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Original Article

# SERUM IRISIN AND LEPTIN LEVELS IN OBESE AND NON-OBESE WOMEN WITH POLYCYSTIC OVARY SYNDROME WITH REFERENCE TO GLUCOSE HOMEOSTASIS

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**ABSTRACT**

**Objective:** This study was aimed to evaluate the effect of serum leptin level on irisin level in relation to glucose homeostasis that to be associated with hormonal changes (Luteinizing hormone (LH), Follicle-stimulating hormone (FSH), Prolactin (PRL), Testosterone (TES)) in obese and non-obese women with polycystic ovary syndrome (PCOS).

**Methods:** Fifty women with polycystic ovaries syndrome (PCOS) and thirty-four apparently healthy control women with regular menstruation (28±2days) were included in this study both of PCOS patients and controls were divided into sub-groups according to their body mass index (BMI) into: twenty-five obese (BMI ≥30) with (BMI= 35.934±0.746) and another twenty-five non-obese polycystic ovaries syndrome women (BMI=25.074±0.456). Whereas, controls were divided as seventeen obese (BMI= 37.140±1.470) and seventeen non-obese (BMI= 25.022±0.683) healthy control women with regular menstruation with an age range (20-40 y) and BMI matching that of the patient groups. Venous blood samples were collected to measure serum levels of luteinizing hormone (LH), follicle stimulating hormone (FSH), LH/FSH, prolactin (PRL), total testosterone (TES), thyroid stimulating hormone (TSH). As well as, fasting glucose, irisin, leptin, and insulin. Besides, estimating Insulin Resistance (HOMA-IR) index, β-cell function was determined using the Homeostasis Model Assessment of β-cell function (HOMA-β).

**Results:** Serum irisin levels were not significantly different from their corresponding controls, in both obese and non-obese PCOS patients. Whereas, serum irisin levels were elevated significantly in both obese (patients and control) as compared to non-obese (patients and controls), respectively. But, serum leptin levels were significantly elevated in obese PCOS patients as compared to their corresponding control group, non-obese control, and non-obese PCOS patients. However, serum leptin levels were not significantly different in non-obese women groups, both the PCOS and controls. The irisin/insulin ratio expressed no significant variations from its corresponding control in non-obese groups. But the obese PCOS patient's values were highly significantly different as compared to their control ($p<0.01$). Furthermore, irisin/insulin ratio was elevated significantly in obese control as compared to non-obese patients ($p = 0.001$), but not with non-obese controls ($p=0.114$). The leptin/insulin ratio was not significantly varied in PCOS groups from their corresponding control in non-obese ($p = 0.094$) but in obese PCOS patients, there was significantly different as compared to its control ($p = 0.01$). Furthermore, leptin to insulin ratio was not significantly different between patients groups (non-obese and obese, $p=0.133$), nor between the studied controls ($p=0.705$).

**Conclusion:** Although serum irisin levels show no significant variation in subjects in relation to PCOS condition, it seems more to be related to BMI, since it's secreted by adipocytes. And because leptin and irisin levels would be elevated in obese subjects that would be related to PCOS pathogenesis. However, irisin/leptin ratio could aid only in the differentiation of patients with PCOS and normal subjects within the same BMI values. Irisin/insulin ratio seems to be a better indicator for PCOS condition regardless to BMI, where it showed significantly lowered values and to be negatively correlated with HOMA-IR in obese and non-obese, and even to be significantly correlated with LH/FSH ratio in obese PCOS patients.

**Keywords:** PCOS, Irisin, Leptin, HOMA-IR, HOMA-β



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## INTRODUCTION

Polycystic ovary syndrome (PCOS) is the most common endocrine abnormality of reproductive-age in women and affects about 5–12% of women worldwide [1-3]. Most PCOS patients suffer oligo-or anovulation, infertility, dysfunctional uterine bleeding, hyperandrogenism, and/or hirsutism [4-9]. In addition, it was estimated that>42% of women with PCOS in the United States are overweight or obese, and have a high risk of developing type 2 diabetes (T2D), atherosclerosis, and cardiovascular events [4, 8-12].

PCOS subjects also appear to have a high risk of suffering lipid metabolism disorder [9, 13]. Although the root causes of PCOS remain to be identified, a popular hypothesis considers androgen excess as the primary defect in PCOS [14,15] and that hyperinsulinemia in PCOS patients could be associated with hyperandrogenism [4,9,16-18]. The hyperinsulinemia may cause hyperandrogenism by inhibiting hepatic synthesis of SHBG and by binding insulin like growth factor-1 (IGF-1) receptors in the ovary leading to increased androgen production by thecal cells. In fibroblasts of 50% PCOS patients (PCOS-ser) there is decreased insulin dependent receptor autophosphorylation of tyrosine residue and increased constitutive receptor serine phosphorylation. These defects may cause insulin resistance in women with PCOS-ser [19].

Energy metabolism and insulin resistance-related proteins, such as leptin, adiponectin, ghrelin and tumor necrosis alpha [4], have been well-studied, and recently an additional exercise-induced peptide known as irisin has been identified [4]. Irisin is an endocrine regulator of metabolism; it's function is to transform white adipose tissue ( WAT ) to brown adipose tissue (BAT), thereby inducing thermogenesis and improve health [20-23]. Irisin (112 amino acid) is a newly identified hormone that is released from skeletal muscle following exercise. This protein is transcribed from the fibronectin type III domain-containing protein 5 (FNDC5) gene and is produced by proteolytic cleavage that releases FNDC5 [23]. In addition to skeletal muscle, FNDC5 mRNA and irisin peptide has been found in human adipose tissue [24], cerebrospinal fluid [25] and breast milk [26]. Irisin is secreted in response to peroxisome proliferator-activated receptor gamma coactivator (PGC-1α) activation via exercise [23]. PGC-1α, as a transcriptional coactivator, is involved in several biological processes associated with energy metabolism [27]. PGC-1α has an important role in the regulation of uncoupling

protein 1 (UCP-1) at the transcriptional level [27], mitochondrial biogenesis and thermogenesis [28, 29].

However, it has been indicated in recent crystal structure and biochemical characterization studies of the FNDC5 ectodomain corresponding to the irisin myokine, that irisin consists of an N-terminal fibronectin III (FNIII)-like domain attached to a flexible C-terminal able to form dimers independently of glycosylation [4]. Irisin conducts many downstream events including osteoblast differentiation, nerve cell and b-cell regeneration and so on [4].

Significantly reduced levels of circulating irisin have been determined in long-term, new onset and undefined T2DM patients compared with nondiabetic controls. This has led to the suggestion that either the diabetic state itself or the metabolic condition which resulted in T2DM is accompanied by lower circulating irisin [4]. Chang *et al.* consider that irisin might contribute to the development of PCOS and may also represent a novel PCOS biomarkers [30]. There have also been reports of an association between lower circulating irisin and the risk of non-alcoholic fatty liver disease and heart failure [4]. It has been reported that irisin improves obesity states and glucose homeostasis, thereby prolonging life expectancy [4].

This study was aimed to evaluate the effect of serum leptin level on irisin level in relation to glucose homeostasis that to be associated with hormonal changes (LH, FSH, Prolactin, Testosterone) in obese and non-obese women with polycystic ovary syndrome (PCOS).

## MATERIALS AND METHODS

### Study population

This study was carried out at Kamal Al-Samarrai Hospital (Center for Infertility treatment and *In vitro* Fertilization "IVF"), for the period from October/2015 to April/2016.

The study was conducted with approval from the committee of human research ethics the ministry of health in Iraq (Ethical approval number 6756; date 18$^{th}$October 2015). Informed consent forms were obtained from each participant before beginning the research. The study included fifty women with polycystic ovaries syndrome (PCOS) and thirty-four apparently healthy control women with regular menstruation (28±2 days). The diagnosis of PCOS was based on the revised Rotterdam Criteria [31]. Patients suffering from Cushing's syndrome, thyroid dysfunctions, androgen-secreting tumor, an enzyme deficiency (21-hydroxylase in particular), decreased ovarian reserve (primary ovarian insufficiency), or type 1 or type 2 diabetes and smoking and alcohol habits were excluded. All subjects did not take medications such as oral contraceptives, metformin or corticosteroids that could interfere with glucose and lipid metabolisms during the recent 3 mo before the study. Both of PCOS patients and controls were divided into sub-groups according to their BMI into twenty-five obese (BMI ≥30) with (BMI= 35.934±0.746) and another twenty-five non-obese polycystic ovaries syndrome women (BMI=25.074±0.456). Whereas, controls were divided as seventeen obese (BMI= 37.140±1.470) and seventeen non-obese (BMI= 25.022±0.683) healthy control women with regular menstruation with an age range (20-40 y) and BMI matching that of the patient groups. Anthropometric measurements (body mass index, height, hip and waist circumference) were measured while participants are wearing lightweight clothing without shoes.

Venous blood samples were collected at 9:00 am after an overnight fasting between the 3rd and 5th days of a spontaneous bleeding episode of the PCOS group and of a menstrual cycle of the controls. After centrifugation to obtain serum, all serum samples were stored at-80 °C until analysis. The data of metabolic and hormonal characteristics of the control and PCOS patients are shown in table 1.

**Table 1: Summary of the studied anthropometric, sex hormones and characteristic metabolic data of the control and PCOS patients**

| Variable | Control | PCOS | P-Value |
|---|---|---|---|
| Number | 34 | 50 | - |
| Age (years) | 33.559±0.937 | 28.220±0.786* | 0.0001 |
| Weight (Kg) | 79.382±3.567 | 76.922±2.161 | 0.534 |
| Height (M) | 1.596±0.009 | 1.590±0.007 | 0.596 |
| Lean body weight (Kg) | 52.992±0.599 | 52.584±0.483 | 0.596 |
| Body mass index (kg/m*2) | 31.081±1.323 | 30.504±0.888 | 0.708 |
| Waist (CM) | 94.735±2.361 | 98.02±2.110 | 0.310 |
| Hip (CM) | 116.588±2.494 | 110.46±1.691* | 0.038 |
| Waist Hip Ratio (WHR) | 0.811±0.007 | 0.885±0.009* | 0.0001 |
| Duration of PCOS(years) | - | 5.244±0.441 | - |
| Family History | - | 0.920±0.039 | - |
| Signs and Symptoms | 0.058±0.041 | 0.880±0.046* | 0.000 |
| Ultrasound for PCOS and Enlargement ovaries | -VE | +VE | - |
| Number of Gestations | 2.724±0.232 | 1.565±0.270* | 0.004 |
| Number of Abortions | 0.1724±0.071 | 1.109±0.229* | 0.002 |
| Number of Parity | 2.552±0.214 | 0.457±0.119* | 0.0001 |
| S. FSH (mIU/ml) | 6.721±0.420 | 4.846±0.240* | 0.0001 |
| S. LH(mIU/ml) | 2.708±0.183 | 5.121±0.484* | 0.0001 |
| LH/FSH Ratio | 0.412±0.017 | 1.080±0.089* | 0.0001 |
| S. Prolactin(ng/ml) | 15.028±1.050 | 22.449±1.516* | 0.0001 |
| S. Total Testosterone(ng/ml) | 0.214±0.025 | 0.481±0.040* | 0.0001 |
| S. TSH(nmol/l) | 1.770±0.163 | 2.166±0.178 | 0.121 |

The data are expressed as the numbers or mean±standard error of mean (SEM).*, * P<0.05 is significantly different

### Chemicals and reagents

The kits used for various analyses were of the highest available sensitivity and specificity. Specific chemicals utilized in this study are listed as below with their suppliers. Glucose kit (Human, Germany), Irisin human kit (Cusabio Biotech co., China), Insulin ELISA kit and Leptin ELISA kit (Demeditec Diagnostics GmbH, Germany), VIDAS® FSH kit, VIDAS® LH kit, VIDAS® Prolactin kit, VIDAS® Testosterone II kit and VIDAS® TSH kit (BioMerieux, France).

### Instruments and equipment

Instruments used in various measurements are listed in table 2.

### Assays

Serum luteinizing hormone (LH), follicle stimulating hormone (FSH), LH/FSH, prolactin(PRL), total testosterone(TES), thyroid stimulating hormone (TSH) were tested by automated quantitative test (ELFA) [32-35]. Fasting blood glucose was evaluated according to the method of Barham and Trindoer (1972) [36]. Serum irisin {Cusabio Biotech co., China;}, Serum leptin {Demeditec Diagnostics GmbH, Germany}; and Serum insulin { Demeditec Diagnostics GmbH, Germany}; were determined with enzyme-linked immuno-sorbent assay (ELISA) according to manufacturers' instructions [37-41].

Estimation of Insulin Resistance (HOMA-IR) index was done with the standard formula: HOMA-IR = fasting concentration of insulin (mIU/ml) x fasting concentration of glucose (mmol/l)/22.520 [42]. the β-cell function was determined using the Homeostasis Model Assessment of β-cell function (HOMA-B) which is calculated from fasting glucose (FG) and fasting insulin (FI) using the following formula {HOMA-B±{ 20 X-FI (μIU/ml)}/{FG (mmol/l)-3.5} [43].

**Table 2: Instruments used in the study and their suppliers**

| Instruments | Suppliers |
|---|---|
| Autovortex SA6 | Stuart Scientific,UK |
| BioTek (ELISA-Plate Washer) | Bio-Tek Instruments, USA |
| BioTek (ELISA-Reader) | Bio-Tek Instruments, USA |
| Cecil Aquarius(CE 7200) Double Beam Spectrophotometer | Cecil Instruments Limited, France |
| Circulating Water bath | Grant, England |
| Eppendorf Centrifuge 5702 | Eppendorf AG 22331 Hamburg, Germany |
| Heidolph Titramax 100 (plate shaker) | Heidolph Instruments, Germany |
| Isotemp Incubator | Fisher scientific, USA |
| KARL KOLB (Deionizer) | Scientific Technical Supplies, Germany |
| Magnetic stirrer (Yellow line MSH basic) | IKA, Germany |
| Micromax ® refrigerated microcentrifuge | Thermo electron, USA |
| Micropipette 10-100 | Slamed, Germany |
| Micropipette 100-1000 | Slamed, Germany |
| Multichannel-Micropipettor 10-1000 µl | Diamond, China |
| VIDAS® PC Autoanalyzer | Biomerieux, Italia |

**Statistical analysis**

Normality of the distribution of the variables was confirmed by the Shapiro-Wilk test. The results were expressed as mean±standard error of mean (SEM) or percent changes. Student t-test and analysis of variance (ANOVA) were used to examine the degree of significance. P-values less than 0.05 were considered significant. Pearson's correlation analysis was employed to study the relationship between serum irisin levels and the studied hormonal and metabolic parameters. The statistical analysis was performed using SPSS, version 22.

**RESULTS**

Serum irisin levels were not significantly different from their corresponding controls, in both obese and non-obese PCOS patients, as shown in table 3. Furthermore, serum irisin levels were elevated significantly in both obese patients and obese control as compared to non-obese patients and non-obese controls, respectively. However, when comparing serum irisin levels between PCOS patients groups (non-obese and obese), these levels were higher in the obese patients as shown in table 3. While, serum leptin levels were significantly elevated in obese PCOS patients as compared to their corresponding control group, non-obese control, and non-obese PCOS patients respectively (18.338±0.538, 17.266±0.718 and 17.173±0.549 ng/ml, $p<0.05$). But, serum leptin levels were not significantly different in non-obese women groups, both the PCOS and controls.

Fasting serum insulin levels were highly significantly elevated in obese PCOS women as compared to their corresponding controls ($p<0.0001$), but there was no significant difference between non-obese PCOS women and their control (13.466±1.017, 10.719±0.440 **µIU/ml**, respectively). Furthermore, serum insulin levels were elevated significantly in obese patients as compared to non-obese patients and non-obese controls ($p<0.0001$, 0.0001, respectively). Even so, there were no significant differences in serum insulin levels between controls groups. (table 3).

The leptin to BMI ratio was significantly different in obese PCOS patients as compared to the corresponding control group, non-obese control, and non-obese PCOS patients respectively ($p<0.05$). Whereas, Leptin to BMI ratio was not significantly different among the non-obese women ($p = 0.978$). But, there was a highly significantly difference between obese control as compared with non-obese control and non-obese patients ($p<0.01$).

The irisin to insulin ratio expressed no significant variations from its corresponding control in non-obese groups. But the obese PCOS patient's values were highly significantly different as compared to its control ($p<0.01$). Furthermore, irisin to insulin ratio was elevated significantly in obese control as compared to non-obese patients ($p = 0.001$), but not with non-obese controls ($p=0.114$). The leptin to insulin ratio was not significant vary in PCOS groups from their corresponding control in non-obese ($p = 0.094$) but in obese PCOS patients, there was significantly different as compared to its control ($p = 0.01$). Furthermore, leptin to insulin ratio was not significantly different between patients groups (non-obese and obese, $p=0.133$), nor between the studied controls ($p=0.705$), as illustrated in table 3.

**Table 3: Summary of serum hormone measurements among various groups**

| Groups (No) variables | Control (Non-Obese) (17) | PCOS (Non-Obese) (25) | Control (Obese) (17) | PCOS (Obese) (25) |
|---|---|---|---|---|
| Irisin(ng/ml) | 83.393±4.498$^{a}$ | 73.370±6.059$^{a}$ | 117.145±9.748$^{b}$ | 109.426±7.134$^{b}$ |
| Leptin(ng/ml) | 17.266±0.718$^{a}$ | 17.173±0.549$^{a}$ | 18.338±0.538$^{a}$ | 21.005±1.196$^{b}$ |
| Insulin(µIU/ml) | 10.719±0.440$^{a}$ | 13.466±1.017$^{a}$ | 12.651±0.860$^{a}$ | 22.002±2.430$^{b}$ |
| Leptin to BMI | 0.689±0.024$^{a}$ | 0.690±0.025$^{a}$ | 0.506±0.024$^{b}$ | 0.588±0.033$^{c}$ |
| Irisin to Leptin | 4.864±0.198$^{a}$ | 4.286±0.335$^{a}$ | 6.335±0.446$^{b}$ | 5.451±0.388$^{a,b}$ |
| Irisin to Insulin | 8.017±0.552$^{a}$ | 6.149±0.723$^{a}$ | 9.835±0.856$^{a,b}$ | 6.041±0.689$^{a}$ |
| Leptin to Insulin | 1.676±0.121$^{ab}$ | 1.392±0.084$^{a}$ | 1.606±0.158$^{a}$ | 1.163±0.114$^{a,b}$ |

Data are presented as mean±SEM, values with different letters are significantly different ($p<0.05$). PCOS= Polycystic ovary syndrome. No=Number

As presented in table 4, glycemic indices shows that fasting serum glucose levels were significantly different in obese PCOS women as compared to their corresponding controls ($p = 0.003$), but there was no significant difference between non-obese PCOS women and their control (4.832±0.100, 5.179±0.195 mmol/l, respectively). Furthermore, serum glucose levels were elevated significantly in obese patients as compared to non-obese patients and non-obese controls ($p<0.0001$, 0.001, respectively). Even so, there were no significant different in serum glucose levels between control groups.

Homeostatic Model Assessment was done by: 1-Estimation of Insulin Resistance (HOMA-IR), Table 4, showed that estimation of insulin resistance HOMA-IR values were highly significantly different in obese PCOS women as compared to their corresponding controls ($p<0.0001$), but there was no significant difference between non-obese PCOS women and their control (2.897±0.231, 2.459±0.136, respectively). Furthermore, HOMA-IR values were elevated significantly in obese patients as compared to non-obese patients and non-obese controls ($p<0.0001$, 0.0001, respectively). Even so, there was no significant different in HOMA-IR values between control groups. 2-Estimation of β-cell Function (HOMA-B) values for both obese and non-obese PCOS women shows that there were no significant different to their corresponding controls. Although HOMA-B values were higher in both PCOS groups but there were no significant variations among all groups, as shown in table 4.

**Correlation studies**

Correlation values that presented in this section were calculated using Pearson' s correlation coefficient, considering P values<0.05 as the level of significance are summarized as follows:

**Table 4: Summary of the studied glycemic Indices among various groups**

| Groups (No) variables | Control (Non-Obese) (17) | PCOS (Non-Obese) (25) | Control (Obese) (17) | PCOS (Obese) (25) |
|---|---|---|---|---|
| Serum Fasting Glucose (mmol/l) | 5.179±0.195[a] | 4.832±0.100[a] | 5.232±0.161[a] | 6.057±0.236[b] |
| HOMA-IR | 2.459±0.136[a] | 2.897±0.231[a] | 2.955±0.234[a] | 6.004±0.798[b] |
| HOMA-B | 203.086±59.96[a] | 257.502±43.85[a] | 168.108±19.43[a] | 199.881±26.56[a] |

Data are presented as mean±SEM, values with different letters are significantly different ($p<0.05$). PCOS= Polycystic ovary syndrome. No=Number, HOMA-IR =Homeostatic Model Assessment-Insulin Resistance, HOMA-β =Homeostatic Model Assessment-βcell function

**Table 5: Pearson's correlation in non-obese controls**

| Variables | Variables that are significantly correlated | | | | | |
|---|---|---|---|---|---|---|
| **HOMA-B** | S. Leptin (ng/ml)<br>r-0.610**<br>p 0.009 | Leptin/BMI<br>r–0.592*<br>p 0.012 | Irisin/Insulin<br>r-.540*<br>p 0.025 | Leptin/Insulin<br>r-0.526*<br>p 0.030 | | |
| **HOMA-IR** | Irisin (ng/ml)<br>r 0.494*<br>p 0.044 | | | | | |
| **Serum Irisin (ng/ml)** | FSG (mmol/l)<br>r 0.599*<br>p 0.011 | Leptin (ng/ml)<br>r 0.645**<br>p 0.005 | HOMA-IR<br>r 0.494*<br>p 0.044 | Leptin to BMI<br>r 0.517*<br>p 0.033 | | |
| **Serum Leptin (ng/ml)** | Weight (Kg)<br>r 0.493*<br>p 0.044 | BMI (kg/m*²)<br>r 0.678**<br>p 0.003 | FSG (mmol/l)<br>r 0.554*<br>p 0.021 | Irisin (ng/ml)<br>r 0.645**<br>p 0.005 | HOMA-B<br>r-0.610**<br>p 0.009 | Irisin to Insulin<br>r 0.595*<br>p 0.012 |
| **Leptin to BMI** | Irisin (ng/ml)<br>r 0.517*<br>p 0.033 | HOMA-B<br>r–0.592*<br>p 0.012 | Irisin to Insulin<br>r 0.483*<br>p 0.049 | | | |
| **Irisin to Insulin** | FSG (mmol/l)<br>r 0.559*<br>p 0.020 | Leptin (ng/ml)<br>r 0.595*<br>p 0.012 | Leptin to BMI<br>r 0.483*<br>p 0.049 | HOMA-B<br>r-0.540*<br>p 0.025 | Glucose to Insulin<br>r 0.792**<br>p<0.000 | |
| **Leptin to Insulin** | Age (years)<br>r 0.494*<br>p 0.044 | HOMA-B<br>r-0.526*<br>p 0.030 | Glucose to Insulin<br>r 0.866**<br>p<0.000 | Leptin to BMI<br>r 0.544*<br>p 0.024 | | |

FSG=Fasting Serum Glucose, HOMA-IR =Homeostatic Model Assessment-Insulin Resistance, HOMA-β =Homeostatic Model Assessment-βcell function, * Correlation is significant at the 0.05 level (2-tailed) ($p<0.05$), ** Correlation is significant at the 0.01 level (2-tailed) ($p<0.01$).

**Table 6: Pearson's correlation in non-obese PCOS women**

| Variables | Variables that are significantly correlated | | | | |
|---|---|---|---|---|---|
| WHR | Duration of fertility (years)<br>r 0.418*<br>p 0.038 | | | | |
| S. Fasting glucose (mmol/l) | Total Testosterone (ng/ml)<br>r-0.454*<br>p 0.023 | | | | |
| serum insulin (µIU/ml) | Signs and Symptoms<br>r-0.710**<br>p<0.000 | Leptin (ng/ml)<br>r 0.410*<br>p 0.042 | | | |
| HOMA-B | Total Testosterone (ng/ml)<br>r 0.614**<br>p 0.001 | | | | |
| HOMA-IR | Signs and Symptoms<br>r-0.752**<br>p<0.000 | Leptin (ng/ml)<br>r 0.468*<br>p 0.018 | Leptin to BMI<br>r 0.427*<br>p 0.033 | Irisin to Insulin<br>r-0.549**<br>p 0.004 | Leptin to Insulin<br>r-0.702**<br>p<0.000 |
| Total Testosterone (ng/ml) | Hip(cm)<br>r-0.405* | FSG (mmol/l)<br>r-0.454* | HOMA-B<br>r 0.614** | | |

| | | | | |
|---|---|---|---|---|
| | p 0.044 | p 0.023 | p 0.001 | |
| Serum Leptin (ng/ml) | Signs and Symptoms | Insulin (µIU/ml) | HOMA-IR | |
| | r-0.501* | r 0.410* | r 0.468* | |
| | p 0.011 | p 0.042 | p 0.018 | |
| Leptin to BMI | height (m) | lean body weight | Signs and | HOMA-IR |
| | r 0.419* | (Kg) | Symptoms | r 0.427* |
| | p 0.037 | r 0.419* | r-0.551** | p 0.033 |
| | | p 0.037 | p 0.004 | |
| Irisin to | HOMA-IR | Glucose to Insulin | | |
| Insulin | r-0.549** | r 0.601** | | |
| | p 0.004 | p 0.002 | | |
| Leptin to Insulin | Age (years) | HOMA-IR | Glucose to Insulin | |
| | r 0.462* | r-0.702** | r 0.823** | |
| | p 0.020 | p<0.000 | p<0.000 | |

WHR=waist hip ratio, FSG=Fasting Serum Glucose, HOMA-IR =Homeostatic Model Assessment-Insulin Resistance, HOMA-β =Homeostatic Model Assessment-βcell function, *Correlation is significant at the 0.05 level (2-tailed) (p<0.05), ** Correlation is significant at the 0.01 level (2-tailed) (p<0.01).

**Table 7: Pearson's correlation in obese controls**

| **Variables** | **Variables that are significantly correlated** | | | | |
|---|---|---|---|---|---|
| WHR | SFG (mmol/l) | S. Prolactin (ng/ml) | HOMA-B | Leptin/BMI | |
| | r 0.734** | r 0.502* | r-0.742** | r-0.487* | |
| | p 0.001 | p 0.040 | p 0.001 | p 0.048 | |
| S. Fasting glucose | BMI (kg/m*2) | Waist (cm) | WHR | S. Prolactin (ng/ml) | S. TSH |
| (mmol/l) | r 0.546* | r 0.525* | r 0.734** | r 0.493* | (nmol/l) |
| | p 0.023 | p 0.031 | p 0.001 | p 0.044 | r 0.614** |
| | | | | | p 0.009 |
| serum insulin (µIU/ml) | No. of Abortions | | | | |
| | r-0.534* | | | | |
| | p 0.040 | | | | |
| HOMA-B | WHR | S. TSH | leptin/Insulin | | |
| | r-0.742** | (nmol/l) | r-0.485* | | |
| | p 0.001 | r-0.541* | p 0.048 | | |
| | | p 0.025 | | | |
| HOMA-IR | No. of Abortions | Irisin/Insulin | leptin/Insulin | | |
| | r-0.608* | r-0.565* | r-0.823** | | |
| | p 0.016 | p 0.018 | p<0.000 | | |
| Total Testosterone (ng/ml) | LDL/HDL | | | | |
| | r-0.525* | | | | |
| | p 0.045 | | | | |
| Serum | No. of Abortions | Leptin (ng/ml) | | | |
| Irisin | r-0.524* | r 0.561* | | | |
| (ng/ml) | p 0.045 | p 0.019 | | | |
| Serum Leptin (ng/ml) | No. of Abortions | Irisin | | | |
| | r-0.593* | (ng/ml) | | | |
| | p 0.020 | r 0.561* | | | |
| | | p 0.019 | | | |
| Leptin to BMI | Weight (Kg) | Waist (cm) | Hip (cm) | WHR | |
| | r-0.777** | r-0.844** | r-0.713** | r-0.487* | |
| | p<0.000 | p<0.000 | p 0.001 | p 0.048 | |
| Irisin to Insulin | HOMA-IR | Glucose/Insulin | | | |
| | r-0.565* | r 0.506* | | | |
| | p 0.018 | p 0.038 | | | |
| Leptin to Insulin | LH (mIU/ml) | HOMA-B | HOMA-IR | Glucose to Insulin | |
| | r 0.490* | r-0.485* | r-0.823** | r 0.925** | |
| | p 0.046 | p 0.048 | p<0.000 | p<0.000 | |

WHR=waist hip ratio, FSG=Fasting Serum Glucose, HOMA-IR =Homeostatic Model Assessment-Insulin Resistance, HOMA-β =Homeostatic Model Assessment-βcell function, No=Number, *Correlation is significant at the 0.05 level (2-tailed) (p<0.05), ** Correlation is significant at the 0.01 level (2-tailed) (p<0.01).

**Table 8: Pearson's correlation in obese PCOS women**

| **Variables** | **Variables that are significantly correlated** | | |
|---|---|---|---|
| WHR | S. Insulin (µIU/ml) | HOMA-B | glucose/insulin |
| | r 0.415* | r 0.595** | r-0.487* |
| | p 0.039 | p 0.002 | p 0.013 |
| S. Fasting glucose | Waist (cm) | | |
| (mmol/l) | r-0.446* | | |
| | p 0.025 | | |

| | | | | |
|---|---|---|---|---|
| insulin (µIU/ml) | WHR<br>r 0.415*<br>p 0.039 | | | |
| HOMA-B | Waist (cm)<br>r 0.537**<br>p 0.006 | WHR<br>r 0.595**<br>p 0.002 | leptin/Insulin<br>r-0.461*<br>p 0.020 | |
| HOMA-IR | Irisin/Insulin<br>r-0.555**<br>p 0.004 | leptin/Insulin<br>r-0.647**<br>p<0.000 | | |
| Total Testosterone (ng/ml) | WHR<br>r 0.520**<br>p 0.008 | S. HDL (mmol/l)<br>r-0.432*<br>p 0.031 | | |
| Serum<br>Irisin (ng/ml) | LH/FSH<br>r 0.405*<br>p 0.045 | | | |
| Irisin/Insulin | S. LH (mIU/ml)<br>r 0.546**<br>p 0.005 | LH/FSH Ratio<br>r 0.474*<br>p 0.017 | HOMA-IR<br>r-0.555**<br>p 0.004 | Glucose/Insulin<br>r 0.502*<br>p 0.011 |
| Leptin/Insulin | HOMA-B<br>r-0.461*<br>p 0.020 | HOMA-IR<br>r-0.647**<br>p<0.000 | | |

WHR=waist hip ratio, HOMA-IR =Homeostatic Model Assessment-Insulin Resistance, HOMA-β =Homeostatic Model Assessment-βcell function, * Correlation is significant at the 0.05 level (2-tailed) (p<0.05), **Correlation is significant at the 0.01 level (2-tailed) (p<0.01).

**DISCUSSION**

In the present research, we studied the PCOS patient and controls based on BMI. Serum irisin level of PCOS women did not show a significant difference compared with control subjects although it was decreased, which is consistent with the finding of Gouni *et al.* [44,45] and Shanshan Gao [9]. But there were significant higher differences between obese and non–obese groups both control and PCOS this explained the correlation with BMI. To date, there have been reports of the positive [21, 45-48], negative [24, 49-51] and no correlations [44, 45, 52, 53] between serum irisin and body mass index (BMI). Decreased levels of circulating irisin have been found in T2DM patients compared with non-diabetic controls [46]. Liu *et al.* reported that type 2 diabetes (T2D) patients have lower concentrations of this hormone [46]. Lower serum irisin was also found in new onset T2DM patients by Choi *et al.* and in undefined type 2 diabetes patients by Moreno-Navarrete *et al.* [24,49], which coincides with the findings of Liu *et al.* (204±72 ng/ml in T2D vs. 257±24 ng/ml in nondiabetic controls). Additionally, studies of circulating irisin in humans indicated that irisin levels decrease in sera of patients with T2D or gestational diabetes mellitus [24, 46, 49, 52, 54, 55]. Similarly, in a study by Park *et al.*, increased levels of serum irisin were determined in patients with metabolic syndrome [21]. Age also seems to associate negatively with irisin levels [56]. Interestingly, Stengel *et al.* also observed that women with anorexia nervosa and low BMI (12.6±0.7 kg/m2) have lower plasma irisin levels than obese patients [24,49]. A surprisingly high level of irisin was observed in the PCOS patients contrary to what is generally seen in patients with diabetes, although they share insulin resistance state [4,30]. Therefore, there is no clear explanation for the role of metabolic changes. Based on these observations, it is reasonable to speculate that serum irisin level is likely to be reduced in PCOS patients.

A positive Pearson's correlation between serum irisin and FSG is consistent with Liu *et al.* [46]. In HOMA-IR, leptin/BMI ratio and strongly positive correlated with serum irisin in non-obese control as well as in obese control which explains the energy metabolism and insulin resistance-related proteins such as (leptin) with irisin [57,58]. Insulin resistance-related proteins have also been reported to play a role in the etiopathogenesis of PCOS [59]. It has been reported that irisin improves obesity-related disorders as glucose homeostasis, thereby prolonging life expectancy [58].

While in obese control a negative correlation between serum irisin with the number of abortions reflect the role of irisin in improving the infertility state in obese and PCOS patient. The only positive correlation of irisin in obese PCOS was with LH to FSH ratio, as a compensatory mechanism towards obesity in PCOS patient. Furthermore, PCOS patients frequently have increased secretion of LH and insulin resistance state [60].

Serum leptin level among non-obese groups show no significant difference [19, 60] but in the obese group, the levels were significantly raised due to the effect of obesity [19]. The absence of increased leptin concentration in non-obese PCOS women diminishes the likelihood of any effect of leptin in PCOS pathophysiology. Rather the correlated factor appeared to be the obesity as judged by BMI. Relation of leptin with obesity in humans was previously established [19, 60]. The positive correlation between leptin and weight and BMI indicate the relationship, also with FSG, HOMA-B reflecting the effect of leptin on glucose homeostasis in non-obese control.

The positive correlation with insulin and HOMA-IR reflect the relation of leptin with insulin and its resistance in non-obese PCOS patient. In addition to its role in the regulation of body energy balance, leptin has been recently suggested to serve as a permissive signal to the reproductive system [60]. Furthermore, the negative correlation with PCOS signs and symptoms confirmed that. Fasting plasma insulin levels correlate with circulating leptin levels, which are elevated in insulin resistant subjects [60].

In obese control, the negative correlation with a number of abortions reflects the role of leptin as a marker for fertility state [60]. As expected, fasting plasma insulin levels were clearly higher in PCOS patients than in control subjects. This was also clearly evident even if BMI was used as a covariate. These results suggest that insulin resistance is not solely dependent on obesity in these patients, but that PCOS also contributes to insulin resistance, as reported earlier [60]. However, as serum leptin levels were similar in PCOS patients and in control subjects, the concept that circulating leptin levels would be elevated in insulin resistant states such as PCOS independent of obesity, is supported by our findings in obese PCOS patient.

Serum leptin concentrations were not different in non-obese PCOS patients and control subjects, although each group had clearly different circulating androgen and gonadotrophin levels. Furthermore, serum leptin was not correlated to serum FSH, LH, testosterone [60].

PCOS has been linked to a higher prevalence of impaired glucose tolerance and T2DM, independent of obesity levels. Although the majority of PCOS patients retain sufficient beta-cell function to prevent deterioration in glucose tolerance, a considerable number, especially those with first-degree relatives with type 2 diabetes, produce an abnormal beta-cell response in response to glucose challenges [4] as seen in the present study. Impaired glucose tolerance has been reported in approximately 30%-40% of PCOS patients and diabetes mellitus type 2 in 7.5%-10% [4].

Estimation of HOMA-IR values indicates that glucose and insulin metabolisms in PCOS patients are significantly less efficient than those

of control women, especially in obese subjects. Which could be related to the adipocyte-derived hormone adiponectin concentrations which are positively correlated with insulin sensitivity [9].

Increased insulin levels and HOMA-IR scores were seen in obese PCOS women compared to controls and non-obese PCOS subjects. HOMA-IR scores were much higher in obese PCOS subjects than the normal range values (2.1-2.7). [9] as seen in our study. Insulin level was not significantly elevated in non-obese PCOS but its value above 13 indicated insulin resistance, and very highly elevated in obese PCOS (22.002±2.43), as shown in table 3.

HOMA-B values were not significantly elevated in obese and non-obese PCOS the elevation as a compensatory mechanism for insulin resistance, in the obese group, we seen the decrease in HOMA-B as the deteriorations in pancreatic B-cell progress due to insulin resistance that leads to high risk of diabetes. There are numerous metabolic consequences of PCOS in addition to the effects on the reproductive system. These include a higher risk of obesity, insulin resistance, type 2 diabetes mellitus and premature arteriosclerosis [4].

As a conclusion, although serum irisin levels show no significant variation in subjects in relation to PCOS condition, it seems more to be related to BMI, since it's secreted by adipocytes. And because leptin and irisin levels would be elevated in obese subjects that would be related to PCOS pathogenesis. However, Irisin/leptin ratio could aid only in the differentiation of patients with PCOS and normal subjects within the same BMI values. Irisin/insulin ratio seems to be a better indicator for PCOS condition regardless to BMI, where it showed significantly lowered values and to be negatively correlated with HOMA-IR in obese and non-obese, and even to be significantly correlated with LH/FSH ratio in obese PCOS patients.

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**CONFLICT OF INTERESTS**

Declared none

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