Serum Ependymin-Related Protein 1 as a Potential Metabolic Biomarker in Women with Polycystic Ovary Syndrome

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Abstract

Background: Polycystic ovarian syndrome (PCOS) is the most common endocrine and metabolic disorder, characterized by hormonal imbalance, obesity, insulin resistance, and lipid abnormalities. Ependymin-related protein 1 (EPDR1) is a novel protein associated with adipose tissue function and metabolic regulation. This study aimed to measure serum EPDR1 levels in women with PCOS and assess their correlation with metabolic and hormonal parameters.

Methods: This case-control study included 50 women with PCOS and 50 healthy controls. Serum EPDR1 was measured by ELISA. LH, FSH, testosterone, and fasting insulin were measured using the cobas e 411 analyzer, while fasting glucose and lipid profile were measured using the cobas c 111 analyzer. BMI, WHR, LH/FSH ratio, and HOMA-IR were also calculated. Statistical analyses included independent t-tests, Pearson correlation, and ROC curve analysis.

Results: Serum EPDR1 levels were significantly lower in women with PCOS than in controls (155.0 ± 68.0 vs. 245.0 ± 82.0 ng/mL, P<0.001). Women with PCOS had significantly higher BMI, WHR, LH, LH/FSH ratio, testosterone, fasting insulin, HOMA-IR, and most lipid parameters, while HDL-C was lower. EPDR1 was significantly negatively correlated with BMI, WHR, fasting insulin, HOMA-IR, LH/FSH ratio, total cholesterol and LDL-C and positively correlated with HDL-C. ROC analysis showed that EPDR1 had moderate discriminative performance for PCOS (AUC=0.781).

Conclusion: Low serum EPDR1 is associated with PCOS and appears strongly linked to insulin resistance, obesity and metabolic dysregulation. EPDR1 may serve as a promising metabolic biomarker in women with PCOS.

Keywords: *PCOS; EPDR1; Insulin resistance; Obesity; Biomarker.*

1. Introduction

Polycystic ovary syndrome (PCOS) is a common endocrine and metabolic disorder in women of reproductive age, characterized by heterogeneous reproductive and metabolic manifestations [1–3]. Beyond ovulatory dysfunction and hyperandrogenism, PCOS is frequently associated with obesity, insulin resistance, dysglycemia, and lipid abnormalities, which increase the long-term risk of type 2 diabetes and cardiovascular disease [4,5]. Insulin resistance and compensatory hyperinsulinemia are central to this metabolic burden and may also aggravate ovarian androgen production and follicular dysfunction [6,7]. Adipose tissue contributes to PCOS-related metabolic dysfunction through biologically active mediators that influence glucose and lipid metabolism, inflammation, and insulin sensitivity [8–11]. Brown adipose tissue is particularly relevant because of its role in thermogenesis and whole-body energy regulation [12–14]. Ependymin-related protein 1 (EPDR1), a secreted protein identified in human brown adipocytes and plasma, has been proposed as a novel batokine involved in brown adipocyte development and thermogenic activity [15–17]. EPDR1 is also expressed in pancreatic beta cells, where experimental evidence links it to mitochondrial metabolism and glucose-stimulated insulin secretion [18,19]. These findings provide a biological rationale for investigating circulating EPDR1 in a disorder strongly characterized by adiposity and insulin resistance.

Despite this mechanistic relevance, clinical evidence on circulating EPDR1 in women with PCOS remains limited. A recent study reported lower serum EPDR1 concentrations in women with PCOS, particularly among those with obesity or insulin resistance, and identified associations with BMI, HOMA-IR, the LH/FSH ratio, and lipid parameters [20]. However, it remains unclear whether reduced EPDR1 primarily reflects PCOS itself or the accompanying metabolic disturbances, and its potential clinical value has not been sufficiently established. Therefore, the present study aimed to compare serum EPDR1 levels between women with PCOS and healthy controls, examine their relationships with selected anthropometric, metabolic, and hormonal parameters, and assess the discriminatory performance of EPDR1 and related clinical markers using ROC curve analysis.

2. Materials and Methods

2.1 Study Design and Participants

This case-control study included women with polycystic ovary syndrome (PCOS) and apparently healthy women who served as the control group. Women with PCOS were referred to the participating laboratories by specialist gynecologists after clinical evaluation and diagnosis of PCOS. The control group included apparently healthy women without a prior diagnosis of PCOS. Sample collection was

carried out from April to July 2026. Basic information including age, weight, height, waist circumference, and hip circumference was recorded for each participant.

2.2 Blood Sample Collection and Serum Preparation

Venous blood was obtained in plain gel tubes without anticoagulant for serum preparation using sterile disposable syringes from all subjects. Blood samples were taken after an overnight fast of about 8-12 hours to determine fasting glucose and insulin. The blood samples were allowed to coagulate and then centrifuged to separate the serum. The serum was placed in clean labeled tubes, divided into appropriate aliquots and stored frozen until biochemical and immunological analyses were carried out. Freezing and thawing of the samples was avoided as much as feasible.

2.3 Measurement of Serum Ependymin-Related Protein 1 (EPDR1)

Serum EPDR1 levels were quantified using a commercially available Human Mammalian Ependymin-Related Protein 1 (EPDR1) ELISA Kit (MyBioSource, Inc., San Diego, CA, USA; Catalog No. MBS9316185). The kit is a quantitative sandwich ELISA for use with human serum. According to the manufacturer, the claimed sensitivity is 5.0 ng/mL, and the detection range is 31.2-1000 ng/mL. Briefly, reagents and serum samples were allowed to reach room temperature before analysis. Standards and samples were added to the appropriate antibody-coated wells as directed by the manufacturer. After the necessary incubation, loose material was removed by washing. Detection reagents were added according to the kit instructions, followed by further incubation and washing. Chromogenic substrate was added for color development, and the reaction was stopped by adding stop solution. EPDR1 concentrations were computed from the standard calibration curve and presented as ng/mL. Optical density was measured using a microplate reader. All assay stages were performed according to the kit's instructions.

2.4 Measurement of Hormonal Parameters and Fasting Insulin

We measured serum luteinizing hormone (LH), follicle-stimulating hormone (FSH), total testosterone, and fasting insulin using the cobas e 411 immunoassay analyzer (Roche Diagnostics, Germany). The cobas e 411 system uses electrochemiluminescence immunoassay technology. Serum samples were analyzed with the corresponding Roche reagents, calibrators, and quality-control materials according to the manufacturer's instructions. The LH/FSH ratio was calculated for each participant as LH divided by FSH.

2.5 Measurement of Biochemical Parameters

Fasting serum glucose and lipid profile parameters were measured using the cobas c 111 automated clinical chemistry analyzer (Roche Diagnostics, Germany). The biochemical parameters included fasting blood glucose, total cholesterol, triglycerides, HDL-C, and LDL-C. Serum samples were analyzed with the corresponding Roche reagents, calibrators, and quality-control materials according to the manufacturer's instructions. Results were expressed in mg/dL.

2.6 Calculation of Insulin Resistance

Insulin resistance was estimated using the Homeostatic Model Assessment for Insulin Resistance (HOMA-IR). When fasting glucose was expressed in mg/dL, HOMA-IR was calculated using the following equation: HOMA-IR = [fasting glucose (mg/dL) x fasting insulin (microIU/mL)] / 405. Higher HOMA-IR values indicate greater insulin resistance.

2.7 Body Mass Index

Body weight was measured in kilograms using a calibrated scale, while height was measured in meters with the participant standing upright without shoes. Body mass index (BMI) was calculated as body weight in kilograms divided by height in meters squared (kg/m2).

2.8 Waist-to-Hip Ratio

Waist and hip circumferences were measured with a flexible, non-stretchable measuring tape while the participant stood in a relaxed position. Waist circumference was measured around the abdomen at the midpoint between the lower margin of the last palpable rib and the top of the iliac crest, at the end of a normal expiration and without compressing the skin. Hip circumference was measured around the widest part of the buttocks with the tape horizontal. Waist-to-hip ratio (WHR) was calculated as waist circumference divided by hip circumference.

2.9 Statistical Analysis

Statistical analysis was performed using IBM SPSS Statistics software. Continuous variables were expressed as mean +/- standard deviation (SD). The independent-samples Student's t-test was used to compare mean values between women with PCOS and healthy controls. Pearson's correlation coefficient (r) was used to evaluate relationships between serum EPDR1 concentrations and the studied clinical, hormonal, and metabolic parameters. Receiver operating characteristic (ROC) curve analysis was performed to evaluate the ability of serum EPDR1, selected hormonal parameters, fasting insulin, and WHR to discriminate between women with PCOS and healthy controls. The area under the ROC

curve (AUC), 95% confidence interval, sensitivity, specificity, and optimal cutoff value were determined. The probability value of $P < 0.05$ was considered statistically significant.

3. Results

The two groups were similar in age, with no significant difference between controls and women with PCOS. In contrast, BMI and WHR were significantly higher in the PCOS group. Hormonal analysis showed significantly higher LH, LH/FSH ratio, testosterone, and fasting insulin in women with PCOS, while FSH did not differ significantly between the groups. The PCOS group also showed higher fasting glucose, HOMA-IR, total cholesterol, triglycerides, and LDL-C and lower HDL-C. Serum EPDR1 was significantly lower in PCOS patients compared with healthy controls.

Table 1. Demographic and anthropometric characteristics of the study groups.

Parameter	Control (n=50) Mean +/- SD	PCOS (n=50) Mean +/- SD	P value
Age (years)	27.80 ± 5.40	28.60 ± 5.80	0.477
BMI (kg/m²)	24.10 ± 3.70	29.00 ± 5.00	<0.001
WHR	0.780 ± 0.055	0.860 ± 0.075	<0.001

Table 2. Hormonal parameters and fasting insulin in the study groups.

Parameter	Control (n=50) Mean +/- SD	PCOS (n=50) Mean +/- SD	P value
LH (mIU/mL)	5.80 ± 1.80	8.90 ± 3.60	<0.001
FSH (mIU/mL)	6.30 ± 1.50	6.00 ± 1.60	0.336
LH/FSH ratio	0.957 ± 0.340	1.609 ± 0.906	<0.001
Testosterone (ng/mL)	0.370 ± 0.110	0.560 ± 0.220	<0.001
Fasting insulin (µIU/mL)	8.70 ± 3.40	14.80 ± 6.50	<0.001

Table 3. Metabolic parameters and serum EPDR1 in the study groups.

Parameter	Control (n=50) Mean +/- SD	PCOS (n=50) Mean +/- SD	P value
Fasting glucose (mg/dL)	88.60 ± 9.00	96.40 ± 14.00	0.001
HOMA-IR	1.906 ± 0.776	3.548 ± 1.647	<0.001
Total cholesterol (mg/dL)	169.20 ± 29.00	188.10 ± 35.00	0.004
Triglycerides (mg/dL)	103.40 ± 38.00	145.60 ± 52.00	<0.001
HDL-C (mg/dL)	52.80 ± 9.50	44.60 ± 9.00	<0.001
LDL-C (mg/dL)	96.70 ± 25.00	116.40 ± 31.00	<0.001
EPDR1 (ng/mL)	245.00 ± 82.00	155.00 ± 68.00	<0.001

Correlation analysis showed that, within the PCOS group, EPDR1 had significant negative correlations with BMI, WHR, fasting insulin, HOMA-IR, LH/FSH ratio, total cholesterol, and LDL-C, while a significant positive correlation was observed with HDL-C. Correlations with age, LH, FSH,

testosterone, fasting glucose, and triglycerides were not statistically significant. In the control group, none of the correlations studied reached statistical significance.

Table 4. Pearson correlation of serum EPDR1 with clinical, hormonal, and metabolic parameters.

Parameter	Control r	Control P	PCOS r	PCOS P
Age (years)	0.03	0.836	0.08	0.581
BMI (kg/m²)	-0.19	0.186	-0.46	<0.001
WHR	-0.14	0.332	-0.39	0.005
LH (mIU/mL)	-0.08	0.581	-0.26	0.068
FSH (mIU/mL)	0.03	0.836	0.12	0.406
LH/FSH ratio	-0.092	0.527	-0.326	0.021
Testosterone (ng/mL)	-0.12	0.406	-0.24	0.093
Fasting insulin (µIU/mL)	-0.2	0.164	-0.42	0.002
Fasting glucose (mg/dL)	-0.1	0.49	-0.23	0.108
HOMA-IR	-0.222	0.122	-0.444	0.001
Total cholesterol (mg/dL)	-0.12	0.406	-0.31	0.028
Triglycerides (mg/dL)	-0.1	0.49	-0.21	0.143
HDL-C (mg/dL)	0.17	0.238	0.36	0.01
LDL-C (mg/dL)	-0.15	0.298	-0.34	0.016

ROC curve analysis showed that WHR had the highest discriminatory performance among the evaluated parameters (AUC = 0.800), followed by EPDR1 (AUC = 0.781), fasting insulin (AUC = 0.780), testosterone (AUC = 0.774), LH (AUC = 0.769), and the LH/FSH ratio (AUC = 0.762). FSH showed poor discriminatory ability and was not statistically significant.

Table 5. ROC curve analysis of EPDR1, hormonal parameters, fasting insulin, and WHR for discrimination of PCOS.

Marker	AUC	95% CI	Cut-off	Sensitivity (%)	Specificity (%)	P value
EPDR1 (ng/mL)	0.781	0.691–0.872	≤191.49	70	70	<0.001
LH (mIU/mL)	0.769	0.677–0.862	>7.87	64	90	<0.001
FSH (mIU/mL)	0.548	0.435–0.661	≤6.14	56	54	0.409
LH/FSH ratio	0.762	0.669–0.856	>1.154	74	78	<0.001
Testosterone (ng/mL)	0.774	0.682–0.866	>0.450	70	84	<0.001
Fasting insulin (µIU/mL)	0.78	0.689–0.871	>12.05	62	88	<0.001

WHR	0.8	0.713–0.888	>0.814	72	78	<0.001

4. Discussion

The present study showed clear differences in metabolic, hormonal, and EPDR1-related parameters between women with PCOS and healthy controls, supporting the view that PCOS is not only a reproductive disorder but also a condition closely linked to metabolic dysfunction. Serum EPDR1 was significantly lower in women with PCOS, while BMI, WHR, LH, LH/FSH ratio, testosterone, fasting insulin, fasting glucose, HOMA-IR, total cholesterol, triglycerides, and LDL-C were significantly higher, and HDL-C was significantly lower; FSH showed no significant difference. The most notable finding was the decrease in serum EPDR1 in PCOS. This is consistent with the study of Ren Xiaopang et al. (2026), who investigated 282 women with PCOS and 60 healthy controls and found decreased serum EPDR1 in PCOS, with additional decreases in those with obesity or insulin resistance [20]. Their investigation also found EPDR1 to negatively correlate with BMI, insulin resistance, LH/FSH ratio, total cholesterol, and LDL-C and to positively correlate with HDL-C, closely mirroring the pattern seen in the present analysis[21]. Biologically, one possible explanation is provided by the study of Deshmukh et al. (2019), who discovered EPDR1 as a new protein secreted by human brown adipocytes and proposed a function in brown adipocyte commitment and thermogenic activity [16]. Reduced circulating EPDR1 may suggest altered adipose tissue function in women with PCOS, as brown adipose tissue contributes to energy expenditure and metabolic homeostasis. This is further reinforced by Cataldo et al. (2022) who found that EPDR1 is implicated in the metabolism and function of pancreatic beta-cells. Downregulation of EPDR1 disrupted mitochondrial respiration and glucose-stimulated insulin release, whereas EPDR1 therapy enhanced beta-cell metabolic function[18]. Therefore, the low EPDR1 found in PCOS may be connected with disturbances in the interaction between adipose tissue, energy metabolism, and insulin regulation, although the current case-control design cannot establish a causal relationship. Women with PCOS also had significantly higher BMI and WHR. This agrees with Zhang et al. (2023), who reported an important relationship between body composition, insulin resistance, and hormonal abnormalities in women with PCOS [5]. The negative correlations between EPDR1 and both BMI and WHR in the present study are particularly interesting because they suggest that EPDR1 may be more closely connected with the metabolic and adiposity component of PCOS than with ovarian dysfunction alone. The hormonal findings also followed a typical PCOS pattern. LH and the LH/FSH ratio were significantly increased, testosterone was higher, while FSH itself did not differ significantly. Ren Xiaopang et al. (2026) reported the same general direction of change for LH,

LH/FSH ratio, and testosterone[20], while Zhang et al. (2023) similarly described higher LH, LH/FSH ratio, and androgen-related abnormalities in women with PCOS[8]. These variations can be explained by changes in hypothalamo-pituitary-ovarian regulation along with the effect of hyperinsulinemia on ovarian androgen production[22]. Interestingly, we found a substantial correlation between EPDR1 and the LH/FSH ratio but not with LH, FSH or testosterone separately. Therefore, EPDR1 may be involved in broader metabolic-endocrine disruption rather than in a specific reproductive hormone. Another important finding in the studies is insulin resistance. Fasting insulin and HOMA-IR were markedly higher in PCOS, whereas fasting glucose showed a smaller but significant increase. This pattern is expected because compensatory hyperinsulinemia may occur before a major rise in fasting glucose. Tilak et al. reported that insulin resistance is strongly linked with both the metabolic and reproductive manifestations of PCOS[23]. The present negative correlations between EPDR1 and fasting insulin and between EPDR1 and HOMA-IR are therefore important, as they provide a direct link between the novel marker and one of the central metabolic disturbances in PCOS. The lack of significant correlations with every parameter should not be considered a weakness. PCOS is heterogeneous and various factors influence lipid concentrations, glucose metabolism, body composition and reproductive hormones. Thus, it is more realistic to expect moderate correlations than very high ones across all variables. ROC analysis provided an additional clinical perspective on the data. WHR had the largest AUC, whereas considerable discriminative ability was observed for EPDR1, fasting insulin, testosterone, LH and the LH/FSH ratio. FSH demonstrated weak discriminative performance, consistent with its non-significant group difference. EPDR1 discriminated moderately between PCOS and healthy controls with an AUC of around 0.78. This value does not support EPDR1 as a stand-alone diagnostic test, but it does suggest possible value as an additional metabolic biomarker. The ROC findings for fasting insulin and the LH/FSH ratio are also supported by Golbahar et al. (2012), who found that insulin and the LH/FSH ratio were useful predictors in women with PCOS, although their AUC values were higher than those found here[24]. Differences in ROC performance between studies can result from population characteristics, diagnostic criteria, obesity prevalence, degree of insulin resistance, laboratory methods, and control selection. Overall, the present findings suggest that reduced serum EPDR1 is associated with PCOS and appears particularly connected with obesity, central adiposity, insulin resistance, and lipid disturbances. Its association with individual reproductive hormones was weaker, while the relationship with the LH/FSH ratio remained significant. The close agreement with the recent EPDR1 study by Ren Xiaopang et al. supports further investigation of this protein in PCOS. However, EPDR1 is still a newly studied biomarker, and available clinical evidence

remains limited. Whether decreased EPDR1 levels contribute to the development of PCOS or simply reflect the metabolic derangements that occur in the disease would require larger studies in other populations and PCOS phenotypes as well as prospective studies.

5. Conclusion

The present investigation demonstrated that serum EPDR1 levels were considerably lower in women with PCOS compared with healthy controls. Lower EPDR1 was predominantly associated with higher body weight, central obesity, insulin resistance and adverse alterations in lipids. The substantial associations with BMI, WHR, fasting insulin, HOMA-IR and lipid profile imply that EPDR1 may be more related to the metabolic component of PCOS than to hormonal alterations individually. ROC analysis also showed that EPDR1 moderately differentiated women with PCOS from healthy controls. These results suggest that the serum EPDR1 could serve as a new metabolic biomarker in PCOS, although larger studies are needed to confirm its clinical relevance.

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