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RESEARCH ARTICLE

Serum PCSK9 in polycystic ovary syndrome: Relationship with body mass index and long-term cardiovascular risk

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ABSTRACT

Objective: To evaluate serum proprotein convertase subtilisin/kexin type 9 (PCSK9) levels in polycystic ovary syndrome (PCOS) patients according to body mass index (BMI) and investigate their association with lipid parameters and long-term cardiovascular risk.

Methods: A total of 80 women with PCOS were divided into two groups: normal weight (BMI < 25, n = 40) and overweight/obese (BMI ≥ 25, n = 40). Serum PCSK9 levels were measured via enzyme-linked immunosorbent assay. Lipid profiles, hormone levels, and 30-year Framingham cardiovascular risk scores were analyzed.

Results: Serum PCSK9 levels were significantly higher in the overweight/obese group (27.6 ng/ml) compared to the normal weight group (9.5 ng/ml) ($p < 0.05$). PCSK9 showed positive correlations with LDL-C, total cholesterol, AMH, and Framingham risk scores. No significant correlation with homeostatic model assessment of insulin resistance or insulin was observed.

Conclusion: Elevated PCSK9 levels in overweight/obese PCOS patients may indicate an increased long-term cardiovascular risk. PCSK9 may serve as a biomarker linking metabolic and reproductive disturbances in PCOS and could be a future therapeutic target.

Keywords: polycystic ovary syndrome, proprotein convertase subtilisin-Kexin type 9 body mass index, cardiovascular disease risk score

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INTRODUCTION

Polycystic ovary syndrome (PCOS) is one of the most common endocrine and metabolic disorders in women of reproductive age. PCOS is a pathology characterized by oligomenorrhea, hyperandrogenism, and polycystic ovaries detected on ultrasonography. PCOS patients present with reproductive (menstrual irregularity, hirsutism, infertility, and pregnancy complications), metabolic (insulin resistance, metabolic syndrome, type 2 diabetes, dyslipidemia, hypertension, and cardiovascular risk factors), and psychological (anxiety, depression, body image) problems.

According to the national cholesterol education program guidelines, approximately 70% of PCOS patients exhibit abnormal serum lipid levels [1]. Dyslipidemia is characterized by high low-density lipoprotein (LDL) and triglyceride levels, low high-density lipoprotein (HDL) levels, and increased total cholesterol and lipoprotein concentrations, which collectively contribute to a high cardiovascular disease risk profile [2]. In patients with PCOS, early determination of cardiovascular and metabolic risks is important to prevent long-term complications.

Proprotein convertase subtilisin/kexin type 9 (PCSK9) was identified as the 9th member of the proprotein convertase family by polymerase chain reaction technique in early 2003 [3]. PCSK9 plays a key role in cholesterol metabolism. In cases of high PCSK9 levels or gain-of-function mutations in PCSK9, it binds to LDL receptors from both intracellular and extracellular pathways and causes the PCSK9-LDLR complex to be destroyed in lysosomes [4]. This causes a decrease in the number of LDL-R on the cell surface and, as a result, an increase in.

LDL-C levels. It has been shown in many studies that PCSK9 elevation causes an increase in the risk of cardiovascular disease [5]. The fact that LDL-C levels can be reduced by 70% with anti-PCSK9 monoclonal antibodies has opened a new path in the treatment of dyslipidemia [6]. Avilorocumab and evolocumab are used by the FDA for the treatment of resistant hypercholesterolemia and familial hypercholesterolemia. While theca and granulosa cells directly take up LDL-C into the cells with LDL-R, LDL-C enters the ovarian follicular fluid through the blood-follicle barrier. Therefore, it is known that lipid metabolism disorders impair ovarian steroid hormone synthesis and prevent follicles from developing and functioning [7]. There are studies indicating that PCSK9 concentrations are higher in PCOS patients and significantly higher in the liver and ovaries of PCOS patients [8, 9]. PCSK9 polymorphisms are currently being investigated as a potential risk factor for the development of PCOS [10]. Alirocumab has been found to attenuate lipid metabolic disorders, serum reproductive hormones, and other pathological changes in ovarian morphology in PCOS mice [9]. These observations raise the possibility of using PCSK9 modulators in PCOS women, focusing on both metabolic profile and hyperandrogenism. In line with this information, we aimed to compare serum PCSK9 levels in normal weight and overweight/obese PCOS patients. As a secondary aim, we investigated the relationship between PCSK9 levels and metabolic parameters and Framingham cardiovascular disease risk scores in patients with PCOS.

MATERIAL AND METHODS

Approval was obtained from Ankara Dr. Zekai Tahir Burak Women's Health Education and Research Hospital Clinical Research Ethics Committee (26/08/2016-17) for the study. Power analysis was performed using the G-power program. A total of 80 PCOS cases, 40 normal weight (body mass index [BMI] < 25 kg/m^2) and 40 overweight/obese (BMI ≥ 25 kg/m^2) patients between the ages of 16 and 36 who applied to our hospital's reproductive endocrinology department and met the inclusion criteria for the study were included in the study.

The cases who did not accept to be included in the study and give written consent were patients younger than 16 and older than 40 years of age, those who used oral contraceptives or other hormonal drugs in the last three months; those who used drugs affecting lipoprotein metabolism or insulin secretion/sensitivity; women who smoke; Cases with endocrine diseases such as diabetes, Cushing's syndrome, thyroid dysfunction, and hyperprolactinemia were excluded from the study. Conditions that should be considered in the differential diagnosis of PCOS such as late-onset congenital adrenal hyperplasia and thyroid dysfunction were excluded.

Rotterdam criteria were used for PCOS diagnosis. PCOS was diagnosed if at least two of the three criteria were met. In our study, 17 adolescent cases between the ages of 16-19 were diagnosed with PCOS regardless of the ultrasonographic appearance of polycystic ovary morphology (PCOM) and if both of the clinical/biochemical hyperandrogenism and ovulation dysfunction criteria were met, women with an mFG score > 8 were considered clinically hirsutistic. Total testosterone above 55 ng/dl in the serum sample taken on the 3rd day of menstruation was accepted as the biochemical hyperandrogenemia limit. Ultrasonographic evaluation was performed using a trans-abdominal transducer (Aplio 500; Toshiba, Japan-2015) at a frequency of 5 megaHertz for the diagnosis of PCOM. The presence of 12 or more follicles with a diameter of 2-9 mm in one or both ovaries on ultrasound was considered as PCOM. Following the general physical examination, gynecological history and demographic characteristics, the patients' age, systolic and diastolic blood pressure, BMI, waist and hip measurements, menstrual patterns, D3 total testosterone, anti-Müllerian hormone [AMH], fasting glucose and insulin values after 8 hours of fasting, homeostatic model assessment of insulin resistance (HOMA-IR), postprandial blood sugar or 75 g oral glucose tolerance test (OGTT) 2nd hour value, serum lipid levels (LDL, very low-density lipoprotein [VLDL], HDL, triglyceride, total cholesterol), ultrasonography findings, serum PCSK9 levels were recorded in the study forms. Because the detection rate is higher in this age group, the 10-year Framingham cardiovascular disease risk for patients over 30 years of age and the 30-year Framingham cardiovascular disease risk for all patients were calculated using the official website www.framinhgamheartstudy.org. Those with a 10-year Framingham risk score of less than 5% and a 30-year Framingham risk score of less than 39% were considered to be at 'low risk' for CVD [11]. BMI was calculated using the formula (weight [kg]/height^2 [m^2]). Patients with a BMI < 25 kg/m^2 were considered normal weight, patients with a BMI of 25-30 kg/m^2 were considered overweight, and patients with a BMI of more than 30 kg/m^2 were considered obese. Waist circumference was measured around the navel using a plastic tape measure. Hip circumference was measured at the widest part of the hip. Waist circumference > 80 cm and waist/hip ratio > 0.85 were evaluated as abdominal obesity. Measurements were made by the same researcher.

Antecubital venous blood samples (approximately 10 ml) were taken from each participant on the morning of the 2nd or 3rd day of the menstrual period, following an 8-hour fasting period, and the blood samples were taken to the laboratory 30 minutes later. Blood samples taken for the measurement of PCSK9 levels were centrifuged at 4000 rpm for 10 minutes, and the serum portion was separated and stored at -80 °C until the study day. After giving at least 8 hours of fasting blood for the 75-gram OGTT evaluation, the patients were given the solutions within 5-10 minutes and blood samples were taken again 2 hours later. Patients who did not accept the 75-gram OGTT (n = 28) were evaluated

with postprandial blood sugar 2 hours after the meal. A 2017 model 'Roche Diagnostic/Cobas 6000e601 Hormone Analyzer' was used to determine basal hormone, total testosterone and insulin serum levels. Insulin resistance was calculated using the hemostatic model formula (HOMA-IR = Fasting glucose [mg/dl] × fasting insulin [mIU/mL]/405). Serum lipid and glucose levels were analyzed with a 2012 model 'Roche Diagnostic Cobas 6000c-5001 Biochemistry Analyzer'. Blood samples taken for the measurement of PCSK9 levels were centrifuged, the serum portion was separated and stored at -80 °C until the day of the study. On the day of the study, serum samples were thawed at room temperature for approximately 4 hours and then measured using the enzyme-linked immunosorbent assay method using a commercial kit (model number: 201-12-2321, 96T Sunred Biological Technology Co. Ltd. Shanghai, China) using the 'Thermo Scientific Varioscan Flash Multimod Reader' device. 8T was used for control.

The sensitivity of the kit was 0.175 ng/ml, and the detection range was 0.2 ng/ml-60 ng/ml. According to the guideline recommendations published by the Turkish Endocrine and Metabolism Association in 2018, dyslipidemia was defined as total cholesterol > 200 mg/dl, triglyceride level > 150 mg/dl, LDL-C level > 130 mg/dl or HDL-C 50 mg/dl <. The 'International Diabetes Federation' criteria were used for the diagnosis of metabolic syndrome. Fasting blood sugar between 100-125 mg/dl was evaluated as 'Impaired Fasting Glucose'. Postprandial blood sugar and 75 g OGTT 2nd hour blood sugar between 140-200 mg/dl were evaluated as 'Impaired Glucose Tolerance'. Fasting insulin level of 20 uIU/ml or HOMA-IR value ≥ 2.5 was defined as insulin resistance. All parameters were compared between the groups.

STATISTICAL EVALUATION

Statistical package for social sciences version 22.0 was used. Normality tests were applied to all (dependent) variables. Whether normal distribution was accepted or rejected was decided by looking at the Kolmogorov-Smirnov (KS) test result (whether p-value > 0.05 for KS test).

Values were given as mean standard deviation in case of normal distribution for BMI < 25 kg/m² group and BMI ≥ 25 kg/m²; in case of non-normal distribution, median (minimum-maximum value). Whether there was a significant difference between the group means (or medians) was considered by independent samples t-test if the dependent variable was normal, and by Mann-Whitney U test statistics if it was not normal. The Chi-square test of independence was used to determine whether the distribution of oligomenorrhea frequencies by group was significant. The non-parametric Kruskar-Wallis method was used to compare three groups. Categorical data were expressed as n (number) and percentages (%). Data were examined at a 95% confidence interval and a p-value of < 0.05 was considered significant. Pearson correlation test was used for correlation.

Table 1. Comparison of demographic, anthropometric, and metabolic parameters of the cases

	Group 1 (n = 40)	Group 2 (n = 40)	p*
Age (year)	22.60±5.01	24.10±4.48	0.162
BMI (kg/m²)	21.56±1.94	32.02±4.80	0.000
Waist circumference (cm)	78.78±8.16	100.80±11.79	0.000
Hip circumference (cm)	99.30±6.02	116.78±8.63	0.000
Waist/hip ratio	0.79±0.06	0.86±0.08	0.000
Systolic blood pressure (mm/Hg)	100.88±9.19	118.00±11.42	0.000
Diastolic blood pressure (mm/Hg)	65.25±7.51	69.50±8.76	0.022
Fasting insulin (uIU/ml)	10.00±6.23	17.00±11.00	0.000
Fasting blood glucose (mg/dl)	88.50±6.0	95.50±15.0	0.004
Postprandial 2nd hour glucose (mg/dl)	96.90±14.94 (n = 10)	94.79±10.65 (n = 18)	0.663
75 gr OGTT 2nd hour (mg/dl)	96.0±35.0 (n = 30)	102.0±39.0 (n = 22)	0.165
HOMA-IR	2.25±1.60	3.80±3.60	0.000
LDL (mg/dl)	85.50±32.94	114.50±39.82	0.000
VLDL (mg/dl)	14.50±13.00	21.00±15.00	0.002
HDL (mg/dl)	56.50±24.00	48.50±19.00	0.041
Total cholesterol (mg/dl)	154.0±41.0	183.00±63.00	0.001
Triglyceride (mg/dl)	72.50±48.0	106.50±85.0	0.000
Total testosterone (ng/ml)	0.40 ± 0.18	0.40 ± 0.20	0.503
AMH (ng/ml)	7.05 ± 3.71	5.25 ±4.59	0.030

Note. *p-value < 0.05 was considered statistically significant

RESULTS

The study was conducted between April 2017 and October 2017 on a total of 80 PCOS patients in the reproductive period and aged between 16-36. 40 patients with BMI < 25 kg/m² constituted the normal weight group (group 1), and 40 patients with BMI ≥ 25 kg/m² constituted the overweight/obese group (group 2).

21% (n = 17) of the total 80 patients were in the 16-19 age group (**Table 1**). According to the phenotypic classification, 86% (n = 69) of the patients were in the phenotype A class, and 14% (n = 11) were in the phenotype C class. Dyslipidemia was detected in 41% (n = 33) of the total 80 patients. Insulin resistance was detected in 20% (n = 20) of the 80 cases according to insulin values and in 60% (n = 48) according to HOMA-IR values. Impaired glucose tolerance was detected in 11% (n = 9) according to FBG and in 7% (n = 6) according to 75 g OGTT results. Metabolic syndrome was detected in 21% (n = 17). The mean age of the cases

Table 1. Comparison of Framingham cardiovascular disease risk scores of cases

Framingham cardiovascular disease risk	Group 1 (n = 40)	Group 2 (n = 40)	p*
10 year (%): Median (min-max)	0.10 (0-0.30) (n = 5)	0.16 (0-0.30) (n = 3)	0.553
30 year (%): Median (min-max)	3.32 (1-7)	6.10 (2-12)	0.000

Note. *p-value < 0.05 was considered statistically significant

Table 3. Comparison of serum PCSK9 levels in PCOS cases, Mann-Whitney U test

Framingham cardiovascular disease risk	Group 1 (n = 40)	Group 2 (n = 40)	p*
PCSK9 (ng/ml): Median (min-max)	9.45 (0.38-69.20)	27.57 (5.50-93.70)	0.009

Note. *p-value < 0.05 was considered statistically significant

Table 4. Comparison of serum PCSK9 levels in normal, overweight, and obese cases

	n	PCSK9 (ng/ml)	Minimum	Maximum	p*
Normal weight group	40	9.45	0.38	69.20	0.013
Overweight group	17	34.70	6.90	93.70	
Obese group	23	12.60	5.50	84.00	
Total	80	25.57	0.38	93.70	

Note. Kruskal-Wallis Test & *p-value < 0.05 was considered statistically significant

included in the study was 23.35 ± 4.78 years; mean BMI was calculated as 26.79 ± 6.40 kg/m^2. The mean ages of group 1 and group 2 were 22.60 ± 5.01 and 24.10 ± 4.48, respectively (mean ± standard deviation), and no statistically significant difference was detected between the two groups. The mean BMI of the cases in group 1 and group 2 was 21.56 ± 1.94 kg/m^2 and 32.02 ± 4.80 kg/m^2, respectively (**Table 1**). Waist and hip circumference, systolic and diastolic blood pressure, fasting insulin values, fasting blood glucose and HOMA-IR mean, LDL, VLDL, Total Cholesterol, Triglyceride of the cases in Group 2 were found to be statistically significantly higher than in the cases in group 1 (p-value < 0.05). No statistically significant difference was found between the two groups in terms of postprandial 2nd hour blood glucose and 75 g OGTT mean, total testosterone levels (p-value > 0.05). AMH levels were found to be statistically significantly higher in Group 1 than in the other group (p-value < 0.05) (**Table 1**).

A total of eight patients (n = 5 for group 1, n = 3 for group 2) were evaluated with a 10-year Framingham risk score because they were older than 30 years. The cardiovascular disease risk was calculated as less than 5% (low risk) in all of these 8 patients. A 30-year Framingham cardiovascular disease risk was calculated according to risk factors in all 80 patients, and the 30-year cardiovascular disease risk was found to be 39% < (low risk) in all patients. In terms of Framingham risk scores, the median for group 1 was 3.32% (1-7), the median for group 2 was 6.10% (2-12), and the risk scores were found to be statistically significantly higher in group 2 cases (p-value < 0.05) (**Table 2**).

The median value for PCSK9 level of 80 PCOS cases was calculated as 25.57 ng/ml (0.38-93.70) (median value for group 1 was 9.45 ng/ml [min-max 0.38-69.20] and for group 2 was 27.57 ng/ml [min-max 5.5-93.70]) (**Table 3**). PCSK9 levels in group 2 cases were found to be statistically significantly higher than in the other group (p-value < 0.05). When subgroup analysis was performed for group 2 as those with BMI between 25-30 kg/m^2 (overweight group) and those with BMI > 30 kg/m^2 (obese group), the PCSK9 median of 17 (21.3%) cases with BMI between 25-30 kg/m^2 was calculated as 34.70 ng/ml, and the PCSK9 median of 23 (28.7%) cases with BMI above 30 kg/m^2 was calculated as 12.60 ng/ml (5.5-84.00). When the Mann-Whitney U test with Benferonni correction was applied for pairwise comparison, there was a separation between PCSK9 levels as overweight = obese > normal weight. This means that the difference between the PCSK9 levels of the overweight group and the obese group was statistically insignificant, while the difference between these two groups and the normal group was significant (p-value < 0.05) (**Table 4**).

According to Pearson correlation analysis, there was a negative correlation between systolic blood pressure values and PCSK9 levels in both groups (p-value < 0.05; r = -0.3). For group 1, a positive correlation was observed between AMH values and PCSK9 levels (p-value < 0.05; r = +0.3). No correlation was found between PCSK9 levels and age, waist, waist/hip ratio, total testosterone (p-value > 0.05). For group 1, a negative correlation was found between serum PCSK9 levels and fasting blood glucose values (r = -0.3); and a positive correlation was found between LDL-C and total cholesterol levels (r = +0.5 and r = +0.3, respectively; p-value < 0.05). For group 2, a negative correlation was found

Table 5. Correlation of anthropometric and metabolic parameters of PCOS cases with serum PCSK9

	Group 1 (n = 40): R (p-value)	Group 2(n = 40): R (p-value)	Total R (p-value): (n = 80)
Age (year)	-.074 (0.649)	-.285 (0.075)	-.132 (0.245)
Systolic blood pressure (mmHg)	**-.343 (0.030)**	-.333 (0.036)	-.066 (0.561)
Waist/hip ratio	.252 (0.117)	-.082 (0.614)	.160 (0.156)
Total testosterone (ng/ml)	.163 (0.315)	-.288 (.071)	- .083 (0.466)
AMH (ng/ml)	*.332 (0.036)*	.139 (0.393)	.164 (0.147)
Fasting blood glucose (mg/dl)	**-.312 (0.050)**	-.154 (0.343)	-.092 (0.419)
Postprandial 2nd hour glucose (mg/dl)	.271 (0.449; n = 10)	-.038 (0.879; n = 19)	.072 (0.709; n = 29)
Insulin (uIU/ml)	-.048 (0.771)	-.020 (0.902)	.046 (0.683)
HOMA-IR	-.062 (0.705)	-.098 (0.547)	-.049 (0.666)
75 gr OGTT 2nd hour (mg/dl)	-.017 (0.928; n = 30)	**-.465 (0.029; n = 22)**	-.228 (0.104; n = 52)
LDL (mg/dl)	**.514 (0.001)**	**.362 (0.022)**	**.460 (0.000)**
HDL (mg/dl)	.304 (0.057)	.318 (0.045)	.214 (0.057)
Triglyceride (mg/dl)	.206 (0.201)	-.163 (0.315)	.103 (0.362)
Total cholesterol (mg/dl)	**.334 (0.035)**	**.128 (0.430)**	**.281 (0.012)**
Framingham 10-year risk (%)	-.687 (0.200; n = 5)	.254 (0.837; n = 3)	- .533 (0.174; n = 8)
Framingham 30-year risk (%)	**.456 (0.004)**	**.339 (0.032)**	**.382 (0.000)**

Note. *p-value < 0.05 was considered statistically significant

between serum PCSK9 levels and 75 g OGTT 2nd hour values (r = -0.4); and a positive correlation was found between LDL-C and HDL-C levels (r = +0.3) (**Table 5**).

According to Pearson correlation analysis, when the entire study group was considered, a positive correlation was found between serum PCSK9 levels and LDL-C and total cholesterol, and 30-year Framingham CVD risk scores (r = +0.4 and r = +0.2, respectively; p-value < 0.05).

DISCUSSION

In our study, serum PCSK9 levels were found to be statistically higher in PCOS patients with a BMI over 25 compared to PCOS patients with normal body weight. In addition, serum PCSK9 levels were found to be positively correlated with 30-year Framingham CVD risk scores, LDL-C, total cholesterol and AMH values.

The aim of our study was to investigate the relationship between obesity, which is thought to negatively affect metabolic risks in patients with PCOS diagnosis, and PCSK9 levels. The high PCSK9 levels in PCOS patients with a BMI ≥ 25 indicate that these individuals have impaired lipid metabolism. The positive correlation between PCSK9 and LDL-C, total cholesterol and Framingham CVD risk scores reveals that this protein is directly related to cardiovascular risk. The correlation with AMH supports the scope of the hypothesis by showing that PCSK9 may be associated with PCOS-specific biomarkers not only at the metabolic but also hormonal levels.

Although there is no study in our country showing the relationship between PCSK9 and PCOS, there are many current studies on this subject in the literature.

The animal study [12] in 2018 is the first study to mention the relationship between PCSK9 and PCOS in the literature. It was shown that hyperhomocysteinemia caused the development of dyslipidemia in 25 PCOS model mice in which they developed PCOS with hyperhomocysteinemia. It has also been shown that hyperhomocysteinemia, testosterone and 5 alpha dihydrotestosterone independently increase PCSK9 expression and reduce LDL-R count. This study shows that one of the key mechanisms in causing dyslipidemia in hyperandrogenism, which is at the center of the pathophysiology of PCOS, is the PCSK9-LDL receptor interaction [12].

It was found that the serum PCSK9 level of 46 PCOS patients was significantly higher than that of 49 healthy controls matched for age and BMI [13]. In 2021, Bizon and colleagues found PCSK9 levels higher in PCOS patients compared to healthy individuals [8]. In 2018, Xavier and colleagues planned a clinical study investigating PCSK9 levels in PCOS patients for the first time [10]. In their study, plasma PCSK9 and PCSK9 gene polymorphisms of 97 PCOS patients and 99 normal healthy individuals were examined, and no significant difference was found between the two groups. Although it was not found a significant difference between PCSK9 levels between the control group and the PCOS group in his study, he divided the total cohort into obese and non-obese to look at the relationship with obesity, and again, no significant difference was found between these two groups [10]. This difference in our study may be due to

sample characteristics, PCOS diagnostic criteria used, serum-plasma difference measured, different sensitivity and specificity of the kit brand, or genetic and metabolic differences between ethnic groups. Studies reporting that PCSK9 levels are particularly elevated in obese individuals have revealed that this protein is associated not only with lipid metabolism but also with metabolic parameters such as insulin resistance and inflammation [14]. In the study in [15] in Slovenia in 2017 on 120 individuals, plasma PCSK9 levels were found to be significantly higher in obese individuals compared to normal weight and overweight groups (p-value < 0.001). In 2024, BMI and HDL were defined as the most significant causal factors of PCOS [16]. However, the fact that PCSK9 levels were evaluated particularly in PCOS patients with high BMI is an important point that distinguishes our study from the existing literature. In line with the literature, the median PCSK9 value for a total of 80 PCOS cases between the ages of 16 and 36 in our study group was 25.57 ng/ml (0.1-93.8 ng/ml); in cases with normal body weight, it was found to be 9.45 ng/ml and in cases with overweight/obese weight, it was found to be 27.57 ng/ml. In our study, serum PCSK9 levels were found to be statistically higher in PCOS cases with a BMI above 25 compared to PCOS cases with normal body weight.

Many studies in mice and humans have shown that hypercholesterolemia develops in mutations resulting in gain of function in PCSK9, and hypocholesterolemia develops in mutations causing loss of function [17-19]. In [10], a relationship was found between PCSK9 levels and total cholesterol and LDL-C in the entire population. These findings are consistent with the results of our study, and a positive correlation was found between PCSK9 and LDL-C and total cholesterol in our PCOS patients.

In [10], it was shown that PCSK9 concentrations were positively correlated with insulin and HOMA-IR values, but not with fasting blood glucose values.

Unlike the literature, in our study, no significant correlation was found between PCSK9 level and fasting insulin and HOMA-IR ($p > 0.05$), while a negative correlation was found between fasting blood glucose and 75 g OGTT 2nd hour values ($p < 0.05$). This difference may be due to characteristics such as the average age of the sample, serum-plasma difference, different sensitivity and specificity of the kit brand, or genetic and metabolic differences. There are conflicting results in the literature in studies on cardiovascular diseases that may develop at older ages in PCOS cases. The women's ischemia evaluation study evaluated a total of 936 women aged 18 and over, who did not have any heart disease between 1996 and 2000, but underwent coronary angiography due to chest pain or clinical suspicion of myocardial infarction. It was shown that women with premenopausal menstrual irregularity or hyperandrogenemia and who were considered to have PCOS had an increased risk of developing cardiovascular disease-related morbidity and mortality in the postmenopausal period [20]. In [21], in which the 31-year follow-up results of 786 PCOS patients were published, it was shown that the risk of developing cardiovascular disease in PCOS patients was not increased compared to the control group. There are several studies in the literature where Framingham risk scores were calculated in PCOS patients. In [22] with the mothers and fathers of 411 PCOS patients, the 10-year Framingham risk scores of the fathers of PCOS patients were found to be higher than those in the control group [22]. In the study in [23], 309 women with PCOS with an average age of 25 were examined and no difference was found in 10-year Framingham risk scores compared to the control group. In our study, 10-year Framingham risk scores were calculated for a total of 8 patients over the age of 30. 30-year Framingham risk scores, which are also used for patients under the age of 30, were calculated for all 80 PCOS patients. All patients were in the 'low-risk' group according to the Framingham system, and the patients did not experience any CVD during the 6-month follow-up period. The fact that our study group did not have additional diseases other than PCOS, the age range was between 16-36, and we did not have any patients over the age of 40 may be related to the low risk of cardiovascular disease. In our study, it was found that serum PCSK9 levels and 30-year Framingham CVD risk scores were positively correlated in both groups. Correlation with Framingham risk score suggests that PCSK9 may not only be a biochemical marker but also a predictor of long-term cardiovascular disease risk. This situation reveals the importance of early cardiovascular screening in women with PCOS and high BMI.

Most of the studies in the field of PCSK9 and PCOS in recent years are animal experiments examining the relationship between PCSK9 and polycystic ovaries and hormonal disorders and the effects of PCSK9 inhibitors in PCOS. In recent years, there have been several studies examining the relationship between PCSK9 and ovaries in mice with PCOS models. In [9], it was shown that abnormally high PCSK9 expression in the blood, liver and ovaries of mice with PCOS may play a role in the pathogenesis of PCOS by affecting lipid metabolism and ovarian function, and that PCSK9 inhibition can partially reverse the pathological changes of PCOS [9]. It is clear that low-dose spironolactone improves PCOS features in letrozole-induced PCOS rats with a PCSK9-dependent mechanism and combats dyslipidemia, liver inflammation and ovarian polycystic appearance in PCOS. In 2025, it was shown that L-Kynurenine reversed lipid, metabolic and ovarian dysfunction in mice with PCOS by activating the AHR-PCSK9 pathway [24]. The positive correlation found between PCSK9 and AMH in our study suggests a possible interaction between lipid metabolism and ovarian function. This means that PCSK9 may have indirect effects not only on metabolism but also on the reproductive system. Our limitations can be evaluated as the fact that our study was

single-centered and our sample size was small, the age range of our study group included adolescence and the reproductive period and we only compared patients with PCOS within themselves. The strengths of our study are that it is the first study conducted in the Turkish population on the relationship between PCOS and PCSK9, that the 30-year Framingham risk scores of all patients were calculated one by one and their relationship with PCSK9 was examined, and that it is the first study in the literature to show the relationship between PCSK9 and AMH. In conclusion, serum PCSK9 levels in women with PCOS during the reproductive period can be used as a marker to determine the risk of developing cardiovascular disease. In addition, due to the PCSK9-LDL receptor interaction in the liver and ovary, PCSK9 antibodies are promising as an alternative treatment option to regulate ovarian functions, especially hypercholesterolemia, in patients with PCOS

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