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Evaluation of Liver Fibrosis in Polycystic Ovary Syndrome by Shear Wave Elastography, FIB-4 Score, and Serum Periostin Levels

ABSTRACT

Objective: In this study, we aimed to demonstrate the presence of liver fibrosis in patients with polycystic ovary syndrome at a relatively early stage of the disease using biochemical data and 2-dimensional shear wave elastography techniques.

Methods: The study included 33 women with polycystic ovary syndrome and 33 healthy women volunteers. Serum androgen and sex hormone binding globulin levels were measured, and then free androgen index was calculated. Periostin and matrix metalloproteinase-3 levels were measured by ELISA method. Sterling formula was used to calculate FIB-4 score. Liver elasticity was evaluated using shear wave elastography.

Results: Periostin and matrix metalloproteinase-3 levels were found to be significantly higher in the polycystic ovary syndrome group compared to the control group ($P < .001$ and $P < .001$, respectively). Serum testosterone level and free androgen index were also significantly higher in the polycystic ovary syndrome group ($P = .044$ and $P = .037$, respectively). However, there was no significant difference between the groups in terms of liver velocity and elasticity ($P = .185$ and $P = .172$, respectively). A positive correlation was found between FIB-4 score and periostin ($r = 0.433$, $P = .012$) and between FIB-4 score and liver elasticity in the PCOS group ($r = 0.374$, $P = .032$).

Conclusion: FIB-4 score was positively correlated with periostin and liver elasticity. These data suggest that in addition to FIB-4 score, serum periostin level and shear wave elastography may help us clinically in the detection of liver fibrosis at patients with polycystic ovary syndrome.

Keywords: FIB-4 score, liver fibrosis, PCOS, periostin, shear wave elastography

Introduction

Polycystic ovary syndrome (PCOS) is a common endocrine disorder that affects women of reproductive age.[1] This syndrome has been associated with many metabolic disorders. Polycystic ovary syndrome has been shown to be an independent risk factor for nonalcoholic fatty liver disease (NAFLD) and its outcomes.[2,3] It has been stated that insulin resistance, inflammation, and hyperandrogenism are the key points for hepatosteatosis and fibrosis in this group of obese or nonobese patients.[4] It is important to know the biochemical and clinical features of NAFLD and its related conditions (such as nonalcoholic steatohepatitis and hepatic fibrosis) and to diagnose it early because these pathologies are mostly reversible.[5] There are scoring systems used for indirect assessment of liver fibrosis. Aspartate aminotransferase-platelet ratio index (APRI) and fibrosis-4 index (FIB-4) are prominent systems in this sense.

Periostin is an extracellular matrix protein thought to be a mediator in hepatic fibrosis.[6] Matrix metalloproteinase (MMP) is a family of enzymes secreted as proenzymes and activated in the extracellular space. With the increase of collagen in the extracellular matrix during fibrogenesis, matrix metalloproteinases, which are responsible for their destruction, also increase. Therefore, the role of MMP enzymes in studies on liver fibrosis has been interesting.[7]

Ultrasonography (US) is frequently used in the early diagnosis of NAFLD and related conditions. However, it is difficult to distinguish hepatosteatosis from liver fibrosis with US imaging.[8] Ultrasonographic imaging of tissue flexibility or stiffness parameters has attracted attention in recent years.[9] Shear wave elastography (SWE) is a new ultrasonographic imaging technique. It offers the opportunity to quantitatively evaluate the difference in elasticity between fibrotic and normal tissue. Its diagnostic importance is increasing.[10]

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Failure to detect NAFLD and hepatic fibrosis in the early period with reliable noninvasive tests leads to the progression of these diseases. However, there is a need for tests and imaging technologies that will allow to evaluate the progression of these diseases and the effectiveness of new treatment agents developed. For these purposes, we evaluated periostin and MMP-3 serum levels, which are biochemical fibrosis markers, and SWE findings together in the early diagnosis of steatosis-based hepatic fibrosis in patients with PCOS. We tried to reveal the relationship of these data with each other and with fibrosis scoring systems, if any.

Materials and Methods

Patients between the ages of 18 and 50 years, who applied to the Endocrinology and Metabolism Diseases and Gynecology and Obstetrics outpatient clinics of our unit, were included in the study. PCOS diagnosis was based on Rotterdam 2003 criteria. Drugs and other diseases that may cause hepatic fibrosis and hepatosteatosis were excluded. The control group consisted of age-matched healthy women who had regular menstrual periods. Accordingly, 33 patients diagnosed with PCOS by a single expert endocrinologist and 33 healthy female volunteers were included. Since we are a research hospital located within the university campus, our study patient group consisted of young and nonobese patients with PCOS. A control group suitable for this group was included. Participants were included in the study with a written informed consent form. The study was approved by the Clinical Research Ethics Committee of our university before the study (Protocol Code: 2018/103).

Anthropometric Measurements

Body weight and fat percentage measurements were evaluated with Tanita body-fat analyzer (Tanita type MC-580, TANİCA Corp., Tokyo, Japan). This device is used to estimate body weight and fat, based on the principles of bioelectrical impedance. Waist circumferences and body mass indexes were recorded.

Collection and Preparation of Blood Samples

Blood samples were taken between the 3 and 7 days of menstrual cycles after 8-10 hours of morning fasting, and the samples were stored at –80° until analysis.

Routine Biochemical Analysis and Score Calculations

For complete blood count (CBC), blood was taken into tubes containing ethylenediamine tetraacetic acid (EDTA) and analyzed on the same day with an automatic CBC device (Mindray Medical International Co., Mindray BC-6800, China) in the routine biochemistry laboratory of our hospital. Among the routine parameters, serum glucose, creatinine, and transaminases (Alanine aminotransferase [ALT] and aspartate aminotransferase [AST]) were measured spectrophotometrically using an autoanalyzer (Siemens Advia 1800, Germany) in the biochemistry laboratory. The homeostatic model assessment for insulin resistance (HOMA-IR), APRI score, and FIB-4 scores were calculated as follows:

1. HOMA-IR=[fasting glucose (mg/dL) × fasting insulin (μgIU/mL)] /405;
2. APRI score = [AST level (IU/L)/AST (ULN, (IU/L))]/platelet count (10^9/L) × 100;
3. FIB-4 score = [Age (years) × AST (IU/L)]/[(platelet count (10^9/L) × (ALT (IU/L)$^{1/2}$)]

Serum follicle stimulating hormone (FSH), luteinising hormone (LH), total testosterone, and insulin levels were determined by immun oassay-chemiluminescence method using an autoanalyzer (Siemens Advia Centaur XP, Germany); SHBG, androstenedione, and dehydroepiandrosterone sulfate (DHEAS) levels were also studied with an autoanalyzer (Siemens Immulite 2000 XP, Germany) by immunoassay-chemiluminescence method. Serum high-sensitivity C-reactive protein (hs-CRP) levels were studied by the nephelometric method (Siemens BNII nephelometer, Germany). This formula was used in the FAI calculation: FAI = (testosterone (nmol/L)/SHBG (nmol/L)) × 100.

Serum periostin and MMP3 levels were studied by ELISA method (Thermo Scientific Multiskan Go, Finland). For both measurements, the samples were studied by dilution, and the results were given by multiplying with the dilution coefficient.

Imaging

Suprapubic pelvic US and 2-dimensional-SWE evaluation of the liver were performed by a single radiologist who is an expert in radiological interpretation. Ultrasound imaging and 2D-SWE examination were performed with Logiq E9 XDCLEAR (GE Healthcare, Milwaukee, Wis, USA) device, using a 4-6 MHz convex probe. The liver was evaluated for steatosis with gray-scale US. Patients who were not found to have hepatosteatosis in the gray-scale evaluation were included in our study. For liver elasticity measurement, a total of 10 measurements were performed on the parenchyma areas away from the vascular structures after the patient hold a deep breath, and the average was taken.

Statistical Analysis

Statistical data were analyzed using the IBM Statistical Package for Social Sciences Statistics for Windows, Version 21.0 (IBM Corp., Armonk, NY, USA). The mean, standard deviation, median first (Q1), and third (Q3) quartile values were used in the expression of continuous variables. After examining the normality of continuous variables according to the groups with the Shapiro–Wilk test, student's *t*-test from parametric tests and Mann–Whitney *U* test from nonparametric tests were used. In addition, Pearson and Spearman rank correlation coefficients were used for correlation analysis. A *P* value of .05 was accepted as the limit of significance for all analyses.

In the post hoc power analysis performed for the aforementioned primary variables, the statistical power was calculated as 99.6% for periostin and 95.2% for MMP-3 (effect size 1.16 and 0.908, respectively).

MAIN POINTS

- Hyperandrogenism and inflammation may cause nonalcoholic fatty liver disease (NAFLD) in patients with polycystic ovary syndrome (PCOS).
- The NAFLD and its negative consequences may become evident during the progression of PCOS.
- Increased insulin resistance and inflammatory response may contribute to hepatic fibrosis in advanced stages of PCOS.
- Periostin and matrix metalloproteinase-3 serum levels were found to be high in patients with PCOS.
- The shear wave elastography technique, when evaluated together with FIB-4 score and serum periostin level, may be helpful in the follow-up of liver fibrosis at patients with PCOS.

Table 1. Anthropometric and Biochemical Characteristics and Hormone Levels of the Groups

Variables	Control Group (n = 33)	Patient Group (n = 33)	Cohen's d	*P*
Age (years)	26.12 ± 4.86	24.93 ± 6.29	0.211	.397[a]
BMI (kg/m^2)	23.46 ± 4.02	24.43 ± 4.98	0.214	.390[a]
Waist circumference (cm)	79.63 ± 11.42	78.81 ± 11.38	0.07	.772[a]
Fat ratio (%)	26.02 ± 4.96	27.50 ± 5.58	0.28	.258[a]
HOMA-IR	1.34 (1.0-2.23)	1.72 (1.13-2.67)	0.430	.276[b]
APRI score	0.17 (0.14-0.19)	0.20 (0.10-0.30)	0.274	.700[b]
FIB-4 index score	0.39 (0.30-0.50)	0.39 (0.25-0.48)	0.101	.580[b]
hs-CRP (mg/L)	0.51 (0.22-2.22)	0.83 (0.13-1.37)	0.316	.430[b]
Androstenedione (ng/mL)	1.10 ± 0.39	1.18 ± 0.45	0.189	.424[a]
Total testosterone (ng/mL)	0.28 ± 0.11	0.34±0.11	0.545	.044[a]
DHEAS (mcg/dL)	182.8 ± 95.09	220.35±118.79	0.348	.161[a]
FAI (nmol/L)	1.80 (0.98-2.33)	2.11 (1.16-3.16)	0.563	.037[b]
Periostin (ng/mL)	20.61 ± 11.32	39.40 ± 19.79	1.16	<.001[a]
MMP-3 (ng/mL)	26.66 ± 10.77	36.83 ± 11.61	0.908	<.001[a]

Data are presented as mean ± SD or median (Q1-Q3).
APRI, Aspartate aminotransferase to platelet ratio index; BMI, body mass index; DHEAS, dehydroepiandrosterone sulfate; FAI, free androgen index; FIB-4, fibrosis-4; HOMA-IR, homeostatic model assessment for insulin resistance; hs-CRP, high sensitivity C-reactive protein; MMP-3, matrix metalloproteinase-3.
[a]Student's *t* test; [b]Mann–Whitney *U* test.

Results

Homogeneity was ensured in our anthropometric measurements, and patients and healthy volunteers from the same age groups with the same measurements were included in the study. No significant difference was found between the groups in the comparison of HOMA-IR, hs-CRP, APRI, and FIB-4 scores, elastography characteristics (Table 1).

When the serum androgen levels and indices were compared between the control and patient groups, total testosterone levels and FAI were found to be significantly higher in the patient group (*P* = .044 and *P* = .037, respectively). However, DHEAS and androstenedione level were similar (Table 1).

Table 2. Intergroup Relationship of Liver Velocity and Liver Elasticity

Variables	Control Group (n = 33)	Patient Group (n = 33)	Cohen's *d*	*P*
Liver velocity (m/s)	1.27 (1.11-1.5)	1.25 (1.09-1.4)	0.336	.185[b]
Liver elasticity (kPa)	6.93 ± 2.83	6.06 ± 2.18	0.344	.172[a]

Data are presented as mean ± SD or median (Q1-Q3).
[a]Student's *t* test; [b]Mann–Whitney *U* test.

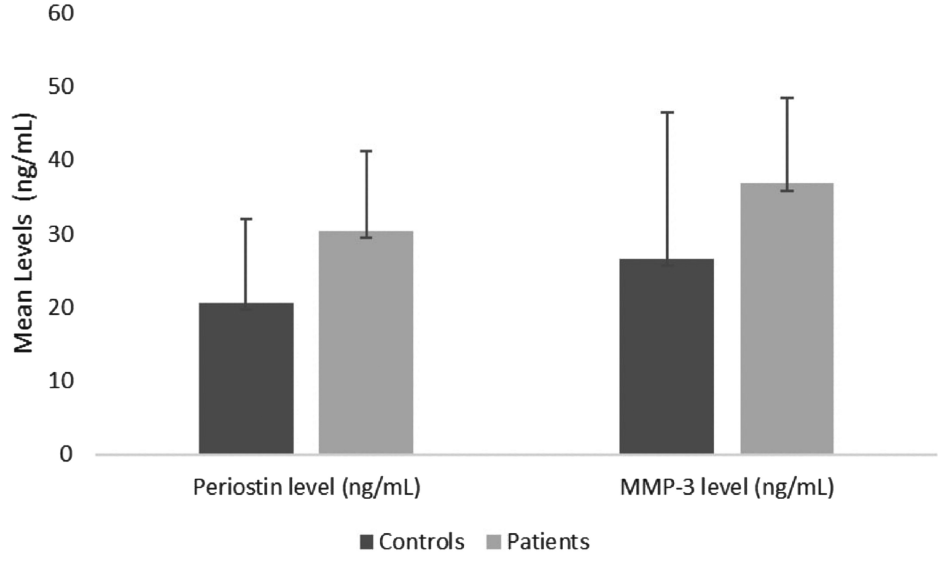

Figure 1. Distribution of periostin (ng/mL) and matrix metalloproteinase-3 (MMP-3; ng/mL) levels according to study groups.

Table 3. HOMA-IR with Liver Elasticity (kPa) in the Study Groups

			Liver Elasticity	Liver Elasticity
Control group	HOMA-IR	r	0.518[c]	-
		P	.002	-
Patient group	HOMA-IR	R	-	−0.133[d]
		P	-	.461

HOMA-IR, homeostatic model assessment for insulin resistance.
[c]Pearson correlation, [d]Spearman Rank Correlation.

Table 4. Relationship between Periostin, MMP-3, and Liver Elasticity in the Study Groups

			Periostin	MMP-3	Liver Elasticity
Control Group	Periostin (ng/mL)	r	-	0.221[c]	0.317[c]
		p	-	.225	.077
	MMP-3 (ng/mL)	r	0.221[c]	-	-0.062[c]
		p	.225	-	.73
	Liver elasticity (kPa)	r	0.317[c]	-0.062[c]	-
		p	.077	.73	-
Patient Group	Periostin (ng/mL)	r	-	0.389[c]	-0.035[c]
		p	-	.025	.847
	MMP-3 (ng/mL)	r	0.389[c]	-	0.126[c]
		p	.025	-	.484
	Liver elasticity (kPa)	r	−0.035[c]	0.126[c]	-
		p	.847	.484	-

MMP-3, matrix metalloproteinase-3.
[c]Pearson correlation.

When the levels of periostin and MMP-3, which are considered as biochemical markers of fibrosis, were compared (Table 1), a statistically significant difference was found between the patient and control groups ($P < .001$ and $P < .001$, respectively). Matrix metalloproteinase-3 (MMP-3) and periostin values were found to be significantly higher in the patient group (Figure 1).

Table 5. Relationship between APRI and FIB-4 Scores and Periostin, MMP-3 and Liver Elasticity

			Periostin	MMP-3	Liver Elasticity
Control Group	APRI score	*r*	−0.239[d]	0.029[d]	−0.265[d]
		P	.188	.874	.137
	FIB-4 score	*r*	−0.160[d]	0.041[d]	−0.248[d]
		P	.383	.822	.164
Patient Group	APRI score	*r*	0.194[d]	0.045[d]	0.233[d]
		P	.278	.802	.192
	FIB-4 score	*R*	0.433[d]	0.214[d]	0.374[d]
		P	.012	.231	.032

APRI, aspartate aminotransferase to platelet ratio index; FIB-4, fibrosis-4; MMP-3, matrix metalloproteinase-3.
[d] Spearman rank correlation.

There was no significant difference in liver velocity and liver elasticity between the patient and control groups (Table 2).

Considering the effect of HOMA-IR on liver elasticity in the groups, it was found to be significant in the control group ($r = 0.518$, $P = .002$) (Table 3).

In addition, the relationship between periostin and MMP-3 was also examined and a positive correlation was found between the 2 in the patient group ($r = 0.389$, $P = .025$). However, no correlation was found between fibrosis markers and liver elasticity (Table 4).

Considering the relationship of APRI and FIB-4 scores with periostin, MMP-3, and liver elasticity in the control and patient groups, FIB-4 score was positively correlated with periostin and liver elasticity in the patient group ($r = 0.433$, $P = .012$ and $r = 0.374$, $P = 0.032$, respectively) (Figure 2; Table 5).

When the effects of total testosterone (ng/mL) and FAI (nmol/L) on the measurement of liver elasticity (kPa) were examined in the groups, a negative correlation was observed between liver elasticity and total testosterone level in the control group ($r = -0.346$, $P = .048$) (Table 6).

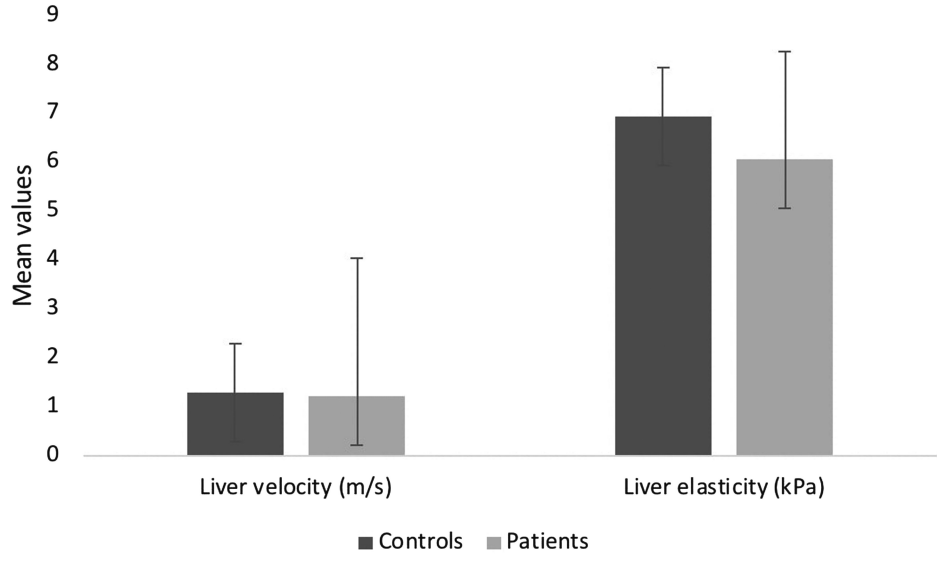

Figure 2. Distribution of liver velocity (m/s) and liver elasticity (kPa) according to the study groups.

Table 6. The Relationship of Total Testosterone and FAI with Liver Elasticity in the Groups

			Liver Elasticity	Total Testosterone	FAI
Control group	Liver elasticity	*r*	-	-0.346[c]	0.018[d]
		P	-	0.048	0.921
	Total testosterone	*r*	−0.346[c]	-	0.586
		P	0.048	-	0
	FAI	*r*	0.018[d]	0.586[d]	-
		P	0.921	<0.001	-
Patient group	Liver elasticity	*r*	-	0.081[c]	−0.034[d]
		P	-	0.655	0.85
	Total testosterone	*r*	0.081[c]	-	0.411[d]
		P	0.655	-	0.017
	FAI	*r*	−0.034[d]	0.411[d]	-
		P	0.85	0.017	-

FAI, free androgen index.
[c]Pearson correlation; [d]Spearman rank correlation.

Discussion

In this study, the body mass index (BMI) values of women in the PCOS and control groups were normal. Waist circumference measurements were also normal according to the reference values of adult females in our country.[11] Although the HOMA-IR index of the PCOS group was higher than that of the control group, there was no significant difference between the study groups. In a study by Uludag et al[12] involving 109 participants with PCOS, HOMA-IR was found to be significantly higher in the PCOS group than that in the control group. When the subanalysis of this study is evaluated, it is seen that the cases with PCOS consisted of overweight and obese patients according to BMI. Homeostatic model assessment for insulin resistance results in the PCOS group with BMI <25 are consistent with our study. In addition, insulin resistance data were significantly higher in the obese group. In another study, in a group similar to our study group for age, waist circumference, and BMI, the HOMA-IR index was found to be normal.[13] Insulin resistance may be found to be increased independently of BMI in patients with PCOS.[14]

If hs-CRP plasma levels, which are considered as low-grade chronic inflammation indicators, are considered, there was no difference between our groups. In the study by Samy et al.[15] it was found that a similar result in the group with a mean BMI matched with our PCOS group. That study divided 108 women with PCOS into 2 groups according to their BMI (group 1 (BMI <27 kg/m^2) and group 2 (BMI >27 kg/m^2)). There was no difference in hs-CRP levels between group 1 and matched healthy controls. In a study conducted by Verit et al,[16] hs-CRP levels increased in PCOS patients with normal serum insulin levels compared to healthy controls. They predicted an increase in BMI and waist circumference as factors affecting this situation. Un et al[17] observed that there was no difference in hs-CRP levels. However, when the obese and nonobese PCOS groups were evaluated in the subanalysis, hs-CRP was found higher in the obese group. Together with the results of the studies in the literature, we believe that an adequate inflammatory response has not yet developed in our PCOS group.

When liver fibrosis scores in our PCOS and control groups were compared, no difference was found. Lerchbaum et al[18] in their study on fatty liver index in PCOS, a total of 611 women with PCOS and 139 BMI matched healthy controls in the same age range were recruited, and no evidence of elevated fibrosis indices was found in PCOS as well as in control group. On the other hand, in another study involving a large number of participants, the FIB-4 score was high in PCOS group.[19,8]

Periostin and MMP-3 levels, which are accepted as biochemical markers of fibrosis, were found higher in our PCOS group. Chen et al[20] included 50 PCOS patients and 30 healthy controls in their cross-sectional study investigating periostin levels in PCOS patients and found that periostin was significantly higher in PCOS patients. No data were found in the literature on the effect of MMP-3 in PCOS. In our study, a positive correlation was found between periostin and MMP-3 in the PCOS group. Tajika et al[21] in a study on the effect of periostin on synoviocytes in knee osteoarthritis showed that periostin facilitates MMP-3 production and MMP-3 levels increase depending on periostin concentration. In a similar study, it was shown that periostin expression induced MMP-3 expression in human osteoarthritis cartilage.[22] Based on these findings, it can be predicted that periostin production is higher in early stages of inflammation and MMP-3 may increase secondary to the effect of periostin in more advanced stages. This assumption is consistent with the results of our study. There was no correlation between both markers and liver elasticity.

A positive correlation was observed between FIB-4 scores and periostin in the PCOS group, but no association with APRI score was detected. Again, in this group, a positive correlation was found between FIB-4 score and liver elasticity. In the study on the diagnosis and staging of early stage fibrosis in chronic Hepatitis B virus (HBV) and hepatitis C virus (HCV) patients, it has been emphasized that the performance of the FIB-4 scoring system is better and more reliable than the APRI system.[23]

There was no significant difference in liver velocity and liver elasticity between the patient and control groups. In the literature, there are many studies on the normal referance values of 2D SWE for liver in the healthy population; however, there is no standardized data yet.[24] In our study, the mean liver elasticity was 6.06 ± 2.18 kPa in our patients and 6.93 ± 2.83 kPa in our control group.

Ferraioli et al.[25] revealed that liver stiffness values changed in parallel with the increase in liver fibrosis. They accepted liver biopsy as the

reference. In this case, the diagnosis of radiological liver fibrosis can be made after the increase in biochemical fibrosis markers.

When the intergroup relationship between androstenedione, total testosterone, DHEAS, and FAI was evaluated, it was found that total testosterone and FAI were higher in the patient group ($P = .044$, $P = .037$, respectively), but although androstenedione and DHEAS were higher in the patient group, the difference between the groups was not significant. Similar to the results of our study, in the study of Rudnicka et al[26] consisting of 227 PCOS patients and 40 healthy controls, total testosterone levels were found higher in the PCOS group. Hyperandrogenism is a risk factor for the development of NAFLD in patients with PCOS.[27] This suggests that hyperandrogenism may be a factor in the increase of fibrosis markers in our study. In our study, no significant difference was found between serum androgen levels and FAI and elastography findings and fibrosis markers.

Obesity, insulin resistance, hyperandrogenism, and inflammation are associated with NAFLD in patients with PCOS.[28,29] Many genes contribute to this condition. We conducted our study in a group of normal weight PCOS patients who were diagnosed in the early stages of disease. In this sense, the absence of insulin resistance and inflammatory response in women with PCOS in the early period is compatible with the literature. We can say that NAFLD and its negative consequences may become evident during the progression of PCOS. The factors that may contribute to this situation in the later stages are increased insulin resistance and inflammatory response.

As a result, serum periostin and MMP-3 levels were higher in the PCOS group. Fibrosis scores were similar. However, a positive correlation was found between FIB-4 score and periostin and between FIB-4 score and liver elasticity in study group. FIB-4 score, serum periostin level, and 2D-SWE may help us in the diagnosis of liver fibrosis in patients with PCOS. Larger-scale studies are needed to evaluate the importance of 2D-SWE in the diagnosis of fibrosis in these cases.

Human Rights Statements and Informed Consent

All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1964 and later versions. Informed consent was obtained from all patients for being included in the study.

Ethics Committee Approval: Ethical committee approval was received from the Ethics Committee of Hatay Mustafa Kemal University (Date: May 1, 2020, Decision No: 2018/103).

Informed Consent: Informed consent forms were obtained from patients and volunteers who agreed to take part in the study.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept – E.G., O.Ö., G.B.; Design – E.G., O.Ö., G.B., G.A.; Supervision – E.G., O.Ö., G.B., G.A.; Materials – E.G., O.Ö., G.B., G.A.; Data Collection and/or Processing – E.G., O.Ö., G.B., G.A.; Analysis and/or Interpretation – E.G., O.Ö., G.B., G.A.; Literature Review – E.G. G.A.; Writing – E.G., O.Ö., G.A.; Critical Review – E.G., G.B., G.A.

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Declaration of Interests: The authors have no conflicts of interest to declare.

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