International Journal of Women's Health

Dovepress
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ORIGINAL RESEARCH

Independent Elevation of Leptin and Reduction of Protective Adipokines in Polycystic Ovary Syndrome: A BMI-Matched Case–Control Study

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Background: Dysregulated inflammatory cytokines and adipokines are implicated in PCOS pathogenesis, but their independent role remains unclear due to the confounding effect of obesity. This study employed a BMI-matched design to specifically investigate adipokine alterations intrinsic to PCOS, independent of body mass.

Patients and Methods: This investigation employed a case-control design and included 70 PCOS patients and 82 healthy controls matched for age and BMI. Serum levels of leptin (LEP), interleukin-6 (IL-6), omentin, adiponectin (ADPN), ghrelin, retinol-binding protein 4 (RBP4), and orexin-A (OXA) were measured. Spearman correlation analysis was used to analyze the correlation between PCOS and glucose and lipid metabolism, reproductive hormones and adipokines. Multivariate logistic regression analysis identified independent risk factors for PCOS. Subsequently, the diagnostic capacity of significant variables was appraised using ROC analysis.

Results: Compared with healthy controls (n = 82), women with PCOS (n = 70) exhibited significantly higher levels of LEP and IL-6, and significantly lower levels of OXA, omentin, and ADPN/LEP ratio ($P < 0.05$). No significant differences were observed in the levels of ADPN, Ghrelin, and RBP4. PCOS positively correlated with HOMA-IR, TG, testosterone (TSTO), Anti-Müllerian Hormone (AMH), LEP, and IL-6, and negatively correlated with omentin, OXA, ADPN/LEP ratio, and HDL-C ($P < 0.05$). Multivariable logistic regression analysis identified LEP as an independent risk factor for PCOS, while omentin and OXA were protective factors ($P < 0.05$).

Conclusion: This study reveals that patients with PCOS exhibit a specific pattern of adipokine dysregulation, independent of obesity, characterized by elevated LEP coupled with reduced omentin and orexin-A, which may play a pivotal role in disease pathogenesis. These findings highlight the potential clinical value of assessing adipokine profiles and developing targeted interventions, thereby offering novel strategies for the diagnosis and treatment of PCOS.

Keywords: PCOS, adipokines, inflammation, metabolic dysregulation

Introduction

Polycystic ovary syndrome (PCOS) is a prevalent endocrine and metabolic disorder, affecting approximately 11–13% of women of reproductive age worldwide and representing a major contributor to infertility.[1] PCOS is linked to a cluster of metabolic disturbances, including obesity, insulin resistance, and aberrant glucose and lipid homeostasis.[2] These disturbances do not occur in isolation. Hyperandrogenism and insulin resistance (IR) further exacerbate metabolic imbalances, while obesity drives the progression of this pathological process by promoting the secretion of adipokine cytokines from adipose tissue.[3] Importantly, PCOS exhibits considerable phenotypic heterogeneity, and its underlying

Received: 13 August 2025
Accepted: 10 November 2025
Published: 19 November 2025

pathophysiological mechanisms remain incompletely understood, posing challenges for accurate diagnosis and targeted therapy.[4]

Adipose tissue functions as an active endocrine organ that synthesizes and secretes a variety of adipokines, thereby exerting critical influences on inflammatory cascades, insulin signaling pathways, and overall metabolic equilibrium.[5] Adipose tissue dysfunction disrupts adipokine secretion and alters their circulating levels, thereby establishing it as a key contributor to PCOS pathophysiology even in non-obese individuals.[6] In obese women with PCOS, a marked decrease in protective adipokines such as adiponectin (ADPN) is often accompanied by elevated levels of pro-inflammatory mediators like leptin (LEP).[7] Even among nonobese PCOS patients, distinct changes in adipokine profiles have been observed. These changes include significantly elevated circulating levels of LEP and resistin, along with reduced ADPN levels.[8] However, research on the adipokine profile in PCOS remains marked by inconsistencies. This heterogeneity likely stems from variations in diagnostic criteria, definitions of obesity, and methodologies for adipokine measurement. Divergent findings have been reported regarding ADPN levels in non-obese young women with PCOS, with some studies indicating elevated levels and others showing no significant difference compared to controls.[9,10] An additional limitation is the narrow scope of previous investigations, which have predominantly focused on classical adipokines such as ADPN and LEP, while the roles of non-classical adipokines, including omentin, orexin-A (OXA), ghrelin, and retinol-binding protein 4 (RBP4), remain inadequately explored. Based on existing research, we conducted a case–control study comparing circulating levels of both classical and novel adipokines in women with PCOS and age- and BMI-matched healthy controls, and evaluated their independent associations with disease status. This study aims to expand current understanding of adipokine dysregulation in PCOS and provide a basis for future mechanistic and translational research on potential metabolic biomarkers and therapeutic targets.

Materials and Methods

Study Participants

A total of 70 women diagnosed with PCOS at the Reproductive Medicine Center of Sichuan Women and Children's Hospital from December 2023 to December 2024 were selected as the study subjects. At the same time, 82 healthy women were recruited as controls. Controls were selected to have a similar age and BMI distribution as the PCOS group (age ±2 years, BMI ±2 kg/m^2). PCOS was diagnosed according to the 2003 Rotterdam criteria:[11] (1) anovulation or oligoovulation (menstrual cycles ≥35 days or fewer than 9 cycles per year); (2) clinical and/or laboratory evidence of hyperandrogenism exceeding normal thresholds; and (3) polycystic ovarian morphology on ultrasonography, defined as the presence of ≥12 follicles measuring 2–9 mm in diameter and/or ovarian volume ≥10 cm^3. The exclusion criteria for both groups were as follows: (1) diagnosis of other endocrine disorders (Cushing's syndrome, thyroid dysfunction, congenital adrenal hyperplasia); (2) presence of systemic inflammatory diseases, diabetes mellitus, or cardiovascular diseases; and (3) use of hormonal medications, insulin-sensitizing drugs, or anti-obesity drugs within the preceding three months.

Ethics Approval and Informed Consent

The study protocol received approval from the Ethics Committee of Sichuan Provincial Women and Children's Hospital (Approval No. 20231012–245). Prior to enrolment, written informed consent was provided by all participants, and the study was carried out in accordance with the principles of the Declaration of Helsinki. As this was not a clinical trial, no clinical trial number is applicable.

Sample Collection and Biochemical Measurement

Blood samples were collected into standard gel-barrier tubes and processed to obtain serum for biochemical assays. A Hitachi 008AS automated analyzer (Tokyo, Japan) was used to conduct all metabolic assays, which quantified fasting plasma glucose (FPG), insulin (FINS), and a comprehensive serum lipid panel comprising low-density lipoprotein cholesterol (LDL-C), triglycerides (TG), total cholesterol (TC), and high-density lipoprotein cholesterol (HDL-C). This study quantified serum levels of testosterone (TSTO), follicle-stimulating hormone (FSH), and luteinizing hormone (LH)

employing a Mindray CL-8000i automated chemiluminescence immunoanalyzer (Mindray, China). A commercially available ELISA kit was used to measure serum levels of Anti-Müllerian hormone (AMH). The precision of the assay was validated with intra-assay and inter-assay coefficients of variation (CV) staying under 6.25% and 8.30%, respectively. Insulin resistance was assessed using the homeostasis model assessment of insulin resistance (HOMA-IR), calculated as: HOMA-IR = [Fasting insulin (μIU/mL) × FPG (mmol/L)] / 22.5. Serum concentrations of adipokines, including OXA, RBP-4, omentin, IL-6, ADPN, LEP, and Ghrelin, were quantified using corresponding enzyme-linked immunosorbent assay (ELISA) kits manufactured by Jianglai Bio (Shanghai, China). Samples were diluted as recommended and incubated with specific capture and detection antibodies according to the manufacturer's instructions. Absorbance was read at 450 nm, and concentrations were determined using standard curves. All assays were performed in duplicate, and intra- and inter-assay CVs were below 10%. The minimum detectable concentrations were: OXA, 31.25 pg/mL; RBP-4, 6.25 ng/mL; omentin, 0.78 ng/mL; IL-6, 3.12 pg/mL; ADPN, 1.56 ng/mL; LEP, 0.15 ng/mL; ghrelin, 0.78 pg/mL.

Statistical Analysis

IBM SPSS Statistics software (version 26.0; Armonk, NY, USA) was used for all statistical analyses. The distribution of continuous variables was assessed using the Kolmogorov–Smirnov test. Data are presented as mean ± standard deviation (SD) for normally distributed variables and as median (interquartile range, IQR) for non-normally distributed variables. Group comparisons were performed using independent samples *t*-test for normally distributed data and the Mann–Whitney *U*-test for non-normally distributed data. A Spearman correlation analysis was performed to assess the relationships between PCOS status and various hormonal, metabolic, and adipokine parameters. We performed multivariable logistic regression analysis, adjusting for key metabolic parameters including age, BMI, and HOMA-IR in the model, to identify independent risk factors for PCOS. To find optimal diagnostic thresholds for each variable, ROC analysis was applied using Youden index maximization, and their sensitivity and specificity in identifying PCOS were assessed. A two-sided $P< 0.05$ was considered statistically significant.

Results

Baseline Characteristics of Participants

A comparative analysis of baseline demographics, endocrine profiles, and metabolic parameters in two groups is presented in Table 1. Age and BMI were not significantly different statistically ($P > 0.05$). Women with PCOS

Table 1 Clinical Information of Polycystic Ovary Syndrome and Control Subjects

Variables	Control (n = 82)	PCOS (n = 70)	*P-value*
Age (years)	29.87 ± 5.154	28.73 ± 3.19	*0.099*
BMI (kg/m^2)	21.65 (19.80, 23.47)	22.60 (20.38, 23.96)	*0.121*
FSH (mIU/mL)	6.52 (4.95, 7.52)	6.30 (5.63, 7.07)	*0.619*
LH (mIU/mL)	5.05 (3.79, 6.96)	9.36 (5.28, 13.93)	*<0.001*
TSTO (ng/mL)	0.256 ± 0.073	0.389 ± 0.157	*<0.001*
AMH (ng/mL)	4.49 (3.00, 5.61)	10.70 (7.39, 18.82)	*<0.001*
FPG (mmol/L)	4.65 ± 0.57	5.04 ± 0.49	*<0.001*
FINS (μIU/mL)	7.75 (6.35, 8.79)	12.18 (7.90, 15.06)	*<0.001*
HOMA-IR	1.58 ± 0.49	2.69 ± 1.36	*<0.001*
TC (mmol/L)	4.52 ± 0.83	4.71 ± 0.96	*0.207*
TG (mmol/L)	0.94 (0.72, 1.43)	1.14 (0.80, 1.88)	*0.016*
HDL-C (mmol/L)	1.65 ± 0.33	1.42 ± 0.34	*<0.001*
LDL-C (mmol/L)	2.53 ± 0.65	2.78 ± 0.75	*0.032*

Abbreviations: AMH, anti-Müllerian hormone; BMI, body mass index; FPG, fasting blood glucose; FINS, fasting serum insulin; FSH, follicle-stimulating hormone; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; LH, luteinizing hormone; TSTO, testosterone; TC, total cholesterol; TG, triglycerides.

https://doi.org/10.2147/IJWH.S560444

demonstrated markedly elevated serum concentrations of LH, TSTO, AMH, FIINS, FPG, HOMA-IR, LDL-C, and TG, alongside a significant reduction in HDL-C, relative to the control group ($P < 0.05$). The observed results align with the well-established endocrine and metabolic profile typically associated with PCOS.[12]

Serum Adipokine Levels

Previous studies have shown that obesity has an impact on the pathophysiological mechanism of PCOS. The levels of adipocyte products secreted by women with PCOS are unbalanced. As previously reported, LEP expression is positively correlated with BMI, while ADPN level is negatively correlated with fat mass, waist-to-hip ratio, and BMI.[6] Therefore, we matched the PCOS and control groups for BMI, thus excluding the confounding effect of obesity on adipokine levels.

The present investigation quantified circulating concentrations of multiple adipokine biomarkers in PCOS sufferers and their matched control group (Figure 1). The findings indicated that serum IL-6 and LEP concentrations were considerably higher in PCOS patients than in the control subjects. ($P < 0.05$). Conversely, circulating levels of Omentin and OXA were substantially lower in the PCOS relative to healthy subjects ($P < 0.05$). Between the groups, no significant differences were found for Ghrelin, ADPN, or RBP4.

Correlation Analysis of Hormones, Metabolic Markers, and Adipokines with PCOS

To further investigate the relationships between PCOS status and key parameters, Spearman's rank correlation analysis was utilized. The results revealed significant positive correlations between PCOS and FINS (r = 0.423, $P < 0.001$), FPG (r = 0.358, $P < 0.001$), HOMA-IR (r = 0.460, $P < 0.001$), and TG (r = 0.195, $P = 0.016$), indicating metabolic dysregulation in PCOS patients. Consistent with previous studies, PCOS was also positively correlated with testosterone (r = 0.493, $P < 0.001$), LH (r = 0.375, $P < 0.001$), and AMH (r = 0.645, $P < 0.001$), reflecting characteristic hyperandrogenism and ovarian dysfunction.[13] Correlation analysis between PCOS and adipokines demonstrated significant positive associations with IL-6 (r = 0.163, $P = 0.044$) and LEP (r = 0.353, $P < 0.001$). Conversely, PCOS was significantly negatively correlated with HDL-C (r = –0.342, $P < 0.001$), omentin (r = –0.313, $P < 0.001$), OXA (r = –0.183, $P = 0.022$), and the ADPN/LEP ratio (r = –0.315, $P < 0.001$).

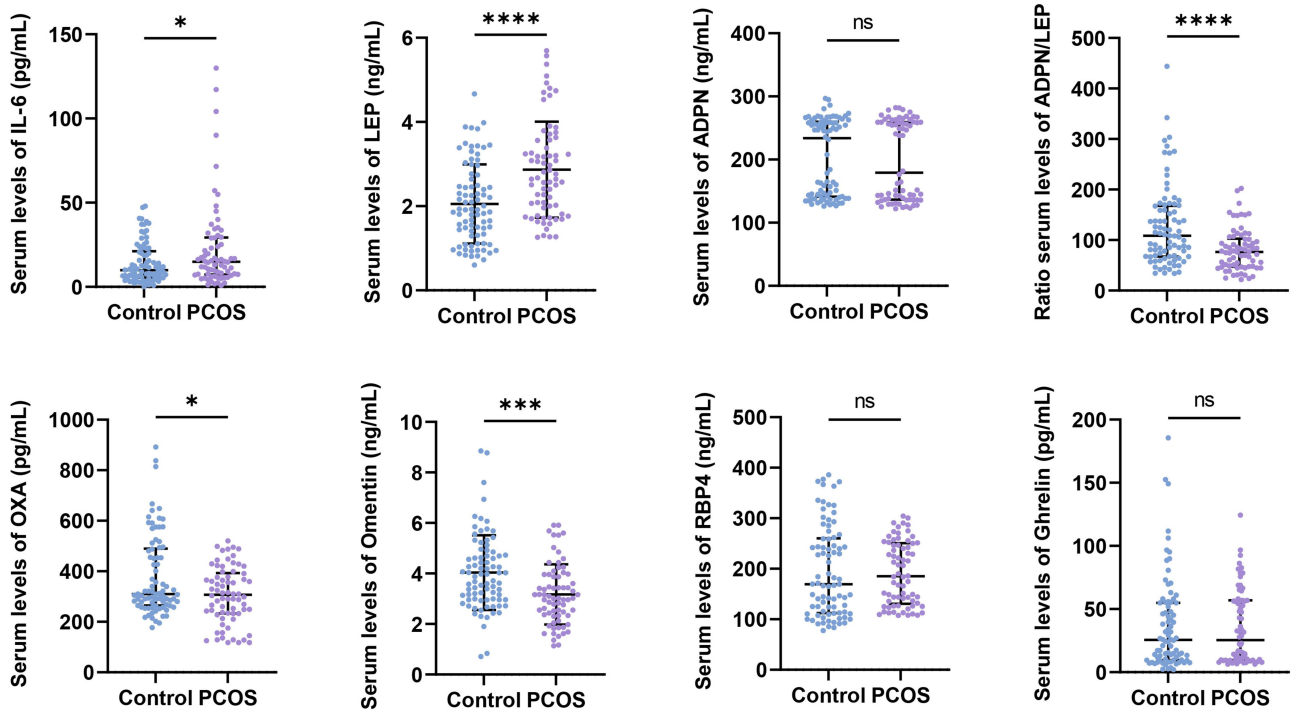

Figure 1 The changes of serum adipocytokine levels in PCOS patients compared with the control group.
Notes: Values for LEP and omentin are expressed as mean ± SD. OXA, IL-6, ADPN, ghrelin, RBP4, and ADPN/LEP ratio are presented as median with interquartile range (IQR). *$P < 0.05$, ***$P < 0.001$ and ****$P < 0.0001$. ns was considered no statistically significant.

Table 2 Comparison of Independent Risk Factor Markers for PCOS

Variable	Adjusted OR	95% CI	*P-value*
Age	0.944	0.846–1.053	*0.300*
BMI	1.041	0.890–1.218	*0.616*
HOMA-IR	4.621	2.335–9.146	*0.001*
IL-6	1.017	0.985–1.050	*0.292*
LEP	2.401	1.193–4.831	*0.014*
Omentin	0.484	0.316–0.741	*0.001*
OXA	0.996	0.992–0.999	*0.018*
ADPN/LEP	0.993	0.982–1.005	*0.235*

Notes: Adjusting for baseline age, BMI and HOMA-IR.
Abbreviations: ADPN, adiponectin; BMI, body mass index; HOMA-IR, homeostasis model assessment of insulin resistance; IL-6, interleukin-6; LEP, leptin; OXA, orexin-A.

Independent Risk Factors for PCOS Based on Hormone and Adipokine Levels

To identify independent factors linked to PCOS, a multivariable logistic regression was constructed. The model was adjusted for age, BMI, and HOMA-IR to control for potential confounding effects. We included adipokines that showed significant intergroup differences, including IL-6, LEP, omentin, OXA, and the ADPN/LEP ratio based on their established role in inflammation and metabolic regulation in PCOS (Table 2). The results showed that LEP was an independent risk factor for PCOS (OR = 2.40, 95% CI: 1.193–4.831, $P = 0.014$), while omentin (OR = 0.48, 95% CI: 0.316–0.741, $P = 0.001$) and OXA (OR = 0.996, 95% CI: 0.992–0.999, $P = 0.018$) served as protective factors.

Diagnostic Performance of Hormone and Adipokine Levels for PCOS

Given that IL-6 and LEP levels are substantially higher and most associated with PCOS risk, we further assessed how these adipokines perform diagnostically compared to conventional endocrine markers (Figure 2, Table 3). AMH was found to have the highest diagnostic accuracy, with an area under the curve of 0.873 ($P < 0.001$), 77.4% sensitivity, and

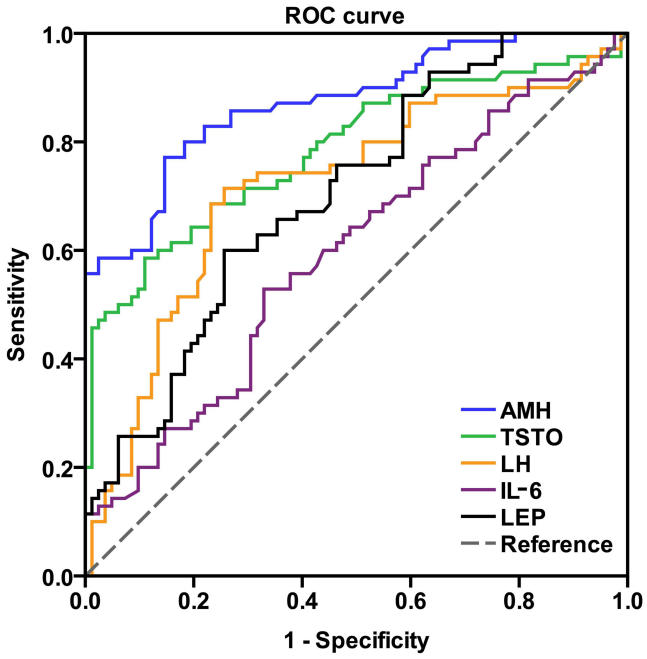

Figure 2 ROC curve of the predictive value of hormone indexes and adipokines for PCOS patients.

https://doi.org/10.2147/IJWH.S560444

Table 3 ROC Curve Analysis of Hormone and Adipokine Markers for PCOS Diagnosis

Variable	Sensitivity	Specificity	Cut Off-*Value*	95% CI	AUC	*P-value*
TSTO	0.589	0.890	0.353 (ng/mL)	0.711–0.861	0.786	*<0.001*
LH	0.714	0.744	6.70 (mIU/mL)	0.633–0.802	0.717	*<0.001*
AMH	0.771	0.854	7.26 (ng/mL)	0.818–0.929	0.873	*<0.001*
LEP	0.600	0.744	2.50 (ng/mL)	0.623–0.786	0.704	*<0.001*
IL-6	0.592	0.671	14.44 (pg/mL)	0.504–0.685	0.595	*0.045*

Abbreviations: AMH, anti-Müllerian hormone; IL-6, interleukin-6; LEP, leptin; LH, luteinizing hormone; TSTO, testosterone.

85.4% specificity. TSTO also showed significant diagnostic value (AUC = 0.786, $P < 0.001$), with sensitivity and specificity of 58.9% and 89.0%, respectively. LEP displayed moderate diagnostic utility (AUC = 0.704, $P < 0.001$), with the most effective cut-off at 2.50 ng/mL. Although IL-6 demonstrated statistically significant diagnostic performance (AUC = 0.595, $P < 0.05$), its clinical applicability appears limited.

Discussion

PCOS is a complex endocrine and metabolic disorder marked by hyperandrogenism, obesity, and adipocyte dysfunction. These characteristics contribute to abnormal adipose tissue distribution and quality, reflecting the interplay between reproductive endocrine dysfunction and broader metabolic disturbances in affected women. Although obesity contributes to PCOS pathogenesis via adipokine dysregulation, substantial evidence confirms distinct pathophysiology in lean PCOS patients relative to obese phenotypes.[6,14] Comprehensive characterization of adipokine profiles in non-obese PCOS is thus critical for elucidating phenotype-specific mechanisms. In this study, an age- and BMI-matched design was employed to effectively control for the confounding effects of obesity on adipokine levels, confirming a characteristic imbalance of adipokines in PCOS patients.

Hyperandrogenemia and insulin resistance represent core features of PCOS, and the hyperandrogenic state may further disrupt adipokine secretion. Adipocytes are actively involved in this process not only through adipokine release but also via the expression of steroidogenic enzymes that contribute to androgen synthesis.[15] Previous studies have confirmed that dysfunctional adipocytes exhibit dysregulated adipokine secretion and interact closely with both adrenal and ovarian steroidogenic cells.[16] In our study, we identified an adipokine imbalance in PCOS patients that was independent of obesity, characterized by elevated levels of pro-inflammatory factors LEP and IL-6 along with reduced levels of protective adipokines omentin and OXA. Concurrently, the PCOS group exhibited significant disturbances in glucose and lipid metabolism, including elevated HOMA-IR, FINS, FPG, and TG levels, accompanied by endocrine abnormalities manifested as increased testosterone, AMH, and LH concentrations.[17] Correlation analyses further revealed positive associations between PCOS status and HOMA-IR, TG, TSTO, AMH, LEP, and IL-6, while demonstrating negative correlations with HDL-C, omentin, OXA, and ADPN/LEP. As metabolically active endocrine cells, adipocytes secrete factors that stimulate testosterone production in adrenal cortical cells and enhance steroidogenesis by regulating enzymes such as 17β-hydroxysteroid dehydrogenase, thereby acting as an important extragonadal source of androgens. This process is modulated by insulin-like growth factors and adipokines and plays a central role in the pathogenesis of PCOS.[18,19] The concurrent elevation of pro-inflammatory adipokines and reduction of protective adipokines, together with metabolic and hormonal disturbances supported by correlation analyses, indicate a complex interplay among adipokines, insulin, and steroid hormones in PCOS.[20] Of particular note, this study observed decreased serum omentin levels, whose deficiency exacerbates glucose-lipid metabolic disorders and insulin resistance. This finding contrasts with the elevated omentin expression observed in follicular fluid and granulosa cells, which may suggest a tissue-specific distribution pattern.[21] Simultaneously, reduced OXA levels promote anovulation and hyperandrogenism through dual mechanisms: disrupting energy homeostasis of the hypothalamic–pituitary–ovarian (HPO) axis at the systemic level and locally promoting granulosa cell apoptosis.[22–24] Furthermore, no significant differences were detected in ghrelin, RBP4, and ADPN levels. Considering that previous literature reports these alterations primarily in overweight PCOS

populations, the strict BMI-matched design employed in our study likely explains the absence of significant differences in these parameters.[25–27] Although growing attention has been paid in recent years to the crosstalk between adipocyte-derived factors and theca or granulosa cells, the specific mechanisms through which adipocyte products influence various steroidogenic cells remain incompletely elucidated, leaving critical knowledge gaps.[28]

Previous studies have demonstrated that adipose tissue exerts systemic metabolic effects through the secretion of multiple adipokines, including LEP and IL-6, both of which are frequently dysregulated in obesity.[29] Recent investigations have revealed significant alterations in the gene expression profile of adipose tissue in PCOS patients, involving multiple pathways such as insulin signaling, lipid metabolism, and inflammatory responses, indicating that adipokine dysregulation may contribute to the pathogenesis of PCOS.[29,30] To further elucidate the role of adipokines in PCOS, this study conducted multivariate regression analysis and identified LEP as an independent risk factor for PCOS after adjusting for BMI, age, and homeostatic model assessment of HOMA-IR. LEP not only influences metabolic status through the regulation of energy balance but also directly participates in reproductive function regulation.[31,32] Its receptors are widely expressed in ovarian tissues, and it directly interferes with follicular development by activating the c-MYC/TERT apoptotic pathway in granulosa cells.[33] Meanwhile, adipose tissue serves as an important source of pro-inflammatory factors and can exacerbate systemic inflammation through positive feedback loops, thereby further promoting the progression of PCOS.[34] The ADPN-to-LEP ratio (ADPN/LEP), as a sensitive indicator for assessing adipose tissue functional imbalance, was significantly decreased in PCOS patients and showed a negative correlation with disease severity.[35] Although this ratio did not emerge as an independent risk factor, it effectively reflects the chronic inflammatory state in PCOS.

Currently, the diagnosis of PCOS primarily relies on the Rotterdam criteria, while AMH has demonstrated substantial value in the diagnosis of PCOS as well as in the evaluation of ovarian reserve and metabolic homeostasis.[11,17] In this study, ROC curve analysis revealed that LEP also exhibits certain diagnostic efficacy for PCOS (AUC = 0.704), providing new perspectives for its auxiliary diagnosis. Research has confirmed that LEP likely plays a critical role in the pathogenesis of PCOS by inducing insulin resistance and promoting hyperandrogenemia.[36] These findings have not only deepened our understanding of PCOS pathogenesis but also provided important evidence for developing novel diagnostic and therapeutic strategies.[37]

This study employed a BMI-matched case-control design to investigate the relationships between LEP, omentin, OXA and PCOS after controlling for obesity-related confounding factors. However, the current investigation was constrained by a limited sample size and the absence of important covariates such as visceral adipose tissue content, which prevented comprehensive elucidation of the mechanistic relationships between these adipokines and PCOS pathogenesis. Therefore, future large-scale, multicenter prospective cohort studies are warranted to validate these findings and explore the underlying biological mechanisms.

Conclusion

This study demonstrated that women with PCOS exhibit dysregulation of multiple adipokines, characterized by elevated IL-6 and LEP levels, reduced omentin and orexin-A (OXA) concentrations, and a decreased adiponectin/leptin ratio. Notably, LEP served as an independent predictor of PCOS, suggesting that it may independently affect the pathological process of PCOS. Considering the heterogeneity of PCOS and the relatively small sample size of this study, the complex interactions among adipokines remain to be elucidated. Future large-scale cohort and mechanistic studies are warranted to further clarify how multiple adipokines collectively contribute to the development and metabolic complications of PCOS.

Funding

This work was supported by Sichuan Medical Association Youth Innovation Project (Q2024012), Sichuan Provincial Science and Technology Department Central Guidance Local Science and Technology Development Project (2024ZYD0067), Sichuan Provincial Cadre Health Research Project (2024-2201), and Chengdu Medical College research project (CYZYB23-03).

Disclosure

The authors report no conflicts of interest in this work.

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