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ORIGINAL ARTICLE

Evaluation of the relationship between serum ferritin and insulin resistance and visceral adiposity index (VAI) in women with polycystic ovary syndrome

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Abstract

Purpose There is a relationship between polycystic ovary syndrome (PCOS) and adipose tissue dysfunction (ADD), but this relationship is not clear. It has been recently shown that iron accumulation in adipose tissue is among the causes of adipose tissue dysfunction. Data on adipose tissue dysfunction in women with PCOS are insufficient. In this study, we aimed to evaluate the relationship between serum ferritin levels (iron accumulation biomarker) and visceral adiposity index (an indicator of adipose tissue dysfunction).

Methods The study is a case–control study. Women with diagnosed PCOS with 2003 Rotterdam Diagnostic Criteria ($n=40$) were compared with non-PCOS group ($n=40$). In this study, the cholesterol ratios, the homeostatic model evaluation index for insulin resistance (HOMA-IR) and the quantitative insulin sensitivity control index were calculated using biochemical parameters, and the visceral adiposity index (VAI) and the lipid accumulation product (LAP) were calculated using both anthropometric and biochemical parameters. In this study, insulin resistance was evaluated by HOMA-IR and adipose tissue dysfunction was evaluated by VAI index.

Results According to the results of this study, women with PCOS have a worse metabolic status than women without PCOS. However, this has been shown only in overweight and obese women, not in women with normal weight.

Conclusion As a result, the presence of obesity in women with PCOS exacerbates metabolic status.

Level of evidence Level V, cross-sectional descriptive study.

Keywords Ferritin · Obesity · Insulin resistance · Polycystic ovary syndrome · Visceral adiposity index

Introduction

Polycystic ovary syndrome (PCOS) is a common metabolic, endocrine and reproductive disorder that affects women of reproductive age. The prevalence of PCOS varies between 6 and 20% depending on the diagnostic criteria used [1]. There are different diagnostic criteria for PCOS which have been set by three organizations: the National Institutes of Health/National Institute of Child Health and Human Disease (NIH/NICHD) in 1990; the European Society for Human Reproduction and Embryology/American Society for Reproductive Medicine (ESHRE/ ASRM) in 2003 (referred to as the Rotterdam criteria) and the Androgen Excess and PCOS Society (AE-PCOS) in 2006 [2, 3]. According to NIH diagnostic criteria, with the exclusion of other disorders associated with androgen excess, PCOS has been identified not only by clinical and/or biochemical findings of hyperandrogenism, but also by the presence of chronic anovulation [4]. Later, with the discovery that ovarian morphology is an important key component for diagnosis, in 2003, under the sponsorship of ESHRE and ASRM, "polycystic ovarian morphology in ultrasonography" was added to the NIH diagnostic criteria and added to the literature as Rotterdam Criteria [5]. According to the Rotterdam Criteria, with the exclusion of other disorders associated with androgen

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excess, the existence of two criteria of clinical and/or biochemical findings of hyperandrogenism, oligo/anovulation, and polycystic ovarian morphology in ultrasonography is sufficient for the diagnosis of PCOS [6]. Finally, according to the AE-PCOS diagnostic criteria, with the exclusion of other disorders associated with androgen excess, the clinical and/or biochemical findings of hyperandrogenism and the coexistence of ovarian dysfunction (polycystic ovarian morphology and/or oligo or anovulation in ultrasonography) are considered sufficient for diagnosis [7].

PCOS is a syndrome characterized by clinical (acne, hirsutism, alopecia) and/or biochemical findings of hyperandrogenism and features of anovulation (amenorrhea, oligomenorrhea, irregular menstrual cycle) along with the appearance of polycystic ovaries on ultrasonography [8]. In addition to these gynecological symptoms, this syndrome presents itself with many metabolic disorders such as increased visceral adiposity, insulin resistance, impaired glucose tolerance, type 2 diabetes, dyslipidemia, chronic low-grade pro-inflammatory condition, and cardiovascular diseases [9]. Especially among these metabolic disorders, insulin resistance and hyperinsulinemia are common in women with PCOS [10]. In order for insulin to act, it is necessary to bind to its specific receptor in the cell membrane, followed by tyrosine phosphorylation of the receptor [11]. However, there are abnormalities in the cellular mechanisms of the receptor functions in women with PCOS [12]. In women with PCOS, serine phosphorylation of the beta subunit of the insulin receptor and the insulin receptor substrate is increased, and thus, trozin autophosphorylation of the insulin receptor is inhibited. As a result, a post-receptor change occurs that prevents signaling pathways bound to the insulin receptor substrate. Serine phosphorylation of the beta subunit of the receptor causes insulin resistance, and serine phosphorylation of the enzyme p450c17 also causes hyperandrogenism [13, 14]. That is, insulin resistance and hyperandrogenism can be independently involved in the pathogenesis of PCOS. In addition, the metabolic and gynecologic features of PCOS form a vicious cycle with each other and sometimes some nutritional factors are involved in this cycle. Insulin resistance, which is at the center of this cycle, is thought to play an important role in the pathogenesis of PCOS by contributing to hyperandrogenism [15]. Insulin resistance and compensatory hyperinsulinemia cause hyperandrogenism by increasing the synthesis of androgen in adipose tissue and ovarian. In addition, hyperinsulinemia causes decreased hepatic synthesis of sex hormone-binding globulin (SHBG), thereby increasing levels of circulating free androgens [12, 16, 17]. DHT (dihydrotestosterone), which is formed by the peripheral conversion of testosterone, triggers insulin resistance by affecting the functions of pancreatic β-cells and causes hypertrophy and lipotoxicity in adipocytes [18]. Hyperandrogenism also triggers the inflammatory process (chronic low-grade inflammation) in PCOS. However, the pro-inflammatory/inflammatory cytokine imbalance in PCOS also causes hyperandrogenism dependent of abdominal obesity and insulin resistance, forming a vicious cycle [19, 20]. On the other hand, nutrient-induced inflammation can induce ovarian androgen production even in the absence of abdominal obesity and insulin resistance in PCOS [19, 21]. Especially, dietary carbohydrate (glucose) induces oxidative stress to stimulate the inflammatory response even in the absence of excess adiposity and insulin resistance. Inflammation-induced hyperandrogenism triggers insulin resistance and compensatory hyperinsulinemia which in turn stimulate further androgen synthesis. This vicious cycle exacerbates the symptoms of PCOS [22]. In this vicious circle in the pathogenesis of PCOS, nutrition can be seen as an additional component in defining a 'deadly quartet' of metabolic risk factors along with insulin resistance, hyperandrogenism and low-grade inflammation [21]. Obesity, a factor worsening the metabolic and gynecological symptoms of this vicious circle, exacerbates hyperandrogenism and menstrual irregularities, which are key features in PCOS [23]. In contrast, body weight loss and maintenance strategies improve all clinical and biochemical characteristics of women with PCOS. Therefore, lifestyle changes (diet, physical activity and behavior changes) and weight maintenance are recommended from the beginning of treatment of women with PCOS [24]. Especially in obese and overweight women with PCOS, it is recommended to include a nutrition program that will lose at least 5–10% of their body weight in initial treatment [25]. However, it is still inconclusive what is the most effective dietary model that should be adopted to lose weight in PCOS [26]. It is suggested that alternative dietary strategies adapted for insulin resistance and type 2 diabetes may be superior in PCOS [27]. Among the different nutritional strategies, Mediterranean Diet is accepted as a health-promoting dietary pattern. Barrea et al. found a direct relationship between PCOS and the adherence to Mediterranean diet. Some foods in this diet show the therapeutic effects by reducing the inflammatory status [26].

The similarity of the metabolic syndrome and the complications associated with PCOS have led to the hypotheses that metabolic disorders in PCOS may be caused by adipose tissue dysfunction (ADD) [28]. There are two types of body fat distribution in adipose tissue: upper body (android or central) and lower body (gynoid or peripheral). The distribution of fat in women's adipose tissue is normally gynoid [29]. However, the distribution of fat mass in postmenopausal women varies from gynoid pattern to android pattern [30]. In addition, even in the fertile period, women with PCOS may tend to have central/android-type fat accumulation. This change is definitively or relatively related to androgen excess in PCOS [31]. The relationship between androgens and body fat distribution led to the hypothesis that androgens have

direct effects on the differentiation of adipocytes [32]. In addition to hyperandrogenism in PCOS, the reduction of catecholamine-induced lipolysis in adipose tissue cells may be associated with hypertrophy in adipose tissue cells. In PCOS, adipose tissue dysfunction is characterized by hypertrophic adipocytes which are more susceptible to fibrosis, apoptosis, inflammation and release of free fatty acids [33, 34]. Furthermore, the secretion of adipose tissue-specific adipokine and pro-inflammatory cytokines is impaired in PCOS [28]. ADD acts as a mediator between abdominal obesity, inflammation, and insulin resistance accompanying PCOS as it causes an increase in the release of pro-inflammatory adipocytokines and a decrease in the release of anti-inflammatory adipocytokines such as adiponectin [35].

Although there is known to be an association between PCOS and adipose tissue dysfunction (ADD), the underlying mechanisms are not fully understood and many hypotheses have been proposed [33]. This study is planned with the knowledge that iron has an effect on adipose tissue functions and that serum ferritin levels are higher in women with PCOS than the healthy control group [35–39]. We thought that there may be a relationship between ferritin and adipose tissue dysfunction in women with PCOS. In explaining this relationship, the knowledge that adipose tissue dysfunction is characterized by adipose tissue-specific insulin resistance and altered adipokine release is fundamental. It is well known that there is a relationship between serum ferritin and insulin resistance [40, 41]. Although this relationship is not fully understood, a reduced ability to burn carbohydrates and altered adipose tissue functions have been suggested as possible mechanisms according to The European Association for the Study of the Liver (EASL) [42]. Apart from this, many hypotheses have been proposed. First, the catalytic effects of iron induce lipid peroxidation, causing inhibition of insulin internalization and actions, and result in hyperinsulinemia and insulin resistance [38, 39]. Second, excess body iron can affect insulin secretion and signaling [43]. Iron in pancreatic β cell is important for normal insulin secretion, either by producing reactive oxygen species (ROS) or by maintaining ATP production in the electron transport chain (ETC) in mitochondria. β cell produces hepcidin, which is secreted out of the cell along with insulin. Hepcidin inhibits iron secretion via ferroportin. That is, in the presence of hyperinsulinemia, iron begins to accumulate in the β cell. Iron accumulation causes β-cell toxicity due to ROS formation via the Fenton reaction. ROS reduces ATP production in the ETC by causing mitochondrial dysfunction, leading to impaired insulin secretion [44]. In addition to β cell, iron accumulation in adipocytes also leads to a decrease in adipogenic capacity, disrupts insulin signaling and adipocyte differentiation and in addition, changes the expression of adipose tissue-specific genes and the release of adipokine (for example, increasing the release of resistin) [41, 45]. Finally, body iron increases the rate of lipolysis of adipose tissue triacylglycerol stores, thereby increasing the level of circulating free fatty acids (FFAs), thereby triggering tissue-specific insulin resistance [46, 47]. As a result, many markers in iron metabolism are associated with adipocyte insulin resistance (defined by the product of fasting insulin and nonesterified fatty acids), an indicator of adipose tissue dysfunction [48, 49].

The relationship between ferritin and adipose tissue dysfunction can also be explained by altered adipokine levels. Adipose tissue is an endocrine organ that secretes many hormones and signaling molecules, collectively called adipokine. These adipokines contribute to insulin resistance with their either pro-inflammatory or inflammatory properties [50]. Adipose tissue is also an organ in which iron regulating proteins (ferritin, hepcidin) are expressed and is the main target organ where iron shows metabolic effects [49, 51]. The investigation of the relationship between serum adipokines and ferritin has been reported to be interesting [52]. Adiponectin is the most studied adipokine for this relationship. There are studies showing an inverse relationship between ferritin and adiponectin [49, 53–55]. Iron is required for the oxidation of lipids in the electron transport chain. As it is known, adiponectin also increases fatty acid oxidation, but its levels are reduced by iron [56]. Iron has an inhibitory effect on adiponectin production, secretion and transcription via the class O of Forkhead box transcription factors (FOXO1)-mediated repression [41, 54]. It is thought that this inhibitory effect may be a compensatory mechanism to protect the organism from additional oxidative stress. That is, iron reduces fatty acid oxidation by reducing adiponectin levels and decreased adiponectin levels may be the cause of adipose tissue dysfunction [56]. As a result, it has been suggested that high levels of serum ferritin may be an indicator of adipose tissue dysfunction [36].

The possible mechanism among metabolic conditions associated with PCOS, body iron accumulation, and adipose tissue dysfunction is given in Fig. 1 [10, 13, 14, 18, 51, 57–71].

This study was planned and conducted to evaluate the relationship between serum ferritin levels and adipose tissue dysfunction (visceral adiposity index) in addition to the relationship between adipose tissue dysfunction and some metabolic disorders accompanying disease in PCOS and control subjects with similar age and BMI.

Materials and methods

Study populations

This is a cross-sectional case–control study aimed to evaluate the relationship between serum ferritin levels and

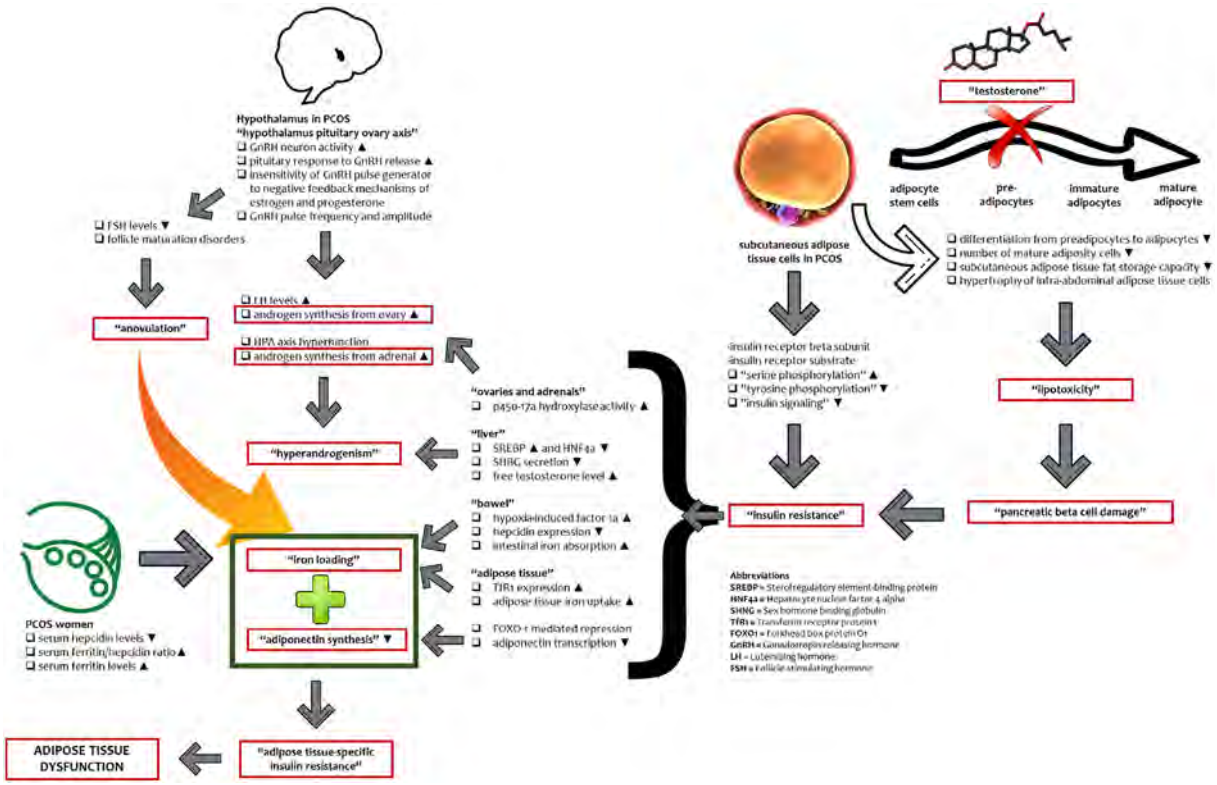

Fig. 1 The possible mechanism among metabolic conditions associated with PCOS, body iron accumulation, and adipose tissue dysfunction

adipose tissue dysfunction (measured by visceral adiposity index) along with the relationship between adipose tissue dysfunction and some metabolic disorders accompanying disease. The study was carried out between April and November 2017 at Gazi University Medical School Hospital, at the Clinic of Obstetrics and Gynecology and Reproduction Treatment Center. The PCOS group included 40 women, between the ages of 18 and 45, who were diagnosed with PCOS with the 2003 Rotterdam Diagnostic Criteria. The non-PCOS group, however, included 40 women, between the ages of 18 and 45, who were not diagnosed with PCOS with the 2003 Rotterdam Diagnostic Criteria and whose menstrual cycles were regular. For the non-PCOS group, women with irregular menstrual cycles, the appearance of polycystic ovaries on ultrasound or the clinical and biochemical signs and symptoms of hyperandrogenism have been excluded from the study. In addition, for the PCOS and non-PCOS group, women using any medication which affects the serum sex hormone profile and body composition as well as depression medication over the last three months; women undergoing pregnancy, lactation or menopause; women with diabetes mellitus or hematological or iron metabolism pathologies; and women with other conditions leading to hyperandrogenism and ovulation dysfunction (such as hypothyroidism, hyperprolactinemia, Cushing's syndrome, congenital adrenal hyperplasia, androgen secretory tumors) have been excluded from the study.

Assessment of participants

Anthropometric measurements [body weight (kg), height (cm), waist circumference (cm), hip circumference (cm)] body composition analysis [body fat percentage (%), and lean body mass (kg)] of all women participating in the study were performed by the researcher. Body weight measurements and body composition analyses of all women were performed using the Tanita BC 532 (Tanita Co., Ltd., Dongguan, China) portable body analyzer [bioelectrical impedance device (BIA)] with light clothing after 8 h of fasting. Height measurement was performed with a stadiometer. At this time, the head should be placed in the Frankfurt plane and participants should breathe deeply with their feet adjacent at the heels, with the back, hips, and heels touching the wall [72].

The BMI values of all women were calculated with the formula body weight (kg) ÷ [length $(m)^2$] [73]. According to the BMI classification made by WHO; a BMI value below 18.50 kg/m^2 is "lean", 18.50–24.99 kg/m^2 is within the range of "normal", 25.00–29.99 kg/m^2 is within the range of "overweight", 30.00–34.99 kg/m^2 is within the range of "1st degree obese", 35.00–39.99 kg/m^2 in the range of

"second degree obese", and 40 kg/m^2 and above is defined as "third degree obese" [74]. In this study, the PCOS and non-PCOS groups were divided into two groups as BMI < 25 kg/m^2 (normal) and ≥ 25 kg/m^2 (overweight or obese). The waist circumference was measured with a flexible but non-stretchable tape passing through the midpoint of the distance between the lowest rib and the crystalline bone according to the WHO recommendation [75]. The hip circumference was measured as the widest area of the hip with the aid of a non-stretching tape, standing side by side with the legs of the participant adjacent. Waist/hip ratios were calculated using these measurements.

Body fat mass index (BFMI) (kg/m^2) was calculated by dividing body fat mass by the square of the height [body fat mass (kg) ÷ height (m)^2]. Lean body mass index (FFMI) (kg/m^2) was calculated by dividing lean body mass by the square of the height [lean body mass (kg) ÷ height (m)^2] [76].

On the day of the questionnaire, a blood sample was taken from the participants after fasting for at least 8 h with the consent of the physician. The analysis of blood in terms of biochemical parameters [fasting blood glucose (mg/dL), serum insulin (μIU/mL), serum ferritin (ng/mL), serum iron and iron binding capacity (pg/mL), HDL cholesterol (mg/dL), LDL cholesterol (mg/dL), total cholesterol (mg/dL), triglyceride (mg/dL)] required for the study was performed by purchasing services from the Biochemistry Laboratory of Gazi University Medical Faculty Hospital. Using these biochemical parameters, homeostatic model evaluation index for insulin resistance (HOMA-IR), the quantitative insulin sensitivity control index (QUICKI), lipoprotein ratios, lipid accumulation product index (LAP), and visceral adiposity index (VAI) were calculated for all participants.

HOMA-IR was calculated using the equation [fasting insulin levels (μIU/mL) × fasting blood glucose levels (mg/dL) ÷ 405] [77]. Although there is no universal HOMA-IR cut-off value for insulin resistance [78], Turkey Endocrinology and Metabolism Society (2009), it is defined as HOMA-IR and insulin resistance is ≥ 2.7 [79]. QUICKI was calculated using the equation "1/log [fasting serum insulin levels (mU/L)] + log [fasting blood glucose levels (mg/dL)] to evaluate insulin sensitivity [9]. The total cholesterol/HDL cholesterol ratio, the LDL/HDL cholesterol ratio, and the triglyceride (TAG)/HDL cholesterol ratio were calculated as lipoprotein ratios [80, 81].

The visceral adiposity index (VAI), considered to be a marker of visceral adipose dysfunction, is a gender-specific mathematical model which includes both anthropometric parameters [(BMI (kg/m^2) and waist circumference (cm)] and functional parameters [serum triglyceride (mmol/L) and HDL cholesterol (mmol/L) levels] [9].VAI index showed a strong association with both insulin sensitivity, evaluated by the hyperinsulinemic-euglycemic clamps technique and visceral adipose tissue, measured by the magnetic resonance imaging (MRI) [82]. Visceral adipose dysfunction is traditionally measured by body mass index (BMI), waist circumference (WC) and waist–hip ratio (WHR). However, BMI is not considered as a good marker since it does not include factors affecting visceral adipose mass and functions. WC is also considered limited marker as it cannot distinguish between subcutaneous and visceral fat area. Visceral adipose tissue can also be evaluated with Magnetic resonance imaging (MRI) and Computed tomography (CT) scan, but both of them are neither easily accessible nor cheap [83]. Therefore, it was planned to use the VAI index for the evaluation of adipose tissue dysfunction in this study. In this study, this index value was calculated using the equation proposed for women [84].

$$\text{VAI} = [\text{waist circumference} \div (36.58 + 1.89 \times \text{BMI})] \times (\text{serum triglyceride} \div 0.81) \times (1.52 \div \text{serum HDL})$$

The lipid accumulation product (LAP) was first described by Kahn in 2005 as an "index based on the combination of waist circumference (cm) and fasting serum triglyceride levels (mmol/L)" [85]. LAP index was calculated using the equation (waist circumference (cm)—58) × fasting triglyceride levels (mmol/L) [9].

Statistical analysis

The SPSS for Windows version 20.0 (SPSS, Inc.; Chicago, USA) was used in performing the statistical analyses. Arithmetic mean ($\bar{x}$) and standard deviation (SD) values were calculated for quantitative variables. In this study, correlation analyses were performed to examine the relationship between two quantitative variables. To evaluate the performance of some anthropometric data and some indexes in the diagnosis of insulin resistance in women with PCOS, ROC curve analyses were performed. All p values of less than 0.05 were considered statistically significant.

Before starting the study, the sample size calculation was made by a statistician in the 95% confidence interval. After the study was completed, power analysis was carried out once again. The post-power value was obtained as 72% with 95% confidence and 0.80 effect size.

Results

Forty women with and without PCOS participated in this study. Comparisons of some biochemical and anthropometric parameters in women with normal body weight and overweight/obese PCOS along with non-PCOS are given in Table 1. The mean age of women with PCOS was 25.25 ± 4.79 and the mean age of women in the non-PCOS group was 24.83 ± 3.17 ($p > 0.05$). The mean BMI was

27.23 ± 6.60 in women with PCOS and 25.37 ± 4.07 kg/m^2 in the non-PCOS group ($p > 0.05$). There was no statistically significant difference in body weight (kg), height (cm), BMI (kg/m^2), waist circumference (cm), hip circumference (cm), waist/hip ratio, and waist/height ratio between normal weight PCOS and non-PCOS women ($p > 0.05$). In contrast, overweight/obese women with PCOS had higher body weight, BMI, waist circumference, waist/hip ratio, and waist/height ratio compared to overweight/obese women with non-PCOS ($p < 0.05$). There was no statistically significant difference in terms of biochemical parameters related to glucose, iron and lipid metabolism, lipoprotein ratios and VAI, and LAP indexes ($p > 0.05$). In contrast, overweight/obese women with PCOS had higher fasting serum insulin levels, HOMA-IR, serum iron binding capacity, lipoprotein ratios, in addition to VAI and LAP index values, while they had lower QUICKI, serum iron, and HDL cholesterol levels compared to overweight/obese women with non-PCOS ($p < 0.05$).

The correlation of VAI and LAP with serum levels of glucose, insulin and ferritin in women with PCOS is given in Table 2. There was a positive correlation between serum

Table 1 Comparison of some biochemical and anthropometric parameters in PCOS and non-PCOS women according to BMI

	BMI < 25 kg/m^2		*p*	BMI ≥ 25 kg/m^2		*p*
	PCOS ($n = 17$)	Non-PCOS ($n = 20$)		PCOS ($n = 23$)	Non-PCOS ($n = 20$)	
	x̄ ± SS	x̄ ± SS		x̄ ± SS	x̄ ± SS	
Anthropometric						
Weight (kg)	56.25 ± 5.940	59.00 ± 5.40	0.150	84.23 ± 13.15	76.16 ± 7.23	0.016
Height (cm)	163.94 ± 6.58	164.25 ± 5.25	0.875	162.91 ± 6.27	162.40 ± 5.39	0.777
BMI (kg/m^2)	20.95 ± 2.06	21.88 ± 1.87	0.139	31.78 ± 4.91	28.86 ± 2.19	0.015
Waist circumference (cm)	75.00 ± 6.69	73.80 ± 6.53	0.586	100.83 ± 10.32	85.90 ± 7.30	0.000
Waist/hip	0.79 ± 0.07	0.75 ± 0.05	0.557	0.87 ± 0.06	0.78 ± 0.07	0.000
Waist/height	0.46 ± 0.06	0.45 ± 0.05	0.331	0.63 ± 0.06	0.54 ± 0.06	0.000
Body fat (%)	22.85 ± 5.15	26.34 ± 4.87	0.061	39.25 ± 4.67	36.32 ± 3.95	0.033
BFMI (kg/m^2)	4.87 ± 1.34	5.83 ± 1.48	0.096	12.67 ± 3.33	10.54 ± 1.71	0.014
Lean body mass (kg)	40.88 ± 2.69	41.15 ± 1.84	0.717	47.90 ± 4.96	46.00 ± 2.37	0.111
FFMI (kg/m^2)	15.24 ± 1.07	15.28 ± 1.06	0.900	18.08 ± 1.79	17.47 ± 0.95	0.168
BFM/FFM	0.33 ± 0.09	0.39 ± 0.10	0.251	0.69 ± 0.13	0.61 ± 0.11	0.038
Biochemical						
Glucose metabolism						
Serum glukoz (mg/dL)	82.14 ± 6.00	85.80 ± 6.11	0.076	88.99 ± 10.53	90.85 ± 8.95	0.542
Serum insulin (μIU/mL)	5.94 ± 2.34	5.49 ± 2.63	0.589	15.64 ± 6.79	11.08 ± 8.82	0.002
HOMA-IR	1.21 ± 0.47	1.19 ± 0.59	0.908	3.51 ± 1.79	2.50 ± 1.99	0.005
QUICKI	0.38 ± 0.03	0.38 ± 0.03	0.786	0.32 ± 0.02	0.35 ± 0.03	0.005
Iron metabolism						
Serum ferritin (ng/mL)	23.70 ± 19.35	15.18 ± 9.12	0.240	27.63 ± 20.97	19.39 ± 14.98	0.289
Serum iron (pg/mL)	88.88 ± 46.00	111.05 ± 33.4	0.099	58.34 ± 23.14	102.55 ± 45.8	0.001
Serum UIBC (pg/mL)	277.91 ± 80.15	266.05 ± 30.0	0.571	335.88 ± 77.89	263.50 ± 50.9	0.000
Lipid metabolism						
Total cholesterol (mg/dL)	170.56 ± 24.19	172.35 ± 21.1	0.812	176.80 ± 38.68	173.03 ± 26.9	0.717
HDL cholesterol (mg/dL)	55.92 ± 7.73	61.60 ± 9.68	0.060	45.03 ± 7.17	58.64 ± 7.15	0.000
LDL cholesterol (mg/dL)	96.86 ± 22.11	94.80 ± 15.57	0.742	108.63 ± 30.88	96.19 ± 24.08	0.153
TAG (mg/dL)	88.91 ± 47.01	79.55 ± 17.95	0.692	128.75 ± 108.8	97.61 ± 30.90	0.575
Lipoprotein rates						
Total/HDL cholesterol	3.10 ± 0.62	2.84 ± 0.33	0.104	3.97 ± 0.86	3.00 ± 0.59	0.000
LDL/HDL cholesterol	1.77 ± 0.54	1.57 ± 0.27	0.156	2.44 ± 0.69	1.67 ± 0.51	0.000
TAG/HDL cholesterol	1.65 ± 0.93	1.34 ± 0.41	0.592	2.92 ± 2.30	1.70 ± 0.55	0.020
Indexes						
VAI	1.34 ± 0.78	1.05 ± 0.36	0.502	2.53 ± 2.11	1.32 ± 0.47	0.003
LAP	17.99 ± 14.06	14.79 ± 8.66	0.522	60.93 ± 46.60	31.60 ± 13.90	0.003

Table 2 The correlation of VAI and LAP with serum levels of glucose, insulin and ferritin in women with PCOS

Variables	VAI		LAP	
	r	*p*	*r*	*p*
Serum glucose (mg/dL)	0.305	0.056	0.368	0.020
Serum insulin (μIU/mL)	0.504	0.001	0.721	0.000
Serum ferritin (ng/mL)	0.270	0.092	0.257	0.109

Pearson correlation coefficient is used to investigate the relationship between two quantitative variables with normal distribution. Spearman correlation coefficient is used to investigate the relationship between two quantitative variables where at least one variable does not have a normal distribution

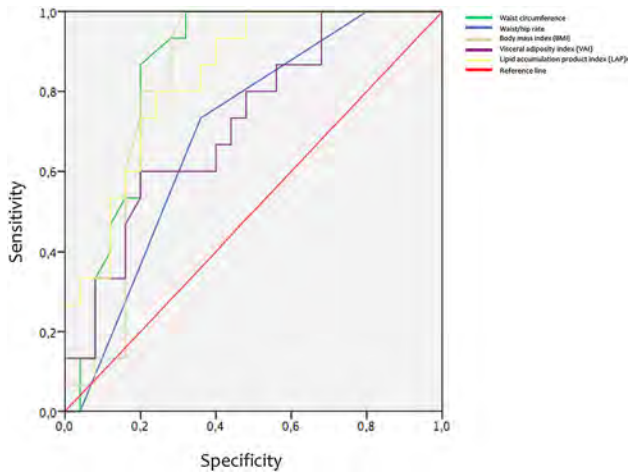

Fig. 2 Cut-off values of VAI, LAP and some biochemical and anthropometric parameters in the determination of insulin resistance in women with PCOS

insulin levels and VAI, and between serum glucose and insulin levels and LAP in women with PCOS ($p < 0.05$).

Cut-off values of VAI, LAP and some biochemical and anthropometric parameters in the determination of insulin resistance in women with PCOS are given Fig. 2. AUC, 95% CI, SS (%), SP (%) and cut-off values of VAI, LAP and some biochemical and anthropometric parameters in determining insulin resistance in women with PCOS are given Table 3. In women with PCOS, the cut-off value of VAI and the cut-off value of LAP were found to be 1.65 and 32.97, respectively.

Discussion

Anthropometric measurements are widely used research tools to assess metabolic risk in women with PCOS [86]. In our study, body weight, BMI, waist circumference, and waist/hip ratios were found to be higher in women with PCOS than in non-PCOS women. However, a statistically significant result was found only in the overweight/ obese group ($p < 0.05$). In literature, body weight, BMI values, and waist circumference findings of women with PCOS are contradictory. In some studies anthropometric measurements did not show significant differences between PCOS and non-PCOS women [76, 87]; while, some studies showed significant differences similar to our study [88, 89]. In our study, body fat percentages were found to be higher in women with PCOS than in non-PCOS women. However, a statistically significant result was found only in the overweight/obese group ($p < 0.05$). In literature, in most studies comparing the body composition of women with PCOS and the non-PCOS group, no statistically significant differences were found between these two groups in terms of body fat percentage, lean body mass, and percentage [90, 91]. However, significant differences were found in some studies similar to our study [76, 92]. Higher body weight and waist circumference along with body fat percentage in women with PCOS can be explained by a decrease in postprandial thermogenesis and basal metabolic rate, impaired gastrointestinal hormone and appetite regulation, insulin resistance, hyperandrogenism, reduced physical activity, and reduced meal frequency. In a study, it was also found that obese women with PCOS had lower postprandial thermogenesis than women with BMI in the matched (obese/lean) PCOS women population. In a study, it was also found that obese women with PCOS had lower postprandial thermogenesis than lean women with PCOS. Hyperandrogenism may also cause weight gain by triggering appetite and bulimic behavior in women with PCOS [93, 94].

In our study, insulin resistance (HOMA-IR) was found to be higher in women with PCOS than in non-PCOS women.

Table 3 AUC, 95% CI, SS (%), SP (%) and cut-off values of VAI, LAP and some biochemical and anthropometric parameters in determining insulin resistance in women with PCOS

Variables ($n = 40$)	AUC	%95 CI		*p*	SS (%)	SP (%)	Cut-off
Waist circumference (cm)	0.837	0.729	0.972	0.000	86.7	80.0	91
Waist/hip	0.699	0.536	0.861	0.037	73.3	64.0	0.85
BMI (kg/m^2)	0.825	0.691	0.960	0.001	93.3	72.0	25.4
VAI	0.721	0.561	0.881	0.020	60.0	76.0	1.65
LAP	0.851	0.716	0.958	0.000	80.0	76.0	32.97

AUC Area under the ROC curve, *CI* confidence interval, *SS* sensitivity, *SP* specificity

However, a statistically significant result was found only in the overweight/obese group ($p < 0.05$). Similar to our study, Durmuş et al. it was shown that women with PCOS have higher HOMA-IR [95]. To achieve insulin action in a healthy metabolism, it must bind to its specific receptor in the cell membrane and phosphorylation of tyrosine. Interestingly, however, serine phosphorylation of the insulin receptor occurs in women with PCOS, resulting in post-receptor abnormalities in insulin action [13].

In addition to insulin resistance, dyslipidemia is one of the common metabolic abnormalities associated with PCOS. In our study, no significant differences were found between normal weight PCOS and non-PCOS groups in terms of serum lipid profiles (total cholesterol, HDL cholesterol, LDL cholesterol, and triglyceride) ($p > 0.05$). On the other hand, significant differences were found only in HDL cholesterol levels between overweight/obese PCOS and non-PCOS groups. Women with overweight/obese PCOS have lower HDL cholesterol levels ($p < 0.05$). In addition to study [96] showing no statistically significant differences in serum lipid profiles between PCOS and non-PCOS women, there are also studies showing that women with PCOS have higher triglyceride levels [97] and lower HDL cholesterol levels [98].

The visceral adiposity index (VAI) is an indicator of adipose tissue dysfunction. It has been suggested that visceral adiposity induces metabolic and endocrine abnormalities that are essential to the progression of PCOS, and therefore assessment of VAI, independent of general obesity, may be important for future therapeutic strategies of PCOS [99]. In our study, VAI was not significantly different from the normal weight PCOS group and the non-PCOS group. However, it was found to be higher in the overweight/obese PCOS group than in the non-PCOS group ($p < 0.05$). Durmus et al. found similar results in our study [95].

The lipid accumulation index (LAP) is presented as an inexpensive research tool to monitor and estimate total body fat accumulation [85]. In our study, the LAP value was found to be significantly higher only in the overweight/obese PCOS group compared to the non-PCOS group ($p < 0.05$). Macut et al. in their study found similar results to our study [100].

Many molecules involved in iron metabolism are identified as potential biomarkers for PCOS [101]. One of these, ferritin, is the main iron-storing protein in maintaining iron homeostasis, and serum ferritin levels are widely used in the clinic routinely as an indicator of body iron stores [37]. In our study, it was found that women with normal weight and overweight/obese PCOS had higher serum ferritin levels. However, this was not statistically significant ($p > 0.05$). Similar to the results of our study in literature [38], there are no differences in the serum ferritin levels between PCOS and non-PCOS groups. However, there are studies [102, 103] showing that women with PCOS have significantly higher serum ferritin levels than non-PCOS women.

Escobar et al. found that overweight/obese women with PCOS had higher serum ferritin levels than the non-PCOS women group. However, there was no statistically significant difference between normal weight PCOS and non-PCOS women [104]. Factors contributing to potential iron overload in women with PCOS include the iron protective effect of reduced menstrual losses associated with oligomenorrhea and/or amenorrhea, obesity and inflammation, insulin resistance, increased hyperandrogenism-induced erythropoiesis, decreased hepcidin expression, and increased Hp2/Hp2 genotype [105]. Insulin resistance and hyperinsulinemia stimulate intestinal iron absorption by increasing the activity of hypoxia-induced factor-1 and reducing hepcidin expression. Through this mechanism, hyperinsulinemia contributes to increased serum ferritin levels seen in PCOS [106]. In our study, although women with PCOS had higher insulin resistance and serum insulin levels compared to non-PCOS women, no significant correlation was found between these parameters and serum ferritin levels ($p > 0.05$).

A study examining the relationship between serum ferritin and adipose tissue dysfunction in the PCOS population is not available in literature. However, a study conducted in a population with vascular disease suggested that free iron may induce adipose tissue dysfunction because of its pro-inflammatory effect on pre-adipose tissue cells [35]. In another study, it was shown that insulin resistance of adipose tissue cells increased by 1.38%, serum non-esterified fatty acid levels increased by 1.94 mmol/L, and that there was a 0.62% decrease in serum adiponectin levels with each 10 mg/L increase in serum ferritin levels. In conclusion, serum ferritin levels may be associated with each parameter of adipose tissue dysfunction [49]. Visceral adiposity index is accepted as an indicator of adipose tissue dysfunction in literature [99]. Therefore, VAI were used in this study to evaluate adipose tissue dysfunction in women with PCOS. In our study, no significant correlation was found between serum ferritin levels and VAI ($p > 0.05$). The reason for this may be the presence of protective mechanisms against iron accumulation (increase in hepcidin synthesis).

In our study, no significant correlation was found between serum ferritin levels and serum insulin levels or serum glucose levels and insulin resistance in women with PCOS ($p > 0.05$). Ko et al. found significant positive correlations between serum ferritin levels and serum insulin levels in addition to serum glucose levels and insulin resistance in obese women with PCOS [105].

In our study, the diagnostic performance of VAI and LAP indexes was evaluated to determine insulin resistance in PCOS. In our study, the optimal cut-off values for determining insulin resistance in women with PCOS were 25.4 kg/m^2 for BMI; 91 cm for waist circumference; 0.85 for waist/hip ratio; 1.65 for VAI index value, and 32.97 for the LAP index value. In our study, LAP has been shown to have

good diagnostic performance. Tehrani et al., found that the optimal cut-off values for determining insulin resistance in women with PCOS were 26.1 kg/m^2 for BMI; 79.5 cm for waist circumference; 0.80 for waist/hip ratio; 1.80 for VAI index value, and 33.80 for the LAP index value. In addition, in this study, it was shown that the LAP index has the highest diagnostic accuracy in determining insulin resistance [107].

Also, Abruzzese et al. reported that the VAI and LAP indexes showed similar diagnostic accuracy in determining insulin resistance and both were good markers for insulin resistance [9].

Conclusions

The aim of this study was to evaluate the relationship among concomitant metabolic conditions, body iron accumulation, and adipose tissue dysfunction in women with PCOS. In this study, it was found that women with PCOS (overweight/obese) had higher insulin resistance and lower HDL cholesterol than non-PCOS women. In parallel with literature, in our study, women with PCOS had more impaired glucose and lipid metabolism. However, no significant difference was found between the serum ferritin levels in PCOS and non-PCOS group. Iron accumulation due to long and irregular menstrual cycles may occur in women with PCOS. However, the presence of protective mechanisms against iron accumulation (such as an increase in the synthesis of hepcidin) can prevent iron accumulation. For this reason, more detailed studies on biochemical parameters such as hepcidin, haptoglobulin, and haptoglobulin genotypes in iron homeostasis in women with PCOS will provide us with clearer mechanisms.

Although the VAI index, which is an indicator of adipose tissue dysfunction, was higher in women with PCOS, there was no correlation between the VAI and serum ferritin levels in this study. In our study, evaluation of adipose tissue dysfunction only with the VAI index is an important limitation. Therefore, further studies are needed to evaluate adipose tissue-specific insulin resistance and serum adiponectin levels associated with adipose tissue dysfunction. Differences between our study and other studies may be caused by small sample size and race differences. In addition, further studies with larger samples and more specific markers are needed to investigate the diagnostic performances of the VAI and LAP indexes and to determine insulin resistance in women with PCOS.

"What is already known on this subject?"

There is a relationship between PCOS and adipose tissue dysfunction, but this relationship is not clear. It has been suggested for years that adipose tissue dysfunction is the basis of metabolic disorders in women with PCOS. It has been recently shown that iron accumulation in adipose tissue is among the causes of adipose tissue dysfunction. However, there is no study that reveals the relationship between adipose tissue dysfunction and iron deposition in women with PCOS.

"What does this study add?"

There is no study on the relationship between the VAI index, which is an indicator of adipose tissue dysfunction, and serum ferritin levels, which is an indicator of iron accumulation, in the population with PCOS. In this study, it is hypothesized that there will be a relationship between them. However, the result of the study was not as expected. There was no correlation between the VAI and serum ferritin levels in this study.

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Author contributions Should individual references be required, all authors listed have contributed sufficiently to the study to be included as authors. However, BBG and YA contributed to the writing of the article. SC and NB contributed to the collecting of the data, if one needs to mention it individually.

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Compliance with ethical standards

Conflict of interest On behalf of all the authors, the corresponding author declares that there is no conflict of interest.

Ethics approval The "Ethics Committee Approval" of the present study was taken from the Zekai Tahir Burak Women's Health Research and Education Hospital, the Directorate of the Clinical Research Ethics Committee dated 18.04.2017 under decision number 65/2017. All procedures performed in studies involving human participants were in accordance with the ethical standards of the institution and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. The reason we got our ethics committee approval from Zekai Tahir Burak Women's Health Research and Education Hospital is because our case group is women with PCOS and this hospital is a branch hospital working in this field. However, considering the location, the case group was taken from Gazi Hospital.

Informed consent Informed consent was obtained from all individual participants included in the study in accordance with the declaration of Helsinki.

Consent to participate The patients have signed an informed consent form indicating that they volunteered to work.

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