ORIGINAL RESEARCH

Bagcilar Med Bull 2025;10(1):15-23
DOI: 10.4274/BMB.galenos.2025.14633

Uric Acid as a Biochemical Marker of Metabolic Dysfunction in Polycystic Ovary Syndrome: Its Association with Insulin Resistance and Adiposity

Polikistik Over Sendromunda Metabolik Disfonksiyonun Biyokimyasal Bir Belirteci Olarak Ürik Asit: İnsülin Direnci ve Adipozite ile İlişkisi

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Abstract

Objective: The association between polycystic ovary syndrome (PCOS), a widespread endocrine disorder in childbearing-aged women, and elevated serum uric acid levels, along with its connection to metabolic disorders, remains an ongoing area of research. This study aimed to examine the associations between serum uric acid, adiposity, body composition, and hormonal parameters in patients with PCOS, while identifying independent predictors and evaluating uric acid's role in metabolic disorders.

Method: The retrospective study included 123 women with PCOS, aged 18 to 35, diagnosed according to the Rotterdam criteria, and 41 age-and body mass index (BMI)-matched controls without PCOS or hyperandrogenism. Exclusion criteria included having chronic diseases and receiving medications that affect hormonal and metabolic parameters or uric acid. Data collected comprised menstrual histories, anthropometric measurements, hormonal, metabolic, and body composition parameters.

Results: Serum uric acid was significantly greater in patients with PCOS than controls (p=0.008). While age and BMI were similar across groups, waist-to-hip ratio was greater in PCOS group (p=0.009). Fasting insulin (p=0.026) and dynamic insulin indices (p=0.001) were elevated in the PCOS group, although homeostasis model assessment of insulin resistance (HOMA-IR) was comparable (p=0.064). No major differences were observed in the body composition or metabolic parameters, including lipid profiles, visceral adiposity index, and lipid accumulation product (LAP). A multiple regression analysis demonstrated that HOMA-IR (B=0.16, p<0.001), BMI (B=0.03, p=0.017), and LAP (B=0.01, p=0.035)

Öz

Amaç: Doğurganlık çağındaki kadınlarda yaygın bir endokrin bozukluk olan polikistik over sendromu (PKOS) ile yüksek serum ürik asit seviyeleri arasındaki ilişki ve bunun metabolik bozukluklarla bağlantısı ilgi çekici araştırma alanı olmaya devam etmektedir. Bu çalışmanın amacı, PKOS hastalarında serum ürik asit düzeyi ile yağlanma, vücut kompozisyonu ve hormonsal parametreler arasındaki ilişkiyi incelemek, bağımsız belirleyicileri tanımlamak ve ürik asidin metabolik bozukluklardaki rolünü değerlendirmektir.

Yöntem: Retrospektif çalışmaya, yaşları 18 ila 35 arasında değişen ve Rotterdam kriterlerine göre tanı konulmuş 123 PKOS hastası kadın ile PKOS veya hiperandrojenizmi olmayan, yaş ve vücut kitle indeksi (VKİ) açısından eşleştirilmiş 41 sağlıklı kadın dahil edilmiştir. Dışlama kriterleri, kronik hastalıklara sahip olunması ve hormonsal ve metabolik parametreleri veya ürik asit seviyelerini etkileyen ilaçların alınmasıdır. Elde edilen veriler hastaların adet geçmişlerini, antropometrik ölçümleri, hormonsal, metabolik ve vücut kompozisyonu parametrelerini içermektedir.

Bulgular: PKOS hastalarında serum ürik asit düzeyleri kontrollere göre anlamlı olarak yüksek saptanmıştır (p=0,008). Yaş ve VKİ açısından gruplar benzer özellikte olmasına rağmen, PKOS hastalarında bel-kalça oranı daha büyüktür (p=0,009). PKOS grubunda açlık insülini (p=0,026) ve dinamik insülin indeksleri (p=0,001) anlamlı derecede yüksek olmasına rağmen insülin direnci için homeostaz model değerlendirmesi (HOMA-IR) benzer bulunmuştur (p=0,064). Lipid profilleri, visseral adipozite indeksi ve lipid birikim ürünü (LAP) dahil olmak üzere metabolik veya vücut kompozisyonu parametrelerinde anlamlı bir farklılık gözlenmemiştir. Çoklu regresyon analizi, HOMA-IR (B=0,16, p<0,001), VKİ (B=0,03,

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Received: 17.01.2025 **Accepted:** 01.03.2025 **Epub:** 05.03.2025 **Publication Date:** 18.03.2025

Cite this article as: Gökkaya N, Aydın K. Uric acid as a biochemical marker of metabolic dysfunction in polycystic ovary syndrome: its association with insulin resistance and adiposity. Bagcilar Med Bull. 2025;10(1):15-23

Abstract

were independent determinants of uric acid, collectively explaining 48.4% of the variance (R^2=0.484, adjusted R^2=0.467).

Conclusion: The study revealed a significant association between increased serum uric acid levels and metabolic problems in PCOS, particularly with insulin resistance and adiposity. Uric acid may be a potential biochemical marker for early metabolic risk assessment in PCOS.

Keywords: Adiposity indices, insulin resistance, polycystic ovary syndrome, uric acid

Öz

p=0,017) ve LAP'nin (B=0,01, p=0,035) ürik asidin bağımsız belirleyicileri olduğunu ve bunların varyansın %48,4'ünü açıkladığını göstermiştir (R^2=0,484, düzeltilmiş R^2=0,467).

Sonuç: Bu çalışma, PKOS hastalarındaki metabolik bozukluklar ile serum ürik asit yüksekliği arasında, özellikle insülin direnci ve adipozite ile anlamlı bir ilişki olduğunu ortaya koymuştur. Ürik asit PKOS'de erken metabolik risk değerlendirmesinde bir potansiyel biyokimyasal belirteç olabilir.

Anahtar kelimeler: Adipozite indeksleri, insülin direnci, polikistik over sendromu, ürik asit

Introduction

Polycystic ovary syndrome (PCOS) is a widespread endocrine disorder that affects women at all stages of their reproductive journey. It is characterized not only by its effects on fertility and physical appearance but also by the associated metabolic disorders. These problems are related to several factors, including hormonal imbalances, ovulation disorders, chronic inflammation, and difficulties with weight management in people with PCOS (1).

Uric acid, a metabolic byproduct of purine degradation, serves a protective role by maintaining oxidative balance within the body under normal physiological conditions. However, when uric acid levels rise, they can exhibit pro-oxidant and pro-inflammatory effects, potentially leading to damage across multiple organ systems. Elevated serum uric acid is linked to increased risks of renal and cardiovascular diseases (2,3). Additionally, it is strongly associated with various metabolic conditions, including diabetes, insulin resistance, obesity, hypertension, and metabolic syndrome conditions often seen in individuals with PCOS (4-8). Furthermore, growing evidence suggests that serum uric acid is frequently elevated in patients with PCOS (9-11).

Hyperandrogenemia, obesity, and hyperinsulinism, all associated with PCOS, are thought to contribute to elevated uric acid levels. While the metabolic complications of PCOS are well documented, the specific role of uric acid in this context remains unclear. Uric acid is not only linked to metabolic risks but also actively participates in a vicious cycle that is believed to mediate the development of insulin resistance and hyperandrogenemia. This may be occurring through mechanisms such as increased oxidative stress, inflammation, and mitochondrial dysfunction (10,12).

To our knowledge, there are no studies that have investigated the combined effects of adiposity indices, body composition, and hormonal parameters established cardiovascular risk indicators on uric acid in women with PCOS. This research aimed to explore the connection between serum uric acid levels and adiposity indicators, body composition, and hormonal factors in patients with PCOS, to identify independent predictors, and to evaluate the potential of uric acid as an early marker of metabolic risk. This could facilitate the development of early intervention strategies to manage hyperuricemia and prevent metabolic disorders.

Materials and Methods

Study Design

The retrospective study involved 123 women aged 18 to 35 years, diagnosed with PCOS according to the Rotterdam criteria, who attended our tertiary outpatient clinic between 2017 and 2019. A control group consisting of 41 age and body mass index (BMI)-matched women without PCOS was also included, with a ratio of one control for every three patients. The data collected encompassed comprehensive menstrual histories, anthropometric measurements, as well as hormonal and metabolic parameters for all participants. Ovarian function in the control group was evaluated by confirming regular menstrual cycles (occurring every 24-36 days) and the absence of signs or symptoms of hyperandrogenism. Furthermore, none of the participants in the control group had any clinical history of endocrine or reproductive disorders, and their hormonal parameters fell within the normal range for reproductive-age women. The study was conducted in agreement with the Declaration of Helsinki II and was approved by University of Health Sciences Turkey, Kartal Dr. Lütfi Kırdar City Hospital Scientific Research Ethics Committee (reference number: 0l0.99/59, date: 24.02.2024). The requirement for written informed consent was waived by the Declaration of Helsinki, as only medical data from patient records were used in this retrospective study.

The exclusion criteria included: i) secondary causes of hyperandrogenemia such as non-classical congenital adrenal hyperplasia, Cushing's syndrome, and androgen-secreting tumors for patients diagnosed with PCOS; ii) a history of hypertension, diabetes, cardiovascular events, oncological diseases, thyroid dysfunction, or hyperprolactinemia; iii) the use of oral contraceptives, anti-androgens, insulin sensitizers, or medications that influence uric acid levels, such as thiazide diuretics or aspirin, within the six months prior to the study; iv) insufficient data.

PCOS Definition Criteria

PCOS was diagnosed in accordance with the 2003 Rotterdam criteria after excluding other potential causes of hyperandrogenemia. The diagnosis required the presence of at least two of the following criteria: [1] Clinical hyperandrogenism or hyperandrogenemia: Clinical hyperandrogenism is assessed using the modified Ferriman-Gallwey score (with hirsutism indicated by a score exceeding 8), while hyperandrogenemia is confirmed through laboratory tests that reveal elevated serum testosterone and dehydroepiandrosterone sulfate (DHEAS) levels. [2] Oligo-ovulation or anovulation, characterized by fewer than nine menstrual cycles per year, cycle lengths outside the range of 26 to 35 days, or luteal phase progesterone levels below 4 ng/mL in regular cycles. [3] Polycystic ovarian morphology, identified via ultrasound as the presence of 12 or more antral follicles (ranging from 2 to 9 mm) or an ovarian volume exceeding 10 mL in at least one ovary.

Measurements and Calculations

Height, weight, waist circumference (measured at the narrowest point between the rib cage and iliac crest during expiration while standing), and hip circumference (measured at the widest point over the femoral trochanters) were recorded. Various adiposity indices, including BMI, waist-to-hip ratio (WHR), waist-to-height ratio (WHtR), visceral adiposity index (VAI), and lipid accumulation product (LAP) were calculated. BMI was determined by dividing weight (in kg) by height squared (in m^2). The VAI was calculated using the formula: [(waist circumference in cm/36.58)+(1.89xBMI)x(triglycerides (TG)/0.81) x(1.52/high-density lipoprotein cholesterol (HDL-C) in mmol/L)]. The LAP was calculated using the formula: [(waist circumference in cm-58)xTG in mmol/L]. The free androgen index (FAI) was derived by dividing total testosterone (TT) by sex hormone-binding globulin (SHBG) and multiplying by 100. Homeostasis model assessment of insulin resistance (HOMA-IR) was estimated using fasting insulin (μIU/mL) and fasting plasma glucose (mg/dL) with the formula fasting insulin x fasting plasma glucose/405. An oral glucose tolerance test (OGTT) was performed to measure plasma insulin and glucose levels at 0, 30, 60, 90, and 120 minutes after administering 75 g of glucose. The areas under the glucose and insulin curves from the OGTT were used to calculate the dynamic insulin secretion index [insulin/glucose area under the curve $(AUC)_{OGTT}$]. Body composition and basal metabolic rate (BMR) were measured using a bioelectrical impedance analysis (BIA) system.

Laboratory Analysis

Laboratory evaluations were conducted between the second and fifth days of spontaneous menstrual cycles, following a minimum fasting period of 10 hours. In individuals with amenorrhea, pregnancy was ruled out before testing. Glucose, total cholesterol (TC), TG, HDL-C, and uric acid levels were determined using an enzymatic colorimetric method on the AU5800 Clinical Chemistry System Analyzer (Beckman Coulter, Florida, USA). The Friedewald formula, TC – HDL-C – (TG/5), was used to calculate low-density lipoprotein cholesterol (LDL-C). Insulin levels were measured using an electrochemiluminescence immunoassay on the E-170 Immunological Analyzer System (Roche Diagnostics, Osaka, Japan). Hormonal assessments included TT, SHBG, DHEAS, estradiol (E2), luteinizing hormone (LH), follicle-stimulating hormone (FSH), 17-hydroxyprogesterone, and prolactin, which were analyzed using the UniCel DXI 800 Access Immunoassay System (Beckman Coulter, Florida, USA). Body composition was evaluated using a BIA system (Tanita BC-418 MA, Tanita Corporation, Tokyo, Japan).

Statistical Analysis

Statistical analyses were conducted using statistical package for the social sciences (SPSS) software version 17.0 (SPSS Inc., Chicago, IL, USA). The Shapiro-Wilk test was applied to assess the normality of the data. Categorical variables were presented as frequencies and percentages, parametric variables were expressed as mean ± standard deviation (SD), and non-parametric variables were presented as median and interquartile range (IQR, 25^{th}-75^{th} percentiles). For group comparisons, the independent samples t-test was employed for parametric data, and the Mann-Whitney U test was utilized for non-parametric data. Correlations were analyzed using Spearman's rank correlation. A multiple linear regression analysis was conducted to identify independent predictors of uric acid levels. Model fitting and residual diagnostics confirmed the validity of the regression model, with residual normality

supporting its appropriateness. The predictor variables included BMI, WHR, WHtR, FAI, HOMA-IR, TG/HDL, VAI, LAP, and body composition parameters, all of which were significantly correlated with uric acid levels. However, due to multicollinearity, VAI, TG/HDL, and body composition parameters were excluded from the analysis. Analysis of variance results were statistically significant across models, highlighting the impact of predictors on uric acid levels, with 5% types-I error level applied to assess statistical significance. The Ins AUC120/Glu AUC120 ratio was analyzed using receiver operating characteristic (ROC) curves. A power analysis was performed using the G*Power (v.3.1.9) program to calculate the power of the study. The analysis was conducted based on the number of patients included in the study, with an effect size of 0.3, an alpha error of 0.05, and a statistical power of 99%.

Results

Clinical Characteristics of Patients with PCOS

In a cohort of patients diagnosed with PCOS, 94% (n=115) exhibited evidence of hyperandrogenism, with 78% (n=96) presenting clinical hyperandrogenism and 66% (n=81) demonstrating hyperandrogenemia. Also, ovulatory dysfunction was observed in 72% (n=89) of the patients, and 87% (n=107) displayed polycystic ovarian morphology through ultrasound imaging.

Adiposity Indices, Hormonal, and Metabolic Features of the PCOS and Control

The characteristics of the PCOS and control groups were comparable in terms of age, BMI, waist circumference, and WHtR. However, WHR was notably greater in patients with PCOS (p=0.009). Hormonal analysis revealed that individuals with PCOS exhibited elevated levels of LH/FSH, TT, and DHEAS (p=0.028, p=0.019, p=0.001), along with decreased levels of SHBG when compared to the controls (p=0.001).

Fasting insulin levels (p=0.026), as well as early-phase and total insulin secretion (Ins AUC30/Glu AUC30 and Ins AUC120/Glu AUC 120) as assessed by the OGTT (p=0.001), were significantly higher in patients with PCOS. However, HOMA-IR values were comparable between the two groups (p=0.064). Figure 1 displays the ROC curve for Ins AUC120/Glu AUC120 with an AUC of 0.695. The metabolic parameters and adiposity indices, including lipid profiles, VAI, and LAP, did not show significant differences. Notably, serum uric acid was elevated in women with PCOS compared to the control group (p=0.008) (Table 1).

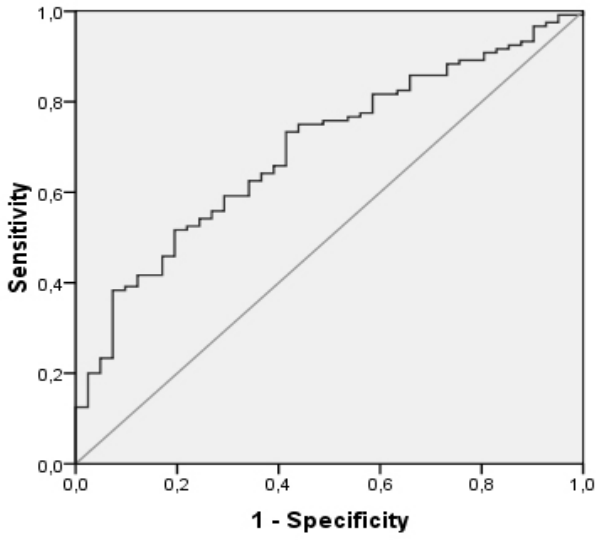

Figure 1. Graph of the InsAUC120/GlucAUC120 ratio (AUC=0.695)

ROC: Receiver operating characteristic, AUC: Area under the curve

Body Composition Parameters of PCOS and Control Groups

In a comparison of body composition parameters between the PCOS group and the control group, no significant differences were observed in fat mass (FM), body fat percentage (PBF), soft lean mass (SLM), total body water (TBW), Trunk FM, or Trunk SLM. However, patients with PCOS demonstrated a higher BMR compared to the control (p=0.033) (Table 2).

Correlations Between Serum Uric Acid and Adiposity Indices, Hormonal Levels, and Body Composition Parameters in Patients with PCOS

In patients with PCOS, a significant positive association was observed between uric acid and various measures of adiposity, including BMI, WHR, and WHtR (p<0.01, r=0.548, 0.374, 0.544 respectively). Furthermore, metabolic parameters and adiposity indices such as the HOMA-IR, TG/HDL ratio, VAI, and LAP showed positive correlations with serum uric acid levels (p<0.01, r=0.511, 0.399, 0.430, 0.587 respectively). Additionally, all body compartments measured by BIA (PBF, FM, SLM, TBW, Trunk FM, Trunk SLM) displayed positive correlations with serum uric acid levels (p<0.01, r=0.448, r=0.532, r=0.503, r=0521, r=0.518, r=0.499 respectively) (Table 3).

Table 1. Adiposity indices, hormonal, and metabolic characteristics of the PCOS and control groups

	PCOS	Control	p-value
	(n=123)	(n=41)	
Age (years)	25 (19-28)	25 (21-28)	0.118
BMI (kg/m²)	27.2 (22.5-31.5)	23.9 (21.1-32.5)	0.347
WC (cm)	85 (77-96)	80 (68-92)	0.071
WHR	0.81 (0.75-0.87)	0.78 (0.73-0.82)	**0.009**
WHtR	0.52 (0.47-0.59)	0.49 (0.43-0.57)	0.105
LH/FSH	0.9 (0.64-1.37)	0.76 (0.59-0.99)	**0.028**
TT (ng/dL)	69.5±90	35.5±12.4	**0.019**
SHBG (nmol/L)	29.4 (17.6-40.7)	46.2 (27.5-69.9)	**0.001**
FAI	2.2 (1.4-3.9)	0.8 (0.5-1.2)	**0.001**
DHEA-S (ug/dL)	314.3±143.2	200±83.1	**0.001**
PRL (ng/mL)	16 (11.5-24.1)	16 (10.7-19.5)	0.519
FPG (mg/dL)	88.1±9.4	91.1±9.3	0.080
FI (uU/mL)	14 (10-19)	10 (8-15)	**0.026**
Ins AUC30/Glu AUC30	0.43 (0.33-0.64)	0.33 (0.26-0.41)	**0.001**
Ins AUC 120/Glu AUC120	0.61 (0.42-0.88)	0.42 (0.32-0.58)	**0.001**
HOMA-IR	2.97 (2.01-4.43)	2.35 (1.61-3.43)	0.064
HbA1c (%)	5.1 (4.9-5.3)	5 (4.9-5.3)	0.880
TG (mg/dL)	80 (62-122)	76 (58-105)	0.294
LDL-C (mg/dL)	105.2±30.3	107±29.5	0.751
HDL-C (mg/dL)	48 (43-57)	53 (44-57)	0.207
TG/HDL-C	1.69 (1.13-2.72)	1.46 (0.99-2.19)	0.151
VAI	3.15 (2.14-5.02)	2.7 (1.79-3.96)	0.080
LAP	28.5 (13.2-48.9)	16.9 (7.6-40.1)	0.053
CRP (mg/L)	3.5 (3.4-3.6)	3.5 (3.3-3.5)	0.380
TSH (mIU/L)	2.13 (1.55-2.95)	2.06 (1.5-3.53)	0.566
Creatinine (mg/dL)	0.63±0.08	0.61±0.1	0.259
Uric acid (mg/dL)	4.46±0.91	4.02±0.79	**0.008**

BMI: Body mass index, WC: Waist circumference, WHR: Waist to hip ratio, WHtR: Waist to height ratio, LH/FSH: Luteinizing hormone to follicle-stimulating hormone ratio, TT, Total testosterone, SHBG: Sex hormone binding globulin, FAI: Free androgen index, DHEA-S: Dehydroepiandrosterone sulfate, PRL: Prolactin, FPG: Fasting plasma glucose, FI: Fasting insulin, Ins AUC30/Glu AUC30: Early phase insulin secretion, Ins AUC 120/Glu AUC120: Total insulin secretion, HOMA-IR: Homeostatic model of assessment-insulin resistance, HbA1c: Glycated hemoglobin, TG: Triglyceride, LDL-C: LDL cholesterol, HDL-C: HDL cholesterol, VAI: Visceral adiposity index, LAP: Lipid accumulation product, CRP: C-reactive protein, TSH: Thyroid-stimulating hormone, PCOS: Polycystic ovary syndrome, values are mean ± standard deviation and median (interquartile range), and p-values are from the samples t-test and Mann-Whitney U test

Multiple Linear Regression Analysis of Independent Factors Influencing Uric Acid Levels in Patients with PCOS Using Stepwise Selection

A multiple regression analysis was conducted to recognize the independent uric acid determinants in patients with PCOS using the stepwise selection method. To avoid multicollinearity, body composition parameters, VAI, and early and total insulin secretion indices were excluded from the regression model. The independent variables included in the analysis were age, BMI, WHR, WHtR, FAI, HOMA-IR, and LAP. Model 1 includes HOMA-IR as the sole predictor, which demonstrates a significant positive association with uric acid levels (B=0.26, p<0.001), explaining 37.3% of the variance (R^2=0.373, adjusted R^2=0.367). Model 2 incorporates both BMI and HOMA-IR, and both predictors remain significant. Together, HOMA-IR (B=0.18, p<0.001) and BMI (B=0.05, p<0.001) account for 45.8% of the variance (R^2=0.458, adjusted R^2=0.447). Model 3 introduces LAP as an additional predictor. All three predictors HOMA-IR (B=0.16, p<0.001), BMI (B=0.03, p=0.017), and LAP (B=0.01, p=0.035) demonstrate statistical significance. Together, they explain 48.4% of the variance in uric acid (R^2=0.484, adjusted R^2=0.467) (Table 4).

Table 2. Body composition parameters of PCOS and control groups

	PCOS	Control	p-value
	(n=123)	(n=41)	
Basal metabolic rate	1314 (1262-1379)	1284 (1231-1328)	0.033
Percentage of body fat (pbf) (%)	33.1 (27.1-38.6)	32.2 (25.6-39.1)	0.612
Total fat mass (kg) (FM)	22.7 (16.3-32.3)	18.5 (15-32.2)	0.301
Fat-free mass (kg) (FFM)	47.6 (42.1-52.8)	45 (41-51.2)	0.240
Soft lean mass (SLM)	43.9±6.2	42.2±6.4	0.146
Total body water (TBW)	34.4±4.9	33.2±5.3	0.195
Trunk fat mass (kg) (Trunk FM)	11.6 (8.3-16.4)	9.9 (7.6-16.8)	0.430
Trunk soft lean mass (kg) (Trunk SLM)	22.1±2.9	21±2.9	0.054

Values mean ± standard deviation and median (interquartile range), and p-values are from the samples t-test and Mann-Whitney U test, p<0.05 is significant, PCOS: Polycystic ovary syndrome

Table 3. Correlations between serum uric acid and adiposity indices, hormonal and body composition parameters in patients with PCOS

Adiposity indices, biochemical and hormonal parameters		Body composition parameters	
BMI	**0.548**[b]	BMR	**0.440**[b]
WHR	**0.374**[b]	PBF (%)	**0.448**[b]
WHtR	**0.544**[b]	FM (kg) (FM)	**0.532**[b]
LH/FSH	**-0.132**[c]	FFM (kg)	**0.533**[b]
FAI	**0.347**[b]	SLM (kg)	**0.503**[b]
HOMA-IR	**0.511**[b]	TBW	**0.521**[b]
Ins AUC 30/Glu AUC30	**0.331**[b]	Trunk FM (kg)	**0.518**[b]
Ins AUC 120/Glu AUC3120	**0.448**[b]	Trunk SLM (kg)	**0.499**[b]
TG/HDL	**0.399**[b]		
VAI	**0.430**[b]		
LAP	**0.587**[b]		

BMI: Body mass index, WHR: Waist to hip ratio, WHtR: Waist to height ratio, FAI: Free androgen index, Ins AUC30/Glu AUC30: Early phase insulin secretion, Ins AUC 120/Glu AUC120: Total insulin secretion, HOMA-IR: Homeostatic model of assessment-insulin resistance, PCOS: Polycystic ovary syndrome, TG/HDL: Triglyceride/HDL cholesterol, VAI: Visceral adiposity index, LAP: Lipid accumulation product, BMR: Basal metabolic rate, PBF: Percentage of body fat, FM: Fat mass, FFM: Fat-free mass, SLM: Soft lean mass, TBW: Total body water, correlation coefficients are presented, [a]: p<0.05, [b]: p<0.01, [c]: p≥0.05

Discussion

In the current research, we found that serum uric acid levels were elevated in women with PCOS compared to BMI-and age-matched controls. Insulin resistance indices emerged as significant predictors of uric acid levels, with BMI and adiposity indices also playing important roles. These findings indicate that uric acid may serve as a valuable marker for metabolic disturbances in PCOS, particularly in relation to insulin resistance and adiposity.

Contrary to studies that identified no significant difference in uric acid levels between individuals with PCOS and non-hyperandrogenemic controls (13), our findings are consistent with previous research demonstrating elevated serum uric acid in PCOS (9-11). Although the increase in uric acid levels has been attributed to various factors, the impact of increased uric acid on the development of PCOS remains debated, especially considering that PCOS encompasses a variety of metabolic disorders.

Insulin resistance and hyperinsulinemia, independent of obesity, play a pivotal role in the development of metabolic disorders in individuals with PCOS. Our study emphasizes the significant impact of insulin resistance on elevated uric acid levels among patients with PCOS. Notably, we observed that HOMA-IR emerged as the strongest independent predictor of serum uric acid levels in this population. These findings align with existing research that links elevated plasma uric acid levels to increased insulin resistance (14,15). A possible explanation for this relationship is that insulin promotes the reabsorption of uric acid in the kidneys, thereby reducing its excretion (16).

Table 4. Multiple linear regression analysis of independent predictors for uric acid levels in patients with PCOS using stepwise selection

Model	B	SE	Beta	95% confidence interval		t	p-value
				Lower limit	Upper limit		
1. Constant	3.58	0.14		3.3	3.86	25.53	0.001
HOMA-IR	0.26	0.03	0.61	0.19	0.32	7.56	0.001
2. Constant	2.5	0.31		1.89	3.11	8.12	0.001
HOMA-IR	0.18	0.04	0.44	0.11	0.26	5.06	0.001
BMI	0.05	0.01	0.34	0.02	0.07	3.86	0.001
3. Constant	2.80	0.33		2.14	3.47	8.41	0.001
HOMA-IR	0.16	0.04	0.37	0.08	0.23	4.03	0.001
BMI	0.03	0.01	0.24	0.01	0.06	2.43	0.017
LAP	0.01	0.00	0.22	0.00	0.01	2.14	0.035

BMI: Body mass index, WHR: Waist to hip ratio, WHtR: Waist to height ratio, FAI: Free androgen index, HOMA-IR: Homeostatic model of assessment-insulin resistance, LAP: Lipid accumulation product, SE: Standard error, PCOS: Polycystic ovary syndrome

Stepwise criteria: Probability of F to enter ≤0.05, probability of F to remove ≥0.1. Independent variables included in the analysis: Age, BMI, WHR, WHtR, FAI, HOMA-IR, LAP.

- Model 1 R^2=0.373, adjusted R^2=0.367
- Model 2 R^2=0.458, adjusted R^2=0.447
- Model 3 R^2=0.484, adjusted R^2=0.467

Moreover, elevated uric acid could induce inflammation and oxidative stress, which, as demonstrated in other studies, may contribute to the development of insulin resistance (17).

The literature presents conflicting evidence regarding the influence of insulin resistance on uric acid levels. According to Luque-Ramírez et al. (13), insulin resistance does not appear to have a direct effect on uric acid levels. In their study, 34 patients with PCOS were treated with either anti-androgenic combined oral contraceptives (COCs) or metformin over a period of 24 weeks. A decrease in serum uric acid was observed in those receiving COC treatment. While metformin did enhance insulin sensitivity, it did not have an impact on uric acid levels, indicating that insulin resistance may not be the primary factor influencing serum uric acid concentrations in this population. Furthermore, uric acid levels in individuals with PCOS were found to be comparable to those in the control. However, participants with obesity exhibited significantly higher uric acid levels across all study groups, regardless of their PCOS status. These findings indicate that hyperandrogenemia and obesity are major determinants affecting serum uric acid in patients with PCOS. In their study analyzing 17,753 adults from Korea, Bae et al. (18) demonstrated that increased BMI, waist circumference, and both general and abdominal obesity are significant risk factors for hyperuricemia in both genders. Similarly, research conducted by Mu et al. (9) revealed that the prevalence of hyperuricemia in patients with PCOS significantly increases with higher BMI levels. These results may be attributed to dysfunctional adipose tissue, which can lead to low-grade chronic inflammation associated with obesity. Consistently, in another study of patients with PCOS who were treated with COCs for six months indicated that laboratory changes were evident exclusively in PCOS patients with obesity, reinforcing the connection between obesity and inflammation (19).

The present study revealed a direct association between serum uric acid and body composition parameters assessed through BIA, indicating both general and abdominal obesity. However, it's important to note that BIA does not differentiate between subcutaneous and visceral adipose tissue (VAT). Zhang et al. (20) explored the relationship between body composition, measured by dual-energy X-ray absorptiometry, and elevated uric acid levels. Their study found that increased VAT mass may exacerbate hyperuricemia, while other adipose tissue compartments did not show a similar effect. LAP and VAI are cost-effective, non-invasive, and easily accessible metrics that incorporate BMI, waist circumference, TG, or HDL cholesterol. These indices are useful for predicting metabolic conditions in women with PCOS and serve as valuable tools for assessing and monitoring VAT changes (21,22). Ribeiro et al. (23) demonstrated that both LAP and VAI effectively screen for and help prevent metabolic syndrome and insulin resistance in individuals with PCOS. Furthermore, both our study and recent literature suggest that LAP is more effective than VAI in predicting visceral adiposity and metabolic disorders (23,24).

The relationship between hyperandrogenemia, a key characteristic of PCOS, and uric acid levels has been investigated in several studies. Findings indicate a positive correlation between elevated testosterone and FAI and increased serum uric acid (9,25). A large-scale study involving 1,183 PCOS patients and 10,772 control subjects without PCOS found that androgens might be a significant mediator in uric acid metabolism (9). Androgens may increase uric acid levels by stimulating renal reabsorption and enhancing hepatic purine nucleotide metabolism (26,27). Similarly, Gong et al. (10) studied 603 PCOS patients and 604 controls, demonstrating that hyperandrogenemia, insulin resistance, and dyslipidemia play roles in raising uric acid levels among patients with PCOS.

Our research distinguishes itself from previous studies by integrating various adiposity markers such as LAP and VAI, along with insulin secretion indices, hormonal and metabolic parameters, and body composition. As far as we know, no prior research has evaluated the combined influence of these factors on uric acid in patients with PCOS. After excluding multicollinear body composition parameters, as well as VAI, and TG/HDL cholesterol from the multivariate regression analysis, we identified HOMA-IR, BMI, and LAP as significant mediators of elevated uric acid. Integrating these metabolic indicators provides a more comprehensive understanding of uric acid metabolism in PCOS.

Study Limitations

This study presents several limitations, such as its retrospective design, which restricts the ability to establish causal relationships, and its single-center nature, which may introduce selection bias. Furthermore, the smaller size of the control group is also a limitation of this research. While BIA is a reliable and accessible method for assessing body composition, its precision in distinguishing between visceral and subcutaneous fat compartments is limited. Additionally, although certain variables were excluded to address multicollinearity, their potential additive value should be examined in larger cohorts.

Conclusion

In conclusion, this study emphasizes the significant relationship between elevated uric acid and metabolic disturbances in PCOS, particularly in relation to insulin resistance and adiposity. These findings suggest that uric acid may serve as a valuable marker for metabolic dysfunction, providing a basis for early risk assessment and intervention. To gain a deeper understanding of the role of uric acid in the pathophysiology of PCOS and its potential as an early predictor of metabolic risk, further prospective long-term analysis with larger cohorts is required.

Ethics

Ethics Committee Approval: This study was approved by University of Health Sciences Turkey, Kartal Dr. Lütfi Kırdar City Hospital Scientific Research Ethics Committee (reference number: 0l0.99/59, date: 24.02.2024).

Informed Consent: The requirement for written informed consent was waived by the Declaration of Helsinki, as only medical data from patient records were used in this retrospective study.

Footnotes

Authorship Contributions

Surgical and Medical Practices: N.G., K.A., Concept: N.G., K.A., Design: N.G., K.A., Data Collection or Processing: N.G., K.A., Analysis or Interpretation: N.G., K.A., Literature Search: N.G., Writing: N.G.

Conflict of Interest: No conflict of interest was declared by the authors.

Financial Disclosure: The authors declared that this study received no financial support.

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