International Journal of Innovative Research in Medical Sciences (IJIRMS)
ISSN (Online): 2455-8737, Vol. 01, Issue 06, August 2016
Available online at – www.ijirms.in

The Prevalence of Metabolic Syndrome in Different Phenotypes of Pcos in Turkish Women

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Abstract:

Background: *Polycystic ovary syndrome (PCOS) is the most common endocrine and metabolic disorder amongst women of reproductive age, with a worldwide.*

Aims: *The aim of this study is to investigate the percentage of Metabolic syndrome (MetS) in different phenotypes of PCOS, as well as several metabolic characteristics.*

Material and Methods: *The study included 128 women with PCOS and 64 controls. The women were grouped into four phenotypes: hyperandrogenism (H) + chronic oligo-/anovulation (CA) + sonographic Polycystic Ovary morphology (PCOM), H-CA, CA-PCOM and H-PCO. The prevalence of MetS was determined for each group, according to the International Diabetes Foundation. Serum levels of glucose and insulin and the lipid profiles were assessed.*

Results: *Although, the prevalence of MetS was found to be higher in H-CA and CA-PCOM phenotypes, a statistically significant difference was observed only in the classical form of PCOS. The patients with CA-PCOM and with the classical form were more insulin resistant. Fasting glucose was found to be higher in all subsets of PCOS. Serum triglyceride levels were also found higher in patients with PCOS, except for the H-PCOM phenotypes.*

Conclusion: *According to this study, we could recommend a screening of the patients with the classical form of PCOS for MetS. An understanding of the exact etiopathogenesis and pathophysiology of PCOS in the future, might help to define the PCOS patients.*

Keywords: Polycystic ovary syndrome, metabolic syndrome, prevalence, phenotypes.

1. INTRODUCTION:

Polycystic Ovary Syndrome (PCOS) is the most common endocrine disturbance, affecting 5%–10% of women of reproductive age, and is characterized by Oligo-anovulation (OA), Hyper-androgenism (HA), and insulin resistance in most patients (1). PCOS is a heterogenic disorder with different clinical aspects. There is a great controversy regarding the diagnosis and classification of PCOS due to this heterogeneity (2). At the same time, genetic factors and epigenetics may predispose women to PCOS, a known hereditary disorder of uncertain etiology (3).

In 2003, the European Society for Human Reproduction and Embryology/American Society for Reproductive Medicine (ESHRE/ASRM) diagnostic criteria were formulated as two of the three criteria of HA, sonographic Polycystic Ovary Morphology (PCOM) and OA. Two new PCOS phenotypes were introduced by this definition; hyper androgenic ovulatory women with PCOM or non-hyper androgenic anovulatory women with PCOM (4). The most recent Androgen Excess and PCOS Society (AE-PCOS Society) criteria recommend that PCOS should be defined as a clinical or biochemical HA, associated with ovulatory dysfunction in the form of OA or PCOM (5). At the Amsterdam ESHRE/ASRM-sponsored PCOS Consensus Workshop Group in 2011, consensus was achieved on the identification of PCOS in the presence of two of the following three criteria: HA, OA and PCOM. (6).

Although, the debate continues about classification and diagnosis, women with PCOS usually show the tendency of having metabolic complications. It is discussed whether all women with PCOS should be screened for MetS and Insulin resistance (IR), since

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they may variants in terms of PCOS phenotype, ethnicity and age. In fact, insulin resistance and compensatory hyperinsulinemia have been proposed as an important factor in the etiopathogenesis of this disorder (7). PCOS women with (O + P) show moderate endocrine and metabolic abnormalities. Though, there were no respectable differences in IR, MetS and glucose intolerance between the four PCOS phenotypes, women with PCOS are at higher risk of impaired glucose tolerance and undiagnosed diabetes (8). Many patients with PCOS have features of the MetS, including insulin resistance, obesity, and dyslipidemia, suggesting an increased risk of cardiovascular disease. At least, one abnormal lipid level is seen in 70% of women with PCOS (9).

There are limited data on metabolic complications of PCOS phenotypes as defined by the Rotterdam criteria. Welt et al. reported that women with HA and OA had greater tendency to develop metabolic disorders. In contrast, patients with oligoanovulatory PCOS without HA, in another study, were reported to have more metabolic disturbance (10). Pehlivanov et al. reported the existence of significant differences in anthropometric, hormonal and metabolic indices between the classical form and the clinical variants of PCOS in a Bulgarian population (11). Shroff et al found that the risk of MetS may vary among the four phenotypes of PCOS based on the Rotterdam criteria (12).

Due to paucity of data, we aimed to investigate the prevalence of MetS in each phenotype of PCOS based on the Rotterdam criteria. As a secondary outcome, we also compared the metabolic and hormonal features of each group in this study.

2. MATERIALS AND METHODS

Subjects and selection of patients participating in the study

The study was organized as a case-control study. The patients with PCOS and admitted to our clinics were invited to participate in the study, until a minimum number of 34 was reached for each PCOS phenotype, according to the Rotterdam criteria. The age range of the patients was between 18 and 40 years. Thereafter, 68 healthy women, who are willing to participate, were randomly selected from an age-matched patient cohort. This cohort consisted of women attending to our outpatient clinics, for reasons other than endocrinopathies, including infertility (8 patients), infectious diseases (27 patients), general control (12 patients), dysmenorrhea and abdomino-pelvic pain (16 patients) and abnormal Pap smears (5 patients). All of the control women had under 8 of the Ferriman-Gallwey score and the transvaginal or transabdominal sonography (Logic 500, General Electric, Milwaukee, USA) revealed no polycystic ovary appearance. Each patient gave a written informed consent and the study protocol was approved by the Institutional Review Board.

The PCOS is diagnosed if any two of the three criteria was present; PCOM, OA and clinical (a Ferriman-Gallwey score > 8; acne, that persist through the second decade of life or through androgenetic alopecia) or biochemical HA, and the exclusion of non-classical congenital adrenal hyperplasia, thyroid dysfunction and hyperprolactinemia. The sonographic diagnosis of PCOM was confirmed, if there were 12 or more follicles measuring 2 mm–9 mm in diameter or having an increased ovarian volume (> 10 cm3). The women with PCOS were divided into four phenotypes according to the clinical characteristics; 1) Patients with OA + HA, 2) Patients with OA + PCOM, 3) Patients with PCOM + HA and 4) Patients with classical form (PCOM + HA + OA). The patients with any known endocrine disorder, including diabetes mellitus were not included in the study, in order to avoid the confusing effects of diabetes on measures of insulin secretion. The patients treated with medications, which are known to alter insulin hemodynamics, lipid profiles or oral contraceptives within three months, were not included, as well.

Participants were classified as having MetS if they met the following criteria suggested by the International Diabetes Foundation (IDF); central obesity defined as waist circumference greater than 80 cm in Europid women, plus any two of the following four factors: raised triglycerides ($\geq$ 150 mg/dl), reduced HDL cholesterol (< 50 mg/dl in females), raised blood pressure (systolic $\geq$ 130 or diastolic $\geq$ 85), and raised fasting plasma glucose ($\geq$ 100 mg/dl) (13).

BMI was calculated as weight (kilograms) divided by the squared height (meters). Waist and hip circumferences were registered and the Waist/Hip ratio (WHR) was calculated.

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Biochemical and Hormonal measures

After an overnight fast, the blood samples were collected for fasting glucose and insulin levels. Thereafter, all subjects underwent a 75 g Oral Glucose Tolerance Test (OGTT). The degree of IR was estimated as follows using the Homeostasis Model Assessment (HOMA) analysis. The HOMA method has been validated to be a good index of insulin resistance in subjects with a broad range of insulin sensitivity, and has a good correlation with the insulin-mediated glucose uptake, calculated by the euglycemic hyperinsulinemic glucose clamp (14).

Assay methods

Plasma glucose levels were determined by the glucose-oxidase method, immediately after the blood samples were obtained. Blood samples for hormones were centrifuged immediately, and serum was stored at –20°C until assayed. Insulin levels were determined by the auto-analyzer following the competitive electro-chemoluminescent immunoassay method (Elecys 2010 RDM, Germany).

Statistical analysis

Assuming a 15% prevalence of MetS in age-adjusted control group (15), and about 45% prevalence of MetS in each PCOS phenotypes (16), the power analysis dictated 64 women in the control group and 32 women in each PCOS subtypes, according to the Rotterdam criteria, at 5% significance level with 80% power (G*Power 3.1.7, Franz Faul, Universität Kiel, Germany). All statistical analyses were performed using the IBM SPSS Statistics v.20 Demo (IBM Corp, New York, US) for Windows. Baseline characteristics were presented as mean± SD for continuous variables; rates and proportions were calculated for categorical data. Normality of distribution for quantitative data was assessed by the Kolmogorov–Smirnov test. Differences between two groups in the univariate analysis were detected by the unpaired Student's t-test for continuous variables (after testing for equality of variance: Levene's test), and by the X^2 test and Fisher's exact test (when appropriate) for categorical variables. The one-way analysis of variance was used for comparison between phenotypes, after testing for the equality of variance. The Fisher's Least Significant Difference (LSD) post hoc correction was applied if the variables had equal variances and the Dunnett post hoc correction was applied if the variables did not have equal variances. Logarithmic or squared-root transformations were applied before ANOVA (Analysis of Variance), to ensure homogeneity of variances, as needed. A *P* value at or below 0.05 was considered as statistically significant.

3. RESULTS

The demographic, clinical and hormonal profile of the 128 PCOS-women and 64 control women are presented in Table 1. The women in PCOS and in control groups did not differ significantly in age and height (Table 1, P > 0.05). Only in the HA+PCOM phenotype was the hip circumference significantly lower than the circumference of the control women, and PCOS women with OA+PCOM and OA+HA+PCOM phenotypes, had significantly higher weight and BMI than the women in the control group (Table 1, P < 0.05). WHR was significantly higher in HA+PCOM and OA+HA+PCOM group than in the controls (P < 0.05). Furthermore, FSH, LH and E2 levels of PCOS women were significantly different than in the control group (P < 0.05, Table 1). No statistically significant differences were observed for these parameters within the phenotypes by the univariate analysis of variance.

Table 1. The baseline characteristics of women (mean, SD)

	OA+HA n = 32	OA+PCOM n = 32	HA+PCOM n = 32	OA+HA+PCOM n = 32	Control n = 64
Age (years)	23.0 (6.0)	25.0 (5.1)	23.4 (4.2)	25.7 (5.7)	24.3 (3.7)
Height (cm)	162.8 (6.7)	162.3 (4.3)	161.2 (7.3)	162.4 (5.3)	161.4 (5.2)
Weight (kg)	67.6 (13.2)	68.5 (13.4) [a]	65.1 (13.4)	71.6 (13.3) [a]	62.8 (14.5)
Body mass index (kg/m^2)	25.3 (4.2)	26.0 (4.6) [a]	25.1 (4.7)	27.5 (5.3) [a]	24.1 (3.3)

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Waist circumference (cm)	81.1 (10.9)	84.0 (11.6)	81.8 (10.0)	86.5 (12.1) [a]	81.4 (10.8)
Hip circumference(cm)	105.2 (9.6)	107.2 (10.4)	102.6 (9.3) [a]	108.7 (10.6)	107.1 (12.8)
Waist-to-hip ratio	0.77 (0.6)	0.78 (0.06)	0.80 (0.05) [a]	0.80 (0.06) [a]	0.76 (0.07)
FSH (mIU/ml)	6.8 (2.3) [a]	6.4 (1.2) [a]	6.1 (2.3)	6.4 (1.6) [a]	5.7 (0.7)
LH (mIU/ml)	6.6 (3.3) [a]	8.4 (4.9) [a]	7.7 (7.1) [a]	8.4 (3.3) [a]	4.0 (1.0)
Estradiol (pg/ml)	49.3 (31.5) [a]	49.5 (38.9) [a]	56.0 (49.0) [a]	46.4 (17.4) [a]	26.6 (5.7)
[a] significantly different from controls, $P < 0.05$, Student's t test no statistically significant difference was observed within the phenotypes, univariate analysis of variance					

Prevalence of the IDF, which defined MetS in PCOS patients, was as follows: 28.1% in OA+HA phenotype, 28.1% in OA+PCOM phenotype, 12.5% in HA+PCOM phenotype and 37.5% in OA+HA+PCOM phenotype (Table 2). The prevalence of MetS was 17.2% in the control group, and only the classical form of PCOS had significantly higher rate of MetS than the controls (P = 0.02, Table 2). Regarding individual components of MetS, only the classical form had statistically significant difference in the serum triglycerides level and systolic or diastolic blood pressure, and marginal significance in the waist diameter, when compared to controls (P < 0.05, Table 2).

Table 2. The prevalence of metabolic syndrome and its components across the groups (n, %)

	OA+HA n = 32	OA+PCOM n = 32	HA+PCOM n = 32	OA+HA+PCOM n = 32	Control n = 64
Metabolic syndrome	9 (28.1)	9 (28.1)	4 (12.5)	12 (37.5) [a]	11 (17.2)
Waist diameter > 80 cm	18 (56.3)	20 (62.5)	15 (46.9)	23 (71.9) [b]	33 (51.6)
Triglycerides ≥ 150 mg/dl	9 (28.1)	7 (21.9)	5 (15.6)	20 (62.5) [a]	12 (18.8)
HDL < 50 mg/dl	7 (21.9)	4 (12.5)	3 (9.4)	6 (18.8)	8 (12.5)
Raised blood pressure	12 (37.5)	11 (34.4)	9 (28.1)	18 (56.3) [a]	14 (21.9)
Fasting plasma glucose ≥ 100 mg/dl	5 (15.6)	6 (18.8)	3 (9.4)	6 (18.8)	8 (12.5)
[a] significantly different from controls; $P < 0.05$, [b] marginal significant difference from controls; $P = 0.057$					

Table 3 presents several metabolic parameters of the groups. The women with PCOS had significantly higher fasting level and 75 g of OGTT glucose (except for OA+HA phenotype) than the control group (P < 0.05, Table 3). Fasting insulin levels did not differ between the groups. HOMA was significantly higher in OA+PCOM and in the classical form than the control group (P < 0.05). Likewise, serum triglycerides levels were significantly higher in all groups, except HA+PCOM, than in the controls. Furthermore, the mean serum triglycerides level in patients with classical form were significantly higher than the patients with OA+HA and HA+PCOM phenotypes (P = 0.02, Table 3). Only the patients with OA+HA had significantly lower HDL cholesterol level than women with HA+PCOM and controls.

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Table 3. The comparison of metabolic parameters of the groups (mean, SD)

	OA+HA n = 32	OA+PCOM n = 32	HA+PCOM n = 32	OA+HA+PCOM n = 32	Control n = 64
Fasting glucose (mg/dl)	90.0 (11.1) [a]	91.6 (9.3) [a]	88.3 (8.9) [a]	92.2 (10.1) [a]	82.0 (7.1)
75 g OGTT glucose (mg/dl)	90.3 (28.3)	94.2 (19.6) [a]	94.3 (20.9) [a]	98.8 (33.9) [a]	84.5 (15.9)
Fasting insulin (µU/ml)	8.5 (5.5)	8.9 (4.6)	8.3 (4.8)	9.2 (6.2)	7.6 (4.5)
HOMA	1.0 (0.7)	1.1 (0.5) [a]	0.9 (0.5)	1.1 (0.6) [a]	0.8 (0.6)
Triglycerides (mg/dl)	108.1 (58.6) [a]	114.3 (57.8) [a]	94.9 (52.8)	137.3 (65.1) [ab]	84.0 (38.5)
HDL cholesterol (mg/dl)	48.7 (12.5) [ac]	54.4 (14.6)	63.9 (18.8)	54.0 (17.9)	58.6 (14.5)

[a] significantly different from controls, $P < 0.05$, Student's t test
[b] significantly different from OA+HA and HA+PCOM, univariate analysis of variance
[c] significantly different from HA+PCOM, univariate analysis of variance

4. DISCUSSION

The present study aimed to characterize the metabolic complications of the four PCOS phenotypes, as proposed by the Rotterdam criteria and their prevalence was compared with the control subjects. We found that the classical phenotype (OA + HA + PCOM) had about a twofold increased risk of MetS compared with the control group. Although, the prevalence of MetS in the OA + HA and OA + PCOM groups were higher than in the control groups, the difference was not statistically significant. The prevalence of MetS in the HA + PCOM group was similar to the control group. Concordant with this finding, the patients with classical form of PCOS had higher metabolic and cardiovascular risk factors, as depicted in Table 2 and 3.

The reported prevalence of metabolic syndrome in women with PCOS varies between 30% and 47% (17) depending on the criteria used for defining both the PCOS and the metabolic syndrome. In women with all three components of the syndrome, metabolic deformities are given at the highest level and has called PCOS phenotype serious metabolic screening may be necessary (8). The metabolic syndrome was present in 64 (46%) of the women with PCOS in a study (18). One of the largest studies by Abrodanidze et al., 43% prevalence of MetS was found in a general PCOS population; however, they did not study the phenotypes of PCOS according to the Rotterdam criteria (16). In fact, they compared the PCOS women with and without MetS, and concluded that women with concurrent PCOS and MetS exhibited, more frequently, the phenotypic feature of acanthosis nigricans, a putative biomarker of insulin resistance. More severe hyperandrogenemia, showed a higher serum free testosterone, and a lower serum SHBG concentrations, than PCOS women without the MetS. Yildiz et al. also suggested an increased risk of MetS in the PCOS, regardless of the diagnostic criteria used for the PCOS (19). Echiburú et al. indicated that metabolic imbalances associated with PCOS are more evident at the early and late reproductive ages. Furthermore, during perimenopause, there is no further impairment of metabolic parameter. Further studies in the late postmenopausal period are needed in order to support whether these women actually develop cardiovascular events and full metabolic disorders (20). Given that such screening programs would place an additional burden on the national budget in developing countries such as Turkey, for this reason, it seems sensible to detect in which risk group the women with PCOS are included, reproductively or metabolically and arrange the screening programs (2). In a community-based study in Turkey in 2013, the prevalence of MetS in women between the ages of 40 and 50 was 36.7%. The prevalence of MetS in Turkish adults aged 40 years or over, currently standing at 53% and shows significant differences across geographic regions (21). Limited number of studies investigated the prevalence of MetS in the PCOS phenotypes

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determined by the Rotterdam criteria. Shroff et al. explained a similar and significantly higher risk of MetS (35% - 44%) in the three PCOS phenotypes than controls, except for the non-hyperandrogenic PCOS phenotype (OA + PCOM, 20%) (12). In contrast, we observed a statistically significant increase in the prevalence of MetS (37.5%), in classical form of PCOS only. Although, the rates of MetS in OA + HA and OA + PCOM (28.1% for both groups) were higher than in the control group, the difference was not statistically significant. The rate of MetS in HA + PCOM women (12.5%) were almost identical to that of the control group (17.5%). Welt et al. found the highest rate of MetS in women in the OA + HA group (22.2%), and the lowest rate in OA + PCOM group (5.6%), however, they did not study the classical form of PCOS (10). The inconsistency in the rates of MetS between this study and in the above-mentioned studies may have several explanations, but generally speaking, the classical form of PCOS usually counter-exists with MetS.

Several factors may affect the prevalence of MetS in PCOS women, including obesity IR and diabetes, as well as different diagnostic criteria for MetS (22,23). Furthermore, the different rates of MetS in these studies may originate from genetic factors and geographic distribution, dietary characteristics, and lifestyle factors in different countries. In the largest study about this subject, Panidis et al. had similar findings with the current study (24). They found that OA + PCOM phenotype had higher fasting glucose levels than the OA + HA subtype. Although, the fasting insulin levels and HOMA were highest in the classical form and in the OA + PCOM phenotype, there were no statistically significant differences between phenotypes regarding these parameters. However, in the subgroup analyses, the differences were more prominent in women with higher BMI, in contrast to the findings of Welt et al. (10).

There are numerous studies in the literature regarding metabolic parameters, including the glucose and insulin levels and lipid profiles in PCOS women. With regard to PCOS phenotypes, majority of previous studies reported that women with the classic phenotype were more insulin resistant than those with either the ovulatory (25, 26) or the normoandrogenic phenotype (27,28). However, several studies did not confirm these findings (12, 24). A comparison between the ovulatory and the normoandrogenic phenotypes, gave even more discordant results (29). Moreover, in the comparison between control women without PCOS, the classic phenotype subgroup generally appeared to be insulin resistant (10, 26, 28).

We found that all phenotypes had minor, but statistically significant differences in the mean fasting glucose levels, when compared with the controls. Likewise, 75 OGTT glucose levels were also significantly higher than the control group, except for the OA + HA phenotype. However, no statistically significant difference was observed in fasting insulin levels. HOMA was higher in OA + PCOM and classical form than in the control group, but there was no statistically significant difference within the phenotypes. Welt et al (10) found no difference in the three subsets of PCOS in regard to the fasting glucose levels, however, they observed that fasting insulin levels were highest in OA + HA (11.7 $\pm$ 10.7 µU/ml) and higher in OA + PCOM (9.9 $\pm$ 17.6 µU/ml), with no difference in HA + PCOM phenotype (6.6 $\pm$ 3.8 µU/ml), when compared to the controls (6.5 $\pm$ 4.0 µU/ml). Panidis et al (24) could not find any statistically significant difference in terms of fasting glucose levels between the control group and the PCOS phenotypes, except for patients with OA + PCOM. Similar to our study, they (24) observed a higher HOMA in OA + HA, OA + PCOM and in the classical form of PCOS than in the controls, but there was no differences observed within the phenotypes.

Lastly, almost all phenotypes in this study had higher triglyceride levels when compared to the controls. The patients with the classical form of PCOS had the highest serum triglyceride level. Interestingly, however, lower HDL cholesterol level was only observed in patients with OA + HA phenotype. In the study of Gluszak et al., there were no statistically significant differences among the phenotypical groups, in terms of lipid profile, although, the levels of total cholesterol and LDL cholesterol were usually higher than normal in the classical form of PCOS (30). These characteristics, which were associated with hypertriglyceridemia and a higher HOMA-IR in the PCOS groups, suggest that these women may be at a higher risk of cardiovascular events (5).

5. CONCLUSION

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Patients with PCOS have different metabolic problems. Efforts to define a specific phenotype of PCOS yielded conflicting results. According to the conclusions of both the ESHRE/ASRM Rotterdam workshop and the AE-PCOS consensus statement, PCOS remains a syndrome and, therefore, no single diagnostic feature is sufficient per se for clinical diagnosis and prediction of tendency to metabolic disorders. However, in the light of the literature and in the current study, we can conclude that the classical form of PCOS has more metabolic abnormalities. Otherwise, prospective studies should be implemented to confirm the findings of cross-sectional studies. A recent suggestion was made to screen all obese women with PCOS for MetS. We could add the classical form of PCOS to this suggestion. Understanding the exact etiopathogenesis and pathophysiology of PCOS in the future, might help to define the PCOS patients under the risk of MetS.

ACKNOWLEDGEMENTS

The authors are grateful to all the patients in the study and thank you very much for their contribution such as in matters; patient selection, literature review, analysis and evaluation results to Yavuz Gozukara, Utku Akgor, Gulcan Akalan and Hakan Aytan.

CONFLICT OF INTEREST

The authors declare that they have no conflict of interests.

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