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ORIGINAL ARTICLE

Increased serum myonectin and irisin levels with myonectin and FNDC5 expressions in polycystic ovary syndrome: a case control study

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ABSTRACT

The aim of this study is to assess the FNDC5 and myonectin expressions and serum levels of myonectin and irisin in women with PCOS. 90 participants were included in this case-control study. 45 of these participants were with PCOS, and 45 of them were healthy volunteers matched for age and body mass index (BMI). Serum irisin and myonectin levels were measured with commercially available enzyme-linked immune sorbent assay (ELISA) kits. Expression of the myonectin and FNDC5 genes were determined by RT-PCR analysis. It was found out that FSI, HOMA-IR, LH, LH/FSH, TT, serum irisin and serum myonectin levels, myonectin mRNA expression, and FNDC5 mRNA expression were higher in the PCOS group, whereas HDL-C level was lower in the PCOS group ($p < .05$). When the groups were compared, it was detected that IR and HA were significantly higher in the PCOS group ($p < .05$). Serum irisin and myonectin levels, and myonectin and FNDC5 mRNA expressions were increased in women with PCOS. These molecules can be target molecules in PCOS pathophysiology and treatment.

IMPACT STATEMENT

- **What is already known on this subject?** Although the aetiology of PCOS is not fully understood, it is thought that insulin resistance may play a critical role. In recent studies, the relationship of cytokines secreted from skeletal muscle with insulin resistance has been shown. The effects of irisin and myonectin, which are members of the myokine family, on lipid and glucose metabolism are known.
- **What do the results of this study add?** Although there are many studies in the literature regarding serum irisin levels in women with PCOS, their results are confusing. There is a study in the literature investigating the relationship between myonectin and PCOS. In our study, we evaluated myonectin and FNDC mRNA expressions in addition to serum irisin and myonectin levels. As a result, we found that markers and their mRNA expressions were lower in patients with PCOS compared to controls.
- **What are the implications of these findings for clinical practice and/or further research?** We think that the results of our study will shed light on future studies. Due to their effects on adipose tissue, these markers may play a role in the aetiology of long-term complications of PCOS. Moreover, they can become pharmacological targets in preventing these complications.

KEYWORDS
Polycystic ovary syndrome; insulin resistance; myonectin; irisin

Introduction

Albeit polycystic ovary syndrome (PCOS) is the most common endocrinological disorder of the reproductive period in women, its diagnosis remains to be a challenge for clinicians due to the different phenotypes of the syndrome as well as its ethnic variations (Bozdag et al. 2016; Gibson-Helm et al. 2017). The diagnosis of PCOS is based on ultrasonographic polycystic ovary image, the presence of oligo/anovulation, and hyperandrogenism (clinical or biochemical) (Group 2004). PCOS is associated with insulin resistance (IR), impaired glucose tolerance, and metabolic syndrome. In addition to infertility, women who meet all PCOS criteria face increased pregnancy complications and the long-term risk of endometrial cancer and cardiovascular disease (Fauser et al. 2012). IR is detected in the majority of women with PCOS, though its impact on the pathophysiology of PCOS is not fully found out (Sirmans and Pate 2013). Furthermore, the correlation between PCOS and IR is not entirely dependent on body mass index (BMI), 30% of lean women with PCOS have IR (Sirmans and Pate 2013). Thus, it can be considered that IR might be a cause, not a result, in the development of PCOS.

It is a well-known fact that sedentary life is a risk factor for chronic and degenerative diseases. Skeletal muscle plays

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an active role in many aspects such as inflammatory and metabolic processes through the myokines it secretes. Moreover, it is a widely accepted fact that the beneficial effects of physical activity are regulated by myokines (Seldin et al. 2012). It is well-documented that irisin formed by the proteolytic process of fibronectin type III domain containing 5 (FNDC5), which is a membrane protein, and myonectin, also known as C1q TNF Related Protein (CTRP15), is essentially secreted from the skeletal muscle (Kishore and Reid 2000; Boström et al. 2012). It has been demonstrated that irisin regulate the formation of adipose tissue, increase energy expenditure, and correct IR and glucose intolerance (Boström et al. 2012). It has been found in previous studies that serum irisin level is lower among patients with Type II diabetes mellitus (T2DM) (Choi et al. 2013). Besides, irisin has been determined to be associated with IR, BMI, and hyperandrogenism in women with PCOS (Li et al. 2015; Wang, Guo, et al. 2018). On the contrary, some studies suggesting that irisin is reduced or unchanged in women with PCOS and is correlated with hyperandrogenism rather than IR (Abali et al. 2016; Wang, Zhang, et al. 2018; Zhang et al. 2018). Information about myonectin is more limited compared to irisin; it is considered that myonectin regulates glucose and lipid metabolism (Seldin et al. 2012). Myonectin levels, which are suppressed during hunger, increase with refeeding and exercise (Seldin et al. 2012). Recombinant myonectin treatment increased fatty acid uptake from the circulation without stimulating lipolysis in animal trials, and likewise, myonectin achieved lipid uptake in hepatocytes and adipocytes in-vitro studies by regulating gene expression (Seldin et al. 2012). In addition to these metabolic effects, it has been found out that myonectin can mediate the beneficial effects of exercise on heart health by reducing inflammation and apoptosis in myocardial ischaemia (Otaka et al. 2018). It has been determined in the studies on T2DM, obesity, and PCOS that the serum level of myonectin was lower compared to the control group (Li et al. 2019; Demir and Guler 2020; Li et al. 2020).

We are of the opinion that the results of a single study on a syndrome with different phenotypes and ethnic variations, such as PCOS, should be verified. In addition to that, serum irisin levels are confusing in women with PCOS. We wanted to increase the power of our study by evaluating together serum levels of two myokines, which we think having parallel effects on glucose and lipid metabolism. The objective of this study is to assess the FNDC5 and myonectin expressions and serum levels of myonectin and irisin in women with PCOS. Moreover, it is to investigate the correlation between metabolic and hormonal effects of PCOS with these parameters.

Materials and methods

Study population

90 participants were included in this case-control study. 45 of these participants were with PCOS, and 45 of them were healthy volunteers matched for age and body mass index (BMI). Approval was obtained from the local Ethics Committee to perform this study, which adhered to the ethical principles of the Declaration of Helsinki at all phases (2017-KAEK-189_2019.02.28_06). Informed consent was obtained from all participants.

PCOS diagnosis was made in accordance with Rotterdam criteria (Group 2004): ultrasonographic polycystic ovary image, presence of oligo/anovulation, and clinical or biochemical hyperandrogenism Women who met at least two of these criteria were considered to be with PCOS. The presence of diabetes mellitus, thyroid diseases, cardiovascular diseases, chronic renal failure, hyperprolactinaemia, Cushing's syndrome, congenital adrenal hyperplasia, and 21-hydroxylase deficiency were considered as exclusion criteria. In addition to that, women who had received hormonal medications and insulin sensitisers were also excluded from the study. It was ensured that women in the control group had regular menstrual cycles and did not use hormonal contraception methods. Height, weight, waist circumference, and hip circumference were measured by a researcher who did not know the data regarding the group of the participants, and Ferriman-Gallwey scoring (FGS) was applied to the participants. Hyperandrogenism was specified as $\geq$8 with FGS. BMI was calculated by dividing the body weight to the square of the body height (kg/m $^{2)}$.

Blood sample collection

Venous blood samples were taken following 8–10 hours of fasting in the early follicular phase of the menstrual cycle (2nd–3rd day). The sample, which was taken into an EDTA tube for the evaluation of myonectin and FNDC5 mRNA, was stored at -80° C. The sample taken to measure the levels of myonectin and irisin was centrifuged at 3000 rpm for 10 minutes and the obtained serum was stored at -80° C.

Metabolic and hormonal analysis

Fasting serum glucose (FSG), total cholesterol (TC), high-density lipoprotein cholesterol (HDL-C), and triglyceride (TG) levels are measured with an autoanalyzer (Aeroset®, Abbott®, IL, USA), while low-density lipoprotein cholesterol The (LDL-C) level was calculated by the Friedewald formula. Fasting serum insulin (FSI), follicle-stimulating hormone (FSH), luteinizing hormone (LH), oestradiol (E2), total testosterone (TT), and dehydroepiandrosterone (DHEA) was measured via electrochemiluminescence immunoassay (ECLIA) technique and using the kits, which were suitable for autoanalyzer (Architect i2000; Abbott Laboratories, Abbott Park, IL, USA). Insulin resistance was assessed using the homeostatic model assessment insulin resistance index (HOMA-IR), and a HOMA-IR of $>$ 2.5 was considered as IR. HOMA-IR was calculated as follows: FSG (mg/dl) x FSI (mU/mL)/405.

Determination of serum irisin and myonectin levels

Serum irisin and myonectin levels were measured with commercially available enzyme-linked immune sorbent assay (ELISA) kits, with a minimum detectable concentration of 0.2 ng/mL and 0.05 ng/mL, respectively, (cat.no E3253Hu, cat.no E4999Hu, Bioassay Technology Laboratory, Shanghai,

Table 1. Comparison of clinical, biochemical and hormonal parameters in PCOS and control groups.

	PCOS	Control	*p*
	n:45	n:45	
Age (years)	25 (6)	27 (8)	.385 [b]
BMI (kg/m^2)	24.50 ± 2.62	24.30 ± 3.22	.746[a]
WHR	0.78 ± 0.10	0.74 ± 0.10	.107[a]
FGS	9 (3)	5 (3)	<.001 [b]
FSG (mg/dL)	85.64 ± 7.84	84.97 ± 7.48	.682[a]
FSI (μIU/mL)	13.21 (8.76)	8.86 (4.90)	<.001[b]
HOMA-IR	2.74 (1.88)	1.85 (1.08)	<.001[b]
Cholesterol (mg/dL)	159.53 ± 29.36	166.03 ± 32.57	.323[a]
Trigliserid (mg/dL)	93.60 (24.30)	83.00 (45.30)	.057[b]
LDL-C (mg/dL)	86.78 (29.02)	90.00 (38.20)	.545[b]
HDL-C (mg/dL)	50.00 (9.60)	54.10 (12.00)	.005[b]
FSH (ng/mL)	5.78 (1.04)	5.87 (1.50)	.521[b]
LH (ng/mL)	8.98 (4.51)	5.49 (1.32)	<.001[b]
E2 (ng/mL)	40.40 (12.21)	38.81 (9.20)	.450[b]
LH/FSH	1.59 (0.78)	0.93 (0.24)	<.001[b]
TSH (μIU/mL)	2.03 (1.02)	2.12 (1.17)	.942[b]
PRL (ng/mL)	11.89 (5.40)	11.02 (3.41)	.096[b]
TT (ng/mL)	0.29 (0.12)	0.20 (0.05)	<.001[b]
DHEA (μg/dL)	252.12 (102.51)	236.81 (109.28)	.460[b]
Myonectin (ng/mL)	96.29 (50.18)	55.64 (20.38)	<.001[b]
Irisin (ng/mL)	699.26 (453.33)	376.89 (229.76)	<.001[b]
Myonectin mRNA	0.90 (0.53)	0.29 (0.33)	<.001[b]
FNDC5 mRNA	1.52 (1.98)	0.29 (0.35)	<.001[b]
IR No	17 (37.8%)	36 (80.0%)	<.001[c]
Yes	28 (62.2%)	9 (20.0%)	
HA No	12 (26.7%)	40 (89.9%)	<.001[c]
Yes	33 (73.3%)	5 (11.1%)	

Data are presented as mean ± SD/median(IQR)/*n*(%). $p < .05$ is significant.
[a]Student t test; [b]Mann-Whitney U test; [c]Chi-Square test.
PCOS: polycystic ovary syndrome; *BMI*: body mass index; *WHR*: waist-hip ratio; *FGS*: Ferriman-Gallwey score; *FSG*: fasting serum glucose; *FSI*: fasting serum insülin; *HOMA-IR*: homeostatic model assessment insulin resistance index; *LDL-C*: LDL cholesterol; *HDL-C*: HDL cholesterol; *FSH*: follicle stimulating hormone; *LH*: luteinizing hormone; *E2*: oestradiol; *LH/FSH*: luteinizing hormone to follicle-stimulating hormone ratio; *TSH*: thyroid stimulating hormone; *PRL*: prolactin; *TT*: total testosterone; *DHEA*: dehydroepiandrosterone; *IR*: insulin resistance; *HA*: hyperandrogenism.

China) according to the manufacturer's instructions. Optical density values for samples and standard samples were detected on Thermo Scientific (USA) Multiscan Go Microplate Reader ELISA reader at 450 nm. The results are presented as ng/mL.

RT-PCR analysis

In order to determine the target gene expression of the myonectin and FNDC5 genes, RNA samples of the patient and control groups were isolated in line with the protocol of the manufacturer (NucleoSpin RNA Blood Extraction Kit, Macherey-Nagel, Germany). The obtained RNAs were converted into cDNA with the reverse transcription kit (High-Capacity cDNA Reverse Transcription Kit, Thermo Fisher, USA), and stored at −20 C following the incubation was completed. The cDNA concentrations of the samples were measured via a fluorometer (QFX, Denovix, USA). cDNA concentrations were equalised to 30 ng/μL in all samples. Primer sets, which have a design suitable for RT-PCR device (Q2000B, LongGene, China) and master-mix kit (S-1001, BIONEER, INC., USA), were utilised. Beta-actin gene was used as the control gene. The cycle of quantification (Cq) for each sample was recorded and 2∘ΔΔCt (threshold cycles) values of the data were analysed. Each sample was run twice, and the mean Ct values were determined.

Statistical analysis

Statistical analysis was performed via the software of SPSS 20 (IBM Corp. released 2011. IBM SPSS Statistics for Windows, version 20.0, Armonk, NY: IBM Corp.). Data are presented as mean ± SD, median (interquartile range), *n* (%). The normality of the distribution for the data was analysed via the Kolmogorov-Smirnov/Shapiro-Wilk's test. Student's t-test or The Mann-Whitney U-test was used to compare the continuous variables of the groups, depending on whether they are normally distributed or not. Univariate correlations were assessed using Spearman's rho test. Categorical data were compared via the Chi-Square test. Logistic regression analysis was used to determine the independent risk factors in PCOS. The diagnostic performance of the parameters was assessed via the receiver operating characteristic (ROC) curve analysis. The results were considered statistically significant at $p < .05$.

Results

The clinical characteristics and biochemical parameters of the studied groups are presented in Table 1. Upon comparing the groups, it was determined that there was no significant difference in mean age, BMI, and WHR, whereas FGS was significantly higher in the PCOS group ($p < .05$). It was found out that FSI, HOMA-IR, LH, LH/FSH, TT, serum irisin and serum myonectin levels, myonectin mRNA expression, and FNDC5 mRNA expression were higher in the PCOS group, whereas HDL-C level was lower in the PCOS group ($p < .05$) (Table 1, Figure 1). When the groups were compared, it was detected that IR and HA were significantly higher in the PCOS group ($p < .05$) (Table 1).

The correlations of serum irisin and serum myonectin levels as well as myonectin and FNDC5 expression with other variables are presented in Table 2. Both myonectin and irisin are positively correlated with FSI, HOMA-IR, and FGS. The same correlation is valid for myonectin and FNDC5 expression. A negative correlation was determined between HDL-C and myonectin as well as irisin. Furthermore, a significant correlation was also determined between these two myokine molecules and LH/FSH as well as FGS. Besides, a positive correlation was found between myonectin and irisin as well as between myonectin expression and FNDC5 expression ($r = 0.236$, $p = .015$; $r = 0.450$, $p < .001$, respectively) (Figure 2). Regression analysis of independent risk factors in PCOS is shown in Table 3.

The optimal ROC cut-off value of myonectin for PCOS was calculated as 70.60 ng/mL with a sensitivity of 88.9% and 75.6% specificity of (AUC: 0.880). The optimal ROC cut-off value of irisin for PCOS was calculated as 485.00 ng/mL with a sensitivity of 80.0% and specificity of 68.9% (AUC: 0.798) (Figure 3).

Discussion

PCOS is a considerable endocrinological disease that impacts women in the reproductive period. PCOS impacts women's health adversely with its short and long-term effects. It is considered that these effects could be mediated by IR

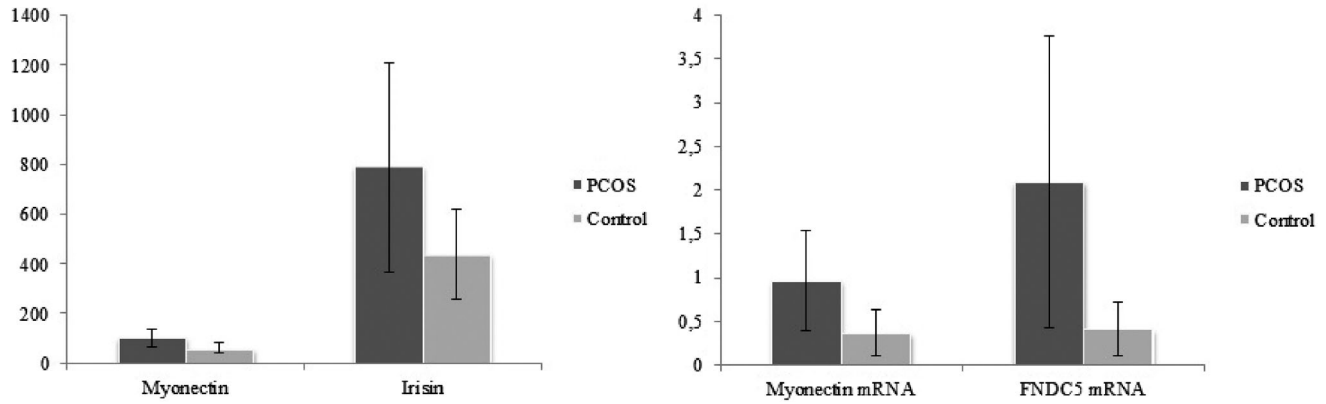

Figure 1. Serum irisin and myonectin levels with FNDC5 and myonectin expressions of the groups.

Table 2. Correlation of serum irisin and myonectin level with glucose metabolism parameters.

	Myonectin	Myonectin mRNA	Irisin	FNDC5 mRNA
Age				
r	−0.189	0.009	0.023	−0.013
p	.075	.930	.828	.901
BMI				
R	0.045	0.097	0.093	0.118
p	.674	.364	.385	.267
WHR				
r	0.184	0.235	0.411	0.368
p	.083	.025	<.001	<.001
FSG				
r	−0.034	−0.005	0.022	−0.009
p	.753	.965	.840	.936
FSI				
r	0.353	0.337	0.511	0.422
p	<.001	.001	<.001	<.001
HOMA-IR				
r	0.345	0.334	0.489	0.406
p	<.001	.001	<.001	<.001
TC				
r	0.011	−0.101	−0.038	−0.037
p	.918	.346	.726	.731
LDL-C				
r	0.018	−0.083	0.009	0.019
p	.869	.435	.929	.858
HDL-C				
r	−0.207	−0.108	−0.221	−0.241
p	.050	.309	.036	.022
TG				
r	0.275	0.182	0.182	0.209
p	.009	.087	.086	.048
FGS				
r	0.496	0.537	0.666	0.819
p	<.001	<.001	<.001	<.001
LH/FSH				
r	0.520	0.469	0.337	0.506
p	<.001	<.001	.001	<.001

Spearman's Rho correlation test.

(Sirmans and Pate 2013). This study compared the levels of myonectin and irisin, which are substantially secreted from skeletal muscle, with the mRNA expressions of these myokines in women with PCOS and healthy women. Serum levels of myonectin and irisin and expression of myonectin and FNDC5 mRNA were determined to be higher in the PCOS group. Serum myonectin and irisin levels as well as HA were detected to be independent risk factors for PCOS.

It is well-known that women with PCOS are at risk for glucose intolerance and T2DM (Celik et al. 2014). This situation increases the cruciality of markers that could be used in the early diagnosis of PCOS. In recent years, there has been a growing body of knowledge that myokines secreted from skeletal muscle could be effective in lipid and glucose metabolism (Boström et al. 2012; Seldin et al. 2012; Choi et al. 2013). Irisin, which is a member of the myokine family, increases total energy expenditure and at the same time creates a defense mechanism against insulin resistance, which is secondary to obesity (Boström et al. 2012). Brown adipose tissue activity has been shown to be decreased in women with PCOS (Shorakae 2019). Considering the results of studies such as ours in which serum irisin levels were found to be high, it can be suggested that there is a lack of response to irisin in the adipose tissue in women with PCOS. The level of irisin is lower in patients with T2DM compared to healthy people (Choi et al. 2013). Serum irisin level has also been associated with dyslipidemia. Wang et al. (2018) demonstrated that women, who have PCOS as well as dyslipidemia, had higher levels of irisin than women with PCOS but without dyslipidemia. Zhang et al. (2018) determined in their study, in which they assessed different PCOS phenotypes, that the difference between irisin levels in the normo-androgenic group and the healthy group was insignificant. However, they indicated that there might be a correlation between the level of irisin and hyperandrogenism. It was underscored in a meta-analysis published in recent years that irisin could impact the development of PCOS, independent of IR (Wang, Zhang, et al. 2018). On the other hand, Masaeli et al. (2019) found out that irisin levels decreased with IR among women with PCOS to whom they treated with metformin for 3 months. There are also differences in the results of studies investigating the correlation between PCOS and irisin. One of these, which was conducted by Abali et al. (2016), found out that irisin was significantly lower in women with PCOS. FNDC5 plays an important role in maintaining metabolic homeostasis. Studies show that FNDC5 has important roles not only in energy metabolism, but also in various processes such as inflammation, proliferation, metastasis and neural differentiation. The FNDC5 transcript is expressed in many tissues, including the ovary, testis, kidney, heart, brain, stomach, and liver (Rabiee et al. 2020). In addition to PCOS' reproductive effects, it has multiple metabolic risk consequences, including obesity, IR, T2DM, and premature atherosclerosis. While most studies report higher irisin levels in women with PCOS than in controls, some other studies have

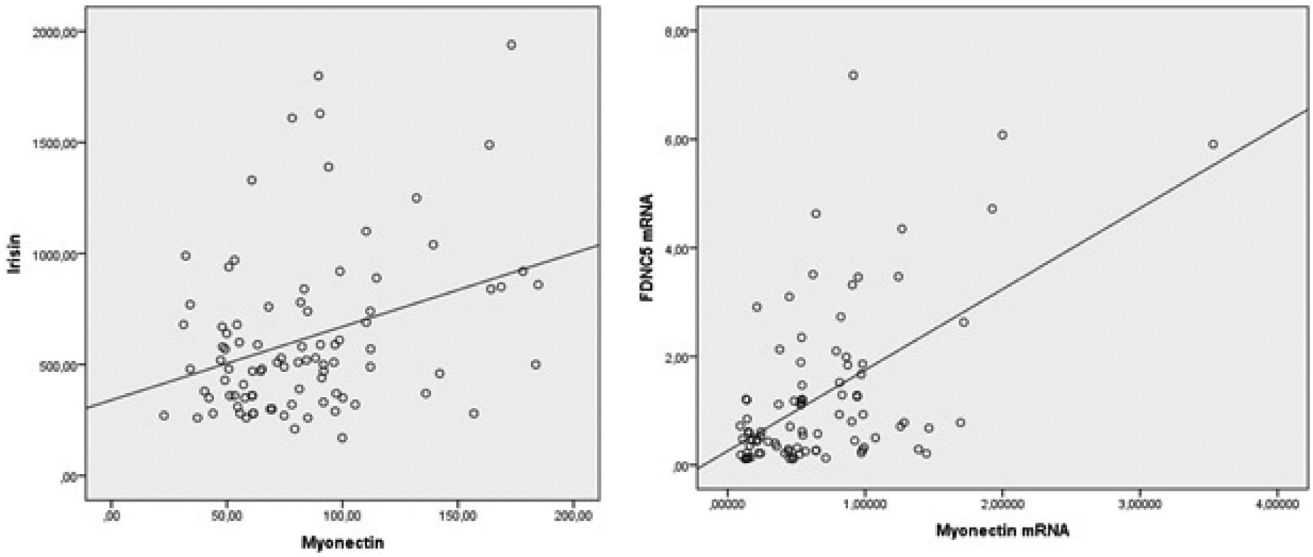

Figure 2. Correlation of biochemical markers.

Table 3. Regression analysis of independent risk factors in PCOS.

			95% Confidence Interval	
Risk Factors	*p* Value	Relative Risk	Lower	Upper
Myonectin	<.001	1.088	1.040	1.138
Irisin	.025	1.005	1.001	1.010
HA	.024	6.298	1.275	31.115
IR	.368	0.493	0.105	2.305

reported similar or lower circulating irisin levels in women with PCOS than in controls. Similar results apply to FNDC5 (Polyzos et al. 2018). These limited results may indicate a possible role of the IR versus FNDC5/irisin pathway in PCOS. We determined in our study that serum irisin level and FNDC5 mRNA expression, which indirectly stimulates the secretion of irisin, was higher in PCOS patients. Moreover, we found a positive correlation between serum irisin level and HOMA-IR and FGS as well. Our results corroborate the hyperirisinemia hypothesis of Park et al. (2013) parallel to insulin resistance, irisin resistance develops, and ultimately, serum irisin levels increase.

Information on myonectin, one of the newly discovered myokines in the literature, is considerably limited compared to irisin. Seldin and Wong (2012) demonstrated that exercise increases myonectin secretion. It was determined in the experimental ischaemic heart disease model that myonectin reduced acute myocardial damage with its antiapoptotic and anti-inflammatory effect. Based on this, it has been revealed that myonectin could mediate the positive effects of exercise on heart health (Otaka et al. 2018). The relationship between exercise and myonectin secretion has not been fully elucidated. In subsequent studies, no correlation was found between exercise and myonectin gene expression and/or serum level (Seldin et al. 2012; Peterson et al. 2014; Kamiński et al. 2019). Myonectin level rises with increasing free fatty acids (Seldin et al. 2012). It is well-documented that free fatty acids could impact the formation of IR (Capurso and Capurso 2012). Toloza et al. (2018) demonstrated in their study with 81 adults that the secretion of myonectin as a compensatory mechanism against insulin resistance might increase. It has been revealed that preoperative decreased myonectin levels started to increase 6 months after surgery among morbidly obese patients who underwent laparoscopic sleeve gastrectomy (Li et al. 2020). It has been suggested that myonectin could have a protective role against obesity (Li et al. 2020). Li et al. (2019) also found similar results in obese patients. Serum myonectin levels were also determined to be lower among patients with T2DM (Li et al. 2019). There is only one study in the literature assessing the serum myonectin levels in women with PCOS. Demir and Guler (2020) determined in their study that myonectin levels were lower in women with PCOS. They have shown that the risk of PCOS increases with decreased myonectin levels (Demir and Guler 2020). The findings of this last study contradict the results of our study. We found a higher serum myonectin level and myonectin mRNA expression in women with PCOS compared to the control group. We found a positive correlation between serum myonectin level and HOMA-IR, FGS, TG, and LH/FSH, and a negative correlation between serum myonectin level and HDL. We consider that the fact that PCOS is a very heterogeneous syndrome and the study group has varying characteristics (such as age, BMI, WHR, etc.) might give rise to these results.

Our study has several limitations. Regarding the first limitation, we have a relatively small sample size. Secondly, our study evaluated the IR via HOMA-IR instead of the insulin clamp technique, which is the gold standard, in the detection of IR. Lastly, we could not establish a causal link as a result of our study. On the other hand, the fact that mRNA expressions were also evaluated together with serum levels of the two markers, which we examined in our study, is a factor that strengthens our study.

In conclusion, serum irisin and myonectin levels, and myonectin and FNDC5 mRNA expressions were increased in women with PCOS. There is a positive correlation between these markers and insulin resistance as well as hyperandrogenism. These molecules can be target molecules in PCOS pathophysiology and treatment. Prospective studies, which have larger sample sizes and are designed according to the heterogeneity of PCOS, are needed to verify our results.

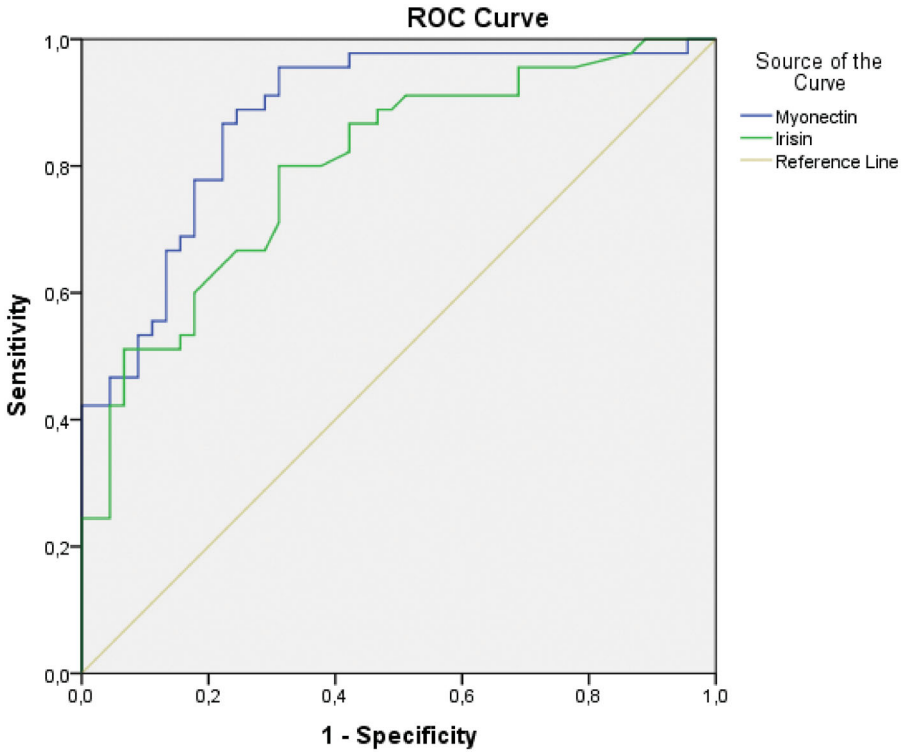

Figure 3. ROC analysis of irisin and myonectin.

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Disclosure statement

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