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Comparison Of Biochemical Markers and Insulin Resistance of Polycystic Ovary Syndrome Patients Diagnosed with the Criteria of Rotterdam, Androgen Excess Society and National Institutes of Health

Rotterdam, Androgen Excess Society ve National Institutes of Health Kriterlerine Göre Tanı Alan Polikistik Over Sendromlu Hastaların Biyokimyasal Değerleri ve İnsülin Direncinin Karşılaştırılması

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Abstract

Objective: There are different criteria to diagnose polycystic ovary syndromes such as Rotterdam Consensus, Androgen Excess Society, and National Institutes of Health. We aimed to investigate the biochemical and insulin resistance-related markers of polycystic ovary syndrome patients according to different diagnostic criteria.

Material and Method: 1299 patients admitted to our clinic retrospectively analyzed. Following the inclusion and exclusion criteria, 200 patients with Rotterdam (Group 1), 182 patients with AES (Group 2), and 180 patients with NIH (Group 3) criteria were included in the study.

Results: Waist/hip ratio among all groups (p1 = 0.002; p2 = 0.0001; p3 = 0.0001), LH/FSH ratio between Group 1 and 3 (p2=0.017), AST between Group 2 and 3 (p3 =0.012), DHEA-S and modified Ferriman–Gallwey score between Group 1 and 2 (p1 = 0.041; p1 = 0.013, respectively) and Group 1 and 3 (p2= 0.003; p2 = 0.04, respectively) were significantly different. A significant difference was detected between Groups 1 and 3 in body mass index ≥ 25 (kg/m^2) (p = 0.006). A significant difference was detected among all groups in waist circumference ≥ 88 cm (p1 = 0.0001, p2 = 0.0012, p3 = 0.004).

Conclusion: The rate of metabolic syndrome was found to be higher in patients diagnosed with Rotterdam criteria, the rate of insulin resistance with NIH criteria, and the rate of dyslipidemia with AES criteria. However, these differences were not statistically significant.

Öz

Amaç: Polikistik over sendromu tanısında Rotterdam Consensus, Androjen Excess Society, ve National Institutes of Health gibi cemiyetlerin farklı kriterleri kullanılmaktadır. Biz bu çalışmada polikistik over sendromu ön tanısıyla kliniğe başvuran hastaların farklı polikistik over sendromu tanı kriterlerine göre biyokimyasal değerlerini ve insülin direncini karşılaştırmayı amaçladık.

Gereç ve Yöntem: Kliniğimize polikistik over sendromu ön tanısıyla başvuran 1299 hasta retrospektif olarak incelendi. Dahil edilme ve dışlama kriterlerinin uygulanmasını takiben Rotterdam kriterleri ile (Grup 1) 200, Androjen Excess Society kriterleri ile (Grup 2) 182, ve National Institutes of Health kriterleri ile (Grup 3) 180 hasta polikistik over sendromu tanısı konularak çalışmaya dahil edildi.

Bulgular: Bel/kalça oranında tüm gruplar arasında (p1=0,002; p2=0,0001; p3=0,0001), LH/FSH oranında Grup 1 ve Grup 3 arasında (p2=0,017), AST Grup 2 ve Grup 3 arasında (p3=0,012), DHEA-S ve modifiye Ferriman–Gallwey skoru Grup 1 ve Grup 2 (sırasıyla p1=0,041; p1= 0,013,) ile Grup 1 ve Grup 3 (sırasıyla p2= 0,003; p2=0,04) arasında istatistiksel olarak anlamlı farklı bulundu. Vücut kütle indeksi≥ 25 (kg/m^2) olan hasta yüzdesi Grup 1 ile Grup 3 arasında istatistiksel olarak anlamlı farklı bulundu (p=0,006). Bel çevresi ≥ 88 cm olan hasta yüzdesinde tüm gruplar arasında istatistiksel olarak anlamlı fark saptandı (Grup 1 ve Grup 2 için p1=0,0001, Grup 1 ve Grup 3 için p2=0,0012, Grup 2 ve Grup 3 için p3=0,004).

Sonuç: Metabolik sendrom görülme sıklığı Rotterdam tanı kriterleri ile, insulin direnci görülme sıklığı National Institutes of Health tanı kriterleri ile, dislipidemi görülme sıklığı ise Androjen Excess Society tanı kriterleri ile polikistik over sendromu tanısı alan kadınlarda istatistiksel anlama ulaşmasa da daha yüksek saptanmıştır.

INTRODUCTION

Polycystic ovary syndrome (PCOS) is a common disorder seen in approximately 10% of young women (1). Hyperinsulinemia and increased production of luteinizing hormone (LH)-dependent androgens in the ovaries have a major effect on PCOS pathogenesis. Hyperinsulinemia stimulates ovarian androgen secretion (2). Estrogen production from peripheral androgens is increased in obese patients with PCOS. In addition, since the level of sex hormone-binding globulin (SHBG) decreases, free testosterone increases (3). Dehydroepiandrosterone sulfate (DHEA-S) was found above normal values in 25% of women with PCOS (4). The increase in body fat mass causes to release insulin and develop insulin resistance. The cause of hyperinsulinemia and insulin resistance in PCOS is not only obesity. Also, insulin-stimulated receptor autophosphorylation was found to be decreased in both obese and lean patients (5).

In addition to insulin and androgens, there are differences in many biochemical markers in PCOS. Abnormal serum gonadotropin levels which are high LH and normal or low follicle stimulating hormone (FSH) are present in 75% of PCOS cases (6). In particular, the increase in the frequency of persistent, rapid LH pulses causes an increase in the LH/FSH ratio in PCOS (7). LH hypersecretion is a characteristic feature of PCOS. Prolactin levels are slightly increased in approximately 25% of patients with PCOS (8). Again, triglyceride (TG), total cholesterol (TC) and low density lipoprotein (LDL)-cholesterol levels increased, and high density lipoprotein (HDL)-cholesterol and apoprotein A-I levels decreased in patients with PCOS (9).

Currently, there are different criteria to diagnose PCOS such as Rotterdam Consensus (10), Androgen Excess Society (AES) (11) and National Institutes of Health (NIH) (12). Herein, we aimed to investigate the biochemical and insulin resistance-related markers of PCOS patients diagnosed with different diagnostic criteria.

MATERIAL and METHOD

In our study, 1299 patients with a pre-diagnosis of PCOS who applied to the Gynecology and Obstetrics Department of our university hospital which is a tertiary center were retrospectively evaluated between April 2011 and August 2012. The patient's history, gynecological examination notes and laboratory examinations were obtained from hospital database.

26 patients whose menstrual cycle was not recorded, 34 patients without ultrasonographic findings, 30 patients without prolactin value, 50 patients without TSH value, and as a result, a total of 140 patients were excluded from the study due to missing data. 207 patients were excluded from the study because of their existing diseases (30 premature ovarian failure, 35 thyroid disease, 35 liver disease, 25 renal disease, 37 diabetes mellitus, 45 other chronic diseases). Patients with only oligomenorrhea (n=151), only polycystic ovarian morphology (n=138), and only hirsutism (n=101) were not included in the study. The remaining 562 patients were included in the study by dividing them into 3 groups according to Rotterdam, AES, and NIH diagnostic criteria.

Rotterdam diagnostic criteria (oligo and/or anovulation; clinical and/or biochemical signs of hyperandrogenism; polycystic ovarian morphology by pelvic ultrasonography after exclusion of other causes of hyperandrogenism, hyperprolactinemia, hyper/hypothyroidism, Cushing's syndrome, and adrenal hyperplasia) were used for Group 1 (10). 200 patients with at least two of these criteria were included in the study with the diagnosis of PCOS.

AES diagnostic criteria (biochemical or clinical hyperandrogenism; oligo-anovulation or polycystic ovaries on ultrasound; exclusion of other diseases such as adrenal hyperplasia, severe insulin resistance syndromes, androgen-secreting neoplasms, idiopathic hirsutism, hyperprolactinemia and thyroid disorders) were used for Group 2 (11). 182 patients with at least two of these criteria were included in the study with the diagnosis of PCOS.

NIH diagnostic criteria (in order of importance: clinical or biochemical hyperandrogenism; oligo-anovulation; exclusion of other known diseases (hyperprolactinemia, Cushing's Syndrome, non-classical congenital adrenal hyperplasia) were used for Group 3 (12). 180 patients were included in the study with the diagnosis of PCOS.

In our study, clinical hyperandrogenism was defined as having a modified Ferriman-Gallewey (mFG) score 8 or higher (13). Total testosterone level higher than 65.8 ng/dL, DHEA-S level higher than 374.9 mg/dL, or free androgen index (FAI) higher than 4.94 was accepted as biochemical hyperandrogenism. Less than eight periods per year or a period longer than five weeks was accepted as oligomenorrhea. Polycystic ovarian morphology was accepted as more than 12 antral follicles in at least one ovary on ultrasonography.

Demographic data, waist and hip circumference, systolic and diastolic blood pressure, mFG score, menstrual pattern and ultrasonography findings of all patients participating in the study were recorded. In addition, endocrine values such as FSH, LH, TT, free testosterone, DHEA-S, SHBG, prolactin, thyroid stimulating hormone (TSH), fasting insulin, fasting glucose, blood urea nitrogen (BUN), creatinine, prolactin, aspartate amino transferase (AST), alanine amino transferase (ALT), C-reactive protein (CRP), lipid profile, oral glucose tolerance test (OGTT) values were noted. FAI was also calculated with the formula TTx100/SHBG.

Body mass index (BMI) of the patients was calculated with the formula of body weight (kg) / height (m^2). BMI between 25 -29 kg/m^2 was considered overweight, and BMI over 30 kg/m^2 was considered obese. Patients with a waist/hip ratio (WHR) greater than 0.85 were considered android obese.

Insulin resistance was evaluated with the homeostatic model assessment of insulin resistance (HOMA-IR = fasting serum insulin (μU/mL) x fasting serum glucose (mg/dL) /450). A HOMA-IR index value above 3.8 was considered as insulin resistance. After a 75-g OGTT, the 120th minute plasma glucose level between 140-199 mg/dL was accepted as impaired glucose tolerance (IGT).

Metabolic syndrome (MetS) was diagnosed if at least three of these features were present: waist circumference ≥ 88 cm, TG level ≥ 150 mg/dL, HDL level <50 mg/dL (or using lipid-lowering medication), blood pressure ≥ 130/85 mmHg

(or using antihypertensive medication), and fasting plasma glucose ≥ 100 mg/dL (14).

Dyslipidemia was diagnosed if at least one of these features was present: LDL ≥ 130 mg/dL, HDL <50 mg/dL, TG ≥ 150 mg/dL, TC ≥ 200 mg/dL, and TC / HDL ≥ 5.6 (15).

Statistical analysis of research data was performed with SPSS Statistics 19 (IBM, Armonk, New York, USA) program. Data for continuous variables were presented as mean (mean) ± standard deviation (sd), median (interquartile range [IQR]) and data for categorical variables as numbers (percentage%). Whether the quantitative variable data showed normal distribution was tested with the Kolmogorov-Smirnov test.

In the comparison of quantitative variables in all groups, one-way analysis of variance (ANOVA) in independent groups, Kruskal Wallis analysis of variance, smallest difference method (LSD) and Mann Whitney U test were used in pairwise comparison of groups. The comparison of qualitative variables according to the groups was done with the chi-square test. $p < 0.05$ was considered statistically significant.

RESULTS

Comparison of demographic and biochemical variables of all groups is summarized in Table 1. A statistically significant difference was found between WHR, AST level, LH/FSH ratio, DHEA-S level, and mFG score (p= 0.0001, p= 0.035, p= 0.041, p= 0.010, and p= 0.007, respectively) of the patients. When the groups were compared in pairs, significant differences were found among all groups in WHR (p1= 0.002; p2= 0.0001; p3=0.0001), Group 1 and 3 in LH/FSH ratio (p2=0.017), Group 2 and 3 in AST value (p3=0.012), Group 1 and 2 (p1=0.041; p1= 0.013, respectively) and Group 1 and 3 (p2= 0.003; p2=0.04, respectively) in DHEA-S value and mFG score [Table 1].

Comparison of obesity and insulin resistance data of all groups is summarized in Table 2. The percentages of patients with BMI ≥ 25 (kg/m^2) were found to be statistically significantly different among the groups (p=0.023). When the groups were compared in pairs, a statistically significant difference was found between Group 1 and 3 in BMI ≥ 25 (kg/m^2) (p2=0.006) [Table 2].

Comparison of metabolic syndrome and dyslipidemia components among the groups is summarized in Table 3. The percentages of patients with a waist circumference of ≥ 88 cm were statistically significantly different among the groups (p=0.002). When the groups were compared in pairs, a statistically significant difference was found among all groups (p1=0.0001; p2=0.0012 3; p3=0.004) [Table 3].

DISCUSSION

PCOS is a chronic disorder characterized with oligo-anovulation, marked increase in androgen levels and increased cardiovascular risk with metabolic disorders such as obesity, dyslipidemia and insulin resistance (16).

In a study comparing PCOS phenotypes with control groups based on the Rotterdam diagnostic criteria in the literature, a significant difference was found in FG score, waist circumference ≥ 88 cm, BMI ≥ 25 (kg/m^2), DHEA-S, testosterone level, FAI (p<0.01) (17). In our study, three different groups were formed based on the Rotterdam, AES, and NIH criteria, and a significant difference was found among the groups in mFG score, waist circumference ≥ 88 cm, BMI ≥ 25 (kg/m^2), and DHEA-S level. However, in our study, a significant difference was not found among the groups in FAI or testosterone levels (p>0.05).

In the literature, it has been shown that metabolic syndrome is more common in PCOS patients diagnosed with AES

Table I. Comparison of demographic and biochemical variables of all groups

Variables	Group1 (mean±sd) (n=200)	Group2 (mean±sd) (n=182)	Group3 (mean±sd) (n=180)	p	p1	p2	p3
Age	25.41±6.36	24.59±6,05	24.18±5.38	0.124	-	-	-
BMI (kg/m^2)	24.82±5.09	24.33±5.20	23.57±4.72	0.054	-	-	-
mFG Score a	12.0 (8)	12.0 (6.25)	13.0 (6)	0.007*	0.013	0.004	0.749
Waist/hip ratio	0.67±0.13	0.72±0.12	0.80±0.22	0.0001*	0.002	0.0001	0.0001
SBP (mmHg)	115.98±12.99	116.29±11.62	114.31±12.37	0.265	-	-	-
DBP (mmHg)	73.79±10.23	72.64±9.67	74.77±11.09	0.151	-	-	-
FSH (mIU/mL)	5.77±1.93	5.71±2.02	5.67±2.04	0.890	-	-	-
LH (mIU/mL)	6.42±3.59	6.54±4.01	7.33±4.42	0.060	-	-	-
LH/FSH	1.20±0.70	1.23±0.78	1.40±0.92	0.041*	0.688	0.017	0.052
TSH (mIU/mL)	1.55±0.88	1.62±0.87	1.58±0.90	0.708	-	-	-
Prolactin (ng/dL)	13.30±7.78	13.12±7.81	13.46±8.30	0.919	-	-	-
Total testosterone (ng/dL)	43.74±25.27	48.84±38.80	45.96±37.44	0.345	-	-	-
Free testosterone (ng/dL)	4.99±7.63	5.26±7.82	6.26±7.34	0.339	-	-	-
BUN (mg/dL)	10.29±2.61	10.34±2.52	10.21±2.43	0.883	-	-	-
Creatinine (mg/dL)	0.73±0.63	0.73±0.63	0.73±0.67	0.992	-	-	-

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AST (U/L)	18.79±5.92	18.35±5.36	19.88±6.04	0.035*	0.460	0.067	0.012
ALT (U/L)	18.08±9.31	17.35±8.64	19.45±9.09	0.083	-	-	-
FAI	5.66±5.06	6.39±5.94	6.20±6.19	0.453	-	-	-
SHBG (nmol/mL)	44.84±36.01	40.10±32.18	39.06±28.46	0.178	-	-	-
DHEA-S (µg/dL)	206.12±96.06	228.72±111.6	238.93±115.0	0.010*	0.041	0.003	0.367
Fasting insulib (µIU/mL)	13.61±12.39	14.72±16.89	13.63±16.45	0.728	-	-	-
Fasting glucose (mg/dL)	92.29±13.76	92.17±13.39	91.83±13.91	0.947	-	-	-
OGTT 1st hour (mg/dL)	128.93±37.26	128.81±35.43	121.64±35.14	0.086	-	-	-
OGTT 2nd hour (mg/dL)	108.00±32.06	105.18±30.19	102.51±31.34	0.231	-	-	-
HOMA-IR	3.76±3.69	4.20±5.54	4.38±6.96	0.533	-	-	-
TC (mg/dL)	165.97±36.87	165.26±35.68	164.27±35.46	0.900	-	-	-
Triglyceride (mg/dL)	107.27±60.37	106.24±60.97	107.42±48.67	0.977	-	-	-
HDL-Cholesterol (mg/dL)	47.98±13.54	46.80±11.58	48.28±12.20	0.487	-	-	-
LDL-Cholesterol (mg/dL)	98.14±30.17	98.69±30.17	98.57±26.64	0.981	-	-	-
VLDL-Cholesterol (mg/dL)	20.89±12.18	21.24±12.41	20.77±9.99	0.923	-	-	-
CRP (mg/dL)	5.94±6.22	5.69±6.38	6.40±5.48	0.531	-	-	-

*Statistically significant (p value <0.05).
p: general comparison among the groups, p1: group1 and group2, p2: group1 and group3, p3: group2 and group3.
a Median (IQR)
BMI: Body mass index; SBP: Systolic blood pressure; DBP: Diastolic blood pressure; FSH: Follicle stimulating hormone; LH: Luteinizing hormone; TSH: Thyroid stimulating hormone; BUN: blood urea nitrogen; AST: Aspartate amino transferase; ALT: Alanine amino transferase; FAI: Free androgen index; SHBG: Sex hormone binding globulin; mFG: modified Ferriman-Gallewey; DHEA-S: Dehydroepiandrosterone sulfate; OGTT: Oral glucose tolerance test; HOMA-IR: Homeostatic model assessment of insulin resistance; TG: Triglyceride; HDL: High density lipoprotein; LDL: Low density lipoprotein; VLDL: Very low density lipoprotein; CRP: C-reactive protein

Table II. Comparison of obesity and insulin resistance among the groups

Variables	Group 1 number (%) n=200	Group 2 number (%) n=182	Group 3 number (%) n=180	P
BMI ≥ 25 (kg/m^2)	79 (39.5%)	59 (32.4%)	47 (26.3%)	0.023*
BMI ≥ 30 (kg/m^2)	30 (15.0%)	25 (13.7%)	18 (10.1%)	0.339
IR (HOMA-IR ≥ 3.8)	71(35.7%)	60 (33.0%)	67 (37.2%)	0.698
IGT	39 (19.5%)	27 (14.9%)	30 (16.7%)	0.470

*Statistically significant (p value <0.05)
BMI: Body mass index; IR: Insulin resistance; HOMA-IR: Homeostatic model assessment of insulin resistance; IGT: Impaired glucose tolerance

Table III. Distribution of metabolic syndrome and dyslipidemia components among the groups

Variables	Group 1 number (%) n=200	Group 2 number (%) n=182	Group3 number (%) n=180	p
Fasting glucose ≥ 100 mg/dL	42 (21.0%)	37 (20.3%)	33 (18.3%)	0.799
Waist circumference ≥ 88 cm	80 (40.0%)	70 (38.5%)	44 (24.4%)	0.002*
Blood pressure ≥ 130/85 mmHg	21 (10.5%)	11 (6.0%)	14 (7.8%)	0.330
HDL-Cholesterol < 50 mg/dL	120 (60.0%)	117 (64.3%)	105 (58.3%)	0.486
TG ≥ 150mg/dL	39 (19.5%)	35 (19.2%)	36 (20.0%)	0.983
TC ≥ 200 mg/dL	40 (20.0%)	39 (21.4%)	36 (20.0%)	0.867
TC /HDL- Cholesterol ≥ 5.6	32 (16.0%)	30 (16.4%)	29 (16.2%)	0.145
LDL- Cholesterol ≥ 130 mg/dL	44 (22.0%)	38 (20.8%)	39 (21.7%)	0.643
MetS	44 (22.0%)	37 (20.3%)	33 (18.3%)	0.619

*Statistically significant (p value <0.05).
HDL: High density lipoprotein; TG: Triglyceride; LDL: Low density lipoprotein; MetS: Metabolic syndrome

criteria (2, 11). In our study, the rate in the general population who were diagnosed with PCOS via Rotterdam diagnostic criteria is compatible with the literature (18). In addition, PCOS patients diagnosed with AES had higher metabolic syndrome rates compared to PCOS patients diagnosed with NIH (20.3% and 18.3%, respectively), and this difference is consistent with previous studies (19, 20). Obesity, insulin resistance and IGT are less common in PCOS patients diagnosed with NIH (14). But, there was no significant difference among the groups in metabolic syndrome rates in our study (p= 0.619). We think that the diagnosis of PCOS with the Rotterdam criteria will be helpful in preventing the long-term effects of PCOS, since metabolic syndrome has a similar frequency in different PCOS phenotypes.

One of the metabolic effects of insulin resistance is on the lipid profile. In a study, women diagnosed with PCOS were evaluated in terms of lipid level, obesity and metabolic syndrome (21). In this study, hypertriglyceridemia, low HDL, high TC, high LDL levels were found in the insulin resistant group, and hypertension, hyperglycemia, obesity and metabolic syndrome were observed to be significantly higher. In many studies, an abnormal lipid profile characterized by increased triglyceride and LDL and decreased HDL has been found in patients diagnosed with PCOS (22). Dyslipidemia is one of the risk parameters in cardiovascular diseases, and high LDL-cholesterol increases the risk of cardiovascular disease 3-7 times (23). In our study, the percentage of HDL-cholesterol < 50 mg/dL, TC ≥ 200 mg/dL, and TC/HDL cholesterol ≥ 5.6 in the AES-PCOS group were found to be higher compared to other groups. However, no significant difference was observed among the groups (p>0.05). Although the incidence of TG ≥ 150 mg/dL in the NIH-PCOS group and LDL-cholesterol ≥ 130 mg/dL in the Rotterdam-PCOS group was found to be higher compared to the other groups, there was still no significant difference among the groups (p>0.05). In the light of all these results, it can be said that the probability of detecting dyslipidemia in PCOS patients diagnosed with AES diagnostic criteria is higher than other criteria.

Recent studies in the literature show that CRP leads to atherothrombosis by directly causing endothelial cell inflammation in the formation of atherosclerosis (24). It is also known that there is a correlation between insulin resistance and hs-CRP levels. The decrease in insulin sensitivity inhibits the physiological role of insulin in the synthesis of acute phase proteins in the liver. Therefore, insulin resistance increases the synthesis of CRP (25). Studies have shown that CRP concentration in women with PCOS can be a risk factor for cardiovascular diseases and type 2 DM (26, 27). In addition, the increase in circulating CRP levels plays an important role in the pathogenesis of PCOS (26). In this respect, CRP values were examined in our study, but no significant difference was found among groups in CRP levels (p>0.05).

There are strengths and limitations of the present study. The major strength was the simultaneous comparison of groups according to three important diagnostic criteria. However, the retrospective design and limited sample size were considered as limitations of our study.

In conclusion, the rate of metabolic syndrome was found to be higher in patients diagnosed with Rotterdam criteria, the rate of insulin resistance with NIH criteria, and the rate of dyslipidemia with AES criteria. However, these differences were not statistically significant.

With further studies, the success of different diagnostic criteria in detecting PCOS-related complications will become clear.

Authors' Contributions: All authors contributed to the research hypothesis formulation, design and organization and supervision. Material preparation was performed by Pınar Kırıcı, Ebru Çelik. Data were collected by Pınar Kırıcı. Statistical analysis were performed by Pınar Kırıcı, Ebru Çelik and Seval Müzeyyen Ecin, The first draft was written by Pınar Kırıcı. The article was edited and finalized by Pınar Kırıcı, Ebru Çelik, Seval Müzeyyen Ecin, Sevil Çiçek. All authors approved the final version of the manuscript.

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