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Research Article

EVALUATION OF SERUM OMENTIN-1 AND APELIN LEVELS AND THEIR ASSOCIATION WITH INSULIN RESISTANCE AND OBESITY IN EGYPTIAN WOMEN WITH POLYCYSTIC OVARY SYNDROME

Zahraa Z. Abd-Elhafez [1]*, Mohamed Ali Mohamed [2], Ashraf T. Abd-Elmouttaleb [3], Doaa M. Abd-Elatif [1]
[1] Department of Biochemistry, Faculty of Pharmacy (Girls), Al-Azhar University, Cairo, Egypt
[2] Department of Obstetrics and Gynecology, Faculty of Medicine, Al-Azhar University, Cairo, Egypt
[3] International Islamic Center for Population Studies and Research, Al- Azhar University, Cairo, Egypt
*Corresponding Author Email: zahraa.abdelhafez@yahoo.com

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ABSTRACT

Polycystic ovary syndrome (PCOS) is the most common endocrine-metabolic disorder in women of reproductive age. Most PCOS patients have a tendency to become obese and insulin resistant. Omentin-1 is an anti-inflammatory adipokine and plays a role in regulating insulin sensitivity. Apelin is a new adipokine which may be a key regulator in glucose and lipid metabolism and may be associated with insulin resistance. This study aimed to evaluate serum levels of Omentin-1 and Apelin to determine their association with obesity and IR in PCOS. A total of eighty subjects divided into four groups: Group I: 20 non-obese control (BMI< 30), Group II: 20 non-obese patient with PCOS (BMI< 30), Group III: 20 obese Control (BMI ≥ 30) and Group IV: 20 obese patient with PCOS (BMI ≥ 30). Serum levels of Insulin, Omentin-1 and Apelin were estimated by ELISA. Homeostasis Model of Assessment-Insulin Resistance (HOMA-IR) was calculated. Results showed a significant decrease in serum levels of Omentin-1 and increase in serum levels of Apelinin (non-obese and obese) PCOS groups when compared to their controls. Within PCOS groups there were significant negative correlations between Omentin-1 and both of HOMA-IR and BMI, while there were significant positive correlations between Apelin and both of BMI and HOMA-IR. In summary serum Omentin-1 and Apelin are directly correlated with IR and obesity in women with PCOS.

Keywords: Polycystic ovary syndrome, Insulin resistance, Obesity, Apelin, Omentin-1.

INTRODUCTION

Polycystic ovary syndrome (PCOS) is a major cause of anovulatory infertility characterized by hormonal and metabolic abnormalities[1]. The underlying mechanisms of metabolic disorders in PCOS are not completely understood. Polycystic ovary syndrome (PCOS) is associated with features linked to metabolic syndrome including visceral adiposity, dyslipidemia and impaired glucose homeostasis. Insulin resistance (IR) is prevalent among women with PCOS independent of obesity and is critically involved in reproductive and metabolic complications[2]. Adipose tissue produces adipocytokines that contribute to the regulation of insulin sensitivity and reproduction[3]. Omentin-1 (also known as intellectin-1) is a newly identified adipokine with a molecular weight of 34 kDa and composed of 313 amino acids[4]. Omentin-1 is the major circulating form; it also has a homologue designated as omentin-2[5]. Omentin-1 has anti-inflammatory and insulin sensitizing roles. The exact role of Omentin-1 in PCOS remains unclear and need more studies[6]. Apelin has been isolated from the bovine stomach extracts as an endogenous ligand of the orphan receptor APJ, which is a G protein-coupled receptor[7]. This peptide is formed of a 77-amino-acid preproapelin precursor and exists in multiple molecular forms with different biological activities[8]. Apelin is shown to possess multiple effects in several organs and tissues, including brain, heart, gut and kidney. Apelin was identified as an adipokine linked to obesity and IR. It stimulates glucose utilization, decreases insulin secretion[9]. Apelin synthesis in adipocytes is stimulated by insulin and apelin plasma levels are markedly increased under conditions such as obesity and type 2 diabetes[10].

MATERIALS AND METHODS

Patients

The present study performed on eighty subjects, their ages ranged between 19-37 years, selected from the outpatients Clinic of Obstetrics and Gynecology Department, Sayed Galal University Hospital, Cairo, Egypt in the period between July 2018 to March 2019. The study was approved by the Institutional Ethical Committee of Faculty of Pharmacy, Al-Azhar University, Egypt [code number: 162; date: 18.12.2017]. Informed written consent was taken from all the subjects. Women with PCOS were diagnosed according to the revised Rotterdam criteria[11], by the presence of two of the following three manifestations: oligo-ovulation/or anovulation, clinical and/or biochemical hyperandrogenism and polycystic ovaries on ultrasound scanning. The control cases had regular menstrual cycles and normal ultrasonography findings on pelvic ultrasound scanning, without clinical or biochemical hyperandrogenism. The cases were not receiving any treatment for at least 3 months. Exclusion criteria for all cases of the study included: age > 40 years, known cardiovascular disease, thyroid disease, other endocrinopathies, history of neoplasms, endometriosis, pregnant females, current smoking, alcohol abuse, type I or type II diabetes, autoimmune diseases, renal impairment, hypertension, oral contraceptive users, insulin sensitizer drugs, hormonal medication for at least 3

months before the study. The final clinical study involved four groups of cases: Group I: consisted of 20 normal weight control cases (BMI < 30), Group II: consisted of 20 normal weight PCOS cases (with BMI < 30), Group III: consisted of 20 control cases with obesity (BMI ≥ 30) and Group IV: consisted 20 obese PCOS cases (with BMI ≥ 30). BMI (kg/m^2) was calculated by dividing weight (kg) by height squared (m^2). Obesity is considered if BMI ≥ 30 kg/m^2 (according to the WHO criteria)[12].

Sampling

10 ml of blood was drawn from each subject after overnight fasting (8-12 hours). The venous blood sample was divided into two tubes. 2 ml were put on fluoride/ oxalate for estimating fasting plasma glucose. The remaining blood was collected in vacutainers without additives, allowed to clot for 30 minutes at room temperature and centrifuged at 3000 RPM for 10 minutes, to obtain supernatant (serum sample) which was labeled and stored at -20°C until analyzed.

Methods of assay

Available commercial kits were used for determination of fasting blood glucose (FBG), total cholesterol (TC), triglycerides (TG), high density lipoprotein (HDL) by enzymatic colorimetric methods using (Spectrum diagnostics®, Egypt), Low-density lipoprotein (LDL) levels were calculated by using Friedewald *et al*., equation[13] LDL (mg/dl) = total cholesterol - [HDL + (triglycerides/5)]. Insulin measured by ELISA using Perfect Ease Biotech (Beijung®, USA), Homeostasis Model of Assessment-Insulin Resistance (HOMA-IR) index for the assessment of insulin resistance, was calculated by using Matthews *et al*. equation[14] HOMA-IR = [glucose (mg/dl) - insulin (IU/ml)]/405.LH measured by ELISA using (Bio Tina GmbH ELISA ®, Germany), FSH measured by ELISA using (Chemux Bio Science ELISA ®, USA), Progesterone and Total testosterone measured by ELISA using (Nova Tecimmundiagnostica GMBH ®, Frankfurt), AMH measured by ELISA using (CUSABIO®, China), Omentin-1measured by ELISA using (Cloud-Clone Crop®, USA), and finally Apelin measured by ELISA using (Cloud-Clone Crop®, USA).

Statistical analysis

The results were expressed as the mean ± standard error of the mean (SEM). Differences between variables were calculated using the Student's t test. Differences between groups were assessed by one-way analysis of variance (ANOVA). Subsequent multiple comparisons between the different groups were analyzed by Tukey (compare all pairs of columns) tests. Pearson's correlations were computed to assess the relationship between variables. Data were statistically analyzed using the (Graph Pad Prism version 5® (Graph Pad Prism software). Values at $P < 0.05$ were considered significant.

RESULTS

As shown in Table 1, the mean values of fasting blood glucose (FBG), fasting insulin, HOMA-IR, Total Cholesterol (TC), Triacylglycerol (TAG), Low density lipoprotein-Cholesterol (LDL-C), LH, Total Testosterone (TT) and AMH showed significant increase in non-obese PCOS patients when compared to the non-obese control and significant increase in obese PCOS patients when compared to the obese control. The mean values of High-density lipoprotein-Cholesterol (HDL-C) showed significant decrease in non-obese PCOS patients when compared to the non-obese control and significant decrease in obese PCOS patients when compared to the obese control. The mean serum levels of FSH and Progesterone showed no significant differences between all groups. The mean serum levels of Omentin-1 showed a statistically significant decrease ($p < 0.0001$) in non-obese PCOS patients (19.47 ± 0.384 ng/ml) compared to non-obese women without PCOS (24.13 ± 0.270 ng/ml) also the mean serum levels of Omentin-1 showed a statistically significant decrease ($p < 0.0001$) in obese women with PCOS (14.94 ± 0.287 ng/ml) compared to their controls (19.88 ± 0.326 ng/ml). Decreased serum Omentin-1 in PCOS woman with or without obesity suggested that Omentin-1 may be involved in the development of the pathogenesis of PCOS. Non-obese women with PCOS demonstrated significantly ($p < 0.0001$) higher Apelin concentrations (1.46 ± 0.081 ng/ml) compared to non-obese women without PCOS (1.01 ± 0.024 ng/ml). Also, obese women with PCOS demonstrated significantly ($p < 0.0001$) higher Apelin concentrations (2.04 ± 0.104 ng/ml) compared to obese women without PCOS (1.37 ± 0.072 ng/ml). Increased serum Apelin in PCOS woman with or without obesity suggested that Apelin may be involved in the development of the pathogenesis of PCOS.

As shown in Table 2 PCOS groups showed no significant differences in FBG, LH, FSH, progesterone, TT and AMH between obese and non-obese PCOS groups PCOS groups showed also a significant increase in obese women when compared to the non-obese women in fasting insulin level, HOMA-IR, Total Cholesterol (TC), Triacylglycerol (TAG) and Low density lipoprotein-Cholesterol (LDL-C). PCOS groups showed also a significant decrease in obese women when compared to the non-obese women in HDL-C. The mean serum levels of Omentin-1 in PCOS groups showed a statistically significant decrease ($p < 0.0001$) in obese women (14.94 ± 0.287 ng/ml) when compared to the non-obese women (19.47± 0.384 ng/ml). The mean serum levels of Apelin in PCOS groups showed a statistically significant increase ($p < 0.0001$) in obese women (2.04 ± 0.104 ng/ml) when compared to the non-obese women (1.46 ± 0.081 ng/ml).

As shown in Table 3 the mean serum levels of Omentin-1 showed a statistically significant decrease ($p < 0.0001$) in PCOS patients (17.15 ± 0.415 ng/ml) compared to women without PCOS (22.05 ± 0.382 ng/ml), also the mean serum levels of Apelin showed a statistically significant increase ($p < 0.0001$) PCOS patients (1.75 ± 0.079 ng/ml) compared to women without PCOS (1.19 ± 0.046 ng/ml).

As shown in Table 4, within PCOS groups, there were significant negative correlations between serum Omentin-1 with BMI, FBG, Fasting insulin, HOMA-IR, TC, TAG, TT and AMH, and significant positive correlation between serum Omentin-1 and HDL-C. As shown in Table 5, there were significant positive correlations between serum Apelin with BMI, FBG, Fasting insulin, HOMA-IR, TC and TAG, and a significant negative correlation between serum Apelin and HDL-C.

Receiver operating characteristics (ROC) curves were carried out to assess the diagnostic performance of Omentin-1 whether it is more sensitive and specific than Apelin or not. A cut off serum Omentin -1 value of 21.8 ng/ml was determined for discriminating between non- obese women with and without PCOS, serum Omentin-1 level of < 21.8 ng/ml predict the presence of PCOS in non-obese women with 100% sensitivity and 100% specificity. A cutoff serum Omentin -1 value of 17.45 ng/ml was determined for discriminating between obese women with and without PCOS, serum Omentin-1 level of < 17.45 ng/ml predict the presence of PCOS in obese women with 100% sensitivity and 95.45% specificity (Figure 3,4) (Table 6, 7). A cutoff serum Apelin value of 1.050 ng/ml was determined for discriminating between non- obese women with and without

PCOS, serum Apelin level of > 1.050 ng/ml predict the presence of PCOS in non-obese women with 90.91% sensitivity and 65.22% specificity. A cutoff serum Apelin value of 1.450 ng/ml was determined for discriminating between obese women with and without PCOS, serum Apelin level of > 1.450 ng/ml predict the presence of PCOS in obese women with sensitivity 95.65% and 68.18% specificity (Figure 5,6) (Table 8,9). The previous results illustrate that serum Omentin-1 is more sensitive rather than serum Apelin.

Table 1: Comparison between statistics of all study groups regarding clinical, biochemical and hormonal data

Parameter	Group I (Non-Obese Control) N = 22	Group II (Non-Obese PCOS) N = 22	P-Value	Group III (Obese control) N = 22	Group IV (Obese PCOS) N = 22	P-Value
	Mean ± SEM	Mean ± SEM		Mean ± SEM	Mean ± SEM	
BMI (kg/m^2)	25.09 ± 0.8498	23.97± 0.7679	NS	35.39 ± 1.065	39.54 ± 1.946	NS
Age (years)	26.7 ± 1.359	24.45±0.777	NS	27.14 ± 1.384	25.13 ± 1.202	NS
FBG (mg/dl)	92.26 ± 2.769	107.9 ± 3.021	^{a}p<0.0001***	94.32 ± 2.629	112.3 ± 2.141	^{b}p < 0.0001 ***
Fasting Insulin (uIU/ml)	8.739 ± 0.6072	15.57 ± 1.312	^{a}p<0.0001***	10.49 ± 1.027	19.94 ± 1.313	^{b}p < 0.0001 ***
HOMA-IR	2.018 ± 0.1678	4.145 ±0.3716	^{a}p<0.0001***	2.404 ± 0.2372	5.493 ± 0.356	^{b}p < 0.0001 ***
Total cholesterol (mg/dl)	140.7 ± 6.283	172.6 ± 172.6	^{a}p<0.0001***	226.5 ± 7.246	272.8 ± 11.59	^{b}p < 0.0001 ***
TG (mg/dl)	86.93 ± 3.974	129.6 ± 4.062	^{a}p<0.0001***	131.2 ± 7.256	184.6 ± 6.301	^{b}p < 0.0001 ***
HDL-C (mg/dl)	62.14 ± 1.847	39.93 ± 0.758	^{a}p<0.0001***	32.86 ± 0.9391	25.76 ± 1.086	^{b}p < 0.0001 ***
LDL-C (mg/dl)	61.17 ± 4.357	106.7 ± 5.305	^{a}p<0.0001***	167.4 ± 6.125	210.1 ± 9.697	^{b}p < 0.0001 ***
LH (mIU/ml)	4.326 ± 0.2194	13.35 ± 0.456	^{a}p<0.0001***	4.995 ± 0.1819	13.81 ± 0.3938	^{b}p<0.0001***
FSH (mIU/ml)	8.413 ± 0.3706	8.736± 0.372	NS	8.786 ± 0.3842	8.491 ± 0.3531	NS
Progesterone (ng/ml)	0.9413 ± 0.0399	0.937 ± 0.049	NS	0.9159 ± 0.04039	0.9691 ± 0.0428	NS
Total Testosterone (pg/ml)	0.2583 ± 0.019	0.622 ± 0.046	^{a}p<0.0001***	0.260 ± 0.0215	0.6343 ± 0.0399	^{b}p<0.0001***
Serum AMH (ng/ml)	4.420 ± 0.1074	13.84 ± 0.621	^{a}p<0.0001***	4.423 ± 0.1721	14.35 ± 0.6179	^{b}p<0.0001***
Omentin-1 (ng/ml)	24.13 ± 0.270	19.47 ± 0.384	^{a}p<0.0001***	19.88 ± 0.326	14.94 ± 0.287	^{b}p<0.0001***
Apelin (ng/ml)	1.01 ± 0.024	1.46 ± 0.081	^{a}p<0.0001***	1.37 ± 0.072	2.04 ± 0.104	^{b}p<0.0001***

BMI: body mass index FBG: fasting blood glucose HOMA-IR: homeostasis model assessment-insulin resistance, TG: triglyceride, HDL-C: High-density lipoprotein-cholesterol, LDL-C: low density lipoprotein-cholesterol, LH: luteinizing hormone, FSH: follicular stimulating hormone, AMH: anti-Mullerian hormone. Data represented as Mean ± SEM: standard error, NS: non-significant (P-Value > 0.05), ***P < 0.0001: Statistically Significant. ^{a}p < 0.0001 group II versus group I, ^{b}p < 0.0001 group IV versus group III

Table 2: Comparison between statistics of the clinical, biochemical and hormonal data of PCOS groups

Parameter	Group II (Non-Obese PCOS) N = 22	Group IV (Obese PCOS) N = 22	P-Value
	Mean ± SEM	Mean ± SEM	
BMI (kg/m^2)	23.97 ± 0.7679	39.54 ± 1.946	P< 0.0001***
FBG (mg/dl)	107.9 ± 3.021	112.3 ± 2.14	NS
Fasting Insulin (uIU/ml)	15.57 ± 1.312	19.94 ± 1.313	p 0.0234*
HOMA-IR	4.145 ± 0.3716	5.493 ± 0.356	p 0.0121*
Total cholesterol (mg/dl)	172.6 ± 172.6	272.8 ± 11.59	P< 0.0001***
TG (mg/dl)	129.6 ± 4.062	184.6 ± 6.301	p< 0.0001***
HDL-C (mg/dl)	39.93 ± 0.758	25.76 ± 1.086	p< 0.0001***
LDL-C (mg/dl)	106.7 ± 5.305	210.1 ± 9.697	p< 0.0001***
LH (mIU/ml)	13.35 ± 0.456	13.81 ± 0.3938	NS
FSH (mIU/ml)	8.736± 0.372	8.491 ± 0.3531	NS
Progesterone (ng/ml)	0.937 ± 0.049	0.9691 ± 0.0428	NS
Total Testosterone (pg/ml)	0.622 ± 0.046	0.6343 ± 0.0399	NS
Serum AMH (ng/ml)	13.84 ± 0.621	14.35 ±0.6179	NS
Omentin-1 (ng/ml)	19.47 ± 0.384	14.94 ± 0.287	p< 0.0001***
Apelin (ng/ml)	1.46 ± 0.081	2.04 ± 0.104	p< 0.0001***

BMI: body mass index FBG: fasting blood glucose HOMA-IR: homeostasis model assessment-insulin resistance, TG: triglyceride, HDL-C: High-density lipoprotein-cholesterol, LDL-C: low density lipoprotein-cholesterol, LH: luteinizing hormone, FSH: follicular stimulating hormone, AMH: anti-Mullerian hormone. Data represented as Mean ± SEM: standard error, NS: non- significant (P-Value > 0.05), *P < 0.05: Statistically Significant, ***P < 0.0001: Statistically Significant

Table 3: Comparison between statistics of PCOS groups and control groups regarding Omentin-1 and Apelin

Parameter	Control groups N = 44	PCOS groups N = 44	P-Value
	Mean ± SEM	Mean ± SEM	
Omentin-1 (ng/ml)	22.05 ± 0.382	17.15 ± 0.415	p < 0.0001***
Apelin (ng/ml)	1.19 ± 0.046	1.75 ± 0.079	p <0.0001***

***P < 0.0001: Statistically Significant

Table 4: Correlations between serum Omentin-1 and other data of PCOS groups (group II and group IV)

Correlation of Omentin-1 with	Group II		Group IV	
	r	P- value	r	P-value
BMI (Kg/m^2)	0.9537***	P < 0.0001	-0.7837***	P < 0.0001
FBG (mg/dl)	-0.9253***	P < 0.0001	-0.9675***	P < 0.0001
Fasting Insulin (uIU/ml)	-0.8617***	P < 0.0001	-0.9006***	P < 0.0001
HOMA-IR	-0.9028***	P < 0.0001	-0.8976***	P < 0.0001
Total cholesterol (mg/dl)	-0.9094***	P < 0.0001	-0.9080***	P < 0.0001
TG (mg/dl)	-0.9190***	P < 0.0001	-0.9211***	P < 0.0001
HDL-C (mg/dl)	0.4333***	P < 0.0001	0.9790***	P < 0.0001
LH (mIU/ml)	-0.04452	P >0.05(0.8440)	-0.2367	P >0.05(0.2768)
FSH (mIU/ml)	-0.2786	P >0.05(0.2094)	-0.09380	P >0.05(0.6703)
Progesterone (ng/ml)	0.01707	P >0.05(0.9399)	0.03468	P >0.05(0. 8752)
Total Testosterone (pg/ml)	-0.9408	P < 0.0001	-0.9615	P < 0.0001
AMH (ng/ml)	-0.9637***	P < 0.0001	-0.9665***	P < 0.0001

BMI: body mass index FBG: fasting blood glucose HOMA-IR: homeostasis model assessment-insulin resistance, TG: triglyceride, HDL-C: High-density lipoprotein-cholesterol, LH: luteinizing hormone, FSH: follicular stimulating hormone, AMH: anti-Mullerian hormone. Data represented as Mean ± SEM: standard error, *** Correlation is significant at P <0.0001.

Table 5: Correlations between serum Apelin and other data of PCOS groups (group II and group IV)

Correlation of Apelin with	Group II		Group IV	
	r	P- value	r	P-value
BMI (Kg/m^2)	0.9557***	P < 0.0001	0.7457***	P < 0.0001
FBG (mg/dl)	0.9465***	P < 0.0001	0.9294***	P < 0.0001
Fasting Insulin (uIU/ml)	0.8778***	P < 0.0001	0.8627***	P < 0.0001
HOMA-IR	0.9072***	P < 0.0001	0.8553***	P < 0.0001
Total cholesterol (mg/dl)	0.8708***	P < 0.0001	0.9471***	P < 0.0001
TG (mg/dl)	0.9920***	P < 0.0001	0.9505***	P < 0.0001
HDL-C (mg/dl)	-0.8843***	P < 0.0001	-0.9219***	P < 0.0001
LH (mIU/ml)	-0.304	0.1688	-0.0619	0.779
FSH (mIU/ml)	0.1245	0.5809	-0.198	0.3651
Progesterone (ng/ml)	-0.2811	0.2051	-0.1023	0.6425
Total Testosterone (pg/ml)	-0.1935	0.3882	-0.1742	0.4268
AMH (ng/ml)	-0.374	0.0864	-0.2889	0.1812

BMI: body mass index FBG: fasting blood glucose HOMA-IR: homeostasis model assessment-insulin resistance, TG: triglyceride, HDL-C: High-density lipoprotein-cholesterol, LH: luteinizing hormone, FSH: follicular stimulating hormone, AMH: anti-Mullerian hormone. Data represented as Mean ± SEM: standard error, *** Correlation is significant at P <0.0001.

Table 6: Characters of Receiver operating characteristics (ROC) curve for Omentin-1 levels in the diagnosis of PCOS in non- obese women

Variable	Cutoff	Sensitivity	Specificity	PPV	NPV
Omentin-1	<21.8	100%	100%	100%	100%

.PPV: positive predictive value, NPV: negative predictive value

Table 7: Characters of Receiver operating characteristics (ROC) curve for Omentin-1 levels in the diagnosis of PCOS in obese women.

Variable	Cutoff	Sensitivity	Specificity	PPV	NPV
Omentin-1	<17.45	100%	95.45%	95.83%	100%

PPV: positive predictive value, NPV: negative predictive value

Table 8: Characters of Receiver operating characteristics (ROC) curve for Apelin levels in the diagnosis of PCOS in non-obese women.

Variable	Cutoff	Sensitivity	Specificity	PPV	NPV
Apelin	>1.050	90.91%	65.22%	71.43%	%88.24

PPV: positive predictive value, NPV: negative predictive value.

Table 9: Characters of Receiver operating characteristics (ROC) curve for Apelin levels in the diagnosis of PCOS in obese women.

Variable	Cutoff	Sensitivity	Specificity	PPV	NPV
Apelin	>1.450	95.65%	68.18%	75.86%	93.75%

PPV: positive predictive value, NPV: negative predictive value

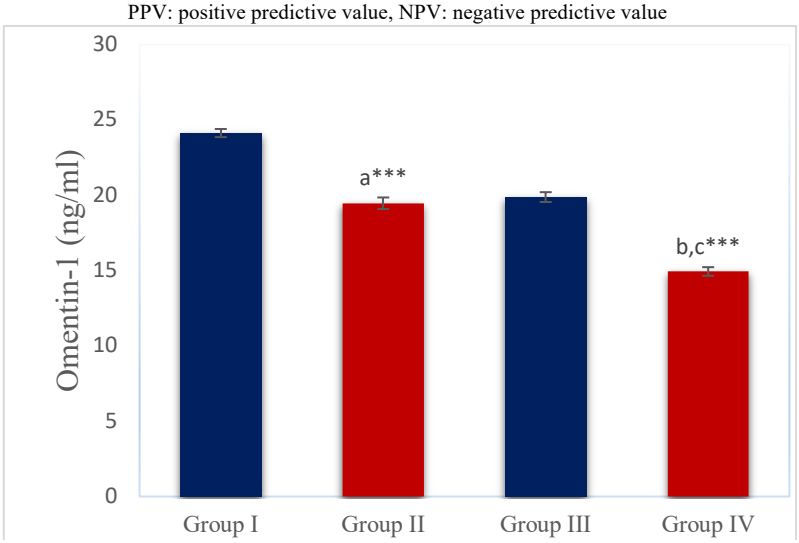

Figure 1: Mean ± SEM of Omentin-1 of all studied groups

***P < 0.0001: Statistically Significant, [a]p < 0.0001 group II versus group I, [b]p < 0.0001 group IV versus group III, [c]p < 0.0001 group IV versus group II

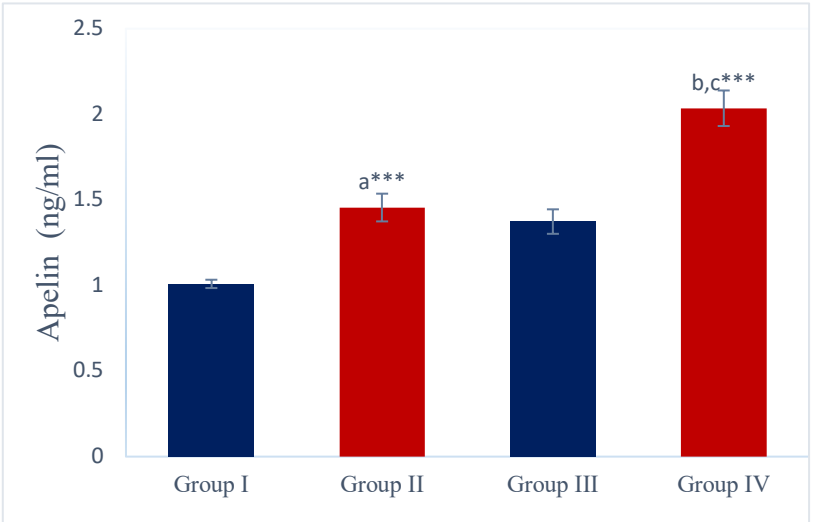

Figure 2: Mean ± SEM of Apelin of all studied groups

***P < 0.0001: Statistically Significant, [a]p < 0.0001 group II versus group I, [b]p < 0.0001 group IV versus group III, [c]p < 0.0001 group IV versus group II

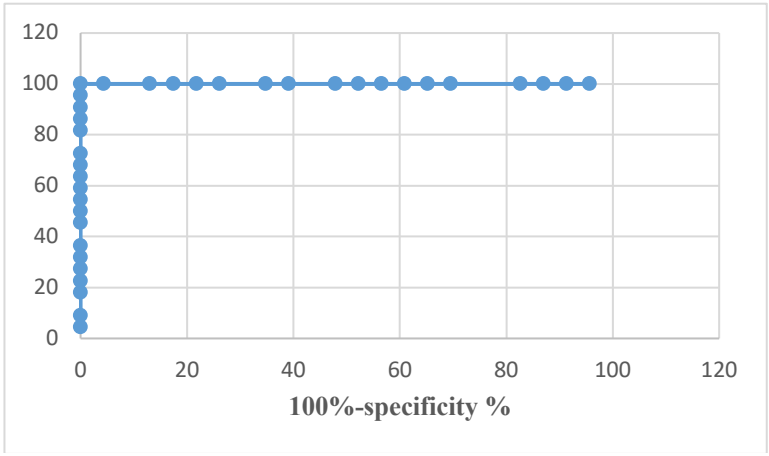

Figure 3: Receiver operating characteristics (ROC) curve for Omentin-1 levels in the diagnosis of PCOS in non-obese women

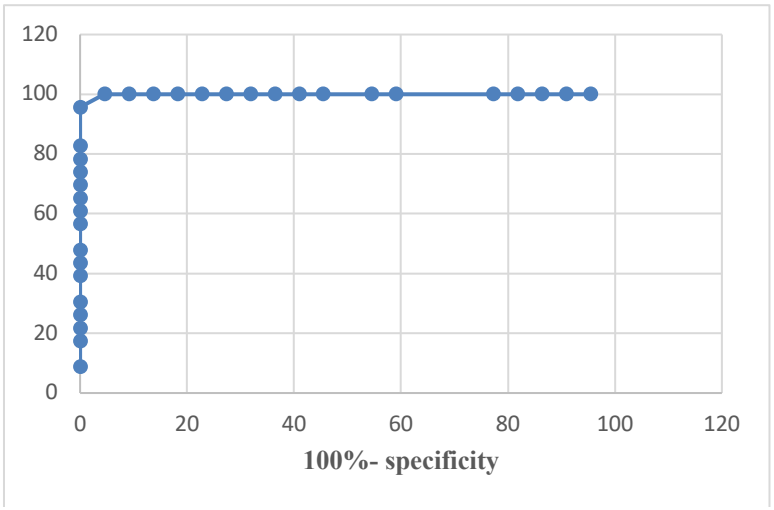

Figure 4: Receiver operating characteristics (ROC) for Omentin-1 levels in the diagnosis of PCOS in obese women

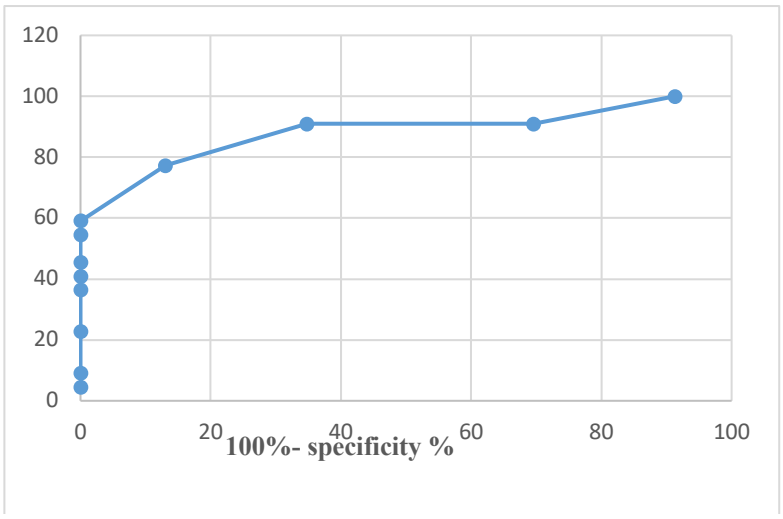

Figure 5: Receiver operating characteristics (ROC) curve for Apelin levels in the diagnosis of PCOS in non- obese women

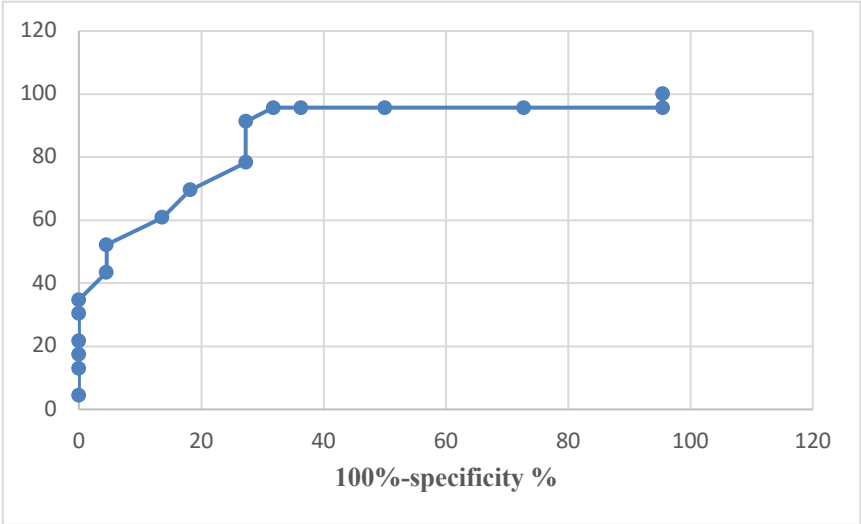

Figure 6: Receiver operating characteristics (ROC) curve for Apelin levels in the diagnosis of PCOS in obese women

DISCUSSION

Regarding insulin resistance assessment this study showed statistically significant higher levels of fasting plasma glucose, fasting insulin and HOMA-IR in non-obese and obese patients when compared with non-obese and obese control subjects respectively. These results are in agreeing with Foda *et al*. and Zhang *et al*.[3,15]. Kyrou *et al*. suggested that this insulin resistance and hyperinsulinemia noticed in PCOS subjects was resulted from over consumption of carbohydrate diet. Many mechanisms have been proposed for the development of IR in PCOS[16]. The main one is a post-binding defect in insulin signaling due to increased serine phosphorylation and decreased tyrosine phosphorylation of insulin receptor[17]. Approximately 90% of obese women with PCOS and 45% of lean women with PCOS have IR[18]. Also, results of a meta-analysis by Rashidi *et al*. Showed that the metabolic and reproductive outcomes in women with PCOS and obese were worsen compared to group with normal weight[19].

Regarding lipid profile, this study showed statistically significant increases in the mean serum levels of total cholesterol (TC), triglycerides (TAG) and low density lipoprotein-cholesterol (LDL-C) but statistically significant decreases in the mean serum levels of high density lipoprotein-cholesterol (HDL-C) in PCOS-obese and PCOS non-obese patients when compared to obese and non-obese controls respectively. PCOS groups showed significant increase in TC, TAG, LDL-C and significant decrease in HDL-C in obese women when compared to the non-obese women, similar results were found in studies done by Foda *et al*[3]. These results agreed with Rashidi *et al*. stated that dyslipidemia pattern in insulin resistance, low levels of HDL and high triglyceride levels pattern are common in women with polycystic ovary syndrome[19]. Agarwal *et al*. suggested that hyperinsulinemia in PCOS may also contribute to the development of dyslipidemia in PCOS patients[20].

Regarding the hormonal profile the present results revealed significant increases in serum LH and total testosterone levels and no significant differences in serum FSH and progesterone levels between PCOS patients compared with control subjects. These results are in agreeing with Hasan and El Hameed, Sun *et al*. and El Omda *et al*.[10,21,22]. Coutinho and Kauffman reported that in the polycystic ovary syndrome LH pulse frequency and amplitude are higher throughout the menstrual cycle in comparison to that observed in healthy women[23]. Spritzer reported that insulin resistance (and compensatory hyperinsulinemia) is an important factor in maintaining hyperandrogenemia by acting directly on theca cells inducing excess androgen production[24]. In this study women with PCOS have higher levels of (AMH) compared with healthy subjects, this result is in agreeing with Liu *et al* and Stracquadanio *et al*. who proposed that serum AMH levels are elevated in patients with PCOS due to increased number of small follicles and an increased secretion within each of these small follicles[25,26].

This study revealed that circulating levels of Omentin-1 show significant decrease in PCOS patients when compared with controls. PCOS groups showed a statistically significant decreased level of Omentin-1 in obese women when compared to the non-obese women. These results are in agreeing with Anagnostis *et al*. Özgen *et al*.[17,18]. Our results show negative correlation between Omentin-1 and HOMA-IR in PCOS groups. Yang's *et al*. study on 153 non obese PCOS patients and 114 aged matched non-obese control and concluded that plasma Omentin-1 concentrations were decreased in the non-obese PCOS group[27]. Insulin resistance could further decrease plasma Omentin-1 in non-obese individuals with PCOS independent of BMI status. Ten articles with 13 studies were included in the meta-analysis of Tang *et al*. which included a total of 1264 subjects (733 patients with PCOS and 531 controls)[28]. The results of this meta-analysis revealed that circulating Omentin-1 levels are significantly lower in women with PCOS compared with normal subjects, which indicated that Omentin-1 may play a role in the pathologic processes of PCOS[28]. Shankar *et al*. found that insulin suppressed Omentin levels[29]. Also they demonstrated that insulin is a potential driver for Omentin regulation under conditions where glucose is stable[29]. Abd-Elbaky *et al*. stated that obesity leads to down regulation of anti-inflammatory factors, such as Omentin, decreased serum Omentin levels observed in obese humans might cause a reduction of insulin-stimulated glucose uptake in visceral and subcutaneous adipocytes and contributing, at least partially, to insulin resistance[30]. All these previous studies showed that the decrease in omentin-1 in patients with PCOS may be a consequence of hyperandrogenism. Moreover, given that this adipokine acts as an insulin-sensitizing agent, low omentin-1 may contribute to IR in patients with PCOS, and a vicious cycle may develop[18]. Shorakae *et al*. reported that Omentin-1 is significantly lower in women with PCOS and correlates significantly with BMI, percentage of body fat, insulin, low density lipoprotein (LDL), triglycerides and total ovarian volume in women with PCOS[31].

Apelin level is related to the occurrence of obesity and IR. There is little data in the literature regarding changes in Apelin level or its relation to PCOS and even the existing published results are in consistent[20]. Altinkaya *et al*. suggested that serum Apelin levels are lower in women with PCOS than in controls[32]. However, BenkSilfeler *et al*. concluded that serum Apelin levels in lean PCOS patients were not significantly different from the control subjects[33]. In the current study, however, serum Apelin levels are significantly higher in PCOS women compared with controls. Moreover, we also observed that Apelin level is significantly and positively correlated with BMI and HOMA-IR. These results are consistent with a previous studies of Sun *et al*. and Cekmez *et al*.[21,34]. Cekmez *et al*. suggested that Apelin level could be used as specific markers for insulin sensitivity and these adipokines may contribute to the pathogenesis of PCOS[34]. Sun *et al*. suggested that Apelin level reduction can reduce the risk of dyslipidemia and IR associated with PCOS[21]. Discrepant findings among the published studies may be attributed to the differences in ethnicity, age, study design, sample size, genetic characteristics of populations, assessment methodology and defining PCOS definitions[2,8]. Hasan and Abd El Hameed concluded that higher serum Apelin levels were found in obese compared to lean PCOS patients. Positive correlations were found between Apelin and BMI, fasting insulin level and HOMA-IR in both obese and lean PCOS subjects[10]. The synthesis of Apelin in adipocytes is triggered by insulin and its plasma levels are reported to increase in association with insulin resistance and hyperinsulinemia[35].

CONCLUSION

The present study showed a significant decrease in serum levels of Omentin-1 and increase in serum levels of Apelinin (non-obese and obese) PCOS groups when compared to their controls. There is a significant negative correlation between Omentin-1 and obesity in women with PCOS, while there is a significant positive correlation between Apelin and obesity in women with PCOS. Additional large-scale studies should be conducted on patients with polycystic ovary syndrome to assess the disease progression relative to insulin resistance, obesity, Omentin-1 and Apelin.

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