RESEARCH ARTICLE

Simultaneous determination and association between serum levels of irisin and chemerin in PCOS

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Abstract

Objective: To determine the serum levels of irisin, chemerin and insulin in women with polycystic ovary syndrome, and to compare their levels with respect to bodyweight and body mass index.

Method: The case-control study was conducted at the Department of Clinical Chemistry, College of Medicine, Mustansiriyah University, Baghdad, Iraq, from December 2020 to February 2022, and comprised healthy controls in group I who were matched for bodyweight and body mass index with polycystic ovary syndrome women in group II. Subjects and cases were inducted using purposive sampling technique Subgroups were also formed on the basis of normal body mass index, and overweight-obese status. Serum irisin, chemerin, insulin and free testosterone levels, anthropometric measurements, lipid profile as well as hormonal and biochemical parameters were noted. Data was analysed using SPSS 25.

Result: Of the 88 subjects, 32(36.4%) were in group I with mean age 25.1±4.7 years, and 56(63.6%) in group II with mean age 25.0±6.3 years (p>0.05). Both the groups were divided into two equal subgroups A and B. Group II had significantly higher mean body mass index (p=0.007) and adult body fat (p=0.018). Group II women had significantly high fasting serum insulin levels (p<0.001) and homeostatic model assessment for insulin resistance values (p<0.001). Serum irisin had significant positive correlation with serum chemerin (p=0.014) in group II. Serum free testosterone, irisin and chemerin were significantly higher (p<0.001) in group II compared to group I except for chemerin which showed no significant differences among women with normal body mass index (p=0.071).

Conclusion: Serum levels of irisin and chemerin could serve as biomarkers of polycystic ovary syndrome.

Key Words: Fibronectins, Insulin, Polycystic Ovary, Overweight, Obesity, Adipose Tissue, Testosterone, Fasting, Lipids.

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Introduction

Polycystic ovary syndrome (PCOS) is defined by a combination of signs and symptoms related to androgen excess and dysfunction of ovaries in the absence of other specific diagnosis[1].

Irisin is a hormone that was discovered in 2012 in the mouse skeletal muscle. It is related to adipomyokines because its actions are in adipose and muscle tissue (adipokine and myokine). Irisin is composed of 112 amino acid residues (12kDa), and the chemical structures of irisin in humans, rats and mice are identical[2].

Interestingly, the chemical structure of irisin showed similarity with insulin (85%), glucagon (90%), and leptin (83%). The determinant factors that influenced the secretion of irisin hormone are age, gender, muscle mass, and the duration, intensity, and type of exercise. The serum levels of irisin in women are less than in men, and they tend to get lower with age. It is a thermogenic protein that converts the white fat into brown fat[3]. One of the characteristic features of PCOS is adiposity, and it is well known that adipose tissue secretes a number of adipocytokines, including leptin, visfatin, resistin, adiponectin, apelin and retinol binding protein-4. The relationships between adipocytokines and the cardinal features of PCOS are usually not universal. Serum adiponectin levels are inversely correlated with insulin resistance (IR) indices, but not with body mass index (BMI) in PCOS patients. Li et al.[4] demonstrated that serum levels of irisin in PCOS women were significantly higher than the corresponding values of normal-weight or overweight women without PCOS.

Chemerin is an adipokine that is encoded by the gene retinoic acid receptor responder-2 (Rarres2), and secreted by the adipose tissue. It is available as prochemerin (inactive form) in several organs and tissues with a molecular weight of 14kD. In the adipose tissue, chemerin

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is secreted as prochemerin, and the protease enzyme keeps it activated through the C-terminal process. Therefore, a number of chemerin isoforms get activated, and this explains the multiple biological effects of chemerin. The serum level of chemerin in obese PCOS women was higher than normal-weight PCOS women in a study which found it to be significantly correlated with glucose, insulin and IR. The systemic level of chemerin remained stable in the form of prochemerin, and it was converted into the active form when needed[5]. One study demonstrated that the expression and regulation of adipokines in PCOS women had variations. The levels of all adipokines except adiponectin were higher in obese PCOS women compared to normal-weight PCOS women, and a higher concentration of chemerin was found in the ovarian granulosa cells compared to follicular fluid[6]. Some studies believed that irisin belonged to myokines, while chemerin belonged to adipokines, therefore, the relationship between them was related to the skeletal muscle and adiposity factors[7].

A recent meta-analysis carried on non-obese women with PCOS found that serum chemerin was significantly increased, while serum irisin did not show significant changes when compared with non-PCOS women[8].

The current study was planned to determine the serum levels of irisin, chemerin and insulin in PCOS women, and to compare their levels with respect to bodyweight and BMI.

Patients and Methods

The case-control study was conducted at the Department of Clinical Chemistry, College of Medicine, Mustansiriyah University, Baghdad, Iraq, from December 2020 to February 2022, and the participants were recruited from the consultant clinics of the Obstetrics and Gynaecology Department of Al-Yarmouk Teaching Hospital, Baghdad, and the General Teaching Hospital, Krikuk, Iraq.

Current samples was raised using purposive sampling technique, those included were healthy controls in group I who were matched for bodyweight and BMI with PCOS women in group II. Subgroups were also formed on the basis of normal BMI, and overweight-obese status.

The patients were diagnosed on the basis of clinical presentation, ultrasound features, and sex hormone profile. Patients with history of complications of obesity, diabetes and cardiovascular diseases, thyroid function disorder, and those on oral anti-diabetic agents were excluded, and so were those using oral contraceptives, ovulation induction and anti-obesity pills for the preceding 2 months.

The Rotterdam criteria[9-10] were used PCOS diagnosis of PCOS patients, with the differentiating features being clinical and/or biochemical signs of hyperandrogenism, oligoovulation and/or anovulation, and polycystic ovarian morphology (PCOM) on ultrasound. Women with at least two of these elements were included in the PCOS group.

Serum levels of irisin and chemerin were determined using enzyme-linked immunosorbent assay (ELISA) sandwich technique with commercial reagents (Human Irisin ab285295, and Chemerin ab155430, Abcam, United Kingdom).

The sample size was determined using G*Power 3.1[11] with power 0.8 and significant level 0.05.

BMI 18-24.99kg/m^2 was considered normal, and BMI ≥25kg/m^2 was considered overweight/obese [12].

For each participant, height, weight, BMI, waist circumference (WC), hip circumference (HC), waist-to-hip ratio (WHR), waist-to-height ratio (WHeR), lipid accumulation product (LAP) and adult body fat (ABF) were noted. Lipid profile and glycaemic indices were determined, and serum levels of insulin, free testosterone, irisin, and chemerin were assessed.

Data was analysed using SPSS 25. Data was expressed as frequencies and percentages, or as mean ± standard deviation, as appropriate. Independent two-sample t-test and Spearman's correlation test were used when applicable. Receiver operating characteristic (ROC) curve analysis were employed. P≤ 0.05 was taken as significant.

Results

Of the 88 subjects, 32(36.4%) were in group I with mean age 25.1±4.7 years, and 56(63.6%) in group II with mean age 25.0±6.3 years (p>0.05). Both the groups were divided into two equal subgroups A and B.

Anthropometric measurements of PCOS patients with normal BMI did not significantly differ from the corresponding values of the healthy subjects (p>0.05) except for mean height (p=0.031). Anthropometric measurements of overweight/obese PCOS patients showed significant higher mean values for body weight (p<0.001), HC (p=0.007), BMI (p<0.001), ABF (p<0.001) and LAP (p=0.041) (Table 1).

In general, PCOS patients regardless of BMI had significantly higher mean BMI (p= 0.07) and ABF (p=0.018) (Figure 1A-B). A positive significant correlation between insulin (p<0.001) and homeostasis model assessment for insulin resistance (HOMA-IR) was observed in PCOS women (p<0.001) (Table 2; Figure 1C). Overweight/obese

Table-1: Anthropometric measurements and related indices.

	Group IA (n=16)	Group IIA (n=26)	p-value	Group IB (n=16)	Group IIB (n=30)	p-value	Group I (n=32)	Group II (n=56)	p-value
Age (year)	25.0±4.9	24.1±6.4	0.616	24.9±4.7	25.7±6.3	0.741	25.1±4.7	25.0±6.3	0.924
Weight (kg)	56.9±6.0	60.2±5.4	0.076	67.8±5.1	77.7±9.8	<0.001	62.7±8.3	69.6±11.9	0.002
Height (m)	1.58±0.06	1.63±0.05	0.031	1.61±0.05	1.62±0.06	0.909	1.60±0.06	1.62±5.9	0.090
Waist circumference cm)	80.4±10.3	84.9±6.9	0.134	92.1±4.8	96.6±9.8	0.406	87.3±12.0	91.2±10.3	0.126
Hip circumference (cm)	87.8±10.3	93.5±10.8	0.100	98.5±8.0	106.7±12.5	0.007	93.0±10.5	100.6±13.4	0.004
Body mass index (kg/m2)	22.6±2.1	22.7±1.8	0.850	26.0±1.4	29.6±3.2	<0.001	24.4±2.5	26.4±4.3	0.007
Conicity index	1.23±0.14	1.28±0.09	0.220	1.30±0.07	1.28±0.10	0.196	1.28±0.13	1.28±0.1	0.936
Waist-hip- ratio	0.92±0.1	0.92±0.1	0.977	0.94±0.09	0.914±0.12	0.205	0.94±0.11	0.92±0.12	0.311
Waist-height- ratio	0.51±0.07	0.52±0.05	0.458	0.57±0.02	0.60±0.05	0.345	0.55±0.07	0.56±0.06	0.244
Adult body fat	32.9±3.0	32.8±3.0	0.949	36.9±2.2	41.4±4.6	<0.001	35.0±3.4	37.4±5.8	0.018
Lipid accumulation product	24.2±20.9	26.5±13.0	0.697	34.0±10.6	45.4±25.8	0.041	29.1±17.0	36.6±22.8	0.084

Group I: Healthy subjects, Group II: Polycystic ovary syndrome patients, A: Normal body mass index, B: Overweight-obese category.

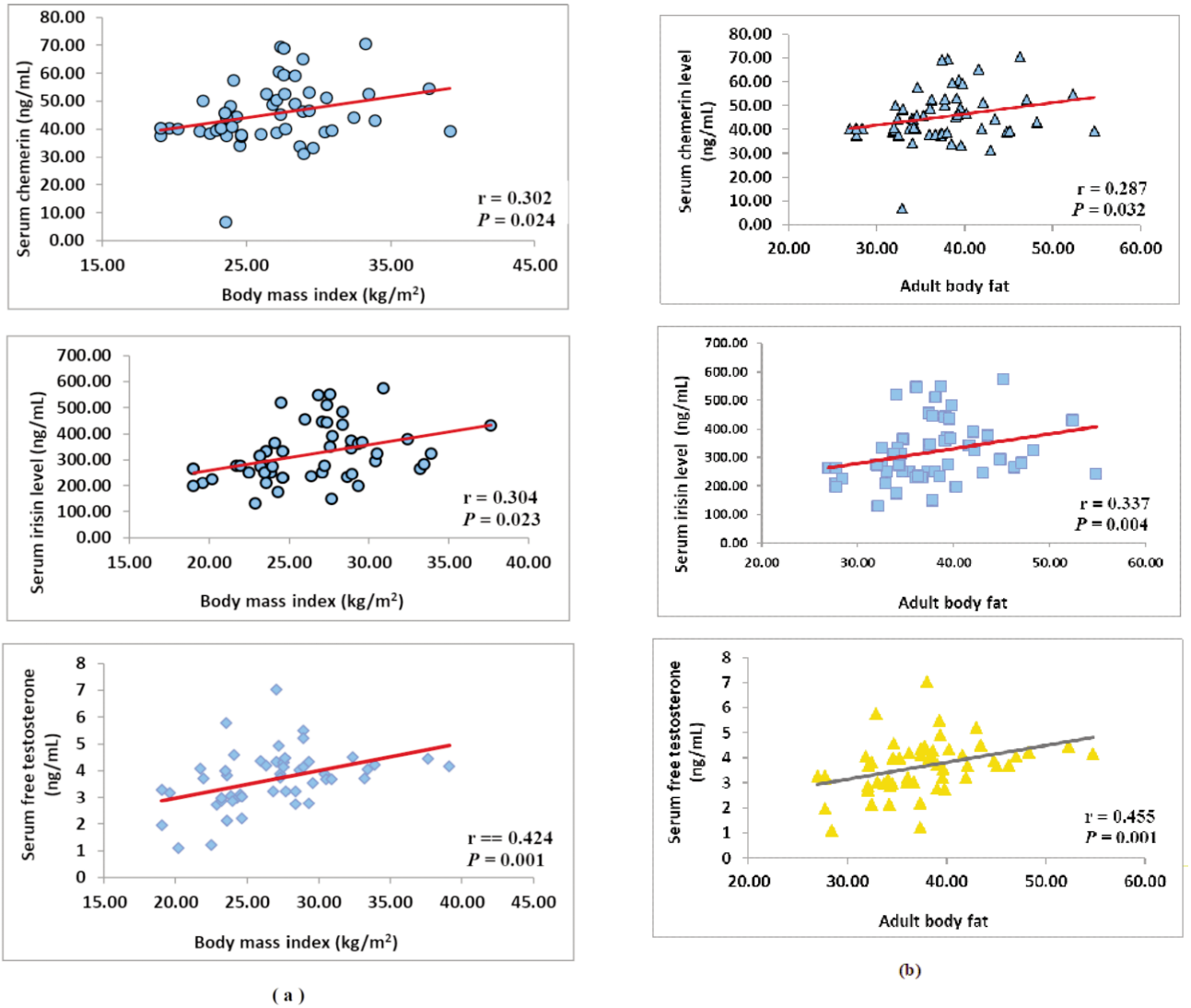
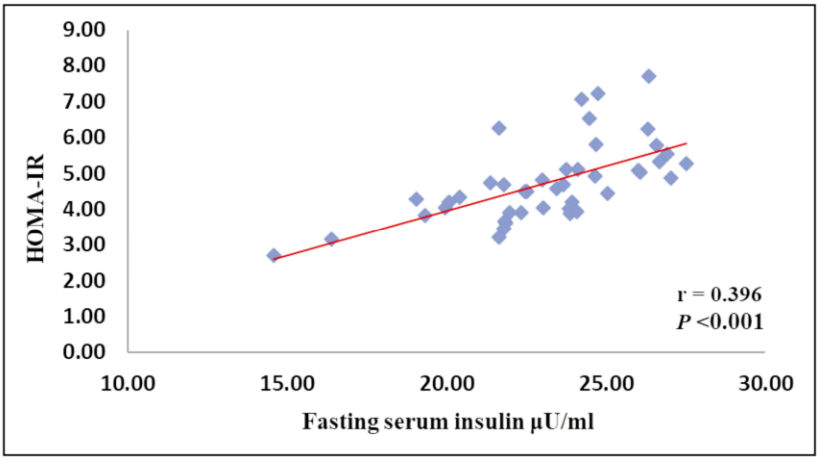


Figure-1: (A) Significant correlation of serum levels of chemerin, irisin and free testosterone with (a) body mass index (BMI), (b) adult body fat (ABF) in polycystic ovary syndrome (PCOS) patients, and (c) significant correlation between serum levels of fasting insulin with homeostatic model assessment for insulin resistance (HOMA-IR) values.



(c)

Figure-1: (c) significant correlation between serum levels of fasting insulin with homeostatic model assessment for insulin resistance (HOMA-IR) values.

women had significantly higher mean values for weight (p<0.001), BMI (p<0.001), WC (p<0.001), HC (p <0.001), WHeR (p<0.001), ABF (p<0.001) and LAP (p<0.001).

Significant higher levels of free testosterone (p<0.001) and irisin (p<0.001) were observed in the 2 subgroups of PCOS women compared to the corresponding subgroups of group I, while the serum levels of chemerin was non-significantly elevated in PCOC patients with normal BMI compared with the corresponding subgroup of group I (Table 3). Overweight/obese PCOS women had significant higher mean values of free testosterone (p<0.001),

Table-2: Serum insulin and HOMA-IR assessment.

	Group IA (n=16)	Group IIA (n=26)	p-value	Group IB (n=16)	Group IIB (n=30)	p-value	Group I (n=32)	Group II (n=56)	p-value
Fasting serum insulin µU/ml	5.3±1.9	22.0±3.2	<0.001	5.7±1.2	23.6±2.2	<0.001	5.5±1.55	22.9±2.8	<0.001
HOMA-IR	1.08±0.39	4.73±1.14	<0.001	1.18±0.25	5.08±1.82	<0.001	1.12±0.32	4.92±1.55	<0.001

Group I: Healthy subjects, Group II: Polycystic ovary syndrome patients, A: Normal body mass index, B: Overweight-obese category. HOMA-IR: Homeostatic model assessment for insulin resistance.

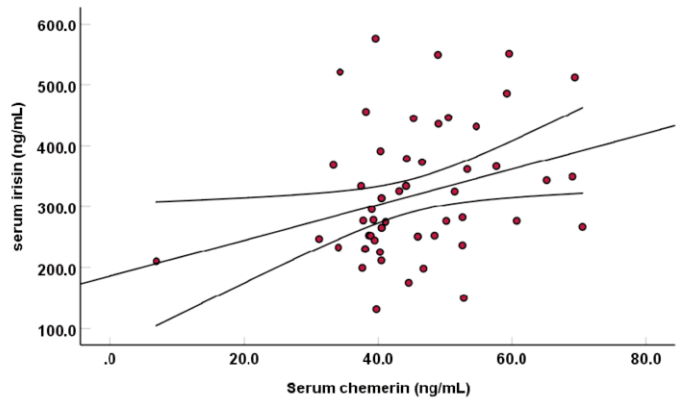


Figure-2: Significant positive correlation between serum irisin and chemerin levels (r=0.332, p=0.014) in patients with polycystic ovary syndrome (PCOS).

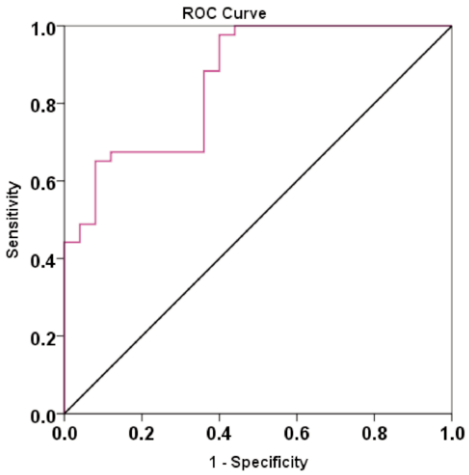


Figure-3: Area under the curve (AUC) of chemirin at a cut-off value of 39.0ng/mL. (AUC: 0.860, confidence interval –CI]: 0.770-0.949, p<0.001).
ROC: Receiver operating characteristic.

Table-3: Serum free testosterone, chemerin and irisin assessment.

	Group IA (n=16)	Group IIA (n=26)	p-value	Group IB (n=16)	Group IIB (n=30)	p-value	Group I (n=32)	Group II (n=56)	p-value
Free testosterone (ng/mL)	1.02±0.27	3.08±0.99	<0.001	1.10±0.23	4.12±0.83	<0.001	1.05±0.025	3.69±1.04	<0.001
Irisin (ng/mL)	191.1±57.8	271.2±73.6	<0.001	195.6±61.6	359.6±111.7	<0.001	192.3±58.0	318.5±105.0	<0.001
Chemerin (ng/mL)	36.8±10.2	40.5±8.4	0.071	39.6±6.9	49.3±10.9	<0.001	38.4±8.9	45.3±10.7	<0.001

Group I: Healthy subjects, Group II: Polycystic ovary syndrome patients, A: Normal body mass index, B: Overweight-obese category.

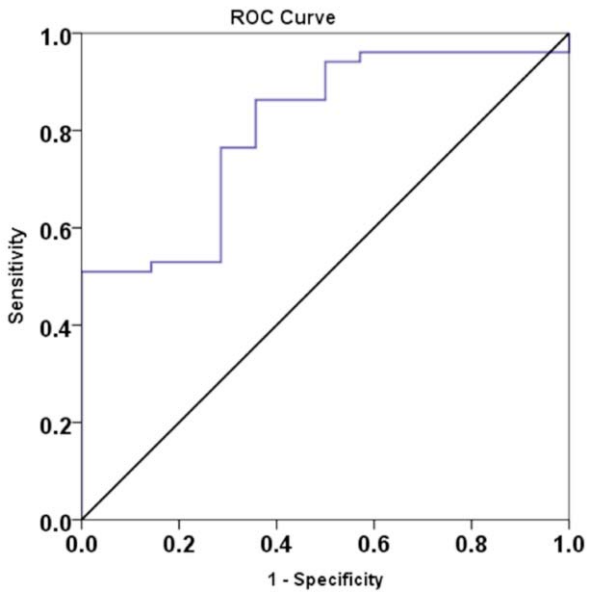


Figure-4: Area under the curve (AUC) of irisin at a cut-off value of 200ng/mL. (AUC: 0.805, confidence interval [CI]: 0.685-0.929, p=0.001). ROC: Receiver operating characteristic.

chemerin (p<0.001) and irisin (p<0.001) compared to overweight/obese women in the control group. Serum chemerin had direct positive correlation with serum irisin (r=0.332, p=0.014) (Figure 2).

ROC analysis showed a significant (p<0.001) area under the curve (AUC) of serum chemerin levels in PCOS patients 0.860 (95% confidence interval [CI]: 0.770-0.949). The sensitivity and specificity were 74.1% and 56.7% at a cut-off level of 39ng/Ml, respectively (Figure 3).

A significant (p=0.001) AUC of serum irisin levels in PCOS patients was found 0.805 (95% CI: 0.685-0.929). The sensitivity and specificity were 72.5% and 73.9% at a cut-off level of 200ng/Ml, respectively (Figure 4).

Discussion

Serum levels of irisin in PCOS subjects have been assessed in several studies with conflicting results. High levels of serum irisin that were observed in the current study indicated poor outcomes for PCOS patients, which was in agreement with previous work[13].

Non-significant correlations between serum irisin levels with insulin and free testosterone levels were observed in the study, which was in contrast to a study[14] which found positive correlations between the indices. This could be related to the characteristics of the patients. Polak et al[15] suggested that serum irisin is a useful biomarker of IR in PCOS, while Luo et al.[16] suggested that irisin had an adverse impact on folliculogenesis, leading to infertility. Although irisin is involved in glucose homeostasis, this does not mean there is a correlation between HOMA-IR and irisin, as the current study found a non-significant correlation between serum irisin levels and HOMA-IR, which was in agreement with Perakakis et al.[17]

The current study did not explore the magnitude of physical exercise the patients were indulging in before the determination of serum irisin. Exercise is the determining factor in the synthesis and release of irisin [18].

Serum chemerin was significantly increased in PCOS, and was positively correlated with irisin, which was in line with earlier findings[19]. It is important to measure serum chemerin in PCOS as chemerin is involved in the osteogenesis, and thereby has an impact on ovarian follicle development. A study demonstrated the link between high serum chemerin with abortion in PCOS women[20]. Accordingly, the positive significant correlation between irisin and chemerin in the current study suggested that both biomarkers had an adverse impact on the development of ovarian follicles in PCOS women, which means both the markers had a therapeutic influence in the pathogenesis of the disease.

In this study, patients with PCOS had significantly higher BMI compared to controls, which is in agreement with Barber T. M.[21] WC values were non-significantly higher among PCOS patients compared to controls both within normal-weight or overweight subgroups. This finding is of great importance as assessment of WC in PCOS could serve as an important surrogate in the assessment of visceral obesity, and may anticipate cardiovascular events in young women[22]. Moreover, the current study showed non-significant difference between PCOS and control groups with respect to conicity index, which is in agreement with Małgorzata Kału˙zna et al.[23], indicating that anthropometric measurements should include other indices beyond the BMI[24].

The other anthropometric measurements that were applied in the current study were ABF and LAP, which were significantly increased in overweight PCOS patients compared to controls. These findings were in agreement with recent studies. [25-26]

Limitation: The current study has its limitations, as some of the indices were not determined, like the oxidised low density lipoprotein (LDL), which is an important determinant of cardiovascular events in young PCOS women. Besides, the study did not explore the element of physical exercises among the subjects. Finally, a small sample limited the generalisability of its findings, especially those related to AUC cut-off levels of irisin and chemerin.

Conclusion

PCOS women had significant higher levels of irisin and chemerin which could serve as biomarkers of PCOS women regardless of their BMI. Significant correlation between irisin and chemerin indicated that both hormones were synthesised and released simultaneously in PCOS, meaning that they were specific for PCOS pathogenesis. According to cut-off values, serum irisin level was found to be more specific predictor of PCOS than serum chemerin. Anthropometric measurements in terms of determination of ABF can be used as a match for PCOS patients. The changes in the serum irisin and chemerin levels in PCOS were not related to BMI as serum chemerin level increased non-significantly in normal weight and overweight women.

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