Original Article

Predictors of Metabolic Syndrome among Polycystic Ovary Syndrome Sisters

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Abstract

Aims: Metabolic syndrome among PCOS sisters may vary depending on the phenotype. The aim of the present study was to analyze the prevalence of metabolic syndrome among different phenotypes of PCOS sisters. **Design:** Case control study. **Materials and Methods:** Two hundred sisters of PCOS patients and 99 age matched healthy controls underwent history, clinical examination, biochemical parameters for metabolic syndrome and hormonal assessment. **Results:** Of 200 sisters, 85 were unaffected (UA group), 21 sisters had hyperandrogenemia (HA group), and 94 sisters had irregular periods or hyperandrogenemia. We observed that the frequency of metabolic syndrome among PCOS sisters was comparable to age and weight matched controls (30% vs 27%). The prevalence of metabolic syndrome was higher in HA and AFFECTED sisters (around 30% in both) compared to UA sisters (20%). The presence of metabolic syndrome was significantly associated with age, BMI, HOMA-IR and free testosterone. After correction for age and BMI, metabolic syndrome was significantly associated with HOMA-IR (*P* - 0.05) and free testosterone (*P* - 0.03). **Conclusion:** Based on above findings, we conclude that affected sisters and those with higher age, BMI and hyperandrogenemia have a high risk of metabolic syndrome compared to unaffected sisters.

Keywords: *Metabolic syndrome, PCOS, PCOS sisters*

Introduction

Polycystic ovary syndrome (PCOS) is a common disorder among women characterized by features of androgen excess, anovulation, and obesity.[1] Women with PCOS also have a high incidence of metabolic abnormalities such as insulin resistance, glucose intolerance, dyslipidemia, and metabolic syndrome.[2-6] PCOS and its associated metabolic abnormalities may cluster in families.[7-9] Some studies from the West have shown that sisters of women with PCOS have hyperandrogenemia, hyperinsulinemia, and increased rates of metabolic syndrome or dyslipidemia compared to unaffected (UA) sisters or healthy controls.[7,10-14] In a recent meta-analysis of metabolic syndrome in first-degree relatives of PCOS patients, it was observed that relative risk of metabolic syndrome among PCOS sisters was 1.5 (confidence interval [CI]: 1.12–2.0).[14]

The presence of metabolic syndrome in sisters with PCOS may differ depending on the phenotype. It is possible that inclusion of symptomatic sisters may have contributed to a high incidence of metabolic syndrome among PCOS sisters compared to healthy controls in some of the above-mentioned studies analyzed in a recent meta-analysis.[7,11] There are only two studies, whereby PCOS sisters were subdivided into symptomatic and asymptomatic groups and assessed for hyperinsulinemia or metabolic syndrome.[12,13] Sam *et al*. observed that metabolic syndrome in affected and hyperandrogenemic sisters with PCOS was more common compared to UA sisters and controls.[12] There is only one Indian study that has assessed the incidence of metabolic syndrome

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among 22 sisters with PCOS without subclassifying them.[15] In the present study, we propose to study the prevalence of metabolic syndrome among different phenotypes of PCOS sisters. The secondary objective of the present study is to assess the predictors of metabolic syndrome in these participants, i.e. impact of age, body mass index (BMI), parental history of diabetes, clinical symptoms, and hyperandrogenemia.

Methodology

Women with PCOS presenting to the endocrinology clinic of this hospital during the study period (2013–2016) were identified. The diagnosis of PCOS was based on the Rotterdam criteria after exclusion of secondary causes. Consenting sisters of patients with PCOS were recruited as participants for the study. Written informed consent was obtained from all participants before their participation in the study. Pregnant, lactating, premenarchal and menopausal sisters or those on oral contraceptive pills, oral hypoglycemics, antihypertensives, or lipid-lowering agents were excluded from the study. This study was approved by the institutional ethics committee. The control group included normal women aged 15–45 years with regular menstrual cycles (27–35 days) and absence of clinical hyperandrogenism (hirsutism, acne, or hair loss). Healthy staff of the hospital was informed about the study. The controls included dieticians, staff nurses, nursing students, or healthy daughters of hospital staff. The selection criteria for the control women were (1) no major medical or psychiatric illnesses, (2) no personal history of hypertension or diabetes, and (3) no intake of medications known to alter sex hormone metabolism or glucose homeostasis for at least 3 months before the study.

Participants (sisters of PCOS) underwent a detailed clinical history and physical examination. Anthropometric measurements including height, weight, waist, and hip measurements were made in all the participants. Waist circumference was measured at the narrowest level between the costal margin and the iliac crest, and the hip circumference was measured at the widest level over the buttocks with the participant standing normally. Blood pressure was determined in the seated position in the right arm as the average of two separate readings obtained two min apart after a 5-min rest. Participants underwent 75-g oral glucose tolerance test after an overnight fast and blood sampling performed at baseline, 1 h, and 2 h after glucose load in the follicular phase (2–7 days of the menstrual cycle). Glucose and lipid profile were analyzed the same day, and samples for insulin and other hormones (including thyroid function tests, cortisol, prolactin, luteinizing hormone [LH], follicle-stimulating hormone [FSH], testosterone, free testosterone, dehydroepiandrosterone sulphate (DHEAS), androstenedione, and 17-Hydroxy progesterone (17-OHP)) were stored at −20°C and analyzed later. Transabdominal ultrasound (Toshiba iStyle using convex Sector probe 3.75 MHZ) was performed in the follicular phase in regularly menstruating females or any day if menstrual cyclicity was more than 2 months. Polycystic ovaries were defined by either 12 or more follicles 2–9 mm in diameter or increased ovarian volume >10 ml.

PCOS sisters and controls were categorized as lean and obese with the BMI cutoff of 23 kg/m^2. Metabolic syndrome was defined as per the NCEP ATP III criteria with modified waist cutoffs as suggested for the Asians.[15] According to these criteria, metabolic syndrome was considered as present if three or more of the following five criteria were fulfilled – (1) waist circumference more than 80 cm, (2) fasting glucose ≥100 mg%, (3) blood pressure measurement more than 130/85 mmHg, (4) triglycerides more than 150 mg%, and (5) high-density lipoprotein (HDL)-cholesterol <50 mg%. PCOS sisters were classified according to the following clinical phenotypes: (1) UA sisters: no hirsutism or hyperandrogenemia and having regular menses every 27–35 days, (2) hyperandrogenic (HA) sisters: sisters who do not have symptoms related to hirsutism or irregular menses but have hyperandrogenemia, and (3) affected (AFF) sisters: those with hirsutism and/or irregular periods. Hyperandrogenemia was defined as androgen levels more than 2 standard deviation (SD) above the mean for levels in control women. Therefore, hyperandrogenemia was considered present if testosterone levels were more than 1.56 nmol/L or free testosterone levels more than 4.55 pg/ml or androstenedione levels more than 4.57 mcg/ml. Homeostatic model assessment for insulin resistance (HOMA-IR) was calculated as follows: serum insulin X serum glucose (mmole/L)/22.5).

Controls underwent anthropometric examination, blood pressure assessment, and sampling post-glucose tolerance test (GTT) for estimation of glucose, lipids, insulin, and other hormones as described for participants above.

Assay

Plasma glucose was determined by the glucose oxidase technique. Serum triglycerides and total cholesterol were measured by enzymatic methods. HDL-cholesterol was measured by a direct method. Very-low-density lipoprotein (LDL) was calculated from the triglyceride fraction (Tg/5). LDL-cholesterol was calculated from

data of the above parameters by Friedwald's equation. LH, FSH, testosterone, prolactin, and thyroid function tests were performed by chemiluminescence (Vitros, ECI, Johnson and Johnson). Plasma insulin, DHEAS, androstenedione, free testosterone, and sex hormone-binding globulin were performed by ELISA (Biorad Evolis, Twin Plus). All hormone assays had inter- and intra-assay coefficients of variation below 10% (3%–9.7%).

Statistical analysis

Data are presented as mean ± SD. Student's *t*-test was used to compare the means of parametric data between PCOS and controls. Normality of the distribution of variables was checked using the Kolmogorov–Smirnov test. Data were log-transformed to achieve homogeneity of variance in variables that were not normally distributed. Chi-square test was performed to compare the categorical variables. ANOVA was performed for comparison of means among the three groups of sisters. *Post hoc* analysis using least significance difference was applied to determine differences among the groups. $P < 0.05$ was considered significant. Binary logistic regression analysis was done for finding the odds ratio with 95% CI. Univariate and multivariate logistic regression modeling was employed to examine predictors of metabolic syndrome such as effect of age, BMI, testosterone, hirsutism, menstrual cyclicity, and androgen levels.

Results

Two hundred and twenty-one PCOS patients were informed about the study. These 221 PCOS patients had 354 sisters. Of 354, 200 sisters were included in the study. One hundred and fifty-four PCOS sisters either refused for sampling or were ineligible to be included [Figure 1]. Ninety-nine age-matched nonhirsute controls having regular periods were also included for analysis. Among 200 sisters, 87 were lean and 113 were obese using a BMI cutoff of 23 kg/m^2. Ninety-four PCOS sisters had complaints of hirsutism and/or irregular periods. Thirty-nine PCOS sisters (19.5%) had complaints of both irregular periods and hirsutism. PCOS sisters had a higher frequency of polycystic ovarian morphology as compared to controls (34% vs. 12%, $P = 0.001$).

Table 1 gives the clinical and biochemical characteristics of PCOS sisters in comparison to normal controls. The average age, BMI, and waist–hip ratio of PCOS sisters were comparable to that of controls. PCOS sisters had a higher menstrual cycle length and greater ovarian volume than controls. PCOS sisters had a higher 1-h insulin compared to the controls while the HOMA-IR and glucose values pre- and post-glucose load were

Table 1: Clinical and biochemical characteristics of polycystic ovary syndrome sisters and controls

	PCOS sisters (*n*=200)	Controls (*n*=99)	*P*
Age (years)	25.42±7.89	26.87±6.03	0.08
BMI (kg/m^2)	24.28±5.01	23.51±4.05	0.15
WHR	0.84±0.005	0.85±0.06	0.13
Menstrual cycles length (days)	42.68±73.32	29.88±1.48	0.014
BP systolic (mmHg)	118.56±10.74	118.74±6.9	0.66
BP diastolic (mmHg)	72.97±7.2	72.02±6.7	0.26
Right ovarian volume (ml)	9.53±5.08	7.91±4.5	0.06
Left ovarian volume (ml)	9.77±6.40	7.22±3.84	0.03
Glucose, h (mg/dl)			
0	84.26±22.78	84.04±9.52	0.59
1	115.32±31.71	115.02±30.99	0.96
2	104.65±41.98	100.05±22.04	0.61
Insulin, h (µIU/ml)			
0	9.10±13.87	6.08±6.42	0.14
1	43.48±33.92	38.47±32.44	0.04
2	30.99±25.71	28.85±30.38	0.14
HOMA IR	2.01±3.44	1.28±1.46	0.18
T3 (pg/ml)	3.63±1.13	3.39±0.71	0.14
T4 (ng/ml)	1.18±0.75	1.21±0.47	0.35
TSH (mIU/L)	3.98±4.37	3.14±2.13	0.03
Prolactin (ng/ml)	18.60±9.49	16.59±8.66	0.06
Cortisol (nmol/L)	241.34±95.07	223.08±86.74	0.21
LH (mIU/ml)	7.57±6.87	8.08±10.02	0.61
FSH (mIU/ml)	5.20±2.21	5.99±3.03	0.01
Testosterone (nmol/L)	0.87±0.49	0.76±0.40	0.06
Free testosterone (pg/ml)	2.65±3.76	1.79±1.38	0.00
SHBG (nmol/l)	62.82±48.76	87.05±60.81	0.01
DHEAS (µg/ml)	1.98±1.53	2.17±1.20	0.28
Androstenedione (ng/ml)	1.77±1.17	1.96±1.10	0.18
17-OHP (ng/ml)	1.05±0.73	0.91±0.88	0.14
Total cholesterol (mg/dl)	158.23±31.97	161.78±33.89	0.42
HDL-cholesterol (mg/dl)	47.71±11.41	46.85±9.85	0.69
LDL-cholesterol (mg/dl)	88.65±25.73	94.86±28.20	0.08
VLDL (mg/dl)	21.42±11.83	20.68±10.83	0.53
TG (mg/dl)	106.43±58.17	101.10±48.45	0.45
Metabolic syndrome, *n* (%)	55 (27.5)	30 (30.3)	0.334
Parental background of DM, *n* (%)	80 (40)	27 (28.15)	0.03
Family background of DM, *n* (%)	111 (55.8)	43 (44.8)	0.05
Family background of HTN, *n* (%)	136 (68.7)	63 (65.6)	0.34
Family background of CAD, *n* (%)	71 (35.5)	22 (23.4)	0.02

PCOS=Polycystic ovary syndrome, BMI=Body mass index, WHR=Waist-to-hip ratio, BP=Blood pressure, HDL=High-density lipoprotein, LDL=Low-density lipoprotein, VLDL=Very LDL, TG=Triglyceride, T3=Triiodothyronine, T4=Thyroxine, TSH=Thyroid-stimulating hormone, LH=Luteinizing hormone, FSH=Follicle-stimulating hormone, SHBG=Sex hormone-binding globulin, DM=Diabetes mellitus, CAD=Coronary artery disease, HTN=Hypertension, DHEAS=Dehydroepiandrosterone sulphate, 17-OHP=17-Hydroxy progesterone, HOMA-IR=Homeostatic model assessment for insulin resistance

comparable in the two groups. The prevalence of metabolic syndrome was comparable in the two groups (30.3% vs. 27.5%, $P = 0.33$). There was a higher frequency of family background of diabetes mellitus and coronary artery disease (CAD) among PCOS sisters in comparison to the controls (56% vs. 45% and 36% vs. 23%, respectively). PCOS sisters had higher testosterone and free testosterone as compared to controls.

Table 2: Comparative clinical and biochemical characteristics of different groups of polycystic ovary syndrome sisters versus controls

	UA sisters (*n*=85)	Hyperandrogenic (HA sisters) (*n*=21)	AFF sisters (*n*=94)	*P*
Age (years)	25.0±7.5	25.62±7.6	25.6±8.36	0.86
Weight (kg/m^2)	58.8±13.9	64.1±14.1	59.7±12.9	0.27
BMI	23.6±4.9	26.1±4.8	24.4±5.0	0.11[a]
WHR	0.83±0.07	0.84±0.07	0.85±0.08	0.22
Menarche	13.2±1.4	12.7±1.0	13.4±1.7	0.13[c]
BP systolic (mm/hg)	119.9±13.2	115.9±10.0	118.4±8.0	0.42
BP diastolic (mm/hg)	72.5±7.1	72.4±7.3	73.4±7.3	0.65
Menstrual cycle length (days)	29.9±2.3	31.3±7.0	56.6±105.4	0.00[b,c]
USG (cc)				
Right ovary	9.80±5.2	7.6±4.2	9.5±5.1	0.73
Left ovary	10.3±7.6	5.8±4.0	9.6±5.4	0.16
Glucose, h (mg/dl)				
0	85.0±32.2	85.8±18.1	83.1±9.9	0.81
1	117.0±33.1	106.6±27.2	115.7±31.3	0.41
2	107.6±53.7	101.4±42.4	102.6±27.3	0.68
Insulin, h (µIU/ml)				
0	7.7±12.9	12.6±22.1	9.4±12.2	0.07[b]
1	40.3±32.6	42.3±36.1	46.5±34.6	0.61
2	29.4±26.1	28.0±22.8	33.1±26.0	0.46
HOMA-IR	1.8±3.8	2.5±4.1	2.0±2.8	0.08[b]
Total cholesterol (mg/dl)	154.4±35.8	157.5±31.2	161.7±28.1	0.31
HDL (mg/dl)	46.5±10.5	45.0±7.5	49.3±12.6	0.14
LDL (mg/dl)	87.0±26.8	91.1±25.7	89.5±24.8	0.71
VLDL (mg/dl)	20.7±12.3	20.7±8.2	22.1±12.0	0.70
TG	104.1±61.5	103.1±40.8	109.2±58.7	0.81
T3 (pg/ml)	3.7±0.6	3.6±0.6	3.5±1.3	0.92
T4 (ng/ml)	1.1±0.4	1.0±0.2	1.2±0.9	0.70
TSH (mIU/L)	3.9±3.2	3.8±2.6	4.0±5.4	0.97
Prolactin (ng/ml)	18.1±10.4	21.2±9.3	18.3±8.5	0.39
Cortisol (nmol/L)	230.4±96.7	293.9±119.3	239.3±84.1	0.02[a,c]
LH (mIU/ml)	7.2±8.4	8.0±7.0	7.7±5.0	0.84
FSH (mIU/ml)	5.4±2.2	5.3±2.4	4.9±2.0	0.47
Testosterone total (nmol/L)	0.6±0.2	1.1±0.7	1.0±0.5	0.00[a,b]
Free testosterone (pg/ml)	1.4±0.9	4.8±5.8	3.2±4.3	0.00[a,b]
SHBG (nmol/l)	71.0±59.4	52.2±35.0	57.7±38.9	0.37
DHEAS (µg/ml)	1.7±0.9	2.9±2.3	1.9±1.6	0.10[a]
Androstenedione (ng/ml)	1.5±0.9	1.6±1.2	1.9±1.3	0.03[b]
17 OHP (ng/ml)	0.9±0.4	1.37±0.8	1.11±0.8	0.03[a]
Metabolic syndrome, *n* (%)	18 (21.2)	7 (33.3)	29 (30.9)	0.27
Family background of DM, *n* (%)	43 (50.6)	13 (62)	55 (58.5)	0.38
Family background of HTN, *n* (%)	59 (71.9)	17 (81)	60 (63.8)	0.25
Family background of CAD, *n* (%)	27 (31.8)	10 (47.6)	34 (36.2)	0.39

[a]*P* value significant if difference significant between UA and HA sisters, [b]*P* value significant if difference significant between UA and AFF sisters, [c]*P* value significant if difference significant between HA and AFF sisters. UA=Unaffected, HA=Hyperandrogenic, AFF=Affected, BMI=Body mass index, WHR=Waist-to-hip ratio, BP=Blood pressure, HDL=High-density lipoprotein, LDL=Low-density lipoprotein, VLDL=Very LDL, TG=Triglyceride, T3=Triiodothyronine, T4=Thyroxine, TSH=Thyroid-stimulating hormone, LH=Luteinizing hormone, FSH=Follicle-stimulating hormone, SHBG=Sex hormone-binding globulin, DM=Diabetes mellitus, CAD=Coronary artery disease, HTN=Hypertension, USG=Ultrasonography, HOMA-IR=Homeostatic model assessment for insulin resistance, DHEAS=Dehydroepiandrosterone sulphate, 17-OHP=17-Hydroxy progesterone

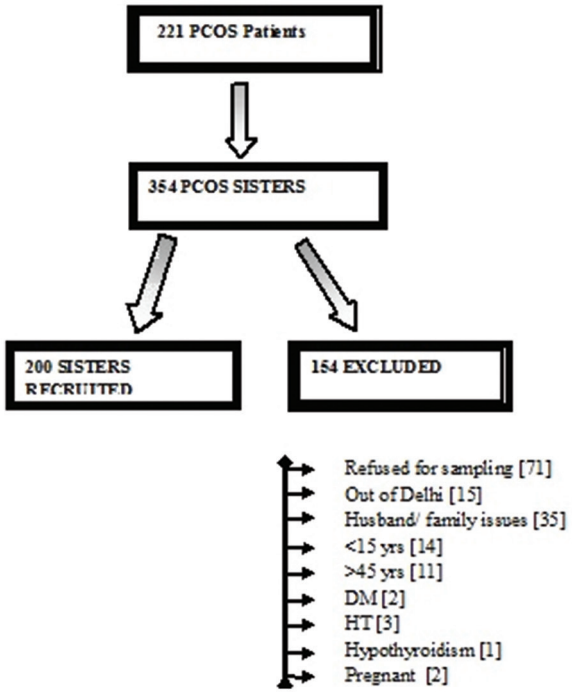

Figure 1: Details of recruitment of polycystic ovary syndrome patients and controls

Around 45% of PCOS sisters had abnormal waist circumference, 38% had low HDL levels, 16% had high triglycerides, 8% were hypertensive, and around 5% had impaired fasting glucose. There was no difference in the relative prevalence of different components of metabolic syndrome among PCOS sisters and controls.

Two hundred sisters were classified into three groups: 89 UA PCOS sisters (UA group), 21 sisters with hyperandrogenemia (HA group), and 94 AFF sisters. Table 2 gives the comparison of clinical and biochemical characteristics among the three groups of PCOS sisters. All the groups were comparable with respect to age. HA sisters had a higher BMI compared to UA sisters. Androgen levels were significantly higher in AFF and HA sisters compared to UA sisters. There was no difference in the glucose levels at 0 h, 1 h, or 2 h in the different groups. Insulin levels at 0 h and HOMA-IR were significantly higher in AFF sisters compared to UA sisters. The prevalence of metabolic syndrome was higher in HA and AFF sisters (around 30% in both) compared to UA sisters (20%) [Figure 2]. A similar trend toward higher prevalence of at least two abnormal metabolic syndrome components was seen in AFF PCOS sisters compared to UA sisters (80.8% in AFF sisters, 76.1% in HA sisters, and 70.5% in UA sisters). Cortisol levels were significantly higher in HA subgroup compared to UA and AFF sisters. There was no difference in the family background of diabetes, hypertension, or CAD in the two groups.

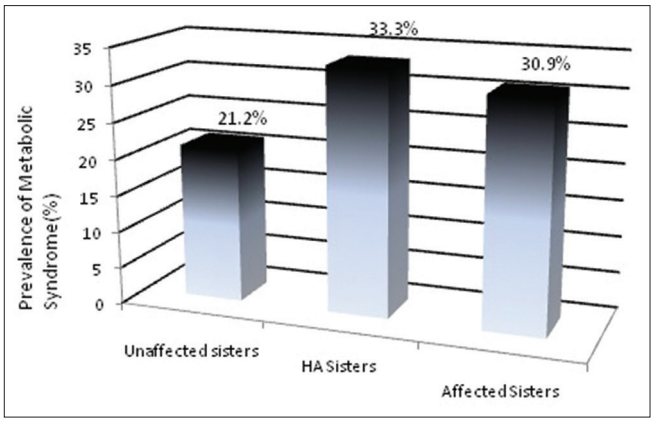

Figure 2: Comparative frequency of metabolic syndrome between different subgroups of polycystic ovary syndrome sisters

Table 3: Association of metabolic syndrome with various clinical and biochemical parameters

Parameters	OR (CI)	*P*
Age (years)	1.072 (1.030-1.11)	0.001*
BMI (kg/m^2)	1.12 (1.05-1.20)	0.00*
Menstrual cycle duration (days)	2.86 (0.616-13.2)	0.18
Hirsutism	0.78 (0.38-1.3)	0.51
Right ovarian volume (cc)	0.86 (1.23-6.13)	0.88
Left ovarian volume (cc)	0.64 (0.110-3.28)	0.62
HOMA-IR	2.37 (1.21-4.64)	0.01*
Total testosterone (nmol/L)	0.61 (0.198-1.89)	0.39
Free testosterone (pg/ml)	2.04 (0.996-4.19)	0.05*
DHEAS (µg/ml)	0.41 (0.158-1.08)	0.073
Androstenedione (ng/ml)	0.56 (0.243-1.31)	0.186
17 OHP (ng/ml)	0.35 (0.134-0.947)	0.03
Family background of DM	1.41 (0.94-2.3)	0.19
Family background of HTN	0.03 (0.37-1.07)	0.08
Family background of CAD	1.05 (0.65-1.8)	0.83

*Significance if *P* value is <0.05. OR=Odds ratio, CI=Confidence interval, BMI=Body mass index, HOMA-IR=Homeostatic model assessment for insulin resistance, DM=Diabetes mellitus, HTN=Hypertension, CAD=Coronary artery disease, DHEAS=Dehydroepiandrosterone sulphate, 17-OHP=17-Hydroxy progesterone

The presence of metabolic syndrome was significantly associated with age, BMI, free testosterone, and HOMA-IR [Table 3]. Forward logistic regression modeling was further used to account for the multicollinearity of the variables. After correction for age and BMI, HOMA-IR (P = 0.046) and free testosterone (P = 0.028) were significantly associated with metabolic syndrome.

Discussion

In the present study, around 20% of sisters had complaints of both irregular periods and hirsutism while 10% had hyperandrogenemia. These results are similar to the study by Legro *et al*. who described

hyperandrogenemia and irregular periods in 22% of sisters.[8] Similar observations regarding the prevalence of PCOS among sisters were reported by Yildiz *et al*. in 23% of sisters and Kahsar-Miller *et al*. in 32% while Azziz and Kashar-Miller noted that as many as 40% of sisters have PCOS.[10,11,16] We also observed that around 45% of sisters had complaints of hirsutism or irregular periods. These rates are much higher than the general population and suggest that genetic component may be involved in this disorder.

In the present study, we observed that the frequency of metabolic syndrome among PCOS sisters was comparable to age- and weight-matched controls (30% vs. 27%). Among all components of metabolic syndrome, centripetal obesity was the most frequent among PCOS sisters (45%), followed by dyslipidemia (38%), hypertension (8%), and impaired fasting glucose (5%). Sam *et al*. reported metabolic syndrome in 19% of PCOS sisters.[12] They observed that the frequency of low HDL was the highest followed by abdominal obesity in 23%. Increased abdominal obesity and metabolic syndrome in our patients as well as controls in spite of a lower BMI (around 24 kg/m^2) compared to a study by Sam *et al*. (BMI around 30 kg/m^2) are indicative of a higher prevalence of centripetal obesity and metabolic syndrome reported in Indian population.[12,17,18]

While 1 h insulin was higher among PCOS sisters in the present study, glucose levels were comparable in the two groups. There was no difference in the lipid parameters between PCOS patients and controls or within the three subgroups of sisters. Joharatnam *et al*. also observed no difference in the lipids between 214 sisters and controls after adjustment of BMI.[19] On the other hand, Sam *et al*. observed that sisters with classical PCOS and HA sisters of PCOS patients had higher cholesterol and LDL-cholesterol compared to UA sisters and control women.[12] However, these patients were more obese (BMI ranging from 29 kg/m^2 to 33 kg/m^2) compared to our patients who had BMI around 24 kg/m^2.

In the present study, AFF and HA sisters had a higher prevalence of metabolic syndrome compared to UA sisters (30% and 33% vs. 20% respectively). AFF PCOS sisters had higher 0 h insulin and HOMA-IR compared to UA sisters. Legro *et al*. reported increased fasting insulin and decreased glucose–insulin ratio in PCOS and HA sisters compared to UA and control women.[13] Sam *et al*. also reported metabolic syndrome in AFF and HA sisters, which was much higher than the UA sisters (52% and 23% vs. 7% respectively).[12] We also observed that asymptomatic PCOS sisters who had mild hyperandrogenemia (HA sisters) were at increased risk of metabolic syndrome.

We observed that metabolic syndrome was significantly associated with free testosterone levels and HOMA-IR after correction for age and BMI. Hyperandrogenemia can cause hyperinsulinemia and insulin resistance by direct effects on skeletal muscle and adipose tissue, through a variety of mechanisms. Animal studies indicate that androgens may increase visceral fat and cause alterations in the insulin receptor and adipokine secretion.[20,21] Higher cortisol in HA sisters could have also contributed to hyperinsulinemia in this subgroup.

This is the first Indian study to recruit such a large number of PCOS sisters and controls. The only previous Indian study included 22 PCOS sisters without recruiting controls.[15] Unlike previous studies, we did not observe a high prevalence of metabolic syndrome among asymptomatic PCOS sisters in comparison to healthy controls. A lack of increased risk of metabolic syndrome among our PCOS sisters could be because of the younger age and leaner BMI (25 years and 24 kg/m^2) compared to PCOS sisters in the West analyzed in a meta-analysis (27–32 years and 26.3–32.9 kg/m^2, respectively).[14] Furthermore, majority of our PCOS sisters were asymptomatic (around 60%). Most of the previous studies have not segregated their PCOS sisters into symptomatic versus asymptomatic sisters. Analysis of metabolic syndrome with reference to HA sisters (asymptomatic but increased androgens) is unique and explored in only two previous studies on PCOS sisters.[12,13] The high risk of metabolic syndrome among this HA subgroup is interesting and needs to be explored further in larger studies. We observed that family background of diabetes, hypertension, or CAD did not affect the risk of metabolic syndrome in PCOS sisters. However, we did not have a complete hormonal or metabolic profile of parents or PCOS probands.

Conclusion

We observed that asymptomatic PCOS sisters did not have a high risk of metabolic syndrome compared to healthy controls. However, symptomatic sisters and those with a higher BMI, high HOMA-IR, and hyperandrogenemia were at increased risk of metabolic syndrome. Asymptomatic sisters with hyperandrogenemia (HA subgroup) also have a higher risk of metabolic syndrome and need to be evaluated for metabolic risk.

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Conflicts of interest

There are no conflicts of interest.

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