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Hyperandrogenism and anthropometric parameters in women with polycystic ovary syndrome

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Abstract

Objective One of the main features of polycystic ovary syndrome (PCOS) is increased adipose tissue, which can result in hormonal disturbances. In the present study, we aimed to investigate which indicator of obesity could better associate with hormonal disturbances in PCOS women.

Methods In this cross-sectional analysis, women with PCOS were included according to the Rotterdam criteria. Fasting blood samples were analyzed for biochemical, metabolic, and hormonal parameters. Anthropometric measures comprised body composition indices (assessed by bioelectric impedance analysis [BIA]), waist circumference, body mass index (BMI), and waist-to-height ratio (WHtR). Linear regression modeling was used to assess the association between anthropometric indices and hormonal imbalance, adjusted for age, mensuration status, and the homeostasis model assessment-estimated insulin resistance (HOMA-IR). Receiver operating characteristics (ROC) curves were utilized to ascertain the sensitivity, specificity, and optimal cut-off points of various anthropometric indices in identifying hyperandrogenism.

Results A total of 129 PCOS women with a median (interquartile range [IQR]) age of 32.0 (23.0–32.0) years and a median BMI of 26.3 (23.00-29.70) kg/m^2 were enrolled. In the adjusted linear regression model, BMI (β = 0.053, $P < 0.001$), waist circumference (β = 0.021, $P = 0.001$), WHtR (β = 3.325, $P = 0.002$), total fat mass (β = 0.021, $P = 0.002$), trunk fat mass (β = 0.038, $P = 0.006$), and leg fat mass (β = 0.045, $P = 0.004$) were positively associated with free androgen index (FAI). In addition, BMI (β=−0.017, $P = 0.003$), waist circumference (β=−0.008, $P = 0.002$), WHtR (β=−1.167, $P = 0.004$), total fat mass (β=−0.008, P=0.003), trunk fat mass (β=−0.017, P=0.001), and leg fat mass (β=−0.018, P=0.004) were negatively associated with the serum level of sex hormone binding globulin (SHBG). WHtR showed the greatest area under the curve (AUC) value (AUC = 0.676, $P = 0.001$) for identifying hyperandrogenism (FAI ≥ 4.97 or total testosterone ≥ 0.7 ng/mL) in PCOS women with corresponding sensitivity of 87.30% and specificity of 39.70%.

Conclusions WHtR is related to hyperandrogenism in PCOS better than other anthropometric measures.

Keywords Polycystic ovary syndrome, Waist-to-height ratio, Androgens, Fat distribution, Obesity

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Introduction

Polycystic ovary syndrome (PCOS) is a heterogeneous metabolic and endocrine disorder, with a prevalence of about 18% among reproductive-age women [1, 2]. PCOS is characterized by polycystic ovarian morphology (PCOM), elevated androgen levels and ovulatory dysfunction [1]. In addition to these presentations, obesity and insulin resistance are common characteristics of PCOS, which can be associated with a pro-inflammatory condition and deteriorate the metabolic and clinical presentations of the disease [3, 4]. Moreover, central adipose tissue distribution, regardless of body mass index (BMI), was found to be one of the characteristics of PCOS [5, 6]. Central adiposity can be linked to insulin resistance and compensatory hyperinsulinemia in PCOS women [7]. Excess insulin secretion acts synergistically with luteinizing hormone (LH) to increase thecal androgen production [8]. Previous reports noted a link between the amount of visceral fat and the levels of androgens in women with PCOS [9, 10]. Additionally, the decreased levels of sex-hormone binding globulin (SHBG) in women with abdominal obesity, may indirectly suggest that increased accumulation of visceral fat is related to elevated levels of free androgens [11].

Measuring the distribution of fat mass by the body composition analysis provides a more detailed body fat assessment compared with BMI and waist circumference [12, 13]. Bioelectrical impedance analysis (BIA) is a convenient, affordable, reliable, and non-invasive technique for measuring body composition and is widely employed in clinical practice [14]. Consequently, we aimed to investigate the relationship between anthropometric indices including waist circumference, BMI, waist-to-height ratio (WHtR), as well as body composition indices measured by BIA and sex-hormone levels among women with PCOS.

Methods

Study design and participants

We conducted a cross-sectional analysis using baseline data from two randomized controlled trials (RCTs) in women with a primary diagnosis of PCOS [15, 16]. RCTs were prospectively performed at three hospitals, affiliated with Tehran University of Medical Sciences, Tehran, Iran. The protocols of the two studies are present at the Iranian Registry of Clinical Trials (irct.ir) with trial registration numbers and date #IRCT2017061917139N2, 17/07/2017 and #IRCT20140406017139N3, 22/12/2018. Informed consents were obtained from all participants and the ethics committee of the Tehran University of Medical Sciences approved the RCTs. The current study was also approved by the ethics committee of Tehran University of Medical Sciences (IR.TUMS.MEDICINE.REC.1400.1186).

Eligibility criteria

Women aged 18–40 years were included in the present study if they were diagnosed with PCOS according to the Rotterdam criteria [17]. The diagnosis of PCOS was made if at least two of the following criteria were met: (1) oligomenorrhea (menstrual cycles longer than 35 days) or amenorrhea (absence of menses for 3–6 months or longer), (2) biochemical (total testosterone > 0.70 ng/mL) and/or clinical (hirsutism, androgenic hair loss, and/or acne) signs of hyperandrogenism, and (3) polycystic ovarian morphology as evidenced by ultrasound exam (ovarian size ≥ 10 ml in at least one ovary and/or presence of ≥ 12 subcapsular follicles in a single ovary at a diameter of 2–9 mm).

Exclusion criteria were as follows: hormonal therapy including OCPs (oral contraceptive pills) or other anti-androgen drugs, use of metabolic altering medications (e.g., glucocorticoid and metformin) within the last month, diagnosis with androgen-secreting tumors, pregnancy, lactation, change of body weight in the previous one months, cigarette smoking or alcohol consumption, and history of glucose intolerance, liver disease and kidney disease or other hormonal disorders (e.g., hyperprolactinemia, abnormal thyroid stimulating hormone (TSH) levels or Cushing's syndrome).

Measurement of clinical and biochemical indicators

All participants underwent a complete medical history and clinical examination, then a trans-abdominal pelvic ultrasonography was done by one of two experienced radiologists using a 3-5.5 MHz curvilinear probe in the early follicular phase of the menstrual cycle in women with regular menstruating or a random day in those with menstrual irregularity. The severity of hirsutism was evaluated quantitatively in every woman via the Ferriman-Gallwey scoring system [18]. Acne was assessed in four grades, as described elsewhere [19].

In addition, after an overnight fast of 10–12 h, blood samples were collected in the early morning and stored at −80 °C until processing. The serum concentrations of follicle-stimulating hormone (FSH), LH, dehydroepiandrosterone sulfate (DHEAS), total testosterone, TSH, prolactin, C-peptide, and fasting insulin levels were measured by the enzyme-linked immunosorbent assay (ELISA) kits (Monobind Inc. Lake Forest, California, USA). SHBG was measured by ELISA kits (Demeditec, Germany). Free androgen index (FAI) was calculated as 3.47 × total testosterone (ng/mL) / SHBG (nmol/L) [20]. To define hyperandrogenism, the cut-off values of 4.97 [21] and 0.7 ng/mL [22] were used to define high FAI and

high total testosterone in PCOS, respectively. Serum levels of fasting blood sugar (FBS) were determined by an auto-analyzer (Cobas c 311, Roche Diagnostics, Risch-Rotkreuz, Switzerland). Serum hemoglobin A1c (HbA1c) was measured by a high-performance liquid chromatography analyzer (Tosoh, Tokyo, Japan). The homeostasis model assessment-estimated insulin resistance (HOMA-IR) was calculated according to the following formula: fasting insulin (μIu/mL) × FBS (mg/dL) / 405 [23].

Anthropometric measurements

Subjects' height was measured by a wall-mounted stadiometer with an approximation of 0.5 cm. BMI value was calculated as weight divided by the square of height (kg/m^2). Waist circumference was measured in standing position, at the approximate mid-point between the lower margin of the last rib and the top of iliac crest. WHtR was calculated by dividing waist circumference by height [24]. Weight and body composition were determined using BIA (Tanita BC-418 MA, Tanita, Tokyo, Japan). Subjects were instructed to fast for at least 4–5 h, not engage in strenuous exercise for 12 h, and avoid caffeine beverages 24 h prior to the BIA measurements. Participants were asked to stand with bare feet on the scale platform including electrodes, which enable the electrical current up one foot and down the other foot. While holding handgrips in hands, arms were in a relaxed position beside the body. Using the BIA system, the total fat mass (kg), leg fat mass (kg), trunk fat mass (kg), and trunk to leg fat mass (kg) were measured taking into account age, height, weight, and level of physical activity.

Statistical analysis

All statistical analyses were performed using SPSS software version 16.0 (SPSS Inc., Chicago, IL, USA). The Kolmogorov-Smirnov test was applied to determine the normality of data distribution. Quantitative data were presented by median (interquartile range [IQR]). Qualitative data were expressed as frequencies and percentages. Non-normally distributed dependent variables were either square-root or log-transformed before the analyses. Linear regression model was used to analyze the association between hormonal parameters and anthropometric parameters. We established four different models using the following adjustments: Model 1: crude model without adjustment; Model 2: adjusted for age; Model 3: adjusted for age and mensuration status; Model 4: adjusted for age, mensuration status and HOMA-IR. Receiver operating characteristic (ROC) curve analyses were also performed to evaluate the discriminating ability of various anthropometric indices in predicting hyperandrogenism. Youden's index was used to identify the optimal cut-off value, sensitivity and specificity for each indicator. P value < 0.05 was accepted as statistically significant.

Results

One hundred and twenty-nine women were enrolled in this study. The median (IQR) age of participants was 32.00 (23.00–32.00) years. Patients had a median BMI of 26.3 kg/m^2 (23.00-29.70). Irregular menstruation cycles and hair loss were observed in 79.8% and 76.4% of patients, respectively. The median acne score was 2.00 (0–2.00). The median (IQR) hirsutism score was 10.00 (6.00–15.00). The median waist circumference and WHtR of participants were 91.00 (83.00-100.75) and 0.57 (0.52–0.63), respectively. The detailed characteristics of patients including the anthropometric indices, metabolic parameters, and hormonal levels are demonstrated in Table 1.

Association between the anthropometric indices and hormonal parameters

In this analysis, we explored the association between the level of total testosterone, FAI, LH to FSH ratio, DHEAS and SHBG with indicators of obesity including BMI, waist circumference, WHtR, total fat mass, trunk fat mass, leg fat mass, and trunk to leg fat mass ratio. Results from the linear regression modeling are demonstrated in Tables 2 and 3. We found that among PCOS patients, BMI (β = 0.053, $P < 0.001$), waist circumference (β = 0.021, $P = 0.001$), WHtR (β = 3.325, $P = 0.002$), total fat mass (β = 0.021, $P = 0.002$), trunk fat mass (β = 0.038, $P = 0.006$), and leg fat mass (β = 0.045, $P = 0.004$) were positively associated with FAI levels in the fully adjusted model (model 4). Moreover, the analyses showed a significant inverse association between the level of SHBG and BMI (β = −0.017, $P = 0.003$), waist circumference (β = −0.008, $P = 0.002$), WHtR (β = −1.167, $P = 0.004$), total fat mass (β = −0.008, P=0.003), trunk fat mass (β = −0.017, P=0.001), and leg fat mass (β = −0.018, P=0.004) in model 4. In contrast, no association was detected between the total testosterone, DHEAS and LH/FSH levels and the anthropometric indices.

The optimum cut-off points, sensitivity, and specificity derived from ROC analyses in predicting hyperandrogenism are shown in Fig. 1. Trunk to leg fat mass ratio was statistically unable to discriminate hyperandrogenism in PCOS. Remaining anthropometric parameters exhibited acceptable discrimination ability [25], with area under the curve (AUC) values between 0.624 and 0.676. WHtR showed the greatest AUC value (AUC = 0.676, $P = 0.001$) in identifying hyperandrogenism in PCOS women with corresponding sensitivity of 87.30% and

Table 1 Demographic, anthropometric and biochemical characteristics of patients with PCOS

Variable	Total ($n=129$)
Age (years)	32.00 (23.00–32.00)
Irregular menstruation, yes	103 (79.80)
Hair loss, yes[a]	84 (76.40)
Acne score	2.00 (0–2.00)
Hirsutism score	10.00 (6.00–15.00)
BMI (kg/m^2)	26.30 (23.00-29.70)
Total fat mass (kg)	23.95 (17.90-32.17)
Trunk fat mass (kg)	13.10 (9.25–18.35)
Leg fat mass (kg)	9.07 (7.42–11.45)
Trunk to leg fat mass ratio	1.42 (1.12–1.63)
Waist circumference (cm)	91.00 (83.00-100.75)
Height (cm)	160.00 (156.00-163.00)
Waist to height ratio	0.57(0.52–0.63)
Total testosterone (ng/mL)	0.40 (0.30–0.60)
FAI	3.31 (1.83–6.78)
LH (mIU/mL)	9.3 (4.30–16.00)
FSH (mIU/mL)	4.20 (5.70–6.80)
LH/FSH ratio	1.79 (0.85–2.97)
SHBG (nmol/L)	41.00 (24.60–82.00)
DHEAS (ng/dL)	150.90 (96.6-200.30)
FBS (mg/dL)	84.00 (80.50–92.00)
Fasting insulin (uIU/mL)	12.10 (8.95–15.80)
C-peptide (ng/mL)	1.00 (0.70–1.55)
HOMA-IR	2.56 (1.78–3.35)
HbA1c (%)	5.30 (5.10–5.50)
Prolactin (ng/mL)	13.20 (10.70-19.25)
TSH (mIU/mL)	2.1 (1.50-3.00)

Each value was represented as median (IQR), except for irregular menstruation (number [%]) and hair loss (number [%])

BMI body mass index, *FAI* free androgen index, *LH* luteinizing hormone, *FSH* follicle-stimulating hormone, *SHBG* sex hormone-binding globulin, *DHEAS* dehydroepiandrosterone sulfate, *FBS* fasting blood sugar, *HOMA-IR* homeostasis model assessment of insulin resistance, *HbA1c*: hemoglobin A1C, *TSH* thyroid stimulating hormone

[a] There was missing data

specificity of 39.70%. The optimal cut-off values to identify hyperandrogenism in PCOS were ˃30.05 kg/m^2 for BMI, ˃87.50 cm for waist circumference, ˃0.52 for WHtR, ˃25.15 kg for total fat mass, ˃12.65 kg for trunk fat mass, and ˃7.10 kg for leg fat mass.

Discussion

In the current study, we evaluated the relationship between representative body composition indices and hormonal parameters and eventually flagged WHtR as a potent indicator of hyperandrogenism. Based on our results, body composition indices are not related to hormonal disturbance of DHEAS, total testosterone levels, and LH/FSH ratio. In agreement with our results, several other studies did not find a significant relationship between BMI and LH/FSH ratio [26–30]. Conversely, another study revealed a negative correlation between BMI and FSH/LH ratio, and individuals with higher LH/FSH ratio tended to have smaller WHR and lower BMI [31]. Yanira et al. also reported an inverse correlation between LH/FSH and BMI in PCOS [32]. Increased levels of LH and LH/FSH ratio are expected in PCOS. This finding may be as a result of abnormal amplitude and frequency of GnRH release from the hypothalamus and subsequent pituitary LH release and androgen stimulation [33]. Based on conflicting findings from various studies, it is still unclear whether observed sex hormone disorders in PCOS are independent of obesity.

In line with our results, previous studies found that despite free testosterone, total testosterone is not related to BMI and waist circumference [34–36]. Antonio et al. reported that increasing levels of free testosterone and decreasing levels of SHBG were associated with higher BMI in subfertile women with oligomenorrhea and suspected PCOS. Moreover, they did not find significant associations between androstenediones or total testosterone levels and BMI, insulin, or insulin resistance [34]. Circulating testosterone is mainly bound to binding proteins like SHBG, cortisol binding protein, and albumin. These binding proteins are required for tissue delivery, transport, metabolism and bioactivity of testosterone [37]. SHBG limits the diffusion of sex steroids into target tissue and modulates the bioactivity of androgens. In women, decreased SHBG levels are expected in obesity, and decreased SHBG level is accompanied by increased free testosterone and androgen excess [38].

Increased circulating levels of DHEAS are reported in about 20–40% of women with PCOS [39]. Here, we observed a negative association between DHEAS levels and anthropometric indices, which was attenuated after adjustment for age. In the same way, Ivandić et al. found that DHEAS did not significantly differ among PCOS women with abdominal obesity, lower-body obesity, or controls [40]. On the other hand, some other studies reported a significant association between DHEAS and anthropometric indices [39, 41]. DHEAS levels are strictly related to age, and serum DHEAS levels decrease by about 40% in healthy, PCOS, and hyperandrogenic women, when moving from their twenties to thirties [39].

In future studies of PCOS women, choosing a restricted age range or adjustment for age may lead to more consistent results regarding the relationship between DHEAS levels and other variables like anthropometric measures.

We also found that BMI, waist circumference, WHtR, total fat mass, leg fat mass, and trunk fat mass were

Table 2 Association between anthropometric indices and hormonal parameters in patients with PCOS

Variable	Total Testosterone		FAI		LH/FSH		SHBG		DHEAS	
	β (SE)	*P* value	β (SE)	*P* value	β (SE)	*P* value	β (SE)	*P* value	β (SE)	*P* value
BMI (kg/m^2)										
Model 1 (unadjusted)	0.003(0.002)	0.190	0.061(0.012)	**< 0.001**	-0.007(0.006)	0.230	-0.021(0.005)	**< 0.001**	-0.109(0.050)	**0.031**
Model 2	0.004(0.002)	0.113	0.064(0.013)	**< 0.001**	-0.006(0.006)	0.330	-0.021(0.005)	**< 0.001**	-0.076(0.051)	0.135
Model 3	0.004(0.002)	0.122	0.062(0.013)	**< 0.001**	-0.007(0.006)	0.264	-0.020(0.005)	**< 0.001**	-0.080(0.051)	0.120
Model 4	0.003(0.003)	0.244	0.053(0.015)	**< 0.001**	-0.011(0.007)	0.121	-0.017(0.006)	**0.003**	-0.070(0.058)	0.233
Waist circumferences (cm)										
Model 1 (unadjusted)	0.001(0.001)	0.390	0.025(0.006)	**< 0.001**	-0.003(0.002)	0.226	-0.009(0.002)	**< 0.001**	-0.050(0.022)	0.027
Model 2	0.001(0.001)	0.233	0.027(0.006)	**< 0.001**	-0.003(0.003)	0.317	-0.009(0.002)	**< 0.001**	-0.034(0.022)	0.131
Model 3	0.001(0.001)	0.228	0.026(0.006)	**< 0.001**	-0.003(0.003)	0.238	-0.009(0.002)	**< 0.001**	-0.036(0.023)	0.119
Model 4	0.001(0.001)	0.479	0.021(0.007)	**0.001**	-0.004(0.003)	0.141	-0.008(0.003)	**0.002**	-0.032(0.026)	0.222
Waist to height ratio										
Model 1 (unadjusted)	0.147(0.163)	0.369	3.783(0.876)	**< 0.001**	-0.436(0.388)	0.264	-1.380(0.334)	**< 0.001**	-8.147(3.452)	0.020
Model 2	0.223(0.170)	0.192	4.157(0.918)	**< 0.001**	-0.359(0.409)	0.382	-1.420(0.352)	**< 0.001**	-5.378(3.553)	0.133
Model 3	0.229(0.173)	0.187	4.032(0.927)	**< 0.001**	-0.439(0.411)	0.288	-1.328(0.352)	**< 0.001**	-5.635(3.597)	0.120
Model 4	0.165(0.195)	0.398	3.325(1.038)	**0.002**	-0.618(0.464)	0.185	-1.167(0.396)	**0.004**	-4.990(4.064)	0.222

Model 1: unadjusted; Model 2 adjusted for age; Model 3 adjusted for age and mensuration status; Model 4 adjusted for age, mensuration status and HOMA-IR

Dependent variables that did not follow a normal distribution were transformed using the log function for SHBG and LH/FSH, and the square root function for FAI, DHEAS, and total testosterone

BMI body mass index, *FAI* free androgen index, *LH* luteinizing hormone, *FSH* follicle-stimulating hormone, *SHBG* sex hormone-binding globulin, *DHEAS* dehydroepiandrosterone sulfate, *HOMA-IR* homeostasis model assessment of insulin resistance, *SE* standard error of mean

positively related to FAI. Moreover, higher BMI, WHtR, waist circumference, total fat mass, trunk fat mass, and leg fat mass were associated with lower concentrations of SHBG.

Obesity can significantly affect the serum concentration of SHBG [42]. BMI is found to be inversely correlated with SHBG concentration [43]. Recent meta-analyses showed that, compared to normal-weight women with PCOS, obese women with PCOS had significantly lower SHBG and higher FAI [44, 45]. In addition to BMI, waist circumference was also shown to be associated with hyperandrogenemia in PCOS [45]. Multiple studies confirmed the critical association of total fat mass, visceral adiposity, and central obesity with the level of androgens among PCOS patients [46–48].

Androgens have been found to cause abdominal accumulation of fat [49] and may induce dysfunction of adipose tissue, resulting in insulin resistance [50]. Previous studies have showed that the expression profile of adipose tissue is altered in women with PCOS, leading to an imbalanced release of adipokines by adipocytes, which negatively influences on the reproductive and endocrine systems. Dysregulated secretion of adipocytes, in addition to heightened inflammatory responses and insulin resistance, may contribute to the development of PCOS and its related clinical manifestations [51, 52]. In women with PCOS, antilipolytic genes and lipogenic enzymes are overexpressed compared with non hyperandrogenic women [53]. On the other hand, obesity also aggravates hyperandrogenism [50]. Increased levels of free fatty acid, as the main manifestation of obesity, decrease glucose uptake in intramyocellular lipids and cause insulin resistance [54]. Moreover, free fatty acids can activate serine/threonine kinases, reduce tyrosine phosphorylation of insulin receptor substrate 1 (IRS-1), and ultimately enhance insulin resistance [55]. Insulin resistance and obesity synergistically stimulate synthesis of androgens in adrenal glands and ovaries, thus creating a cycle that further increases abdominal obesity [50, 56]. Therefore, one of the factors that contribute to hyperandrogenism in PCOS is insulin resistance [4]. However, it is unclear whether adiposity and obesity contribute to the development of PCOS, independently from their effect on insulin sensitivity [57]. Here, we found that the association between anthropometric indices and androgen levels persisted after adjustment for HOMA-IR, suggesting that the associations could be independent of insulin resistance. González et al. reported that inflammation may directly contribute to ovarian dysfunction and hyperandrogenism, independently from insulin sensitivity [58]. Other mechanisms including increased activity of the hypothalamic-pituitary-adrenal axis

Table 3 Association between bioelectrical impedance indices and hormonal parameters in patients with PCOS

Variable	Total Testosterone		FAI		LH/FSH		SHBG		DHEAS	
	β (SE)	*P* value	β (SE)	*P* value	β (SE)	*P* value	β (SE)	*P* value	β (SE)	*P* value
Total fat mass (kg)										
Model 1 (unadjusted)	0.001(0.001)	0.539	0.026(0.006)	**<0.001**	-0.003(0.003)	0.204	-0.009(0.002)	**<0.001**	-0.049(0.023)	**0.033**
Model 2	0.001(0.001)	0.402	0.027(0.006)	**<0.001**	-0.003(0.003)	0.280	-0.009(0.002)	**<0.001**	-0.036(0.022)	0.108
Model 3	0.001(0.001)	0.421	0.026(0.006)	**<0.001**	-0.003(0.003)	0.212	-0.009(0.002)	**<0.001**	-0.039(0.023)	0.093
Model 4	0.000(0.001)	0.773	0.021(0.006)	**0.002**	-0.005(0.003)	0.083	-0.008(0.003)	**0.003**	-0.035(0.026)	0.183
Trunk fat mass (kg)										
Model 1 (unadjusted)	0.000(0.002)	0.952	0.048(0.012)	**<0.001**	-0.007(0.005)	0.184	-0.020(0.005)	**<0.001**	-0.120(0.047)	**0.011**
Model 2	0.000(0.002)	0.837	0.051(0.012)	**<0.001**	-0.006(0.006)	0.271	-0.021(0.005)	**<0.001**	-0.089(0.047)	0.059
Model 3	0.000(0.002)	0.875	0.049(0.013)	**<0.001**	-0.008(0.006)	0.184	-0.020(0.005)	**<0.001**	-0.097(0.048)	0.046
Model 4	-0.001(0.003)	0.760	0.038(0.014)	**0.006**	-0.010(0.006)	0.096	-0.017(0.005)	**0.001**	-0.091(0.052)	0.085
Leg fat mass (kg)										
Model 1 (unadjusted)	0.001(0.003)	0.794	0.057(0.015)	**<0.001**	-0.009(0.007)	0.181	-0.022(0.006)	**<0.001**	-0.079(0.058)	0.172
Model 2	0.001(0.003)	0.688	0.058(0.015)	**<0.001**	-0.008(0.007)	0.226	-0.022(0.006)	**<0.001**	-0.057(0.056)	0.312
Model 3	0.001(0.003)	0.706	0.057(0.015)	**<0.001**	-0.009(0.007)	0.189	-0.021(0.006)	**<0.001**	-0.060(0.057)	0.296
Model 4	0.000(0.003)	0.985	0.045(0.015)	**0.004**	-0.011(0.007)	0.118	-0.018(0.006)	**0.004**	-0.045(0.060)	0.454
Trunk to leg fat mass ratio										
Model 1 (unadjusted)	-0.024(0.031)	0.437	0.140(0.176)	0.428	0.005(0.076)	0.953	-0.117(0.067)	0.082	-0.765(0.660)	0.248
Model 2	-0.020(0.031)	0.516	0.142(0.178)	0.426	0.015(0.076)	0.846	-0.112(0.067)	0.098	-0.518(0.643)	0.421
Model 3	-0.023(0.032)	0.476	0.098(0.181)	0.589	0.000(0.078)	0.998	-0.091(0.068)	0.186	-0.588(0.658)	0.374
Model 4	-0.026(0.032)	0.418	0.050(0.175)	0.775	-0.004(0.078)	0.963	-0.077(0.067)	0.255	-0.534(0.661)	0.420

Model 1: unadjusted; Model 2 adjusted for age; Model 3 adjusted for age and mensuration status; Model 4 adjusted for age, mensuration status and HOMA-IR

Dependent variables that did not follow a normal distribution were transformed using the log function for SHBG and LH/FSH, and the square root function for FAI, DHEAS, and total testosterone

FAI free androgen index, *LH* luteinizing hormone, *FSH* follicle-stimulating hormone, *SHBG* sex hormone-binding globulin, *DHEAS* dehydroepiandrosterone sulfate, *HOMA-IR* homeostasis model assessment of insulin resistance, *SE* standard error of mean

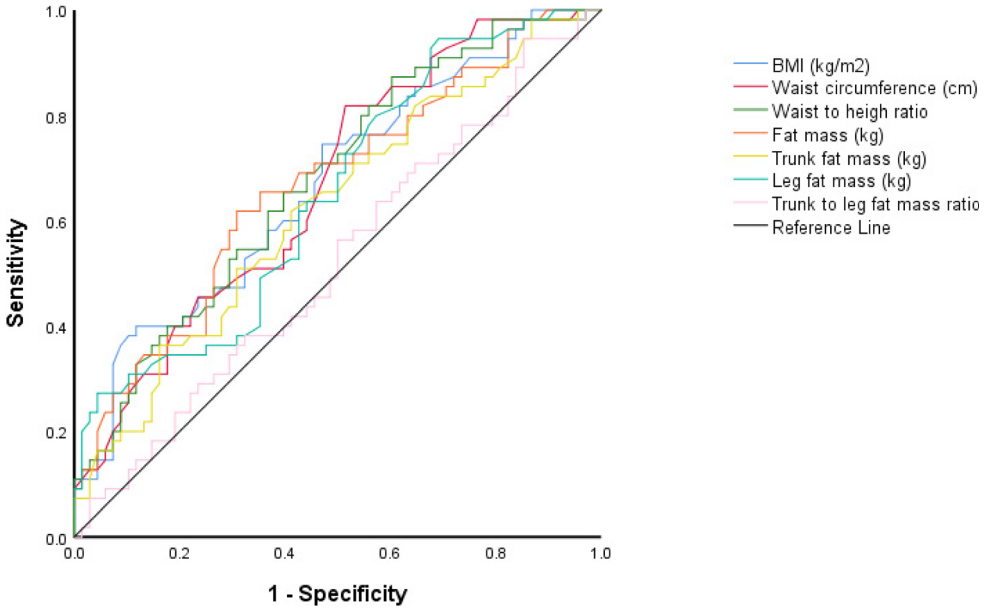
and opioid system, lower rate of SHBG synthesis, and higher rate of estrogen production may be additional explanations by which obesity is linked to the development of hyperandrogenism in PCOS [4]. Nevertheless, PCOS women with normal BMI may present clinical and/or biochemical evidence of hyperandrogenism [42]. This phenomenon can be explained by androgen receptor gene polymorphism as well as greater population of small subcutaneous abdominal adipocytes, which may limit subcutaneous adipose storage and promote the accumulation of more metabolically active visceral fat [59, 60].

Further research targeting the link between obesity and hyperandrogenism in PCOS is warranted.

Most previous studies used BMI as a measure of overall adiposity. Waist circumference is also a simple measurement to characterize central adiposity and offers additive and independent information to BMI for predicting health outcomes [61]. Increased waist circumference is associated with all-cause and cardiovascular mortality, after adjustment for BMI. There is a consensus on the inclusion of this measurement in routine clinical practice in order to counsel patients on obesity-related health problems [62]. In the present study, WHtR was strongly related to hyperandrogenism in PCOS women. WHtR included both height and waist circumference and appears to be a more precise indicator to specify metabolic risk and central adiposity than the commonly used BMI, or waist circumference [63–65].

Prior research in other populations confirmed the benefits of WHtR use over other anthropometric indices in the evaluation of metabolic risk in both healthy and PCOS women [63, 66, 67]. Here, we further confirmed its superior applicability in determining hyperandrogenism in PCOS women.

Our study provided a perspective on the association between the alterations in body composition and hormonal imbalances in PCOS. We select a homogeneous sample of patients with respect to the diagnosis, past medical history, and the taken medications, which can be considered as the strength of our study. However, due to some limitations, the findings should be interpreted with caution. Firstly, the cross-sectional design,



Parameter	AUC	95% CI	SE	P value	Optimum cut-off	Sensitivity (%)	Specificity (%)
BMI (kg/m^2)	0.669	0.573-0.764	0.049	0.001	30.05	40.00	88.20
Waist circumference (cm)	0.667	0.573-0.762	0.048	0.001	87.50	81.80	48.50
Waist to height ratio	0.676	0.582-0.770	0.048	0.001	0.52	87.30	39.70
Total fat mass (kg)	0.668	0.572-0.764	0.049	0.001	25.15	61.80	69.10
Trunk fat mass (kg)	0.624	0.525-0.723	0.050	0.018	12.65	61.80	58.80
Leg fat mass (kg)	0.649	0.553-0.746	0.049	0.004	7.10	94.50	30.90
Trunk to leg fat mass ratio	0.523	0.420-0.626	0.052	0.658	0.96	94.50	14.70

AUC: area under the curve, CI: confidence interval, SE: standard error of mean, BMI: body mass index

Fig. 1 ROC curve analysis for comparison between different anthropometric parameters in determining hyperandrogenism (FAI ≥ 4.97 or total testosterone ≥ 0.7 ng/mL) in PCOS

makes it difficult to find a causal relationship between body composition indices and hormonal parameters in women with PCOS. Secondly, the sample size was limited, which can affect the generalizability of the findings. Therefore, larger studies with prospective designs should be conducted to confirm our findings. Thirdly, while the BIA system is a common and validated method for estimating body composition, it is not as accurate as dual x-ray absorptiometry (DEXA) and DEXA is still the gold standard for measuring the body composition parameters. Therefore, future investigations might examine the connection between hormonal changes and body composition indices by using the DEXA method.

Conclusions

In the present study, we found that indices of adiposity were significantly associated with FAI and SHBG, while body composition indices were not related to hormonal disturbance of total testosterone levels and LH/FSH ratio. There was a negative association between DHEAS and anthropometric indices, which was attenuated after adjustment for age. This highlighted the importance of considering age while investigating DHEAS in PCOS women. In addition, we demonstrated that localized and total fat mass distribution measured by BIA had no superiority to simple measures of body composition. Accordingly, BMI, WHtR, and waist circumference can be used as indicators of hyperandrogesnim in PCOS women. Among these indices and based on regression analysis, the WHtR appeared to be a potent indicator of hyperandrogenism. Moreover, WHtR was more sensitive but less specific than BMI and waist circumference to identify hyperandrogenism in PCOS women.

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Authors' contributions
Authors' contributions: A.M. Study conception and design, Acquisition of data, Analysis and interpretation of data, Drafting of manuscript, Critical revision, M.N. Drafting of manuscript, M.S.H. Critical revision, Z.H. Acquisition of data, M.R.M.T. Critical revision, M.M. Drafting of manuscript, Critical revision, S.M.S.J. Study conception and design, Analysis and interpretation of data, Drafting of manuscript, Critical revision. All authors have read the manuscript and approved the manuscript.

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Availability of data and materials
The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate
The study was performed in accordance with the Helsinki Declaration and informed consents were obtained from all participants and the ethics committee of the Tehran University of Medical Sciences approved the RCTs. The current study was also approved by the ethics committee of Tehran University of Medical Sciences (IR.TUMS.MEDICINE.REC.1400.1186).

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

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