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Metabolic Heterogeneity of Polycystic Ovary Syndrome Phenotypes: A Comparative Analysis of Hormonal and Biochemical Parameters

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Abstract Polycystic ovary syndrome (PCOS) is characterized not only by reproductive dysfunction but also by marked metabolic disturbances. The aim of this study was to conduct a comparative analysis of the hormonal and metabolic profiles in women with different PCOS phenotypes, defined according to the Rotterdam criteria (ESHRE/ASRM, 2003). Materials and Methods: The study included 151 reproductive-aged women, divided into four phenotypes. The analysis included measurements of body mass index (BMI), insulin, HOMA-IR, lipid profile, androgens, and sex hormone-binding globulin (SHBG). Results: The most pronounced metabolic disturbances were observed in patients with phenotype A (HA+A+PCO), including elevated levels of insulin and triglycerides and reduced SHBG. Even phenotype D (A+PCO), traditionally considered metabolically favorable, showed significant signs of insulin resistance. Logistic regression revealed that triglyceride level was the only statistically significant predictor of severe insulin resistance (HOMA-IR > 3.5). Conclusion: These findings underscore the need for metabolic monitoring in all PCOS phenotypes and the importance of using phenotypic classification not only for reproductive assessment but also for metabolic stratification.

Keywords Polycystic ovary syndrome, Phenotypes, Insulin resistance, Triglycerides, SHBG

1. Introduction

Polycystic ovary syndrome (PCOS) is one of the most common endocrine disorders affecting women of reproductive age. In addition to classical gynecological manifestations such as chronic anovulation and hyperandrogenism, PCOS is characterized by pronounced metabolic abnormalities. These include insulin resistance, abdominal obesity, dyslipidemia, and an increased risk of developing type 2 diabetes and cardiovascular disease.

According to the Rotterdam criteria (ESHRE/ASRM, 2003), PCOS can be classified into four phenotypes, based on the combination of three key features: hyperandrogenism, ovulatory dysfunction, and polycystic ovarian morphology. Each phenotype is associated with varying degrees of hormonal and metabolic disturbance. However, it remains unclear how clinically meaningful these differences are—and whether there are distinct interaction patterns between the hormonal background and metabolic status for each phenotype. One of the most intriguing questions is the relationship between hyperandrogenism and insulin resistance within the different PCOS variants.

Based on this, the aim of our study was to conduct a comparative analysis of hormonal and metabolic parameters in women with different PCOS phenotypes and to identify potential patterns in their interrelationships. Particular attention was paid to identifying statistically significant correlations between androgen levels, lipid metabolism parameters, and insulin resistance markers. Additionally, factors associated with pronounced insulin resistance (defined as HOMA-IR > 3.5) were analyzed separately.

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2. Materials and Methods

The study included data from 151 women of reproductive age with a confirmed diagnosis of polycystic ovary syndrome (PCOS) according to the Rotterdam criteria [12]. Based on phenotypic classification, the participants were divided into four groups: Phenotype A: a combination of hyperandrogenism (HA), anovulation (A), and polycystic ovarian morphology (PCO); Phenotype B: hyperandrogenism and anovulation (HA + A); Phenotype C: hyperandrogenism and polycystic morphology (HA + PCO); Phenotype D: anovulation and polycystic morphology (A + PCO).

The clinical and laboratory parameters included in the analysis were: Body mass index (BMI), insulin levels, glucose, HOMA-IR (calculated as glucose × insulin / 22.4), total testosterone, sex hormone-binding globulin (SHBG), luteinizing hormone (LH), follicle-stimulating hormone (FSH), total cholesterol (TC), high-density lipoprotein (HDL), low-density lipoprotein (LDL), and triglycerides (TG).

Table 1. Comparison of Mean Hormonal and Metabolic Parameters Across PCOS Phenotypes

Parameter	Phenotype A	Phenotype B	Phenotype C	Phenotype D
BMI (kg/m²)	29,5	27,1	28,8	26,9
HOMA-IR	4,1	3,2	3,9	2,8
Insulin (μU/mL)	16,4	12,8	15,1	10,7
TG (mmol/L)	1,9	1,5	1,8	1,3
SHBG (nmol/L)	35,2	44,5	36,8	49,1
Testosterone (nmol/L)	2,4	2,1	2,2	1,6

BMI – body mass index; HOMA-IR – homeostasis model assessment of insulin resistance; TG – triglycerides; SHBG – sex hormone-binding globulin.

Statistical analysis included both descriptive and inferential methods. Data were presented as medians, quartiles, means, and standard deviations. Comparison of indicators between PCOS phenotypes was performed using the non-parametric Kruskal–Wallis test. Spearman's rank correlation coefficient was used to assess relationships between hormonal and metabolic parameters. Severe insulin resistance was defined as HOMA-IR > 3.5. To identify factors associated with severe insulin resistance, a logistic regression model was built, with calculation of corresponding coefficients and p-values.

3. Results

The study included 151 reproductive-aged women with a confirmed diagnosis of polycystic ovary syndrome (PCOS), who were classified into four phenotypes according to the Rotterdam criteria (ESHRE/ASRM, 2003). The distribution by phenotype was as follows: Phenotype A (hyperandrogenism + anovulation + polycystic ovarian morphology) included 61 participants (40.4%), Phenotype B (hyperandrogenism + anovulation) — 21 participants (13.9%), Phenotype C (hyperandrogenism + polycystic ovarian morphology) — 41 participants (27.2%), Phenotype D (anovulation + polycystic ovarian morphology) — 28 participants (18.5%).

Analysis using the Kruskal–Wallis test revealed statistically significant differences among PCOS phenotypes in several hormonal and metabolic parameters (Table 1).

Among the hormonal parameters, the most pronounced differences were found in total testosterone levels, which were highest in phenotype A, moderate in phenotypes B and C, and lowest in phenotype D ($p < 0.001$). SHBG (sex hormone-binding globulin) levels were significantly lower in phenotypes A and C compared to B and D ($p = 0.004$). Differences were also observed in the LH/FSH ratio ($p < 0.05$), mainly due to elevated LH levels in the hyperandrogenic phenotypes.

Among the metabolic parameters, the most marked differences were seen in body mass index (BMI), which was highest in phenotype A ($p = 0.02$), as well as in insulin and HOMA-IR levels, which were significantly elevated in phenotypes A and C compared to D ($p < 0.001$ and $p = 0.003$, respectively). Triglyceride (TG) levels were also higher in phenotype A, with statistically significant differences across groups ($p = 0.014$). As for LDL and HDL levels, there was a trend toward a more atherogenic profile in phenotypes A and C, although these differences did not reach statistical significance.

For each group of patients with different PCOS phenotypes, an analysis of hormonal and metabolic correlations was conducted. In phenotype A (HA + A + PCO), the most pronounced imbalances were observed: body mass index (BMI) positively correlated with triglycerides (TG) ($r = 0.63$; $p = 0.006$) and total cholesterol (TC) ($r = 0.55$; $p = 0.02$), and negatively with sex hormone-binding globulin (SHBG) ($r = –0.50$; $p = 0.03$). Insulin and HOMA-IR were positively associated with TG ($r = 0.52$ and $r = 0.59$, respectively; $p < 0.05$), and negatively associated with SHBG ($r = –0.72$ and $–0.65$; $p < 0.01$). SHBG showed the greatest number of inverse correlations—with BMI, insulin, HOMA-IR, and TG—which confirms the presence of a distinct insulin–SHBG–TG axis and points to the high metabolic vulnerability of this phenotype. In phenotype B (HA + A), the correlations were less pronounced, but certain patterns were retained. BMI negatively correlated with SHBG ($r = –0.83$; $p = 0.0053$) and positively with FSH ($r = 0.83$; $p = 0.0053$). Total cholesterol (TC) positively correlated with LDL ($r = 0.79$; $p = 0.01$), which may indicate the development of dyslipidemia. Thus, this phenotype demonstrates moderate metabolic involvement with an emphasis on BMI and lipid markers. In phenotype C (HA + PCO), distinct correlation clusters were identified: BMI, insulin, and HOMA-IR showed strong positive associations with LDL ($r \approx 0.9$; $p < 0.05$). Testosterone positively correlated with LDL ($r = 0.9$; $p = 0.0374$), while SHBG negatively correlated with LH ($r = –0.9$; $p = 0.0374$). These findings suggest a significant contribution of hyperinsulinemia and lipid metabolism disorders to the pathogenesis of this phenotype, even in the absence of ovulatory dysfunction. Despite the absence of hyperandrogenism, phenotype D (A + PCO) demonstrated a pronounced picture of insulin resistance: BMI, insulin, and HOMA-IR were significantly correlated with TG ($r = 0.89$; 0.84; and 0.79, respectively; $p < 0.01$). A surprising direct correlation was found between testosterone and SHBG ($r = 0.73$; $p = 0.0158$), and between testosterone and LH ($r = 0.95$; $p < 0.001$), suggesting compensatory activity of the hypothalamic-pituitary axis in the setting of latent insulin

resistance. Thus, phenotype-specific correlation analysis revealed unique metabolic profiles and possible pathogenic mechanisms in each group. To evaluate the factors associated with severe insulin resistance (HOMA-IR > 3.5), a logistic regression model was built, incorporating both hormonal and metabolic predictors. According to the results, triglyceride level (TG) was the only statistically significant predictor, being reliably associated with a high risk of marked insulin resistance (OR = 2.76; p = 0.0024). Other variables, including BMI, testosterone, SHBG, LH, FSH, and other lipid fractions, did not demonstrate statistically significant contributions to the model. This underscores the diagnostic value of triglycerides as a marker of metabolic risk in PCOS.

Table 2. Logistic Regression Coefficients for Predicting HOMA-IR > 3.5

Parameter	Coefficient	p-value
BMI	-0.0310	0.6848
Testosterone	-0.0049	0.9936
SHBG	-0.0057	0.7851
LH	-0.0558	0.4287
FSH	0.3681	0.1266
Total Cholesterol	-0.1314	0.8651
HDL	0.7288	0.4815
LDL	0.5749	0.5698
Triglycerides	2.7620	0.0024*

*BMI – body mass index; SHBG – sex hormone-binding globulin; LH – luteinizing hormone; FSH – follicle-stimulating hormone; HDL – high-density lipoprotein; LDL – low-density lipoprotein;*Statistically significant predictors (p < 0.05) are marked with an asterisk.*

4. Discussion

The results of this study highlight the clinical and metabolic heterogeneity of polycystic ovary syndrome (PCOS). Phenotypic stratification allows for the consideration of not only reproductive features but also the degree of metabolic vulnerability, which is important for prognosis, clinical management, and individualized therapy.

Women with the classic full phenotype (A) demonstrated the most pronounced insulin resistance, hyperinsulinemia, and dyslipidemia. HOMA-IR, insulin levels, and triglycerides were significantly elevated, while sex hormone-binding globulin (SHBG) was significantly reduced. The observed positive correlations between BMI, HOMA-IR, and TG, along with inverse correlations with SHBG, confirm the existence of an insulin–SHBG–triglyceride axis characteristic of the high-risk PCOS phenotype [2,4,5].

Despite the presence of both hyperandrogenism and anovulation, phenotype B (HA + OA) showed only moderate metabolic disturbances. The inverse correlation between SHBG and BMI, as well as the positive correlation between total cholesterol and LDL, indicate the presence of early signs of dyslipidemia even against a relatively favorable metabolic background. These data support the necessity of metabolic monitoring in all PCOS phenotypes, regardless of clinical severity [6].

In patients with phenotype C (HA + PCO), positive associations were found between testosterone, BMI, HOMA-IR, and lipid markers (including LDL and triglycerides), emphasizing the role of hyperandrogenism in shaping an atherogenic profile. An inverse correlation between LH and SHBG was also identified, which may reflect gonadotropin dysregulation. This hormonal–metabolic profile deserves attention not only in the reproductive but also in the cardiometabolic context [8,9].

Phenotype D (OA + PCO), which lacks hyperandrogenism, is traditionally considered metabolically favorable. However, in our study, it also showed strong positive correlations between BMI, insulin, HOMA-IR, and triglyceride levels. These results emphasize that the absence of hyperandrogenism does not preclude the presence of insulin resistance, reinforcing the relevance of metabolic screening across all PCOS phenotypes [9,11].

In the logistic regression model aimed at identifying predictors of severe insulin resistance (HOMA-IR > 3.5), the only statistically significant predictor was triglyceride level (p = 0.0024). Neither BMI, nor testosterone, SHBG, nor other lipid parameters reached statistical significance. This confirms that triglycerides and derived indices such as the TyG index are more sensitive markers of metabolic disturbances in PCOS than traditional anthropometric measures [12].

5. Conclusions

The results obtained emphasize the need for metabolic monitoring in all PCOS phenotypes, including those not accompanied by hyperandrogenism. The level of sex hormone-binding globulin (SHBG) may serve as a routine and sensitive marker of insulin resistance. In addition, triglycerides represent a simple and clinically significant indicator of metabolic risk in women with PCOS. These findings support the use of phenotypic classification not only for reproductive assessment, but also for understanding metabolic risks and guiding individualized treatment strategies.

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