RECIPROCAL ACTION OF PENTRAXIN-3 AND CRP IN WOMEN WITH POLYCYSTIC OVARY SYNDROME

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The aim of this study was to investigate the relationship between pentraxin-3 and other biochemical parameters in women with polycystic ovary syndrome (PCOS). We compared 58 women with PCOS to 34 body mass index- and age-matched normally menstruating healthy controls. Women with PCOS had significantly higher DHEA-S, free testosterone, LH and FAI, but lower pentraxin-3 levels when compared to healthy controls (0.86±0.21 and 0.91±0.14 respectively, p=0.014). Levels of CRP and lipoprotein-a were higher in the PCOS group. Overweight PCOS had significantly higher insulin, HOMA-IR, FAI, free testosterone and CRP and statistically significantly lower HDL and SHBG levels when compared to controls. Pentraxin-3 levels of obese and normal weight PCOS were similar. CRP and pentraxin-3 might contribute reciprocally to metabolic events and chronic low-grade inflammation in women with PCOS.

Polycystic ovary syndrome (PCOS) is the most common endocrinopathy of women at reproductive age presenting with oligo-amenorrhea, hyperandrogenism (hirsutism, acne and alopecia) and polycystic ovaries at ultrasound (1). It has a wide spectrum of clinical presentations and the presence of insulin resistance (IR) and obesity affect the clinical phenotype of patients. This implicates IR as the major underlying pathological mechanism in PCOS (2). PCOS shares many common features with metabolic syndrome (MS) (3) and both of the syndromes pose a greater risk of future cardiovascular disease (CVD). Central obesity is common in both PCOS and MS and is associated with a chronic low-grade systemic inflammatory state (4). Acute-phase proteins indicating a low-grade inflammatory state increase in response to interleukin-6 released from adipose tissue (5). C-reactive protein (CRP) is an acute-phase protein, a marker commonly used to determine inflammation and is a part of the pentraxin family. The pentraxin family is made of short and long pentraxins. CRP is located in the short pentraxin group and pentraxin-3 is located in the long pentraxin group (6). In contrast to CRP, which is produced almost exclusively from hepatocytes (7), pentraxin-3 is produced by a wide range of cells including adipocytes, as a response to tissue damage at the site of inflammation (6, 8). Pentraxin family is involved with the recognition of pathogens and apoptotic cells (9), then they activate the classical complement pathway. CRP promotes clearance of apoptotic cells, but soluble pentraxin-3 opposes this action (10). On the contrary, endogenous pentraxin-3 when expressed on cell surface acts as a signal for phagocytosis of apoptotic cells (11). Thus, pentraxin-3 plays a role in tuning inflammation.

Key words: inflammation, pentraxin-3, polycystic ovary syndrome, lipoprotein-a, CRP

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Previous studies showed that patients with MS had higher pentraxin-3 levels that increased with the severity of MS (12). A recent study detected higher pentraxin-3 levels in women with PCOS (13). In this study we investigated the relationship between pentraxin-3 levels and other biochemical parameters of women with PCOS.

MATERIALS AND METHODS

The study was constructed as a cross-sectional study. Patients attending the gynecology outpatient clinics of Istanbul Bilim University School of Medicine were requested to participate the study. The study was approved by the Institutional Review Board, was in agreement with the Declaration of Helsinki (1975) and all of the involved patients gave their informed consent. The diagnosis of PCOS was made according to 2003 Rotterdam ESHRE/ASRM PCOS Consensus Workshop Group criteria (14) when at least two of the following 3 criteria were present: oligomenorrhea-amenorrhea, clinical or biochemical signs of hyperandrogenism and the presence of polycystic ovaries (PCO) on transabdominal, transvaginal or transrectal ultrasonography (presence of an ovary with 12 or more follicles measuring 2-9 mm in diameter). Clinical hyperandrogenism was defined as the presence of a Ferriman-Gallwey score >8. The control group was composed of patients without any menstrual irregularities, without any clinical or biochemical signs of hyperandrogenism. Cases and controls 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. For at least 3 months prior to the study, none of the cases or controls were on any medications including oral contraceptives, glucocorticoids, lipid-lowering, antiobesity, antidiabetes, antiandrogenic, antihypertensive or ovulation-inducing agents.

All of the patients underwent physical examination and appropriate laboratory tests were performed. Body mass index (BMI) was calculated as body weight in kilograms divided by height in meter squared (kg/m^2). Patients were also separated into two groups according to their BMI. Seventeen patients with PCOS were overweight-obese (BMI$\geq$ 25) and 41 were normal (BMI$<$ 25). In the control group 8 patients were overweight-obese (BMI$\geq$ 25) and 26 were normal (BMI $<$25). Weight, height and waist and hip circumferences were measured. Waist circumference (WC) was obtained as the smallest circumference at the level of umbilicus. Hip circumference (HC) was obtained as the widest circumference at the level of the buttocks. Waist-to-Hip ratio (WHR) was calculated by dividing WC to HC. Serum samples were obtained from all of the study group in the early follicular phase after an overnight of fasting, during the 3rd-4th days of the cycle. Levels of fasting plasma glucose, insulin, total cholesterol, high-density lipoprotein (HDL), low density lipoprotein (LDL), triglycerides (TG), luteinizing hormone (LH), follicle stimulating hormone (FSH), prolactin, thyroid stimulating hormone (TSH), dehydroepiandosterone sulfate (DHEAS), free testosterone (FTest), cortisol, freeT4, 17-OH progesterone, sex-hormone binding globulin (SHBG), free androgen index (FAI), CRP (cobas integra 400, Roche) and Lp-a (cobas integra 800, Roche) were measured. Insulin resistance was calculated by homeostasis model assessment (HOMA) index with the formula: HOMA-IR= fasting plasma immunoreactive insulin (μU/mL)x fasting serum glucose (mg/dL)/405. Levels of pentraxin 3 were studied from serum samples stored at -80°C with ELISA (Human Pentraxin-3 Immunoassay Aviscera Bioscience, CA, USA) with intraassay and interassay coefficients of variations of 4-6% and 8-10%, respectively.

Statistical analyses were performed using the Number Cruncher Statistical System (NCSS) 2007& Power Analysis and Sample Size (PASS) 2008 Statistical Software (Utah, USA). Data showing normal distribution of parameters were compared with Student's *t*-test, data showing non-normal distribution of parameters were compared with Mann Whitney U test, relation of pentraxin-3 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

In Table I we compared the anthropometric and biochemical properties of women with PCOS and the control group. Women with PCOS had significantly higher DHEAS, F.Test, LH, FAI and their pentraxin-3 levels were significantly lower (0.86±0.21 and 0.91±0.14, respectively, p=0.014). We compared women with PCOS according to their BMI (normal and overweight): overweight PCOS had significantly higher WHR (p=0.001), F.Test (p=0.040), insulin (p=0.001), HOMA-IR (p=0.001), FAI (p=0.013), CRP (p=0.05) and significantly lower HDL (p=0.001)) and SHBG (p= 0.001); Pentraxin-3 levels did not differ when compared according to BMI. We compared the control group according to

Table I. *Anthropometric and biochemical properties of the study group.*

	PCOS (n=58)	CONTROLS (n=34)	p-value
	Mean±SD (Median)	Mean±SD (Median)	
Age (years)	25.84±5.3	28.26±6.78	0.080
Weight (kg)	63.75±12.72	60.75±10.18	0.244
Height (cm)	163.86±6.27	164.76±6.44	0.511
Body Mass Index (kg/m^2)	23.70±5	22.41±3.17	0.133
Waist-Hip ratio	0.83±0.06	0.81±0.07	0.219
Fasting Blood Glucose (mg/dl)	92.69±6.73	90.82±6,29	0.195
[b]Triglyceride (mg/dl)	81.07±65.75 (60)	65.15±25.16	0.329
High Density Lipoprotein (mg/dl)	58.33±16.27	58.21±13.52 (58)	0.973
Low Density Lipoprotein (mg/dl)	101.02±28.51	96.29±26.3	0.437
[b]Dehydroepiandosterone sulfate (ug/ml)	261.41±83.1 (266.2)	226.43±135.77 (200)	0.010*
[b]Free Testosterone (ng/dl)	0.61±0.31 (0.57)	0.45±0.35 (0.35)	0.006**
Insulin (uU/ml)	9.74±4.99 (8.28)	9.08±4.43 (8.32)	0.536
[b]Lipoprotein-a (mg/dl)	20.57±22.99 (9.7)	18.41±21.83 (8.9)	0.808
[b]C-Reactive Protein (mg/l)	2.21±3.8 (0.7)	1.69±3.56 (0.4)	0.174
Follicle Stimulating Hormone (mIU/ml)	6.33±1.77	7.25±2.83	0.058
Luteinizing Hormone (mIU/ml)	8.54±4.14	5.82±2.37	0.001**
[b]HOMA-IR	2.25±1.21 (2.01)	2.26±1.59 (1.83)	0.859
[b]SHBG (nmol/ml)	52.35±33.77 (41.76)	58.78±35.67 (46.74)	0.220
[b]Free Androgen Index	3.9±2.64 (3.31)	2.42±1.83 (2.19)	0.006**
[b]Pentraxin-3 (ng/ml)	0.86±0.21 (0.81)	0.91±0.14 (0.89)	0.014*

Student's t-test [b]Mann-Whitney U test SHBG: sex Hormone Binding Globulin
HOMA-IR: Homeostatic Model Assessment of Insulin Resistance
**p<0.05 *p<0.01*

Table II. *Normal weight PCOS compared with normal weight controls and overweight PCOS compared with overweight controls.*

	Normal weight PCOS compared with normal weight controls (BMI<25)			Overweight PCOS compared with overweight controls (BMI≥25)		
	PCOS (n=41)	Controls (n=26)	p-value	PCOS (n=17)	CONTROLS (n=8)	p-value
[a]Age (years)	25.63±4.72	27.27±6.53	0.275	26.35±6.63 (23)	31.5±7.01 (33.5)	0.115
[a]Weight (kg)	57.80±7.44	56.48±6.65	0.463	78.09±11.37 (74)	74.62±6.55 (74)	0.705
[a]Height (cm)	165.12±6.39	164.31±6.40	0.613	160.82±4.93 (160)	166.25±6.78 (167)	0.069
[a]Body Mass Index (kg/m)	21.02±2.1	21.02±1.75	0.999	30.17±3.88 (28.86)	26.92±2.43 (25.72)	0.012*
[a]Waist-Hip Ratio	0.81±0.06	0.8±0.07	0.410	0.89±0.06 (0.88)	0.86±0.06 (0,86)	0.357
[a]Fasting Blood Glucose (mg/dl)	91.83±6.39	90.92±6.70	0.584	94.76±7.28 (94)	90.5±5.15 (91)	0.189
Triglyceride (mg/dl)	66.53±25.68 (58)	64.15±23.75 (57)	0.783	115.29±108.39 (106)	68.38±30.89 (56)	0.256
[a]High Density Lipoprotein (mg/dl)	62.32±15.53	57.52±12.13	0.193	48.71±14.16 (46)	60.38±18.01 (59.5)	0.096
[a]Low Density Lipoprotein(mg/dl)	95.05±21.46	90.74±22.32	0.439	115.41±37.86 (106)	113.63±31.65 (112)	0.521
Dehydroepiandosterone sulfate (ug/ml)	261.63±80.68 (279.3)	233.7±143.45 (188.15)	0.014*	260.88±91.26 (257.9)	202.81±112.151 (222)	0.415
Free Testosterone (ng/dl)	0.55±0.27 (0.51)	0.43±0.34 (0.33)	0.022*	0.76±0.36 (0.8)	0.52±0.4 (0.46)	0.240
Insulin (uU/ml)	7.66±3.33 (6.70)	8.57±3.25 (8.14)	0.132	15.06±4.63 (15.14)	10.69±7.05 (8.87)	0.032*
Lipoprotein-a (mg/dl)	17.43±17.44 (9.85)	18.43±23.35 (8.9)	0.823	27.96±32.02 (8.9)	18.32±17.62 (8.9)	0.815
C-Reactive Protein (mg/l)	1.49±3.07 (0.62)	1.93±4.03 (0.4)	0.662	3.93±5.12 (1.1)	0.93±1(0.45)	0.080
Follicle Stimulating Hormone (mIU/ml)	6.17±1.84 (6.13)	7.21±3.14 (6.72)	0.134	6.69±1.58 (6.27)	7.36±1.57 (7.14)	0.322
Luteinising Hormone (mIU/ml)	9.28±4.31 (7.60)	5.86±2.38 (5.32)	0.001**	6.73±3.11 (6.2)	5.68±2.46 (5.08)	0.351
HOMA-IR	1.74±0.79 (1.56)	2.22±1.57 (1.83)	0.096	3.46±1.21 (3.35)	2.41±1.75 (1.91)	0.036*
SHBG (nmol/ml)	58.87±30.21 (47.24)	61.16±36.86 (47.74)	0.929	37.40±37.58 (26.74)	50.28±32.11 (39.93)	0.039*
Free Androgen Index	3.19±1.9 (2.91)	2.25±1.62 (2.07)	0.040*	5.50±3.38 (4.98)	2.93±2.48 (2.64)	0.098
Pentraxin-3 (ng/ml)	0.86±0.24 (0.81)	0.89±0.09 (0.89)	0.035*	0.85±0.14 (0.81)	0.98±0.23 (0.88)	0.130

aStudent's t-test Mann-Whitney U Test SHBG: Sex Hormone Binding Globulin; HOMA-IR: Homeostatic Model Assessment of Insulin Resistance
**p<0.05 **p<0.01*

their BMI (normal and overweight) but only LDL level of the overweight group was significantly higher, overweight PCOS had higher pentraxin-3 levels but levels were not statistically significant. We compared PCOS and controls with normal BMI (Table II): women with PCOS had significantly higher DHEAS, F.Test, LH, FAI and significantly lower pentraxin-3 levels (0.86±0.24 and 0.89±0.09 respectively, p=0.035). We compared overweight PCOS and controls (Table II): women with PCOS had significantly higher insulin, HOMA-IR and significantly lower SHBG levels, pentraxin-3 levels were higher in the control group but did not reach statistical significance (0.85±0.14 and 0.98±0.23 respectively, p=0.13).

Women with PCOS and WHR<0.8 had significantly higher HDL and SHBG, lower insulin and HOMA-IR when compared to women with WHR ≥ 0.8. Pentraxin-3 levels were higher in the PCOS group with WHR<0.8, but did not reach statistical significance (0.96±0.31 and 0.83±0.17 respectively, p=0.159). Pentraxin-3 levels of the control group did not change when compared according to WHR, (0.91±0.13 when WHR<0.8 and 0.92±0.15 when WHR ≥ 0.8, p=0.957).

Pentraxin-3 level of women with PCOS did not change when stratified according to HOMA-IR, PCOS with HOMA-IR ≥ 2.75 and <2.75 had pentraxin levels of 0.81±0.11 and 0.87±0.24 respectively, p=0.317).

Pentraxin-3 levels were correlated statistically significantly with Lp-a levels in women with PCOS (r=0.33, p=0.012) and with weight (r=-0.535, p=0.027) and LDL (r=-0.642, p=0.005) in obese PCOS. There was no statistically significant correlation between pentaxin-3 and the other parameters in any of the groups.

DISCUSSION

In this study we detected significantly lower pentraxin-3 levels in women with PCOS when compared to the control group. The only previous study comparing pentraxin-3 levels of women with PCOS and controls, showed increased levels of pentraxin-3 in PCOS (13). Levels of pentraxin-3 were also reported to increase in metabolic syndrome (MS) (12, 15). Experimental studies about pentraxin-3 found that it had antiinflammatory and cardioprotective properties (16) and other experimental studies about CRP revealed its proatherogenic properties (17). Studies with MS patients found higher CRP and lower pentraxin-3 levels when compared to the control group (18, 19). Therefore pentraxin-3 was proposed to be a molecule balancing the proinflammatory and antiinflammatory stimuli, in this way it might be protecting the cells from damage (16).

In this study levels of pentraxin-3 did not change when women with PCOS were stratified according to BMI, but overweight women with PCOS had significantly higher CRP levels. After stratification according to BMI, normal weight controls had significantly higher pentraxin-3 levels when compared to normal weight PCOS, but pentraxin-3 levels of overweight PCOS and overweight controls did not differ. In a previous study on patients with MS, BMI correlated positively with CRP and negatively with pentraxin-3 levels (18). We did not find a correlation between BMI and pentraxin-3 or CRP in women with PCOS and controls. Previously, the presence of a chronic inflammatory state in women with PCOS was suggested by high levels of CRP (20, 21), others reported non-significantly increased CRP levels in PCOS (22) as in our study. This might suggest the presence of a difference in the mechanism of chronic inflammatory state of women with PCOS. Low levels of pentraxin-3 may prevent limitation of inflammation, thereby accelerating the associated tissue damage and atherosclerosis in women with PCOS.

We detected a positive correlation between pentraxin-3 and levels of Lp-a in the women with PCOS group, but in the overweight PCOS group, pentraxin-3 was correlated negatively with LDL and body weight, which may be due to the statistically relative increment of LDL in overweight cases.

Obese PCOS patients had higher CRP and Lp-a levels compared to obese controls, but the BMI of the obese PCOS group were higher and therefore the results must be interpreted with caution. In previous studies, women with PCOS demonstrated significantly elevated Lp(a) concentrations (23, 24). In this study, although not statistically significant, CRP and Lp-a levels were higher in women with PCOS when compared to BMI matched controls.

Elevated baseline levels of Lp-a were reported to be associated with an increased risk of fatal and non-fatal coronary artery disease (25). A proinflammatory stimulus might result in an increased cardiovascular risk due to increased Lp-a levels in PCOS patients.

A recent study detected a positive correlation between pentraxin-3 levels and insülin resistance (IR) in women with PCOS (13). On the contrary, there was no relationship between pentraxin-3 and HOMA-IR in our study, and nor was there any difference in pentraxin-3 levels when women with PCOS were stratified according to HOMA-IR. Other previous studies also reported no association between IR and pentraxin-3 (15, 26). Levels of pentraxin-3 correlated negatively with IR both in lean and obese subjects in previous studies (27, 28). Miyaki et al. proposed low pentraxin-3 levels as the triggering factor for obesity-induced IR (29).

We compared BMI and age-matched cases and controls. But the differences in BMI and number of subjects between obese PCOS and obese controls are limitations of this study. Also the cross-sectional nature of the study prevents detecting a cause and effect relationship. Pentraxin-3 might be a molecule contributing to pathophysiology of PCOS by preventing apoptosis of atretic follicles and this can be the subject of future studies.

Based on the results of this study, we can postulate a reciprocal contribution of CRP and pentraxin-3 to metabolic events and chronic low-grade inflammation in women with PCOS. Pentraxin-3 might be a molecule contributing to pathophysiology of PCOS. Further studies are warranted to prove reproducibility of our results.

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