Academic Science Journal (ASJ)
Vol. 4, No. 2, April 2026, pp. 131~138
DOI: 10.24237/04.02.784

The Renin-Angiotensin System and Metabolic Dysfunction in PCOS: Associations between Angiotensin Peptides, HOMA-IR, and BMI

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Article Info

Article history:

Received 14,09, 2025
Revised 01, 11, 2025
Accepted 11,01, 2026
Published 30, 04,2026

Keywords:

Polycystic Ovary Syndrome,
Renin Angiotensin System,
Metabolic dysfunction,
BMI,
IR.

ABSTRACT

Polycystic Ovary Syndrome (PCOS) is a multifactorial disorder that affects both the metabolic and endocrine systems, characterized by chronic anovulation, hyperandrogenism, and insulin resistance. It is strongly associated with obesity, diabetes, and metabolic disturbances, with evidence suggesting that androgens may directly stimulate the renin–angiotensin system (RAS). This case–control study aimed to investigate the correlation of angiotensin peptides, HOMA-IR, and BMI in women with PCOS. A total of 90 reproductive-age women were enrolled, including 45 newly diagnosed PCOS patients (according to Rotterdam criteria) and 45 age-matched healthy controls. The levels of renin, angiotensin II, angiotensin 1–7, fasting insulin, and BMI were measured, and statistical analyses were performed using SPSS. Group comparisons were performed using the Mann–Whitney U test and independent samples t-test, whereas one-way ANOVA was applied to evaluate variations across BMI categories within the PCOS cohort. Correlations were evaluated using Spearman's and Pearson's methods, with statistical significance set at $p < 0.05$. Compared with controls, PCOS patients showed no significant differences in renin ($p = 0.254$) and angiotensin II ($p = 0.114$) levels, whereas HOMA-IR, angiotensin 1–7, and BMI were significantly elevated (all $p < 0.01$). Correlation analysis within the PCOS group revealed a negative relationship between renin and HOMA-IR ($p = 0.045$, $r = –0.3$). These findings highlight RAS alterations in PCOS, particularly reduced angiotensin 1–7 levels, which may indicate impaired protective RAS activity and its association with insulin resistance. Furthermore, elevated angiotensin II levels in women over 25 years suggest potential age-related RAS dysregulation, reinforcing the role of RAS imbalance in PCOS pathophysiology.

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1. INTRODUCTION

Polycystic Ovary Syndrome (PCOS), which is a highly prevalent reproductive endocrinopathy that affects about 8-18% women of reproductive age, is characterized by chronic anovulation, insulin resistance (IR) and hyperandrogenism[1]. Although several diagnostic criteria have been proposed for PCOS, the Rotterdam criteria remain the most widely adopted. Based on the criteria, PCOS is diagnosed if 2 of the 3 criteria—bio-chemical and/or clinical hyper-androgenism, oligo/anovulation, and polycystic ovarian morphology (PCOM) [2]—are met. Nevertheless, up to 70% of women with PCOS might go undetected [3]. Hypertension, central obesity, hyperlipidemia, and hyperglycemia are all part of metabolic syndrome (MetS), which is a group of metabolic risk factors. The precise aetiology of MetS is unknown [4]. PCOS is a major contributor to infertility as well as a risk factor for other metabolic diseases, including endometrial carcinoma, type 2 diabetes mellitus (T2DM), and cardio-vascular disease [5]. PCOS affected 66 million people globally in the year 2019[6]. There are regional and age-based variations in PCOS prevalence and incidence rates. However, PCOS incidence and prevalence rates are generally steadily rising[7].

The annual economic cost of PCOS has been estimated to be $8 billion by the year 2020[8]. Yet, neither the European Medicines Agency nor the US FDA have approved any particular medication as of 2024 [9]. Symptom-oriented and off-label medications, including letrozole, metformin, clomiphene, and oral contraceptives, are prescribed to PCOS patients [10]. It is essential to thoroughly investigate the epidemiological features of PCOS to give the government a basis for decisions about the allocation of medical

Numerous organs and tissues were shown to have RAS. A localized renin–angiotensin system, known as the ovarian renin–angiotensin system (OVRAS), has been identified within the adult ovary[11]. Together with the circulating endocrine RAS, the RAS system is composed of a number of active substances and enzymes. In the local RAS system, which regulates electrolytes and blood pressure, the active peptides Angiotensin (1-7) (Ang-(1-7)) and Angiotensin II (Ang II) appear to have unique actions[12]. It is mostly found in the uterus, ovary, and placenta in the female reproductive system. As a result, along with such characteristics, angiotensin as well as its receptors in the reproductive system appear to be involved in physiological processes regarding the uterus and placenta and reproductive activities, like follicle growth and development. Furthermore, alterations in RAS components have the potential to cause pathological conditions like cancer and reproductive diseases[13]. Although Ang- (1–7) and Ang II appear to have antagonistic actions in the majority of tissues, this is not necessarily the case in the reproductive system, in which they have comparable pathological and physiological roles[14]. It was clarified how variations in local activity RAS components in a number of diseases affecting the reproductive system, such as cancer and diseases linked to infertility, affect the onset and progression of those diseases[13]. Research on the alterations in RAS component expression in patients who have PCOS was conducted[15]. Alphan et al. found that blood total renin concentrations have been higher in patients who have PCOS when compared with the non-PCOS patients[16]. A survey had discovered that obese women with PCOS had higher total renin concentration levels, which have been associated with the free testosterone as well as the fasting insulin levels. The activity of Angiotensin-Converting Enzyme (ACE) and Ang II levels have been significantly higher in PCOS patients, but there has not been any significant difference in plasma renin activity between the controls and PCOS women[17]. These results indicate that the RAS is active in PCOS patients, Angiotensin Peptides, HOMA-IR, and BMI correlation in PCOS were the focus of the presented research.

Previous studies have mainly examined the local ovarian RAS and its effect on angiotensin receptors and ovarian function. However, the metabolic role of RAS components and their contribution to the pathophysiology of PCOS remain poorly understood. This study focused on the metabolic implications of RAS dysregulation, exploring how changes in angiotensin peptides may influence insulin resistance and metabolic balance in women with PCOS. To the best of our knowledge, it is also among the first to measure Ang-(1-7) levels in PCOS patients. We recommend that future research include the measurement of ACEs to better understand its potential effect on angiotensin peptide levels and the overall RAS activity in PCOS. One of the main challenges was collecting samples from newly diagnosed, treatment-naïve PCOS patients to avoid interference with biomarker levels.

2. METHOD

2.1. Study Configuration and Design

The case control study's time frame has been from December-2024 to Marach-2025. This research was conducted in accordance with the guiding principles of the Declaration of Helsinki. Each one of the patients visited the private gynecological clinics in Fallujah, Iraq, and has been diagnosed with PCOS based on Rotterdam criteria. A total of 90 volunteers has taken part in this study, 50% of them had received a PCOS diagnosis recently. The other 50% of the women, who were apparently in good health, represented the controls. Demographic data, including age (ranging from 18 to 40 years), body mass index (BMI; calculated as weight in kilograms divided by height in meters squared), and waist circumference (waist circumference was assessed at the midpoint between the lower margin of the last rib and the iliac crest), were recorded for all participants. Women had been classified to have normal weight if their BMIs were between 18.50 and 24.90kg/m2, obese if they were over 30kg/m2, and overweight if they were between 25 and 29.9 kg/m2. Cushing's syndrome, androgen-secreting tumors, congenital adrenal hyperplasia, hyperprolactenemia, thyroid problems, hyperprolactinemia, and other illnesses with similar clinical presentations have not been allowed to take part in this study. Additionally, patients with chronic diseases who were receiving medications such as immunosuppressants, antidiabetic agents, or antihypertensive drugs were not included.

2.2. Sample collection

Each participant provided a 5 mL blood sample at 9:00 a.m. Plasma was separated by centrifugation at 3000 rpm for 10 minutes and subsequently stored at –20°C until analysis. All participants were informed to fast from food for at least 8 hours prior to blood collection**.** Plasma levels of total testosterone, renin, luteinizing hormone (LH), follicle-stimulating hormone (FSH), Ang II, and Ang (1–7) were quantified using ELISA kits (ELK Bio-Technology, China).

Fasting plasma glucose was measured via biochemical analysis (Cobas® Pure, Germany), and fasting insulin levels were determined using an ELISA kit (Reed Bio-Technology, China). Homeostatic Model Assessment of Insulin Resistance (HOMA-IR) was calculated as fasting insulin (μIU/mL) × fasting glucose (mmol/L) / 22.5.

2.3. Ethical approval

This study received ethical approval from the Ethics Committee of the College of Pharmacy, University of Baghdad (Approval No. REC032446A, dated October 20, 2024). All participants gave verbal consent after being fully informed about the study's objectives and intended benefits.

2.4. Statistical analyses

SPSS v. 23 software has been used for conducting statistical analyses. The Shapiro-Wilk test has been utilized for the assessment of the normality levels. The variables have been displayed as median (interquartile range) or mean ± standard deviation. The median values of renin, Ang II, age, Ang (1–7), HOMA-IR, LH, FSH, and total testosterone between the two groups were compared using the Mann–Whitney U test, whereas the mean values of BMI, fasting plasma glucose, and waist circumference were compared using the independent samples t-test. One-way ANOVA was conducted to compare the levels of renin, angiotensin II, and angiotensin 1–7 among PCOS patients with normal weight, overweight, and obesity. The correlation between the variables under study was evaluated using Spearman's and Pearson's correlations. P-values below 0.05 have been regarded significant.

3. RESULTS AND DISCUSSION

3.1. Biochemical, Hormonal, and Anthropometric Characteristics of PCOS Patients

Table 1 lists bio-chemical, demographic, and hormonal features of the controls and the PCOS group. Age has been matched between those two groups. Compared with the controls, PCOS patients had much higher fasting insulin and HOMA-IR levels. BMI, LH/FSH ratio, total testosterone, and waist circumference levels have been substantially greater in PCOS-afflicted women than in control ($p < 0.01$). Ang (1–7) was considerably greater in the controls when compared to PCOS patients, although there has not been any significant difference in levels of serum renin or Ang II between the groups.

In order to examine the impact of BMI and age on renin, Ang II, and Ang (1–7) levels in PCOS group, the groups were separated based on age into two groups: those aged > 25 and those aged ≤ 25. Renin and Ang (1–7) concentrations did not differ significantly between groups, but Ang II concentrations were significantly higher in the group aged over 25 ($p = 0.039$), shown in Table 2.One-way ANOVA was conducted to compare the levels of renin, Ang II, and Ang (1–7) among PCOS patients with normal weight, overweight, and obesity. Levene's test indicated homogeneity of variances ($p > 0.05$ for all variables). The analysis showed no statistically significant differences between groups in renin Ang II and Ang (1–7). shown in Table 3.

Table 1. The demographic, biochemical data and hormonal profiles of studied groups

	PCOS (n=45)	Control (n=45)	*P*-value
Age, years	25 (19-29.5)	25 (22-28)	0.961
BMI (Kg/m2)	30 ± 5.32	26.91± 3.2	<0.01*
Waist circumference (cm)	90.98 ± 6	85 ± 3.69	<0.01*
Fasting plasma glucose, mmol/L	4.76 ± 0.37	4.69 ± 0.38	0.395
Fasting insulin, μIU/mL	24.3 (16.9-27.2)	10.4 (8.4-14.6)	<0.01*
HOMA-IR	4.91 (3.2-5.8)	2.21 (1.7-5.11)	<0.01*
FSH, mIU/ml	4.41 (1.3-6.8)	3.6 (3.3-6)	0.171
LH, mIU/ml	5.9 (2.2-11.5)	4.4 (3.4-5.7)	0.29
LH/FSH ratio	1.66 (0.98-1.09)	1.02(1.22-2.1)	<0.01*
Total Testosterone, ng/ml	1.27(0.51-2.21)	0.39(0.34-0.62)	<0.01*
Renin, pg/ml	18.5(13.4-31.4)	25(16.1-35.15)	0.254
Ang II, pg/ml	68.8 (28.3-89.5)	59.2 (20-82.4)	0.114
Ang (1–7) pg/ml	18.1(16.8-19.4)	21.2(18-27.7)	<0.01*

Where n=number; PCOS= Polycystic ovary syndrome; HOMA-IR= Homeostatic Model Assessment for Insulin Resistance; FSH = Follicle-stimulating hormone; LH=Luteinizing Hormone.

Data shown as mean ± SD and median (the interquartile range)
**P<0.050 has been significant.*

Table 2. The levels of renin, Ang II and Ang (1-7) according to age in PCOS

Parameters	PCOS age ≤ 25 years (n=23)	PCOS age > 25 years (n=22)	*P*-value
Renin, pg/ml	18.8 (13.21-31.27)	16.71 (13.7-31.27)	0.785
Ang II, pg/ml	54 ± 32	73.9 ± 30	0.039*
Ang (1-7), pg/ml	17.9 (16.2-22.48)	18.1 (17.02-19.07)	0.794

Where n=number; PCOS= Polycystic ovary syndrome
Data represented as mean ± SD and median (the interquartile range)
**P<0.050 has been significant.*

Table 3. Comparison of Renin–Angiotensin System Components among PCOS Patients According to BMI Categories

Variable	Normal weight (n=7)	Overweight (n=13)	Obese (n=25)	F(df)	p-value
Renin, pg/ml	13.3 ± 6.5	33.3 ± 19.0	25.6 ±25.5	F(2,42)=1.93	0.158
Ang II, pg/ml	60.1± 33.2	63.1 ± 26.7	67.6 ±28.7	F(2,42)=0.38	0.686
Ang (1-7), pg/ml	24.2± 20.5	17.6 ± 6.9	24.8 ±27.9	F(2,42)=0.46	0.636

**No statistically significant differences were observed between groups (p > 0.05 for all comparisons).*

3.2. Correlation studies between HOMA-IR and Fasting insulin levels with renin, angiotensin II and angiotensin (1-7) levels of PCOS patients

The correlations between the patients investigated characteristics and their HOMA-IR as well as fasting insulin levels were displayed in Table 4. HOMA-IR revealed a negative correlation with renin levels (r = -0.3, p = 0.045) and no significant correlation with Ang II or Ang (1–7) levels. There has been a significant negative correlation (r = -0.352, p = 0.001) between fasting insulin level and concentrations of Ang (1–7).

Table 4. Correlations of HOMA-IR and Fasting insulin level with the studied variables of PCOS

Parameters	HOMA-IR	Fasting insulin levels		
	Correlation	*P*-value	*correlation*	*P*-value
renin	-0.3	0.045*	0.072	-0.19
Ang II	0.09	0.556	0.092	0.546
Ang (1-7)	0.189	0.213	-0.352	0.001*

**P<0.05 has been significant.*

3.3 Correlation studies between BMI and renin, angiotensin II and angiotensin (1-7) levels of PCOS patients

Table 5 showed the correlations of BMI with the studied variables of the patients. Regarding the BMI, it showed no significant correlation with renin, angiotensin II and angiotensin (1-7) levels.

Table 5. Correlations of BMI with the studied variables of PCOS

	correlation	*P*-value
Renin	0.023	0.881
Ang II	0.12	0.432
Ang (1-7)	0.052	0.736

**P<0.05 was significant.*

3.4. DISCUSSION

PCOS is still a syndrome with a complicated pathophysiology that is regulated through various hormones as well as impacted by a number of environmental and genetic variables[18]. A number of hormone markers were suggested as PCOS diagnostic techniques, including LH, testosterone, and FSH. Nonetheless, it seems that these hormones fluctuate over the menstrual cycle and have inconsistent diagnostic effectiveness[19]. Enhanced knowledge of the variations in hormonal and biochemical indicators between Healthy Controls and PCOS patients was one of the primary results of this study.

According to this research, in comparison with the control group, women with PCOS have noticeably higher levels of HOMA-IR, BMI, total testosterone, fasting insulin, LH, and the LH/FSH ratio. This is consistent with findings from Haolin Zhang et al. and Terhi T. Piltonen et al. they show the same outcomes[20,21]. The results confirm the documented connection between metabolic, endocrine and PCOS dysfunctions. There is still much to learn about RAS origin, physiological function, and hormonal action in PCOS. Nonetheless, a number of studies indicate that the MetS is associated with an overactive RAS[22] and a number of metabolic manifestations, including IR and obesity, are linked to PCOS[23]. As demonstrated by previous studies, there is a correlation between components of RAS and insulin resistance in patients with PCOS[17]. This association underscores the complex interaction between metabolic dysfunction and hormonal regulation in the pathophysiology of PCOS. In the present study, plasma renin and Ang II levels did not differ significantly between groups, which contrasts with some previous reports suggesting that PCOS may involve overactivation of components of RAS associated with insulin resistance [24]. Women who have PCOS had significantly greater renin levels than the control group[25,13] , according to Jorly Mejia-Montilla et al. and Alphan et al., whereas Soheila Arefi et al. demonstrated that the PCOS group had much higher levels of Ang II compared to the control group[17]. Compared to PCOS patients, the control group had considerably greater levels of Ang (1–7). This research raises the possibility that women with PCOS may have an imbalance in RAS's protective arm. As far as we are aware, no prior study has directly measured Ang (1–7) levels in PCOS patients. This is because Ang 1–7 has anti-inflammatory, insulin-sensitizing, and vasodilator effects [26], and its lower levels might contribute to important PCOS features like chronic inflammation and IR. The absence of significant differences in renin and Ang II levels between the groups might be attributed to localized ORAS activity that is not captured in serum measurements, potential changes in ACE2 activity influencing Ang 1–7 synthesis, or variations in individual and hormonal profiles. Furthermore, the relatively small sample size may have limited the ability to detect minor differences.

Further subgroup analysis within the PCOS group based on age (≤ 25 vs. > 25 years) and BMI categories (normal weight, overweight and obese) revealed a significant increase in Ang II levels among patients aged > 25 years. However, no significant differences have been noted in renin or Ang (1-7) levels across age or BMI subgroups. These findings suggest that age may influence Ang II levels in PCOS, while BMI does not appear to have a notable effect on RAS components in this study.

Regarding the correlation between renin levels and HOMA-IR in PCOS patients, renin levels were inversely correlated with HOMA-IR ($r = –0.3$, $p = 0.045$), indicating that individuals with higher renin levels exhibited lower IR as assessed by HOMA-IR. This finding is somewhat unexpected, as previous studies in patients with T2DM have reported positive correlations between renin levels, hyperglycemia, and insulin resistance [27]. These results suggest that renin may not serve as a direct mediator of insulin resistance in PCOS, or that its role is more complex and warrants further investigation.

The association between Ang II and HOMA-IR was weak and not significant ($r = 0.09$, $p = 0.556$) indicating that angiotensin II might not be a significant effective factor for IR in PCOS women. Contrary to earlier research, which found a link between IR and Ang II in patients with T2DM, this result is surprising[28]. A compensatory response regarding the RAS to counterbalance metabolic disturbances was indicated by the positive correlation between the Ang (1-7) level and HOMA-IR ($r = 0.189$, $P = 0.213$), yet this finding was not statistically significant. On the contrary with earlier findings that found oral treatment with A-1317 (Ang (1-7) analogue) was more effective in lowering body mass increase, improving IR, b-cell functionality, and liver damage[29], this suggests that Ang (1-7) may have a weak relationship with IR in PCOS. There was no statistically significant correlation between Ang II and Ang (1–7) levels as well as HOMA-IR; this discrepancy could be explained by variations in sample size, study population, or methodological factors like assay sensitivity as well as timing of sample collection. To elucidate the nature of this link, more research is necessary.

Comparing to earlier research that found insulin increases circulating Ang II levels as well as renin activity[30], both Ang II ($r = 0.092$, $p = 0.546$) and renin ($r = 0.072$, $p = 0.19$) did not significantly correlate with fasting insulin levels, indicating that such peptides are most likely not directly impacting fasting insulin levels in PCOS patients. Additionally, a significant negative correlation was seen between Ang (1-7) and fasting insulin ($r = -0.352$, $P = 0.0010$), suggesting that a higher level of Ang (1-7) may be associated with a

lower level of fasting insulin, this finding is intriguing because it suggests that Ang (1–7) can provide protection against IR in PCOS.

According to Fernando P. DOMINICI et al., Ang-(1–7) improves insulin action through mechanisms such as enhancing insulin signaling, blocking Ang II's negative effects, and improving insulin delivery to tissues. These discoveries highlight the potential of targeting the ACE2/Ang-(1–7)/Mas receptor axis as a therapeutic strategy for metabolic syndrome and T2DM [31]. BMI did not exhibit a statistically significant correlation with renin, Ang II, or Ang (1–7), as indicated in (Table 5). This finding suggests that BMI may not have a substantial impact on renin, Ang II, and Ang (1–7) in PCOS women in the current research. Obesity is linked to elevated levels of serum renin as well as Ang II, which contradicts earlier results. Probably as a result of the elevated sympathetic tone in obese people, plasma renin levels rise in obesity.[32] Furthermore, obese people have higher levels of plasma Ang II after beta adrenergic stimulation than lean people do[32]. Overweight and obesity were linked to lower Ang 1–7 levels in the circulation and higher Ang II levels[33]. Numerous factors, such as variations in population ethnicity, study design or genetic background, BMI distribution, hormone profiles, and sample size, can account for this discrepancy. The observed inconsistencies might be caused by variances in the date of sample collection as well as variations in laboratory procedures, like the specificity and sensitivity of the tests performed. These elements underscore the necessity for more extensive, standardized research to validate such correlations and the complexity related to the RAS's function in metabolic control in PCOS patients.

4. CONCLUSION

With a focus on RAS, the current study advances our knowledge of the metabolic as well as hormonal characteristics of women with PCOS. The findings coincided with a number of existing findings in the literature, particularly in terms of the correlation between IR, obesity and metabolic dysfunction in PCOS. Nevertheless, the absence of differences in plasma renin and Ang II levels between PCOS patients and healthy controls and a significantly lower level of Ang (1-7) was detected in the PCOS group. This may reflect a disruption in the alternative, protective arm of the RAS, which is known for its anti-inflammatory and insulin-sensitizing effects. Furthermore, the observed negative correlation between Ang (1-7) and fasting insulin suggests a potential link between reduced Ang (1-7) activity and insulin resistance in PCOS. Notably, Ang II levels were significantly higher among PCOS patients aged > 25 years, indicating a possible age-related upregulation of the classical RAS pathway. These findings highlight the complexity of RAS regulation in PCOS and suggest that both age and insulin dynamics may modulate its activity.

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