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**RESEARCH ARTICLE**

# Correlation between Hyperandrogenism and Endothelin-1 Levels with Cardiovascular Risks in Lean Women with PCOS

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**ABSTRACT**

Hyperandrogenism, a key factor in the pathophysiology of PCOS, affects 60–80% of PCOS cases. While PCOS is primarily associated with reproductive disorders, it is also linked to metabolic dysfunction, which heightens cardiovascular disease (CVD) risks. Endothelin-1 (ET-1), a biomarker involved in atherosclerotic lesion formation, is considered predictive of future CVD events.This study aimed to evaluate the relationship between hyperandrogenism and cardiovascular risks in non-obese PCOS patients, with a focus on endothelial dysfunction markers such as ET-1. A cross-sectional observational study was conducted on 38 non-obese PCOS patients, divided into hyperandrogenism (HA) and non-hyperandrogenism (non-HA) groups. Physical examinations assessed FG Score, waist circumference (WC), and waist-to-hip ratio (WHR). ET-1 levels were measured using the ELISA method. Statistical analyses were performed with SPSS version 21. The WC and WHR comparisons between HA and non-HA groups showed no significant differences (WC: 80.68 ± 9.47 vs. 80.02 ± 9.25, p = 0.838; WHR: 0.84 ± 0.03 vs. 0.83 ± 0.07, p = 0.781). However, ET-1 levels were significantly higher in the HA group (12.11 ± 6.86 vs. 7.31 ± 4.56, p = 0.021). Systolic blood pressure was positively correlated with FG Score (r = 0.413, p = 0.010), while no significant relationships were observed between FG Score and ET-1, WC, WHR, or diastolic blood pressure. The HA PCOS group demonstrated elevated ET-1 levels and cardiometabolic markers (WC, WHR, BP) compared to the non-HA group. A significant association was found between hyperandrogenism and systolic blood pressure, highlighting its role in cardiovascular risk.

## INTRODUCTION

Polycystic ovary syndrome (PCOS) is an endocrine disorder that affects 20% of women in their reproductive years (Lizneva et al., 2016). It is not limited to the obese population, as approximately 20–50% of those with PCOS have a BMI within the normal range (Atnil et al., 2022). The approach to diagnosing PCOS has shifted over the years, but currently, the Rotterdam criteria are the most widely used. At least two of the following three traits are needed to meet these criteria: clinical signs of

hyperandrogenism, ovulatory disorders characterized by oligomenorrhea or amenorrhea, and ultrasound findings of polycystic ovaries (The Rotterdam ESHRE/ASRM-sponsored PCOS consensus workshop group, 2004). Among the various signs and symptoms, hyperandrogenism plays a major part in PCOS pathophysiology, affecting approximately 60–80% of women with the condition (Ye et al., 2021). Hyperandrogenism is the final outcome of various proposed mechanisms, ultimately resulting in ovulatory dysfunction. This is supported by the classification of PCOS phenotypes, which display a spectrum of clinical severity, with hyperandrogenism present in the three initial phenotypes exhibiting more severe clinical symptoms.

In addition to dominant reproductive disorders, PCOS is also closely associated with metabolic dysfunction, which can lead to cardiovascular disease (CVD). Women with PCOS exhibit unfavorable cardiometabolic biomarker profiles. Beyond general biomarkers such as BMI, visceral fat, insulin resistance, and dyslipidemia, inflammatory processes also contribute to the development of CVD, increasing the prevalence of metabolic syndrome. These biomarkers are interrelated, creating a complex relationship that culminates in cardiovascular health disorders (van der Ham et al., 2022; Nasir et al., 2024). Insulin resistance, for example, is closely linked to the acceleration of atherogenesis, making coronary artery calcification common in PCOS-affected women (González et al., 2009; Jam et al., 2014). Notably, insulin resistance is not exclusive to obese women with PCOS; approximately 20–25% of non-obese PCOS women also experience insulin resistance (Taylor et al., 2019).

As a complex syndrome, it is critical to elucidate the pathophysiological pathways that contribute to specific cardiovascular risks in PCOS. Hyperandrogenism, in particular, is suspected to be a primary cause of endothelial dysfunction in PCOS-affected women, independent of obesity as a risk factor. The balance between vascular constriction and dilation is closely linked to endothelial dysfunction. Endothelin-1 (ET-1) serves as an indicator of endothelial dysfunction due to its role in maintaining this balance. ET-1 is a major factor behind the formation of atherosclerotic lesions and is considered a predictor of future CVD events (Bohm & Pernow, 2007). Research by Usselman et al. indicated that endothelial dysfunction, characterized by increased ET-1 levels, was less prevalent in the control group than in the HA PCOS group (Usselman et al., 2019). Similarly, Wenner et al. observed elevated ET-1 levels in obese PCOS-affected women in comparison to obese controls (Wenner et al., 2013). Other clinical parameters analyzed in this context include the waist circumference (WC) and waist-to-hip ratio (WHR). Saxton et al. (2019) reported that an increased WHR indicates excessive adipose accumulation in visceral tissue, contributing to CVD through mechanisms similar to those associated with ET-1. This involves a disruption of the balance between vasodilation and vasoconstriction, which eventually leads to cardiovascular events (Saxton et al., 2019).

The discussion above demonstrates that changes in serum ET-1 levels can serve as predictors and clinical markers for assessing the risk of CVD in PCOS-affected women. Over time, these findings could form the basis for individualized monitoring and targeted management of PCOS.

## MATERIALS AND METHODS

### Subjects

In this cross-sectional observational analytic research, all procedures were supervised and approved by the Ethical Committee of the Faculty of Medicine, Universitas Airlangga (reference No. 74/EC/KEPK/FKUA/2024). A total of 38 subjects were gathered using the purposive random sampling method and separated into two groups according to the presence of hyperandrogenism. The inclusion criteria were women aged 18–35 years with a non-obese BMI (18–27) and PCOS diagnosed based on the Rotterdam criteria. Exclusion criteria included the use of medications for PCOS in the past three months, diabetes mellitus or hypertension under treatment, and hyperandrogenism caused by other conditions such as congenital adrenal hyperplasia,

hypothyroidism, androgen-producing tumors, hyperprolactinemia, excessive exercise, Cushing's syndrome, and pregnancy.

### Data Collection

Anamnesis, physical examination, and ultrasound were performed to diagnose PCOS using Rotterdam criteria. The cutoff for the FG score was adjusted for the Asian population, with an FG score ≥ 5 considered as hyperandrogenism (Li et al., 2012). Anthropometric measurements were conducted to assess BMI, waist-to-hip ratio (WHR), and waist circumference (WC). According to the national local guidelines on nutritional status, BMI ≥ 27.00 was categorized as obesity; thus, the inclusion criteria used a BMI range of 18–27. WC was defined as the circumferential diameter between the lower corner of the iliac crest and the costae. WHR was calculated as the ratio of waist circumference to hip circumference. Hip circumference was defined as the circumferential diameter at the level of the greater trochanter. Endothelin-1 levels were measured using the ELISA technique from serum specimens collected from all subjects. Hypertension was defined based on the ACC/AHA guidelines, with a cutoff of ≥ 130/80 mmHg. All examinations and measurements were performed by the same team of operators.

### Data analysis

The research data were analyzed using SPSS Statistics. Each variable underwent univariate analysis, which included descriptive analysis, a homogeneity test using Levene's test, and a normality test using the Shapiro-Wilk test. Data were considered homogenous and/or normally distributed if the p-value was greater than 0.05. For data that follows a normal distribution, the appropriate analysis would involve an independent T-test. However, if the data does not follow a normal distribution, the Mann-Whitney test would be used instead. A p-value under 0.05 was the cutoff for statistical significance in this study.

## RESULTS

The research was conducted at Klinik Kehamilan Sehat, Kendangsari Mother and Children Hospital, and El-Shafi Clinic, Surabaya, from May–June 2024. The total sample consisted of 38 subjects selected according to the inclusion and exclusion criteria and were separated into two groups: PCOS with hyperandrogenism and PCOS without hyperandrogenism (Table 1).

**Table 1. Subject characteristics**

| Variable | Group | N | Minimum | Maximum | Mean | Std. Deviation |
|---|---|---|---|---|---|---|
| Age | HA | 19 | 19 | 34 | 27.42 | 3.288 |
| | Non-HA | 19 | 24 | 35 | 29.05 | 4.636 |
| BMI | HA | 19 | 20.08 | 25.97 | 23.48 | 1.990 |
| | Non-HA | 19 | 17.97 | 25.96 | 23.96 | 2.118 |

Comparative analysis employing the Mann-Whitney test showed a p-value < 0.05 (p = 0.000), indicating a substantial variation between the FG Score values of the HA and non-HA PCOS groups. A p-value > 0.05 (p = 0.838) was obtained from a comparative analysis using the Mann-Whitney test, indicating that there was no substantial variation between the WC values of the HA and non-HA PCOS groups. The Shapiro-Wilk analysis revealed that the distribution of ET-1 levels in the HA PCOS group was abnormal, with a p-value of 0.003. In contrast, the p-value for the distribution of ET-1 levels in the non-HA PCOS group was 0.559. A comparative analysis conducted employing the Mann-Whitney

test yielded a p-value of 0.021, showing a substantial difference between the Endothelin-1 levels of the HA PCOS group and the non-HA PCOS group (Table 2).

**Table 2. Comparative analysis of variables**

| Variable | HA | Non-HA | p-value |
|---|---|---|---|
| FG Score | 6–12 (9.00) | 0–5 (3.00) | 0.000* |
| Waist Circumference | 68–103 (80.68) | 62–95 (80.02) | 0.838 |
| Waist-to-Hip Ratio | 0.78–0.92 (0.84) | 0.71–0.92 (0.83) | 0.781 |
| ET-1 Level | 3.36–33.98 (12.11) | 0.66–15.59 (7.31) | 0.021* |

The Chi-square test analysis revealed a substantial connection between blood pressure and hyperandrogen conditions, with a p-value of 0.008 ($p < 0.05$) (Table 3). The examination of the association between blood pressure and elevated Endothelin-1 levels (cutoff ET-1 levels > 6.03) using the Chi-square test yielded an insignificant connection, with a p-value of 0.062 ($p > 0.05$) and a correlation coefficient of 0.290. The ROC (Receiver Operating Characteristic) curve quantified the diagnostic efficacy of ET-1 levels. According to the test, ET-1 levels had an area under the curve (AUC) of 0.719 (0.550–0.852) with a p-value of 0.008, suggesting that the ROC test result was statistically substantial. The determined cutoff value was more than 6.03 pg/mL, with a sensitivity of 89.47% (confidence interval: 66.9%–98.7%) and a specificity of 47.37% (confidence interval: 24.4%–71.1%) (Table 4) (Figure 1).

**Table 3. Correlation analysis between hypertension and hyperandrogenism**

| Blood Pressure | HA | | Non-HA | | p-value |
|---|---|---|---|---|---|
| | N | % (in group) | N | % (in group) | |
| Hypertension | 7 | 36.8 | 0 | 0 | 0.008 |
| Normal | 12 | 63.2 | 19 | 100.0 | |
| | | | | | |

**Table 4. Correlation analysis between ET-1 level and hypertension.**

| ET-1 level | With risk (ET-1 > 6.03) | | Without risk (ET-1 < 6.03) | | r | p-value |
|---|---|---|---|---|---|---|
| | N | % | N | % | | |
| Hypertension | 7 | 18.4 | 0 | 0 | 0.290 | 0.062 |
| Normal | 20 | 31.5 | 11 | 50.0 | | |

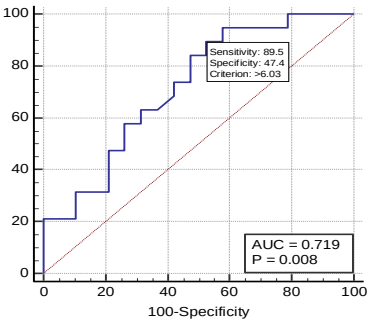


**Figure 1. ROC curve for ET-1 levels (Endothelin-1)**

The correlation coefficient between FG Score and waist circumference in the HA PCOS group was -0.181, indicating a weak connection. Nevertheless, the p-value of 0.278 suggested that this connection was not statistically substantial ($p > 0.05$). The correlation coefficient between FG Score and waist-to-hip ratio in the HA PCOS group was -0.122, indicating a moderate connection. The p-value of 0.467 suggested that this connection was not statistically substantial ($p > 0.05$). The results

of the FG Score connection test with ET-1 levels yielded a correlation coefficient of 0.563. The investigation of the connection between FG Score and Endothelin-1 levels using the Spearman test showed an insignificant connection, with a p-value of 0.563 ($p > 0.05$), indicating that the link was not statistically substantial ($p > 0.05$). The correlation coefficient value was 0.097. The analysis of the connection between FG Score and blood pressure in the HA PCOS group using the Pearson test revealed a substantial connection. The p-value for systolic blood pressure was 0.010, indicating a strong relationship with a correlation coefficient of 0.413. However, for diastolic blood pressure, the connection was found to be insignificant, with a p-value of 0.052 and a correlation coefficient of 0.317.

**Table 5. Correlation analysis between FG score and cardiometabolic markers**

| Variable | r | p | Description |
|---|---|---|---|
| Waist Circumference | -0,181 | 0.278 | Not Significant |
| Waist-to-Hip Ratio | -0.122 | 0.467 | Not Significant |
| ET-1 Level | 0.097 | 0.563 | Not Significant |
| Systolic Blood Pressure | 0.413 | 0.010 | Significant |
| Diastolic Blood Pressure | 0.317 | 0.052 | Not Significant |

## DISCUSSION

Based on the hypothesis of this study, the non-HA PCOS group demonstrated lower Endothelin-1 levels and cardiovascular risk in comparison to the HA PCOS group. In line with this hypothesis, the non-HA PCOS group exhibited lower Endothelin-1 levels, a marker of endothelial dysfunction, and cardiometabolic markers consisting of blood pressure, waist-to-hip ratio, and waist circumference in comparison to the HA PCOS group. A comparison of endothelial dysfunction markers and cardiovascular risk showed statistically significant results for Endothelin-1, waist-to-hip ratio, and blood pressure. However, the waist circumference marker did not demonstrate statistically substantial differences. High blood pressure is one of the main contributors to heart and blood vessel development, and approximately 30% of PCOS-affected women have hypertension as opposed to the general female population aged 20–34 years. The causes of hypertension in PCOS are multifactorial. Several recent studies suggest that hyperandrogenism, chronic inflammation, and immune responses can trigger endothelial dysfunction and kidney disorders, which mediate hypertension and contribute to cardiovascular disease (Moulana, 2023).

In this study, the numerical comparison of WC and WHR between the HA and non-HA PCOS groups showed statistically insignificant differences (WC 80.68 ± 9.47 vs. 80.02 ± 9.25, $p = 0.838$; WHR 0.84 ± 0.03 vs. 0.83 ± 0.07, $p = 0.781$). These results differ from a 2021 study by Bhattacharya et al., which also assessed anthropometric values in PCOS patients. In that study, the subject groups were separated into a PCOS group and a control group, and significant differences were observed in WHR values (0.91 ± 0.10 vs. 0.83 ± 0.05, $p = 0.001$). The WC value in Bhattacharya et al.'s study also demonstrated a significant variation between the PCOS and control groups (95.11 ± 11.11 vs. 77.84 ± 10.01, $p = 0.001$). Similarly, a study carried out in China demonstrated a significant difference in WC between the PCOS and control groups (89.67 ± 13.93 vs. 75 ± 7.11, $p = 0.001$) (Bhattacharya et al., 2021; Dou et al., 2016). This discrepancy may arise from differences in group classifications, as previous studies categorized subjects into PCOS and non-PCOS groups and included individuals with obesity.

A study assessing increased intra-abdominal fat reserves in normoweight PCOS-affected women supports the findings of the current study. Dumesic et al. also noted no substantial difference in WC between the PCOS and non-PCOS groups in normoweight subjects (74.8 ± 2.2 vs. 75.9 ± 1.2, $p = 0.6$). Although anthropometric measurements in Dumesic's study showed no significant results, an assessment of fat reserves using Total-body DXA examination revealed significant differences in fat

mass and total body fat percentage between the PCOS and non-PCOS groups. This suggests that conventional anthropometric examinations may not adequately represent fat reserves in the normoweight population (Dumesic et al., 2016).

In this study, blood pressure varied substantially between the non-HA and the HA PCOS groups ($p = 0.008$). An elevated prevalence of hypertension was noted in the HA PCOS group (36.8%, 7/19) compared to the non-HA PCOS group, where no cases of hypertension were found (0/19). Research on hypertension in PCOS has produced mixed results. Several studies have found significant differences in systolic blood pressure between PCOS and control groups (Tang et al., 2020; Zhang et al., 2018). However, other studies have reported that diastolic and systolic blood pressure varied substantially in PCOS (Bahadur et al., 2021; Sachdeva et al., 2019; Tavares & Rêgo Barros, 2019). Studies examining differences in hypertension incidence between these two groups are relatively rare. Two studies reported lower diastolic and systolic blood pressure in the normoandrogenic phenotype and control groups compared to other PCOS phenotypes (Krentowska & Kowalska, 2022). This is further supported by a study in Iran, which found higher systolic blood pressure in PCOS phenotype I compared to the normoandrogenic phenotype (Jamil et al., 2015).

In this study, the results align perfectly with the hypothesis. The non-HA PCOS group demonstrated substantially lower Endothelin-1 (pg/ml) levels than the HA PCOS group ($7.31 \pm 4.56$ vs. $12.11 \pm 6.86$, $p = 0.021$). A 2019 study assessing Endothelin-1 levels (pg/ml) similarly found higher levels in the PCOS group as opposed to controls ($7.86 \pm 1.13$ vs. $4.82 \pm 0.19$, $p < 0.001$) (Rashad et al., 2019). However, earlier research in 2011 showed different results, with no substantial variation between the PCOS group and controls ($11.77 \pm 3.27$ vs. $9.83 \pm 2.91$, $p = 0.343$) (Foltyn et al., 2011).

Based on the hypothesis of this study, there is a connection between hyperandrogenism, assessed using the FG-Score, and cardiovascular risk markers, including the endothelial dysfunction marker ET-1, and cardiometabolic markers such as blood pressure, waist-to-hip ratio, and waist circumference, in non-obese PCOS-affected women with hyperandrogenism. A statistically significant connection was found between the systolic blood pressure and FG-Score ($r = 0.413$; $p = 0.010$), but the connections between the FG-Score and ET-1 levels, WC, WHR, and diastolic blood pressure were not significant (ET-1 levels: $r = 0.097$, $p = 0.563$; WC: $r = -0.181$, $p = 0.278$; WHR: $r = -0.122$, $p = 0.467$; diastolic BP: $r = 0.317$, $p = 0.052$). Several studies have demonstrated a strong connection between hyperandrogenism and hypertension, but the molecular mechanisms underlying the role of androgens in cardiovascular disease development remain unclear (Moulana, 2023). In PCOS, hyperandrogenism can increase carotid intima-media thickness and calcification in coronary arteries and the aorta, suggesting androgen-induced atherosclerosis. A 2018 study also found that androgens can induce endothelial dysfunction. Endothelial dysfunction, as an early marker of cardiovascular disease, is independent of obesity status in PCOS. Impaired vasodilation and endothelin-1 release can exacerbate endothelial injury (Ye et al., 2021).

Several studies have established a correlation between hyperandrogenism and elevated blood pressure in PCOS patients. However, most research focuses on the general PCOS population, often including those with obesity, which can confound the outcomes. The effect of hyperandrogenism on blood pressure in non-obese PCOS women remains controversial and underexplored. A study assessing hypertension in non-obese PCOS women reported similar findings. Mellembakken et al. observed higher diastolic and systolic blood pressure in PCOS-affected women compared to controls. Bivariate analysis demonstrated a positive connection between blood pressure and hyperandrogenism, assessed using total testosterone levels and the androgen index (Mellembakken et al., 2021). Chen et al. conducted a study on 151 Taiwanese women with PCOS, with an average reproductive age of <30 years and FG-Score >8. Their results showed a significant connection between hyperandrogenism and increased systolic and diastolic blood pressure, along with metabolic parameters such as waist circumference, BMI, and HOMA-IR. Few studies have

investigated the impact of hyperandrogenism in non-obese PCOS populations, making this study a novel contribution. An interesting finding by Özkan et al. highlighted the concept of masked hypertension in PCOS patients, indicating that cardiovascular risks may develop insidiously in this population. (Chen et al., 2007; Özkan et al., 2020)

In a study by Usselman et al., higher ET-1 levels were observed in the PCOS group with hyperandrogen as opposed to the non-obese control group. Based on existing studies, endothelial dysfunction in hyperandrogenic PCOS is suspected to be mediated through the NO pathway influenced by androgens. Androgen exposure can disrupt endothelial NO release and is closely associated with inflammation, oxidative stress, and NF-κB activation (Usselman et al., 2019). Regarding the connection between FG-Score and other cardiovascular markers, the results of this study differ from findings in a study that examined the relationship between clinical hyperandrogenism, assessed using the FG-Score, and anthropometric/metabolic parameters in PCOS women. Khan et al. reported a strong positive connection between FG-Score and both waist circumference and waist-to-hip ratio ($r = 0.468$, $p = 0.000$; $r = 0.397$, $p = 0.001$). Similarly, Sales et al. observed a positive Pearson correlation between FG-Score, BMI, and abdominal circumference. These findings suggest that abdominal adiposity is correlated with hirsutism (Khan et al., 2019; Sales et al., 2015). The FG-Score can also be used to evaluate the connection between hyperandrogenism and cardiovascular risk factors in PCOS women. Differences in subject groups, particularly the inclusion of obese individuals in previous studies, may explain discrepancies with the present findings.

## LIMITATIONS

This study is an analytical observational study with a cross-sectional design, meaning it cannot establish causal relationships between the variables studied. Additionally, this study did not assess other risk factors for cardiovascular events, such as laboratory androgen levels or laboratory and imaging lipid profile examinations.

## CONCLUSION

This study revealed that women with hyperandrogenic polycystic ovary syndrome (HA PCOS) had higher levels of certain cardiometabolic and endothelial markers compared to the non-hyperandrogenic (non-HA) group, with notable findings on blood pressure and Endothelin-1 levels. However, results for other cardiometabolic markers such as waist circumference (WC) and waist-to-hip ratio (WHR) did not exhibit statistically significant differences between the groups.

## AUTHOR'S CONTRIBUTIONS

AT, AYP, and JYA were responsible for conception and design of the study. AT were collecting patient samples and clinical data and preparing for laboratory investigations. AT and JYA collaboratively drafted the manuscript. AT handled statistical analysis, data interpretation, and preparation of the manuscript for submission to an international journal. All authors contributed to critically revising the manuscript and approved the final version.

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