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Serum chemerin levels in women with polycystic ovary syndrome

[Polikistik over sendromlu kadın hastalarda serum chemerin seviyeleri]

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ABSTRACT

Objective: The aim of this study is to investigate the association of serum chemerin levels with metabolic parameters of women with polycystic ovary syndrome. Chemerin is an adipocytokine associated with adiposity, insulin resistance and metabolic syndrome, all of which are frequently observed in polycystic ovary syndrome.

Methods: This is a prospective case-control study. We compared the metabolic, biochemical and anthropometric parameters of 35 women with polycystic ovary syndrome and 30 body mass index and age matched controls.

Results: Chemerin levels of women with polycystic ovary syndrome were similar to that of the control group. Chemerin levels correlated positively with DHEAS (r=0.427, p=0.011) and LH (r=0.407, p=0.015) levels in women with polycystic ovary syndrome. There was a negative correlation between chemerin and lipoprotein-a levels in normal weight women with polycystic ovary syndrome (r=-0.426, p=0.043) and there was a negative correlation between chemerin and triglyceride levels in overweight women with polycystic ovary syndrome (r=-0.669, p=0.024). In obese control group chemerin correlated positively with C-reactive protein levels (r=0.738, p=0.037).

Conclusion: In this study we could not detect a definitive role of chemerin in the pathophysiology of polycystic ovary syndrome, but its probable role in the development of the syndrome should be investigated with more detailed studies in the future.

Key Words: Chemerin, Polycystic Ovary Syndrome, CRP, body mass index

Conflict of Interest: The authors have no conflict of interest.

ÖZET

Amaç: Bu çalışmanın amacı serum chemerin seviyeleri ile polikistik over sendromlu hastaların metabolik parametreleri arasındaki ilişkiyi araştırmaktır. Chemerin adipozite, insulin rezistansı ve metabolik sendrom ile ilişkilidir ve bulgulara polikistik over sendromunda da sık rastlanır.

Metod: Bu çalışma prospektif bir vaka-kontrol çalışması olarak planlandı. Kliniğimize başvuran 35 polikistik over sendromlu hastanın metabolik, biyokimyasal ve antropometrik parametrelerini, yaş ve vücut kitle indeksleri eşleştirilmiş 30 kontrol hastasıyla karşılaştırdık.

Bulgular: Polikistik over sendromlu hastaların serum chemerin seviyeleri ile kontrol grubunun serum chemerin seviyeleri benzerdi. Polikistik over sendromlu hastalarda serum chemerin seviyeleri, DHEAS (r=0.427, p=0.011) ve LH (r=0.407, p=0.015) seviyeleri ile korele idi. Normal kilolu polikistik over sendromlu kadınlarda serum chemerin ile lipoprotein-a seviyeleri arasında negatif korelasyon tespit edildi (r=-0.426, p=0.043), kilo fazlası olan polikistik over sendromu hastalarında ise chemerin ve trigliserit seviyeleri arasında negatif korelasyon tespit edildi (r=-0.669, p=0.024). Obez kontrol grubunda serum chemerin seviyeleri ile C-reaktif protein seviyeleri arasında pozitif korelasyon tespit edildi (r=0.738, p=0.037).

Sonuç: Bu çalışmada chemerinin polikistik over sendromunun patofizyolojisinde açık bir rol oynadığı gösterilemedi, fakat sendromun gelişimine olası katkıları gelecekteki daha ayrıntılı çalışmalarla araştırılmalıdır.

Anahtar Kelimeler: Chemerin, polikistik over sendromu, CRP, vücut kitle indeksi

Çıkar Çatışması: Yazarların çıkar çatışması yoktur.

Introduction

The most common endocrinopathy in women of reproductive age is the polycystic ovary syndrome (PCOS) [1,2]. Women with PCOS seem to have an adverse cardiovascular risk profile [3] and this can be attributed to the increased prevalence of metabolic syndrome (MS) in women with PCOS [4]. Although not included in the diagnostic criteria of PCOS, obesity and insulin resistance (IR) affect nearly 2/3 of the women with PCOS [5] and characterize most of the patients with MS. Adipose tissue, especially visceral adipose tissue is an active endocrine organ secreting proinflammatory adipocytokines together with the macrophages infiltrating adipose tissue, these adipocytokines also lead to IR [6]. A recently identified adipocytokine, chemerin is highly expressed in liver and adipose tissue and is associated with adiposity, IR and MS risk factors, all of which are frequently observed in women with PCOS [7,8]. Chemerin also acts as a chemoattractant for macrophages and it leads to adipocyte differentiation [9]. The aim of this study is to investigate the association of chemerin with metabolic parameters of women with PCOS.

Materials and Methods

The study was constructed as a case-control study. Serum samples of patients attending gynecology outpatient clinics of İstanbul Bilim University were used. Serum samples were collected for another study approved by the Institutional Review Board of İstanbul Bilim University, all of the involved patients have given their written informed consent. The study protocol was in agreement with the Declaration of Helsinki, 1975. The diagnosis of PCOS was made according to 2003 Rotterdam ESHRE/ASRM PCOS Consensus Workshop Group criteria [10], when at least two of the following 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). We established a control group from patients without any menstrual irregularities, without any clinical or biochemical signs of hyperandrogenism. We excluded cases and controls with systemic diseases as diabetes mellitus, cardiovascular diseases, hypertension, thyroid diseases, chronic renal failure, malignancy, Cushing syndrome, congenital adrenal hyperplasia, hyperprolactinemia and gastrointestinal malabsorptive diseases. To avoid drug misinterpretations, medications of cases or controls were stopped for at least 3 months before the study including oral contraceptives, glucocorticoids, lipid-lowering, antiobesity, antidiabetes, antiandrogenic, antihypertensive or ovulation-inducing agents.

Table 1. Clinical, hormonal and metabolic features of women with PCOS and controls

	PCOS (n=35)	Controls (n=30)	[a]*p*
	Mean±SD (Median)	Mean±SD (Median)	
Age (years)	26.31±5.26	28.40±7	***0.186***
Weight (kg)	64.93±8.18	62.70±9.13	***0.303***
Height (cm)	163.69±6.11	165.63±6.13	***0.206***
BMI (kg/m^2)	24.06±3.09	22.94±2.98	***0.144***
Waist-Hip Ratio	0.84±0.05	0.82±0.07	***0.194***
Fasting Blood Glucose (mg/dl)	93.54±6.77	90.76±6.49	***0.100***
[b]Triglycerides (mg/dl)	70.34±31.12 (60)	65.70±25.93 (57)	***0.797***
High density Lipoprotein (mg/dl)	56.06±14.5	58.34±13,26	***0.516***
Low Density Lipoprotein (mg/dl)	98.40±22.67	97.71±26,08	***0.910***
[b]Dehydroepiandosterone sulfate (ug/ml)	257.62±87.66 (266.3)	229.11±142.07 (1921)	***0.047****
[b]Free Testosterone (ng/dl)	0.66±0.33 (0.5)	0.47±0.36 (0.3)	***0.013****
[b]Insulin (uU/ml)	10.09±5.07 (9.4)	9.44±4.49 (8.5)	***0.756***
[b]Lipoprotein-a (mg/ml)	19.70±23.77 (9.8)	18.87±22.97 (8.9)	***1.000***
[b]C-Reactive Protein (mg/l)	2.03±3.59 (0.7)	1.68±3.76 (0.3)	***0.197***
[b]Follicle Stimulating Hormone (mIU/ml)	6.36±1.61 (6.2)	7.09±2.7 (6.8)	***0.140***
[b]Luteinising Hormone (mIU/ml)	8.99±4.55 (7.5)	5.76±2.46 (4.9)	***0.001****
[b]HOMA-IR	2.35±1.26 (2.2)	2.37±1.65 (1.9)	***0.757***
[b]Sex Hormone Binding Globulin (nmol/ml)	48.82±32.85 (38.2)	56.34±33.64 (46.7)	***0.156***
[b]Free Androgen Index	4.30±2.96 (3.5)	2.52±1.87 (2.2)	***0.007****
[b]Chemerin (ng/ml)	184.30±48.89 (193.7)	187.50±49.88 (187.9)	***0.762***

[a]Student t test; [b]Mann-Whitney U test; *p<0.05; **p<0.01.

Table 2. Women with PCOS stratified according to body mass index

	Normal (n=24)	Overweight (n=11)	*p*
	Mean±SD (Median)	Mean±SD (Median)	
Age (years)	26.42±4.92 (25.5)	26.09±6.20 (23)	***0.695***
Weight (kg)	61.58±6.95 (60)	72.23±5.54 (71.5)	***0.001****
Height (cm)	165.04±6.56 (165)	160.73±3.77 (160)	***0.074***
Body Mass Index (kg/m^2)	22.27±1.4 (21.7)	27.96±1.87 (27.5)	***0.001****
Waist-Hip Ratio	0.83±0.04 (0.8)	0.87±0.07 (0.8)	***0.084***
Fasting Blood Glucose (mg/dl)	91.92±5.85 (91)	97.09±7.53 (96)	***0.040****
Triglyceride (mg/dl)	69±28.77 (60)	73.27±37.08 (56)	***0.957***
High density Lipoprotein (mg/dl)	60.38±13.86 (59)	46.64±11.42 (46)	***0.010****
Low Density Lipoprotein (mg/dl)	98.25±24.86 (101)	98.73±18.08 (98)	***0.972***
Dehydroepiandosterone sulfate (ug/ml)	249.18±81.81 (275.3)	276.03±100.93 (258.1)	***0.859***
Free Testosterone (ng/dl)	0.58±0.27 (0.5)	0.83±0.39 (0.7)	***0.080***
Insulin (uU/ml)	8.41±3.96 (7.3)	14.12±5.37 (13.8)	***0.002****
Lipoprotein-a (mg/ml)	14.91±16.59 (10)	29.73±33.1 (8.9)	***0.645***
C-Reactive Protein (mg/l)	1.26±1.7 (0.7)	3.71±5.72 (0.6)	***0.434***
Follicle Stimulating Hormone (mIU/ml)	6.43±1.83 (6.3)	6.21±1.04 (6.1)	***0.558***
Luteinising Hormone (mIU/ml)	10.07±4.63 (8.3)	6.62±3.49 (5.8)	***0.013****
HOMA-IR	1.91±0.92 (1.6)	3.31±1.4 (3.3)	***0.002****
Sex Hormone Binding Globulin (nmol/ml)	59.01±34.4 (47.1)	26.6±12.5 (23.7)	***0.001****
Free Androgen Index	3.41±2.03 (3.1)	5.94±3.72 (4.9)	***0.063***
Chemerin (ng/ml)	193.76±42.98 (197.4)	163.66±56.53 (169.4)	***0.145***

Mann-Whitney U Test; *p<0.05; **p<0.01.

We made physical examination of all patients and blood for appropriate laboratory tests were drawn in the early follicular phase after an overnight of fasting, during the 3rd-4th days of the cycle. We measured weight, height and waist and hip circumferences. Hip circumference (HC) was obtained as the widest circumference at the level of the buttocks. Waist circumference (WC) was obtained as the smallest circumference at the level of umbilicus. Waist-to-Hip ratio (WHR) was calculated by dividing WC to HC. Body mass index (BMI) was calculated as body weight in kilograms divided by height in metre squared (kg/m²). 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), total testosterone, cortisol, free T4, 17-OH progesterone, sex-hormone binding globulin (SHBG), CRP (Cobas integra 400, Roche) and Lp-a (Cobas integra 800, Roche) were measured. Free testosterone was calculated with the formula of Vermulen which includes total testosterone (Cobas E411, 0.025-15, 1.2-4.7), SHBG and albumin [11]. All hormonal parameters were studied with enzymatic chemilıminescence and other parameters were studied with spectrophotometric analysis. Level of chemerin was studied from serum samples stored at -80ºC with ELISA (Human Chemerin Immunoassay Aviscera Bioscience, CA, USA) with intraassay and interassay coefficients of variations of 4-6% and 8-10% respectively. 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. Free androgen index (FAI) was calculated with the formula= 100x total testosterone/SHBG.

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 Student's T-test, data showing non-normal distribution of parameters were compared with Mann Whitney U test, relation of chemerin with other parameters was investigated with Spearman's and Pearson's correlation analyses. At a confidence interval of 95% p-values<0.05 were considered statistically significant.

Results

Table 1 showed the clinical, hormonal and metabolic features of the cases and controls, there was no difference in chemerin levels of the two groups. Women with PCOS had statistically significantly higher DHEAS, Free Testosterone, LH and FAI. Cases and controls were seperated into two groups according to their BMI. Eleven patients with PCOS were overweight-obese (BMI≥ 25kg/m²) and

Table 3. Control group stratified according to body mass index

	Normal (n=22)	Obese (n=8)	*p*
	Mean±SD (Median)	Mean±SD (Median)	
Age (years)	27.27±6.8 (24.5)	31.5±7.01 (33.5)	***0.239***
Weight (kg)	58.36±5.19 (57)	74.62±6.54 (74)	***0.001****
Height (cm)	165.41±6.04 (166.5)	166.25±6.78 (167)	***0.671***
Body Mass Index (kg/m^2)	21.49±1.45 (21)	26.92±2.43 (25.7)	***0.001****
Waist-Hip Ratio	0.81±0.07 (0.8)	0.86±0.06 (0.8)	***0.054***
Fasting Blood Glucose (mg/dl)	90.86±7.04 (92)	90.5±5.15 (91)	***0.826***
Triglyceride (mg/dl)	64.73±24.63 (57)	68.38±30.89 (56)	***0.907***
High density Lipoprotein (mg/dl)	57.57±11.43 (58)	60.38±18.01 (59.5)	***0.751***
Low Density Lipoprotein (mg/dl)	91.65±21.49 (90)	113.63±31.65 (112)	***0.025****
Dehydroepiandosterone sulfate (ug/ml)	238±67±152.71 (178.3)	202.81±112.15 (222)	***0.944***
Free Testosterone (ng/ml)	0.46±0.35 (0.3)	0.52±0.4 (0.4)	***0.799***
Insulin (uU/ml)	8.96±3.17 (8.5)	10.69±7.05 (8.8)	***0.788***
Lipoprotein-a (mg/dl)	19.08±25.1(8.9)	18.32±17.62 (8.9)	***0.961***
C-Reactive Protein (mg/l)	1.95±4.34 (0.3)	0.93±1 (0.4)	***0.962***
Follicle Stimulating Hormone (mIU/ml)	6.99±3.02 (6.6)	7.36±1.57 (7.1)	***0.573***
Luteinising Hormone (mIU/ml)	5.79±2.51 (4.9)	5.68±2.46 (5)	***0.851***
HOMA-IR	2.35±1.65 (1.9)	2.41±1.75 (1.9)	***0.815***
Sex Hormone Binding Globulin (nmol/ml)	58.36±34.66 (47.7)	50.28±32.11 (39.9)	***0.277***
Free Androgen Index	2.38±1.66 (2.1)	2.93±2.48 (2.6)	***0.885***
Chemerin (ng/ml)	183.97±46.42 (183.2)	197.18±60.79 (224.2)	***0.223***

Mann-Whitney U Test; *p<0.05; **p<0.01.

24 were normal weight (BMI< 25kg/m²). In the control group 8 patients were overweight-obese (BMI≥ 25kg/m²) and 22 were normal weight (BMI <25 kg/m²). In Table 2 overweight PCOS were compared to normal weight PCOS: Overweight PCOS had statistically significantly higher fasting blood glucose (p=0.04), insulin (p=0.002), HOMA-IR (p=0.002) and lower HDL (p=0.01) and SHBG (p=0.04) levels. Chemerin levels of the 2 groups were similar. In Table 3 overweight controls were compared to normal weight controls: Overweight controls had statistically significantly higher LDL levels (p=0.025). Chemerin levels of the 2 groups were similar. When we compared normal weight PCOS to normal weight controls, Free Testosterone (p=0.048) and LH (p=0.04) levels of women with PCOS were statistically significantly higher and chemerin levels of the 2 groups were similar. When we compared overweight PCOS to overweight controls, only SHBG level of women with PCOS were statistically significantly lower than controls (p=0.016) and chemerin levels of the 2 groups were similar. Women with PCOS and controls were stratified into two groups according to their HOMA-IR and chemerin levels did not differ when HOMA-IR was ≥2.75 or <2.75, both in PCOS and controls. Mean chemerin level of controls with HOMA-IR ≥2.75 and <2.75 were (p=0.965). Mean chemerin level of PCOS with HOMA-IR ≥2.75 and <2.75 were (p=0.570).

Chemerin correlated positively with DHEAS (r=0.427, p=0.011) and LH (r=0.407, p=0.015) in women with PCOS. There was a negative correlation between chemerin and Lp-a in normal weight PCOS (r=-0.426, p=0.043) and there was a negative correlation between chemerin and TG in overweight PCOS (r=-0.669, p=0.024). In obese controls chemerin levels correlated positively with CRP (r=0.738, p=0.037).

Discussion

In this study we did not detect any difference in chemerin levels of women with PCOS and the control group. A previous study in overweight PCOS detected increased serum chemerin levels when compared to BMI matched controls [12]. Bearing the results of this study in mind, we compared our overweight PCOS to overweight controls, although not statistically significant, overweight women with PCOS had lower chemerin levels. Some of the previous studies related chemerin to obesity related parameters as IR and BMI and some did not [8,12,13], therefore chemerin is most probably not a mediator of obesity. In the aforementioned study, level of chemerin was reported to decrease after treatment with metformin, and the change in chemerin levels was attributed to decreased IR [12]. Other studies correlated chemerin with IR and showed that chemerin levels changed with improvement in IR parameters after life-style intervention [14,15]. HOMA-IR of our cases and controls were matched and chemerin levels did

not differ between the groups with and without IR, and chemerin levels were not associated with IR. Some of the previous studies rejected the association between chemerin and IR parameters [8,13]. Chemerin is secreted from adipocytes, but not from macrophages infiltrating adipose tissue or skeletal muscle cells [16]. Skeletal muscle is the major site of peripheral IR. Skeletal muscle cells were reported to have chemerin receptors and chemerin was reported to decrease insulin stimulated glucose uptake in skeletal muscle cells [16]. As a result the role of chemerin in the pathophysiology of IR and PCOS is still controversial.

Bozaoglu et al found similar chemerin levels in diabetics and healthy controls and chemerin levels were related to BMI, TG levels and blood pressure in healthy controls [8]. In the current study chemerin correlated negatively with TG levels in normal weight PCOS, there was no correlation with TG levels in other groups. Chemerin was associated with TG levels in some other reports [17,18].

In the current investigation chemerin correlated positively with CRP in obese controls, this may indicate an action as a marker of inflammation in obese subjects rather than being a marker of obesity. Chemerin may act as a chemoattractant protein generated in inflammatory conditions to recruit macrophages. Weigert et al found higher chemerin levels in diabetics (increased BMI) and obese patients when compared to normal weight controls, but the effect was attributed to inflammation [19]. Other investigations also proposed a relationship between chemerin and markers of inflammation in obese or diabetic subjects [20,21]. Interestingly chemerin levels of our patients with PCOS were not related to CRP levels. Chemerin was also correlated with CRP in MS patients whom have similarities to PCOS [22]. Chemerin levels were related to markers of inflammation in studies with different designs after exclusion of other contributers [23-25].

Additionally, in our study, we found that chemerin was seemed to be positively correlated with DHEAS and LH. Although, our data showed no definitive role of chemerin in the pathophysiology of PCOS, further clinical and experimental studies has to be done as previously in some studies chemerin was shown to be regulating some steroid hormones in preantral follicles and granulosa cells [26,27].

In conclusion chemerin might be a multipotential adipocytokine with various actions, but not a direct mediator of obesity.

Conflict of Interest

There are no conflicts of interest among the authors.

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