RESEARCH ARTICLE / *Araştırma Makalesi*

Endocan As A Potential Marker of Early Endothelial Dysfunction In Polycystic Ovary Syndrome (PCOS)

Polikistik Over Sendromunda (PKOS) Erken Endotel Disfonksiyonunun Potansiyel Belirleyicisi Olarak Endocan

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Abstract

Objective Polycystic ovary syndrome (PCOS) is a common endocrinological disease in women of reproductive age and has a wide range of metabolic effects. Chronic low-grade inflammation and endothelial dysfunction plays a key role in the pathogenesis of PCOS and they are associated with an increased risk of cardiovascular disease. Endocan, is an inflammatory marker showing endothelial dysfunction. The aim of our study, to compare serum endocan levels in PCOS and healthy control groups and to determine the relationship between some cardiovascular risk factors and serum endocan levels.

Materials and Methods This case-control study included 52 PCOS patients and 59 age-matched healthy controls. Patients were diagnosed as PCOS based on 2003 Rotterdam criteria. Demographic data, history of menstrual irregularity and infertility, polycystic ovary appearance in ultrasonography and hirsutism status were recorded. Endocan levels of PCOS patients and controls were compared. Data analysis was performed by using SPSS-22 for Windows (Statistical Package for Social Science, SPSS Inc. Chicago IL, USA*Z).

Results The median (IQR) value of serum endocan level was 420.7 ng/L (355.2-570.3) in the PCOS group and 320.0 ng/L (219.9-455.9) in the control group (p=0.003). While there was no significant correlation between serum endocan and some cardiovascular risk factors such as waist circumference, hip circumference, BMI, LDL, triglyceride, systolic and diastolic arterial tension but a positive correlation was found between homeostatic model assessment insulin resistance (HOMA-IR) (r= 0.276, p= 0.003).

Conclusion Serum endocan levels are higher in PCOS patients, in line with the literature. Endocan level shows a significant correlation with insulin resistance, one of the metabolic parameters. This may be a sign of early endothelial dysfunction in PCOS.

Keywords endocan; endothelial dysfunction; polycystic ovary syndrome; inflammation

Öz

Amaç *Polikistik over sendromu (PKOS), üreme çağındaki kadınlarda sık görülen endokrinolojik hastalıktır. PKOS'ta izlenen kronik düşük dereceli inflamasyon ve endotel disfonksiyon artmış kardiyovasküler hastalık riski ile ilişkilidir. Endocan, endotel disfonksiyonunu gösteren inflamatuar bir belirteçtir. Çalışmamızda PKOS ve sağlıklı kontrol grubunu serum endocan düzeyleri açısından karşılaştırmayı ve kardiyovasküler risk faktörleri ile serum endocan düzeyleri arasındaki ilişkiyi belirlemeyi amaçladık.*

Gereç ve Yöntemler *Bu vaka-kontrol çalışmasında, 52 PKOS hastası ve yaş eşleştirilmiş sağlıklı 59 bireyden oluşan kontrol grubu yer almaktadır. Hastalara, 2003 Rotterdam kriterlerine göre PCOS tanısı kondu. Demografik veriler, menstruel düzensizlikler, infertilite öyküsü, ultrasonografide polikistik over görünümü ve hirsutizm varlığı kaydedildi. PCOS hastaları ve kontrol grubunun serum Endocan düzeyleri karşılaştırıldı. Veri analizi Windows için SPSS-22 (Statistical Package for Social Science, SPSS Inc. Chicago IL, USA*Z) kullanılarak yapıldı.*

Bulgular *Serum endocan düzeyi ortanca (IQR) değeri PKOS grubunda 420,7 ng / L (355,2-570,3), kontrol grubunda ise 320,0 ng / L (219,9-455,9) idi (p = 0,003). Serum endocan ile bel çevresi, kalça çevresi, BMI, LDL, trigliserit, sistolik ve diyastolik arteriyel basınç gibi bazı kardiyovasküler risk faktörleri arasında anlamlı bir ilişki bulunmazken, insülin direnci (HOMA-IR) ile arasında pozitif korelasyon saptandı (r = 0.276, p = 0,003).*

Sonuç *Çalışmamızda, serum endocan düzeyleri literatürle uyumlu olarak PKOS hastalarında daha yüksek saptanmıştır. Endocan düzeyi, metabolik parametrelerden biri olan insülin direnci ile anlamlı bir korelasyon göstermektedir. Bu bulgular, PKOS' ta erken endotel disfonksiyonunun bir işareti olarak yorumlanabilir.*

Anahtar Kelimeler *endocan; endotel disfonksiyonu; polikistik over sendromu; inflamasyon*

INTRODUCTION

Polycystic ovary syndrome (PCOS) is an endocrinological disease that affects 6-18% of women of reproductive age and has a wide range of metabolic effects.[1,2] It is the most common cause of infertility in women.[3] The main clinical features of PCOS are ovulatory dysfunction and hyperandrogenism, and these findings may persist throughout the reproductive period. Its etiology is unknown and causes long-term health problems. PCOS is associated with an increased risk of metabolic syndrome, type 2 diabetes, cardiovascular disease, and endometrial cancer.[2,4,5]

Because of these effects, the diagnosis of PCOS should not be ignored. Chronic low-grade inflammation is involved in the pathogenesis of obesity-related diseases. PCOS is also an obesity-related disease and is a proinflammatory condition. A great deal of literature has been published showing that many inflammatory cytokines or molecules such as interleukin-1, interleukin-6, C- reactive protein (CRP), and tumor necrosis factor- alpha (TNF-alfa) are altered in relation to PCOS.[6-10] Endothelial dysfunction is associated with an increased risk of cardiovascular disease, and there are many studies associated with this in PCOS.7,11-13 Although there are conflicting information about the definite increase in cardiovascular mortality in PCOS, which is a premenopausal disease, it is an indisputable fact that cardiovascular disease risk factors frequently accompany PCOS.[4,14]

Endocan (Endothelial cell Spesific Molecule-1; ESM-1), a proteoglycan found in serum and produced by the endothelium, is an inflammatory marker showing endothelial dysfunction.[15-17]

Endocan has been studied in many chronic inflammatory diseases and cancers, and similar studies have been conducted in PCOS. In these studies, endocan levels in PCOS, as in other chronic diseases, were found to be higher than healthy control groups.[1,13,16,18-20] The aim of this study is to compare the endocan level in PCOS patients with the healthy control group and to show the relationship between some cardiovascular risk indicators accompanying PCOS and endocan level.

MATERIALS and METHODS

Study design

This research is a case-control study conducted between January 01, 2017 and December 31, 2018. Our study was evaluated by the Clinical Research Ethics Committee of Health Sciences University Yıldırım Beyazıt Dışkapı Training and Research Hospital and ethics committee approval was obtained with the decision number 24/30, dated 30.06.2015. In addition, the research was carried out in accordance with the Declaration of Helsinki Principles (www.wma.net/e/policy/b3.htm). The study included 52 PCOS patients and 59 age-matched healthy controls. Between the two groups, some cardiovascular risk parameters such as insulin resistance and arterial blood pressure were compared, as well as age, anthropometic measurements, biochemical markers and hormones associated with hirsutism. In addition, to make a comparison according to their body mass index (BMI), both groups were subgrouped within themselves: normal (BMI <25 kg/m2), overweight (BMI = 25-29.9 kg/m2) and obese (BMI≥30 kg/m2). Since there were no obese patients in the control group, it was categorized only as normal and overweight. Serum endocan levels were compared both between groups and between BMI subgroups.

Diagnosis and case selection

Demographic data, history of menstrual irregularity and infertility, polycystic ovary appearance in ultrasonography and hirsutism status were recorded. Hirsutism scoring was done according to Modified Ferriman Gallwey Scoring System.[21] Oligomenorrhea is defined as menstrual intervals over 35 days, and amenorrhea is defined as not having periods for more than 6 consecutive months. PCOS diagnoses were made based on Rotterdam and Androgen Excess Society diagnostic criteria, if in the pelvic or transvaginal ultrasound, 2-9 mm twelve or more preantral

follicle appearance or ovarian volume was more than 10 ml and/or chronic oligo-anovulation (oligomenorrhea) and clinical and/or laboratory hyperandrogenism findings were detected.[22,23] Women under 18 years of age, pregnant women, postmenopausal women, other causes of ovarian and non-ovarian hyperandrogenism (congenital adrenal hyperplasia, idiopathic hyperandrogenism, adrenal and ovarian tumors, etc.), patients using drugs such as oral contraceptives, anti-androgen pills and synthetic steroids, and patients with acute or chronic inflammatory diseases were not included in the study. Those with known cardiovascular disease or predominant risk for cardiovascular disease were also excluded.

Laboratory parameters

Biochemistry and follicular phase hormonal parameters were taken in the follicular phase of the menstrual cycle (within the first 7 days of menstruation). It was sampled at any time in oligomenorrheic patients. All baseline blood tests were performed between 08:00 and 10:00 in the morning, following an 8-hour fasting period. Serum samples for the endocan were first stored for coagulation and then centrifuged at 4000 xg for 15 minutes at + 4 ° C. The serum samples obtained were divided into aliquots and stored in a freezer at -80˚C until analysis. Subsequently, endocan was studied with elisa method with "Human ESM1 / Endocan, PicoKine™, EK0752" kit belonging to "Boster Biological Technology USA". Its sensitivity is <10 pg/ml, the measurement range is 31.2pg / ml-2000pg / ml. Routine biochemistry, thyroid function tests, follicular phase hormonal panel, total testosterone, dehydroepiandosterone sulfate (DHEA-S) and basal 17 OH-P levels at diagnosis were also recorded.

Statistical Analysis

Data analysis was performed by using SPSS-22 for Windows (Statistical Package for Social Science, SPSS Inc. Chicago IL, USA®Z). The variables were investigated using visual (histograms, probability plot) and analytical methods (Kolmogorov-Simirnov/Shapiro-Wilk's test) to determine whether or not they are normally distributed. We performed analyses to describe and summarize the distributions of variables. Continuous variables were reported as the median and interquartile range (IQR). We use the Mann-Whitney U test to compare continuous nonparametric variables. When investigating the changes in serum endocan by groups (PCOS or control), the effects of BMI was adjusted using ANCOVA tests. While investigating the associations between non-normally distributed and/or ordinal variables, the correlation coefficients and their significance were calculated using Spearman test. The statistically significant two tailed p-value was considered as <0,05.

RESULTS

The median age (interquartile range=IQR) is 22 (19-27.75) in the PCOS group and 25 (22-30) in the control group (p=0.130). Other baseline characteristics and descriptive statistics between both groups were summarized in table 1. The median (IQR) value of serum endocan level was 420.7 ng/L (355.2-570.3) in the PCOS group and 320.0 ng/L (219.9-455.9) in the control group (p=0.003) (figure 1).

Serum endocan levels were 311.42 ng/L in those with normal BMI (n= 46) in the control group and 376.64 ng/L in those overweight (n=13), and this difference was not significant (p= 0.149). Similarly, serum endocan levels were not different in subgroups formed according to BMI in PCOS group (p= 0.923) (table 2). In addition, when examining the difference between serum endocan levels compared to PCOS and control groups, it was evaluated whether BMI had an effect on this and it was found that it did not affect the endocan levels in the groups (p=0.837). No correlation was found between the serum endocan level and the total testosterone level (r= 0.022, p= 0.826), which is within the PCOS diagnostic criteria. While there was no significant correlation between serum endocan and some cardiovascular risk factors such as waist circumference (r= 0.172, p= 0.072), hip circumference (r= 0.169, p= 0.076), BMI (r= 0.154, p= 0.107), LDL (r= 0.008, p= 0.933), triglyceride (r=

0.053, p= 0.579), systolic (r= 0.077, p= 0.423) and diastolic arterial tension (r= 0.081, p= 0.397), a positive correlation was found between homeostatic model assessment insulin resistance (HOMA-IR) (r= 0.276, p= 0.003) (table 3).

Table 1. Baseline characteristics of PCOS and control group and differences between groups.

	Median (interquartile range) *		
	PCOS (n=52)	Control (n=59)	p value
Age** (min-max)	23.5±5.3 (18-37)	24.1±3.9 (18-38)	0.130
BMI (kg/m2)	26.44 (22.36-30.48)	22.03 (19.84-24.44)	<0.001
Waist circumference (cm)	88.50 (76.75-97.75)	73.00 (67.00-80.00)	<0.001
Hip circumference (cm)	102 (95-110)	95 (91-101)	0.002
Waist/hip circumference ratio	0.850 (0.819-0.895)	0.766 (0.714-0.822)	<0.001
Fasting blood glucose (mg/dL)	80. (75-88)	78 (72-83)	0.058
İnsülin (fasting) (mIU/L)	15.10 (11.92-20.60)	8.70 (6.40-10.50)	<0.001
HOMA-IR*	3.03 (2.17-4.10)	1.64 (1.28-2.10)	<0.001
TG (mg/dL)	93 (69-149.25)	76 (57-106)	0.031
HDL (mg/dL)	50 (45-58)	52 (50-60)	0.033
LDL (mg/dL)	96 (86-115.5)	89 (77-100)	0.007
Cholesterol (mg/dL)	161 (146-178)	155 (142-180)	0.434
FSH (IU/L)	5.50 (4.55-6.77)	5.00 (4.50-7.30)	0.614
LH (IU/L)	5.55 (3.90-12.07)	5.00 (3.80-7.00)	0.185
Serum estradiol (pg/mL)	48.50 (35.75-67.25)	96 (54.30-125)	<0.001
Total testosterone (ng/dL)	64.88 (47.28-85.33)	31.60 (23.00-35.00)	<0.001
Ferriman-Gallway score	14 (12-16.75)	7 (6-8)	<0.001
Systolic blood pressure (mmHg)	115 (100-130)	100 (95-120)	0.001
Diastolic blood pressure (mmHg)	75 (70-80)	70 (65-80)	0.052

*Since it does not show normal distribution, all data are expressed as median (interquartile range).
** mean
BMI; Body mass index, HOMA-IR; homeostasis model assessment of insulin resistance, FSH; follicle-stimulating hormone, LH; luteinizing hormone, HDL; high-density lipoprotein, LDL; low-density lipoprotein, TG; triglyceride

Table 2. Serum endocan levels were compared between groups according to body mass index.

	Endocan (ng/L)			
	Normal (BMI<25 kg/m2)	**Overweight (BMI=25-29.99kg/m2)**	**Obese (BMI≥30 kg/m2)**	**p value**
Control*	**311.42** (218.00-448.21) (n= 46)	**376.64** (284.51-510.60) (n= 13)	- - (n= 0)	0.149
PCOS*	**413.39** (313.20-599.41) (n= 21)	**454.75** (344.29-547.52) (n= 17)	**424.05** (356.43-580.72) (n= 14)	0.923

*Results for continuous variables were expressed as medians and interquartile ranges.
PCOS; Polycystic ovary syndrome, BMI; Body mass index

Table 3. Correlation analysis between serum endocan level and other cardiovascular risk factors.

	r value	p value
BMI	0.154	0.107
Waist circumference	0.172	0.072
Hip circumference	0.169	0.076
HOMA-IR	0.276	0.003
FGS	0.236	0.013
TG	0.053	0.579
HDL	-0.195	0.041
LDL	0.008	0.933
Total testosterone	0.022	0.826
Systolic blood pressure	0.077	0.423
Diastolic blood pressure	0.081	0.397

BMI; Body mass index, HOMA-IR; homeostasis model assessment of insulin resistance, FGS; Ferriman-Gallwey skoru, HDL; high-density lipoprotein, LDL; low-density lipoprotein, TG; triglyceride

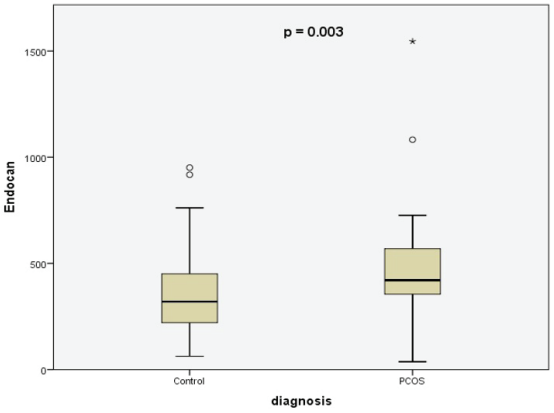

Figure 1. Serum endocan levels of PCOS and control groups are shown schematically.

DISCUSSION

In our study, as expected, serum endocan level was found higher in PCOS patients than healthy control group with similar age distribution. However, endocan level did not change with the increase of BMI in both the PCOS group and the control group. This result is inconsistent with some studies showing the relationship between PCOS and endocan. In a study, it was found that PCOS patients had higher endocan levels than healthy control group, and it was reported that the endocan level decreased with increasing BMI.[1] This is actually a contradictory result showing that Endocan and the severity of obesity act in the opposite direction rather than together. However, there are studies showing that endocan and BMI are positively correlated in PCOS patients.[2]

Obesity is a traditionally known increased cardiovascular mortality risk factor.[24] In our study, the median baseline BMI level of PCOS patients was higher than the control group. However, no correlation was found between endocan and BMI regardless of the group. These results indicate that the inflammation associated with endothelial dysfunction in PCOS patients is caused by reasons other than obesity.

Endocan is now accepted as a marker of inflammation that is associated with endothelial dysfunction.[15,25] At the same time, there are studies showing that there is endothelial dysfunction in PCOS.[26,27] Therefore, studies investigating the relationship between PCOS and cardiovascular disease and mortality have been conducted.[4] In these studies, no relationship was found between cardiovascular mortality and PCOS diagnostic criteria such as menstrual irregularity and anatomical ovarian changes, but a positive relationship was found with hyperandrogenism. However, some risk factors such as obesity, dyslipidemia, insulin resistance, waist circumference, hip circumference and arterial hypertension have been shown to be associated with cardiovascular disease, although they are not among the diagnostic criteria of PCOS.[4,28,29]

In our study, almost all of these cardiovascular risk factors show a negative change in the PCOS group compared to the control group, only HOMA-IR showed a positive correlation with endocan among these differences. In the current study, selected PCOS patients were young, and many of the risk factors mentioned above may not have contributed to endothelial dysfunction, which is an important part of the development of cardiovascular disease. Insulin resistance is a risk factor that prepares and contributes to the development of subclinical atherosclerosis, which is an early stage indicator of endothelial dysfunction.[30] A positive correlation between HOMA-IR and serum endocan level has also been shown.[2] Therefore, the correlation between serum endocan and only HOMA-IR among the risk factors may be related with the early stage of endothelial dysfunction.

This study has some limitations. The first of these is the small number of PCOS patients and the lack of information about the PCOS phenotype. Second, the case-control randomization according to BMI was not done correctly and BMI of groups did not match. As the last limitation, high-sensitivity C-reactive protein (hs-CRP) was not evaluated in our study.

In conclusion, serum endocan levels are higher in PCOS patients, in line with the literature. Endocan level shows a significant correlation with insulin resistance, one of the metabolic parameters. This may be a sign of early endothelial dysfunction in PCOS.

Conflict of Interest

There is no conflict of interest to be declared.

Authors' contributions

All authors contributed to this project and article equally. All authors readand approved the final manuscript.

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