The Relationship between Polycystic Ovary Syndrome and Serum Periostin Level

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ABSTRACT

Objective: To determine the changes of circulating periostin levels in polycystic ovary syndrome (PCOS) and its relationship with metabolic disorders.

Study Design: Cross-sectional study.

Place and Duration of Study: Konya Research and Training Hospital, Turkey between September 2018 and April 2020.

Methodology: Patients with PCOS were compared with healthy individuals as control. The demographics, laboratory findings, anthropometric measurements, the levels of serum periostin and carotid intima media thickness (CIMT) were evaluated and compared.

Results: There was no significant difference between patients with PCOS (n = 53) and controls (n = 35), according to demographic and laboratory findings and anthropometric measurements. The CIMT in patients with PCOS and control groups were measured as 0.5 ± 0.06 mm and 0.43 ± 0.1 mm, respectively ($p < 0.003$). The levels of periostin in the patients with PCOS and control groups were found to be 6.43 ± 6.19 ng/mL and 3.61 ± 3.79 ng/mL, respectively ($p < 0.018$). No statistically significant correlations were found according to periostin levels and metabolic variables.

Conclusion: Although there was no significant correlation between the periostin levels and the metabolic variables in patients with PCOS as compared to those without the periostin levels, but CIMT were higher in PCOS group.

Key Words: *Atherosclerosis, Carotid intima-media thickness, Insulin resistance, Periostin protein, Polycystic ovary syndrome.*

How to cite this article: Gonulalan G, Guney I, Sackan F, Acar S. The Relationship between Polycystic Ovary Syndrome and Serum Periostin Level. *J Coll Physicians Surg Pak* 2021; **31(11)**:1291-1295.

INTRODUCTION

Polycystic ovary syndrome (PCOS) is the most frequently seen reproductive disease with metabolic dysfunction in premenopausal women. PCOS is defined with ovulatory dysfunction, polycystic ovaries, biochemical and/or clinical signs of hyperandrogenism.[1] It represents with polycystic ovaries, menstrual irregularities, infertility, androgen excess, insulin resistance, central obesity, dyslipidaemia and increased type 2 diabetes frequencies.[2] Previously studies showed that subclinical inflammation was frequently seen in PCOS and it was associated with insulin resistance.[3,4]

Periostin is a matricellular protein, which compounds 836 amino acids weighing 90kD.[5] It was first described with expression in the periosteum of long bones, and and it is related with extracellular matrix components such as collagen I, tenascin-C, and fibronectin fibrinogenesis.

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Received: May 15, 2021; Revised: September 30, 2021; Accepted: October 06, 2021
DOI: https://doi.org/10.29271/jcpsp.2021.11.1291

It is thought that periostin regulates cellular adhesion, migration, proliferation, differentiation.[6,7] It also plays role in pathologic processes such as fibrosis, atherosclerosis, tumorigenesis and metastasis. It was found that periostin levels were strongly correlated with chronic inflammation and insulin resistance. Insulin resistance is an important factor in stimulating testosterone secretion by theca cells of the ovaries which represents the clinical signs of hyperandrogenism.[8-10]

Although it has not been clearly defined, it is thought that chronic inflammation has a role in PCOS physiopathology. Previous studies have shown that women with PCOS had fibrosis in both ovaries. Periostin might be an important factor in development of fibrosis and increased testosterone secretion in polycystic ovaries.

Thus, the aim of this study was to determine the alterations of serum periostin levels and its relationship with metabolic disorders in PCOS.

METHODOLOGY

This study was designed as an observational cross-sectional study. Sample size was calculated according to frequency of PCOS and the population of the city in 2018. The informed and written consents of the patients were signed by the patients

before the beginning of study. The study was approved by the local Ethics Committee of the Karatay University (2018-021) and was performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments. The cost of tests was paid by the Institution (TUEK 48929119/774). None of the patients had a payment for the tests.

The subjects included 53 patients with PCOS and a control group of 35 healthy volunteers in between September 2018 and April 2020. The patients, who were admitted to outpatient clinic of Endocrinology and Metabolism Disorders with the symptoms of menstrual irregularity and/or hyperandrogenism, were randomly included. Age and body mass index (BMI)-matched 35 healthy premenopausal women visiting the outpatient clinic for general check-up, were included as the control group. All patients and healthy individuals were aged between 18 and 45 years. The clinical, biochemical and hormonal values and ultrasonography findings of the ovaries were detected as normal in control group. They did not have any chronic medication and metabolic disease history. The patients with history of coronary artery disease, cerebrovascular event, heart failure, vascular disease, renal failure, immunological disease, ovarian tumor, and endocrine diseases such as diabetes mellitus, congenital adrenal hyperplasia, hyperprolactinemia, cushing syndrome and hypothyroidism were excluded from the study.

PCOS was diagnosed according to the 2003 Rotterdam criteria.[11] Any patient with two of the three criteria, namely oligo-anovulation, clinical and/or biochemical hyperandrogenism or polycystic ovarian morphology on ultrasound, were diagnosed as PCOS.

During the first examination, carotid intima media thicknesses (CIMT) of the patients were measured from the common carotid artery by the same investigator with LOGİQ P5 B-Mode Ultrasonography device TM. The average of three measurements at 1 cm proximal to the bifurcation of both common carotid arteries was accepted as CIMT measurement.

After fasting overnight for 8-12 hours, venous blood samples were taken between 08.00 a.m. and 09.00 a.m. at the 3^{rd}-5^{th} day of the menstrual circle. The levels of fasting blood glucose, fasting blood insulin, luteinizing hormone (LH), follicle stimulating hormone (FSH), estradiol (E2), total testosterone, dehydroepiandrosterone-sulfate (DHEAS) and lipid profile such as high density lipoprotein cholesterol (HDL-C), low density lipoprotein cholesterol (LDL-C), triglyceride(TG) were examined. The cut-off points of TG, LDL-C and HDL-C were accepted as 150mg/dL, 130mg/dL and 50 mg/dL respectively. The levels of serum periostin were determined by Elisa method (Catalogue No: E-EL-H2452): Intra-assay co-efficent variation (CV<10%).

All measurements were done by the same investigator. Anthropometric Measurements included the weight, height, and waist and hips circumference. BMI was calculated by dividing body weight (Kg) by the square of height (m^2). Waist circumference was measured at the midpoint between iliac crests and the lowest rib at standing position. Hip circumference was measured at the widest part of the hips. The average of these two values was taken as the waist-hip-ratio (WHR). Waist-height-ratio was also calculated by averages of these two values.

LAP and VAI were calculated to evaluate the abdominal adiposity.[12,13] Both of them was calculated with following formulae:

VAI (Females) = [waist circumference (cm)/ (36.58+ (1.88×BM)] × (triglyceride/0.81) × (1.52/HDL-K).

LAP (Females) = (waist circumference (cm)-58) × Triglyceride.

Software SPSS version 22.0 for Windows XP was used for the statistical analysis of study. Student's t-test was used to compare the normally disturbed variables, whereas the Mann-Whitney U-test was used for non-normally disturbed variables. Results of parametric variables were presented as mean ± standard deviation. Pearson correlation test was used for correlation analysis of periostin and metabolic variables in PCOS group. The level of $p \leq 0.05$ was accepted as statistical significance.

RESULTS

In the study, 53 patients with PCOS aged 18 to 45 years and 35 healthy volunteers in the control group were included. Demographic and anthropometric measurements of the groups were given in Table I. The laboratory findings of the groups were given in Table II. There was no statistical significant difference between control and PCOS groups, according to demographic, laboratory findings and anthropometric measurements.

Homeostasis model assessment (HOMA) formula [Fasting insulin (µU/mL) × Fasting Glucose (mg/dl)/405)] was used in calculation of Insulin resistance. The collection and analysis of these data were done by the same investigators.

Table I: The demographic and anthropometric properties of patients.

Variables	Control group (n=35)	PCOS group (n=53)	*P*
Age (years)	27.3±5.9	25.8±7.1	0.299
Weigth (kg)	71.97±17.15	73.89±18.16	0.643
Height (cm)	162.55±6.25	162.91±5.63	0.791
BMI (kg/m^2)	29.97±6.72	28.22±6.64	0.698
WC (cm)	85.06±12.57	87±11.71	0.494
WHtR	0.52±0.08	0.53±0.07	0.563
HC (cm)	103.74±11.83	105.04±12.14	0.644
WHR	0.82±0.07	0.83±0.06	0.516
CIMT (mm)	0.43±0.1	0.5±0.06	0.003
SBP (mmHg)	110.77±7.6	111.43±9	0.864
DBP (mmHg)	67.69±9.27	67.14±7.56	0.895
LAP	50.52±42.74	39.84±26.91	0.250
VAI	2.55±1.78	2.28±2.18	0.645

p value <0.05 was considered statistically.
BMI: Body mass index; HC: Hip circumferences; WC: Waist circumference; WHtR: Waist-to-height ratio; WHR: Waist-to-hip ratio; SBP: Systolic blood pressure; DBP: Diastolic blood pressure; VAI: Visceral adiposity index; LAP. lipid accumulation index; CIMT: arotid intima media thickness.

The average age of the patients with PCOS and control groups were 25.8 ± 7.1 and 27.3 ± 5.9 years, respectively without statistical significance (p=0.299). There was significant difference between the patients with PCOS and the control group in terms of waist circumference, body mass index, waist/height ratio, waist/hip ratio, total cholesterol, TG, LDL-C and HDL-C (p values being 0.494, 0.351, 0.563, 0.516, 0.865, 0.320, 0.761, and 0.668, respectively). Likewise, a considerable difference could not be found between two groups in terms of HOMA-IR.

Table II: The laboratory findings of patients.

Variables	Control group (n=35)	PCOS group (n=53)	*P*
HS-CRP	5.49±9.58	2.86±3.19	0.137
Periostin (ng/mL)	3.61±3.79	6.43±6.19	0.042
FBG (mg/dL)	86.29±7.93	88.83±12.4	0.292
TC (mg/dL)	184.32±28.13	185.55±35.31	0.865
TG (mg/dL)	127.5±80.82	107.57±75.15	0.320
HDL (mg/dL)	47.14±9.45	48.32±11.11	0.668
LDL (mg/dL)	113.26±21.84	115.06±29.39	0.761
FSH (mIU/mL)	6.92±3.42	6.47±2.55	0.486
LH (mIU/mL)	10.21±8.7	8.72±7.3	0.382
Estradiol (pg/ml)	122.03±108.29	88.28±99.95	0.012
Total Testosterone	45.26±12.69	47.08±21.07	0.932
Fasting Insulin (μU/mL)	13.5±8.86	14.42±11.61	0.698
DHEA-S (mg/dL)	287.15±120.71	252.02±135.54	0.228
HOMA-IR	2.92±2.06	3.26±3.03	0.964

p value <0.05 was considered statistically.
TC: Total cholesterol; TG: triglyceride; HDL-C: High density lipoprotein; LDL-C: Low density lipoprotein; LH: luteinizing hormone; FSH: follicle stimulating hormone; HOMA-IR: HOMA of insulin resistance index; hs-CRP: high sensitive C reactive protein; FBG: fasting blood glucose.

On the other hand, the CIMT in patients with PCOS and control groups were measured as 0.5 ± 0.06 mm and 0.43 ± 0.1 mm, respectively and the difference was statistically significant (p<0.01). The levels of periostin in the patients with PCOS and control groups were found as 6.43 ± 6.19 ng/mL and 3.61±3.79 ng/mL, respectively. The increased level of periostin in PCOS was also statistically significant (p=0.018).

The correlations between periostin and metabolic parameters are shown in Table III. There were no statistically significant correlations between periostin and metabolic variables according to correlation tests.

DISCUSSION

PCOS is characterised by metabolic disorders and reproductive pathologies. However, the pathophysiology of PCOS has not been completely clarified; chronic inflammation might be an important factor. In previous studies, it was shown that periostin might be associated with inflammation, insulin resistance, glucose metabolism and lipid metabolism.[14] Thus, the authors aimed to investigate the relationship with periostin and metabolic parameters in patient with PCOS.

Sarapatkova *et al*. showed that triglyceride levels were in normal ranges in both PCOS and control groups; but there was statistically higher triglyceride level in PCOS group. They also found insignificant differences between groups according to levels of total cholesterol, LDL and HDL in their study.[15] Similarly, there was no statistically significant differences according to triglyceride, total cholesterol, HDL and LDL levels between PCOS and control groups in the present study.

In previous studies, periostin promoted inflammation; and fibrosis were shown in cases such as myocardial infarction, cardiac hypertrophy, idiopathic lung disease, asthma, sclerosing skin, hepatic fibrosis, muscular dystrophy and kidney diseases.[16] Chen *et al*. reported that there were positive correlations between levels of periostin and BMI, uric acid, hs-CRP.[17] However, the authors could not find any significant correlation between these variables and periostin in this study. Chen *et al.* were also reported that LAP and HOMA–IR predicted the level of periostin independently. Periostin might be one of the pathogenic factors on obesity, abnormal fat distribution and impaired glucose metabolism observed in PCOS.[17] On the other hand, there was no correlation between periostin and LAP and HOMA–IR in this study. The levels of periostin in patients with PCOS were found higher in comparison with the control group in our study. According to Pearson correlation analysis, there was no any significant correlation between the level of periostin and BMI, waist circumference, HOMA-IR, TG, TC, HDL, LDL and LAP in this study. The lack of significant correlation between Periostin levels and other variables might be due to the fact that the mean age and BMI values of groups were similar in this study.

The subclinical inflammation is one of the significant pathogenic factors in patients with PCOS. It has been shown that the increased levels of inflammatory cytokines such as DHEAS, hs-CRP, TNFα, IL6, IL1β, monocyte chemotactic protein, macrophage inflammatory protein 1α were seen in patients with PCOS.[18,19] On the other hand, there was no any significant difference between the patients with PCOS and the control group, according to the levels of DHEAS and hs-CRP in this study. In previous studies, it was shown that subclinical inflammation had an important role on development of atherosclerosis and CIMT was an indicator of subclinical atherosclerosis.[20,21] In this study, the mean level of CIMT of patients in PCOS group was significantly higher than control PCOS group. However, the CIMT was not significantly correlated with inflammatory cytokines. It was thought that subclinical atherosclerosis might be related to the metabolic pathologies in PCOS.

Periostin promotes inflammation and fibrosis in various organs, according to the development of different diseases. It affects the levels and activity of fibrinogenic cytokines and growth factors due to the activation of integrin receptors.[6,16] Previous studies were reported that there were increased periostin levels in patients with insulin resistance, chronic inflammation and impaired lipid metabolism.[14,22] Development of insulin resistance was reported as an important factor in pathophysiology of PCOS.[8,9,23] Periostin might promote insulin resistance with pro-inflammatory activity in PCOS. It was reported that overproduction and secretion of testosterone from the theca cells of the ovaries were induced by insulin resistance. Therefore insulin resistance and increased testosterone secretion were responsible for the clinical symptoms of hyperandrogenism in PCOS.[10,17]

Table III: The pearson correlation test of periostin and metabolic risk factors.

	BMI	WHR	TC	TG	HDL	LDL	HOMA-IR
Periostin	0.031	0.003	-0.073	-0.045	0.165	-0.103	0.052
P	0.789	0.978	0.503	0.711	0.174	0.342	0.637
	LH	**FSH**	**Estradiol**	**Total Testosterone**		**FBG**	
Periostin	0.017	0.076	0.022	-0.212		0.112	
P	0.880	0.485	0.841	0.052		0.301	
	WC	**WHtR**	**CIMT**	**HOMA-IR**	**DHEA-S**		**Fasting Insulin**
Periostin	0.005	-0.006	0.022	0.009	-0.150		0.047
P	0.966	0.959	0.860	0.933	0.169		0.667

BMI: Body mass index; WC: Waist circumferences; HC: Hip circumferences; WHR: waist-to-hip ratio; SBP: systolic blood pressure; DBP: diastolic blood pressure; TC: Total cholesterol; TG: triglyceride; VAI: visceral adiposity index; LAP: lipid accumulation product; LH: Luteinizing hormone; FSH: Follicle stimulating hormone; HOMA-IR: HOMA of insulin resistance index; CIMT: Carotid intima media thickness; FBG: Fasting blood glucose.

In this study, the mean CIMT values and periostin levels of patients with PCOS were significantly higher than control group. On the other hand, testosterone levels of the two groups were similar. It was thought that periostin increased in PCOS according to the subclinical inflammation. However, there was no significant difference between groups, according to testosterone levels and insulin resistance. Similar BMI values of groups might be responsible for similar HOMO-IR values and insulin resistance. Periostin did not affect the testosterone and insulin resistance at the early stage of PCOS. The increased periostin levels might be a factor for the inflammation and development of insulin resistance at the following period of PCOS.

There were some limitations in this study. One of them was a small number of cases. The authors also could not evaluate the other inflammatory cytokines to investigate the inflammatory process of PCOS. Patients with PCOS did not undergo ovarian biopsies to investigate the structural changes in ovaries, according to periostin levels, due to ethical reasons. The authors believe that the relationship between periostin levels and metabolic pathologies in PCOS will be defined by future studies.

CONCLUSION

The mean periostin levels and CIMT values of patients with PCOS were significantly higher. Increased periostin and insulin resistance might be responsible for the subclinical inflammation and hyperandrogenism symptoms in PCOS. Although the authors could not find any correlation between periostin levels and the metabolic parameters, future studies about the periostin levels and PCOS disease might give new ideas to explain this relationship in PCOS.

ETHICAL APPROVAL:

The study was approved by the local Ethics Committee of the Karatay University (2018-021) and was performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments.

PATIENTS' CONSENT:

The informed and written consents of the patients were signed by the patients before the beginning of study.

CONFLICT OF INTEREST:

The authors declared no conflict of interest.

AUTHORS' CONTRIBUTION:

GG: Designed, directed and coordinated the study, created study plan, selected patients, analysed the data and written the article.

IG: Analysed the data, designed, directed and coordinated the study.

FS: Selected patients, collected samples and analysed the data.

SA: Selected patients, collected samples.

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