

The novel predictor of metabolic risk in patients with polycystic ovary syndrome: could it be the visceral adiposity index?

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Abstract. – OBJECTIVE: Polycystic ovary syndrome (PCOS) is the most common endocrinological disorder in women of reproductive age, often accompanied by high androgen levels, irregular menstrual cycles and polycystic ovaries. In addition, patients with PCOS also present with an increase in abdominal adipose tissue and insulin resistance. Recently, the gender-specific mathematical formulation called visceral adiposity index (VAI) has been widely used in assessing cardiometabolic risk. This study aimed at comparing the VAI values of patients with PCOS, patients with idiopathic hirsutism (IH) and a control group.

PATIENTS AND METHODS: We obtained demographic data, laboratory results and anthropometric measurements of patients from the hospital database. We retrospectively grouped all cases included in the study as PCOS (n = 52), IH (n = 57) and control (n = 58) according to the diagnoses. We also took venous samples for hormone and biochemical tests in the early follicular phase of the menstrual cycle, at least 8-10 hours after fasting in the early morning hours. Finally, we evaluated the variables using SPSS 22.0 software (IBM Corp., Armonk, NY, USA).

RESULTS: We included 167 female individuals in the study. Of these, 57 (34.1%) were diagnosed with IH, while 52 (31.1%) were diagnosed with PCOS. The control group comprised 58 (34.8%) healthy female individuals. The median age of the study group was 25 years [interquartile range (IQR) = 8 years]. The age, height, weight, body mass index (BMI) and waist circumference values of the groups were similar. We found that the VAI values among the groups were significantly different ($p = 0.028$). Post-hoc analysis determined that this was due to the difference between the group with PCOS and the control group. In addition, we found significantly high HOMA-IR, fasting insulin and androgen levels in the group with PCOS ($p < 0.001$).

CONCLUSIONS: After comparing data in groups with similar BMI levels, we found significantly high VAI values in patients with PCOS. The results reinforce the idea that VAI is a useful marker easily obtained in daily practice for assessing the cardiometabolic risk of patients with PCOS.

Key Words:

Cardiometabolic risk, Insulin resistance, Polycystic ovary syndrome, VAI.

Introduction

Approximately 7% of women in their reproductive years have hyperandrogenemia¹. This is commonly caused by polycystic ovary syndrome (PCOS), followed by idiopathic hirsutism (IH), congenital adrenal hyperplasia and androgen-secreting tumors. Despite different diagnostic criteria defining this condition, namely clinical or laboratory hyperandrogenism, the presence of polycystic appearance of the ovaries on pelvic ultrasonography and irregular menses are often accompanied by PCOS². PCOS is associated with an increased risk of metabolic syndrome, cardiovascular disease, type 2 diabetes, endometrial cancer, infertility and hypertensive disorders in pregnancy³⁻⁶. IH is a disorder demonstrated by an increase in male-like terminal hair in androgen-sensitive body areas, as well as the normal ovarian function and serum androgen levels⁷.

Visceral adipose tissue secretes proinflammatory cytokines such as leptin, adiponectin, TNF-alpha and resistin. The increase in these cytokines and insulin resistance constitute the basic pathophysiology of PCOS^{8,9}. Obesity is a

common comorbidity, but PCOS can also be observed in patients with different phenotypic characteristics, such as those with normal body mass index (BMI).

The visceral adiposity index (VAI), a gender-specific mathematical formulation, helps detecting the presence of metabolic syndrome, insulin resistance, cardiometabolic complications and visceral adipose tissue dysfunction. Previous clinical studies^{10,11}, which evaluated visceral adipose tissue using computed tomography (CT) in patients with PCOS, found that VAI values correlated with adipose tissue mass. As shown later in an equation, VAI comprises anthropometric measurements (BMI and waist circumference) and functional parameters [Triglyceride (Tg) and high-density lipoprotein (HDL)]¹². Analyzing visceral adipose tissue and body composition requires various methods, such as CT, magnetic resonance imaging and bioelectric impedance analysis. However, their high cost, technical difficulties and inaccessibility limit their routine use. Alternatively, VAI can be easily obtained through a polyclinic physical examination and laboratory test. Previous studies¹³⁻¹⁶ have demonstrated the relationship between VAI and increased cardiometabolic risks.

This study aimed at comparing levels of VAI, which is a cardiometabolic risk indicator, in patients' groups with IH and PCOS, as well as in the control group.

Patients and Methods

We conducted the study based on the principles of the Declaration of Helsinki and obtained the Ethics Committee Approval (Decision No. 2021-145) from the Afyonkarahisar Health Sciences University. We obtained informed consent from all individual participants included in the study.

We grouped all cases included in the study into the group with PCOS (n = 52), group with IH (n = 57) and the control group (n = 58). We used the Endocrine Society Clinical Practice Guideline as a guide for diagnosing PCOS¹⁷. For diagnosing IH, we considered the absence of PCOS characteristics on pelvic ultrasound (≥ 10 small follicles that are 2-8 mm in size in both ovaries), presence of normal serum androgen levels and ovarian function.

We used transabdominal ultrasonography to evaluate ovarian pathologies and performed the

examination with the help of a single radiology operator. We evaluated the degree of hirsutism and menstrual pattern for the clinical diagnosis. We also defined oligomenorrhea as having a menstrual interval of > 35 days, whereas amenorrhea as the absence of menstruation for > 3 months in women who have a regular cycle and > 6 months in women who have irregular menses. We determined hirsutism according to the Modified Ferriman Gallwey Scoring System: a total of ≥ 8 points taken from nine different body surfaces were defined as hirsutism.

We took fasting blood samples at the early follicular phase of the menstrual cycle. In addition, we excluded Cushing's syndrome by administering 1 mg of dexamethasone suppression test in patients with PCOS and IH.

We measured the waist circumference (WC) on the basis of the midpoint between the lower margin of the last palpable rib and the top of the iliac crest. Finally, we excluded patients with thyroid dysfunction, prolactinoma, chronic diseases and history of using hormone replacement therapy for any reason from the study.

Since VAI is a gender-specific mathematical formulation, we calculated the VAI level for women using the formula given below.

$$VAI = \left[\frac{WC}{(39.68 + (1.88) \times BMI)} \right] \times \left[\frac{TG}{1.03} \right] \times \left[\frac{1.31}{HDL} \right]$$

WC: cm, BMI: kg/m², Tg and HDL: mmol/l.

Statistical Analysis

We presented categorical variables as percentages and frequencies, used χ^2 test to compare categorical variables between groups and checked the compliance of continuous variables to normal distribution using visual histograms and the Shapiro-Wilk's test. We then compared normally distributed continuous variables through the analysis of variance (ANOVA) test and continuous variables not normally distributed through the Kruskal-Wallis' test. We conducted post-hoc analysis for VAI using pairwise comparisons and Bonferroni correction. We used the receiver operating characteristic (ROC) curve to find the predictive power of VAI for the group with PCOS and the control group. We selected the best cut-off value using the Youden index. All *p*-values are two-sided, and *p* < 0.05 was considered significant. We used SPSS 22.0 software (IBM Corp., Armonk, NY, USA) for analyses.

Table I. Group comparison of general characteristics.

	IH (IQR)	PCOS (IQR)	Control (IQR)	<i>p</i>
Age (years)	25 (5)	24.5 (6)	26 (7)	0.267
Height (mt)	1.62 (0.07)	1.61 (0.05)	1.62 (0.09)	0.078
Weight (kg)	63 (10)	67 (13)	63.5 (13)	0.148
BMI (kg/m ²)	24.7 (3.75)	25.9 (4.92)	24.41 (3.94)	0.315
WC (cm)	86 (22)	89 (14)	84.5 (8)	0.078
IP (n-%)	6-10.5	41-78.8	0	< 0.001

E2, estradiol; FSH, follicle stimulating hormone; HDL-C, high density lipoprotein cholesterol; HOMA-IR, homeostatic model assessment insulin resistant; IH, idiopathic hirsutism; IQR, interquartile range; e, low density lipoprotein cholesterol; LH, luteinising hormone; PCOS, polycystic ovary syndrome; TSH, thyroid stimulating hormone.

Results

We conducted the study with 167 women. Of these, 57 (34.1%) had IH, whereas 52 (31.1%) had PCOS. In addition, 58 (34.8%) women were in the control group. The median age of the study group was 25 years [interquartile range (IQR) = 8 years].

The participants were matched in age, height, weight, BMI and WC. We found that irregular period was significantly high in patients with PCOS. Table I shows the group comparison of general characteristics.

Table II shows the group comparison of the laboratory results. We found that the VAI values were significantly different between the groups ($p = 0.028$). Figure 1 demonstrates the VAI value comparison between groups. Post-hoc analysis (pairwise comparison and Bonferroni correction) showed that VAI levels of the group with PCOS were higher than those of the control group (Table III).

In addition, ROC analysis showed that a VAI value of 4.55 predicted PCOS with 86.5% sensitivity and 48.3% specificity [$p = 0.022$, AUC (95% CI): 0.627 (0.520-0.734)] (Figure 2).

Discussion

To evaluate the cardiometabolic risk in patients with PCOS at an early stage, we found that the VAI level was significantly higher in patients with PCOS than in the healthy control group. Similarly, Amato et al¹¹ and Agrawal et al¹⁸ found that VAI levels of patients with PCOS were significantly high, whereas Androulakis et al¹⁹ showed a significant relationship between PCOS disease severity and high VAI levels. In addition, Durmus et al²⁰ found that VAI values were similar between the groups they studied.

In this study, we found that BMI and WC values were similar between the groups. On the contrary, LDL-C, which was not included in the for-

Table II. Group comparison of laboratory results.

	IH (IQR)	PCOS (IQR)	Control (IQR)	<i>p</i>
Glucose (mg/dl)	91 (9)	80.5 (13)	78 (9)	< 0.001
LDL-C (mg/dl)	100 (28)	96 (29.3)	90 (23.5)	0.026
HDL-C (mg/dl)	50 (9)	48 (5)	50 (8)	0.054
Triglyceride (mg/dl)	125 (25)	127 (20)	120 (18)	0.053
Insulin	8.72 (IQR = 3.7)	15.1 (IQR = 8.7)	6.65 (IQR = 4.1)	< 0.001
LH	4.89 ± 2.9	7.97 ± 5.5	6.82 ± 6.2	0.485
FSH	5.42 (2.5)	5.5 (2.2)	5 (2.5)	0.655
E2	35 (16.5)	48.5 (31.5)	91.5 (69.5)	< 0.001
Total Testosterone	42.9 (15)	45 (46.2)	30.9 (13)	< 0.001
HOMA-IR	1.93 (0.9)	3.03 (1.9)	1.6 (0.75)	< 0.001

Abbreviations: E2, estradiol; FSH, follicle stimulating hormone; HDL-C, high density lipoprotein cholesterol; HOMA-IR, homeostatic model assessment insulin resistant; IH, idiopathic hirsutism; IQR, interquartile range; e, low density lipoprotein cholesterol; LH, luteinising hormone; PCOS, polycystic ovary syndrome; TSH, thyroid stimulating hormone.

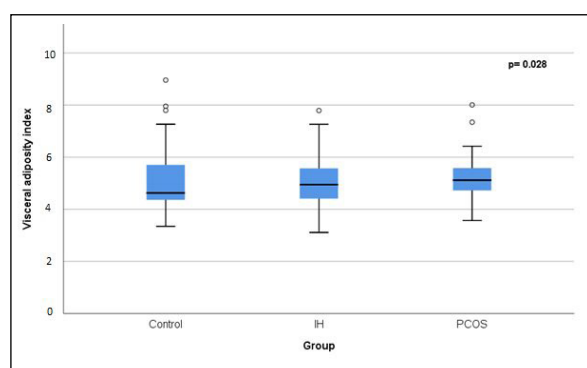


Figure 1. Group comparison of VAI.

mulation, was significantly high in the group with PCOS. A previous study²¹ showed that LDL-C, especially in small dense LDL-C (sdLDL-c), is considered to be a potent atherogenic lipid that can induce the development of cardiovascular diseases. In our study, we think that the high values of VAI and LDL-C in patients with PCOS support the accuracy of the study results.

Zheng and Li²² found that the VAI is an indicator of the presence of insulin resistance in patients with PCOS. Similarly, we found that both HOMA-IR and VAI values were significantly higher in patients with PCOS than in other groups. Although WC and BMI values were similar between the groups, the significant difference in insulin resistance suggested that PCOS develops as a result of a number of genetic and/or molecular mechanisms involved in etiopathogenesis^{23,24}. In addition, previous studies²⁵⁻²⁷ have shown that insulin resistance is an obesity-independent risk factor for developing cardiovascular diseases in PCOS. Despite the similarity in BMI values between the groups, we think that the significant increase in insulin resistance may have been caused by the significant difference in the VAI levels in patients with PCOS.

Moreover, HOMA-IR and VAI values of the IH group were similar to those of the control group. Previous studies^{28,29} have demonstrated the positive relationship between insulin resistance and the presence of hyperandrogenemia and irregular

Table III. Visceral adiposity index post-hoc.

Pairwise comparisons	Adjusted <i>p</i>
Control-PCOS	0.023
Control-IH	0.916
PCOS-IH	0.985

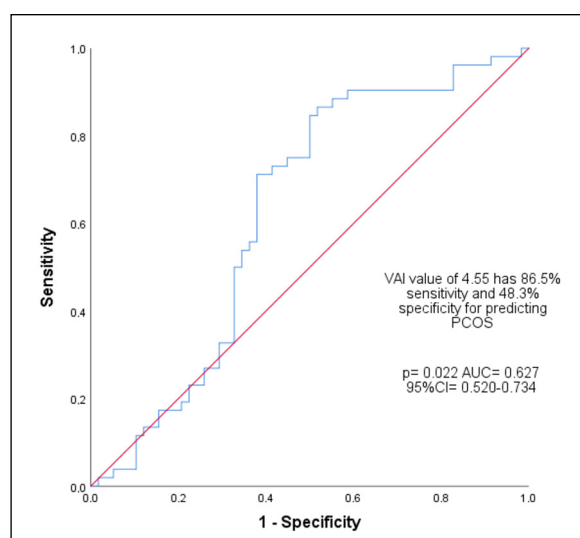


Figure 2. VAI predictivity evaluation in the group with PCOS and the control group using ROC curve analysis [*p* = 0.022, AUC (95% CI): 0.627 (0.520-0.734)].

menstrual cycle in patients with PCOS. In addition, high androgen levels have been demonstrated to induce insulin resistance. For example, after administering anti-androgen therapy, the androgen effect in patients decreased, while insulin sensitivity increased³⁰. Our study results support the results of literature in showing the possible metabolic adverse effects of hyperandrogenemia.

Other studies^{10,13} revealed the optimal level of VAI in patients with PCOS. In this study, VAI value of 4.55 was shown to predict PCOS with 86.5% sensitivity and 48.3% specificity.

The limitations of our study include not being able to study androstenedione, 17-OH progesterone and DHEA-S tests used in evaluating extraovarian androgen production. In addition, we did not use biochemical markers for cardiac risk assessment in the retrospective study design. In recent years, some studies^{31,32} have demonstrated the role of vitamin D and alpha lipoic acid replacement to reduce the cardiometabolic disturbances in PCOS patients. However, the treatment section was not involved in our study design. On the contrary, to the best of our knowledge, this study is the first comparing VAI values of patients with IH and PCOS, as well as healthy controls.

Conclusions

Comparing the VAI values of groups with similar BMI, we found that patients with PCOS

showed significantly high VAI values. Our study supports VAI as a useful risk marker that is easily obtained in daily practice for assessing cardiometabolic risk in patients with PCOS.

Conflict of Interest

The Authors declare that they have no conflict of interests.

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Ethics Approval

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Informed Consent

Informed consent was obtained from all individual participants included in the study.

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