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Metabolic Disorders among Phenotypes of Polycystic Ovary Syndrome

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Abstract

Background: Polycystic Ovary Syndrome (PCOS) is a disorder of uncertain etiology, and is also associated with a number of metabolic perturbations. Metabolic features of different phenotypes remain debatable. Thus, the study was aimed at observing the pattern of metabolic profiles among the phenotypes of PCOS.

Methods: A total of 125 reproductive-aged women were included in this cross-sectional study. Of these, 100 women with PCOS (age, mean ± SD: 23 ± 5 years; body mass index, BMI: 27.6 ± 4.6 kg/m^2) diagnosed on the basis of Rotterdam criteria (divided into four phenotypes) and 25 healthy control (age, mean ± SD: 24 ± 5 years; BMI: 24.2 ± 4.9 kg/m^2) were recruited. PCOS phenotypes were defined as: A (oligo-anovulation + hyperandrogenism + PCO), B (oligo-anovulation + hyperandrogenism), C (hyperandrogenism + PCO) and D (oligo-anovulation + PCO). Glucose was measured by glucose oxidase method, and lipids were measured by automated analyzer, while hormones were analyzed using chemiluminescent immunoassay.

Result: Frequency of PCOS phenotypes were highest for A (57%), followed by D (16%), B (14%) and C (13%). Highest value of fasting insulin was observed in phenotype A followed by D, B and C and all were higher than control. The overall frequency of Insulin Resistance (IR) was 66% and Metabolic Syndrome (MetS) was 44% in women with PCOS. Logistic regression showed that age ≥25 years, Waist circumference ≥80 cm, BMI≥25 kg/m^2 and Ferriman-Gallwey (FG) score were associated with risk of MetS. Using IR as a dependent variable phenotype A, B, C and D were associated with 17-fold, 13-fold, 11-fold and 9-fold increased risk of developing IR compared to control. Phenotype A and B but not C or D were good predictors for MetS. Phenotype A and B had much higher risk than that of control.

Conclusions: Women with PCOS have increased cardiometabolic risk compared to healthy control. Among the phenotypes, A and B have worse metabolic profiles.

Keywords: Hyperandrogenism; Insulin resistance; Metabolic syndrome; PCOS phenotypes

Introduction

Polycystic ovary syndrome (PCOS) seems increasing day by day. It is a heterogeneous disorder of uncertain etiology. However, there is strong evidence that complex interactions between genetic, environmental and behavioral factors contribute to causing this syndrome [1]. In addition to chronic anovulation and androgen excess, PCOS is also associated with a number of metabolic perturbations. Irrespective of Body Mass Index (BMI), these women have an increased risk of Insulin Resistance (IR), glucose intolerance, type 2 Diabetes Mellitus (T2DM), dyslipidemia, subclinical atherosclerosis, and vascular dysfunction, all of which lead to cardiovascular diseases [2,3]. The diagnostic criteria of PCOS have evolved over the years [4-6]. To this end, the phenotypes are divided into four diagnostic groups: phenotype A (biochemical/clinical hyperandrogenism and oligo/anovulation with polycystic ovaries (PCO) on ultrasound); phenotype B (biochemical/clinical hyperandrogenism and oligo/anovulation without PCO); phenotype C (biochemical/clinical hyperandrogenism and PCO but with normal ovulation); phenotype D (oligo/anovulation and PCO but without any biochemical/clinical hyperandrogenism) [7].

IR plays an important role in pathogenesis and development of other metabolic complications in women with PCOS. Prevalence of IR is around 70%, and risk of Metabolic Syndrome (MetS) is 11-fold higher in women with PCOS compared with aged matched controls [8,9]. However, there are controversies on presence of IR in different phenotypes of PCOS. The majority of this data regarding IR and

metabolic features of PCOS based on studies defining women with PCOS with hyperandrogenism. There are limited data on metabolic features in women belonging to the newer phenotypes as defined by the Rotterdam criteria, [5] especially normoandrogenic phenotype [10]. Some studies suggest that normoandrogenic phenotype is characterized by less severe endocrine and metabolic abnormalities, [7,11] whereas, other observations suggest that higher IR exhibit a stronger correlation with the higher prevalence of obesity in these PCOS women than the phenotypes per se [12,13].

The present study was undertaken to observe and compare the pattern of IR and metabolic complications in different phenotypes of women with PCOS in Bangladesh.

Methods

This study was conducted in the Department of Endocrinology, Bangabandhu Sheikh Mujib Medical University (BSMMU), Dhaka. Using a formula and based on a previous study, estimated required sample size of each subgroup was 48 (with 80% power and 5% significant level) [14]. But for limitation of resources, 100 Bangladeshi women of age 16-35 years with PCOS based on the basis of Revised Rotterdam Consensus 2003 criteria [5,7] were recruited. Control group included 25 age matched healthy women having regular menstrual cycle, no history of clinical and biochemical hyperandrogenism, no polycystic ovary morphology on ultrasonography, and without clinical evidence of any endocrine diseases. Patients with following diseases were not included: primary amenorrhea, hyperprolactinemia diagnosed by the presence of serum prolactin values greater than 25 ng/ml, hypothyroidism, considered by serum Thyroid Stimulating Hormone (TSH) greater than 5 μIU/ml and non-classical congenital adrenal hyperplasia which was diagnosed in case of basal or adrenocorticotrophic hormone stimulated 17-OH progesterone greater than 10 ng/ml [15].

Women on medication for <6 months prior to the study (including oral contraceptives, glucocorticoids, metformin, ovulation induction agents, and estrogenic or anti-androgenic drugs or any medication for dyslipidemia or anti-obesity drugs) or suffering from other systemic diseases (e.g. chronic kidney disease, liver diseases etc.) were also excluded in the study. Prior to commencement, the research protocol was approved by the Institutional Review Board (IRB). Informed written consent was taken from all subjects.

Anthropometric measurements were taken by the same investigator and hirsutism was assessed using a modified Ferriman-Gallwey (FG) method [16]. For total testosterone, follicle-stimulating hormone, luteinising hormone, TSH and prolactin samples were collected on any day between 2nd-7th of a spontaneous bleeding episode or randomly in the case of amenorrhea. Trans-abdominal (in unmarried) or transvaginal ultrasonography was performed preferably in early follicular phase. Samples for glucose (fasting and 2 hours after 75 g glucose load) as well as Fasting Insulin (FI) and lipid were taken, centrifuged and preserved at -20°C until assay. Plasma glucose was assayed by glucose oxidase method whereas insulin by Chemiluminescent Microparticle Immunoassay (CMIA, Architect Plus ci4100) and lipids by automated analyzer (Architect Plus ci8200).

Oligomenorrhea/anovulation was defined as delayed menses >35 days or <8 spontaneous hemorrhagic episodes/year, clinical hyperandrogenism (hirsutism using modified FG score of >8) or biochemical hyperandrogenism (total testosterone >48 ng/dl), polycystic ovarian morphology on ultrasonography (12 or more follicles in each ovary measuring 2-9 mm in diameter, and/ or increased ovarian volume >10 cm^3). We used the surrogate markers to define IR; however there is no universal consensus regarding cut-off points for two of the most used parameters to detect IR: FI and the Homeostatic Model Assessment of IR (HOMA-IR). To date no studies have been reported to establish cut-off points for these two markers in Bangladeshi women, thus on the basis of previous studies [14,17] IR was diagnosed by the presence of one or more of the following: FI >20 μu/ml, fasting glucose/insulin ratio (FG/FI ratio) <4.5, HOMA-IR >3.8 in this study; HOMA-IR was calculated using the formula=fasting glucose (mmol/L) × fasting insulin (μU/ml)/22.5 [18]. MetS was defined following the definition provided by the modified National Cholesterol Education Program Adult Treatment Panel III (NCEP ATP III) [19]. Prediabetes were defined as follows: Impaired Fasting Glucose (IFG) when Fasting Plasma Glucose (FPG) was between 5.6-6.9 mmol/L and Impaired Glucose Tolerance (IGT) when the 2-h Plasma Glucose (2-h PG) value during a 75 g Oral Glucose Tolerance Test (OGTT) was between 7.8-11.0 mmol/L. Diabetes mellitus was confirmed by FPG ≥ 7.0 mmol/L, a 2-h PG value during a 75 g OGTT of ≥ 11.1 mmol/L [20].

Data were expressed either as frequency or mean ± SD. One-way ANOVA and Chi square test were done to compare the clinical and biochemical characteristics between the different PCOS phenotypes. When more than 20% of the expected counts were less than 5, Fisher's exact test was applied. Logistic regression analysis was used to determine the predictors of MetS and IR with phenotypes and clinical parameters as independent variables. A p-value of <0.05 was considered as statistically significant. All data were processed using SPSS version-22.0.

Result

The frequencies of phenotype A-57%, phenotype B-14%, phenotype C-13% and phenotype D-16%. Comparison of the clinical characteristics and metabolic parameters (mean ± SD) among the subgroups and control are shown in table 1. There was no difference among the PCOS phenotypes for Body Mass Index (BMI), Waist Circumference (WC), waist:hip ratio (p=not significant); but each PCOS subgroups had significant difference with control (p<0.05). As expected FG score and total testosterone of phenotype A, B, C were significantly higher than D as well as control (p<0.001), but not among themselves (phenotype A, B, C).

There were statistically significant difference among phenotypes and control (phenotype A *vs* B *vs* C *vs* D *vs* control) for FI (p<0.001), FG/FI ratio (p=0.002), HOMA-IR (p<0.001), Total Cholesterol (TC) (p=0.041) and Low Density Lipoprotein (LDL) (p=0.033). However, fasting glucose (mmol/L), 2-h glucose (mmol/L), Triglycerides (TG) (mg/dl) and High Density Lipoprotein (HDL) (mg/dl) showed no statistical difference among the phenotypes and control (p=not significant for all). Highest value of FI was observed in phenotype A followed by D, B and C. It was significantly differed from control (p<0.05), except phenotype C which did not differ significantly from control. Among the subgroups, only phenotype A significantly differed from phenotype C (p<0.05). Similarly some significant differences were observed among the phenotypes and control for FG/FI ratio, HOMA-IR, TG and LDL.

Frequencies of prediabetes, DM, IR and MetS of the PCOS phenotypes are shown in table 2. Comparison of the frequencies (phenotype A *vs* B *vs* C *vs* D *vs* control) for prediabetes (p=0.004), IR (p<0.001), and MetS (p=0.013) were significantly higher in PCOS phenotypes than control; but among the phenotypes, frequencies did not differ significantly. When compared for glycemic status, IR and MetS, there were statistical difference for prediabetes (p=0.002) and IR (p=0.003) in the younger age group of 16-20 years and for the MetS in the age group 26-30 years (p=0.019), but none of the variable in other age groups (Table 3).

Table 1: Comparison of clinical characteristics and metabolic parameters of different phenotypes of PCOS and control.

Parameters	A n=57	B n=14	C n=13	D n=16	E-Control n=25	p-value
Age (years)	22.9 ± 5	23.8 ± 3	24.6 ± 6	21.8 ± 4.8	23.9 ± 4.5	0.487
BMI (Kg/m^2)	27.5 ± 4.8^{e}	27.2 ± 4.2	27.5 ± 5.1^{e}	28.47 ± 4.2^{e}	24.2 ± 4.9^{a,c,d}	0.029
WC (centimeter)	87.2 ± 10^{e}	88.2 ± 12^{e}	90.3 ± 13^{e}	89.4 ± 7.7^{e}	78.7 ± 10.6^{a,b,c,d}	0.002
W:H ratio	0.86 ± 0.05^{e}	0.87 ± 0.07^{e}	0.88 ± 0.07^{e}	0.87 ± 0.04^{e}	0.82 ± 0.05^{a,b,c,d}	0.002
Systolic BP	115.9 ± 14	120.7 ± 13^{c}	108.4 ± 9.8^{b}	115.6 ± 14.6	113.4 ± 13	0.199
Diastolic BP	80.7 ± 8.5^{e}	81 ± 7.7^{e}	78 ± 4.8	79 ± 6.6	74.4 ± 10.2^{a,b}	0.032
FG score	7.9 ± 4.4^{d,e}	7.6 ± 5.9^{d,e}	7.3 ± 2.6^{d,e}	0^{a,b,c}	0^{a,b,c}	<0.001
Total testosterone (ng/dl)	85.82 ± 28.44^{d,e}	82.84 ± 22.7^{d,e}	76.09 ± 27.5^{d,e}	34.35 ± 5.17^{a,b,c}	32.61 ± 1.62^{a,b,c}	<0.001
Fasting glucose (mmol/l)	4.99 ± 1.0	4.96 ± 0.6	5.77 ± 3.2	5.08 ± 0.7	4.7 ± 0.5	0.255
2-h glucose (mmol/L)	8.07 ± 3.5	7.2 ± 1.2	8.4 ± 6.7	7.9 ± 2.2	6.1 ± 0.9	0.143
Fasting insulin (µU/ml)	23.1 ± 11.3^{c,e}	17.9 ± 7.3^{e}	15.1 ± 8.7^{a}	19.3 ± 9.9^{e}	11.4 ± 4.3^{a,b,d}	<0.001
FG/FI	4.1 ± 2.7^{b}	6.5 ± 8.0^{a}	6.3 ± 5.7	5.4 ± 3.9^{e}	8.2 ± 2.3^{d}	0.002
HOMA-IR	5.26 ± 3.0^{c,e}	3.95 ± 1.74	3.59 ± 1.99^{a}	4.57 ± 2.8^{e}	2.44 ± 1.1^{a,d}	<0.001
Cholesterol (mg/ml)	185.2 ± 42^{e}	179.8 ± 34	177.3 ± 56	193.9 ± 34^{e}	158.4 ± 30^{a,d}	0.041
Triglycerides (mg/dl)	132.4 ± 62^{e}	125 ± 75	149.3 ± 177^{e}	130.5 ± 72	92.9 ± 47^{a,c}	0.261
HDL (mg/dl)	39.6 ± 10.8	39.4 ± 6.7	40.8 ± 8	37.6 ± 8	41.6 ± 7.2	0.730
LDL (mg/dl)	119 ± 38^{e}	119 ± 23^{e}	116 ± 48	130 ± 27^{e}	97 ± 23^{a,b,d}	0.033

Data were expressed as mean ± SD. p-values were calculated using one-way ANOVA followed by multiple comparisons (post hoc test).

^{a}p<0.05 versus phenotype A PCOS; ^{b}p<0.05 versus phenotype B PCOS; ^{c}p<0.05 versus phenotype C PCOS; ^{d}p<0.05 versus phenotype D PCOS; ^{e}p<0.05 versus control; PCOS: Polycystic ovary syndrome; Phenotype A:Oligo-anovulation+hyperandrogenism+polycystic ovary; phenotype B: Oligo-anovulation+hyperandrogenism; phenotype C: hyperandrogenism+polycystic ovary; phenotype D: Oligo-anovulation+polycystic ovary; E: Control; BMI: Body Mass Index; WC: Waist Circumference; W:H: Waist-Hip; BP: Blood Pressure; FG: Ferriman-Gallwey; FG/FI: Fasting Glucose/Fasting Insulin; HOMA: Homeostatic Model Assessment of Insulin Resistance; HDL: High Density Lipoprotein; LDL: Low Density Lipoprotein.

Table 2: Glycemic status and insulin resistance in PCOS phenotypes and control.

Variables	All PCOS n=100	A n=57	B n=14	C n=13	D n=16	E-Control n=25	p*
Prediabetes	40(40)	23(40.4)	4(28.6)	3(23.1)	10(62.5)	2(8)	0.004
DM	9(9)	6(10.5)	1(7.1)	1(7.7)	1(6.3)	0	0.573
Insulin resistance	66(66)	40(70.2)	9(64.3)	8(61.5)	9(56.3)	3(12)	<0.001
Metabolic syndrome	44(44)	29(50.9)	6(42.9)	3(23.1)	6(37.5)	3(12)	0.013

Data were expressed as frequency, percentage. p-values were calculated using Chi-square test.
DM: Diabetes Mellitus; Phenotype A: Oligo-anovulation+hyperandrogenism+polycystic ovary; phenotype B: Oligo-anovulation+hyperandrogenism; phenotype C: Hyperandrogenism+Polycystic ovary; phenotype D: Oligo-anovulation+polycystic ovary; E: Control;
*p-values for PCOS phenotypes *vs* controls.
Among phenotypes: Frequencies did not differ significantly for prediabetes (p=0.128); DM (p=0.941); insulin resistance (p=0.740) and metabolic syndrome (p=0.297).

Logistic regression analysis showed that age ≥25 years (OR=3.111; 95% CI for OR 1.38-6.97; p=0.006), WC ≥80 cm (OR=32.00; 95% CI for OR 4.195-244.109; p=0.001), BMI≥25 (OR=4.179; 95% CI for OR 1.73-10.08; p=0.001) and FG score (OR=1.088; 95% CI for OR 1.010-1.172; p=0.026) were associated with risk of having MetS (Table 4). Using IR as a dependent variable, phenotype A (OR=17.25; 95% CI 4.459-65.443; P<0.001), B (OR=13.20; 95% 2.592-67.233; p=0.002) and C (OR=11.733; 95% 2.266-60.745; p=0.003) were shown to be associated with 17-fold, 13-fold and 11-fold increased risk of developing IR, while phenotype D (OR=9.429; 95% 1.983-44.827; p=0.005) was associated with 9-fold increased risk in comparison to control group (Table 5). Phenotype A had 7 times (OR=7.59; 95% CI 2.04-28.24; p=0.002) and phenotype B had 5 times (OR=5.50; 95% CI 1.10-27.37; p=0.037) higher risk for developing MetS in comparison to control group (Table 6).

Discussion

The present study expressed four phenotypes of PCOS, which had discordant cardio metabolic risk profiles. Phenotypes with hyperandrogenism and oligo-anovulation with or without polycystic ovarian morphology (phenotype A and B respectively) had the worst metabolic presentation, in agreement with other reports [16-25]. IR raises the risk of IGT, DM, hyperlipidemia, hypertension, abdominal obesity and risk of cardiovascular disease.

Different studies showed that 35-40% of women with PCOS had IGT and 7-10% had T2DM [26,27]. In the present study the overall frequencies of DM as well as prediabetes were 9 and 40% respectively. Among the subgroups, frequency of prediabetes was highest in phenotype D (62.5%), followed by phenotype A (40%), B (23%), and C (23%). Whereas, highest frequency of DM was observed in phenotype

Table 3: Metabolic status in age groups of PCOS phenotypes and control.

Age groups	A n=57	B n=14	C n=13	D n=16	E-Control n=25	p
16-20 years	**n=20**	**n=3**	**n=3**	**n=7**	**n=8**	
Prediabetes	11(55)	0	0	6(85.7)	0	0.002
DM	3(15)	0	0	1(14.3)	0	0.681
Insulin resistance	16(80)	2(66.7)	2(66.7)	5(71.4)	0	0.003
MetS	10(50)	1(33.3)	0	2(28.6)	0	0.080
21-25 years	**n=21**	**n=7**	**n=5**	**n=6**	**n=10**	
Prediabetes	4(19)	2(28.6)	1(20)	2(33.3)	1(10)	0.813
DM	2(9.5)	0	1(20)	0	0	0.460
Insulin resistance	12(57.1)	4(57.1)	2(40)	2(33.3)	2(20)	0.330
MetS	9(42.9)	2(28.6)	1(20)	1(16.7)	1(10)	0.359
26-30 years	**n=11**	**n=4**	**n=3**	**n=3**	**n=5**	
Prediabetes	7(63.6)	2(50)	1(33.3)	2(66.7)	0	0.173
DM	0	1(25)	0	0	0	0.221
Insulin resistance	7(63.6)	3(75)	2(66.7)	2(66.7)	0	0.117
MetS	5(45.5)	3(75)	0	3(100)	0	**0.019**
31-35 years	**n=5**	**n=0**	**n=2**	**n=0**	**n=2**	
Prediabetes	1(20)	-	1(50)	-	1(50)	0.638
DM	1(20)	-	0	-	0	0.638
Insulin resistance	5(100)	-	2(100)	-	1(50)	0.140
MetS	5(100)	-	2(100)	-	2(100)	-

Data were expressed as frequency, percentage. p-values were calculated using Fisher's exact test.
DM: Diabetes Mellitus; MetS: Metabolic Syndrome; Phenotype A: Oligo-anovulation+hyperandrogenism+ polycystic ovary; phenotype B: Oligo-anovulation+hyperandrogenism; phenotype C: hyperandrogenism+polycystic ovary; phenotype D: Oligo-anovulation+polycystic ovary; E: Control.

Table 4: Logistic regression showing the predictive association of clinical variables and presence of metabolic syndrome.

Independent variable	B	p-value	OR	95% CI	
				Lower	Upper
Age ≥ 25 years	1.135	**0.006**	3.111	1.388	6.973
WC ≥ 80cm	3.466	**0.001**	32.000	4.195	244.109
BMI ≥ 25	1.430	**0.001**	4.179	1.731	10.088
FG score	0.084	**0.026**	1.088	1.010	1.172
F/H of DM	0.053	0.904	1.054	0.450	2.467

Values were calculated using binary logistic regression analysis.
WC: Waist Circumference; BMI: Body Mass Index; FG: Ferriman-Gallwey; F/H: Family history; DM: Diabetes Mellitus; HOMA-IR: Homeostatic Model Assessment of Insulin Resistance; B: Coefficient for the constant; OR: Odd ratio; CI: Confidence Interval.

Table 5: Logistic regression of insulin resistance as a dependent variable and phenotype-control as independent variable.

Independent variable	B	p-value	OR	95% CI	
Phenotype-Control		**<0.001**		**Lower**	**Upper**
A	2.848	<0.001	17.255	4.549	65.443
B	2.580	0.002	13.200	2.592	67.233
C	2.462	0.003	11.733	2.266	60.745
D	2.244	0.005	9.429	1.983	44.827
Control (reference)			1.000		
Constant	-1.992	0.001	0.136		

A (10%) while other phenotypes had almost similar frequency (6-7%). It is well established that PCOS even in their twenties, demonstrates a cluster of metabolic and cardiovascular disturbances [26,28]. Palmert et al. [29] found that IGT was present in eight of 27 (29.6%), and T2DM was present in two of 27 (7.6%) adolescent girls with PCOS [19]. We also found similar results in our study. These observations indicate the potential benefit of performing a 75 g 2-h OGTT in all PCOS patients irrespective of age to assess the clinical prognosis and management plan. There were no significant differences in fasting blood glucose levels identified between the PCOS phenotypes and the control groups in some previous studies, [23,30] while some others showed higher blood glucose levels in phenotype B and phenotype C compared to control subjects [31]. We did not find any differences in serum glucose levels among the PCOS phenotypes, which is consistent with previous studies [16,32].

We used FI level, FG/FI ratio and HOMA-IR as a surrogate marker for assessing the IR. There were overall significant differences among phenotypes and control for these markers. Highest value of FI was observed in phenotype A followed by phenotype D, B and C. Jamil et al. [14] did not, however, find any significant differences in FI levels among the PCOS phenotypes. Regarding FG/FI ratio Shroff, et al. [31] reported the highest FG/FI ratio in the control group and the lowest ratio in the phenotype A which is compatible with the present study. For assessing IR, euglycemic hyperinsulinemic clamp method is the gold standard. HOMA-IR calculation correlates very well with euglycemic hyperinsulinemic clamp method, and is often used as a surrogate marker [33]. We found highest HOMA-IR in phenotype A and lowest in phenotype C. Phenotype A and D also significantly differed from healthy control for HOMA-IR. Similar to us, in a study comparing HOMA-IR scores, the highest values was detected in the

Table 6: Logistic regression analysis for metabolic syndrome as a dependent variable and phenotype-control as independent variable.

Independent variable	B	p-value	OR	95% CI	
				Lower	Upper
Phenotype-Control		**<0.001**			
A	2.028	0.002	7.595	2.043	28.242
B	1.705	0.037	5.500	1.105	27.374
C	0.788	0.382	2.200	0.376	12.868
D	1.482	0.065	4.400	0.911	21.248
Control (reference)			1.000		
Constant	-1.992	0.001	0.136		

Values were calculated using binary logistic regression analysis.

Phenotype A: Oligo-anovulation+hyperandrogenism+polycystic ovary; phenotype B: Oligo-anovulation+hyperandrogenism; phenotype C: hyperandrogenism+polycystic ovary; phenotype D: Oligo-anovulation+polycystic ovary; B: Coefficient for the constant; OR: Odd Ratio; CI: Confidence Interval.

phenotype A and the lowest values were detected in the phenotype C and control groups, [23] though some studies did not find so [31]. On the other hand, Chae et al. [34] did not find any differences in HOMA-IR scores among the PCOS phenotypes, although there were significant differences between PCOS phenotypes and the control group. The overall prevalence of IR in PCOS ranges from 44 to 70% [8,35] we also found similar frequency (66%) in our study.

Among the phenotypes, frequency of IR was highest in phenotype A followed by phenotype B, C and D, respectively. Similar findings were also observed by Jamil et al. [14], Kauffman et al. [32] and Li et al. [35]. On the other hand, using surrogate markers one study observed that polycystic ovaries with ovulatory cycles and anovulation and polycystic ovaries without hyperandrogenism show little or no evidence of IR [36]. A comparison of markers of IR among the different PCOS phenotypes conducted by Panidis et al. [12] revealed that phenotype A was associated with higher prevalence of IR and more pronounced hyperandrogenemia than phenotype B. In contrast, phenotype C was not associated with IR. Genetic variation, environmental factors and variations in inclusion criteria are possible reasons for the differences among studies. Using IR as a dependent variable, regression analysis revealed all the phenotypes to have increased risk of developing IR compared to control. Phenotype A and B, but not C or D were good predictors for MetS. These findings were comparable to others [16].

In the present study, women with PCOS showed significantly higher level of TC, TG and LDL than control without variability among the phenotypes, a finding similar to that of Jamil et al. [14] and Yilmaz et al. [25]. These observations suggest that lifestyle, physical activity, and dietary habits play role in determining lipid concentrations rather than androgen level. According to NCEP ATP III criteria, we found 44% of PCOS women had MetS. Age ≥ 25 years, WC ≥ 80 cm, BMI ≥ 25 and FG score had independent predictability over MetS in PCOS, which correlates with other study [17].

We acknowledge limitations to our approach as well. In this cross sectional study, samples were collected from a single tertiary level hospital. Furthermore the sample size was small and control groups were not BMI matched. In addition, for assessing insulin resistance we used surrogate markers instead of gold standard hyperinsulinemic euglycemic clamp method. The strength of the study is the inclusion of an aged matched control group, and PCOS subjects were not preselected to have biochemical hyperandrogenism or any other specific characteristics, and therefore, represent the general population.

Conclusions

Our study exhibits that PCOS women with phenotype A and B have worse metabolic profiles compared with phenotype C and D, though there are no significant differences in the prevalence of IR and MetS among the phenotypes. Large scale population based studies are needed to elucidate these concerns.

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