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ORIGINAL ARTICLE

SERUM ADIPONECTIN IN WOMEN WITH POLYCYSTIC OVARY SYNDROME

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Abstract:

Background: *An imbalance of different adipocytokines may play a role in the pathogenesis of PCOS. This study aimed to observe the association and diagnostic utility of adiponectinin PCOS and its manifestations.* **Methods:** *This cross-sectional study included 40 newly diagnosed females of reproductive age (18-40 years) with PCOS on the basis of international evidence-based guidelines and an equal number of matched healthy control. Along with clinical information, blood was drawn for biochemical and hormonal analysis. Glucose was measured by glucose oxidase, lipid by glycerol phosphate dehydrogenase peroxidase, all hormones by CMIA, and adiponectin by ELISA method. Insulin resistance was measured by homeostasis model assessment (HOMA-IR) and defined with a cut-off of 2.6.* **Results:***Patients with PCOS had lower serum adiponectin than controls without significant differences even irrespective of body mass index status(ns for all). Adiponectin levels had no significant associations or correlations with any manifestations among patients with PCOS (ns for all). ROC curve analysis showed that serum adiponectin could not be used as a marker of PCOS. It was a poor marker of both metabolic syndrome [AUC (95% CI): 0.64 (0.46-0.81] and insulin resistance [AUC (95% CI): 0.61 (0.44-0.79)] in patients with PCOS.***Conclusion:** *Our study failed to find any significant association between adiponectin and PCOS and its characteristics. Serum adiponectin could not be used as a marker of PCOS. It was a poor marker of insulin resistance and metabolic syndrome among patients with PCOS.*

Keywords: *Polycystic ovary syndrome, Adiponectin, Insulin resistance, Metabolic syndrome.*

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Introduction:

Polycystic ovary syndrome (PCOS) is one of the most common reproductive endocrinopathies in females with unknown pathophysiology. Recently it is thought that the condition originates during fetal life (developmental origin) in genetically susceptible persons and several maladaptive postnatal adaptations occur in response to exposure to the modern environment (evolutionary hypothesis).[1] These maladaptations include the cardinal features of PCOS (hyperandrogenism and insulin resistance) as a result of escape from the accumulation of excess hepato-visceral fat.[2] This proinflammatory central fat mediates its effects by producing an imbalance in several adipocytokines production with modulation in ovarian and adrenal tissue steroidogenesis.[3]On the other hand, these adipocytokines also contribute to insulin resistance and compensatory hyperinsulinemia, and stimulation of androgen production. Thus a vicious cycle is produced by the

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visceral fat and androgen-producing glands that maintain the condition.[4]So, the role of adipocytokines in the pathogenesis of PCOS is very important.

Adiponectin is the most abundant adipokineand is also produced from other tissues. It hasseveral circulating molecular weight forms with different tissue-specific efficacy. It directly acts in different metabolic tissues including the liver, skeletal muscles, vasculature, etc. mediated by its receptors.[5] It has a protective role against insulin resistance, inflammation, atherogenesis, etc. This 'guardian angel' cytokine is thus reduced in these conditions.[6] Hence, the replacement of this adipokine in diseases with these conditions such as obesity, diabetes mellitus, and cardiovascular (CV) diseases is a potential therapeutic target.[7] PCOS is also a metabolic disorder and transplantation of brown adipose tissue as well as replacement of adiponectin ameliorate PCOS too.[8]

PCOS is a heterogeneous disorder with higher metabolic as well as androgenic features in patients from South-Asian backgrounds.[9]However, the association between PCOS and adiponectin is not well documented in this region. Besides, the association between adiponectin with different manifestations of PCOS along with its diagnostic role is not adequately reported in the literature. We aimed to assess the association and diagnostic role of adiponectin with PCOS as well as its manifestations.

Methods:

This cross-sectional study was done in the Endocrinology department of a University hospital during the period from March 2019 to September 2020. The study protocol was approved by the institutional review board of the University. Informed consent was taken from each participant. The sample size was calculated from the following formula: $n= \{(Z_\alpha+ Z_\beta)^2 \times (\sigma_1^2 + \sigma_2^2)\} \div (\mu_1 - \mu_2)^2$. At a 95% confidence interval (Z_α=1.96), 95% power (Z_β=1.64), and taking the mean±SD from a previous study the minimum sample size was 37.[10] We included 40 females with PCOS and an equal number of matched healthy control.

Newly diagnosed adult females of reproductive age (18-40 years) with PCOS on the basis of international evidence-based guidelines were enrolled consecutively by purposive sampling.[11] Participants having a regular menstrual cycle and insignificant hirsutism were enrolled as control. Participants having similar endocrine disorders, systemic disorders, or a history of taking hormonal contraceptives, antiandrogens, insulin sensitizers, ovulation-inducing drugs, anti-lipid, or antiobesitywithin 3 months of enrollment were excluded. Each participant was asked about their reproductive history (menstrual cycle, subfertility, menstrual regulation/ abortion). Height (cm), weight (kg), waist circumference (WC, cm), hip circumference (HC, cm), blood pressure (BP, mm-Hg), hirsutism by modified Ferriman-Gallwey (mFG) score were measured, and the presence of acne and acanthosis nigricans were noted. Body mass index (BMI, kg/m^2), waist/hip ratio (WHR), and waist/height ratio (WHtR) were calculated. A BMI ≥25 kg/m^2 was taken as obesity.[12] A mFG score ≥6 was considered significant hirsutism.[11]Venous blood was collected in a fasting state and during the follicular phase of the menstrual cycle (days: 2 – 5) to measure glucose (fasting plasma glucose, FPG), lipid profile (total cholesterol, TC; HDL-cholesterol; triglyceride, and LDL-cholesterol from Friedwald formula), insulin, total testosterone (TT), sex hormone binding globulin (SHBG), dehydroepiandrosterone sulfate (DHEAS), luteinizing hormone (LH), follicle-stimulating hormone (FSH), and adiponectin levels. An oral glucose tolerance test (OGTT) was done to measure glucose (2H-OGTT). Free androgen index was calculated [FAI= (TT in nmol/L÷SHBG in nmol/L)×100%] and a FAI e"5% was considered hyperandrogenemia.[13] Insulin resistance was measured by homeostasis model assessment [HOMA-IR=(fasting insulin in μIU/mL × FPG in mmol/L)÷22.5, and a HOMA-IR ≥2.6 was considered insulin resistance (IR).[14]A LH/FSH ratio (LFR) >2 was taken as an altered ratio.[15] Abnormal glycemic status was defined by the presence of at least impaired fasting glucose (IFG ≥5.6 mmol/L) &/or impaired glucose tolerance (IGT ≥7.8 mmol/L).[16] Metabolic syndrome (MS) was diagnosed by the presence of at least any 3 out of 5 components.[17]Ultrasonography of the ovaries was done during the follicular phase of the menstrual cycle for the presence of polycystic ovarian morphology (PCOM).

Glucose was measured by glucose oxidase, lipid by glycerol phosphate dehydrogenase peroxidase, and all hormones including SHBG by chemiluminescence microparticle immunoassay method. The adiponectin samples were measured using ACRP30 ELISA kit, a nonradioactive quantification of Human Adiponectin (DRG International Inc., USA) with the analytical sensitivity of 0.493 ng/mL, intra-assay coefficient of variation (CV) of 2.8% – 3.9%, and inter-assay CV of 5.9% – 6.4%.

Data were analyzed using SPSS software version 25.0. Qualitative data were expressed in frequency (%), and quantitative data were expressed in mean±SD or median (IQR) depending on their distribution. A comparison between the two groups was done by independent samples t-test or Mann-Whitney U test

for medians and distribution. A comparison among more than two groups was analyzed by Kruskal-Wallis one-way ANOVA for medians and distribution. The correlations between adiponectin with clinical and laboratory variables were done by Spearman's correlation test. A receiver operating characteristics (ROC) curve analysis was done to see adiponectin as a marker of PCOS, and a marker of MS and IR in patients with PCOS. Statistical significance was set with a two-tailed p-value below 0.05.

Results:

The characteristics of the study population showed that patients with PCOS had significantly poor metabolic features (higher BMI, WC, WHR, WHtR, SBP, DBP, 2H-OGTT, TC, LDL-C, fasting insulin, but lower HDL-C), higher androgenic features (higher TT, DHEA-S, but lower SHBG), and higher LFR than controls. Age, FPG, and triglyceride were statistically similar among the study groups (Table-1).

Table-I

Characteristics of the study population (n=80)

Variables	PCOS (n=40)	Control (n=40)	p
Age, years	23.0	24.5	0.654*
	(20.0-29.8)	(21.0-29.0)	0.455†
Body mass index, kg/m^2	29.0±5.7	22.8±3.1	<0.001‡
Waist circumference, cm	92.1±13.1	77.9±8.9	<0.001‡
Waist/hip ratio	0.91	0.87	0.014*
	(0.85-0.93)	(0.82-0.89)	0.001†
Waist/height ratio	0.6±0.1	0.5±0.1	<0.001‡
Systolic blood pressure, mm-Hg	120.0	110.0	0.002*
	(100.0-120.0)	(100.0-110.0)	0.005†
Diastolic blood pressure, mm-Hg	80.0	67.5	<0.001*
	(70.0-85.0)	(60.0-70.0)	<0.001†
Serum luteinizing hormone/ follicle-stimulating hormone ratio	2.0	1.1	0.001*
	(1.1-2.6)	(0.7-1.5)	<0.001†
Serum total testosterone, ng/ml	4.6	2.0	<0.001*
	(3.1-9.8)	(1.7-2.6)	<0.001†
Serum sex hormone binding globulin, nmol/L	10.4	37.1	<0.001*
	(8.1-20.7)	(24.4-66.1)	<0.001†
Serum dehydroepiandrosterone sulfate, µgm/dL	233.1±121.3	157.0±76.3	<0.001‡
Fasting plasma glucose, mmol/L	5.0	5.2	0.370*
	(4.8-5.5)	(4.8-5.5)	0.582†
2 hours after OGTT glucose, mmol/L	7.5	6.9	0.014*
	(6.2-8.7)	(6.1-7.2)	0.016†
Serum total cholesterol, mg/dL	188.5	165.5	0.074*
	(172.5-210.8)	(149.5-187.5)	0.002†
Serum HDL-cholesterol, mg/dL	46.0	42.0	0.074*
	(40.3-52.5)	(35.8-47.8)	0.019†
Serum LDL-cholesterol, mg/dL	119.5	99.0	0.044*
	(102.3-135.5)	(89.8-121.3)	0.003†
Serum triglyceride, mg/dL	131.3±53.4	117.0±59.7	0.264‡
Fasting plasma insulin, µIU/mL	11.4	8.4	<0.001*
	(10.0-22.7)	(6.3-10.1)	<0.001†

Mann-Whitney U test for medians* and distribution†, and independent samples t-test were done

Patients with PCOS had lower serum adiponectin than controls without significant differences [PCOS vs. control: 6.8 (4.9-10.2) vs. 7.0 (5.1-8.6), µgm/mL, median (IQR), p=0.823 (medians), p-0.969 (distributions)]. Similarly, they had also higher percentages of low adiponectin levels (<4 µgm/mL), again without significant differences (17.5% vs. 5.0%, p=0.154) with control participants (Figure-1). There were no significant differences in serum adiponectin levels (µgm/mL) when the study groups were compared considering BMI subgroups also [PCOS vs. control- nonobese (<25 kg/m^2): 6.7 (5.0-9.5) vs. 7.2 (5.7-8.7), p=0.785; obese (25 kg/m^2): 6.8 (4.4-10.4) vs. 4.7 (4.4-8.7), p=0.541, median (IQR)].

Serum adiponectin levels were compared between groups of different characteristic features of PCOS. None of the variables had any significant associations with adiponectin in patients with PCOS (Table-II).

Table-II

Serum adiponectin levels with different characteristics in patients with PCOS (n=40)

Variables	Groups	No.	S. adiponectin, µg/mL	p
Menstrual cycle	Irregular	35	7.4 (5.0-10.3)	0.4680.092
	Regular	5	4.0 (3.1-11.5)	
Subfertility	Present	10	4.6 (3.5-9.5)	0.7150.109
	Absent	30	7.3 (5.4-10.4)	
Menstrual regulation/ abortion	Present	7	5.9 (3.8-7.7)	0.4050.293
	Absent	33	7.4 (4.9-10.7)	
Hirsutism	Significant (≥8)	39	7.2 (4.9-10.3)	1.0000.473
(Modified Ferriman-Gallwey score)	Insignificant (<8)	1	5.0	
Acne	Present	23	7.7 (5.0-11.5)	0.5220.107
	Absent	17	5.9 (3.9-8.9)	
Acanthosis nigricans	Present	28	8.0 (5.1-10.5)	0.3010.122
	Absent	12	5.3 (3.3-7.9)	
Body mass index(Kg/m^2)	Obese (≥25)	30	6.8 (4.4-10.4)	0.7151.000
	Nonobese (<25)	10	6.7 (5.0-9.5)	
Androgenemia	Hyperandrogenemia (≥5.0)	30	6.8 (4.8-10.5)	0.7151.000
(Free androgen index, %)	Normoandrogenemia (<5.0)	10	6.8 (4.5-10.2)	
Polycystic ovarian morphology	Present	32	6.8 (4.9-10.5)	0.6930.561
	Absent	8	7.1 (1.9-9.7)	
LH/FSH ratio	Altered (>2.0)	21	6.4 (4.5-9.5)	0.4270.569
	Normal (≤2.0)	19	7.9 (5.0-10.6)	
Glycemic status	Abnormal	24	7.6 (5.0-10.9)	0.3330.331
(FPG ≥5.6 &/or 2H-OGTT≥7.8 mmol/L)	Normal	16	6.0 (4.6-8.9)	
Insulin resistance (HOMA-IR)	Present (≥2.6)		10	6.0 (4.6-8.8)
0.3430.221				
	Absent (<2.6)	20	8.2 (4.9-11.2)	
Metabolic syndrome	Present (≥3/5)	18	5.9 (4.3-8.9)	0.3400.147
(No. of component)	Absent (<3/5)	22	7.8 (5.0-11.1)	
Phenotypes	A	27	7.4 (5.5-10.6)	0.3500.137
	B	8	7.1 (1.9-9.7)	
	C	5	4.0 (3.1-11.5)	

LH (Luteinizing hormone); FSH (follicle-stimulating hormone); FPG (fasting plasma glucose); OGTT (oral glucose tolerance test)

Mann-Whitney U test or Kruskal Wallis test for medians and distributions were done

The correlations between serum adiponectin with different clinical and laboratory variables are shown in Table-III. There were no significant correlations between serum adiponectin with any of the studied variables (ns for all).

ROC curve analysis showed that serum adiponectin could not be used as a marker of PCOS [area under the curve, AUC (95% confidence interval, CI): 0.50 (0.37-0.63); standard error, SE: 0.07; p=0.969). It was a poor marker of both metabolic syndrome [AUC (95% CI): 0.64 (0.46-0.81; SE: 0.09, p=0.142] and insulin resistance [AUC (95% CI): 0.61 (0.44-0.79); SE: 0.09; p=0.218] in patients with PCOS (Figure-2 and Figure-III).

Table-III

Correlation of Serum adiponectin with clinical and laboratory variables in patients with PCOS (n=40)

Determinants of 'ρ'	ρ	p
Age, years	-0.3	0.079
Body mass index, kg/m^2	-0.1	0.850
Waist circumference, cm	-0.3	0.120
Waist/hip ratio	-0.1	0.904
Waist/height ratio	-0.2	0.144
Systolic blood pressure, mm-Hg	-0.1	0.434
Diastolic blood pressure, mm-Hg	-0.1	0.629
Modified Ferriman-Gallwey score	0.1	0.505
LH/FSH ratio	0.1	0.435
S. total testosterone, ng/mL	-0.1	0.382
S. sex hormone binding globulin, nmol/L	-0.1	0.382
S. dehydroepiandrosterone, µgm/dL	-0.1	0.786
Fasting P. glucose, mmol/L	-0.2	0.294
2-hours after OGTT glucose, mmo/L	-0.1	0.440
S. total cholesterol, mg/dL	-0.1	0.623
S. HDL-cholesterol, mg/dL	0.1	0.702
S. LDL-cholesterol, mg/dL	0.1	0.779
S. triglyceride, mg/dL	-0.2	0.345
S. fasting insulin, µIU/mL	-0.3	0.084

Spearman's correlation test was done

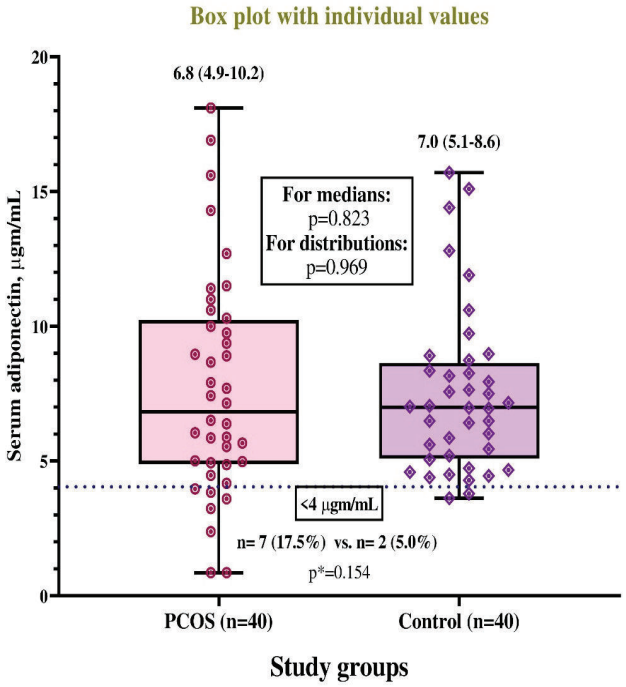

Fig.--1: *Serum adiponectin levels and category in the study population (n=80)*

Mann-Whitney U test (medians and distributions) and *Fisher's exact test were done

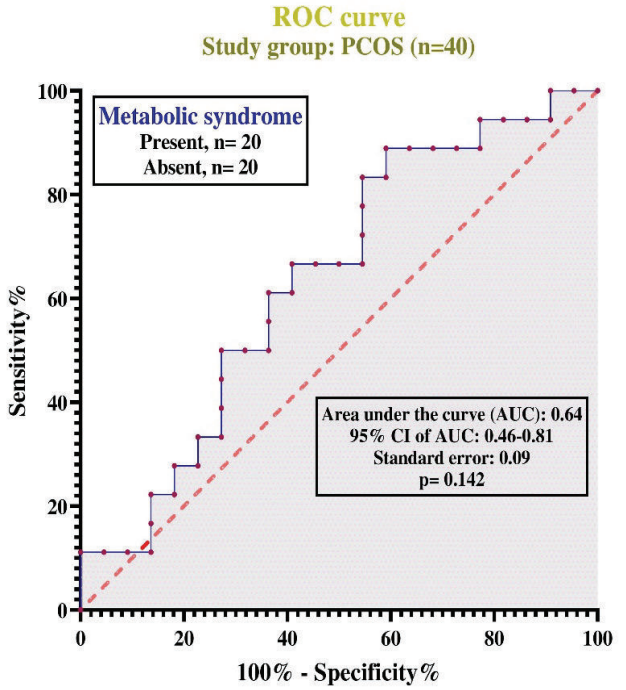

Fig.-2: *Serum adiponectin as a marker of metabolic syndrome in patients with PCOS (n=40)*

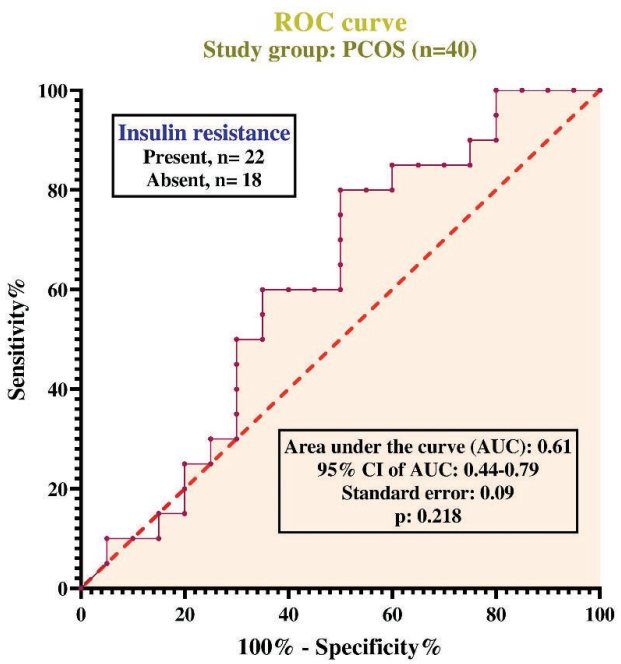

Fig.-3: *Serum adiponectin as a marker of insulin resistance in patients with PCOS (n=40)*

Discussion:

This study failed to show any significant association of serum adiponectin in patients with PCOS or any significant association or correlation with any studied features in patients with PCOS. Furthermore, serum adiponectin could not be used as a marker of PCOS. However, it was a poor marker for metabolic syndrome and insulin resistance in patients with PCOS.

We found a little bit lower but statistically similar levels of adiponectin despite poorer metabolic status in patients with PCOS than in the control group. Our finding is similar to some studies' observations.[18-20]However, systematic reviews and meta-analyses showed lower adiponectin levels irrespective of obesity status in women with PCOS.[21,22] We also found a higher percentage of hypoadiponectinemia(17.5%) in the PCOS group than in the control group but again with an insignificant association. A study conducted among 49 Indian women found 22.0% of patients with PCOS with hypoadiponectinemia. However, this study did not include a control population.[23]

We did not find any significant association between adiponectin and any diagnostic features and phenotypes in patients with PCOS. Several studies and a meta-analysis also found an insignificant association between adiponectin and different androgens including TT.[21,24,25]In contrast, several studies found a significant association between them.[25,26]Karkanaki et al. (2009) found lower adiponectin levels in phenotype A and B than in phenotype D. They hypothesized a negative association of irregular cycle and hyperandrogenism with adiponectin, and no association with PCOM.[26] However, in our study, there were no patients with phenotype D and other phenotypes had similar levels of adiponectin.

We did not find any significant association between adiponectin and any metabolic features including insulin resistance in patients with PCOS. Several studies also found an insignificant association between serum adiponectin and different metabolic features.[18,19,24,28] However, contradictory findings were observed by others.[21,25] Several studies showed that high molecular adiponectin rather than total adiponectin is associated with PCOS and its features.[29,30] Again, an insignificant association was also observed.[31]

Serum adiponectin could not be used as a marker of PCOS in our study.A similar finding was also observed in several studies.[10,32,33] We found adiponectin as a poor marker for IR and MS in women with PCOS. However, the role of adiponectin as a marker of IR and MS remains controversial.[34]

Conclusion:

Our study did not find any significant association between adiponectin and PCOS and its characteristics indicating an insignificant/minor role of adiponectin in the pathogenesis of PCOS. Serum adiponectin could not be used as a marker of PCOS. It was a poor marker of insulin resistance and metabolic syndrome among patients with PCOS.

Limitations:

Small sample size and this single hospital based study did not reflect exact scenario of the whole community. Patients from all socioeconomic status and all parts of the country did not come to seek medical attention in the study place.

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Authors' Contributions:

IAJ, HB, MAH were responsible for conception and design, obtaining funds, data interpretation, manuscript drafting and manuscript editing, and final approval data acquisition, data interpretation and critical revision for important intellectual content conception and design, obtaining funds, data

interpretation, manuscript editing, and final approval. IAJ, MSM, EURC were responsible for data analysis and statistical analysis. IAJ and MAH were responsible manuscript writing and editing. IAJ and MAH were responsible for data collection. All authors have read and approved the final version of the manuscript.

Data Availability:

The datasets analysed during the current study are not publicly available due to the continuation of analyses but are available from the corresponding author on reasonable request.

Conflict of Interest:

The authors stated that there is no conflict of interest in this study

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Ethical consideration:

The study was conducted after approval from the ethical review committee. IRB clearance from BSMMU (No. BSMMU/2019/3865, Date: 11/04/2019). The confidentiality and anonymity of the study participants were maintained

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