Phenotypic subgroups of polycystic ovary syndrome have different intra-renal resistance symptoms

Fenotypowe podgrupy zespołu policystycznych jajników mają różne objawy wewnątrznerkowej oporności

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Abstract

Objective: *The polycystic ovary syndrome (PCOS) is known to be related with increased metabolic and cardiovascular risks. Various phenotypic subgroups of PCOS have been proven to have metabolic and endocrine disorders with varying degrees of severity. However, intra-renal vascular resistance, which is an indirect indication of atherosclerosis, remains unknown in PCOS subgroups. In this study we examined whether PCOS subgroups have different intra-renal resistance symptoms.*

Material and Methods: *98 PCOS patients (diagnosed according to the Rotterdam criteria) 30 controls were included in the study. The diagnosis of PCOS was established in the presence of at least two of the following criteria: 1- oligo and/or amenorrhea (OM); 2- clinic and/or biochemical signs of hyperandrogenism (HA); 3- polycystic ovarian morphology (PCO) detected by transvaginal ultrasonography. 37 patients (Group 1) met all three criteria (HA+OM+PCO), 29 patients (Group 2) met two of the criteria including hyperandrogenism (HA+OM or HA+PCO) and the remaining 32 patients (Group 3) had no hyperandrogenism but fulfilled the other two criteria; PCO+OM. Renal Doppler ultrasonography and hormonal/ biochemical analyses were carried out. The first outcome measure was designated as the differences in the renal resistive index (RRI) values of the groups, and the second outcome measure was designated as the relation of RRI with the insulin resistance and lipid profile.*

Results: *In Group 1, the RRI and the homeostasis model assessment of insulin resistance (HOMA-IR) values were significantly higher than in Group 3 and controls (P < 0.031, P < 0.001, respectively, after adjusting for age and BMI). The RRI and HOMA-IR values in Group 3 were similar to those of the control group. It was determined that RRI has a positive correlation with HOMA-IR (r=0.784, P<.0001) and BMI (r=0.645, P<.0001).*

Conclusions: *In this study, we demonstrated that PCOS subgroups have metabolic and endocrine disorders and cardiovascular risks of varying degrees of severity. Moreover, we showed that there was no increase of metabolic and cardiovascular risks in PCOS patients without hyperandrogenism.*

Key words: **Polycystic Ovary Syndrome** / **phenotypic subgroups of PCOS** / / **insulin resistance** / **renal resistive index** /

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Streszczenie

Cel pracy: *Zespół policystycznych jajników jest związany ze zwiększonym ryzykiem metabolicznym i sercowo-naczyniowym. Fenotypowe podgrupy w obrębie zespołu PCO charakteryzują się zaburzeniami metabolicznymi i endokrynnymi o różnym stopniu nasilenia. Jednak wewnątrznerkowa oporność naczyniowa, która jest pośrednim wykładnikiem miażdżycy, pozostaje nieznana w podgrupach zespołu PCO. W badaniu ocenialiśmy czy podgrupy zespołu PCO mają różne objawy wewnątrznerkowej oporności.*

Materiał i metoda: *do badania włączono 98 pacjentek z zespołem PCO (zdiagnozowanym według kryterium z Rotterdamu) oraz 30 pacjentek kontrolnych. Rozpoznanie zespołu PCO postawiono na podstawie obecności przynajmniej dwóch z poniżej wymienionych kryteriów: 1-oligo i/lub amenorrhea (OM); 2-kliniczne lub biochemiczne objawy hiperandrogenizmu (HA); 3-policystyczny obraz jajników (PCO) w przezpochwowym badaniu ultrasonograficznym. Grupę 1 stanowiło 37 pacjentek, które spełniły wszystkie kryteria diagnostyczne (HA+OM+PCO), grupa 2 to 29 pacjentek z dwoma kryteriami, w tym kryterium hiperandrogenizmu (HA+OM lub HA+PCO), pozostałe 32 pacjentki to grupa 3 – bez hiperandrogenizmu ale z dwoma pozostałymi kryteriami; PCO+OM. Przeprowadzono badanie dopplerowskie nerek i hormonalno-biochemiczną ocenę. Jako pierwszą zmierzono różnicę pomiędzy grupami w indeksie oporu nerkowego (RRI), następnie oceniono związek pomiędzy RRI a insulinoopornością i profilem lipidowym.*

Wyniki: *W grupie 1, RRI i wskaźnik oceny insulinooporności (HOMA-IR) były istotnie wyższe niż w grupie 3 oraz kontrolnej (p<0.031, p<0.001, odpowiednio po uwzględnieniu wieku i BMI). W grupie 3 i kontrolnej uzyskano podobne wyniki RRI i HOMA-IR. Znaleziono pozytywną korelację RRI z HOMA-IR (r=0.784, p<0.0001) oraz BMI (r=0.645, p<0.0001).*

Wnioski: *W naszym badaniu wykazaliśmy, że podgrupy zespołu PCO charakteryzują się zaburzeniami metabolicznymi i ryzykiem sercowonaczyniowym o różnym nasileniu. Co więcej, u pacjentek z zespołem PCO bez hiperandrogenizmu nie wystąpiło nasilenie ryzyka metabolicznego i sercowonaczyniowego.*

Słowa kluczowe: **zespół policystycznych jajników** / **fenotypy zespołu PCO** /
/ **insulinooporność** / **wskaźnik oporu nerkowego** /

Introduction

Polycystic Ovary Syndrome (PCOS), which is characterized by oligomenorrhea and hyperandrogenism, is the most widely encountered endocrine pathology among women of reproductive age. The prevalence of PCOS, the diagnostic criteria of which remain a source of controversy, is 6-8% [1] according to NIH and 18% according to the Rotterdam diagnostic criteria. In contrast to the Androgen Excess Society (AES), which accepts hyperandrogenism as an essential characteristic of PCOS, a new phenotypic subgroup of PCOS without hyperandrogenism has been defined according to the expanded diagnostic criteria of Rotterdam [3].

Most women with PCOS have certain metabolic disorders along with their endocrine disorders [4]. The most important metabolic disorders include insulin resistance (IR), which results in hyperinsulinemia, and atherogenic dyslipidemia [5]. Literature reports that 50-70% of all women with PCOS have varying degrees of insulin resistance [6, 7]. If hyperandrogenism is used as a diagnostic criterion for PCOS, insulin resistance and hyperinsulinemia are encountered much more frequently [8]. It has been shown in studies so far that metabolic syndrome and insulin resistance are encountered significantly less frequently in PCOS patients who are normoandrogenic [9, 10].

Renal resistive index (RRI) reflects the renovascular resistance, which is an early marker of vascular damage. RRI is accepted as a reliable marker for atherosclerosis [11]. The increase in RRI displays a significant correlation with the severity of systemic atherosclerosis [12]. The correlation between insulin resistance and RRI has been demonstrated in patients with type-2 diabetes and metabolic syndrome [11, 13].

The metabolic and cardiovascular effects of PCOS are hotly debated today. Although there is no conclusive evidence that PCOS increases the risk of atherosclerosis [14], it has been shown that most of the clinical and subclinical markers of atherosclerosis are altered in patients with PCOS [15, 16]. The state of the intra-renal vascular resistances, which is an indirect indication of atherosclerosis, remains unknown in PCOS subgroups.

In this study we compared intra-renal resistance symptoms of PCOS phenotypic subgroups. Moreover, the relation between renal resistive index and insulin resistance was examined.

Material and Methods

The patients were selected from amongst those who presented at the infertility polyclinic of Baskent University Hospital, Konya. The suitability for inclusion in the study was evaluated in 120 patients diagnosed with PCOS according to the Rotterdam. 22 patients were excluded: 16 did not meet the suitability criteria, and 6 who refused to take part. The remaining 98 women with PCOS were included in the study. For the control group, 35 women with infertility reasons other than PCOS were evaluated for their suitability in the study. Three of these did not satisfy the necessary criteria and 2 refused to participate. The remaining 30 patients were included in the study as controls.

In accordance with the Rotterdam criteria, the diagnosis of PCOS was established in the presence of at least two of the following three criteria:

1 – oligo and/or amenorrhea (OM);
2 – clinic and/or biochemical signs of hyperandrogenism (HA);

3 – polycystic ovarian morphology (PCO) detected by transvaginal ultrasonography.

37 of the 98 POCS patients (Group 1) met all three criteria (HA+OM+PCO), 29 patients (Group 2) met two of the criteria including hyperandrogenism (HA+OM or HA+PCO) and the remaining 32 patients (Group 3) had no hyperandrogenism but fulfilled the other two criteria; PCO+OM.

In this case-controlled study, the women with PCOS, separated into phenotypic subgroups according to the Rotterdam criteria, were compared with those in the control group with regard to their intra-renal vascular and insulin resistances, as well as lipid profiles. The first measure of result was designated as the differences in the renal resistive index (RRI) values of the groups, and the second measure of result was designated as the relation of RRI with the insulin resistance and lipid profile. The number of cases was determined through power analysis.

The criteria for inclusion in the study were: 19-37 years of age, 19-40 BMI, no history of endocrine diseases such as type-2 DM or hyperprolactinemia, no hypertension, no medical treatment for PCOS (Ocs, antiandrogenics, insulin sentisizers, antiplatelets) in the last three months before the study. Smokers, pregnant or breastfeeding women were also excluded from the study.

The diagnosis of PCOS was made according to the criteria of the Rotterdam ESHRE/ASRM-sponsored PCOS consensus workshop group (2004).

With the exclusion of other conditions that could cause menstrual irregularity and androgen excess, patients who presented with two out of three of the following criteria were diagnosed with PCOS:

1 – oligo and/or anovulation (menstrual cycle between 35-50 days or secondary amenorrhea and/or anovulation);

2 – clinic and/or biochemical signs of hyperandrogenism [Ferriman-Gallway modified score ≥ 8 and/or acne, and /or hyperandrogenemia: total testosterone >0,6 ng/ml (2 nmol/l);

3 – polycystic ovaries, identified by transvaginal ultrasonography (presence of ≥ 12 follicles in each ovary, measuring 2-9 mm in diameter and/or increased ovarian volume >10cm³) [17].

Insulin resistance was calculated using the homeostasis model assessment of insulin resistance (HOMA-IR), with the following equation: HOMA-IR = [(fasting glucose in mg/ dL x 0.05551) x fasting insulin in µU/mL] /22.5 [18]. Waist circumference was measured at the umbilicus and the hip circumference was measured at the most prominent buttock level. The waist-to-hip ratio was considered to be the measure of body fat distribution.

In this study, the renal Doppler ultrasonography was carried out by a single diagnostic medical sonographer who had no information about the clinical state of the patients. All subjects had normal kidney functions. Patient anamneses confirmed they had not consumed drinks with caffeine or alcohol, smoked or performed heavy exercise in the last 24 hours before the test. The Doppler examination was carried out in the morning after a night of fasting and following a 30-minute rest.

The ultrasonographic examination was carried out by means of an ultrasound device with a duplex Doppler and B-mode apparatus equipped with a 5 MHz convex probe (Sonoline Antares, Siemens, Germany). RRI of each patient was calculated by taking the mean of the three separate measurements made at the level of the interlobar arteries for each kidney: peak systolic speed – end diastolic speed / peak systolic speed [19].

All the blood samples were collected after a night of fasting. The hormonal and biochemical examination of the samples was performed on the same day as the ultrasonographic examination. Fasting glucose, high-density lipoprotein [HDL] cholesterol, low-density lipoprotein [LDL] cholesterol, triglyceride levels were measured with original kits, using an Abbott-Aeroset autoanalyzer (Chicago, IL, USA). Serum levels of luteinizing hormone [LH] and insulin were measured by a microparticle enzyme immunoassay method in an AXSYM autoanalyzer (Abbott Laboratories, IL, USA). Serum total testosterone and thyroid stimulating hormone levels were measured by a solid-phase competitive chemiluminescent enzyme immunoassay in an Immulite 2000 autoanalyzer using BIODPC reagents (Bio DPC, Los Angeles, CA, USA).

After the Ethical Committee of Baskent University confirmed the working protocol, the written informed consent was obtained from the patients.

Statistical analyses

Statistical analyses were performed using SPSS 10.0 (SPSS for Windows 10.0; Chicago, IL, USA). The ANOVA test was used to investigate whether there were any differences between the groups. Normality of the data was evaluated by the Kolmogorov-Smirnov test with Lilliefors correction. Differences among the groups were assessed by the t-test for normally distributed continuous variables and by the Mann-Whitney U test with a Bonferroni correction for non-normally distributed continuous variables.

Due to age and BMI influence on the fasting insulin and lipid profiles, analyses were optionally adjusted for age and BMI. A p-value < 0.05 was considered significant. The correlation test necessary for the second hypothesis was carried out using the Pearson's correlation analysis.

Results

The clinical features, metabolic and hormonal states and renal Doppler parameters of the patients are shown in Table I. There turned out to be statistically significant differences between the groups in their RRI, PSV, HOMA IR and lipid profile values when these were subjected to the one-way ANOVA test. In those PCOS patients with all three criteria (Group 1), RRI and HOMA IR levels were higher than in the Group 3 PCOS patients without hyperandrogenism as well as in the control group (P <0.005, P <0.001, P <0.031, respectively, after adjustment for age and BMI). In Group 1 PCOS patients the AFC, WHR, LH, insulin, total testosterone and triglyceride levels were higher while HDL was lower (Table I).

In contrast, between 2 and 3 PCOS groups on one hand and the control group on the other, no difference was observed in the monitored variables (parameters) save for the AFC. When the variables of all the patients in the study were subjected to correlation analysis, there turned out to be a significant correlation between the RRI and HOMA IR (r = 0.665, P <0.000), insulin (r = 0.703, P <0.000) and BMI values (r = 0.555, P <0.000) (Table II).

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Table I. Clinical characteristics and endocrine, metabolic, renal Doppler parameters of PCOS phenotypic subgroups with the control group.

	[PCO+HA+OM] Grup1 (n=37)	[HA+OM, HA+PCO] Grup 2 (n=29)	[PCO+OM] Grup 3 (n=32)	Control group (n=30)	One-way ANOVA P-value*	One-way ANOVA P-value adjusted**
Age (years)	25.5±4.7	25.27±2.29	26.1±3.0	27.3±4.1	0.068	-
BMI (kg/m²)	30.7±5.9 c	29.1±7.1	26.0±5.9	26.7±6.1	0.018	-
WHR	0.79±0.05 e	0.79±0.05	0.77±0.04	0.76±0.03	0.032	**0.048**
AFC	53.5±16.9 e	47.6±23.9 d	54.8±35.3 b	20.3±5.8	<0.001	**<0.001**
RRI	0.66±0.03 e, c	0.64±0.04	0.63±0.04	0.62±0.04	0.006	**0.031**
PSV	87.7±17.5 e	99.3±8.05	94.5±21.6	101.3±21.9	0.013	**0.015**
Glucose (mg/dL)	96.79±9.14 e	93.41±6.15	94.00±5.84	92.26±4.46	0.025	**0.024**
Insulin (µU/mL)	14.90±6.29 a,c,e	9.80±6.12	10.19±6.35	10.34±4.84	<0.001	**0.005**
HOMA-IR	3.51±1.43 a,c,e	2.29±1.39	2.26±1.27	2.22±0.99	<0.001	**0.001**
HDL (mg/dL)	42.21±10.60 e,c	43.55±10.91 d	49.11±7.71	52.04±7.40	0.004	**0.019**
LDL (mg/dL)	115.74±24.3 a	103.68±33.7	101.94±23.8	96.26±15.7	0.012	**0.016**
Triglycerides (mg/dL)	139.58±80.6 c e	113.32±74.9	96.78±42.4	102.26±37.1	0.034	**0.096**
Total Testosterone (ng/mL)	0.78±0.37 c,e	0.61±0.32	0.54±0.31	0.53±0.14	<0.001	**<0.001**
TSH (µU/mL)	5.20±11.89	4.86±6.29	2.47±1.95	1.89±1.75	0.358	**0.171**
LH (mIU/mL)	9.70±4.37 e	12.28±6.07 d	10.45±6.20 b	4.05±1.95	<0.001	**0.001**

PCO: polycystic ovaries; OM: oligo-or amenorrhea; HA: hyperandrogenism; ANOVA: analysis of variance; BMI: body mass index; WHR: waist-hip ratio; AFC: antral follicle count; RRI: renal resistive index; PSV: peak systolic velocity; HOMA-IR: homeostasis model assessment of insulin resistance; HDL: high-density lipoprotein; LDL: low-density lipoprotein; TSH: thyroid-stimulating hormone; LH: luteinizing hormone.
a [PCO+HA+OM] vs.[HA+OM, HA+PCO], b [PCO+OM] vs. Control, c [PCO+HA+OM] vs. [PCO+OM], d [HA+OM, HA+PCO] vs. Control, e [PCO+HA+OM] vs. Control.

Analysis of variance (ANOVA) was used for differences between the groups. Pair-wise comparisons among the groups were assessed with the Mann-Whitney U test with Bonferroni correction. All values are given as mean±SD. p<0.05 was considered statistically significant.
* One-way ANOVA P-values (unadjusted) across the control group, [PCO+HA+OM], [HA+OM, HA+PCO], [PCO+OM] phenotypic subgroups.
** One-way ANOVA P- values (adjusted for age and BMI) across the control group, [PCO+HA+OM], [HA+OM, HA+PCO], [PCO+OM] phenotypic subgroups.

Discussion

Diagnostic symptoms as well as metabolic and cardiovascular effects of PCOS are still debated. Its phenotypic spectrum has been expanded through the Rotterdam criteria. After this change in the diagnostic criteria, metabolic anomalies came to be observed with less frequency and severity in patients newly diagnosed with PCOS [20]. PCOS is known to be related with deep insulin resistance, which is accompanied by obesity, as well as with defects in insulin secretion [18]. It is thought that insulin resistance is the primary biochemical defect that lies beneath epidemic obesity accompanied by cardiovascular disorders and type-2 diabetes [21]. Insulin resistance is linked with upset glucose metabolism as well as with many other metabolic anomalies such as dyslipidemia, inflammation and hypercoagulability [21]. It is accepted that insulin resistance has a pathophysiological role in the development of a cardiometabolic state [22, 23]. Increased atherosclerosis linked with insulin resistance is a result of the vascular effect of these metabolic anomalies or of the molecular pathology linked with the insulin receptor signal [24].

It is not fully known to what extent the phenotypic subgroups in PCOS are affected by cardiovascular risks. So far studies have shown that insulin resistance is higher in hyperandrogenic than normoandrogenic PCOS patients [9, 10, 22].

Our findings represent a continuation and confirmation of the previous studies on this subject. Our study has shown that insulin resistance and intra-renal resistance are higher in the PCOS patients with all three criteria than in the PCOS subgroup without hyperandrogenism as well as in the control group (Table I).

We also demonstrated the existence of a positive correlation between the intra-renal resistance and insulin resistance in PCOS patients.

Intra-renal resistance reflects systemic vascular damage. Increased intra-renal resistance, at least in the early phase, can be taken as an indication of the functional and reversible modification of intra-renal vasoconstriction [25]. Studies have shown that RRI is increased in patients with insulin resistance as well as in those with type-2 diabetes, hypertension or chronic kidney failure [11, 13].

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Table II. Relationships of RRI with HOMA-IR and other study variables in all patients.

		RRI	PSV	Insulin	HOMA-IR
Age (years)	r	,050	-,064	,100	,108
	p	,591	,488	,279	,241
BMI (kg/m²)	r	,555	-,174	,635	,616
	p	,000	,058	,000	,000
WHR	r	,325	-,126	,419	,471
	p	,000	,171	,000	,000
AFC	r	,097	-,004	,064	,081
	p	,293	,970	,490	,384
RRI	r	1	-,335	,703	,665
	p		,000	,000	,000
PSV	r	-,335	1	-,418	-,410
	p	,000		,000	,000
Glucose (mg/dl)	r	,083	-,129	,147	,314
	p	,371	,163	,111	,001
Insulin (µU/mL)	r	,703	-,418	1	,980
	p	,000	,000		,000
HOMA-IR	r	,665	-,410	,980	1
	p	,000	,000	,000	
HDL (mg/dl)	r	-,370	,144	-,312	-,341
	p	,000	,118	,001	,000
LDL (mg/dl)	r	,244	,051	,299	,265
	p	,007	,582	,001	,004
Triglycerides (mg/dl)	r	,295	-,070	,371	,387
	p	,001	,448	,000	,000
Total Testosterone (µU/mL)	r	,265	-,128	,238	,268
	p	,004	,164	,009	,003
TSH	r	,037	,005	-,051	-,026
	p	,693	,955	,585	,782
LH (mIU/mL)	r	,013	,037	,021	,035
	p	,884	,688	,822	,707

In obese or overweight patients with metabolic syndrome, RRI has been found to be linked with increased carotid intima-media thickness, which is accepted in turn to be linked with upset endothelial function [11].

Reports so far have confirmed that PCOS patients with all three criteria have lower insulin sensitivity [10, 20]. We found that PCOS patients with all three criteria have greater intra-renal and insulin resistance as well as more atherogenic dyslipidemia than the PCOS subgroup without hyperandrogenism and the controls. In the light of these findings, the PCOS subgroup with all three criteria seems to be the worst phenotype as far as cardiovascular risk is concerned, while the PCOS subgroup without hyperandrogenism appears to suffer from a lighter form of the illness.

In this study, we showed that PCOS phenotypic subgroups are heterogeneous with regard to the intra-renal resistance, which shows the vascular effects of insulin resistance. Undoubtedly, a more flexible approach is needed in the management of the metabolic effects of PCOS. PCOS subgroups have different clinical features and metabolic and cardiovascular risk factors of different degrees.

Conclusions

In conclusion, women with PCOS do not all have the same metabolic and cardiovascular risk profile. Clinical subgroups of PCOS should be taken into consideration when assessing patient risk. There is also a need for further studies that examine the link between insulin resistance and other markers of atherosclerosis.

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Declaration of Interest

The authors declare no conflict of interest.

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