# Kallistatin Levels in Polycystic Ovary Syndrome: A Novel Biomarker for Insulin Resistance and Metabolic Dysregulation: A Case-Control Study

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**Abstract-** Polycystic ovary syndrome (PCOS) is the most prevalent endocrine disorder among women of reproductive age. Characterized by a heterogeneous constellation of hormonal, metabolic, and reproductive abnormalities, PCOS manifests through three cardinal features: oligo‑ or anovulation, clinical or biochemical hyperandrogenism, and polycystic ovarian morphology. This disorder is associated with major metabolic consequences, such as an increased risk of developing metabolic syndrome. This study aimed to investigate the potential role of kallistatin as a biomarker for PCOS, focusing on its association with insulin resistance (IR) and its regulatory function in inflammation. In this study, 30 healthy controls were matched with 60 patients with PCOS based on BMI, height, weight, and age. The study was carried out in the Fertility Center, Department of Gynecology, at Al‑Zahraa Teaching Hospital and Al‑Sadr Medical City from January 10, 2024, to January 24, 2025. Kallistatin levels were measured using ELISA, and insulin resistance was determined using the HOMA‑IR index. The study compared metabolic and hormonal parameters between 60 PCOS patients and 30 healthy controls. Significant differences ($P$<0.001) were observed: PCOS patients exhibited elevated insulin levels (14.91±3.01 vs. 8.22±2.47) and HOMA‑IR (3.77±1.01 vs. 1.74±0.52), along with reduced kallistatin levels (2.34±0.76 vs. 5.59±1.58 ng/ml). A notable correlation was found between kallistatin levels and both insulin resistance and lipid profiles. This study provides compelling evidence for the potential role of kallistatin as a biomarker for PCOS. The findings revealed significantly lower kallistatin levels in PCOS patients than in healthy controls, suggesting its potential utility in the diagnosis and prognosis of the condition.

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**Keywords:** Kallistatin level; Polycystic ovary syndrome (PCOS); Insulin resistance (IR); Lipids profile

## Introduction

Polycystic Ovary Syndrome (PCOS) is a complex endocrine disorder affecting women of reproductive age, characterized by oligo- or anovulation, hyperandrogenism, and/or polycystic ovarian morphology. Globally, this condition affects approximately 5-10% of women and has both reproductive and metabolic aspects associated with substantial health risks (1). Recent studies have highlighted the pathophysiological cascade linking PCOS with various metabolic disorders, such as insulin resistance and low-grade inflammation.

Moreover, the diagnosis of PCOS is often delayed due to a lack of awareness. Because many of these metabolic abnormalities are influenced by hormonal factors, they are important to address, as they increase the risk of cardiovascular disease and type 2 diabetes in women with PCOS. This underscores the need for early diagnosis and intervention (2).

PCOS involves a complex network of genetic, endocrine, and environmental factors. Two core types of

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hormonal dysregulation characterize the condition: impaired sensitivity to insulin or leptin and altered hypothalamic–pituitary communication. Many women with PCOS show increased levels of luteinizing hormone (LH) due to enhanced pulsatile secretion of gonadotropin-releasing hormone (GnRH), which leads to altered feedback in reproductive hormones (3).

When LH levels exceed follicle-stimulating hormone (FSH) levels, the ovaries produce more androgens. Additionally, many women develop hyperinsulinemia due to decreased insulin sensitivity. Insulin increases the bioavailability of androgens by promoting their synthesis in ovarian cells and by reducing the production of sex hormone-binding globulin (SHBG). The presence of these two factors contributes to the hyperandrogenism that characterizes this disorder (4).

### Effect of insulin on metabolism

Testosterone production increases in response to elevated insulin levels. Insulin resistance (IR) and hyperandrogenism are the two main hormonal abnormalities that contribute to the development of PCOS (5,6). Excess insulin stimulates the ovaries to produce higher levels of androgens, leading to hyperandrogenism and related metabolic complications, thereby creating a detrimental cycle of hormonal and metabolic dysfunction.

Women with PCOS—particularly those exhibiting hyperandrogenism—often present with cardiovascular risk factors, including dyslipidemia and chronic inflammatory conditions, which further increase their susceptibility to type 2 diabetes (7,8).

Kallistatin, a 58 kDa endogenous acidic glycoprotein comprising 427 amino acids and belonging to the serine proteinase inhibitor (SERPIN) superfamily (9), exhibits pleiotropic functions that are critical to both physiological homeostasis and pathological processes. Its structure includes two functionally distinct domains: (1) a catalytic region that inhibits tissue kallikrein activity while promoting the activation and expression of endothelial nitric oxide synthase (eNOS), sirtuin 1 (SIRT1), and SOCS3, a regulator of cytokine signaling, as referenced in study (9); and (2) a separate domain with heparin-binding properties that interferes with signaling pathways driven by growth factors and inflammatory mediators, such as vascular endothelial growth factor (VEGF), tumor necrosis factor-α (TNF-α), high-mobility group box-1 (HMGB1), and epidermal growth factor (EGF).

Emerging evidence highlights the clinical relevance of kallistatin in PCOS, a prevalent endocrine disorder in women of reproductive age, with recent studies demonstrating correlations between altered kallistatin levels and PCOS pathophysiology (10). Kallistatin, a unique inhibitor of tissue kallikrein and serine proteinases, is present in human plasma and is also associated with vasodilation. In addition to its anti-inflammatory, anti-apoptotic, anti-fibrotic, antioxidant, and anti-angiogenic properties, kallistatin may protect against aging, cellular senescence, and vascular damage through the generation of nitric oxide (NO) (11).

This study aimed to investigate the potential role of kallistatin as a biomarker for PCOS, focusing on its association with insulin resistance (IR) and its regulatory function in inflammation.

## Materials and Methods

A total of 60 samples were collected from women of reproductive age (20-43 years) during their visits to the gynecology departments of Al-Zahraa Teaching Hospital, Al-Furat Al-Awsat Hospital, and the Al-Sadr Medical City Fertility Center from October 1, 2024, to January 24, 2025. These women were diagnosed with PCOS by gynecologists based on the Rotterdam-2003 criteria, which include hyperandrogenism, oligo- or anovulation, the presence of at least 12 follicles (2–9 mm in diameter), and an ovarian volume exceeding 10 ml on ultrasonography (12). Demographic data, laboratory findings, family history, and blood pressure (BP) data were collected using a structured questionnaire.

Inclusion criteria required participants to be married and meet the Rotterdam-2003 diagnostic standards (13). Exclusion criteria eliminated women with a history of smoking, chronic conditions (e.g., diabetes, autoimmune diseases, thyroid disorders, hypertension, cardiovascular diseases, chronic renal failure, or malignant tumors), or the use of medications such as lipid-lowering agents, ovulation stimulants, corticosteroids, or anti-diabetic drugs.

Additionally, a control group of 30 healthy, fertile women aged 20-43 years was selected, with no history of smoking, regular menstrual cycles, normal ovarian morphology, and no underlying medical conditions, as confirmed by gynecological evaluation. Both groups were matched for age and reproductive status to ensure comparability.

### Sample collection

Samples from healthy women were collected from the same hospital settings as the PCOS patients (Al-Zahraa Teaching Hospital, Al-Furat Al-Awsat Hospital, and

Al-Sadr Medical City Fertility Center). Five milliliters of blood were drawn from each participant’s vein on the second day of her menstrual cycle and placed in a gel tube for serological and immunological testing.

An ELISA kit was used to perform the human kallistatin assay at the BT laboratory. ELISA kits [ELabscience, USA] were employed to measure fasting insulin (FINS), while an immunofluorescent technique [Minividas, BioMérieux, France] was used to measure LH, FSH, and total testosterone levels.

Insulin resistance (IR) was determined using the Homeostatic Model Assessment for Insulin Resistance (HOMA-IR) formula:

HOMA-IR=[insulin (µU/ml) × glucose (mg/dL)] / 405.

According to the World Health Organization (WHO), definitions of overweight and obesity are based on Body Mass Index (BMI) classifications (14).

**Statistical analysis**

Data were analyzed using SPSS® statistical software to evaluate the characteristics of the PCOS cohort and the control group. Independent t‐tests were used to assess differences in mean values between the two groups. Pearson’s correlation analysis was performed to determine the associations between kallistatin concentrations and indicators related to PCOS and insulin resistance, with $P<0.05$ considered statistically significant (15).

## Results

Table 1 shows the major differences between the two groups across several variables. Despite having the same mean age, women with PCOS had higher BMIs and waist‐to‐hip ratios, indicating greater abdominal adiposity and a higher prevalence of overweight/obesity. These findings are consistent with previous studies suggesting that obesity and abnormal fat distribution are common features of PCOS.

Furthermore, a noticeably higher percentage of women in the PCOS group experienced menstrual irregularities and excessive hair growth. Irregular menstruation and hirsutism are well‐known clinical manifestations of PCOS and are often associated with ovarian dysfunction and elevated testosterone levels.

A notable disparity also existed in the number of children between the two groups, with a greater proportion of nulliparous women in the PCOS group. This finding aligns with the well‐established association between reduced fertility and PCOS.

**Table 1. The Comparison between of following parameters of study groups**

| Demographic features | | Studied groups | | | | ***P*** |
|---|---|---|---|---|---|---|
| | | **PCOS patients N=60** | | **Healthy control N=30** | | |
| | | **N** | **%** | **N** | **%** | |
| **Age [year]** | **Mean ± SD** | 28.15±5.96 | | 27.6±4.93 | | 0.663$^a$ |
| | **≤ 25 years** | 22 | 36.70% | 10 | 33.30% | $X^2$ = 0.097<br>0.755$^b$ |
| | **> 25 years** | 38 | 63.30% | 20 | 66.70% | |
| **BMI [kg/m$^2$]** | **Mean ± SD** | 28.42±4.44 | | 26.14±2.85 | | 0.004$^a$ |
| | **Normal weight** | 13 | 21.70% | 10 | 33.30% | $X^2$ = 5.883<br>0.053$^b$ |
| | **Overweight** | 27 | 45.00% | 17 | 56.70% | |
| | **Obesity** | 20 | 33.30% | 3 | 10.00% | |
| **Hirsutism** | **Yes** | 52 | 86.70% | 0 | 0.00% | $X^2$ = 61.579<br>0.0001$^b$ ** |
| | **No** | 8 | 13.30% | 30 | 100.00% | |
| **Menstrual cycle** | **MC. Regular** | 12 | 20.00% | 28 | 93.30% | $X^2$ = 43.56<br>0.0001$^b$ ** |
| | **MC. Irregular** | 48 | 80.00% | 2 | 6.70% | |
| **No. Children** | **Non** | 34 | 56.70% | 0 | 0.00% | $X^2$ = 28.407<br>0.0001$^b$ ** |
| | **One** | 17 | 28.30% | 18 | 60.00% | |
| | **Two** | 7 | 11.70% | 11 | 36.70% | |

n: number of cases; SD: standard deviation; ** $P$<0.00: statistical significance. a: Independent sample t-test. b: Chi-square. NS: Not Significant

Table 2 presents a comparison between the two groups of women with PCOS and the healthy control group. The study compared metabolic and hormonal parameters between 60 PCOS patients and 30 healthy controls, revealing significant differences. PCOS patients showed elevated fasting blood sugar, insulin, HOMA‑IR, total cholesterol, triglycerides, and LDL levels, along with reduced HDL and kallistatin levels. These findings indicate the presence of insulin resistance, dyslipidemia, and altered kallistatin regulation in PCOS, highlighting systemic metabolic and hormonal disruptions.

The results of the multiple linear regression analysis, with kallistatin (ng/mL) as the dependent variable, are presented in Table 3. The remaining factors served as independent variables, meaning their potential to predict kallistatin levels was evaluated.

According to the analysis, kallistatin showed statistically significant associations with the following variables (*P*<0.05):

- Age: Positive association. Kallistatin levels were generally higher in older individuals.

- BMI: Positive correlation. Higher BMI values were associated with higher kallistatin levels.
- Insulin resistance (IR): Negative correlation. Higher IR values were associated with lower kallistatin levels.

**Table 2. Metabolic and hormonal differences between PCOS patients and healthy controls**

| **Parameters** | | **PCOS patients N=60** | **Healthy control N=30** | ***P*** |
|---|---|---|---|---|
| **FBS [mg/dl]** | Mean ± SD | 104.32±15.23 | 86.47±7.08 | <0.001$^a$ ** |
| **Insulin [µU/ml]** | Mean ± SD | 14.91±3.01 | 8.22±2.47 | <0.001$^a$ ** |
| **HOMA-IR** | Mean ± SD | 3.77±1.01 | 1.74±0.52 | <0.001$^a$ ** |
| **TC [mg/dl]** | Mean ± SD | 226.57±27.47 | 178.67±7.93 | <0.001$^a$ ** |
| **TG [mg/dl]** | Mean ± SD | 168.15±16.25 | 106.63±12.02 | <0.001$^a$ ** |
| **HDL [mg/dl]** | Mean ± SD | 28.63±2.44 | 36.23±2.06 | <0.001$^a$ ** |
| **LDL [mg/dl]** | Mean ± SD | 152.22±11.81 | 128.27±2.73 | <0.001$^a$ ** |
| **LH [mIU/ml]** | Mean ± SD | 10.12±1.84 | 4.21±1.4 | <0.001$^a$ ** |
| **FSH [mIU/ml]** | Mean ± SD | 6.13±1.48 | 4.23±1.2 | <0.001$^a$ ** |
| **Total Testosterone [ng/ml]** | Mean ± SD | 2.11±0.86 | 0.73±0.48 | <0.001$^a$ ** |
| **Kallistatin [ng/ml]** | Mean ± SD | 2.34±0.76 | 5.59±1.58 | <0.001$^a$ ** |

n: number of cases; SD: standard deviation; statistical significance ** *P*<0.001. a: Independent sample t-test

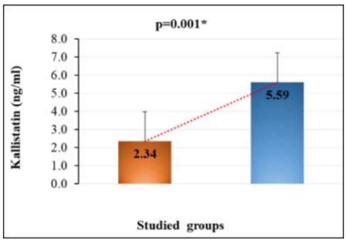

**Figure 1.** Comparison between kallistatin levels in patients with PCOS & HC

**Table 3. Correlation glycemic profile and lipid profide with kallistatin**

| **Parameters** | **Dependent Variable: Kallistatin [ng/ml]** | | | | |
|---|---|---|---|---|---|
| | **B** | **t** | ***P*** | **95.0% CI** | |
| **Age [year]** | 0.402 | 3.911 | 0.001* | 0.025 | 0.077 |
| **BMI[kg/m^2]** | 0.298 | 2.251 | 0.029* | 0.005 | 0.096 |
| **LH [mIU/ml]** | -0.064 | -0.568 | 0.573 | -0.121 | 0.068 |
| **FSH [mIU/ml]** | -0.100 | -0.938 | 0.353 | -0.161 | 0.059 |
| **Testosterone [ng/ml]** | 0.027 | 0.266 | 0.791 | -0.158 | 0.206 |
| **FBS [mg/dl]** | -0.194 | -0.880 | 0.383 | -0.032 | 0.012 |
| **Insulin [µU/ml]** | 0.359 | 1.312 | 0.196 | -0.048 | 0.229 |
| **HOMA-IR** | -0.775 | -2.105 | 0.041* | -1.141 | -0.026 |
| **TC [mg/dl]** | 0.213 | 1.953 | 0.057 | 0.000 | 0.012 |
| **TG [mg/dl]** | 0.019 | 0.193 | 0.848 | -0.008 | 0.010 |
| **HDL [mg/dl]** | 0.089 | 0.815 | 0.419 | -0.041 | 0.096 |
| **LDL [mg/dl]** | 0.034 | 0.358 | 0.722 | -0.010 | 0.015 |

B: effect size. T: predicted value. CI: Confidence interval

The results of the correlation analysis and diagnostic performance evaluation appear in Table 4 and Table 5, respectively. In Table 4, no significant correlation was observed between kallistatin concentrations and variables such as LH, FSH, testosterone, TC, TG, HDL, and LDL. In contrast, there is a significant inverse relationship (decrease) between kallistatin levels and both FBS (R= -0.599, *P*=0.0001) and insulin (R= -0.346, *P*=0.007). This strong inverse correlation is further illustrated in Figure 2, which highlights the relationship between HOMA-IR and kallistatin. Furthermore, the diagnostic utility of these markers is presented in Table 5, supported by the ROC curve analysis shown in Figure 3. The data demonstrate that kallistatin has a high diagnostic accuracy (Area=0.97, *P*=0.0001) with a cutoff value of <3.90 ng/ml, yielding a sensitivity of 0.98 and a specificity of 0.10.

**Table 4. The table shows a strong inverse relationship between kallistatin concentration and HOMA-IR level**

| Parameters | Kallistatin [ng/ml] | |
|---|---|---|
| | R | *P* |
| **LH [mIU/ml]** | 0.148 | 0.260 |
| **FSH [mIU/ml]** | 0.136 | 0.302 |
| **Testosterone [ng/ml]** | -0.163 | 0.212 |
| **FBS [mg/dl]** | -0.599** | 0.0001 |
| **Insulin [µU/ml]** | -0.346** | 0.007 |
| **TC [mg/dl]** | 0.082 | 0.535 |
| **TG [mg/dl]** | -0.137 | 0.297 |
| **HDL [mg/dl]** | 0.153 | 0.244 |
| **LDL [mg/dl]** | -0.004 | 0.978 |

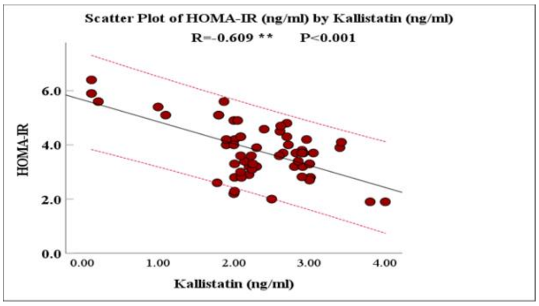

**Figure 2.** This plot shows the correlation between HOMA-IR and kallistatin

**Table 5. ROC curve parameters of study groups**

| Markers | Area | *P* | 95% CI | | Cutoff | Sens* | Speci* |
|---|---|---|---|---|---|---|---|
| | | | Lower Bound | Upper Bound | | | |
| **LH [mIU/ml]** | 1.00 | 0.0001 | 0.99 | 1.00 | >7.41 | 0.93 | 0.00 |
| **FSH [mIU/ml]** | 0.84 | 0.0001 | 0.75 | 0.92 | >5.54 | 0.63 | 0.10 |
| **Testosterone [ng/ml]** | 0.91 | 0.0001 | 0.86 | 0.97 | >1.41 | 0.78 | 0.10 |
| **Kallistatin [ng/ml]** | 0.97 | 0.0001 | 0.93 | 1.01 | <3.90 | 0.98 | 0.10 |

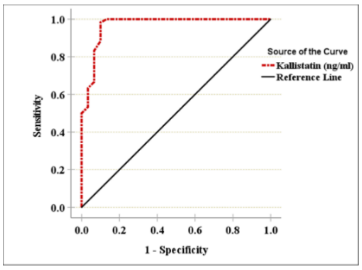

**Figure 3.** The ROC curve kallistatin

## Discussion

PCOS is a complex hormonal disorder of unknown etiology, with contributing factors that include inflammation, vascular injury, oxidative stress, and genetics (16,17). Because PCOS extends beyond a solely gynecological diagnosis, a comprehensive evaluation is necessary (18).

One of the hallmark features of PCOS is insulin resistance, which plays a central role in its pathogenesis. IR is characterized by reduced sensitivity of tissues—particularly skeletal muscle, adipose tissue, and the liver—to insulin. As a result, the body produces excess insulin to compensate for impaired glucose uptake and utilization (19).

The metabolic components of PCOS are further complicated by the close relationship between hyperinsulinemia and the development of obesity (21). Visceral fat accumulation is a primary risk factor for PCOS, and the disorder is worsened by the metabolic consequences of obesity, including IR and impaired lipid metabolism. Adipose tissue contributes to a pro‑inflammatory environment, particularly in obesity, by producing pro‑inflammatory cytokines and oxidative stress markers (22).

Prolonged exposure to elevated blood glucose and lipid levels in women with PCOS can lead to oxidative stress, potentially damaging vital organs such as peripheral tissues and pancreatic beta cells, which in turn reduces insulin production and sensitivity (23). Inflammation within adipose tissue may create a vicious cycle in which inflammation disrupts normal lipid metabolism, increases IR, and accelerates PCOS progression. The role of inflammation in PCOS has drawn significant attention, as women with the condition consistently exhibit elevated levels of inflammatory markers (24).

Research indicates that individuals with PCOS exhibit markedly reduced levels of kallistatin in comparison to healthy individuals, suggesting that kallistatin may serve as a biomarker or a pathophysiological factor in PCOS. A recent cohort study conducted by Yurtkal *et al.*, reported a significant reduction in serum kallistatin levels among patients with PCOS compared with age- and body mass index-matched controls, underscoring its potential utility as a diagnostic biomarker.

This study highlights a notable correlation between kallistatin—a serine proteinase inhibitor known for its anti-inflammatory and antioxidative functions—and the pathophysiological mechanisms associated with PCOS. Reduced kallistatin levels may contribute to the systemic inflammation and metabolic dysregulation characteristic of the syndrome (25).

However, conflicting findings across studies—such as the report by Calan *et al.*, which involved women with PCOS and matched controls—demonstrated significantly elevated circulating kallistatin levels in the PCOS group compared with controls, suggesting a potential association between kallistatin and PCOS pathogenesis (24). This highlights inconsistencies in the current evidence. These discrepancies imply a complex and multifactorial relationship between kallistatin and PCOS, one that may be influenced by factors such as metabolic heterogeneity, inflammatory status, or methodological variations.

Although the precise mechanistic role of kallistatin in PCOS remains incompletely understood, emerging data position it as a plausible biomarker and a potential contributor to the syndrome’s pathophysiology. Kallistatin, an endogenous protein, is a potential regulator of inflammatory processes and oxidative damage, both of which are likely involved in the pathophysiology of PCOS characterized by insulin resistance, atherosclerosis, inflammation, and oxidative stress. Kallistatin has been shown to reduce inflammation by inhibiting pro-inflammatory and oxidative stress signaling (26). However, there is a negative correlation between IR, fasting insulin, and plasma kallistatin levels (27).

## Limitations

This study has several limitations. The small sample size reduces statistical power and limits generalizability. Although BMI was matched between groups, residual confounding by adiposity cannot be ruled out. The single-center nature of the study (Al-Zahraa Teaching Hospital and affiliated centers) introduces potential selection bias and limits external validity, as the findings may not be generalizable to a more diverse population. Furthermore, the cross-sectional design does not allow for causal inferences regarding the relationship between kallistatin and PCOS pathophysiology. These limitations highlight the need for larger, multicenter studies with appropriate adjustment for confounders.

This study identified kallistatin as a potential prognostic and diagnostic biomarker for PCOS, with significantly decreased serum kallistatin levels in patients suffering from the disease compared with healthy controls. Kallistatin was inversely associated with IR, dyslipidemia, and hyperandrogenism, suggesting that kallistatin deficiency may aggravate IR and inflammatory disturbances that play a key role in the pathogenesis of PCOS. These correlations support the hypothesis that kallistatin dysregulation contributes to endocrine–metabolic dysfunction.

By elucidating the role of kallistatin in PCOS pathophysiology, this study provides novel insights into its clinical utility for risk stratification and diagnostic evaluation, while emphasizing the need for further validation in diverse cohorts to address existing inconsistencies and optimize its translational applicability.

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