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Article

Visceral Adiposity Index (VAI) Levels in Patients with Different Phenotypes of Polycystic Ovary Syndrome (PCOS)

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Abstract

Background and Objectives: We aimed to compare visceral adiposity index (VAI) levels among polycystic ovary syndrome (PCOS) subtypes in this study. **Materials and Methods:** A total of 180 PCOS patients and 51 controls were included. Patients were divided into the following subtypes: Phenotype A (n=96); clinical and/or biochemical hyperandrogenism (HA)+oligo-anovulation (OA)+polycystic ovarian morphology (PCOM); Phenotype B (n=19); HA+OA; Phenotype C (n=35); HA+PCOM; and; Phenotype D (n=30); OA+PCOM. VAI was calculated for women by the following formula:
$$\text{VAI} = \frac{\text{Waist circumference (cm)}}{36.58 + (1.89 \times \text{Body mass index (kg/m}^2))} \times \left[\frac{\text{triglyceride (mmol/L)}}{0.81} \times \left(1.52 \times \frac{\text{High density lipoprotein-cholesterol (mmol/L)}}{\text{HDL}} \right) \right]$$
 Results: In the total PCOS patients; VAI levels were higher than controls [1.21 (0.39-10.89) and 0.85 (0.32-1.87); respectively] (p<0.001). VAI levels were higher in Phenotype A [1.46 (0.39-10.89)] and Phenotype B [1.31 (0.43-4.39)] than in controls [0.85 (0.32-1.87)], and also higher in Phenotype A than in Phenotype C [1.00 (0.41-4.79)] and Phenotype D [1.01 (0.4-3.21)] (p=0.003 and p=0.001; respectively). While present in 38 patients (21.1%) in the PCOS group; there was no metabolic syndrome (MetS) in controls (p<0.001). In Phenotypes A; B; and D; while more patients had MetS than controls (p<0.001; 0.004; and 0.021; respectively); more patients had MetS in Phenotype A; compared to Phenotypes C and D (p=0.003 and p=0.021; respectively). Given ROC analysis; the VAI cut-off value in predicting MetS in the PCOS group was 1.66 (sensitivity: 94.74% and specificity: 83.1%). **Conclusions:** PCOS phenotypes characterized by HA and OA; particularly Phenotypes A and B; are associated with higher VAI values and an increased frequency of MetS; underscoring the importance of early metabolic assessment in these patient groups

Keywords: phenotype; polycystic ovary syndrome; subtype; visceral adiposity index

1. Introduction

Polycystic ovary syndrome (PCOS) is one of the most common metabolic disorders and affects 5-20% of women of childbearing age [1,2]. The general characteristics of the condition are oligo-anovulation (OA), clinical or biochemical hyperandrogenemia (HA), and the appearance of polycystic ovaries (PCO) on ultrasonography (USG), and the diagnosis is performed under the Rotterdam criteria [1,2]. Such components of metabolic syndrome (MetS) as obesity, especially abdominal obesity, dyslipidemia, high blood sugar, and hypertension (HT) are frequently witnessed in patients with PCOS [3–7].

Until recent years, only the presence or absence of PCOS was considered significant. However, due to the heterogeneity in clinical features and metabolic disturbances, patients are now classified

into four phenotypic groups based on specific criteria: Phenotype A in which HA, OA, and the appearance of PCO in the ovaries exist on USG (PCOM); Phenotype B with HA and OA; Phenotype C characterized by HA and PCOM; and, Phenotype D characterized by OA and PCOM [8]. In PCOS, as the letters of phenotypes progress from A to D, the severity and frequency of accompanying metabolic disorders and inflammation decrease.

Based on the literature, it would be more appropriate to evaluate visceral obesity instead of generalized obesity in predicting cardiovascular morbidity and mortality [9]. Even if PCOS patients are of normal weight, the frequency of central obesity has been reported to be higher in these patients [10]. Compared with generalized obesity, central obesity is more associated with MetS components leading to cardiovascular morbidity and mortality, such as insulin resistance (IR), Type 2 diabetes mellitus (DM), HT, and dyslipidemia [11–13]. Although waist circumference (WC) provides a simple measure of central obesity, it may be confounded by increases in subcutaneous fat, which has fewer adverse metabolic effects, as well as by variations in ethnicity and gender. Although such methods as computerized tomography (CT) and dual-energy X-ray absorptiometry (DXA) have been recommended to assess the actual amount of visceral fat tissue, the radiation risk and cost of such methods restrict the use of CT and DXA [14,15]. Instead, the visceral adiposity index (VAI), an indicator of visceral fat function calculated from anthropometric [body mass index (BMI) and waist circumference (WC)] and biochemical [high-density lipoprotein (HDL) cholesterol and triglyceride (TG)] parameters, has been recommended for early detection and assessment of cardiovascular risk in various populations [16–20]. In one of our previous studies, while finding VAI levels to be similar between non-obese PCOS patients and the controls, we also detected higher VAI values in obese PCOS patients than in obese controls [21].

In the presented study, however, we aimed to compare VAI levels, an indicator of visceral adiposity, in PCOS patients having different phenotypes.

2. Materials and Methods

The presented study with a prospective and case-controlled design was conducted in the Departments of Internal Medicine, Endocrinology and Metabolism Diseases, and Gynecology and Obstetrics of the Training and Research Hospital at Usak University between April 1st, 2022, and July 20th, 2023. *The study was performed in line with the principles of the 1961 Declaration of Helsinki and its later amendments. Approval was granted by the Ethics Committee of the Medical School of Usak University (Date: 25/05/2022 and no: 90-90-13). Informed consent was obtained from all individual participants included in the study.* Those admitted to the hospital due to such complaints as pubescence, acne, menstrual irregularity, or infertility and diagnosed with PCOS under the 2003 Rotterdam criteria [1,2] were included in the study, based on the biochemical, hormonal, and USG examinations.

PCOS was diagnosed in the presence of two of these three criteria: 1) OA, 2) Clinical (hirsutism and/or acne) and/or biochemical signs of HA, and 3) Appearance of PCO on USG, and in the absence of other clinical conditions, such as Cushing's syndrome, congenital adrenal hyperplasia or androgen-secreting tumor [2]. The patients were divided into four phenotypes [8]: Phenotypes A, B, C, and D included 96, 19, 35, and 30 PCOS patients, respectively (Figure 1). Even so, the control group was composed of 51 age-matched women between 18-35 years (Figure 1), without diagnoses of PCOS and any known cancers, liver and kidney failures, taking no medication to affect IR, with no active infection, hirsutism and acne, PCO on USG, and having normal menstrual cycle. Height, weight, and WC were measured in all participants, with height and weight recorded in underwear. Hair assessment was repeated by the same researcher (CD). WC was measured as the minimum size between the iliac crest and lateral costal margin. BMI was calculated as weight (kg) divided by height square (m²). To measure the levels of androgen, all blood samples were drawn in the morning after overnight fasting between the 3rd and 5th days of the menstruation, separated by centrifugation, and stored in deep freeze at -70°C until being analyzed. The levels of androgen were measured in none of the controls.

All cases were re-evaluated in terms of PCOM by the same researcher (OO) using a transabdominal USG with a transducer frequency of 3-6.6 mHz and/or a transvaginal USG with a transducer frequency of 3-5 mHz probe using the Mindray DC-7 device (Shenzhen Mindray Bio-Medical Electronics Co., Ltd. Shenzhen, PRC), and the presence of 12 or more follicles in each ovary measuring 2-9 mm in diameter, and/or increased ovarian volume >10 mL was accepted to be compatible with PCOM.

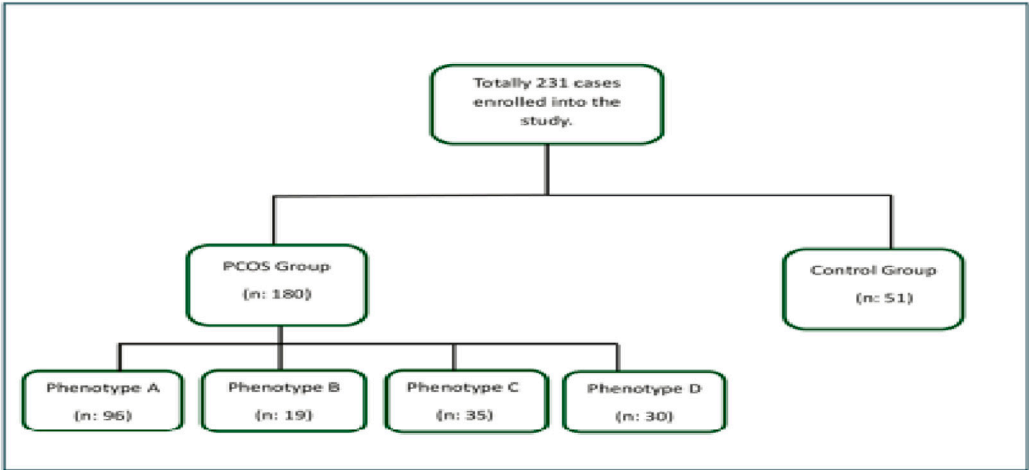


Figure 1. Flowchart of the study population.

Glucose levels [normal range (NR), 70-105 mg/dL] were measured by Olympus AU 5800 (Beckman Coulter Inc. USA) through the hexokinase method. Insulin levels were measured by Immulite 2000 (Siemens Healthcare Diagnostics, Siemens AG, Germany) with the chemiluminescence method, and the intra- and inter-assay coefficients of the variations for insulin were found as 4.6 and 5.9, respectively. While HDL-cholesterol levels were measured by Olympus AU 5800 (Beckman Coulter Inc. USA) with the immune reaction (antigen-anticore complex), the levels of TG were assessed with a routine enzymatic method using an auto-analyzer by Olympus AU 5800 (Beckman Coulter Inc. USA). Even so, the luteinizing hormone (NR: 1.9-12.5 IU/L), follicle-stimulating hormone (NR: 2.59-10.2 IU/L), estradiol (NR: 19.5-144.2 pg/mL) and total testosterone (NR: 12-60 ng/dL) were evaluated through the chemiluminescent immunoassay method on the Abbot Advia Centaur (Tarrytown, NY, USA) device. Also, dehydroepiandrosterone-sulfate levels (NR: 1.9-12.5 IU/L) were measured using the Chemiluminescent immunoassay method with the Siemens Immulate 2000 device (Cary, NC, USA), and 17 OH-progesterone (NR: <2.6 ng/mL) and free testosterone (NR: <4.2 pg/mL) were evaluated using the Chemiluminescent immunoassay method with the Snibe Maglumi 4000 plus (Shenzhen, China) device. However, MetS was diagnosed under the criteria by the National Cholesterol Education Program Adult Treatment Panel (NCEP-ATP) III [22].

While IR was calculated by homeostasis model assessment-insulin resistance (HOMA-IR) [fasting plasma glucose (mmol/l) x fasting serum insulin (μIU/mL)/22.5], VAI was calculated for women by the formula of $(WC/[36.58+(1.89 \times BMI)]) \times [(TG \text{ (mmol/l)}/0.81) \times (1.52 \times HDL\text{-cholesterol (mmol/l)})]$ [17].

Statistical Analysis

The statistical analyses of the data were carried out with the Statistical Package for Social Sciences for Windows, version 22.0 (SPSS, IBM Corp. Armonk, NY, USA). The analyses of data normality were conducted using *Shapiro-Wilk tests*. In group comparisons, the *student t-test* was used for continuous variables with normal distribution, and the *Mann-Whitney-U test* was used for the

variables without normal distribution. While *Fisher’s exact test* was used for the comparisons of binary groups for categorical variables, *Pearson’s chi-square test* was used for the comparisons of more than two groups. Additionally, normally distributed continuous variables were given as *mean±standard deviation (SD)*, and non-normally distributed continuous variables were presented as *median (min: max)*. However, the *receiver operating characteristic (ROC) analysis* was carried out to calculate the values of sensitivity, specificity, and *area under curve (AUC)*. Upon finding the *AUC* value to be significant, the *Youden J index* and cut-off *VAI* values were calculated to find the cut-off *VAI* value predicting the presence of *MetS*. The statistical significance of the findings was evaluated at a 95% *confidence interval (CI)*, and a *p*-value of ≤ 0.05 was accepted to be significant.

3. Results

A total of 231 participants, 180 patients with *PCOS*, and 51 healthy controls were included in the study. Compared the total *PCOS* group, including all *PCOS* patients, with the controls; *BMI* levels, weight, *WC*, insulin, *TG*, and *HOMA-IR* levels were found to be higher, and *HDL* cholesterol levels were detected to be lower (all $p<0.001$) (Table 1). Additionally, the levels of *VAI* levels were also higher in the total *PCOS* group than in the controls [1.21 (0.39-10.89) and 0.85 (0.32-1.87), respectively] ($p<0.001$) (Table 1, Figure 2).

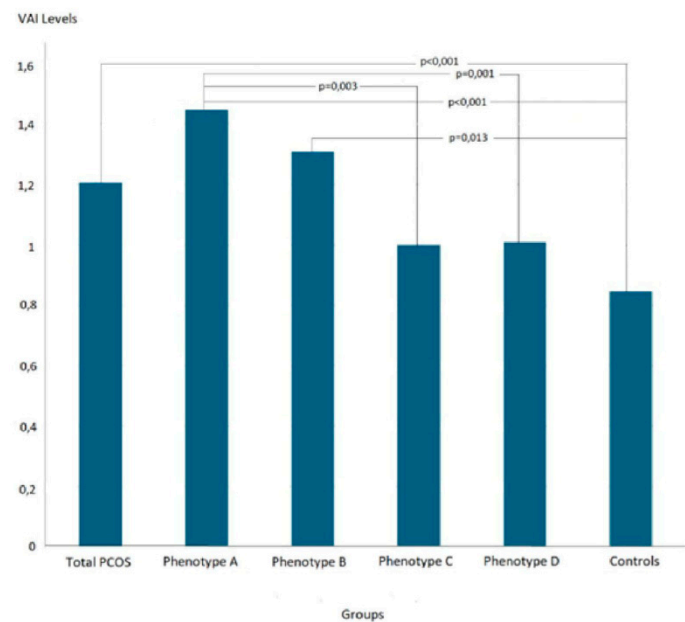


Figure 2. Visceral adiposity index (VAI) levels in total polycystic ovary syndrome (PCOS) patients and PCOS subtypes;.

Table 1. Some demographic and laboratory data of the cases.

	Tot al PC OS n=1 80	Pheno type A n=96	Pheno type B n=19	Pheno type C n=35	Pheno type D n=30	Con trol Gro up n=5 1	p1	p2	p3	p 4	p 5	p 6	p7	p 8	p 9	p 10	p 11
Age (year)	24 (18- 35)	25 (18- 35)	22 (18- 34)	25 (18- 35)	24 (20- 35)	23 (22- 33)	.45 7	.19 1	.19 1	.9 50	.4 08	.1 03	.35 3	.9 54	.3 22	.0 99	.5 00

Weigh t (kg)		70.5 (45- 129)	65 (44- 103)	60 (44- 98)	63.5 (44- 116)	58 (47- 79)	<.0 01	<.0 01	.06 5	.3 51	.0 25	.0 82	<.0 01	.0 22	.2 73	.8 05	.3 04
BMI (kg/m ²)	25. 49 (15. 59- 50. 22)	27.19 (17.15 - 49.77)	24.83 (15.78 - 39.84)	22.14 (15.59 - 34.08)	24.88 (17.19 - 50.22)	21.4 8 (17. 78- 27.3 4)	<.0 01	<.0 01	.02 8	.1 46	.0 06	.1 11	<.0 01	.0 31	.1 74	.7 66	.1 84
WC (cm)	83. 5 (58- 129)	89 (61- 129)	82 (60- 120)	77 (58- 105)	78 (60- 116)	75 (59- 100)	<.0 01	<.0 01	.04 1	.2 37	.1 60	.0 65	<.0 01	.0 05	.2 69	.6 89	.5 62
Glucos e (mg/d L)	89 (56- 142)	90 (56- 142)	88 (75- 109)	88 (66- 103)	88 (78- 103)	87 (73- 98)	.08 2	.05 4	.20 4	.5 88	.3 27	.9 76	.28 0	.5 21	.4 62	.6 22	.7 32
Insulin (μU/m L)	12. 3 (2- 100 .5)	13.6 (3.6- 100.5)	13.5 (4.4- 35.7)	10.1 (2.5- 37.8)	9.6 (2- 30.5)	7.3 (2.8- 22)	<.0 01	<.0 01	<.0 01	.0 10	.0 24	.8 10	.00 9	.0 06	.0 94	.0 71	.7 97
HOM A-IR	2.7 5 (0.3 8- 25. 57)	2.96 (0.77- 25.57)	3.06 (0.92- 7.31)	2.30 (0.55- 7.54)	2.13 (0.38- 6.55)	1.63 (0.5 8- 4.35)	<.0 01	<.0 01	<.0 01	.0 12	.0 24	.7 75	.00 8	.0 08	.0 94	.0 71	.8 13
HDL- cholest erol (mmol /L)	1.4 (0.9 - 2.4)	1.3 (0.9- 2.4)	1.4 (0.9- 1.9)	1.6 (1- 2.2)	1.5 (1- 2.4)	1.6 (1.1- 2.3)	<.0 01	<.0 01	<.0 01	.4 93	.1 24	.7 37	.00 1	.0 21	.0 22	.0 71	.6 17
Triglyc eride (mmol /L)	0.9 (0.3 - 5.6)	1.1 (0.3- 5.6)	0.8 (0.5- 2.4)	0.9 (0.4- 2.8)	0.8 (0.5- 1.8)	0.8 (0.3- 1.5)	<.0 01	<.0 01	.21 2	.1 49	.3 43	.1 23	.01 0	.0 02	.7 51	.5 72	.6 50
VAI	1.2 1 (0.3 9-	1.46 (0.39- 10.89)	1.31 (0.43- 4.39)	1.00 (0.41- 4.79)	1.01 (0.4- 3.21)	0.85 (0.3 2-	<.0 01	<.0 01	.01 3	.1 17	.2 44	.3 31	.00 3	.0 01	.2 89	.1 24	.8 03

	10.89)					1.87)										
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Results are given as median (minimum-maximum), * Mann-Whitney Test, [§]Kruskal Wallis Test. p1: Total PCOS cases vs Controls, p2: Phenotype A vs Controls, p3: Phenotype B vs Controls, p4: Phenotype C vs Controls, p5: Phenotype D vs Controls, p6: Phenotype A vs Phenotype B, p7: Phenotype A vs Phenotype C, p8: Phenotype A vs Phenotype D, p9: Phenotype B vs Phenotype C, p10: Phenotype B vs Phenotype D, p11: Phenotype C vs Phenotype D. BMI: Body Mass Index, WC: Waist Circumference, HOMA-IR: Homeostasis Model Assessment of Insulin Resistance, HDL: High-Density Lipoprotein, VAI: Visceral Adiposity Index.

Compared PCOS subtypes with controls, BMI levels were determined to be higher in Phenotype A, Phenotype B, and Phenotype D than those in the controls ($p<0.001$, $p=0.028$, and $p=0.006$, respectively), and also higher in Phenotype A compared to Phenotype C ($p<0.001$) and Phenotype D ($p=0.031$). However, the levels of WC were higher in Phenotype A ($p<0.001$) and Phenotype B ($p=0.041$), compared to the controls, and also higher in Phenotype A than those in Phenotype C ($p<0.001$) and Phenotype D ($p=0.005$). Compared PCOS patients with the controls, Phenotype A was detected to have higher levels of weight, insulin, HOMA-IR, and TG (for all; $p<0.001$); Phenotype B to have higher insulin and HOMA-IR levels ($p<0.001$ and $p<0.001$, respectively); Phenotype C to have higher insulin ($p=0.010$) and HOMA-IR ($p=0.012$); Phenotype D to have higher insulin ($p=0.024$) and HOMA-IR ($p=0.024$) levels. Even so, Phenotype A and Phenotype B were found to have lower HDL-cholesterol levels (for both, $p<0.001$) (Table 1). The levels of insulin, HOMA-IR, and TG were higher in Phenotype A than in Phenotype C ($p=0.009$, $p=0.008$, and $p=0.010$, respectively) and Phenotype D ($p=0.006$, $p=0.008$, and $p=0.002$, respectively). In contrast, HDL-cholesterol levels were lower in Phenotypes C and D ($p=0.001$ and $p=0.021$, respectively). In addition, the levels of HDL-cholesterol were lower in Phenotype B than in Phenotype C ($p=0.022$).

When PCOS subtypes were compared to the controls, VAI levels were observed to be higher in Phenotypes A [1.46 (0.39-10.89)] and B [1.31 (0.43-4.39)] than in the controls [0.85 (0.32-1.87)] (Table 1). When intergroup comparisons were performed among PCOS subtypes, VAI levels were found higher in Phenotype A than in Phenotypes C [1.00 (0.41-4.79)] and D [1.01 (0.4-3.21)] ($p=0.003$ and $p=0.001$, respectively).

In the presented study, while 38 patients (21.1%) in the PCOS group had MetS, none of those in the controls were found to have MetS ($p<0.001$) (Table 2). More patients in Phenotypes A, B, and D had MetS, compared to the controls ($p<0.001$, 0.004, and 0.021, respectively). In addition, more patients in Phenotype A had MetS, compared to Phenotypes C and D ($p=0.003$ and $p=0.021$). Given the findings of ROC analyses, the VAI cut-off value in predicting MetS in the PCOS patient group was found to be 1.66 (sensitivity: 94.74% and specificity: 83.1%, AUC: 0.952, standard error (SE): 0.0153, Youden J index=0.7784, and $p<0.001$) (Figure 3 a and b).

When the correlation analysis was performed, there was a positive correlation between VAI and age levels (Spearman's Rho 0.214, $p=0.001$) and HOMA-IR (Spearman's Rho =0.348, $p<0.001$) (Table 3).

Table 2. The relationship between visceral adiposity index levels and some parameters.

	Spearman's rho	P
Age	0.214	0.001
Glucose	0.077	0.246
HOMA-IR	0.348	<0.001

HOMA-IR: Homeostasis Model Assessment of Insulin Resistance.

Table 3. The relationship between visceral adiposity index levels and some parameters.

	Total PCOS n=180	Phenotype A, n=96	Phenotype B, n=19	Phenotype C, n=35	Phenotype D n=30	Controls n=51	p1	p2	p3	p4	p5
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Presenc e of MetS, n (%)	38 (21.1)	30 (31.3)*§	3 (15.8)	2 (5.7)*	3 (10)§	0 (0)	<0.00 1	<0.00 1	0.00 4	0.08 4	0.02 1
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p1; Total PCOS cases vs Controls, p2; Phenotype A vs Controls, p3 , Phenotype B vs Controls, p4; Phenotype C vs Controls, p5; Phenotype D vs Controls. For comparisons between other groups: Phenotype A vs B p= 0.173, *Phenotype A vs C p= 0.003, §Phenotype A vs D p= 0.021, Phenotype B vs C p= 0.222, Phenotype B vs D p= 0.547, Phenotype C vs D p= 0.517. Mets: Metabolic Syndrome.

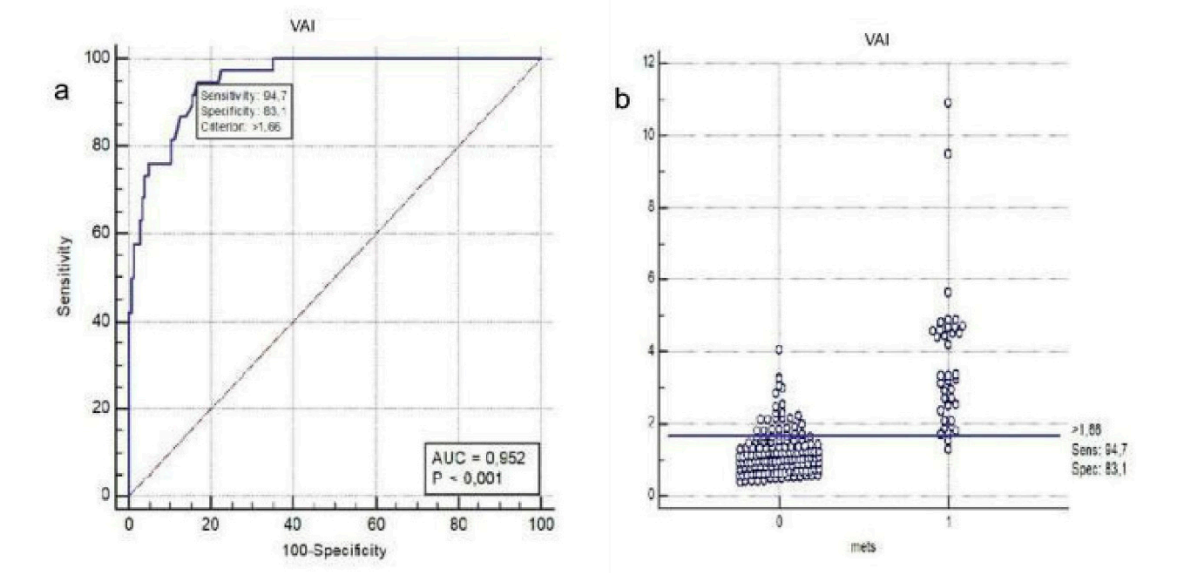


Figure 3. The receiver operating characteristic (ROC) curves of visceral adiposity indexes (VAI) in predicting metabolic syndrome (MetS) in patients with polycystic ovary syndrome (PCOS), (a) Scattering graph of VAI, (b) According to the determined VAI cut-off value.

4. Discussion

In the presented study, VAI levels were evaluated across different PCOS phenotypes. VAI was higher in the total PCOS group, as well as in Phenotypes A and B compared to controls, and higher in Phenotype A compared to Phenotypes C and D. Additionally, the prevalence of MetS was greater in the total PCOS group and in Phenotypes A, B, and C than in controls. The VAI cut-off value for predicting MetS in PCOS patients was calculated as 1.66

IR and MetS components are frequently present in patients with PCOS [3–6,23]. Also, IR is considered one of the specific features of PCOS, independent of adiposity [7]. On the other hand, hyperinsulinism existing in PCOS leads to a vicious cycle in these patients, triggering hyperandrogenism [23]. Due to the heterogeneity of clinical features and metabolic disturbances, PCOS patients are classified into distinct phenotypes. Metabolic complications are more common in Phenotype A, which represents the classic PCOS features, and in Phenotype B, characterized by HA and OA. The severity and frequency of metabolic disturbances and inflammation progressively decrease from Phenotype A to D. [8]. Patients with PCOS tend to accumulate more central and visceral fat, particularly in the trunk and upper body, compared to BMI-matched controls, which contributes to increased proinflammatory activity, insulin resistance (IR), diabetes mellitus (DM), dyslipidemia, and hypertension (HT), ultimately elevating the risk of atherosclerosis and cardiovascular mortality [17,24]. Although waist circumference (WC) provides a simple measure of central obesity, VAI has been shown to better reflect cardiometabolic risk by distinguishing between subcutaneous and visceral adiposity [17].

In the presented study, VAI levels were also found higher in all PCOS patient groups and Phenotype A and B subtypes than in the controls and also in Phenotype A, compared to Phenotype

C and D subtypes (Table 1, Figure 2). In the study performed by Amato et al. [25], on a total of 220 Sicilian PCOS patients (82 with Phenotype A, 43 with Phenotype B, 52 with Phenotype C, and 43 with Phenotype D) and 144 controls, VAI levels were found to be 2.45 ± 1.63 , 2.49 ± 1.46 , 1.68 ± 1.0 , 2.25 ± 1.40 , and 1.62 ± 0.84 in Phenotypes A, B, C, D and controls, respectively. In the same study, the researchers also reported that oligomenorrheic phenotypes had higher VAI levels. The levels of VAI determined by Amato et al. [25] are 1.5-2 times higher than those found in our patient and control groups, which may be attributed to the fact that both studies were conducted in different ethnic groups. In another study by Agrawal et al. [26], in which VAI levels were evaluated in 100 PCOS patients with different phenotypes and 50 healthy controls, it was reported that VAI levels were higher in all PCOS patients than in controls, and also higher in Phenotype A than in Phenotype D, which is consistent with our study findings (VAI levels in all PCOS cases: Phenotypes A, B, C and D, and controls: 2.07, 2.46, 2.48, 1.47, 1.7, and 1.27, respectively). When patients were classified by cardiometabolic risk, Agrawal et al. reported that 56% were in the risk group and 12% in the high-risk group overall. Among Phenotype A cases, 64% were in the risk group and 24% in the high-risk group; for Phenotype B, 17% and 50%; for Phenotype C, 67% were in the risk group; and for Phenotype D, 53% and 2%, respectively [26]. However, the small number of patients in the study by Agrawal et al., especially in Phenotype B and Phenotype C (six and three patients, respectively), makes it difficult to analyze the study accurately. In addition, the lack of comparisons of VAI levels in PCOS subtypes with the controls can be considered another limitation. In the study by Ramezani Tehrani et al. [27], although women with PCOS were older and had higher BMI and waist circumference compared to healthy controls, VAI levels were found to be similar between PCOS subgroups and the control group. Considering that the prevalence of obesity and visceral adiposity increases with age [27] and that both BMI and WC levels are the components of the VAI formula, it can be interpreted that such differences affected the study findings.

In our study, the HOMA-IR index, an indicator of IR in the total PCOS patient group and all phenotypic subtypes, was found to be higher than the control group. Upon the comparisons of subtypes, HOMA-IR levels were detected to be higher in Phenotype A than in Phenotypes C and D; even so, no difference was found in HOMA-IR levels among other subtypes. Phenotypes A and B are severe subtypes of PCOS [26,28], and as PCOS subtypes progress from A to D, the severity of metabolic disorders decreases. In their study, although not attributing to HOMA-IR levels in terms of PCOS subtypes, Agrawal et al. emphasized a strong correlation between VAI and HOMA-IR levels as a result of correlation analysis ($r=0.455$, $p<0.001$) [26]. On the other hand, Amato et al. reported that HOMA-IR levels were significantly higher only in Phenotype B compared to controls ($p=0.037$), while Phenotype C demonstrated a lower Matsuda insulin sensitivity index ($p=0.02$) [25]. As opposed to the findings by Amato et al. Ramezani Tehrani et al. reported that when HOMA-IR levels were taken as ≥ 2.3 , IR was present in more patients in all three PCOS subgroups compared to controls although HOMA-IR levels in PCOS subtypes were similar to those in the controls.

In our study, while 38 patients (21.1%) in the total PCOS group had MetS, no MetS was detected in the control group ($p<0.001$) (Table 2). When the subtypes were examined, the frequency of MetS was 31.3% in Phenotype A including the component of OA, 15.8% in Phenotype B, and 10% in Phenotype C, and this rate was higher than that in the controls ($p<0.001$, $p=0.004$ and $p=0.021$, respectively). In addition, given the intergroup comparisons of PCOS subtypes, more patients in Phenotype A had MetS than in Phenotypes C and D ($p=0.003$ and $p=0.021$). When the findings of ROC analysis were investigated, we found the VAI cut-off value as 1.66 (sensitivity: 94.74% and specificity: 83.1%) in predicting MetS in the PCOS patient group (Figure 3 a and b). Amato et al. [25] reported that the frequency of MetS was significantly higher only in Phenotypes A ($p=0.005$) and B ($p=0.024$) compared to controls. They also observed that MetS prevalence was higher in OA-containing phenotypes, consistent with our study findings. Although MetS prevalence was elevated in Phenotype D as well, this difference did not reach statistical significance. Furthermore, a limitation of their study was the absence of direct comparison of MetS prevalence among PCOS subtypes. In our study, the small number of patients in the control group and the absence of patients with MetS

among the controls were other limitations. In planning the study, our primary aim was to compare VAI levels among PCOS phenotypes; therefore, the patients in the study were appropriate for our inclusion criteria and the predicted number of patients. After adding the controls, 51 control cases meeting the criteria were included in the study. In the study by Shreenidhi et al. [29], which compared VAI and lipid accumulation product (LAP) levels in PCOS patients classified as metabolically healthy (MH-PCOS) and metabolically unhealthy (MU-PCOS) according to NCEP-ATP III criteria, 38% of patients were in Phenotype A, 3% in Phenotype B, 12% in Phenotype C, and 47% in Phenotype D. MU-PCOS cases were most frequently observed in Phenotypes A (43%) and D (36.3%). Shreenidhi et al. also found the VAI cut-off value to be ≥ 2.767 [(sensitivity: 84.09%, specificity: 85.26%, AUC: 95%CI:0.89 (0.82-0.95)] in distinguishing MU and MH-PCOS in the Asian-Indian population, and reported that the risk of having MetS increased by 9.42 (95%CI: 3.25-27.26) times above this value. In their study where VAI levels were compared, Shreenidhi et al. found no difference between the subtypes (from Phenotype A to D: 2.3, 2.1, 1.57, and 2.12, respectively), and no relationship between VAI and HOMA-IR levels [30]. On the other hand, Ramezani Tehrani et al. reported the VAI cut-off value as 3.1 (sensitivity: 81% and specificity: 78%, AUC: 0.8) in predicting MetS [29].

As parallel to the positive correlation between VAI and HOMA-IR levels reported in several previous studies [26,31,32], there was also a positive correlation between VAI and HOMA-IR (*Spearman's Rho*=0.348, $p<0.001$) levels in our study, However, while finding no relationship between VAI and HOMA-IR ($r=0.12$, $p=0.08$) levels, Shreenidhi et al. [30] detected a relationship between LAP and VAI ($r=0.23$, $p=0.001$) levels.

5. Conclusions

In the presented study, we evaluated VAI levels in different phenotypic PCOS subtypes and demonstrated that PCOS subtypes containing components such as HA and OA had higher VAI levels than the controls and other subtypes. We also determined that more patients in these groups had negative metabolic disorders such as MetS and IR. Therefore, our study presents the findings emphasizing the importance of taking the necessary precautions and the need to combat possible metabolic disorders early and effectively in PCOS patients, especially in phenotypes containing such components as HA and OA.

Supplementary Materials: The following supporting information can be downloaded at the website of this paper posted on Preprints.org. Table 1: Some demographic and laboratory data of the cases; Table 2: The relationship between visceral adiposity index levels and the presence of metabolic syndrome; Table 3: The relationship between visceral adiposity index levels and some parameters; Figure 1- Flowchart of the study population; Figure 2- Visceral adiposity index (VAI) levels in total polycystic ovary syndrome (PCOS) patients and PCOS subtypes; Figure 3- The receiver operating characteristic (ROC) curves of visceral adiposity indexes (VAI) in predicting metabolic syndrome (MetS) in patients with polycystic ovary syndrome (PCOS), (a) Scattering graph of VAI, (b) According to the determined VAI cut-off value.

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Data Availability Statement: Dataset available on request from the authors.

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Abbreviations

The following abbreviations are used in this manuscript:

VAI	Visceral adiposity index
PCOS	Polycystic Ovary Syndrome
HA	Hyperandrogenism
OA	Oligo-anovulation
PCOM	Polycystic ovarian morphology
BMI	Body mass index
HDL	High density lipoprotein
MetS	Metabolic Syndrome
ROC	Receiver Operating Characteristic
USG	Ultrasonography
PCO	Polycystic ovaries
HT	Hypertension
IR	Insulin resistance
DM	Type 2 diabetes mellitus
WC	Waist circumference
CT	Computerized tomography
DXA	Dual-energy X-ray absorptiometry
NCEP-ATP	National Cholesterol Education Program Adult Treatment Panel
HOMA-IR	Homeostasis model assessment-insulin resistance
TG	Triglyceride
NR	Normal range
SD	Standard deviation
AUC	Area under curve
CI	Confidence interval
LAP	Lipid accumulation product
MH-PCOS	Metabolically healthy Polycystic Ovary Syndrome
MU-PCOS	Metabolically unhealthy Polycystic Ovary Syndrome

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