
Range	4–25	4–25	
Insulin resistance			
Mean ± SD	1.73 ± 0.52	2.34 ± 0.64	0.012* S
Range	1–3	1–3	
Resistance (>2)	11 (27.5 %)	16 (40.0 %)	0.237** NS
No resistance (<2)	29 (72.5 %)	24 (60.0 %)	

*FBS, fasting blood glucose; n, number of cases; PCOS, polycystic ovary syndrome; SD, standard deviation. *Independent samples t-test; **Chi-square test; S, significant at P ≤ 0.05; NS, not significant at P > 0.05; HS, highly significant at P ≤ 0.01.*

TABLE 4. Control and PCOS-based Hormonal Levels According to Body Mass Index (Normal versus Obese).

Characteristic	Control normal n = 17	Control obese n = 23	PCOS normal n = 18	PCOS obese n = 22	P
Leptin ng/ml	9.81 ± 2.74	23.87 ± 5.33	11.22 ± 2.86	31.34 ± 5.06	< 0.001* HS
FSH	6.18 ± 0.86	5.84 ± 0.82	5.52 ± 0.87	5.15 ± 1.09	0.021* S
LH	5.14 ± 0.97	6.04 ± 0.98	6.17 ± 0.69	6.38 ± 1.22	0.027* S
Free testosterone pg/ml	1.24 ± 0.45	1.24 ± 0.43	1.09 ± 0.26	1.28 ± 0.34	0.414* NS
TSH	4.14 ± 0.84	4.13 ± 0.81	3.81 ± 0.51	3.78 ± 0.67	0.227* NS

Data were expressed as mean ± standard deviation. FSH, follicular stimulating hormone; LH, luteinizing hormone; n, number of cases; PCOS, polycystic ovary syndrome; TSH, thyroid stimulating hormone.
**One-way ANOVA followed by LSD multiple comparison test; NS, not significant at P > 0.05; HS, highly significant at P ≤ 0.01; S, significant at P ≤ 0.05.*

DISCUSSION

Chronic anovulation and hyperandrogenemia are the main characteristics of the PCOS-based anovulatory conditions, which appear gradually with the age advancement and increase in adipose tissue that is associated with leptin and its receptor activity. The demographic (age and BMI) alterations showed no significance in the PCOS and non-PCOS groups.

The study by Diamanti-Kandarakis et al. on 192 women in reproductive age (17–45 years) did not record an alteration in mean age between non-PCOS women read against PCOS women, but higher BMI was found among PCOS women.[6]

TABLE 5. Fasting Blood Glucose Level, Insulin Level, and Insulin Resistance in Controls and PCOS Patients According to Body Mass Index (Normal versus Obese).

Characteristic	Control normal n = 17	Control obese n = 23	PCOS normal n = 18	PCOS obese n = 22	P
FBS mmol/l					
Mean ± SD	5.44 ± 0.79	5.59 ± 0.72	5.68 ± 0.73	6.47 ± 0.93	<0.001* HS
Insulin level mUI/l					
Mean ± SD	6.61 ± 1.43	16.87 ± 3.52	6.56 ± 1.69	15.09 ± 5.27	<0.001* HS
Insulin resistance					
Mean ± SD	1.28 ± 0.26	2.47 ± 0.40	1.38 ± 0.34	2.30 ± 0.43	<0.001* HS
Insulin resistance, n (%)	0 (0.0 %)	11 (47.8 %)	1 (5.6 %)	15 (68.2 %)	<0.001** HS
No insulin resistance, n (%)	17 (100.0 %)	12 (52.2 %)	17 (94.4 %)	7 (31.8 %)	

Data were expressed as mean ± standard deviation. n, number of cases; PCOS, polycystic ovary syndrome.
**One-way ANOVA followed by LSD multiple comparison test; NS, not significant at P > 0.05; HS, highly significant at P ≤ 0.01.*

In this study, the SLL was significantly elevated among PCOS patients read against non-PCOS patients. This agrees with the finding Mohiti-Ardekani et al., which showed that there was an elevated SLL in women with PCOS patient compared with the normal control non-PCOS patients.[7]

Baig et al. found no significance between non-PCOS women and PCOS participants regarding SLLs.[8]

This study also showed that the serum level of LH was significantly higher and FSH amounts were in lower reads in the PCOS patients ($P \leq 0.05$) than those from the control women, but there was no free testosterone– and TSH-based significant difference between the non-PCOS and PCOS females, and this fact is in agreement with the findings by Daghestani et al., which showed that patients in the PCOS group exhibited increased LH/FSH ratio, decreased progesterone, and increased testosterone, as these women do not ovulate on a monthly basis. This difference in the results maybe probably due to the small sample size of the study.[9]

A study by Turner et al. concluded that the PCOS and non-PCOS LH/FSH ratio showed no differences between the groups (1.6 vs 1.2).[10]

This study showed that in PCOS patients, the mean FBS and insulin levels were considerably elevated compared to non-PCOS group, and IR in the PCOS participants was higher than that from the non-PCOS females.

The study by Zhang et al. showed that the FBG, fasting insulin, and insulin resistance in PCOS group were elevated than those in non-PCOS health group.[11]

While the study by Tomlinson et al. reported that there were normal fasting glucose levels despite increased postprandial glucose amounts in PCOS females.[12]

Ludwig et al. unveiled that PCOS- and non-FCOS-based FBS concentration showed no differences.[13]

Legro et al. found that IR was expected if the insulin levels were > 20 μU/mL. A ratio <4.5 showed sensitivity of >90% in identifying IR.[14]

A PCOS- and non-PCOS significant link was detected, in the present work, between leptin

amounts and BMI, as PCOS- and non-PCOS obese-based SLL were significantly elevated ($P \leq 0.01$). This agrees with the findings by Glintborg et al. which showed that PCOS- and non-PCOS obese-based SLL was significantly elevated, due to more leptin release from fatty tissues.[15]

Olszanecka-Glinianowicz et al. showed an elevated PCOS-based SLL on comparing age with BMI. In addition, obese-PCOS and non-PCOS-based SLL were significantly elevated as compared to that from lean females.[16]

However, the study by Ramanand et al. indicated no PCOS-SLL-based significant alteration regarding age and BMI.[17]

This study showed that the LH level was higher with obese (non-PCOS and PCOS) group than that from normal BMI females ($P \leq 0.05$), and FSH level was higher in non-PCOS than PCOS women. A study by Moran et al. suggested that there is no link between BMI- and IR-LH/FSH ratio.[18]

A study by Kiddy et al. showed that obese PCOS FSH-BMI link was inversely correlated[19], and the study by Dinka et al. reported PCOS-BMI-hormonal features with no association.[20]

This study showed that FBS level was significantly elevated in obese PCOS patients than normal BMI PCOS patients ($P \leq 0.01$), and fasting insulin level was significantly elevated in obese non-PCOS and PCOS patients (16.87 ± 3.52μ UI/L and 15.09 ± 5.27 μUI, respectively), compared to normal BMI control and PCOS patients ($P \pm 0.01$). Insulin resistance was significantly elevated in obese non-PCOS and PCOS patients (2.47 ± 0.40 and 2.30 ± 0.43, respectively), compared to normal BMI (non-PCOS and PCOS patients), and 47.8% of the obese non-PCOS patients had higher insulin resistance than normal PCOS and non-PCOS BMI patients (5.6% and 0.0%, respectively; $P \leq 0.01$) .

Park et al. in his study unveiled the elevation in obese-PCOS hyperandrogenemia, IR, and relative hyperglycemia, FBG, and decreases in sex hormone binding globulin (SHBG).[21]

However, Yildirim et al. reported higher fasting insulin levels in non-obese PCOS women when compared with the usual weight non-PCOS subject.[22]

Crowther et al. unveiled that IR was linked to obesity and increases in insulin levels.[23]

A study by Moller et al. reported that IR and inherited disorders in insulin or insulin receptor revealed significant positive correlation. If these disorders are absent, leptin acts in IR development in obese females.[24]

Furthermore, the study by Cohen et al. showed that leptin inhibits insulin binding in adipocytes and attenuates several insulin-induced activities in hepatocytes. Thus, high SLL is related to obesity, high levels of insulin, and IR.[25]

It was believed that more adipose tissue generates more SLLs, resulting in IR in BMI-based PCOS women, as showed in the study by Cheng et al., which reported that the SLLs were elevated in IR females. This study reported a strong link between PCOS participant–based SLL and IR.[26]

CONCLUSIONS

In obese patients, serum leptin levels significantly correlated with BMI with the presence of hyperinsulinemia and elevated insulin resistance.

ETHICAL APPROVAL

The study protocol was approved by the Iraqi Ethical Committee at the Departments of Obstetrics and Gynecology, College of Medicine, University of Al-Qadisiyah, Iraq.

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None

CONFLICTS OF INTEREST

The author declares no conflict of interest.

INFORMED CONSENT

The patients' consent (written form) was collected from all subjects, who enrolled in the current study.

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