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Association Between Renin-Angiotensin System Peptides and Inflammatory Cytokines in Polycystic Ovary Syndrome

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ABSTRACT

Background & Objective: Polycystic Ovary Syndrome (PCOS) involves chronic inflammation and alterations in the Renin-Angiotensin System (RAS). This study was conducted with aim to examine the relationship between key RAS peptides and pro-inflammatory cytokines in PCOS.

Materials & Methods: This case-control study was conducted between December 2024 and March 2025 at Fallujah Teaching Hospital for Women and Children, in Fallujah, Anbar, Iraq. Ninety reproductive-aged women (18-40 years) were enrolled, including 45 newly diagnosed PCOS patients and 45 healthy controls. Anthropometric, metabolic, and reproductive parameters were evaluated. Serum levels of Angiotensin II, Angiotensin (1-7), IL-6, and TNF-α were measured. Data were analyzed using IBM SPSS Statistics (version 27.0) and independent t-test or Mann–Whitney U test, ANCOVA, Spearman correlation, ROC analysis, and regression model. $P<0.05$ was considered statistically significant.

Results: Pro-inflammatory cytokines were elevated in the PCOS group (serum concentrations of IL-6 (8.2 vs 4.1 pg/mL, P=0.013) and TNF-α (8.0 vs 1.7 pg/mL, P=0.039), whereas Ang (1-7) levels were lower (18.1 vs 21.2 pg/mL, $P<0.01$) compared with controls); however, after BMI adjustment, IL-6 became borderline and TNF-α lost statistical significance. Correlation analysis revealed LH and FSH were moderately correlated with TNF-α (r=0.479 and r=0.464, respectively; both P=0.001). ROC analysis identified AMH as the strongest discriminator for PCOS (AUC=0.866), followed by total testosterone (AUC=0.765), while Angiotensin (1-7) showed moderate diagnostic accuracy with an inverse relationship (AUC=0.718).

Conclusion: This study identified alterations RAS in women with PCOS, evidenced by lower Ang (1-7) levels, along with associations between inflammatory markers and reproductive hormones. Further prospective studies are required to confirm these findings.

Keywords: Polycystic ovary syndrome, Renin-angiotensin system, Cytokines, Angiotensin II, Angiotensin 1-7

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1. Introduction

Polycystic Ovary Syndrome (PCOS) has a global prevalence affecting up to 6-10% of reproductive aged women that is one of the most common endocrine-metabolic disorders in this population (1-3). It is a heterogeneous condition characterized by hyperandrogenism, oligo-anovulation, and polycystic ovarian morphology, often accompanied by insulin resistance and obesity (4). The etiology of PCOS is multifactorial and not fully elucidated, involving genetic predispositions and environmental/lifestyle factors. In recent years, chronic low-grade inflammation has been recognized as a key feature of PCOS pathophysiology (5,6). Circulating pro-inflammatory cytokines such as Interleukin-6 (IL-6) and Tumor Necrosis Factor-Alpha (TNF-α) are frequently elevated in PCOS women (7), and have been implicated in the development of insulin resistance (8) and other metabolic disturbances associated with the syndrome (9). These cytokines can also interact with the hypothalamic-pituitary-ovarian axis, potentially affecting ovarian function and contributing to hyperandrogenemia and anovulation.

Another system that may link metabolic and reproductive aspects of PCOS is The Renin-

Angiotensin System (RAS) **(10)**. Beyond its classical role in blood pressure regulation **(11)**, the RAS is expressed in ovarian tissue and influence follicular development and steroidogenesis **(12)**. Angiotensin II (Ang II), the main effector peptide of the RAS, can promote oxidative stress and inflammation via the angiotensin type-1 receptor **(13)**. Some studies have reported elevated Ang II levels in women with PCOS, correlating with insulin resistance **(14)**. Angiotensin-(1-7) (Ang (1-7)), produced from Ang II by Angiotensin-Converting Enzyme 2 (ACE2), counter-regulates Ang II actions by exerting anti-inflammatory, vasodilatory, and insulin-sensitizing effects **(15)**. An imbalance between the "harmful" Ang II (acting via the AT-1 receptor) and the "protective" Ang (1-7) (acting via the Mas receptor) could therefore contribute to the chronic inflammation and metabolic derangements in PCOS women **(16)**. However, while Ang II has been studied to some extent in PCOS, Ang (1-7) has received little attention; to our knowledge, no prior study has directly measured Ang (1-7) levels in PCOS patients **(17,18)**.

Given the intertwined roles of inflammation and the RAS in metabolism and ovarian function, we hypothesized that women with PCOS have altered levels of RAS peptides and inflammatory cytokines that are inter-related and linked to PCOS clinical features. This study was conducted with aim to compare serum concentrations of Ang II, Ang (1-7), IL-6, and TNF-α between PCOS patients and healthy controls; also to examine correlations between these RAS components, inflammatory markers, and key reproductive hormones; and to evaluate the diagnostic performance of these biomarkers (individually and in combination) for distinguishing PCOS. We seek to improve understanding of PCOS pathophysiology and identify potential markers for clinical assessment of PCOS-related inflammation and RAS imbalance.

2. Materials and Methods

This case–control study was conducted between December 2024 and March 2025 at Fallujah Teaching Hospital for Women and Children, a tertiary care center in Fallujah, Anbar, Iraq. A total of 90 reproductive-aged women (18-40 years) were enrolled, including 45 newly diagnosed patients with PCOS and 45 age-matched healthy controls.

PCOS was diagnosed according to the Rotterdam 2003 criteria **(19)**, requiring at least two of the following: oligo/anovulation, clinical and/or biochemical hyperandrogenism, or polycystic ovarian morphology on ultrasound. Controls had regular menstrual cycles, no clinical hyperandrogenism, and normal ovarian morphology.

Women were excluded if they were pregnant, menopausal, had endocrine disorders that could mimic PCOS (e.g., Cushing's syndrome, thyroid dysfunction, congenital adrenal hyperplasia), diabetes mellitus, or chronic inflammatory diseases, or had used hormonal or insulin-sensitizing medications within the preceding three months. All participants provided a medical history and underwent a standardized physical examination.

Age and anthropometric measurements, including weight, height, and waist circumference, were recorded for all participants. On the third day of the menstrual cycle, 5 mL of venous blood was collected following an overnight fast of at least 8 hours. Fasting plasma glucose was measured using the cobas® pure analyzer (Germany). Serum insulin levels were determined using a commercial ELISA kit (Reed Biotech, China), and insulin resistance was estimated using the Homeostatic Model Assessment for Insulin Resistance (HOMA-IR).

Reproductive hormones, including Luteinizing Hormone (LH), Follicle-Stimulating Hormone (FSH), total testosterone, and Anti-Müllerian Hormone (AMH), as well as inflammatory cytokines (IL-6 and TNF-α) and renin-angiotensin system peptides (Ang II and Ang (1-7)), were quantified using ELISA kits (ELK Biotechnology, China). To minimize posture-related activation of the renin–angiotensin system, participants rested in a supine position for at least 15 minutes prior to blood sampling.

Data were analyzed using IBM SPSS Statistics (version 27.0), with JMP Pro 18 and GraphPad Prism 10 used for supplementary analyses and data visualization. Continuous variables were expressed as mean±Standard Deviation (SD) for normally distributed data or median with interquartile range (IQR) for non-normal distributions. $P<0.05$ was considered statistically significant.

Between-group comparisons were performed using the independent-samples t-test or Mann-Whitney U test. Analysis of covariance (ANCOVA) was conducted to adjust for the potential confounding effect of BMI. Non-normally distributed variables were log-transformed or rank-transformed prior to analysis when necessary.

Spearman's rank correlation was used to evaluate the relationships among inflammatory markers, renin–angiotensin peptides, reproductive hormones, and metabolic parameters within the PCOS group. Diagnostic performance was assessed using receiver operating characteristic (ROC) curves, with the Area Under the Curve (AUC) and 95% confidence intervals calculated. Optimal cutoff values were determined using Youden's index.

Univariate logistic regression analyses were performed to estimate Odds Ratios (ORs) and corresponding 95% confidence intervals for associations between clinical and biochemical variables and the likelihood of PCOS.

3. Results

A total of 45 women with PCOS and 45 age-matched healthy controls were included in this study. Women with PCOS had significantly higher BMI, waist circumference, fasting insulin, HOMA-IR, LH/FSH ratio, total testosterone, and AMH levels compared with controls (P<0.001) (Table 1). Serum concentrations of IL-6 and TNF-α were also elevated in the PCOS group (IL-6: 8.2 vs 4.1 pg/mL, P=0.013; TNF-α: 8.0 vs 1.7 pg/mL, p=0.039), whereas Ang (1-7) was lower (18.1 vs 21.2 pg/mL, P<0.01). Ang II showed no significant difference between the two groups. After adjusting for BMI using ANCOVA, the difference in IL-6 became borderline (P=0.050), while TNF-α was no longer statistically significant (P=0.068).

Data are presented as mean±Standard Deviation (SD) for normally distributed variables and median (interquartile range) for non-normally distributed variables in the unadjusted columns, and as mean±Standard Error (SE) in the adjusted columns.

In the PCOS group, Spearman's rank correlation analysis (Figure 1) revealed a very strong positive correlation between BMI and waist circumference (r=0.990, P<0.001). Fasting insulin was also strongly correlated with HOMA-IR (r=0.959, P<0.001). Associations involving gonadotropins showed a strong positive correlation between FSH and LH (r=0.936, P<0.001), while FSH was inversely correlated with the LH/FSH ratio (r=–0.329, P=0.027). Both FSH and LH demonstrated moderate positive correlations with TNF-α (r=0.464 and r=0.479, respectively; both P=0.001). Additionally, age was positively correlated with Ang II levels (r=0.334, P=0.025). No other correlations reached statistical significance.

ROC curve analysis (Figure 2) demonstrated that AMH had the highest discriminative ability for PCOS (AUC=0.866, sensitivity=62.2%, specificity=100%; P<0.001). Total testosterone also showed good diagnostic performance (AUC=0.765, sensitivity=66.7%, specificity=84.4%; P<0.001). IL-6 and TNF-α showed modest diagnostic value (IL-6 AUC= 0.652, P=0.009; TNF-α AUC= 0.626, P=0.037), while Ang (1-7) displayed moderate accuracy with an inverse association (AUC=0.718, sensitivity=86.7%, specificity=64.4%; P<0.001).

In the univariate logistic regression analysis (Figure 3), BMI (OR=1.287, P<0.001), waist circumference (OR=1.253, P<0.001), fasting insulin (OR=1.174, P<0.001), and HOMA-IR (OR=2.261, P<0.001) were significantly associated with PCOS. Additionally, LH (OR=1.182, P=0.012), LH/FSH ratio (OR=793.494, P<0.001), total testosterone (OR=4.323, P<0.001), AMH (OR=3.115, P<0.001), IL-6 (OR=1.125, P=0.015), and TNF-α (OR=1.089, P=0.007) also showed significant associations. However, age, fasting glucose, FSH, Ang II, and Ang (1-7) were not significantly associated with PCOS (P>0.05).

Table 1: Comparison of anthropometric, biochemical, and hormonal parameters between the control and PCOS groups, with unadjusted and BMI-adjusted analyses

Variables	Control (Unadjusted) (n=45)	PCOS (Unadjusted) (n=45)	Control (Adjusted) (n=45)	PCOS (Adjusted) (n=45)	P-value	
Age (year)	25(22-28)	25(19-29.5)	-	-	0.961	*
BMI (kg/m²)	26.91±3.2	30±5.32	-	-	<0.001	*
Waist Circumference (cm)	85±3.69	90.98±6	-	-	<0.001	*
FBG (mmol/L)	4.69±0.38	4.76±0.37	4.67±0.06	4.79±0.06	0.188	**
Fasting Insulin (µIU/mL)	10.4(8.4-14.6)	24.3(16.9-27.2)	12.0±0.81	21.0±1.44	<0.001	***
HOMA-IR	2.21(1.7-5.11)	4.91(3.2-5.8)	2.47±0.17	4.44±0.3	<0.001	***
FSH (mIU/ml)	3.6(3.3-6)	4.41(1.3-6.8)	4.28±0.49	3.25±0.37	0.102	***
LH (mIU/ml)	4.4(3.4-5.7)	5.9(2.2-11.5)	42.7±4.16	48.3±4.16	0.364	****
LH/FSH ratio	1.02(1.22-2.1)	1.66(0.98-1.09)	26.9±2.97	64.1±2.97	<0.001	****
Total Testosterone (ng/ml)	0.39(0.34-0.62)	1.27(0.51-2.21)	35.2±3.68	55.8±3.68	<0.001	****
AMH (ng/ml)	1.9(1.35-2.65)	5.2(2.85-8.5)	26.4±3.13	64.6±3.13	<0.001	****
IL-6 (pg/ml)	4.1(0.85-7.75)	8.2(2.15-9.75)	39.5±4.03	51.8±4.03	0.05	****
TNF-α (pg/ml)	1.7(1.1-6.45)	8(1.16-14.4)	39.9±4.09	51.1±4.09	0.068	***8
Ang II (pg/ml)	53.1±5.17	63.8±4.86	55.0±5.33	61.9±5.33	0.393	**
Ang (1-7) (pg/ml)	21.2(18-27.7)	18.1(16.8-19.4)	54.8±3.87	36.2±3.87	0.002	****

* Independent t-test (unadjusted), ** ANCOVA adjusted for BMI, *** ANCOVA on log-transformed dependent variable adjusted for BMI, and **** Rank-transformed ANCOVA adjusted for BMI.

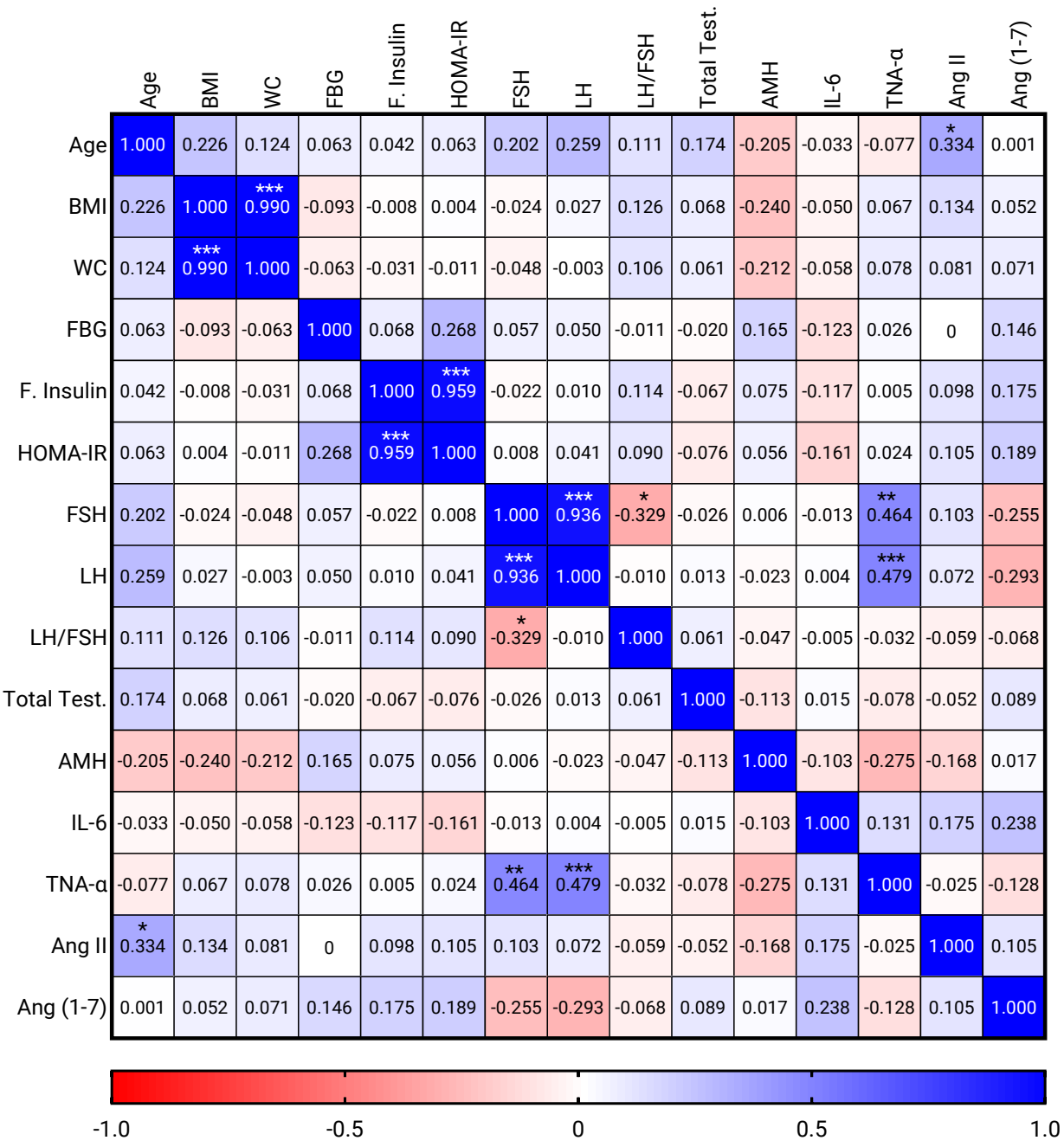


Figure 1. Spearman's correlation matrix of anthropometric, biochemical, and hormonal parameters in the PCOS group. Color intensity represents the strength and direction of correlation, with blue indicating positive correlations and red indicating negative correlations. P<0.05 (*), p<0.01 (**), and p<0.001 (***) denote statistical significance

WC: Waist Circumference, FBG: Fasting Blood Glucose, F. Insulin: Fasting Insulin, Total Test: Total Testosterone

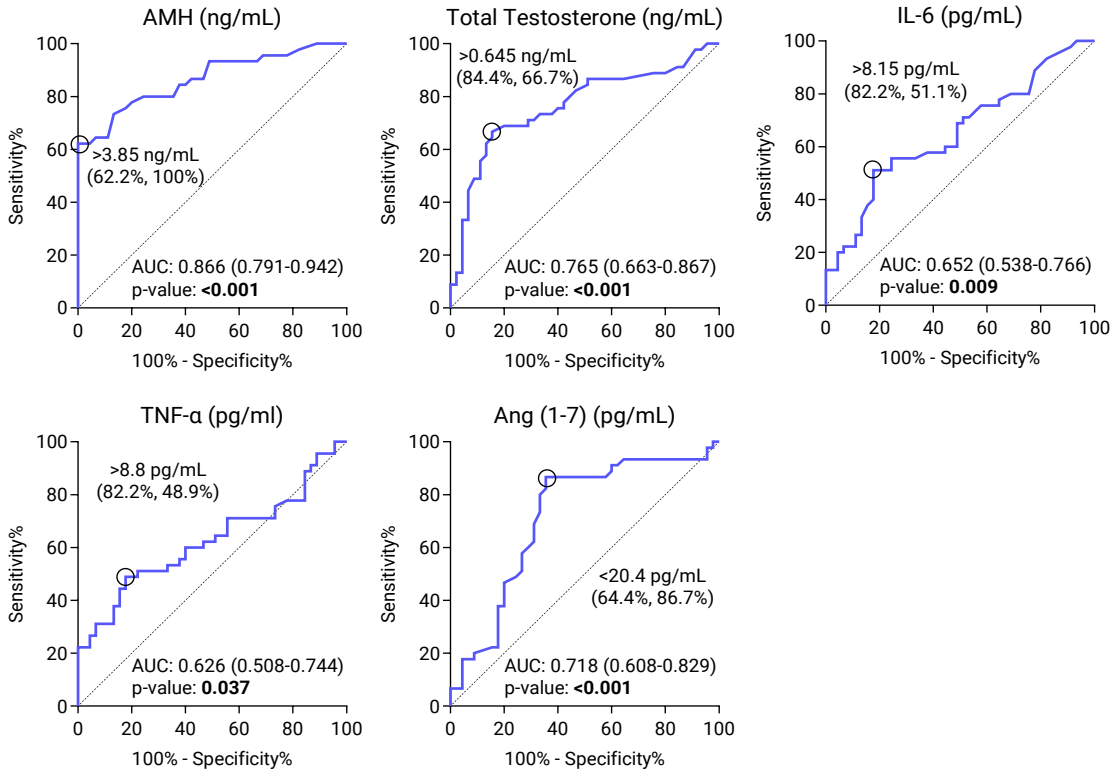


Figure 2. ROC curves for AMH, total testosterone, IL-6, TNF-α, and angiotensin 1-7 in differentiating women with PCOS from controls. The optimal cutoff value for each biomarker (indicated on the curve) was determined using Youden's index, with corresponding specificity and sensitivity shown in parentheses. The AUC with 95% CI and P-value is provided for each marker

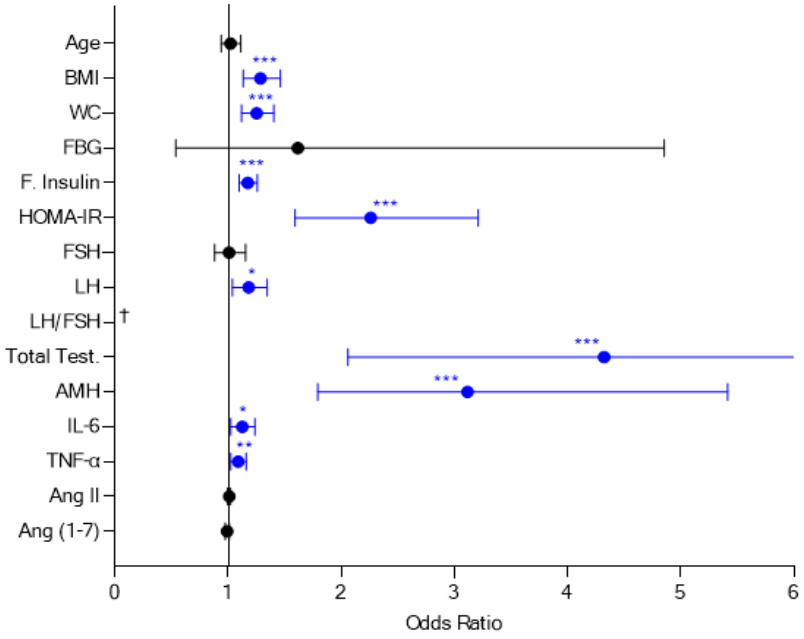


Figure 3. Forest plot of OR with 95% CI from univariate logistic regression analyses. Blue points indicate statistically significant predictors (*P<0.05, **P<0.01, ***P<0.001), while black points indicate non-significant variables. The † symbol marks the LH/FSH ratio, whose OR (793.5; 95% CI: 35.60-17,687) exceeded the plot scale and is therefore not shown in full

4. Discussion

Inflammatory Profile in PCOS

The present study provides a comprehensive investigation of the interrelationships between RAS peptides and inflammatory cytokines in PCOS, offering insights into the pathophysiological mechanisms that may link metabolic inflammation to reproductive dysfunction. Our findings suggest that women with PCOS exhibit a pro-inflammatory profile accompanied by hormonal and metabolic abnormalities. Higher circulating levels of IL-6 and TNF-α were observed in women with PCOS compared with healthy controls, suggesting a potential association between low-grade inflammation and metabolic or reproductive features of PCOS, consistent with recent meta-analyses demonstrating elevated inflammatory markers across diverse PCOS populations, this inflammatory profile has been previously linked to insulin resistance and may partially explain the increased cardiovascular and metabolic risk observed in women with PCOS **(7)**. However, after adjustment for BMI, the association between IL-6 and PCOS became borderline, while TNF-α was no longer statistically significant. These findings suggest that excess adiposity may substantially contribute to the observed inflammatory pattern, indicating that the inflammatory changes may not be solely attributable to PCOS. A similar finding was reported by Niu et al., **(20)**, who investigated follicular fluid cytokine profiles in PCOS patients with and without metabolic syndrome. Their study reinforces the concept that obesity may be a key confounding factor in PCOS-associated inflammation. While they found elevated TNF-α levels in PCOS patients with metabolic syndrome, this group also had substantially higher BMI compared to both controls and non-metabolic syndrome PCOS patients. Importantly, they demonstrated a positive correlation between TNF-α and triglyceride levels, providing mechanistic support for the metabolic basis of inflammation in PCOS. Consistent with our results, several studies have reported no significant differences in IL-6 levels between women with PCOS and controls after adjusting for metabolic factors, emphasizing the importance of considering these parameters when interpreting inflammatory biomarkers. Nevertheless, the literature remains inconclusive **(7)**. While some investigations have demonstrated elevated IL-6 and TNF-α levels in PCOS patients independent of BMI, others have failed to observe such differences, highlighting the ongoing debate regarding the extent to which PCOS itself contributes to systemic inflammation **(7)**.

RAS Dysregulation and Clinical Implications

In the present study, Ang II levels were not significantly associated with PCOS. This finding differs from that of some earlier studies reporting increased Ang II activity in women with PCOS and proposing a potential role of the RAS in metabolic dysregulation **(14,21,22)**. Our null finding for Ang II may be due to several factors. First, differences in patient populations, study methodologies, or assay techniques could contribute to discrepant results. Second, it is possible that systemic Ang II levels do not fully capture tissue-specific RAS activity; for example, ovarian or adipose tissue RAS could be upregulated in PCOS without a measurable rise in circulating Ang II **(23,24)**. Local tissue RAS systems can operate independently of systemic circulation, with adipose tissue and ovarian tissue both hosting functional local RAS that may not be reflected in circulating levels **(12,25)**. Third, a prior study **(14)** reporting elevated Ang II in PCOS often involved populations with significantly higher BMI differences between groups. Interestingly, a modest positive correlation was identified between age and Ang II levels among women with PCOS, suggesting a possible age-related pattern in RAS activity. This observation may reflect cumulative cardiometabolic alterations over time or age-related variability in PCOS manifestations. However, this relationship should be interpreted cautiously given the cross-sectional nature of the study, and further longitudinal research is needed to clarify the temporal dynamics of RAS activity in this population.

A key finding of our study is the significantly lower level of Ang (1-7) in PCOS women [18.1 (16.8-19.4) vs 21.2 (18-27.7) pg/mL, $P<0.01$]. This represents novel clinical evidence that PCOS is associated with deficiency in the ACE2/Ang (1-7)/Mas axis. Ang (1-7) is known to oppose many actions of Ang II, including mitigating inflammation, promoting vasodilation, and improving insulin sensitivity **(15)**. The reduced Ang (1-7) levels in PCOS may be associated with both the inflammatory state and insulin resistance characteristic of the syndrome. This finding aligns with recent single-cell RNA sequencing studies demonstrating local RAS dysregulation in ovarian tissue of PCOS patients **(18)**. Future research should explore the nature of the association between Ang (1-7) deficiency and PCOS, determining whether it reflects a feature of the condition or arises as a consequence, and whether strategies aimed at restoring Ang (1-7) activity may have potential therapeutic value.

Diagnostic Performance of Biomarkers

In the present study, ROC analysis provided important insights into the diagnostic utility of various biomarkers for PCOS. Among them, AMH showed a strong association with PCOS (AUC=0.866), suggesting its value as part of contemporary diagnostic assessments. These findings support its consideration alongside other clinical parameters, while acknowledging that biomarker performance may vary across populations and study settings **(26)**. Total testosterone also showed good discriminative ability (AUC=0.765), though practical implementation remains challenging due to assay standardization issues. In contrast, IL-6 and TNF-α demonstrated only

modest diagnostic value (AUC=0.652 and 0.626, respectively), despite being elevated on average in PCOS. This limited diagnostic performance may be attributed to the considerable overlap in cytokine levels between the PCOS and control groups, potentially influenced by the effects of obesity in both populations. These findings are consistent with recent systematic reviews showing that while inflammatory markers are consistently elevated in PCOS populations, their utility for individual patient diagnosis remains limited **(27)**. Inflammatory biomarkers may have greater value in phenotyping PCOS patients, monitoring treatment responses, or risk stratification for metabolic complications rather than primary diagnosis.

Notably, Ang (1-7) demonstrated moderate discriminative ability with an inverse association (AUC=0.718). Lower concentrations were more frequently observed among women with PCOS, which may point toward alterations within RAS. However, its moderate performance, together with assay complexity and cost considerations, may limit its feasibility as a routine diagnostic marker. Nevertheless, these findings may suggest important pathophysiological implications, indicating that RAS dysfunction in PCOS involves altered balance between opposing pathways rather than simple overactivity of the classical RAS.

Mechanistic Insights

Inflammation-Reproductive Axis Interactions

One notable observation from the correlation analysis in the present study was the positive association between TNF-α and gonadotropins among women with PCOS. TNF-α showed moderate correlations with both LH and FSH. This pattern may reflect a potential interaction between inflammatory pathways and hypothalamic–pituitary function in PCOS. Mechanistically, TNF-α produced by adipose tissue, ovaries, or other sources could act centrally to modulate GnRH secretion or pituitary responsiveness **(27)**. Experimental studies have demonstrated that TNF-α can alter hypothalamic dopaminergic activity and sensitize the pituitary to GnRH, potentially contributing to the characteristic LH hypersecretion and altered gonadotropin pulsatility in PCOS **(28)**. Our findings may suggest a potential association between metabolic inflammatory processes and neuroendocrine alterations in PCOS, highlighting a possible interplay between the metabolic and reproductive features of the syndrome. This inflammation-gonadotropin axis may partially explain why weight loss and anti-inflammatory interventions can improve reproductive outcomes in PCOS patients **(29,30)**.

The strong positive correlation observed between FSH and LH in our PCOS cohort, although anticipated, reflects the close association between these gonadotropins in this population. The inverse correlation between FSH and LH/FSH ratio is mathematically expected but clinically relevant, as the LH/FSH ratio remains an important diagnostic and phenotyping tool in PCOS.

We did not observe significant correlations between IL-6 and reproductive hormones, consistent with some **(31)** but not all previous studies **(32,33)**. IL-6 is strongly associated with insulin resistance and is elevated in obesity regardless of PCOS status **(34)**, which may explain why its correlations with reproductive parameters are less consistent. The differential behavior of these inflammatory cytokines indicates that TNF-α may be a more closely associated with hypothalamic-pituitary-gonadal axis disturbance, while IL-6 predominantly reflects systemic metabolic inflammation **(7)**.

The absence of correlations between systemic RAS peptides and ovarian hormones suggests that circulating RAS measurements may not fully reflect intra-ovarian RAS activity. Local tissue RAS systems can operate independently of systemic activity **(23)**, and ovarian RAS components influence follicular development, steroidogenesis, and ovulation rates in animal models **(35,36)**. Our finding of reduced circulating Ang (1–7) may reflect a global deficiency, but tissue-specific studies measuring follicular fluid concentrations or ovarian expression would provide more mechanistic insight.

This study had several important limitations that should be acknowledged. First, our sample size of 45 cases and 45 controls, while adequate for detecting major differences, may limit the generalizability and statistical power for detecting weaker associations or subgroup analyses. Larger multi-center studies would strengthen confidence in these findings. Second, the cross-sectional design of the study precludes determination of causality or temporal relationships between inflammatory markers, RAS peptides, and PCOS features. Longitudinal studies tracking changes in these biomarkers over time or in response to interventions would provide mechanistic clarity. Third, as a single-center study conducted in Iraq, our results may be influenced by specific genetic, ethnic, or environmental factors that limit generalizability to other populations. Fourth, we did not control for potentially important confounders including dietary intake, physical activity levels, or menstrual cycle phase at blood sampling, which could introduce variability particularly in inflammatory markers. Fifth, our focus on systemic biomarkers may not reflect tissue-specific activity, especially in ovarian tissue where local RAS and inflammatory systems may operate differently. Finally, while adjusted for BMI in our analyses, we did not account for other potential confounders such as body fat distribution, or detailed medication histories.

5. Conclusion

This study demonstrated altered renin-angiotensin system components in women with PCOS, evidenced

by lower Angiotensin (1-7) levels compared with controls. The associations observed between inflammatory markers and reproductive hormones highlight a potential interplay between immune and endocrine pathways in the syndrome. While traditional biomarkers such as AMH and total testosterone showed superior diagnostic performance, inflammatory markers may offer complementary value in the clinical evaluation of PCOS.

Overall, these findings reinforce the concept of PCOS as a multifactorial condition characterized by interconnected metabolic, hormonal, and inflammatory disturbances. Further large-scale prospective studies are warranted to confirm these associations and to better define their clinical relevance.

6. Declarations

Acknowledgments

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Ethical Considerations

This study was performed according to the Helsinki Declaration. The study protocol was approved by the University of Baghdad College of Pharmacy Ethics Committee (ethical code: REC032446A), and all participants gave informed written consent prior to enrollment.

Authors' Contributions

A.J.A contributed to data curation, formal analysis, investigation, resources, software, validation, visualization, writing- original draft, and writing- review & editing. S.S.A performed conceptualization, validation, methodology, project administration, and writing- review & editing.

Conflict of Interest

The authors declare no conflict of interest.

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