C-reactive protein and lipoprotein-a as markers of coronary heart disease in polycystic ovary syndrome

Polikistik over sendromlu hastalarda koroner kalp hastalıklarının belirteci olarak c-reaktif protein ve lipoprotein-a bakılması

Nilgün Güdücü, Herman İşçi, Alin Başgül Yiğiter, İlkkan Dünder

Department of Obstetrics and Gynecology, İstanbul Bilim University Avrupa Florence Nightingale Hospital, İstanbul, Turkey

Abstract

Objective: The aim of this study was to investigate the risk factors of coronary heart disease, CRP and Lipoprotein-a in polycystic ovary syndrome patients.

Material and Methods: Prospectively collected data of polycystic ovary syndrome patients (n=62) and control group (n=40) were compared.

Results: PCOS patients had higher HOMA-IR, CRP, DHEAS, free testosterone, FAI, LH and prolactin levels when compared to the control group. Lipoprotein-a levels did not differ between the groups. The obese PCOS group had statistically significantly higher fasting blood glucose, total cholesterol, triglyceride, free testosterone, insulin, CRP and HOMA-IR and statistically significantly lower HDL and SHBG when compared to normal weight PCOS persons. Fasting blood glucose, total cholesterol, LDL, SHBG, CRP, Lipoprotein-a, FSH, LH, TSH, DHEAS and prolactin levels did not differ between the normal weight and obese control groups.

Conclusion: CRP levels increase in polycystic ovary syndrome patients and can be used as a marker of coronary heart disease. Future studies can be directed at treatments to decrease CRP levels, including antiinflammatory treatments.

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Key words: Polycystic ovary syndrome, obesity, CRP, lipoprotein-a, coronary heart disease

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Özet

Amaç: Bu çalışmanın amacı polikistik over sendromlu hastalarda koroner kalp hastalıkları risk faktörlerini, CRP ve Lipoprotein-a araştırmaktı.

Gereç ve Yöntemler: Prospektif olarak polikistik over sendromlu (n=62) ve kontrol grubunun (n=40) kan örnekleri çalışıldı.

Bulgular: Polikistik over sendromlu hastalarda HOMA-IR, CRP, DHEAS, serbest testosteron, FAI, LH and prolaktin seviyeleri yüksek, FSH ve SHBG seviyeleri ise düşük bulundu. Lipoprotein-a gruplarda farklı değildi. Obez polikistik over sendromlu hastalarda açlık kan şekeri, total kolesterol, trigliserit, serbest testosteron, insulin, CRP ve HOMA-IR daha yüksek, HDL ve SHBG daha düşük bulundu. Açlık kan şekeri, total kolesterol, LDL, CRP, SHBG, Lipoprotein-a, FSH, LH, TSH, DHEAS ve prolaktin seviyeleri obez ve normal kilolu kontrol gruplarında benzerdi.

Sonuç: CRP polikistik over sendromlu hastalarda yükselir ve koroner kalp hastalıklarının belirteci olarak kullanılabilir. Gelecekte CRP'nin düşürülmesine yönelik, antienflamatuar tedavileri de içeren araştırmalar planlanabilir. (J Turkish-German Gynecol Assoc 2012; 13: 227-32)

Anahtar kelimeler: Polikistik over sendromu, obesite, lipoprotein-a, koroner kalp hastalığı, CRP

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Introduction

Polycystic ovary syndrome (PCOS) is a heterogenous disease characterized by hyperandrogenism, chronic oligo-anovulation, infertility and insulin resistance (IR) (1). This common endocrinopathy, encountered in 5-10% of women of reproductive age (2), necessitates exclusion of other etiologies of hirsutism and anovulation. The wide-spectrum of the disease and the changing nature of the clinical presentation with weight fluctuations may be challenging. Most women with PCOS present with features of metabolic syndrome (MS), including abdominal obesity, IR, hypertension and dyslipidemia (3). PCOS patients were reported to have an increased prevalence of MS, about 2-3 times higher than age-matched controls (3, 4). Metabolic syndrome is a known risk factor for coronary heart disease (CHD), and PCOS patients are a group of young women with a high risk of early-onset CHD (5). In a recent study women with PCOS were reported to have an increased incidence of cardiovascular events and a lower event free survival (6). Lipoprotein-a (Lp-a) is a genetically determined LDL-like atherogenic lipoprotein (7). The aim of this study was to investigate the previously suggested biochemical markers of CHD in women with PCOS, namely C-reactive protein (CRP) and Lp-a (8, 9).

Material and Methods

This is a prospective cross-sectional study carried out in İstanbul Bilim University School of Medicine, Department of Obstetrics and Gynecology Clinics between April 2010

Address for Correspondence: *Nilgün Güdücü, Hüseyin Cahit Yalçın Sk. No: 1 Fulya, İstanbul, Turkey*
Phone: +90 533 640 40 10 e.mail: nilgun.kutay@gmail.com

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and December 2011. The study was in agreement with the Declaration of Helsinki, 1975 and all of the involved patients gave their informed consent. Some of the data used in this study was used in another study which has been reported previously.

The study group consisted of 62 women with PCOS and 40 healthy, normally menstruating women without any concomitant disease. All PCOS patients were diagnosed as PCOS according to the 2003 Rotterdam ESHRE/ASRM PCOS Consensus Workshop Group criteria (10) if at least two of the following criteria were present: oligo/amenorrhea, clinical or biochemical hyperandrogenism and PCO on ultrasonography. Clinical hyperandrogenism was defined as the presence of a Ferriman-Gallwey score>8. PCO was defined as the presence of an ovary with 12 or more follicles measuring 2-9mm in diameter. All subjects in the control group had a normal pelvic ultrasound, regular periods and no clinical or biochemical hyperandrogenism. Patients with systemic diseases such as diabetes mellitus, cardiovascular diseases, hypertension, thyroid diseases, chronic renal failure, malignancy, Cushing syndrome, congenital adrenal hyperplasia, hyperprolactinemia and gastrointestinal malabsorptive diseases were excluded. None of the patients were on any medications for at least 3 months before the study including oral contraceptives, glucocorticoids, lipid-lowering, antiobesity, antidiabetes, antiandrogenic, antihypertensive or ovulation-inducing agents.

All the patients underwent a physical examination and appropriate laboratory tests were performed. BMI was calculated as body weight in kilograms divided by height in square metres (kg/m^2). Patients were also separated into two groups according to their body mass index (BMI). Twenty-one patients with PCOS were obese (BMI≥ 25) and 41 were non-obese (BMI< 25). In the control group, 11 patients were obese (BMI≥ 25) and 29 were non-obese (BMI <25). Weight, height and waist and hip circumferences were measured. Waist circumference (WC) was obtained as the smallest circumference at the level of the umbilicus. Hip circumference (HC) was obtained as the widest circumference at the level of the buttocks. Serum samples were obtained from all women in the early follicular phase after an overnight fast, during the 3^{rd}-4^{th} days of the cycle. Levels of fasting plasma glucose, insulin, total cholesterol, high-density lipoprotein (HDL), low density lipoprotein (LDL), triglycerides (TG), LH, FSH, prolactin, TSH, dehydroepiandosterone sulfate (DHEAS), free testosterone, cortisol, freeT4, 17-OH proges-

Table 1. Anthropometric, biochemical and hormonal characteristics of the study groups

	PCOS n=62	Control n=40	
	Mean±SD (Median)	Mean±SD (Median)	p
Age (years)	24.77±4.85	28.13±5.66	0.002**
Height (cm)	163.37±6.48	162.98±6.76	0.768
Weight (kg)	64.60±14.88	61.82±14.69	0.357
Waist/Hip ratio	0.81±0.09	0.79±0.06	0.197
BMI (kg/m^2)	24.15±5.35	23.35±5.33	0.465
Fasting glucose(mg/dL)	91.95±6.99	90.35±7.22	0.267
Insulin (uU/mL)	11.41±6.89	8.73±3.85	0.014*
Total Cholesterol (mg/dL)	162.39±36.32	162.41±28.92	0.998
Triglyceride (mg/dL)	69.23±30.30	65.67±25.23	0.540
HDL (mg/dL)	56.60±15.97	54.42±13.67	0.479
LDL (mg/dL)	93.62±27.24	99.70±27.24	0.275
+DHEAS (ug/dL)	273.98±109.45 (280.55)	235.63±103.69 (219.00)	0.036*
+F. Testosterone (ng/dL)	0.73±0.54 (0.63)	0.38±0.23 (0.30)	0.001**
FSH (mIU/mL)	5.46±1.39	6.87±2.08	0.001**
LH (mIU/mL)	8.72±4.17	6.15±2.50	0.001**
Prolactin(ng/mL)	20.87±9.21	16.53±6.16	0.006**
TSH (uIU/mL)	2.43±1.221	2.13±1.07	0.198
HOMA-IR	2.58±1.71	2.01±1.07	0.042*
+SHBG (nmol/mL)	44.44±25.5 (35.59)	50.39±22.98 (42.42)	0.029*
FAI	4.31±2.78	2.36±1.52	0.017*
+Lipoprotein-a (mg/dL)	24.69±20.05 (18)	22.11±28.77 (9.7)	0.097
+CRP (mg/dL)	0.27±0.28 (0.16)	0.19±0.25 (0.10)	0.046*

Student t Test, +Mann Whitney U Test, *p<0.05, **p<0.01

terone, sex-hormone binding globulin (SHBG), CRP (cobas integra 400, Roche) and Lp-a (cobas integra 800, Roche) were measured. Insulin resistance was calculated by the homeostasis model assessment (HOMA) index with the formula: HOMA-IR=fasting plasma immunoreactive insulin (μU/mL)x fasting serum glucose (mg/dL)/405, after excluding those with a serum glucose>200mg/dL, using insulin and thiazolidine.

Statistical analyses were performed using the Number Cruncher Statistical System (NCSS) 2007& Power Analysis and Sample Size (PASS) 2008 Statistical Software (Utah). Data showing normal distribution of parameters were compared with the Student's t-test, data showing non-normal distribution of parameters were compared with Mann Whitney U test, relation of CRP and Lp-A with other parameters was compared with Spearman's correlation analysis. At a confidence interval of 95%, p-values<0.05 were considered statistically significant.

Results

The anthropometric, biochemical and hormonal data of the groups were shown in Table 1. BMI, waist to hip ratio (WHR), fasting plasma glucose, total cholesterol, TG, HDL, LDL, lipoprotein-a (Lp-a), insulin and TSH levels were similar in the PCOS and control groups. PCOS patients had higher HOMA-IR, CRP, DHEAS, free testosterone, FAI, LH and prolactin levels when compared to the control group and lower FSH and SHBG levels. Lp-a levels did not differ between the groups.

Lp-a correlated negatively with DHEAS and positively with LDL in the control group, but did not correlate with any parameter in women with PCOS (Table 2). CRP correlated positively with weight, BMI, insulin, LDL and HOMA-IR in women with PCOS, with weight, WHR, BMI, insulin, TG and HOMA-IR in the control group and correlated negatively with HDL in the control group (Table 2).

The obese PCOS group had statistically significantly higher fasting blood glucose, total cholesterol, triglyceride, free testosterone, insulin, CRP and HOMA-IR and statistically significantly lower HDL and SHBG when compared to the normal weight PCOS controls (Table 3). Lp-a, FSH, LH, TSH, DHEAS and prolactin levels did not differ between the PCOS groups (Table 3). Obese controls had statistically significantly higher triglyceride, insulin, free testosterone and HOMA-IR and statistically significantly lower HDL when compared to normal weight controls (Table 4). Fasting plasma glucose, total cholesterol, LDL, SHBG, CRP, Lp-a, FSH, LH, TSH, DHEAS and prolactin levels did not differ between the normal weight and obese control groups (Table 4).

Table 2. Correlations according to Lipoprotein-a and CRP between the groups

	Lipoprotein-a				CRP			
	PCOS		Control		PCOS		Control	
	r	p	r	p	r	p	r	p
Age	-0.111	0.400	0.159	0.335	-0.056	0.672	0.186	0.250
Weight	0.127	0.337	0.229	0.162	0.411	0.001**	0.457	0.003**
Waist/Hip ratio	0.049	0.711	0.231	0.158	0.032	0.808	0.314	0.049*
Height	0.155	0.241	-0.049	0.769	-0.053	0.689	0.041	0.800
BMI	0.094	0.480	0.252	0.121	0.389	0.002**	0.503	0.001**
Fasting glucose	-0.026	0.847	0.051	0.760	0.189	0.147	0.202	0.212
Insulin	0.143	0.285	0.209	0.202	0.421	0.001**	0.453	0.003**
T. Cholesterol	0.115	0.474	0.095	0.625	0.267	0.092	0.041	0.833
Triglyceride	-0.008	0.950	0.148	0.367	0.113	0.390	0.404	0.010*
HDL	0.156	0.239	-0.223	0.173	-0.090	0.495	-0.325	0.041*
LDL	-0.017	0.899	0.333	0.038*	0.295	0.022*	-0.025	0.877
DHEAS	-0.022	0.868	-0.407	0.010*	0.172	0.189	0.073	0.657
F. Testosterone	-0.252	0.056	-0.063	0.706	0.151	0.253	0.256	0.116
FSH	0.155	0.245	0.157	0.340	0.086	0.518	-0.016	0.920
LH	-0.052	0.697	0.078	0.639	-0.017	0.900	0.004	0.980
Prolactin	-0.064	0.638	-0.242	0.138	-0.058	0.667	-0.202	0.211
TSH	-0.233	0.078	0.031	0.849	-0.123	0.354	0.051	0.756
HOMA-IR	0.169	0.200	0.232	0.156	0.372	0.003**	0.467	0.002**
SHBG	0.086	0.697	0.191	0.273	-0.234	0.271	-0.150	0.384
FAI	-0.122	0.571	-0.252	0.384	0.170	0.416	0.059	0.834

r: Spearman's correlations, *p<0.05, **p<0.01

Table 3. Comparison of parameters according to BMI in PCOS patients

n=62	BMI<25	BMI>25	p
	Mean±SD (median)	Mean±SD (median)	
Fasting glucose (mg/dL)	90.39±5.98	95±7.92	0.013*
Insulin (uU/mL)	9.14±5.26	16.07±7.61	0.000**
T. Cholesterol (mg/dL)	153.75±27.09	181±46.87	0.023*
Triglyceride (mg/dL)	62.61±22.03	82.80±39.88	0.045*
HDL (mg/dL)	59.49±16.63	50.70±12.98	0.043*
FSH (mIU/mL)	5.49±1.57	5.43±0.98	0.859
LDL (mg/dL)	87.32±3.41	106.55±32.82	0.008**
+DHEAS (ug/dL)	266.60±114.04 (282.10)	288.40±101 (278)	0.337
+F. Testosterone (ng/dL)	0.59±0.45 (0.50)	1.03±0.59 (0.87)	0.001**
LH (mIU/mL)	9.30±4.48	7.62±3.35	0.138
Prolactin (ng/mL)	22.23±10	18.33±7.06	0.119
TSH (uIU/mL)	2.27±1.04	2.73±1.46	0.211
HOMA-IR	1.95±1.02	3.80±2.11	0.002**
+SHBG (nmol/mL)	57.90±24.50 (47.30)	24.24±6.71 (23.61)	0.001**
FAI	3.04±1.66	6.35±3.073	0.002**
+Lipoprotein-a (mg/dL)	24.64±20.55 (18.50)	24.80±19.49 (17.60)	0.542
+CRP (mg/dL)	0.20±0.24 (0.11)	0.42±0.31 (0.42)	0.001**
Student t Test, +Mann Whitney U Test, *p<0.05, **p<0.01			

Table 4. Comparison of parameters according to BMI in the control group

n=40	BMI<25	BMI>25	p
	Mean±SD	Mean±SD	
Fasting glucose (mg/dL)	89.90±5.90	91.55±10.19	0.526
Insulin (uU/mL)	7.8±3.18	11.13±4.56	0.013*
T. Cholesterol (mg/dL)	161.64±28.62	164.86±32.06	0.803
Triglyceride (mg/dL)	59.00±19.67	83.27±30.50	0.005**
HDL (mg/dL)	57.80±10.73	45.55±16.93	0.009**
LDL (mg/dL)	96.93±27.34	107±26.82	0.303
+DHEAS (ug/dL)	230.75±103.15 (218)	248.50±109 (220)	0.671
+F. Testosterone (ng/dL)	0.34±0.22 (0.30)	0.51±0.24 (0.53)	0.035*
FSH (mIU/mL)	6.73±2.19	7.24±1.81	0.494
LH (mIU/mL)	6.33±2.68	5.67±2.00	0.464
Prolactin (ng/mL)	16.58±5.21	16.40±6.33	0.933
TSH (uIU/mL)	1.93±0.74	2.65±1.57	0.166
HOMA-IR	1.76±0.80	2.66±1.41	0.016*
+SHBG (nmol/mL)	53.63±25.71 (43.31)	40.68±4.64 (41.81)	0.083
FAI	2.17±1.95	2.66±054	0.565
+Lipoprotein-a (mg/dL)	20.47±32.31 (8.9)	26.28±17.32 (21)	0.058
+CRP (mg/dL)	0.14±0.15 (0.10)	0.33±0.39 (0.13)	0.098
Student t Test, +Mann Whitney U Test, *p<0.05, **p<0.01			

Discussion

Although there is no standard evaluation for cardivascular risk assessment, CRP is a known predictor of future CHD risk (11) and Lp-a was reported to be associated with coronary heart disease (9). High sensitivity CRP is a marker of inflammation, an acute phase reactant that is synthesized in the liver as a response to tumor necrosis factor-a (TNF-α) and interleukin-6 (11). CRP was also shown to play a role in cardiovascular events by complement activation, adhesion molecule expression and promotion of LDL uptake by macrophages (12). In this study, we detected increased CRP levels in PCOS patients, as reported previously (13,14). In our study, PCOS patients had statistically significantly increased CRP levels and obese PCOS patients had higher CRP levels than non-obese PCOS. We did not find such a relationship in the control group. Both non-obese and obese PCOS were reported to have higher CRP concentrations when compared to the control groups with similar BMI (8, 15). Gen et al. (16) reported similar CRP levels in non-obese PCOS and healthy women. These findings suggest an increased body weight as the major determinant of metabolic abnormalities related to CHD in PCOS women, as reported previously (16, 17) and CRP as the marker of increased CHD risk.

A significant correlation was previously reported between CRP and IR in PCOS patients (13-15). In our study, CRP correlated with IR both in PCOS patients and control group. In PCOS patients correlation of CRP with IR was independent of WHR, but in the control group it was related to the presence of abdominal obesity. These findings suggest an increased risk of CHD in PCOS patients independent of abdominal obesity.

Hyperandrogenic women not fulfilling PCOS criteria were reported to have CRP levels similar to the control group (18). There was no correlation between CRP levels and androgens in our study, as reported previously (13).

We hypothetized that by measuring Lp-a levels, cardiovascular risk factors not related to insulin resistance could be determined and treatment strategies could be developed. We found similar Lp-a levels in PCOS patients and healthy controls without concomitant disease. Moreover Lp-a plasma levels showed no variation when groups were compared according to the BMI and had no correlation with other metabolic parameters. Patients with MS, a syndrome with features similar to PCOS, were reported to have higher Lp-a levels when compared to the control group (19). Previously, PCOS patients were shown to have increased concentrations of Lp-a (9). In our study there was no difference in Lp-a levels between PCOS patients and controls. Elevated plasma levels of Lp-a have been suggested to increase the risk of CHD in a way independent of insulin resistance (20). Other studies suggested modifications in Lp-a by glycation, this modification was reported to increase the risk of CHD both in type 1 and type 2 diabetic women (9, 21, 22). Obese PCOS were reported to have higher Lp-a levels when compared to non-obese PCOS, while other studies found elevated Lp-a both in non-obese and obese PCOS (23, 24). In our study, there was no correlation between Lp-a levels and IR markers. In our control group, Lp-a levels correlated positively with LDL and negatively with DHEAS levels. These findings obscure the suggestion of Lp-a as a marker of CHD in PCOS patients. As Lp-a is genetically and racially determined (7), these findings may be unique to our population.

Insulin resistance is a common feature of PCOS, it affects about half the women with PCOS, whether obese or non-obese (25). PCOS patients were reported to have a form of IR intrinsic to PCOS (26). Forty percent of obese PCOS patients developed diabetes or impaired glucose tolerance until the age of 26 years (27). Obesity acts as an additive factor, increasing IR (25). Our PCOS patients had higher IR when compared to the control group.

Conclusion

CRP levels were increased in PCOS patients and the increase was higher in obese PCOS patients. Weight loss may decrease CHD risk in PCOS patients and CRP can be used as a marker of CHD. The role of antiinflammatory drugs in decreasing CRP and CHD of PCOS patients can be studied in the future clinical trials.

Conflict of interest

No conflict of interest was declared by the authors.

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