

Clinical and hormonal characteristics of women with various phenotypes of polycystic ovary syndrome

Senem Arda Duz, Gorkem Tuncay, Abdullah Karaer

Department of Gynecology and Obstetrics, Faculty of Medicine, Inonu University, Malatya, Turkey

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Abstract

Aim: The goal of this study is to identify clinical and hormonal characteristics of women with various phenotypes of polycystic ovary syndrome.

Material and Methods: One hundred seventy eight cases, between the ages 18-30, diagnosed with PCOS, up to Rotterdam criteria, in our clinic between February 2015 -November 2018 were recruited in this cross sectional study.

Results: The number was declined 89 by using National Institutes of Health criteria, 132 up to Androgen Excess and PCOS Society criteria. 34.83% of the patients were phenotype A, 15.16% were phenotype B, 24.15% were phenotype C and 25.84% were phenotype D. When we compared the different phenotypes with each other, body mass index, fasting glucose, postprandial glucose, fasting insulin and homeostatic model assessment for insulin resistance were found to be higher in phenotype A. In addition, luteinizing hormone and luteinizing hormone to follicle stimulating hormone ratio was higher in phenotype D than in B and C. When multivariate analysis was performed, body mass index was found to be as a single statistically significant predictive factor on IR.

Conclusion: Body mass index was the most effective factor on insulin resistance and the mean body mass index was significantly higher in phenotype A.

Keywords: Hirsutism; hyperandrogenism; insulin resistance; phenotype; polycystic ovary syndrome

INTRODUCTION

Polycystic ovary syndrome (PCOS) is a disorder that affects usually reproductive aged women and insulin resistance (IR) and hyperinsulinemia often accompany (1). PCOS has numerous symptoms like irregular cycles, characterized anovulation and hirsutism besides other clinical metabolic disorders like hyperandrogenemia, dyslipidemia and IR. In addition, infertility is an important problem in PCOS diagnosed women. Besides, in the following years PCOS diagnosed women are likely to face with type 2 diabetes mellitus (DM) (2), coronary heart disease, cerebrovascular morbidity (3), atherogenic dyslipidemia (4), anxiety and depression (5). Also, during pregnancy the risk for gestational diabetes mellitus, macrosomia, small-for-gestational age infants, pre-eclampsia and perinatal mortality increases in PCOS diagnosed women (6).

It is still uncertain that PCOS is a single clinical disorder or is an association of different disorders with similar clinical presentations (7). Today there are 3 different diagnostic criteria systems for diagnosis of PCOS. The

National Institutes of Health (NIH) criteria include only hyperandrogenism (HA) and oligo-anovulation (OA) for the diagnosis of PCOS (8). Androgen Excess and PCOS Society (AE-PCOS), stipulates the presence of hyperandrogenism for diagnosis, coexisting OA and/or polycystic ovary morphology (PCOM) in ultrasound (9). The components for diagnosing of this disorder according to Rotterdam criteria are: (i) OA, (ii) clinical and/or biochemical HA and (iii) polycystic ovaries (≥ 12 follicles measuring 2-9 mm in diameter, or ≥ 10 ml ovarian volume in at least one ovary) (10). The presence of at least two of this three components is required for diagnose. Although PCOS is a common disorder, the definition and pathophysiology of PCOS is still unclear. Because of the heterogeneity of diagnosis criteria, the National Institute of Child Health and Human Development of the US National Institutes of Health (NIH) consensus panel proposed the use of the phenotype classification. According to this phenotype classification system the presence of HA + OA + PCOM is defined as phenotype A; the presence of HA + OA is defined as phenotype B, the presence of HA + PCOM is defined as phenotype C, and the presence of OA + PCOM defined

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Corresponding Author: Senem Arda Duz, Inonu University, Faculty of Medicine, Department of Gynecology and Obstetrics, Malatya, Turkey E-mail: senem_arda@yahoo.com

as phenotype D (11). It is still not clear, whether these different phenotypes are genuine PCOS as reported by Stein and Leventhal (12), or are distinct clinical disorders with analogue clinical symptoms.

The goal of our study was to identify clinical and hormonal characteristics of women with different phenotypes of polycystic ovary syndrome.

MATERIAL and METHODS

Study population

One hundred seventy eight cases, between the ages 18-30, diagnosed with PCOS in our clinic between February 2015 and November 2018 were enrolled in this cross sectional study. This study was designed retrospectively and the data of the participants were obtained from the medical records. This trial has validated by the Inonu University ethics committee (protocol no:2018/23-5).

Women with congenital adrenal hyperplasia or adrenal tumors, thyroid dysfunction, hyperprolactinemia, and chronic systemic disorder such as type 1 or 2 DM or hypertension were excluded. The use of oral contraceptive pill in the last 3 months was another exclusion criterion.

For diagnosis of PCOS we used the Rotterdam criteria (10). Menstrual cycles longer than 35 days were defined as oligomenorrhea, and no menstrual bleeding for 3 consecutive cycles, defined as amenorrhea. We evaluated the hirsutism, a clinical symptom of hirsutism, by using Ferriman- Gallwey scoring system (13) and a score higher than 8 was addressed as hirsutism. The existence of at least 12 peripheral placed follicles having a size between 2 and 9 mm in ultrasound diagnosis of ovaries has defined as polycystic features.

Weight, height and age of the patients were recorded during the physical examination.

Body mass index (BMI) was calculated as: $BMI = \text{weight (kilograms)} / \text{square of height (meters)}$.

Metabolic and hormonal assessment

Blood assay for metabolic markers and hormones were collected on any day between the 2nd-5th day of period, between 08:00 am and 10:00 am, after an at least 8-hour-overnight fasting. Serum fasting glucose and postprandial 2nd hour glucose, fasting insulin, HbA_{1c} levels, and serum follicle stimulating hormone (FSH), luteinizing hormone (LH), sex hormone binding globulin (SHBG), dehydroepiandrosterone sulphate (DHEA-S) and total testosterone levels were measured.

IR was determined with Homeostatic Model Assessment for Insulin Resistance (HOMA-IR) and calculated with the following formula (14): $HOMA-IR = \text{fasting glucose (mg/dL)} \times \text{fasting insulin } (\mu\text{IU/ml}) / 405$.

Free androgen index (FAI) was used to determine biochemical HA and calculated as: $FAI = 100 \times \text{total testosterone (nmol/L)} / \text{SHBG (nmol/L)}$.

Statistical analysis

Statistical Package for Social Sciences soft-ware 17.0 (SPSS, Inc., Chicago, IL) was used for statistical assessment. Kolmogorov-Smirnov test was used for distribution type of variables. Student's-t test was used for the parameters which had normal distribution and Mann-Whitney-U test was used for the parameters which did not have normal distribution. The categorical data was analyzed by Chi-square test. All data were referred to median (interquartile range) or mean \pm standard deviation (SD). The relation between IR and the age, BMI, and phenotype was analyzed with multinomial logistic regression analysis. A p value < 0.05 was evaluated as statistically significant.

RESULTS

According to Rotterdam criteria (phenotype A+B+C+D) 178 women with PCOS were incorporated in this study. 34.83% of the cases were phenotype A (n=62), 15.16% were phenotype B (n=27), 24.15% were phenotype C (n=43), and 25.84% were phenotype D (n=46). The number was declined 132 according to (AE-PCOS) criteria (phenotype A+B+C) and 89 according to NIH criteria (phenotype A+B).

The age, BMI, hirsutism score, hormonal parameters and biochemical parameters of the study participants and the differences between phenotypes were listed in Table 1. When we compared the different phenotypes with each other, BMI was found to be higher in phenotype A than in B. There was no statistically significant difference regarding to BMI between other phenotypes.

LH to FSH ratio was found to be higher in phenotype A and D than in B and C. But the difference in LH to FSH ratio between phenotype A and D was statistically insignificant.

The hirsutism score and FAI were significantly lower in phenotype D than in A, B, and C and SHBG levels were significantly higher in phenotype D than in A, B, and C. Total testosterone levels were significantly lower in phenotype D than in A and C.

Fasting glucose levels were higher in phenotype A than in B and D. Postprandial glucose levels were significantly higher in phenotype A than in C and D. Fasting insulin levels and HOMA-IR were found to be higher in phenotype A than in D. Finally HbA_{1c} levels were higher in phenotype A than in B.

The participants were categorized according to their BMI such as BMI was less than 25kg/m², those between 25-29.9 kg/m², and those 30 kg/m² or more. The patients with BMI \geq 30 kg/m² have higher HOMA-IR than the patients with BMI \leq 25kg/m² and BMI between 25-29.9 kg/m². Regardless of the phenotype, IR was 100% in women with BMI \geq 30 kg/m², 54.8% in women with BMI between 25-29.9 kg/m² and 20.5% in women with BMI \leq 25kg/m². When multivariate analysis was performed, BMI was found to be as a single statistically significant predictive factor on IR.

Table 1. Results of four phenotypes and the comparison of phenotypes with each other

	Phenotype A Median (interquartile range)	Phenotype B Median (interquartile range)	Phenotype C Median (interquartile range)	Phenotype D Median (interquartile range)	p1	p2	p3	p4	p5	p6
Age	20.5(19-23)	21(20-22)	21(19-24)	21(19-22)	0.76	0.93	0.94	0.83	0.97	0.88
Height (m) [†]	1.61±0.5	1.61±0.06	1.61±0.03	1.61±0.05	0.28	0.28	0.82	0.71	0.71	0.31
Weight (kg)	61.5(53.7-71)	57(48-63)	57(51-66)	57.5(51.8-68)	0.03*	0.09	0.15	0.5	0.34	0.77
BMI (kg/m ²)	23.4(20.4-27.6)	21.5(19.6-24)	21.5(20.2-26.3)	22.1(20-25.5)	0.02*	0.13	0.14	0.3	0.34	0.94
Hirsutism score	13(10-16)	12(12-16)	14(12-16)	2(2-5)	0.89	0.47	<0.001*	0.55	<0.001*	0.01*
Total testosterone (ng/dl)	51(39.9-60.9)	44(37-58.6)	43.1(35.2-60.7)	41.3(34.8-49.6)	0.26	0.25	0.02*	0.86	0.45	0.029*
SHBG (nmol/l)	21.4(15.7-30.7)	19.6(14.6-26.4)	19.3(17.2-25.9)	34.6(30.8-51.3)	0.48	0.8	0.004*	0.78	<0.001*	0.001*
FAI	6.7(4.4-13.5)	8.5(4-12.1)	8.2(5.2-10.1)	4.4(3-6.6)	0.99	1	0.015*	0.82	0.01*	0.003*
DHEA-S (µg/dl)	270.9(270.4-319)	269(179-350)	277.5(202.2-324)	225(155-296)	0.92	0.93	0.054	0.86	0.15	0.06
FSH (mIU/ml) [†]	5.9±1.6	6.4±1.4	6.4±1.7	6.2±1.7	0.32	0.1	0.54	0.83	0.72	0.31
LH (mIU/ml)	6.9(4.6-11.2)	5.5(3.5-8.5)	5.7(4.1-8.5)	7.1(4.6-12.1)	0.065	0.07	0.7	0.61	0.02*	0.04*
LH/FSH	1.2(0.8-2.2)	0.82(0.38-2.3)	0.8(0.6-1.4)	1.3(0.8-1.7)	0.01*	0.01*	0.85	0.59	0.009*	0.01*
Fasting glucose (mg/dl)	86(82-89)	83(76-86)	83(79-88)	83(78-87)	0.03*	0.14	0.03*	0.59	0.81	0.73
Postprandial glucose (mg/dl)	91(86-97.7)	89(86-102)	86(84-92)	88(76-92)	0.91	0.03*	0.03*	0.07	0.07	0.99
Insulin (µIU/ml)	11.1(8.9-17.1)	11.1(6.5-14.7)	11.1(8.2-15)	8.9(5.6-14.9)	0.26	0.42	0.04*	0.44	0.53	0.14
HOMA-IR	2.4(1.9-3.5)	2.2(1.3-2.6)	2.2(1.6-3)	1.7(1.1-3.1)	0.16	0.3	0.03*	0.39	0.62	0.18
HbA1C	5.3(5.2-5.7)	5.3(5.2-5.3)	5.3(5.2-5.6)	5.3(5.2-5.5)	0.014*	0.41	0.28	0.09	0.12	0.8

*Statistically significant

[†]Normally distributed variables according to Kolmogorov-Smirnov test (mean±SD)

BMI:Body Mass Index, DHEA-S:Dehydroepiandrosterone Sulphate, FAI:Free Androgen Index, Fsh:follicle Stimulating hormone, HOMA-IR:Homeostatic Model Assessment For Insulin Resistance, LH:Luteinising Hormone, SHBG:Sex Hormone Binding Globulin, p1: Comparison of Phenotype A and B, p2: Comparison of Phenotype A and C, p3: Comparison of Phenotype A and D, p4: Comparison of Phenotype B and C, p5: Comparison of Phenotype B and D, p6: Comparison of Phenotype C and D

DISCUSSION

In this study phenotype A was the most frequent phenotype of PCOS and followed by phenotype D, C, and B. Also some studies reported phenotype A as the most frequent phenotype (15-17) except studies from Iran (18) and China (19). Mehrabian et al. reported phenotype D as the most frequent phenotype and followed by A, B, and C, respectively (18). Zhang et al. found out in their case-control study among 719 women with PCOS, phenotype D as the most frequent phenotype and followed by A, C, and B, respectively (19). Yildiz et al. reported from Turkey phenotype C as the most frequent phenotype and followed by A, D, and B, respectively (20).

In this study we found that BMI of the women in phenotype A was higher than in phenotype B. Pehlivanov and Orbetzova reported the women in phenotype A and B were more obese (21). Also some studies reported the BMI of the women in phenotype A is higher than in other phenotypes (22,23). However some studies reported no differences about IR and BMI according to phenotypes (24,25).

In this trial we found LH and LH to FSH ratio significantly higher in phenotype D than other phenotypes. Incompatible with this study, Jamil et al. reported significantly higher LH to FSH ratio and total testosterone in phenotypes A and B and although the result was statistically insignificant they reported lower LH and LH to FSH ratio in phenotype D (23). In addition, Yilmaz et al. reported that LH to FSH ratio was higher in phenotype A, B and C than D (15).

We found no difference in this study according to hirsutism score, total testosterone and FAI between phenotypes A and B, A and C, and B and C. However, these parameters were statistically significantly lower in phenotype D than other phenotypes, as expected. Some studies reported mildly increase in serum androgens and hirsutism score in phenotype C than in A and B (22,26). Pehlivanov and Orbetzova reported the women in phenotype A and B were more hyperandrogenic than phenotype C and D (21).

Fasting glucose, postprandial glucose, HOMA-IR and fasting insulin were found to be significantly higher in phenotype A in this study, similar to some other studies (21-23,26), but this can be defined by the individuals' differences in body weight. Clark et al. reported higher fasting insulin levels in phenotype A and B compared with D. When data were adjusted for BMI, they reported no differences among PCOS phenotypes (27).

Chang et al. reported both biochemically detected HA and hirsutism were the greatest risk factor for hyperinsulinemia (7). Some studies reported increased HOMA-IR in hyperandrogenic women with PCOS than normoandrogenic women, like our study (20,28,29). Clark et al. also reported women with hirsutism alone had higher HOMA-IR and fasting insulin, than women with PCOM alone but the results was statistically insignificant when data were adjusted for BMI (27).

CONCLUSION

In conclusion, phenotype A is the most common phenotype of PCOS. Regardless of the phenotype, the individuals with $BMI \geq 30 \text{ kg/m}^2$ have higher HOMA-IR than the individuals with $BMI \leq 25 \text{ kg/m}^2$ and BMI between 25-29.9 kg/m^2 . Therefore, BMI is a better predictive factor for IR than phenotype.

Competing interests: The authors declare that they have no competing interest.

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