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Cardiovascular and Metabolic Risk Profiles Across Different Phenotypes of Polycystic Ovary Syndrome

Polikistik Over Sendromu Fenotipleri Arasında Kardiyovasküler ve Metabolik Risk Profillerinin Karşılaştırılması

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Abstract

Aim: Polycystic ovary syndrome (PCOS) is a heterogeneous endocrine disorder affecting 5–10% of women of reproductive age and is increasingly recognized as a female-specific cardiometabolic condition. Although metabolic risk factors such as insulin resistance, dyslipidemia, and hypertension are well established in PCOS, their distribution across distinct phenotypes remains controversial.

Material and Method: In this retrospective study, 240 women diagnosed with PCOS based on the 2003 Rotterdam criteria and 116 healthy controls aged 18–42 years were evaluated. Patients with PCOS were categorized into four phenotypes: (i) hyperandrogenism+oligo/anovulation+polycystic ovaries (HA+OA+PCO), (ii)hyperandrogenism+oligo/anovulation (HA+OA), (iii)hyperandrogenism+polycystic ovaries (HA+PCO), and (iv)polycystic ovaries+oligo/anovulation (PCO+OA). Anthropometric measurements, hormonal profiles, lipid panels, glucose-insulin parameters, and HOMA-IR indices were compared between groups.

Results: Compared with controls, women with PCOS had significantly higher triglycerides, fasting insulin, HOMA-IR, total testosterone, DHEAS, and LH/FSH ratio, while HDL cholesterol was lower (all $p<0.05$). Waist-to-hip ratio was elevated in the PCOS group despite similar BMI. Mean systolic BP was comparable, whereas diastolic BP was slightly lower in PCOS; both SBP and DBP varied significantly across phenotypes. Lipid and hormone profiles did not differ among subgroups. Although glucose and overall HbA1c were similar between PCOS and controls, HbA1c was significantly higher in the PCO+OA subgroup compared with HA+OA.

Conclusion: PCOS is associated with adverse cardiometabolic risk factors independent of phenotype. These findings underscore the need for early cardiometabolic screening in all women with PCOS, while larger multicenter studies are warranted to delineate subtle inter-phenotypic variations.

Keywords: Polycystic ovary syndrome, phenotypes, insulin resistance, cardiovascular risk, metabolic syndrome

Öz

Amaç: Polikistik over sendromu (PCOS), üreme çağındaki kadınların %5–10'unu etkileyen heterojen bir endokrin bozukluktur ve giderek kadınlara özgü bir kardiyometabolik durum olarak tanınmaktadır. İnsülin direnci, dislipidemi ve hipertansiyon gibi metabolik risk faktörleri PCOS'ta iyi tanımlanmış olsa da, bunların farklı fenotipler arasındaki dağılımı tartışmalıdır.

Gereç ve Yöntem: Bu retrospektif çalışmada, 2003 Rotterdam kriterlerine göre PCOS tanısı almış 240 kadın ve 18–42 yaş aralığında 116 sağlıklı kontrol değerlendirildi. PCOS'lu hastalar dört fenotipe ayrıldı: (i) hiperandrojenizm+oligo/anovulasyon+polikistik overler (HA+OA+PCO), (ii) hiperandrojenizm+oligo/anovulasyon (HA+OA), (iii) hiperandrojenizm+polikistik overler (HA+PCO), (iv) polikistik overler+oligo/anovulasyon (PCO+OA). Gruplar arasında antropometrik ölçümler, hormonal profiller, lipid panelleri, glukoz-insülin parametreleri ve HOMA-IR indeksleri karşılaştırıldı.

Bulgular: Kontrollerle karşılaştırıldığında, PCOS'lu kadınlarda trigliserid, açlık insülini, HOMA-IR, total testosteron, DHEAS ve LH/FSH oranı anlamlı derecede yüksek; HDL kolesterol ise daha düşüktü (tümü $p<0,05$). VKİ benzer olmasına rağmen bel/kalça oranı PCOS grubunda daha yüksekti. Ortalama sistolik kan basıncı benzerken, diyastolik kan basıncı PCOS'ta biraz daha düşüktü; hem SBP hem de DBP fenotipler arasında anlamlı farklılık gösterdi. Lipid ve hormon profilleri alt gruplar arasında farklılık göstermedi. Glukoz ve HbA1c genel olarak PCOS ve kontroller arasında benzer olsa da, HbA1c PCO+OA alt grubunda HA+OA'ya göre anlamlı derecede yüksekti.

Sonuç: PCOS, fenotipten bağımsız olarak olumsuz kardiyometabolik risk faktörleri ile ilişkilidir. Bu bulgular, tüm PCOS'lu kadınlarda erken kardiyometabolik taramanın önemini vurgulamaktadır. İnter-fenotipik ince farklılıkları ortaya koymak için daha geniş çok merkezli çalışmalara ihtiyaç vardır.

Anahtar Kelimeler: Polikistik over sendromu, fenotipler, insülin direnci, kardiyovasküler risk, metabolik sendrom

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INTRODUCTION

Polycystic ovary syndrome (PCOS) is the most prevalent endocrine disorder among women of reproductive age, with an estimated prevalence of 5–10% depending on diagnostic criteria and population studied.[1] Traditionally defined by chronic anovulation, hyperandrogenism, and polycystic ovarian morphology, PCOS is now recognized as a complex, multisystem disorder with significant reproductive, metabolic, and cardiovascular implications.[2,3]

Since the introduction of the Rotterdam criteria in 2003, four distinct phenotypes have been identified: (i) hyperandrogenism, oligo/anovulation, and polycystic ovaries (classic PCOS, HA+OA+PCO); (ii) hyperandrogenism with oligo/anovulation (HA+OA); (iii) hyperandrogenism with polycystic ovaries (HA+PCO); and (iv) polycystic ovaries with oligo/anovulation but without hyperandrogenism (PCO+OA). These phenotypes exhibit variable reproductive and metabolic features, yet their relative cardiometabolic risk profiles remain incompletely defined.[4]

Insulin resistance is considered a core pathophysiological mechanism in PCOS, reported in up to 70% of affected women regardless of body mass index. Hyperinsulinemia exacerbates androgen excess by stimulating ovarian theca cells, while simultaneously reducing hepatic sex hormone-binding globulin (SHBG) synthesis, thereby increasing free testosterone levels.[5] In parallel, PCOS is associated with adverse lipid profiles, elevated blood pressure, and impaired glucose tolerance, all of which contribute to long-term cardiovascular disease (CVD) risk.[6]

Despite the clear metabolic burden of PCOS, whether these risks are uniformly distributed across all phenotypes is debated. Some studies suggest that "classic" phenotypes (HA+OA+PCO and HA+OA) carry the highest cardiometabolic risk, while "non-hyperandrogenic" phenotypes, particularly PCO+OA, may exhibit milder metabolic disturbances.[7,8] However, other reports have failed to demonstrate significant inter-phenotypic differences, highlighting the need for further clarification.[9,10]

Therefore, the present study aimed to compare cardiovascular and metabolic risk parameters across different PCOS phenotypes in a Turkish cohort, using retrospective clinical and biochemical data. By elucidating phenotype-specific risk profiles, this study seeks to refine risk stratification and inform tailored clinical management strategies.

MATERIAL AND METHOD

Study Design and Participants

This retrospective study was conducted at the Namık Kemal University Non-interventional Clinical Researches Ethics Committee (Date: 26/09/2013, Decision No: 2013/108), between January 2010 and October 2013. A total of 356 women aged 18–42 years were evaluated, including 240 patients with PCOS and 116 age-matched healthy controls. PCOS was diagnosed according to the 2003 Rotterdam criteria, requiring the presence of at least two of the following: (i) oligo/anovulation, (ii) clinical or biochemical hyperandrogenism, and (iii) polycystic ovarian morphology on ultrasound.

Inclusion and Exclusion Criteria

Eligible participants were women aged 18–42 years, either diagnosed with PCOS according to the Rotterdam criteria or serving as age-matched healthy controls, who voluntarily agreed to participate. Women with thyroid dysfunction, hyperprolactinemia, congenital adrenal hyperplasia, Cushing's syndrome, ovarian or adrenal androgen-secreting tumors, diabetes mellitus, cardiovascular disease, chronic systemic or autoimmune disorders, hepatic or renal impairment, or neoplastic conditions were excluded. Additional exclusion criteria were pregnancy, use of hormonal or metabolic treatments within the preceding six months, and refusal to provide informed consent.

Phenotype Classification

PCOS patients were stratified into four phenotypes:

- **Group 1 (HA+OA+PCO):** hyperandrogenism + oligo/anovulation + polycystic ovaries (n=149)
- **Group 2 (HA+OA):** hyperandrogenism + oligo/anovulation (n=32)
- **Group 3 (HA+PCO):** hyperandrogenism + polycystic ovaries (n=27)
- **Group 4 (PCO+OA):** polycystic ovaries + oligo/anovulation without hyperandrogenism (n=32)

Clinical and Anthropometric Assessment

All participants underwent a detailed evaluation that included obstetric and gynecological history, menstrual pattern, reproductive background, medical history, medication use, and assessment of hyperandrogenism. Height and weight were measured, and body mass index (BMI, kg/m^2) was calculated. Waist circumference was measured at the midpoint between the lowest rib and the iliac crest during normal expiration, and hip circumference was measured at the widest point over the greater trochanters to derive the waist-to-hip ratio (WHR). Systolic and diastolic blood pressures were recorded in the seated position using a calibrated sphygmomanometer. Hirsutism was assessed using the modified Ferriman–Gallwey (mFG) scoring system across nine anatomical regions, with a score ≥8 considered diagnostic. Additional features of hyperandrogenism—including acne, seborrhea, androgenic alopecia, voice deepening, and weight gain—were also systematically documented.

Ultrasonographic Evaluation

Transvaginal ultrasonography was applied whenever feasible, whereas virginal women were assessed transabdominally. Polycystic ovarian morphology was defined as ≥12 follicles measuring 2–9 mm and/or ovarian volume >10 mL in at least one ovary. Bilateral ovarian volumes were calculated for all participants.

Laboratory Analyses

Venous blood samples were collected between 08:00 and 09:30 a.m. during the early follicular phase (cycle days 3–5) after an overnight fast. Samples were kept at cold temperature, centrifuged at 4000 rpm for 5 minutes, and the plasma fraction was used for biochemical measurements. Serum fasting glucose, total cholesterol, triglycerides (TG), high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C), and HbA1c were determined using enzymatic methods (Roche Diagnostics, Cobas e311 autoanalyzer).

Hormonal assays, including follicle-stimulating hormone (FSH), luteinizing hormone (LH), estradiol, total testosterone (TT), dehydroepiandrosterone sulfate (DHEAS), prolactin, thyroid-stimulating hormone (TSH), free T3 (FT3), and free T4 (FT4), were performed by electrochemiluminescence immunoassay (Roche Cobas e411). All analyses were conducted at the Multidisciplinary Laboratory of Tekirdağ Namık Kemal University Faculty of Medicine and the Biochemistry Laboratory of Tekirdağ Namık Kemal University Research and Training Hospital. Results were reported in standard clinical units (e.g., glucose: mg/dL; insulin: µIU/mL; HbA1c: %; lipid profile: mg/dL; reproductive hormones: µIU/mL, pg/mL, ng/dL, or µg/dL).

Oral Glucose Tolerance Test (OGTT) and Insulin Resistance

Following three days of a normal diet and usual activity, a 10–12 h fast was required prior to testing. A baseline venous sample was collected for fasting glucose and insulin, followed by ingestion of 75 g glucose dissolved in 300 mL water. A second blood sample was collected at 120 minutes. According to the 2011 American Diabetes Association (ADA) criteria, impaired fasting glucose was defined as 100–125 mg/dL, impaired glucose tolerance as 140–199 mg/dL at 120 minutes, and diabetes mellitus as fasting glucose ≥126 mg/dL or 120-min glucose ≥200 mg/dL.

Insulin Resistance Assessment

A HOMA-IR cut-off value of 2.5 was used to define insulin resistance, consistent with prior studies and recommended thresholds in non-diabetic reproductive-age women.11,12 Diagnostic criteria for glucose tolerance were based on the American Diabetes Association guidelines, which provide standardized definitions for impaired fasting glucose and impaired glucose tolerance.

Insulin resistance was estimated using the homeostasis model assessment (HOMA-IR) formula:

$$\text{HOMA-IR} = \frac{\text{Fasting glucose (mg/dL)} \times \text{Fasting insulin (µIU/mL)}}{405}$$

A HOMA-IR value >2.5 or fasting insulin ≥20 µIU/mL was accepted as evidence of insulin resistance.

Statistical Analysis

Data analysis was performed using SPSS version 19.0 (IBM Corp., Armonk, NY, USA). Continuous variables are presented as mean ± standard deviation (SD) or mean ± standard error of the mean (SEM) where indicated. The distribution of data was evaluated using the Shapiro–Wilk test, and homogeneity of variances was examined with Levene's test. For comparisons between the PCOS and control groups, Student's t-test was applied for normally distributed variables, and the Mann–Whitney U test was used for non-parametric variables. For comparisons among PCOS subtypes, one-way analysis of variance followed by Tukey's post hoc test was performed when assumptions were met. When assumptions of normality or homogeneity were violated, the Kruskal–Wallis test with Dunn–Bonferroni correction was applied. A two-tailed p-value <0.05 was considered statistically significant.

RESULT

Between January 2010 and October 2013, we retrospectively reviewed medical records of 356 women evaluated at the Department of Obstetrics and Gynecology, Namık Kemal University: 240 with polycystic ovary syndrome (PCOS) aged 18–42 years and 116 without PCOS as controls. PCOS cases were stratified into four phenotypes: Group 1 (HA+OA+PCO), 149 patients (62.1%); Group 2 (HA+OA), 32 patients (13.3%); Group 3 (HA+PCO), 27 patients (11.3%); and Group 4 (PCO+OA), 32 patients (13.3%) (**Table 1**).

Table 1: Number and percentage distribution of PCOS phenotypes.

Group	Number of Patients (n)	Percentage (%)
Group 1 (HA+OA+PKO)	149	62.1
Group 2 (HA+OA)	32	13.3
Group 3 (HA+PKO)	27	11.3
Group 4 (PKO+OA)	32	13.3

Note: Group definitions are provided in the Materials and Methods section.

Demographic characteristics

As shown in **Table 2**, the mean age of the control group was significantly higher than that of the PCOS group (p=0.005). No significant difference was observed in systolic blood pressure, whereas diastolic blood pressure was significantly lower in the PCOS group compared with controls (p=0.039). Although BMI was slightly higher in the PCOS group, the difference was not significant. By contrast, WHR was significantly higher in the PCOS group (p<0.001).

As shown in **Table 3**, there were significant differences in both systolic and diastolic blood pressures across the PCOS subtypes (p=0.005; p=0.021, respectively). Post hoc Tukey comparisons indicated that systolic BP was significantly lower in the HA+OA+PCO group compared with the HA+OA (p=0.035) and HA+PCO (p=0.048) subtypes. For diastolic BP, the HA+OA+PCO phenotype exhibited significantly lower values compared with the HA+OA group (p=0.045). No other pairwise differences reached statistical significance (all p>0.05) (**Figure 1**).

Table 2. Comparison of demographic characteristics between PCOS and control groups

Demographic characteristics	PCOS (N=240)	Control (N=116)	P
Age (years)	24.71±5.36	26.43±5.51	0.005*
SB (mmHg)	111.22±12.57	110.3±13.34	0.893
DB (mmHg)	70.01±9.53	72.28±9.94	0.039*
BMI (kg/m2)	26.03±7.55	24.61±4.90	0.066
WHR	0.81±0.074	0.76±0.071	<0.001*

Mean ± SD: mean ± standard deviation. Statistically significant at *p<0.05.

Table 3. Comparison of demographic characteristics among PCOS subtypes

Demographic characteristics	Subtype 1 (HA+OA+PCO) n=149	Subtype 2 (HA+OA) n=32	Subtype 3 (HA+PCO) n=27	Subtype 4 (PCO+OA) n=32	p value
Age (years)	24.55±5.20	24.18±5.45	27.03±6.38	24.06±4.75	0.111
Systolic BP (mmHg)	109.06±11.77	115.31±13.19	115.18±14.51	113.9±12.09	0.007*
Diastolic BP (mmHg)	68.52±9.05	73.75±9.06	73.14±10.1	70.56±10.41	0.021*
WHR	0.81±0.08	0.81±0.06	0.79±0.06	0.80±0.05	0.604
BMI (kg/m^2)	25.98±8.17	24.74±8.20	26.62±5.00	27.04±5.50	0.646

Mean ± SD: mean ± standard deviation. *Statistically significant at p<0.05 (ANOVA).

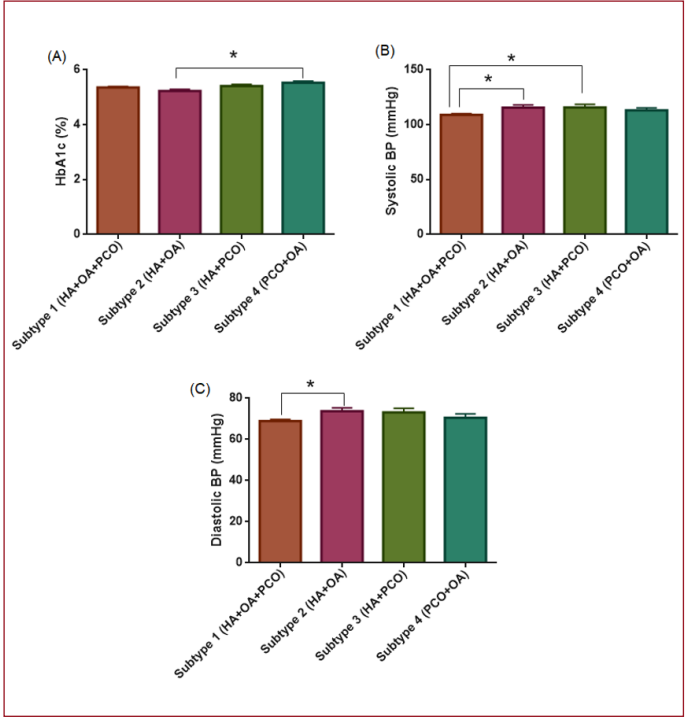

Figure 1. Comparison of metabolic and hemodynamic parameters across PCOS subtypes.
(A) HbA1c levels were significantly higher in the PCO+OA phenotype compared with the HA+OA group (*p<0.05).
(B) Systolic blood pressure (BP) was significantly lower in the HA+OA+PCO subtype compared with the HA+OA and HA+PCO groups (*p<0.05).
(C) Diastolic BP was significantly lower in the HA+OA+PCO phenotype compared with the HA+OA group (*p<0.05).
Data are presented as mean ± SEM. *p<0.05, statistically significant.

Lipid profile

As shown in **Table 4**, no significant differences were detected in total cholesterol or LDL levels between the groups, indicating that these parameters were not influenced by PCOS status. In contrast, triglyceride levels were significantly higher in the PCOS group compared with controls (p=0.001), suggesting a greater tendency toward hypertriglyceridemia in women with PCOS. Moreover, HDL levels were significantly lower in the PCOS group than in the control group (p<0.001), reflecting a more atherogenic lipid profile in patients with PCOS.

As shown in **Table 5**, no significant differences were observed among the PCOS subgroups in triglyceride, total cholesterol, or LDL levels (p>0.05). HDL values also showed no statistically significant variation across the subgroups (p=0.127), although the third subgroup tended to have slightly higher HDL concentrations. Overall, the lipid profile did not differ significantly between PCOS phenotypes, indicating that dyslipidemia was a common feature regardless of subgroup classification.

Table 4. Comparison of lipid profiles between PCOS and control groups

Lipid profile	PCOS (N=240)	Control (N=116)	P
Total cholesterol (mg/dl)	177.77±39.88	174.34±36.80	0.436
TG (mg/dl)	105.82±60.62	85.46±36.79	0.001*
LDL (mg/dl)	110.53±32.48	116.51±110.14	0.439
HDL (mg/dl)	47.92±12.23	53.08±12.74	<0.001*

Mean ± SD: mean ± standard deviation. *Statistically significant at p<0.05.

Table 5. Comparison of lipid profiles among PCOS subtypes

Lipid profile	Subtype 1 (HA+OA+PCO) n=149	Subtype 2 (HA+OA) n=32	Subtype 3 (HA+PCO) n=27	Subtype 4 (PCO+OA) n=32	p value
TG (mg/dl)	110.70±62.70	100.15±55.45	97.00±76.07	96.23±36.30	0.457
Total cholesterol (mg/dL)	178.26±40.78	174.89±39.00	178.36±43.50	177.85±34.74	0.979
LDL (mg/dl)	111.59±35.21	108.81±30.50	108.08±24.28	109.41±27.84	0.932
HDL (mg/dl)	47.26±12.34	46.56±11.78	53.12±12.54	47.96±11.30	0.127

Mean ± SD: mean ± standard deviation. *Statistically significant at p<0.05 (ANOVA).

Hormonal parameters

As shown in **Table 6**, both total testosterone and DHEAS levels were significantly elevated in the PCOS group compared with controls (p<0.001 and p=0.015, respectively), highlighting the hyperandrogenic profile that characterizes the syndrome. In addition, the LH/FSH ratio was markedly higher in women with PCOS (p<0.001), consistent with the well-known disruption of gonadotropin secretion patterns in this disorder. Together, these findings underscore the hormonal imbalance that differentiates PCOS patients from healthy controls.

As shown in **Table 7**, no significant differences were detected among PCOS subtypes in terms of total testosterone, DHEAS, or LH/FSH ratio (all p>0.05). This suggests that hyperandrogenism and altered gonadotropin dynamics, which are hallmarks of PCOS, were consistently present across phenotypes rather than being restricted to a specific subgroup. Such findings indicate that the endocrine disturbances underlying PCOS are shared features, independent of clinical presentation.

Table 6. Comparison of hormone parameters between PCOS and control groups

Hormones	PCOS (N=240)	Control (N=116)	p value
TT (ng/mL)	38.71±18.81	29.33±11.92	<0.001*
DHEAS (µg/dL)	227.41±101.72	200.58±86.57	0.015*
LH/FSH ratio	1.57±0.99	0.96±0.80	<0.001*

Mean ± SD: mean ± standard deviation. *Statistically significant at p<0.05.

Table 7. Comparison of hormone parameters among PCOS subtypes

Hormones	Subtype 1 (HA+OA+PCO) n=149	Subtype 2 (HA+OA) n=32	Subtype 3 (HA+PCO) n=27	Subtype 4 (PCO+OA) n=32	p value
TT (ng/mL)	40.66±17.68	35.47±20.13	38.30±22.26	33.47±18.75	0.172
DHEAS (µg/dL)	235.68±95.35	226.69±95.49	229.36±142.09	187.97±91.50	0.121
LH/FSH ratio	1.67±1.10	1.37±0.87	1.28±0.74	1.56±0.67	0.160

Mean ± SD: mean ± standard deviation. *Statistically significant at p<0.05 (ANOVA).

Diabetes and insulin resistance parameters

As shown in **Table 8**, fasting glucose, postprandial glucose, and HbA1c values did not differ significantly between women with PCOS and controls, suggesting preserved glucose homeostasis in this young cohort. In contrast, fasting insulin levels were significantly higher in the PCOS group (p=0.002), and HOMA-IR values were also elevated (p=0.001), indicating increased insulin resistance. These findings highlight subclinical metabolic alterations in PCOS, marked by hyperinsulinemia and insulin resistance despite normal glycemic indices.

As shown in **Table 9**, no significant differences were observed among PCOS subtypes in fasting glucose, postprandial glucose, insulin, or HOMA-IR values (all p>0.05), indicating that overall glucose homeostasis and insulin resistance were comparable across phenotypes.

Table 8. Comparison of diabetes-related parameters between PCOS and control groups

Diabetes parameters	PCOS (N=240)	Control (N=116)	p-value
Glucose (mg/dL)	90.36±8.42	90.98±8.16	0.513
Postprandial glucose (mg/dL)	102.21±29.34	97.40±25.91	0.133
Insulin (µIU/mL)	9.62±7.99	7.13±4.71	0.002*
HbA1c (%)	5.36±0.40	5.42±0.32	0.206
HOMA-IR	2.22±2.04	1.54±1.14	0.001*

Mean ± SD: mean ± standard deviation. *Statistically significant at p<0.05.

Table 9. Comparison of insulin resistance parameters among PCOS subtypes

Insulin resistance parameters	Subtype 1 (HA+OA+PCO) n=149	Subtype 2 (HA+OA) n=32	Subtype 3 (HA+PCO) n=27	Subtype 4 (PCO+OA) n=32	p value
Glucose (mg/dL)	90.49±9.10	89.42±6.78	90.33±9.28	90.70±5.72	0.923
Postprandial glucose (mg/dL)	102.23±30.65	102.58±33.62	100.37±20.86	103±25.61	0.984
Insulin (µIU/mL	10.25±8.94	8.24±5.92	6.93±4.35	10.30±6.98	0.160
HbA1c (%)	5.35±0.42	5.22±0.36	5.40±0.34	5.52±0.34	0.028*
HOMA-IR	2.40±2.35	1.84±1.36	1.58±1.04	2.32±1.58	0.170

Mean ± SD: mean ± standard deviation. *Statistically significant at p<0.05.

HbA1c Findings

In our study, HbA1c levels differed significantly among PCOS phenotypes (p=0.028), with the Subtype 2 (HA+OA) subgroup showing lower values compared with the Subtype 4 (PCO+OA) subgroup (p=0.013). This result is notable in that it questions the assumption that non-hyperandrogenic phenotypes exhibit a metabolically milder profile. Since HbA1c reflects long-term glycemic control, the elevated levels in the PCO+OA phenotype suggest that this subgroup may also be prone to subclinical glucose dysregulation, even in the absence of overt abnormalities in fasting or postprandial glucose.

DISCUSSION

This study evaluated cardiometabolic risk factors across different phenotypes of polycystic ovary syndrome (PCOS) in a Turkish cohort of 240 women with PCOS and 116 healthy controls. The main findings were that PCOS patients exhibited higher triglycerides, fasting insulin, HOMA-IR, total testosterone, DHEAS, and LH/FSH ratio, alongside lower HDL cholesterol, compared with controls. These results confirm that PCOS, regardless of phenotype, is associated with an adverse cardiometabolic profile. Inter-phenotypic analysis revealed no major differences, except for higher HbA1c in the PCO+OA subgroup compared with HA+OA, and modest differences in blood pressure between subtypes.

Compared with controls, PCOS patients did not exhibit higher mean BMI, indicating that obesity is not universal in this population. However, waist-to-hip ratio was significantly elevated, reflecting disproportionate central adiposity. This observation is consistent with evidence that PCOS favors visceral fat accumulation even among normal-weight women.[4,13,14] Mechanistically, hyperandrogenism and hyperinsulinemia may drive abdominal fat deposition, while visceral adipose tissue itself contributes to systemic insulin resistance and adverse lipid alterations.[4,15] These findings highlight central obesity as a key metabolic risk factor in PCOS.

Phenotype-based comparisons revealed no significant differences in BMI or WHR across subgroups, indicating that central adiposity is largely phenotype-independent. Notably, even the non-hyperandrogenic PCO+OA phenotype showed similar fat distribution, contrasting with prior reports describing greater adiposity in hyperandrogenic phenotypes and a leaner profile in this subgroup.[4,16] In our cohort, however, PCO+OA did not exhibit a metabolically favorable pattern, as both BMI and WHR were comparable to other phenotypes. These findings underscore visceral adiposity as a common feature across PCOS subtypes and support its role as a core driver of metabolic risk.[15,16]

In line with this, women with PCOS exhibited a more atherogenic lipid profile than controls, characterized by elevated triglycerides and reduced HDL cholesterol, consistent with the dyslipidemia frequently reported in PCOS.[18,19]

Importantly, lipid disturbances did not differ significantly between phenotypes, implying that dyslipidemia is a common metabolic signature across all PCOS subtypes.[20] Reports suggest a prevalence of dyslipidemia in up to ~70% of women with PCOS, typically manifesting as reduced HDL and elevated triglycerides.[21] Taken together, our findings support the notion that insulin resistance and central adiposity, rather than phenotype, are central determinants of lipid abnormalities in PCOS.

Mean SBP was similar between PCOS and controls (~111 vs 110 mmHg, p≈0.89), while DBP was unexpectedly lower in PCOS (70.0 vs 72.3 mmHg, p=0.039). This contrasts with the anticipated link between PCOS and hypertension.[19,22] A likely explanation is the younger age of the PCOS group (~24.7 vs ~26.4 years), as even small differences can affect blood pressure. Exclusion of women with cardiovascular disease or diabetes and the generally young, normotensive sample may also explain the absence of elevated BP. Thus, hypertensive effects of PCOS may emerge later with advancing age or longer disease duration, beyond what our cross-sectional cohort could capture.

Within the PCOS cohort, significant differences in blood pressure were observed across phenotypes. The classic HA+OA+PCO group exhibited the lowest systolic and diastolic pressures, whereas the non-PCO hyperandrogenic subtypes (HA+OA and HA+PCO) showed the highest mean values. The normoandrogenic PCO+OA phenotype demonstrated intermediate levels, indicating that the absence of hyperandrogenism does not necessarily confer protection against subtle BP elevations. Although all values remained within the normotensive range, this gradient suggests that androgen excess may contribute to modest increases in blood pressure, potentially through endothelial dysfunction, activation of the renin–angiotensin system, and sympathetic overactivity.[23] Our results are consistent with prior evidence linking hyperandrogenemia to elevated blood pressure independent of adiposity[24] and meta-analyses showing an overall increased risk of hypertension in PCOS.[25,26] These findings reinforce the importance of both phenotype-specific and general cardiovascular monitoring in women with PCOS.

In our cohort, women with PCOS exhibited the characteristic hormonal abnormalities of the syndrome, with significantly higher total testosterone, DHEA-S, and LH/FSH ratios compared to controls. These findings are consistent with the concept of functional ovarian hyperandrogenism as a central pathophysiological feature of PCOS.[27-30] Recent studies further corroborate the presence of elevated androgen levels and increased LH/FSH ratios in affected women.[31-33] Elevated DHEA-S has also been documented in large PCOS cohorts, reflecting the contribution of adrenal hyperandrogenism.[34] Moreover, insulin resistance exacerbates androgen excess by stimulating ovarian theca cell activity and suppressing hepatic SHBG production, thereby amplifying the hyperandrogenic milieu.

Despite normal glucose values, PCOS women had significantly higher fasting insulin and HOMA-IR, consistent with compensatory hyperinsulinemia and intrinsic insulin resistance.[35,36] This abnormality was evident across all phenotypes, including phenotype D, challenging the notion of a metabolically "benign" variant. Our findings align with recent data showing insulin resistance in 50–80% of PCOS women, independent of BMI.[3,37] Mechanistically, hyperinsulinemia exacerbates androgen excess while reduced insulin sensitivity promotes visceral adiposity, reinforcing a vicious cycle.

A novel observation was the higher HbA1c in phenotype D compared with phenotype B, despite all means being within the normal range. This suggests subtle glycemic impairment in women without overt hyperandrogenism, in line with reports of phenotype-dependent but overlapping metabolic risk.[4,38,39] Differences may reflect age, adiposity, or delayed diagnosis in less symptomatic phenotypes. Regardless, elevated HbA1c emphasizes the need for metabolic screening in all women with PCOS, including those lacking clinical hyperandrogenism.

While HbA1c was significantly higher in the PCO+OA phenotype compared with HA+OA, all mean values were within the normal clinical range (<5.7%). Thus, the difference may not represent overt hyperglycemia but could indicate subtle alterations in long-term glucose handling, possibly related to insulin signaling inefficiency or delayed diagnosis in non-hyperandrogenic phenotypes.

Our findings align with those of Carmina et al.[4], who showed that metabolic disturbances, including dyslipidemia and insulin resistance, were shared across all PCOS phenotypes in a Mediterranean cohort. Likewise, Wen et al.[39] found comparable insulin resistance indices among Chinese women, indicating that non-hyperandrogenic phenotypes may also exhibit early glycemic alterations. The higher HbA1c in our PCO+OA group underscores the need for metabolic monitoring even in normoandrogenic patients and challenges the notion of a metabolically "benign" phenotype, emphasizing phenotype-independent strategies for cardiometabolic prevention in PCOS.

Taken together, these findings highlight the systemic nature of PCOS, with diastolic hypertension and central adiposity serving as early, phenotype-independent indicators of cardiovascular risk. Early recognition of these traits may guide phenotype-specific risk stratification and timely interventions.

From a clinical perspective, these findings support universal screening for metabolic risk factors in all women with PCOS, regardless of phenotype. Early identification of insulin resistance, dyslipidemia, and hypertension could guide preventive strategies, including lifestyle interventions and pharmacologic management. Given that PCOS affects women in their reproductive years, addressing metabolic health has implications not only for long-term cardiovascular outcomes but also for fertility and pregnancy complications.

This study has some limitations. First, its retrospective design may introduce selection bias. Second, the sample sizes of the phenotypic subgroups were unequal, which may have reduced statistical power to detect subtle inter-phenotypic differences. Third, the study population was limited to a single tertiary center in Türkiye, which may restrict generalizability. Finally, we did not assess emerging markers of cardiovascular risk such as inflammatory cytokines, adipokines, or vascular imaging parameters, which could provide more comprehensive risk profiling.

CONCLUSION

In summary, women with PCOS demonstrated significantly higher insulin resistance, adverse lipid profiles, and hyperandrogenemia compared with controls, independent of phenotype. Although phenotypic differences were limited, the presence of elevated HbA1c in the PCO+OA subgroup suggests that even non-hyperandrogenic PCOS phenotypes may carry metabolic risk. These findings underscore the importance of cardiometabolic screening in all PCOS patients and highlight the need for larger, multicenter, prospective studies to clarify inter-phenotypic variability.

ETHICAL DECLARATIONS

Ethics Committee Approval: Ethical approval was obtained from the Namık Kemal University Non-interventional Clinical Researches Ethics Committee (Date: 26/09/2013, Decision No: 2013/108).

Informed Consent: Because the study was designed retrospectively, no written informed consent form was obtained from patients.

Referee Evaluation Process: Externally peer-reviewed.

Conflict of Interest Statement: The authors have no conflicts of interest to declare.

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Author Contributions: All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

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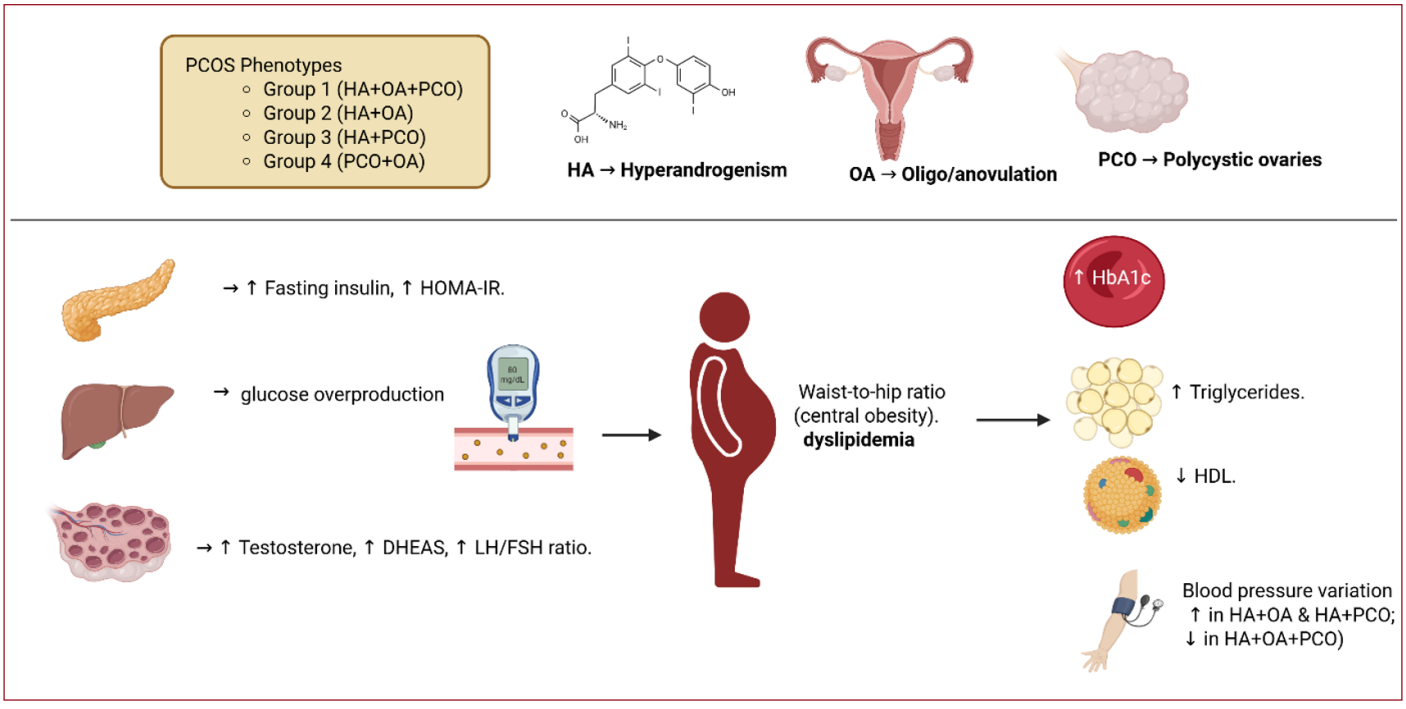

Graphical abstract
Cardiometabolic risk profiles across PCOS phenotypes.
The figure illustrates the major biological sources (pancreas, liver, ovary), intermediate mechanisms (central obesity, dyslipidemia), and clinical outcomes (↑ HbA1c, ↑ triglycerides, ↓ HDL, and blood pressure variation), highlighting that all PCOS phenotypes exhibit adverse metabolic risk.

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