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NEÜ YAYINEVİ

Serum Irisin Levels in Newly Diagnosed Type 2 Diabetes Mellitus and Prediabetic Patients

Yeni Tanı Tip 2 Diyabetes Mellitus ve Prediyabetik Hastalarda Serum İrisin Düzeyleri

Ahmet Yavuz[1], Zumrut Mine Isik Saglam[2], Ebru Kavak Yavuz[3], Melike Dogruel Yilmaz[4], Ezgi Degerli[5], Zeynep Karaali[6]

[1]*Necmettin Erbakan University, Meram Faculty of Medicine, Department of Gastroenterology, Konya, Turkey*
[2]*Ministry of Health Istanbul Training and Research Hospital, Clinic of Biochemistry, Istanbul, Turkey*
[3]*Ministry of Health Ankara City Hospital, Clinic of Hematology, Ankara, Turkey*
[4]*Ministry of Health Aydın State Hospital, Clinic of Internal Medicine, Aydın, Turkey*
[5]*Istanbul University, Cerrahpasa Faculty of Medicine, Department of Medical Oncology, Istanbul, Turkey*
[6]*Ministry of Health Başakşehir Çam and Sakura City Hospital, Clinic of İnternal Medicine, İstanbul, Turkey*

Address correspondence to: Ahmet Yavuz, Necmettin Erbakan University, Meram Faculty of Medicine, Department of Gastroenterology, Konya, Turkey
e-mail: ahmedyvz133@hotmail.com

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Öz

Amaç: Kas hücrelerinden salınan, miyokin grubu içerisinde yer edinen, kas ile yağ dokusu arasında mesajcı olarak görev yapan irisin hormonunun insülin direncinde, glukoz ve enerji metabolizmasının düzenlenmesinde aktif bir rol oynadığı gösterilmiştir. Çalışmamızda irisin molekülünün glukoz metabolizması ile olan ilişkisinin incelenmesi amaçlanmıştır.
Hastalar ve Yöntem: Çalışmaya, Nisan 2017 ve Eylül 2017 arasında İç Hastalıkları Polikliniğine başvurmuş 29 yeni tanı tip 2 diyabetes mellitus hastası, 41 yeni tanı prediyabet hastası ve 28 sağlıklı kontrol grubu dahil edildi. Serum irisin düzeyleri, laboratuvar bulguları ve metabolik parametreler ölçülerek kaydedildi.
Bulgular: Tip 2 diyabetes mellitus hasta grubunun serum irisin ortalaması prediabetik hastalara ve kontrol grubuna göre istatistiksel olarak anlamlı yüksekti (p=0,015 p<0,001). Prediyabetik hastaların irisin ortalaması kontrol grubuna göre daha yüksekti, ancak bu iki grup arasında istatiksel olarak anlamlı fark saptanmadı. İrisin düzeyi ile plazma açlık glukozu, HbA1c, total kolesterol, LDL, TG ile pozitif yönde HDL ile negatif yönde istatistiksel olarak anlamlı ilişkili saptandı.
Sonuç: Bizim çalışmamız irisinin Tip 2 DM hastalarında artan insülin rezistansına kompansatuvar cevap olarak glukoz metabolizmasını düzenleyici şekilde artış gösterdiğini desteklemektedir. Çalışmamızda yer alan insülin direncine sahip prediyabetik hastalarda irisin ortalaması düzeyi kontrol grubuna göre yüksekti ancak istatiksel olarak iki grup arasında anlamlı fark saptanmadı. İrisinin insülin direnci üzerine olumlu sonuçları olduğu düşünülmekle birlikte etkisinin daha belirgin olarak anlaşılabilmesi için daha geniş ve daha farklı değişkenlerin göz önüne alındığı çalışmalara ihtiyaç vardır.

Anahtar Kelimeler: İrisin, prediyabet, tip 2 diyabetes mellitus

Abstract

Aim: Irisin molecule is in the group of myokins, it is released from muscle cells and a messenger between muscle and fat tissue. It is shown that irisin peptide has an important role in insulin resistance, glucose and energy metabolism. In our study we aimed to show irisin molecule's relationship with glucose metabolism.
Patients and Methods: The study included 29 newly diagnosed type 2 diabetes mellitus patients, 41 newly diagnosed prediabetes patients and 28 healthy control groups who applied to the Internal Medicine Outpatient Clinic between April 2017 and September 2017. Serum irisin levels, laboratory findings and metabolic parameters were measured and recorded.
Results: The mean plasma irisin level of the type 2 diabetes mellitus patient group was statistically significantly higher than the prediabetic patients and the control group (p=0.015 p<0.001). Although the mean plasma irisin level of prediabetic patients was higher than the control group, no significant difference was found. A statistically significant correlation was found between plasma irisin level and plasma fasting glucose, HbA1c, total cholesterol, LDL, TG in a positive way and HDL in a negative way.
Conclusion: Our study supports that plasma irisin increases in a compensatory response to the increased insulin resistance in Type 2 DM patients in a way that regulates glucose metabolism. Although in our study the mean irisin level in prediabetic patients was higher than the control group, no statistically significant difference was found between the two groups. Even tough irisin is thought to have positive results on insulin resistance, studies that larger and consider more different variables are needed in order to understand its effect more clearly.

Key words: Irisin, prediabetes, type 2 diabetes mellitus

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INTRODUCTION

Diabetes mellitus (DM) is a chronic metabolic disorder that results from defects in insulin secretion, effect, or both, and clinically progresses with hyperglycemia. Conditions, where plasma glucose values are higher than normal limits but do not reach the diagnostic limits of diabetes, are called prediabetes (1). The rate of diabetes development in prediabetic patients is stated to be 74% in some publications. (2). In recent studies, it has been determined that hormone-like molecules are released from muscle cells. These molecules are called myokines. The most known of these myokines are IL-6 (interleukin-6), leukemia inhibitory factor (LIF), IL-8 (interleukin-8), IL-15 (interleukin-15), and irisin (3, 4, 5). It has been shown that irisin, which is in the myokine group, is released into the blood as a hormone from the muscle cell with the activation of the fibronectin type III domain containing 5 (FNDC5) gene in case of increased expression of PGC (peroxisome proliferator-activated receptor-gamma coactivator)-1alpha in the muscle cell as a result of exercise (3). There are also studies showing that irisin is released from adipose tissue, which shows that iris may also be an adipokine (6, 7). It has been shown that irisin hormone, which is released from muscle cells, is in the myokine group, and acts as a messenger between muscle and adipose tissue play an active role in insulin resistance, regulation of glucose, and energy metabolism (3, 8). Although many studies have been done on irisin and glucose metabolism before, conflicting results have been obtained (9-11). Newly diagnosed type 2 DM patients, newly diagnosed prediabetic patients and healthy adults as the control group were included in our study. Irisin levels were checked. It was aimed to elucidate the relationship between the irisin molecule and glucose metabolism.

PATIENTS AND METHODS

Approval was obtained for the study with the decision numbered 473 of the ethics committee of non-drug clinical studies on 05.04.2017. Our study is a cross-sectional study and included newly diagnosed type 2 diabetes patients, prediabetes patients who did not use any antidiabetic medication, and as a control group healthy adults who applied to our Internal Diseases Polyclinic between April 2017 and September 2017.

Written informed consent was obtained from all patients eligible for the study seen in the outpatient clinic, and their demographic data such as age and gender were recorded. ADA (American Diabetes Association) criteria for the diagnosis of diabetes mellitus (FPG≥126 mg/dl or plasma glucose value at any time of the day>200 mg/dl or second-hour plasma glucose value in OGTT >200 mg/dl or HbA1c ≥%6,5) was taken as the basis. Type 1 diabetics were not included in the study. ADA criteria (FPG: 100-125 mg/dl and/or second-hour plasma glucose value in OGTT: 140-199 mg/dl and/or HbA1c: 5.7-6.4%) were used for the diagnosis of prediabetes (12).

The height and weight values of all patients were recorded. Body mass indexes (BMI) were calculated using the formula [BMI= Weight (kg) / (height)2 (m)]. Fasting plasma glucose and insulin values of prediabetic and type 2 diabetic patients were evaluated. HOMA-IR values of the patients were calculated using the formula (HOMA-IR=Fasting Glucose(mg/dl) X Fasting Insulin(uIU/ml)/405). GFR (glomerular filtration rate) values were calculated using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) formula.

Patients under the age of 18, over the age of 75, with chronic renal failure (GFR: <60 ml/min), with a diagnosis of malignancy, with chronic liver disease, with a diagnosis of acute coronary syndrome, with a diagnosis of autoimmune disease and pregnant patients were not included. While determining the exclusion criteria, conditions that would be effective in terms of results from previous irisin studies were taken into consideration.

Samples were taken from venous blood and placed in tubes containing potassium EDTA for irisin. The samples taken were centrifuged at 1000xg speed for 10 minutes within half an hour and stored at -80°C. Serum irisin level was measured in all study patients by ELISA method (ELABSCIENCE E-EL-H2254 Fibronectin type III domain-containing protein 5 ELISA kit [irisin]).

Plasma fasting glucose (PAG), insulin, HOMA-IR, glycosylated hemoglobin (HbA1c), urea, creatinine, total cholesterol, HDL-cholesterol, LDL-cholesterol, VLDL-cholesterol, triglyceride, aspartate transaminase (AST), and alanine transaminase (ALT) were measured and recorded in the prediabetic and type 2 diabetes patient group after eight hours of fasting. PAG, urea, creatinine, total cholesterol, HDL-cholesterol, LDL-cholesterol, VLDL-cholesterol, triglyceride, aspartate transaminase (AST), and alanine transaminase (ALT) were measured in the healthy control group after eight hours of fasting. Analysis of blood samples was done in the biochemistry laboratory of our hospital.

Statistical analysis

SPSS 15.0 for Windows program was used for statistical analysis. Descriptive statistics; numbers and percentages for categorical variables; mean, standard deviation, minimum and maximum for numerical variables were given. Comparisons of numerical variables in independent groups were made with the One Way ANOVA test when the normal distribution condition was provided, and with the Kruskal Wallis test when the normal distribution condition was not provided. The rates in the groups were compared with the Chi-Square Test. The relationships between numerical variables were studied by Spearman Correlation Analysis since the parametric test condition was not provided. Risk factors likely to affect serum irisin levels were analyzed by linear regression analysis. Statistical alpha significance level was accepted as p<0.05.

RESULTS

41 Prediabetic (41.83%) patients (9 female patients, 32 male patients), 29 (29.59%) patients (16 female patients, 13 male patients) with type 2 DM, and as the healthy control group 28 (%28,57) people (8 women, 20 men) totally 98 people who met the inclusion criteria of our study were included. The data of the patients who participated in the study and control groups are shown in Table 1. A statistically significant difference was found in the gender ratios of the groups (p=0.012). The female sex ratio of Type 2 DM patients was higher than the prediabetic and control groups (Type 2 DM vs. Prediabetes p=0.004 Type 2 DM vs. control p=0.042); also a statistically significant difference was not found between the prediabetic group and control group (prediabetes vs. control p=0.531). There was a statistical difference in the mean age, BMI, and PAG of the groups (p<0.001 for all). No statistically significant difference was found between mean insulin levels of type 2 DM and prediabetic patients (p=0.206). Homa IR and HbA1c averages of type 2 DM patients were statistically significantly higher than the prediabetic patients (p<0.001 for both). There was a statistically significant difference in the mean of T. cholesterol, HDL, LDL, TG, irisin of the groups (T. cholesterol p=0.001 for all others, p<0.001); (Table-1).

The mean age and BMI of type 2 DM and prediabetic patients were statistically significantly higher than the control group (p<0.001 p=0.001 p<0.001 p<0.001). There was no statistically significant difference between the mean age and BMI of type 2 DM and prediabetic patients (p=0.085 p=0.202). The mean PAG of type 2 DM patients was significantly higher than the prediabetes and control groups (p <0.001). The mean PAG of the prediabetic patients was significantly higher than the control group (p< 0.001); (Table-1).

The mean total cholesterol of prediabetic patients was statistically significantly higher than the control group (p<0.001). No statistically significant difference was found in the mean total cholesterol levels of type 2 DM patients compared to the prediabetic and control groups (p=0.300 p=0.058). The mean HDL in type 2 DM patients was statistically significantly

Table 1. Clinical, laboratory and demographic characteristics of the patients

Type 2 DM	Prediabetes	Control						
		n	%	n	%	n	%	P
Gender	Male	13	44,8	32	78,0	20	71,4	0,012
	Female	16	55,2	9	22,0	8	28,6	
		Mean.±SD	Min-Maks	Mean.±SD	Min-Maks	Mean.±SD	Min-Maks	P
Age		51,7±8,5[a]	32-63	48,7±7,6[a]	35-64	37,6±12,9[b]	22-62	<0,001
BMI (kg/m^2)		32,8±6,3[a]	19,4-45,8	31,1±5,5[a]	20,4-48,4	26,5±3,4[b]	19,9-33,5	<0,001
PFG (mg/dl)		187,6±86,3[a]	126-436	112,8±6,4[b]	101-125	89,2±5,8[c]	80-99	<0,001
Insulin (uIU/ml)		15,3±13,4[a]	4,1-67	18,9±53,5[a]	4,1-351			0,206
Homa IR		6,5±4,8[a]	1,8-22,3	5,2±14,5[b]	1,15-95			<0,001
HbA1c (%)		8,5±1,9[a]	6-13,7	5,9±0,4[b]	5-6,4			<0,001
		Mean.±SD	Median	Mean±SD	Median	Mean.±SD	Median	
Total cholesterol (mg/dl)		199,4±38,9[a]	201	214,1±43,8[b]	210	174,4±37,3[a]	185	0,001
HDL (mg/dl)		41,3±9,1[a]	43	49,5±10,6[b]	48	54,9±13,7[b]	57,5	<0,001
LDL (mg/dl)		122,5±29,4[a]	122	136,5±36,6[a]	137	100,6±32,6[b]	98,5	<0,001
TG (mg/dl)		177,5±80,4[a]	168	141,0±64,3[a]	127	95,5±52,7[b]	75,5	<0,001
Irisin (ng/ml)		8,75±3,97[a]	10,07	6,41±3,91[a]	6,77	4,34±2,65[b]	3,56	<0,001

BMI: Body mass index, DM: Diabetes mellitus, PFG: Plasma fasting glucose

lower when compared to the prediabetic and control groups, no statistically significant difference was found when the HDL averages of the prediabetic and control groups were compared (p=0.123). LDL and TG mean of type 2 DM and prediabetic patients were statistically significantly higher than the control group (p=0.040 p<0.001 p<0.001). The mean LDL of type 2 DM patients was statistically indifferent compared to prediabetic patients (p=0.204). The mean TG of type 2 DM patients was statistically indifferent compared to prediabetic patients (Bonferroni corrected p=0.14). The irisin levels of the groups are shown in figure-1. The mean irisin of the type 2 DM patient group was statistically significantly higher than the prediabetic patients and the control group (p=0.015 p<0.001). When the mean irisin of the prediabetic patients was compared with the control group, no statistically significant difference was found (Bonferroni corrected p=0.123); (Table-1).

In the entire study group, irisin level was found to be significantly positively correlated with age, HbA1c, Total Cholesterol, LDL, TG, and significantly negatively correlated with HDL. A statistically significant positive correlation was found between irisin and PAG levels in diabetic and prediabetic patients; (Table-2).

In the linear regression analysis, which included gender, age, BMI, Homa-IR, HbA1c, HDL, LDL, TG variables as possible risk factors to affect serum irisin level, none of these factors were detected as independent risk factors for serum irisin level.

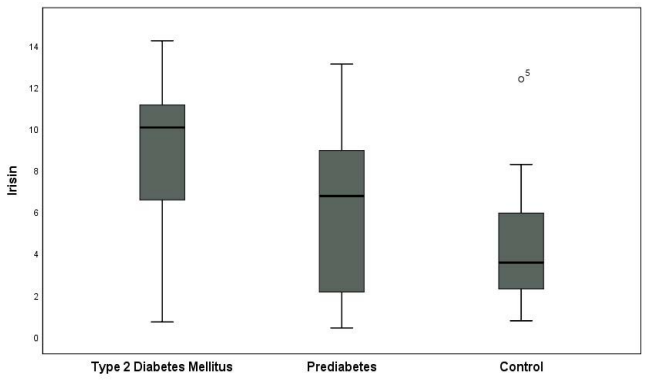

Figure 1. Serum irisin levels of the groups.

Table 2. Correlation analysis results

	Irisin	
	rho	**P**
Age	0,253	0,012
BMI (kg/m^2)	0,155	0,127
HbA1c (%)	0,316	0,008
Total cholesterol (mg/dl)	0,243	0,016
HDL (mg/dl)	-0,270	0,007
LDL (mg/dl)	0,249	0,014
TG (mg/dl)	0,210	0,038
PFG (mg/dl)	0,455	<0,001
Insulin (uIU/ml)	0,026	0,831
Homa IR	0,207	0,085

BMI: Body mass index, PFG: Plasma fasting glucose

DISCUSSION

In our study, the mean serum irisin levels of the newly diagnosed type 2 DM patient group were statistically significantly higher when compared to the newly diagnosed prediabetic patients and the control group. The mean irisin of the prediabetic patients was higher than the control group, but no statistically significant difference was found between these two groups.

It has been shown that the irisin hormone plays an active role in insulin resistance and regulation of glucose and energy metabolism (3, 8). Recent mouse studies have shown that irisin supports the survival of pancreatic β-cells by protecting them from apoptosis, inducing insulin synthesis and secretion, and improving insulin sensitivity (13, 14).

Some studies have shown that irisin affects glucose homeostasis by increasing the expression of Glucose transporter-4 (GLUT-4) and mitochondrial biogenesis. (15,16). Many clinical studies have been conducted to examine the relationship of irisin with glucose metabolism, insulin resistance, and type 2 diabetes; but conflicting results have been obtained. Choi et al. (9) found that the plasma irisin levels of newly diagnosed type 2 DM patients were lower than the control group with normal glucose tolerance, and there was a negative correlation between HbA1c and plasma glucose levels with irisin. In a study conducted by Duran et al. (17) on women in 2015 in our country, plasma irisin levels of prediabetic patients with impaired fasting glucose + impaired glucose tolerance and patients with type 2 DM were found to be significantly lower when compared with the control group with normal glucose tolerance, and It has been suggested that the irisin gradually decreases with the progression of glucose intolerance and type 2 DM. In a study by Mostafa et al. (18), serum irisin levels

were found to be lower in newly diagnosed type 2 DM patients compared to the healthy control group. However, some studies have reported contradictory results regarding irisin. In the study of Rana et al. (10), plasma irisin levels in type 2 DM patients were found to be significantly higher than in the healthy control group A positive correlation was found between BMI and HbA1c values and irisin. In the study of Garcia et al. (19), plasma irisin levels of type 2 DM patients were found to be higher than the non-diabetic control group, and it was stated that there was a positive correlation between plasma irisin level and plasma fasting glucose. In a study by AlKhairi et al. (20), serum irisin levels were found to be higher in type 2 DM patients compared to the healthy control group. In the prospective cohort study conducted by Huh et al. (21) increased risk of developing type 2 DM was found in people with high irisin levels in a 2.6-year follow-up. A positive correlation was found between irisin level with HbA1c and plasma postprandial glucose. In a study by He et al. (22), it was shown that the risk of developing type 2 DM increased in prediabetic patients with high serum irisin levels in a 3-year follow-up. In our study, it was determined that irisin level was positively correlated with glucose, HbA1c, T. Cholesterol, LDL, TG and negatively correlated with HDL. In a recent study, it has been shown that in cases where oxidative stress, inflammation, and free fatty acids are increased such as DM, obesity, metabolic syndrome, the stimulation of PGC1-α in the muscle stimulates the increase of irisin level and stimulates the release of UCp1 from brown adipose tissue and reducing insulin resistance (8). In our study, it supports the fact that irisin increases in a compensatory response to increased insulin resistance in Type 2 DM patients in a way that regulates glucose metabolism.

In our study, no statistically significant relationship was found between irisin and BMI. There are conflicting results regarding the relationship between irisin and BMI. In some studies, irisin was positively correlated with BMI (23), and in some studies, irisin was negatively correlated with BMI (24). As in our study, there are also studies showing that the iris is unrelated to BMI (25).

There were some limitations in our study. Firstly, since it was a cross-sectional study, prospective metabolic status and irisin levels of the patients could not be followed up. Secondly, the number of our patients was limited. Third, the exercise status of the patients was unknown, so it was not possible to comment on whether irisin levels were affected by this situation.

In conclusion, the realization that irisin is released from the muscles as a result of exercise and turns white fat cells into brown fat cells has led to new hopes in metabolic diseases as a new molecule. However, due to the contradictory results of the studies, it has not yet taken its place in diagnosis or treatment. Our study supports that irisin regulates glucose metabolism as a compensatory response to increased insulin resistance in Type 2 DM patients. Although irisin is thought to have positive results on insulin resistance, studies that take into account wider and different variables are needed to understand its effect more clearly and to use it in diagnosis and treatment.

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Address correspondence to: *Ahmet Yavuz, Necmettin Erbakan University, Meram Faculty of Medicine, Department of Gastroenterology, Konya, Turkey*
e-mail: *ahmedyvz133@hotmail.com*

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