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Serum irisin levels in patients with polycystic ovary syndrome

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Abstract. – OBJECTIVE: Polycystic ovary syndrome (PCOS) is clinically heterogeneous endocrine disorders. Insulin resistance-related proteins play a role in the etiopathogenesis of PCOS. Irisin is a newly identified myokine which act like adipokines. Irisin has been shown to be associated with the insulin resistance and metabolic syndrome.

The purpose of this study was to determine the serum levels of irisin in PCOS patients and evaluate the correlations with other metabolic and hormonal parameters.

PATIENTS AND METHODS: Thirty-five PCOS patients and 35 matched healthy controls were enrolled to study. Serum irisin levels, anthropometric, hormonal and metabolic parameters including HOMA-IR were measured. Linear regression analysis was employed to study the relationship between irisin and hormonal and metabolic parameters.

RESULTS: Serum irisin level in PCOS patients (mean value; 0.491±0.145 μg/mL) was significantly elevated when compared to control group (mean value 0.281±0.138 μg/mL) ($p < 0.001$). Linear regression analysis showed that serum irisin was positively associated with body mass index, luteinizing hormone, fasting insulin and total cholesterol in the overall patient population but not for PCOS group alone ($p < 0.05$).

CONCLUSIONS: Serum irisin level of PCOS patients was high compared to that of healthy control subjects. In patients with PCOS, this situation may be due to insulin resistance, when there is leptin resistance or metabolic syndrome.

Key Words:
Polycystic ovary syndrome, Metabolic syndrome, Insulin resistance, Irisin.

Background

The first reports of polycystic ovary syndrome (PCOS) in modern medical literature were by Stein and Leventhal in 1935, with descriptions of 7 women with the complaints of amenorrhea, hirsutism, and enlarged ovaries with multiple cysts[1]. PCOS is a common endocrine disorder, with a prevalence of approximately 7% in reproductive age women. It is now recognized as a common, heterogeneous, inherited disorder characterized by hyperandrogenemia, menstrual irregularities, chronic anovulation, polycystic ovaries and reduced fertility[2,3]. A joint ASRM/ESHRE publication gave the definition of this pathology, which is now accepted globally. For a confirmed diagnosis, 2 of the following 3 clinical criteria are essential: oligomenorrhoea, hyperandrogenism or polycystic appearance of the ovaries on transvaginal ultrasonography[4]. There are numerous metabolic consequences of PCOS in addition to the effects on the reproductive system. These include a higher risk of obesity, insulin resistance (IR), type 2 diabetes mellitus (T2DM) and premature arteriosclerosis[5-7].

Characterized by reduced efficiency of insulin in the regulation of blood sugar levels, insulin resistance is a pathological condition, which develops in response to the complex interaction of the metabolic and inflammatory mediators of energy balance. The energy metabolism and insulin resistance-related proteins, such as leptin, adiponectin, ghrelin and tumor necrosis alpha[8], have been well-studied, and recently an additional exercise-induced peptide known as irisin has been identified[9]. Insulin resistance-related proteins such as adiponectin and ghrelin have also been reported to play a role in the etiopathogenesis of PCOS[10]. It has been reported that irisin improves obesity states and glucose homeostasis, thereby prolonging life expectancy[9]. The initial description of this protein was as a cleavage product of the type I membrane protein fibronectin type III domain-containing 5

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(FNDC5)[9]. However, it has been indicated in recent crystal structure and biochemical characterization studies of the FNDC5 ectodomain corresponding to the irisin myokine, that irisin consists of an N-terminal fibronectin III (FNIII)-like domain attached to a flexible C-terminal able to form dimers independently of glycosylation[11].

Irisin has attracted great attention since its discovery as it is thought that this peptide could play an important role in both animal and human physiology and biology[12]. To date, however, the benefits to humans which could be attributable to irisin remain unclear[12], and the effects of exercise training on FNDC5 gene expression and irisin levels are as yet, undefined[9]. Irisin was first defined as an exercise-induced hormone secreted by muscle[9]; then relationships with other myokines were determined and it has since been described as behaving in the same way as an adipokine expressed and secreted by white adipose tissue[13]. Irisin conducts many downstream events including osteoblast differentiation, nerve cell and b-cell regeneration and so on[14].

Significantly reduced levels of circulating irisin have been determined in long-term, new onset and undefined T2DM patients compared with nondiabetic controls. This has led to the suggestion that either the diabetic state itself or the metabolic condition which resulted in T2DM is accompanied by lower circulating irisin[15-17]. There have also been reports of an association between lower circulating irisin and the risk of non-alcoholic fatty liver disease and heart failure[18,19].

The aim of this study was to determine the serum levels of irisin in patients with polycystic ovary syndrome (PCOS), to compare these levels and to understand the correlations with other metabolic and hormonal parameters.

Patients and Methods

Approval for the study was granted by the Institutional Review Board of Sakarya University Medical School and informed consent was obtained from all participants. This prospective study comprised 35 PCOS patients and 35 matched healthy controls. The diagnosis of PCOS was made by the presence of any 2 of the following 3 criteria: (1) clinical and/or biochemical evidence of hyperandrogenism; (2) chronic oligo-/anovulation; and/or (3) polycystic ovaries on ultrasound[4]. PCO was defined as the presence of 12 or more follicles in each ovary, each measuring 2-9 mm in diameter, and/or increased ovarian volume > 10 ml[4]. Patients suffering from Cushing's syndrome, thyroid dysfunctions, androgen-secreting tumor, enzyme deficiency (21-hydroxylase in particular), decreased ovarian reserve (primary ovarian insufficiency), or type 1 or type 2 diabetes were excluded. None of the subjects were taking any medication for at least 3 months before the study. All the patients had clinical and/or biochemical hyperandrogenism and chronic anovulation, and 80% of the patients had polycystic ovaries on ultrasound.

The control group consisted of healthy women who had regular menstrual cycles (28 ± 2 days, blood progesterone levels measured between the 18th and 21st days of the menstrual cycle, > 10 ng/ml in two consecutive cycles) without clinical or biochemical hyperandrogenism or polycystic ovary and with no history of any drug intake for at least 3 months. Additional exclusion criteria for both groups were smoking and alcohol consumption.

All of the study groups were tested within 3rd to 5th days of menstruation. Anthropometric measurements (body mass and height) and waist circumference were measured with participants wearing lightweight clothing without shoes and body mass index (BMI) was calculated according to the standard formula.

Blood samples were collected at 9:00 am after an overnight fast between the 3rd and 5th days of a spontaneous bleeding episode of the PCOS group and of a menstrual cycle of the controls. In all the women, basal serum levels of follicle-stimulating hormone (FSH), luteinizing hormone (LH), thyroid stimulating hormone (TSH), prolactine (PRL), total testosterone (T), free testosterone (fT), fasting glucose (fGlu), fasting insulin (fI) and dehydroepiandrosterone sulfate (DHEA-S) were measured. Serum total cholesterol, high-density lipoprotein (HDL) cholesterol, low-density lipoprotein (LDL) cholesterol and triglycerides levels were also measured. Of the hormonal parameters, LH, FSH, T, DHEA-S, fI, fT PRL and TSH were analyzed by immune chemiluminescence method (Roche-Hitachi Modular Analytics E-170, Indianapolis, IN, USA) and the biochemical parameters were studied by enzymatic colorimetric methods (Olympus AU 600 Tokyo/Japan). HOMA-IR index was calculated with the standard formula: HOMA-IR = fasting concentration of insulin (mIU/ml) x fasting concentration of glucose (mmol/l)/22.5[20].

Irisin concentrations in the blood samples were measured in the same experimental series using commercial ELISA kits (cat no: EK-067-52; lot no: 603894) (Phoenix Pharmaceuticals, Belmont, CA, USA).

Statistical Analysis

Normality of the distribution of the variables was confirmed by the Shapiro-Wilk test. Unpaired *t*- and Mann-Whitney U tests were used for variables with normal and not normal distribution, respectively. Values were given as mean ± SD unless stated otherwise. Pearson correlation analysis was employed to study the relationship between irisin and hormonal and metabolic parameters. Multivariate linear regression models were used to study which variables were independently associated with irisin. A value of $p < 0.05$ was considered statistically significant. Data analysis was performed using the Statistics Package for Social Sciences version 15.0 (SPSS, Chicago, IL, USA).

Results

The anthropometric data of the control and PCOS patients are shown in Table I. The mean age of the control group was 26.83 ± 7.02 yrs, mean body weight was 58.14 ± 6.82 kg, mean BMI was 22.79 ± 2.64, and waist/hip (W/H) ratio was 0.72 ± 0.01. In the PCOS patient group, the mean age was 24.51 ± 5.29 yrs, mean body weight was 68.97 ± 9.81 kg, mean BMI was 26.74 ± 3.40, and W/H ratio was 0.80 ± 0.01.

The hormonal values of the PCOS and control patients are shown in Table I. The LH, fT, T values of the PCOS patients was significantly higher than were those of the control group ($p < 0.5$).

The metabolic status of the PCOS and control patients are shown in Table II. In the control group, the fGlu and fI values were determined as mean 90.57 ± 12.18 mg/dL and 5.09 ± 2.66 μU/mL respectively and in the PCOS group, as 97.69 ± 25.39 mg/dL and 13.96 ± 8.34 μU/mL respectively. The PCOS patients exhibited significantly higher levels of fGlu and fI compared with those of the control group ($p < 0.5$).

HOMA-IR values were, then, compared between the two groups for the assessment of insulin resistance. The highest HOMA-IR levels i.e. maximum insulin resistance was observed in the PCOS group (9.94 ± 6.28) while the lowest values were observed in the control group (2.19 ± 1.49) ($p < 0.001$).

The mean serum irisin level was determined as 0.491 ± 0.145 μg/mL for PCOS patients and 0.281 ± 0.138 μg/mL for the control group. As a result of this, the PCOS patients had significantly elevated levels of fasting irisin compared to the control subjects (Figure 1).

Linear regression analysis showed that fasting irisin was positively associated with BMI, LH, fI and total cholesterol in the overall patient population (Table III, $p < 0.05$). As we done the analysis for the groups, there was only negative association between irisin and fI was found (Table IV, $p < 0.05$).

Table I. The anthropometric data and hormonal status of the control and PCOS patients.

	Control	PCOS	p
Age (year)	26.83 ± 7.02	24.51 ± 5.29	0.15
Weight (kg)	58.14 ± 6.82	68.97 ± 9.81	0.00*
BMI	22.79 ± 2.64	26.74 ± 3.40	0.00*
W/H Ratio	0.72 ± 0.01	0.80 ± 0.01	0.00*
FSH(mIU/mL)	4.93 ± 1.32	4.31 ± 1.46	0.57
LH (mIU/liter)	4.33 ± 1.55	7.61 ± 3.03	0.00*
Estradiol (pg/mL)	36.74 ± 10.82	42.06 ± 14.56	0.29
TSH (uIU/mL)	1.56 ± 0.85	1.69 ± 0.79	0.32
Prolactin (ng/mL)	21.32 ± 8.84	22.17 ± 9.64	0.64
Free testosterone (pg/ml)	2.83 ± 1.68	4.93 ± 3.45	0.01*
Testosterone (ng/mL)	0.41 ± 0.15	0.88 ± 0.39	0.00*
DHEA-S (ng/ml)	334.72 ± 132.84	310.99 ± 117.82	0.67

Abbreviations: PCOS, polycystic ovary syndrome; BMI, body mass index; W/H, waist/hip; FSH, follicle-stimulating hormone; LH, luteinizing hormone; TSH, thyroid stimulating hormone; DHEA-S, dehydroepiandrosterone sulfate.

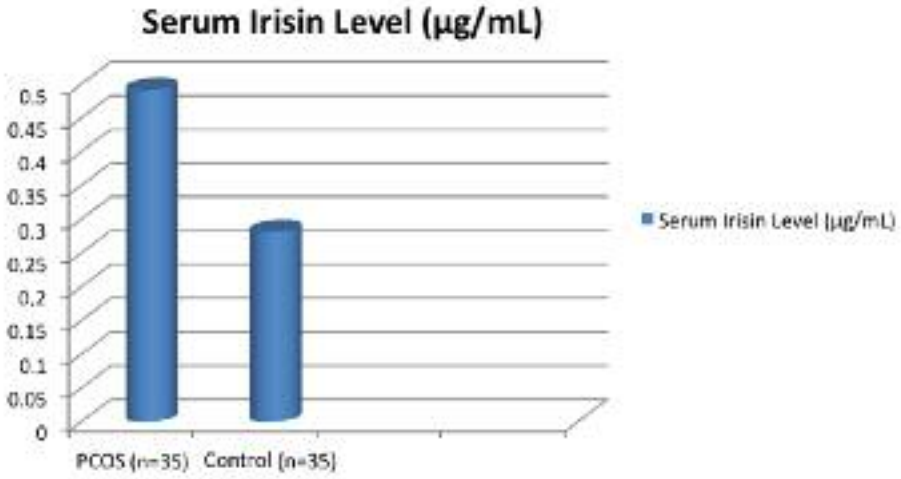

Figure 1. The mean serum irisin level for PCOS and Control Groups.

Discussion

According to the ASRM/ESHRE criteria definition, PCOS is frequently associated with insulin resistance and metabolic syndrome[4]. In a study of NHANES III[21], girls with PCOS were observed to be 4.5 times more likely to have Metabolic Syndrome (MBS) after adjustment for BMI and with every quartile increase in bioavailable testosterone, MBS was 3.8 times higher in girls with PCOS after adjustment for BMI.

Insulin has a key role in carbohydrate metabolism and insulin resistance is associated with PCOS at a reported prevalence of 50%-70% occurring independently of obesity[22]. Increased serine phosphorylation and reduced tyrosine phosphorylation, which is a specific abnormal pattern of insulin receptor phosphorylation, seems to be responsible for the insulin resistance observed in PCOS[23]. It has been widely accepted that insulin signal transduction might be diminished in PCOS.

PCOS has been linked to a higher prevalence of impaired glucose tolerance and T2DM, independent of obesity levels. Although the majority of PCOS patients retain sufficient beta-cell function to prevent deterioration in glucose tolerance, a considerable number, especially those with first-degree relatives with type 2 diabetes, produce an abnormal beta-cell response in response to glucose challenges[24]. Impaired glucose tolerance has been reported in approximately 30%-40% of PCOS patients and diabetes mellitus type 2 in 7.5%-10%[25]. In a meta-analysis[26], a subgroup analysis of BMI-matched studies reported the OR for impaired glucose tolerance to be 2.54 (95% CI 1.54-4.47) for women with PCOS. The same meta-analysis[26] evaluated the prevalence of

Table II. The metabolic status data of the control and PCOS patients.

	Control	PCOS	p
LDL cholesterol (mg/dL)	109.53 ± 31.68	105.79 ± 32.96	0.50
HDLcholesterol (mg/dL)	54.80 ± 12.18	49.40 ± 10.16	0.59
Total cholesterol (mg/dL)	163.66 ± 44.22	187.69 ± 44.33	0.12
Triglycerides (mg/dL)	82.54 ± 27.67	98.51 ± 47.47	0.00*
Fasting insulin (µU/mL)	5.09 ± 2.66	13.96 ± 8.34	0.00*
Fasting glucose (mg/dL)	97.69 ± 25.39	90.57 ± 12.18	0.28
HOMA-IR	2.19 ± 1.49	5.56 ± 3.28	0.00*
Irisin (µg/mL)	0.28 ± 0.14	0.49 ± 0.14	0.00*

Abbreviations: LDL, Low-density lipoprotein; HDL, high-density lipoprotein.

Table III. Linear regression analysis of the variable according to Irisin

	Total (n = 70)		Control (n = 35)		PCOS (n = 35)	
	r	p	r	p	r	p
Age (year)	-0.75	0.270	0.218	0.108	-0.136	0.217
BMI	0.292	0.007*	-0.064	0.360	-0.68	0.348
FSH(mIU/mL)	-0.108	0.188	-0.28	0.438	0.104	0.275
LH (mIU/liter)	0.446	0.000*	0.192	0.138	0.149	0.197
Fasting insulin (μU/mL)	0.359	0.001*	-0.350	0.021*	-0.42	0.405
Total cholesterol (mg/dL)	0.227	0.030*	0.05	0.489	0.156	0.185
Triglycerides (mg/dL)	0.177	0.072	-0.107	0.274	0.165	0.172
HDLcholesterol (mg/dL)	-0.190	0,600	-0.136	0.221	0.09	0.480
LDL cholesterol (mg/dL)	-0.70	0.270	0.251	0.76	0.125	0.237

Abbreviations: PCOS, polycystic ovary syndrome; BMI, body mass index; FSH, follicle-stimulating hormone; LH, luteinizing hormone; LDL, Low-density lipoprotein; HDL, high-density lipoprotein.

type 2 diabetes in BMI-matched studies and reported a higher prevalence of T2DM in PCOS (OR 4.0, 95% CI 1.97-8.1).

Several adipose-derived hormones, such as adiponectin and leptin are responsible for the modulation of insulin sensitivity. Adiponectin, which has antidiabetic properties, is considered to be an insulin sensitizer and reduced levels of adiponectin are known to be associated with obesity and insulin resistance[27]. Both leptin and adiponectin are proteins with an established relationship to insulin resistance and irisin seems to have an additional role in the process of insulin resistance. Besides that another adipocyte derived polypeptide of resistin does not seem to be involved in the pathogenesis of PCOS regarding insulin resistance[28]. As a muscle-derived factor, irisin is secreted from muscle after the shedding of the extracellular portion of the type I membrane protein FNDC5.

Decreased levels of circulating irisin have been found in T2DM patients compared with non-diabetic controls[16]. Liu et al[16] reported a significantly lower level of circulating irisin in long-term T2DM patients compared with a non-diabetic control group. Lower serum irisin was also found in new onset T2DM patients by Choi et al[15] and in undefined type 2 diabetes patients by Moreno-Navarrete et al[29].

While Timmons et al[30] stated that there was no relationship between irisin and BMI in diabetic populations, this has been contradicted by consistent recent reports of a positive relationship between serum irisin and BMI[16,31]. In an experimental animal model, Boström et al[9] obtained convincing results that adenovirus-mediated

Table IV. Linear regression analysis of the variable according to Irisin

	Total (n = 70)		Control (n = 35)		PCOS (n = 35)	
	r	p	r	p	r	p
Age (year)	-0.75	0.270	0.218	0.108	-0.136	0.217
BMI	0.292	0.007*	-0.064	0.360	-0.68	0.348
FSH(mIU/mL)	-0.108	0.188	-0.28	0.438	0.104	0.275
LH (mIU/liter)	0.446	0.000*	0.192	0.138	0.149	0.197
Fasting insulin (μU/mL)	0.359	0.001*	-0.350	0.021*	-0.42	0.405
Total cholesterol (mg/dL)	0.227	0.030*	0.05	0.489	0.156	0.185
Triglycerides (mg/dL)	0.177	0.072	-0.107	0.274	0.165	0.172
HDLcholesterol (mg/dL)	-0.190	0,600	-0.136	0.221	0.09	0.480
LDL cholesterol (mg/dL)	-0.70	0.270	0.251	0.76	0.125	0.237

Abbreviations: PCOS, polycystic ovary syndrome; BMI, body mass index; FSH, follicle-stimulating hormone; LH, luteinizing hormone; LDL, Low-density lipoprotein; HDL, high-density lipoprotein.

irisin overexpression leads to improved glucose tolerance and increased energy expenditure in mice.

In the current study, a surprisingly high level of irisin was observed in the PCOS patients contrary to what is generally seen in patients with diabetes. There is no clear explanation of this and as has been previously stated, PCOS is a condition associated with metabolic disease. In a study by Park et al[32], increased levels of serum irisin were determined in patients with metabolic syndrome.

The increase observed in serum fasting irisin level in the PCOS patients compared to the control subjects can, therefore, be associated with metabolic syndrome, which is itself associated with PCOS. Another view is that the elevated serum irisin level may be a protection in the prediabetic state of PCOS, before DM develops.

Liu et al[16] determined a significantly positive association of serum irisin with fasting plasma glucose. The negative correlations of serum irisin level with 2 hr plasma glucose (OGTT), HbA1c and triglyceride were determined, but after multiple regression analysis, only the negative association of 2 hr plasma glucose persisted[15].

However, it has also been suggested that the elevated irisin level may represent a state of "irisin resistance"[33], resembling that of insulin resistance, fibroblast growth factor 21 resistance[34], and leptin resistance[35], where high circulating hormone levels fail to induce the desired physiological effect.

An alternative theory has also been proposed that, irisin resistance might develop in PCOS similar to leptin resistance seen in patients with obesity and/or metabolic syndrome[36].

Conclusions

The results of this study showed that the serum irisin level of PCOS patients was found high compared to that of healthy control subjects. In patients with PCOS, this situation may be due to insulin resistance, when there is leptin resistance or metabolic syndrome.

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Conflict of Interest

The Authors declare that they have no conflict of interests.

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