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Lipid Profile In Relation To Anthropometric Indices and Insulin Resistance in Overweight Women with Polycystic Ovary Syndrome

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ABSTRACT

Background: The present study was aimed to investigate lipid profile in relation to anthropometric indices and insulin resistance in overweight or obese women with polycystic ovary syndrome (PCOS).
Methods: In this cross-sectional study, lipid profile and anthropometric indices including body mass index (BMI), waist and hip circumference, waist to hip ratio (WHR), and waist to height ratio (WHtR) were evaluated in 63 overweight or obese PCOS patients subdivided into insulin-resistant (IR) and non-insulin-resistant (NIR) groups. IR was defined as homeostasis model of insulin resistance (HOMA-IR) ≥3.8.
Results: Fasting insulin concentration and HOMA-IR were higher (P<0.001) and high-density lipoprotein cholesterol (P=0.012) was lower in IR group. All of the anthropometric measures other than WHR and BMI showed significant correlations with several lipid parameters. Amongst, WHtR showed the strongest correlation with total cholesterol (TC) (r=0.37; P=0.004) and low-density lipoprotein cholesterol (LDL-C) (r=0.33; P=0.011) in the whole PCOS patients.
Conclusion: Anthropometric characteristics (especially BMI and hip circumference) are more important parameters correlated to lipid profile than IR in overweight or obesePCOS patients, confirming the importance of early treatment of obesity to prevent dyslipidemia in the future.

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Introduction

Polycystic ovary syndrome (PCOS) is a heterogeneous gynecological disorder that includes oligo/anovulation, clinical or biochemical hyperandrogenism and/or polycystic ovaries. It affects 5% to 10% of women at reproductive age[1]. PCOS is associated with a wide range of endocrine and metabolic abnormalities including obesity, insulin resistance, and metabolic syndrome (MetS)[2].

Insulin resistance (IR) is considered as an important factor in the pathogenesis of PCOS which affects the long-term health[3].

IR plays a significant role in the development of dyslipidemia. About 70% of PCOS women have at least one abnormal lipid constituent[4]. Obese women with PCOS are more prone to dyslipidemia, particularly elevated triglycerides (TG) and decreased high-density lipoprotein cholesterol (HDL-C)[5]. However, much of the atherogenic lipoprotein pattern in PCOS has been related to obesity[6].Cibula et al. showed the effect of obesity on lipid profile and hyperlipoproteinemia in PCOS women[7]. Obesity, rather than the pattern of menstrual cycle determines lipid profile and insulinemia in aging PCOS women[8]. In addition, regional distribution of body fat deposit plays a key role in plasma lipids and cardiovascular risk[9]. Recently, it was reported that an abnormal postprandial lipid pattern is a trait of abdominal obesity even without fasting hypertriglyceridemia[10]. Therefore, obesity likely plays a significant role in the pathogenesis of the syndrome[11].

About half of PCOS patients have obesity[12], especially central obesity that worsens its phenotype[13]. Women with PCOS have a similar amount of total and trunk fat, but a higher quantity of central abdominal fat compared with weight-matched healthy women[14]. Indeed, central fat excess may be associated with insulin resistance and low-grade chronic inflammation[14] and with metabolic dysfunction in PCOS women[15]. In addition, excess intra-abdominal fat is associated with greater risk of obesity-related morbidity than is overall adiposity[16]. Thus, measurements of waist circumference and waist to hip ratio (WHR) have been suggested as alternatives to body mass index (BMI). Several studies on adults have reported a stronger positive association between cardiovascular risk factors such as hypertension, lipid and glucose concentrations with abdominal adiposity (measured by waist circumference (WC) or WHR) than with overall adiposity (as measured by BMI) [17-18], although BMI has also been reported as being one of the most important risk factors for type 2 diabetes[19].

Women with PCOS have a 7.4-fold relative risk for myocardial infarction because of the prevalence of dyslipidemia, glucose intolerance, insulin resistance, hypertension[20], and central obesity[21].

Concerning the well-proven relationship between insulinresistance and obesity[11], the relative contribution of these twofactors to lipid profile in PCOS seems to be pivotal to better understand this heterogeneous syndrome.

The present study was aimed to investigate the influence of anthropometric indices and insulin resistance on lipid profile in overweight or obese PCOS patients subdivided into insulin-resistant (IR) and noninsulin-resistant (NIR) groups.

Materials and Methods

Patient population

This cross-sectional study was carried out from January 2011 to August 2012 in Gynecology and Endocrinology Outpatient Clinics of Tabriz University of Medical Sciences, Iran. The study included 63 overweight or obese patients diagnosed as PCOS. The research protocol was approved by the Ethics Committee of the University (ethical code=906). Written informed consent was obtained from all the participants.

The diagnosis of PCOS was confirmed according to the revised Rotterdam criteria[22], in which the presence of any two out of the three following criteria were required: (1) Oligo- and/or anovulation (<8 menstrual periods per year) [23], (2) clinical and/or biochemical signs of hyperandrogenism, including hirsutism (Ferriman-Gallwey score> 8) and (3) polycystic ovaries on sonography (i.e., at least 1 ovary containing 12 or more peripheral follicles measuring 2–9 mm in diameter and/or ovarian volume of at least 10 mL)[24] and exclusion of other etiologies (congenital adrenal hyperplasia, androgen-secreting tumors, and Cushing's syndrome). Vaginal or transabdominal pelvic sonography, as appropriate, was performed only on patients who did not fulfill the diagnostic criteria. The inclusion criteria were any PCOS pa-

tient diagnosed by the above mentioned criteria with age range between 17 to 37 years old, BMI range between 25 to 39 kg/m^2, and taking no medicines at least 2 months before the study. Any patient with a disease affecting metabolic parameters including hypoglycemia, Diabetes Mellitus, Cushing's syndrome, androgen secreting tumors or congenital adrenal hyperplasia, hyperparathyroidism, hyperprolactinemia, thyroid disorders, hypertension and etc. were excluded from the study. Patients taking drugs or any dietary supplements within the two months before the study were also excluded. Indeed, history of being on a special diet such as weight loss diet during the 6 months before the onset of the study was regarded as excluded criteria.

The obtained data for medical history included questions about age, intake of drugs, smoking and alcohol consumption. Dietary intake was measured using a 3-day food record. Blood pressure (BP) was measured after a 10-min rest period using digital automatic blood pressure monitor, Omron, Japan. Systolic BP above 140 mmHg and diastolic BP above 90 mmHg were regarded as hypertension[25]. Subjects were weighed to within 100 g in light clothing without shoes. Height was measured to the nearest 0.1 cm using a wall-mounted stadiometer. BMI was calculated as weight (kg) divided by the square of height (m). For further analysis, the patients were also subdivided into 2 subgroups of BMI: the overweight group (BMI range, 25-29.9 kg/m^2) or the obese group (BMI≥30 kg/ m^2)[26]. Lipid profile was also compared between these two subgroups. Waist circumference (WC) (cm) was measured at a level midway between the lower rib margin and iliac crest[27] and hip circumference (HC) at the widest point between the iliac crest and buttock[21]. The circumferences were measured in a standing position and to the nearest 1 mm. The waist circumference was divided by the hip circumference as well as by height to give waist to hip ratio (WHR) and waist to height (WHtR) ratios, respectively.

The standard oral glucose tolerance test (OGTT) was performed two hours after administration of 75 gram glucose for all the patients[28]. The homeostasis model of insulin resistance (HOMA-IR) was calculated as [fasting plasma glucose concentration (mmol/L)×fa-sting serum insulin concentration (μU/mL)/-22.5][29].IR was defined as HOMA-IR value≥3.8 (30). Impaired glucose tolerance (IGT) was defined as an elevated fasting glucose ($110\ mg/dL \leq G_0 \leq 125\ mg/dL$) or an elevated 2-hour glucose (140mg/dL $G_{120-} \leq 199\ mg/dL$) [30]. Diabetes was defined as fasting plasma glucose above 126 mg/dl[31]. Hyperandrogenemia was considered as either serum testosterone level above 2.08 nmol/l and/or serum dehydroepiandrosteronesulphate (DHEAS) level above 7800 nmol/l[32]. Increased serum 17-OHP was defined in levels above 2 ng/ml to exclude congenital adrenal hyperplasia[33].

Laboratory measurements

After a 12-hour overnight fast, 10 ml blood was obtained in the follicular phase of the menstrual cycle (i.e. serum progesterone level lower than 2.5 ng/ml) [34]. In terms of high progesterone level, the whole measurements were repeated after one or two weeks. The whole blood samples were centrifuged at 3000 rpm for 5 min. The samples were analyzed either immediately or during the first week after conservation at -20 °C.

Serum glucose, total cholesterol (TC), TG, and HDL were analyzed using the standard enzymatic method (Pars Azmoon kit, Pars Azmoon Inc., Tehran, Iran) (glucose: CV inter-assay=0.90%, TC: CV inter-assay=1.1%, TG: CV inter-assay=1.6%, and HDL: CV inter-assay=1.8%). LDL-C was calculated with the Friedewald(35) Formula: LDL= [TC]-[HDL]-[TG]/5.0 (mg/dL). DHEAS (DRG Instruments GmbH, Germany, CV inter-assay=4.8%), and plasma insulin levels (Liaison®; DiaSorin S.P.A., Saluggia, Vercelli, Italy, CV inter-assay=3.9%) were measured using chemiluminescence methods.

Statistical analysis

The Kolmogorov-Smirnov test was used to check for the normality of the data; all data were normally distributed. Data were

expressed as mean±SD for continuous variables. Independent samples t-test was used to compare continuous variables. Correlations between lipid profile and anthropometric indices were examined using Pearson's correlation coefficients. Partial correlations were performed to determine these associations after controlling for age and serum DHEAS level as confounders. $P<0.05$ was set as significant.

Results

Thirty-six percent of PCOS patients with overweight or obesity had HOMA-IR≥3.8 and formed insulin-resistant group. Furthermore, only 5 out of 63 PCOS patients had glucose intolerance (BS2h=142-215 mg/dl); however, none were diabetic. None of the PCOS patients were taking drugs at least 2 months before the study. Further, nobody smoked or consumed alcohol before or during the study. In addition, none of the patients were hypertensive. The mean age and BMI of the patients were 26.9±5.7 years and 31.4±3.8 kg/m^2, respectively. General characteristics and anthropometric indices of the patients in the IR and the NIR groups are shown in Table 1.The IR and NIR groups did not differ in terms of age and systolic or diastolic blood pressure (Table1). There was no significant difference in energy intake, using a 3-day food record, between the two groups (2382 in the IR *vs.* 2355 kcal/day in the NIR group). The mean BMI was similar between the two groups (32.27±3.46in the IR *vs.* 30.91±3.88 kg/m^2 in the NIR group, Table 1; $P=0.175$).

More than half of the patients were similarly hyperandrogenic in the IR and NIR groups ($P=0.55$). Around 80% of the IR and NIR groups were hirsute. The two groups had similar oligo/anovulation pattern (95% in both groups).

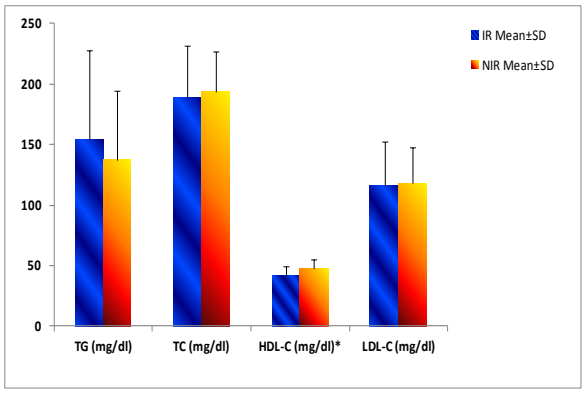

Fig. 1: Mean (SD) of Lipid profile between IR- and NIR- PCOS patients (* $P<0.05$)
TC=Total cholesterol; HDL-C=High-density lipoprotein cholesterol; LDL-C=Low-density lipoprotein cholesterol

Obesity was significantly more prevalent in the IR compared to the NIR group (77% *vs.* 50%, $P=0.038$). Waist circumference was non-significantly higher in the IR group compared with the NIR group ($P=0.072$). Fasting insulin concentration and HOMA-IR were significantly higher ($P<0.001$) in the IR compared with the NIR group (Table 1).

Table 1: General characteristics and anthropometric indices between IR and NIR PCOS women

Variables	IR group (n=23) Mean±SD	NIR group (n=40) Mean±SD	*P-value*
Age (yr)	26.96±6.58	26.80±5.29	0.918
Blood pressure (mmHg)			
Systolic	113.17±7.73	111.12±9.34	0.443
Diastolic	76.35±9.70	72.50±9.43	0.184
Energy (kcal/day)	2382.17±530	2355.91±655	0.630
Fasting insulin (µU/mL)	23.19±7.44	12.72±6.032	<0.001
HOMAIR	5.18±1.53	2.60±0.76	<0.001
BMI (kg/m^2)	32.27±3.46	30.91±3.88	0.175
WC (cm)	96.20±7.67	93.19±8.88	0.205
HC (cm)	108.35±6.70	104.34±9.46	0.067
WHR	0.88±0.03	0.89±0.04	0.577
WHtR	0.612±0.054	0.589±0.062	0.184

*Independent samples *t*-test, IR= insulin-resistant; NIR= noninsulin-resistant; HOMA-IR= homeostasis model of insulin resistance; BMI= body mass index; WC=waist circumference; HC= hip circumference; WHR=waist to hip ratio; waist to height ratio

Variables	All patients (n=63)	IR group (n=23)	NIR group (n=40)	*P*- value
TG (mg/dl)				
≥150	25 (39.7)	10 (43.5)	15 (37.5)	0.643
<150	38 (60.3)	13 (56.5)	25 (62.5)	
TC (mg/dl)				
≥200	24 (38.1)	10 (43.5)	14 (35)	0.508
<200	39 (61.9)	13 (56.5)	26 (65)	
HDL-C (mg/dl)				
<50	45 (73)	19 (82.6)	26 (65)	0.139
≥50	18 (27)	4 (17.4)	14 (35)	
LDL-C (mg/dl)				
≥100	45 (72.6)	16 (69.6)	29 (74.4)	0.685
<100	18 (27.4)	8 (30.4)	10 (25.6)	

IR= insulin-resistant; NIR= noninsulin-resistant; TG= triglycerides; TC=Total cholesterol; HDL-C=High-density lipoprotein cholesterol; LDL-C=Low-density lipoprotein cholesterol

The mean of lipid profile is presented in Figure 1. Overall, the mean of TG was higher and the mean of HDL-C was lower in the IR than the NIR group. However, only the mean of HDL-C was statistically significant (41.78±7.54 mg/dl in the IR *vs.* 47.25±8.38 mg/dl in the NIR group, Figure 1; *P*=0.012). Frequency of lipid abnormalities in the whole PCOS patients and also between the IR and NIR groups is presented in Table 2.

For further analysis, lipid profile, fasting insulin, and HOMA-IR were compared between the two subgroups of overweight and obese PCOS patients. Although TG, TC, and LDL-C were higher and HDL-C was lower in the IR than the NIR group (Fig. 1), no significant difference was observed in lipid profile between these two subgroups of the patients (data not shown). However, fasting insulin (18.42±9.61 *vs.* 13.43±4.42; *P*=0.008) and HOMA-IR (3.86±1.92 μU/mL *vs.* 3.04±1.07 μU/mL; *P*=0.036) were significantly higher in obese PCOS patients than overweight PCOS women. For the whole PCOS patients, BMI showed a significant correlation with TC only after adjustment for age and DHEAS level as confounders. Waist circumference significantly correlated with TC (r=0.32, *P*=0.015) and LDL-C (r=0.28; *P*=0.030); however, it became non-significant after controlling for the confounders. Hip circumference was significantly associated with TG (r=0.26; *P*=0.044). It was also significantly correlated with TC (r=0.27; *P*=0.036) and LDL-C (r=0.24; *P*=0.049) (Fig. 2). Nevertheless, only the association of hip circumference with TG remained significant after adjustment (r=0.31; *P*=0.021). In addition, WHtR correlated significantly with TC (r=0.37; *P*=0.004) and LDL-C (r=0.33; *P*=0.011) (Fig. 2). The results of partial correlation also showed a significant association of WHtR with TC (r=0.33; *P*=0.016) as well as with LDL-C (r=0.30; *P*=0.034).

We also tried to find such correlations in subgroups of PCOS population (i.e. the IR and the NIR groups) (Table 3 and 4). TC as well as LDL-C showed significant correlations with all of the anthropometric indices except for WHR in the NIR group (Table3). After controlling for the effects of age and DHEAS, only the associations of BMI and hip circumference with TC and LDL-C remained significant in the NIR group (*P*<0.05) (Table4).

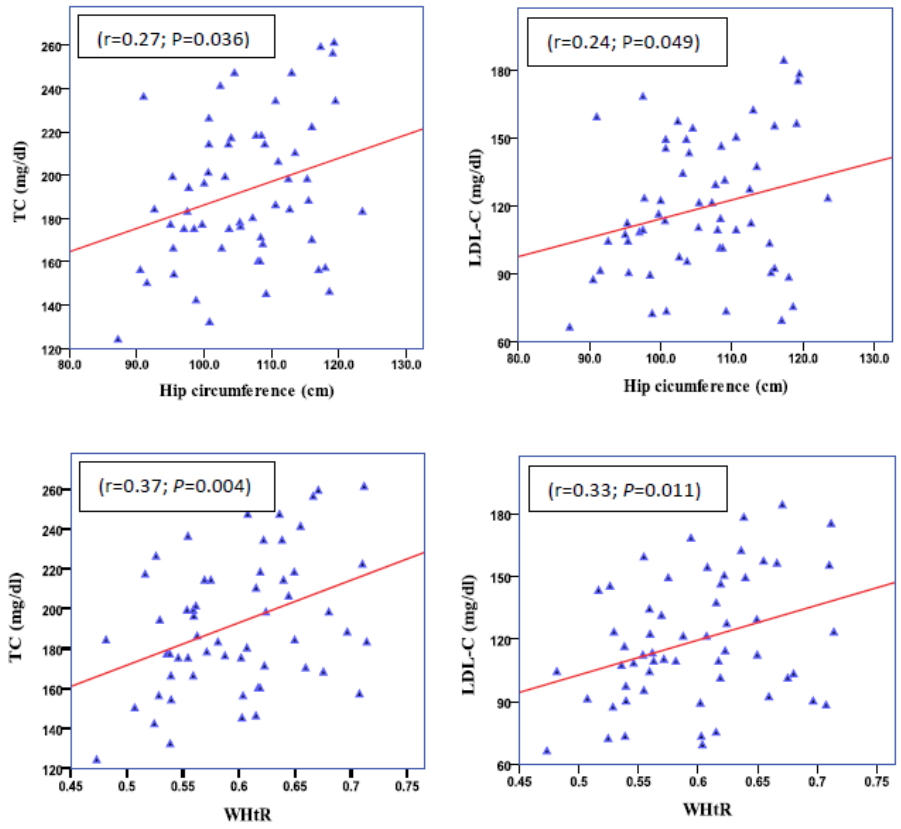

Fig. 2: Correlation coefficients of hip circumference and WHtR with TC and LDL-C in the whole PCOS patients

Table 3: Pearson correlation coefficients for the associations between lipid profile and anthropometric indices in IR and NIR PCOS women

Variable	IR group (n=23)				NIR group (n=40)			
	TG	TC	HDL-C	LDL-C	TG	TC	HDL-C	LDL-C
BMI (kg/m²)	0.09	-0.03	0.05	-0.09	0.12	0.38*	0.01	0.40*
WC (cm)	0.38	0.12	-0.22	0.01	0.07	0.42**	0.09	0.42*
HC (cm)	0.40	-0.09	-0.26	-0.23	0.15	0.43**	-0.02	0.43**
WHR	0.14	0.35	-0.02	0.36	-0.12	0.03	0.21	0.03
WHtR	0.23	0.24	0.02	0.17	0.15	0.44**	0.11	0.41*

* *P*-value<0.05/** *P*-value<0.01

Table 4: Partial correlation coefficients for the association between lipid profile and anthropometric indices in IR and NIR PCOS women (controlling for the effects of age and DHEAS)

Variable	IR group (n=23)				NIR group (n=40)			
	TG	TC	HDL-C	LDL-C	TG	TC	HDL-C	LDL-C
BMI (kg/m²)	0.03	-0.02	0.08	-0.05	0.30	0.39*	-0.01	0.33*
WC (cm)	0.38	0.12	-0.32	0.04	0.09	0.26	0.04	0.25
HC (cm)	0.39	-0.13	-0.34	-0.26	0.22	0.39*	-0.10	0.39*
WHR	0.11	0.38	-0.07	0.42	-0.12	-0.27	0.28	-0.29
WHtR	0.19	0.28	-0.03	0.25	0.20	0.32	0.02	0.27

* *P*-value<0.05

Discussion

The present study was aimed to investigate the relation of anthropometric indices and insulin resistance with lipid profile in overweight or obese women with PCOS. The prevalence of IR was 36.5% among the PCOS patients. According to our findings, IR is at least, partly, related to obesity and not attributed solely to PCOS. Since in our study, insulin concentration and HOMA-IR were significantly higher in the obese PCOS patients compared to the overweight women. On the other hand, the mean BMI (though non-significantly) was higher in the IR than NIR patients, a finding which is consistent with previous studies[36-38]. In fact, as mentioned earlier, abdominal obesity can result in higher insulin concentration[39]; and the resultant hyperinsulinemia may encourage further obesity[40]. As IR occurs in obese as well as lean subjects with PCOS, it is seemingly independent of obesity[41-43]. Nonetheless, any degree of obesity is liable to trigger reduced insulin sensitivity.

Our results also showed that among lipid profile, only HDL-C was significantly lower in the IR group (Fig. 1). The finding about HDL-C is in line with prior studies[36-37 ,44-46]. In the study conducted by Rabinson et al. [45], the authors suggested that low HDL-C was associated with insulin sensitivity rather than BMI. They concluded that PCOS was accompanied by biochemical risk factors for premature vascular disease, which could not be explained by obesity alone. In our study, elevated LDL-C level was not found in the insulin-resistant patients like the study by Kalra et al. [37] who compared lipid profile between insulin-resistant and non insulin-resistant PCOS groups. In another study, no significant correlation was observed between HOMA-IR and LDL-C[44]. However, in a large study of non-Hispanic white women[4], in which obese PCOS patients were compared to obese controls, elevations in LDL-C levels were the dominant lipid abnormality in women with PCOS, independent of obesity. Of course, the level of HDL-C was also elevated in the obese PCOS women; however, the characteristic dyslipidemia of IR was not observed.

In our study, though obesity was more common in the IR group *(P*=0.038), however, the two groups were similarly obese. Obesity has an important impact on lipid profile. Dyslipidemia of obesity is characterized by increased TG, low levels of HDL-C, increased subfractions of small, dense LDL, and increased levels of apolipoprotein B-100[47-48].

Around 50% of PCOS patients are overweight or obese with accumulation of abdominal fat[49]. Cibula et al. showed the effect of obesity on lipid profile and hyperlipoproteinemia in PCOS women[7]. Researchers demonstrated that lipid and lipoproteins did not differ in obese, overweight and non obese PCOS patients compared with control subjects, while HDL-C was decreased in obese PCOS and obese control women[50-51]. In non obese patients with PCOS, serum TG levels correlated with visceral fat and preperitoneal fat thickness. The authors concluded that intra-abdominal, preperitoneal, and visceral fat accumulation may contribute to the development of lipid metabolism disorders in non obese women with PCOS[52].

Among anthropometric measures, WHtR showed the strongest correlation with lipid profile components (r=0.37; *P*=0.004 for TC) and (r=0.33; *P*=0.011 for LDL-C) compared with BMI, WC, and HC in the whole patients (Fig. 2). Costa et al. indicated that WHtR and WC are more accurate than WHR to predict metabolic syndrome in Brazilian PCOS women[53]. Jiang et al. showed that BMI alone is not a significant contributory factor causing impaired glucose tolerance in PCOS women. WHtR is one more significant and predictive index for the occurrence of abnormal glucose tolerance[54]. In a research on the anthropometric indices of visceral obesity and cardiovascular risk factors among PCOS patients, both WHtR and WC but not WHR showed to be good markers of adverse metabolic profile in women with PCOS[55]. The results of a meta-analysis support the superiority of measures of centralized obesity, especially WHtR, over

BMI, for detecting cardiovascular risk factors in both men and women[56]. WHtR and WC are strongly associated with cardiovascular risk factors than WHR[55]. BMI, WHR and WHtR significantly correlated with fasting blood sugar (FBS), TC and TG using partial correlation test. Amongst, the highest correlation was observed for WHtR than BMI and WHR[57]. WHtR was a valuable obesity index for predicting lipidemia, diabetes, and hypertension[57].

In our unpublished data on this population, serum DHEAS level correlated significantly with some of the anthropometric measures like a previous study[55]. Therefore, we controlled the effects of DHEAS level, too. After removing the effects of confounders (age and serum DHEAS level), WHtR again showed the strongest association with TC (r=0.33; *P*=0.016) and LDL-C (r=0.30; *P*=0.034) in the overall patients. When divided the patients into IR and NIR groups, only the correlation of BMI and hip circumference with TC and LDL-C was significant in the NIR group. Hip circumference in women is a stronger independent predictive risk factor for total death and development of CVD or CHD than either BMI or waist circumference[58]. Dyslipidemia is common in women with PCOS, mainly due to low HDL-C levels and BMI has a significant impact on this abnormality (46). In a study on Chinese population, general adiposity was the only obesity determinant of LDL-cholesterol[59].

A relatively limited sample population was included in the present study due to taking into account a vast number of effective confounders as inclusion criteria. The controversies which exist in different studies may result from different diagnostic criteria used for PCOS, inclusion of women with different BMIs, and probable use of progestin for menstrual induction preceding the study. However, in the present investigation, diagnosis of PCOS was based on the Rotterdom criteria, widely used in most researches. Moreover, only overweight or obese patients at a limited age range (i.e.17-37 years) were recruited. Finally, no hormonal treatment (i.e. progestin) was used for menstrual induction before the study.

Conclusion

Our study suggests that anthropometric characteristics (especially BMI and hip circumference) are more important parameters correlated to lipid profile than IR in PCOS patients, approving the importance of early treatment of obesity to prevent further cardiometabolic complications in the future.

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Competing interests

The authors declare that there is no conflict of interest.

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