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Original Article

The association between serum irisin levels and cardiovascular disease in diabetic patients

Zahra Mazloum Khorasani [a], Ramin Khameneh Bagheri [b], Mohammad Ali Yaghoubi [a, c], Saeed Chobkar [d, *], Monavvar Afzal Aghaee [e], Mohammad Reza Abbaszadegan [f], Amirhossein Sahebkar [g, h, i]

[a] Metabolic Syndrome Research Center, Mashhad University of Medical Sciences, Mashhad, Iran
[b] Department of Cardiology, School of Medicine, Mashhad University of Medical Sciences, Mashhad, Iran
[c] Birjand University of Medical Sciences, Birjand, Iran
[d] School of Medicine, Mashhad University of Medical Sciences, Mashhad, Iran
[e] Department of Social Medicine, School of Medicine, Mashhad University of Medical Sciences, Mashhad, Iran
[f] Department of Genetics, School of Medicine, Mashhad University of Medical Sciences, Mashhad, Iran
[g] Neurogenic Inflammation Research Center, Mashhad University of Medical Sciences, Mashhad, Iran
[h] Biotechnology Research Center, Pharmaceutical Technology Institute, Mashhad University of Medical Sciences, Mashhad, Iran
[i] School of Pharmacy, Mashhad University of Medical Sciences, Mashhad, Iran

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ABSTRACT

Background: Cardiovascular disease is the most common cause of mortality and morbidity in diabetic patients. Insulin resistance has been shown to be reduced by the secretion of irisin from muscle and adipose tissues. This study was aimed at determining the relationship between serum irisin levels and angiographically defined coronary artery disease (CAD) in type II diabetic patients.
Methods: In this case-control study, 30 diabetic subjects with angiographically defined CAD were compared with 30 age- and sex-matched diabetic subjects without CAD in terms of clinical and laboratory parameters including serum irisin levels.
Results: Serum levels of Irisin were significantly higher in the diabetic group without CAD compared with the group with CAD ($P = 0.048$). Serum irisin levels showed a significant positive correlation with BMI ($r = 0.374$, $P = 0.004$) and fasting insulin ($r = 0.303$, $P = 0.021$), and a significant negative correlation with diabetes duration ($r = -0.384$, $P = 0.002$). Based on the results of the binary logistic regression model, circulating levels of irisin were associated with the presence of CAD in diabetes ($p = 0.038$) after adjusting for potential confounders.
Conclusion: Serum irisin levels were lower in the diabetic patients with cardiovascular complication compared with the uncomplicated diabetic patients. Therefore, additional larger scale studies are needed to determine the role of irisin in monitoring CAD in diabetic patients.

1. Introduction

Cardiovascular disease (CVD) is the leasing cause of mortality and morbidity in diabetic patients [1]. Diabetes increases the risk of CVD by 1.5–2 times in men and 2 to 3 times in women, and elevates the risk of atherosclerotic disease by 2–3 folds in diabetic compared with non-diabetic subjects [2]. Diabetes is closely linked to insulin resistance, which is likewise associated with the risk of CVD development beginning at the pre-diabetes stage [2]. Accordingly, hyperinsulinemia is considered as a plausible link between hyperglycemia and CVD [2]. Cardiovascular involvement in diabetes can also be triggered by endothelial dysfunction which is the first pathological event in vascular injury characterized by reduced nitric oxide production [3].

In the last decade, muscle and adipose tissues have been identified as regulators of endocrine metabolism in the body [4]. The skeletal muscle is an endocrine organ that secretes a number of myokines including follistatin, myostatin, activin A and irisin,

* Corresponding author. School of Medicine, Mashhad University of Medical Sciences, Mashhad 9177948564, Iran.
E-mail address: chobkar.saeed@gmail.com (S. Chobkar).

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which appear to play a vital role in coordinating the activity and metabolism of other endocrine organs [5]. Many biological processes related to energy metabolism are regulated by peroxisome proliferator-activated receptor-γ coactivator 1α, which also stimulates several muscle gene products such as fibronectin type III domain-containing protein 5 (FNDC5) [6]. FNDC5 is released into the circulation after exercise and produces a derivative called irisin [6]. Irisin is a polypeptide hormone containing 112 amino acids secreted from muscle and adipose tissues into the bloodstream. It converts white adipocytes into brown adipocytes and reduces insulin resistance both *in vitro* and *in vivo* [3,6]. Increasing thermogenesis is a suggested mechanism through which irisin can improve insulin sensitivity and reduce blood glucose level and body weight [6,7].

In a sedentary lifestyle, serum irisin levels are associated with the parameters of cardiometabolic risk such as insulin level, body mass index (BMI), and the homeostasis model assessment of insulin resistance (HOMA-IR) [8]. Insulin resistance can result in micro- and macroangiopathy, peripheral arterial disease, vascular dysfunction, hypertension, and endothelial cell and cardiomyocyte dysfunction; these conditions ultimately lead to an increased risk of coronary artery occlusion, heart attacks, and heart failure, indicating a direct relationship between insulin resistance and coronary artery disease [8]. A positive relationship has also been suggested to exist between plasma irisin levels and BMI. Irisin is a physiological protective factor against obesity, and its increase improves body weight gain. In obese individuals, physiological irisin is unable to maintain a balance between stored and consumed energy, thus driving skeletal muscle and adipose tissues to secrete irisin for the purpose of modifying stored fat [9]. Finding new methods for early diagnosis of metabolic syndrome and diabetes can be helpful in preventing and timely treatment of their complications especially cardiovascular events.

Given the above-mentioned properties of irisin, it can be considered as a potential target for monitoring and intervention in people with type II diabetes and cardiovascular complications [10]. It may also be studied as a new target for the treatment of obesity and its comorbidities such as diabetes and non-alcoholic fatty liver disease. Despite this potential, however, many questions remain unanswered as to the benefits of irisin as a treatment target. An important issue in this regard is the role of irisin in metabolic syndrome and its related complications, especially cardiovascular disease [9]. In the present study, we investigated the relationship between serum irisin levels and cardiovascular disease in patients with type II diabetes.

2. Materials and methods

2.1. Study design and setting

This case-control study was conducted on a total of 60 subjects, who were previously or newly diagnosed as having type II diabetes on the basis of the criteria of the American Diabetes Association. The subjects were selected through Simple Sampling from among the diabetic patients referred to diabetes and cardiology clinics of Qaem Hospital and the endocrine clinic of Hazrat Rasoul Hospital in Mashhad. Sampling was conducted from 22 August 2016 to 23 September 2017. To determine the relationship between irisin hormone levels and cardiovascular involvement, the patients were divided into two groups: group A, which comprised 30 diabetic patients who exhibited no symptoms of cardiac involvement and had normal EKG levels and negative exercise tests; and group B, which consisted of 30 diabetic patients with CVD diagnosed through angiography. All the patients were homogenized for age and gender.

2.2. Inclusion and exclusion criteria

The inclusion criteria were people with type II diabetes and an age range of 18–70 years, and the exclusion criteria were patients with end-stage renal failure (glomerular filtration rate < 30 mL/min) or undergoing dialysis, liver failure or active liver disease, evidence of active infection, professional athletes, and engagement in heavy exercise three days prior to the sampling.

This research was approved by the Ethics Committee of Mashhad University of Medical Sciences, and ethical consent was obtained from all the patients before the initiation of the study.

2.3. Data collection

Information on all the patients' baseline demographic characteristics (including age and gender), medical history (including Duration of diabetes), symptoms of cardiovascular involvement (including chest pains or shortness of breath during activity), and physical attributes (including height, weight, waist circumference, systolic and diastolic blood pressure) was first obtained. Then, tests were performed to determine fasting plasma glucose (FPG) and 2-h plasma glucose (2-h PG), serum triglyceride levels, low-density lipoprotein (LDL) and high-density lipoprotein cholesterol, glycated hemoglobin (HbA1c), creatinine, and random urinary albumin excretion (UAE). The fasting insulin levels of the patients who did not receive insulin were measured via quantitative luminescent analysis. These patients' HOMA-IR was also calculated on the basis of the serum levels of fasting glucose and fasting insulin. The formula used in the calculation was as follows: fasting glucose (mg/dL) × fasting insulin (μU/mL)/405.

Blood samples (5 mL) were taken from the patients. Plasma was then separated from the samples and kept at −20 °C for the measurement of irisin levels. After sample collection, irisin level (ng/mL) was measured by enzyme-linked immunosorbent assay using an irisin kit (Crystal Day Biotech Co, Shanghai, China.). The measurements were carried out in the Genetics Laboratory of the School of Medicine at Mashhad University of Medical Sciences.

2.4. Statistical analysis

The normal distribution of quantitative variables was evaluated using the Kolmogorov–Smirnov test. Continuous variables were reported in terms of mean and standard deviation. Median (interquartile range) was also reported in cases with non-normal distribution. Comparisons between groups of normally distributed variables and non-normally distributed variables were performed using the independent-samples *t*-test and Mann–Whitney *U* test, respectively. Categorical variables were reported using the number (%) and the chi-square test was used to compare them between the two groups.

Spearman's correlation coefficient was used to evaluate the correlation between irisin and quantitative variables. Binary logistic regression analysis was conducted to investigate the predictive effect of irisin on cardiovascular involvement in the presence of potential confounding factors.

The role of irisin in predicting cardiovascular involvement in diabetic patients was also analyzed using receiver operating characteristic (ROC) curve and the optimal cutoff was determined using the Youden index. A p-value of less than 0.05 was considered significant. Statistical analysis was performed using the SPSS version 18.

3. Results

In this study, 60 diabetic patients in two groups with and

without CVD were studied (in each group of 30 patients). Mean age of the 60 participants in this study was 56.1 ± 8.6 years. The type of cardiovascular involvement in diabetic patients with CVD was 1-vessel disease (8 (26.7%)), 2-vessel disease (16 (53.3%)) and 3-vessel disease (6 (20.0%)) (Fig. 1). There was no significant difference between the two groups in terms of sex (P = 0.079), age (P = 0.163), BMI (P = 0.519), duration of diabetes (P = 0.828), atorvastatin use (>0.99), and the level of laboratory findings of creatinine (P = 0.591), UAE (P = 0.528), triglyceride (P = 0.228), LDL (P = 0.051), 2-h PG (P = 0.087), Fasting insulin (P = 0.538) and HOMA-IR (P = 0.879). Waist circumference (P = 0.024), FPG (P = 0.043) and HbA1c (P = 0.033) were significantly higher in diabetic patients with CVD than the diabetic patients. HDL levels were significantly higher in diabetic patients than in diabetic patients with CVD (P = 0.002). The levels of irisin were significantly higher in the diabetic group than the group of the diabetic patients with CVD (P = 0.048). The demographic and laboratory findings of the subjects in the study are presented in Table 1.

The relationship between serum irisin levels and demographic and laboratory factors in the 60 diabetic patients was evaluated by using the Spearman's correlation coefficient. Specifically, irisin levels had a significantly positive correlation with BMI (r = 0.374, P = 0.004), fasting insulin (r = 0.303, P = 0.021), and a significantly negative correlation with diabetes duration (r = −0.384, P = 0.002). The Results also indicated serum irisin levels had a negative correlation with age (r = −0.232, P = 0.074) and LDL (r = −0.214, P = 0.100). Results of the Spearman's analysis of the correlation between quantitative variables and Irisin are presented in Table 2.

Sex, waist circumference, LDL-C, HDL-C and FPG were identified as potential confounding factors. The Results of the binary logistic regression analysis with adjusted effects of the confounding factors are presented in Table 3. Base on result of binary logistic regression model, levels of circulating irisin were associated with cardiovascular involvement in diabetes (p = 0.038) after adjustment for the aforementioned confounders.

The receiver operating characteristic (ROC) curve was used to predict cardiovascular involvement in the diabetic patients by using the levels of circulating irisin. The Results indicated an area under the ROC curve of 64.8% (95% confidence interval = 50.7–79.7), an optimal cut-off point of 3.5 ng/mL with a sensitivity of 90%, and a specificity of 53.3% (Fig. 2).

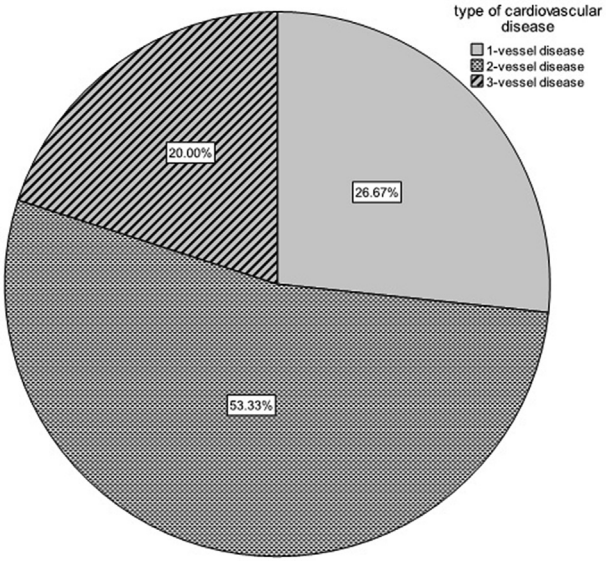

Fig. 1. Type of coronary artery disease in diabetic patients with CVD group.

Table 1
Comparison of demographic and laboratory findings of the diabetic patients with and without CVD.

	Diabetic N = 30	Diabetes with CVD N = 30	P value
Sex (men, %)	9 (30.0%)	13 (43.3%)	0.079
Age (years)	54.5 ± 8.6	57.7 ± 8.6	0.163
Waist circumference (cm)	99.5 ± 7.2	104.8 ± 9.8	0.024
BMI (kg/m2)	29.2 ± 2.6	28.6 ± 3.7	0.519
Duration of diabetes (years)	8.9 ± 9.4	9.4 ± 6.9	0.828
Systolic BP (mmHg)	122.8 ± 10.5	125.5 ± 16.9	0.649
	120 (10.0)	122.5 (30.0)	
Diastolic BP (mmHg)	76.5 ± 7.3	77.9 ± 8.4	0.551
	80 (10.0)	80 (15.0)	
Cr (mg/dL)	1.1 ± 0.1	1.2 ± 0.2	0.591
UAE	36.1 ± 54.9	51.4 ± 95.3	0.517
	21.0 (23.8)	15.9 (25.6)	
Triglycerides (mg/dL)	163.5 ± 69.3	142.0 ± 67.7	0.228
LDL (mg/dL)	99.6 ± 22.4	86.8 ± 27.3	0.051
HDL (mg/dL)	45.5 ± 10.1	36.9 ± 9.7	0.002
Atorvastatin use (yes, %)	21 (70.0%)	21 (70.0%)	>0.99
FPG (mg/dL)	150.8 ± 36.5	176.7 ± 58.0	0.043
2-h PG (mg/dL)	217.7 ± 72.0	252.0 ± 57.2	0.087
HbA1C (%)	7.0 ± 1.5	7.8 ± 1.05	0.033
Fasting insulin (mU/L)	13.8 ± 9.0	12.1 ± 11.4	0.538
HOMA-IR	5.3 ± 3.9	5.1 ± 4.8	0.879
Irisin (ng/mL)	8.0 ± 6.6	5.4 ± 5.0	0.048
	5.5 (5.3)	3.7 (4.1)	

Data are n (%) or Mean ± SD or Medians (interquartile ranges).
BMI: Body mass index, BP: Blood pressure, Cr: Creatinine, UAE: Urinary albumin excretion, LDL: Low-density lipoprotein, HDL: High-density lipoproteins, FPG: Fasting plasma glucose, 2-h PG: 2-h plasma glucose, HbA1c: Hemoglobin A1c, HOMA-IR: Homeostasis model assessment of insulin resistance.

Table 2
Analysis of the correlation between quantitative variables and Irisin.

Variables	Correlation Coefficients	P-Value
Age (years)	−0.232	0.074
Waist Circumference (cm)	0.103	0.441
BMI (kg/m^2)	0.374	0.004
Duration of diabetes (years)	−0.384	0.002
Systolic BP (mmHg)	−0.085	0.519
Diastolic BP (mmHg)	−0.118	0.370
Cr (MG/DL)	−0.042	0.751
UAE	−0.093	0.494
Triglycerides (mg/dL)	−0.093	0.478
LDL (mg/dL)	−0.214	0.100
HDL (mg/dL)	−0.019	0.883
FPG (mg/dL)	−0.145	0.270
2-h PG (mg/dL)	−0.146	0.338
HbA1c (%)	−0.153	0.244
Fasting insulin (mU/L)	0.303	0.021
HOMA-IR	0.165	0.215

BMI: Body mass index, BP: Blood pressure, Cr: Creatinine, UAE: Urinary albumin excretion, LDL: Low-density lipoprotein, HDL: High-density lipoproteins, FPG: Fasting plasma glucose, 2-h PG: 2-h plasma glucose, HbA1c: Hemoglobin A1c, HOMA-IR: Homeostasis model assessment of insulin resistance.

4. Discussion

In our study, the level of irisin was significantly higher in the diabetic group without CAD compared with the group of the diabetic patients with CAD. Until now, the association between irisin and various diseases, including diabetes [11,12], obesity [13], and cardiovascular diseases [14–17] has been reported. Based on the previous studies, irisin has been significantly lower in diabetic and myocardial infarction patients compared with controls [12,14–20]. Our study is the first designed to investigate the association between circulating irisin levels and CAD in diabetic patients.

Irisin is a newly discovered myokine that is cleaved and secreted

Table 3
Results of univariate and multivariate logistic regression on the relationship between irisin and cardiovascular involvement in diabetes.

	Univariate		Multivariate	
	P value	OR (95%CI)	*P* value	Adjusted OR (95%CI)
Sex	0.966	0.968 (0.210–4.466)	0.194	1.052 (0.974–1.136)
Waist circumference (cm)	0.029	1.108 (1.011–1.215)	0.457	1.082 (0.879–1.331)
LDL-C (mg/dL)	0.574	0.991 (0.960–1.023)	0.931	0.997 (0.929–1.069)
HDL-C (mg/dL)	0.012	0.896 (0.822–0.976)	0.018	0.969 (0.945–0.995)
FPG (mg/dL)	0.064	1.014 (0.999–1.030)	0.243	0.964 (0.906–1.025)
Irisin (ng/mL)	0.038	0.869 (0.761–0.993)	0.127	0.912 (0.811–1.026)

BMI: Body mass index, LDL: Low-density lipoprotein.

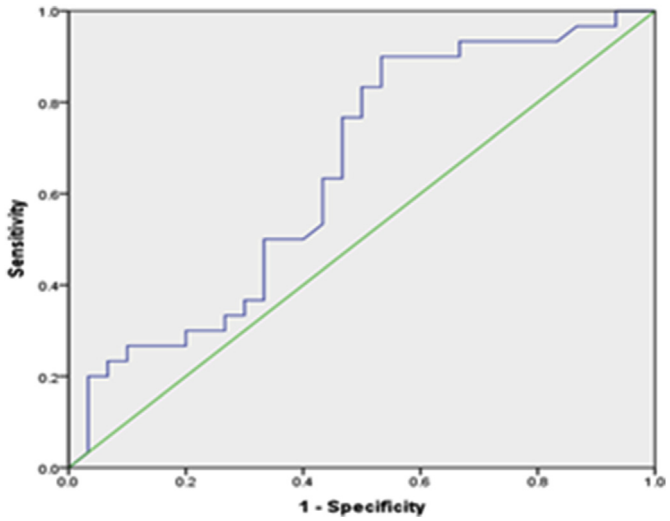

Fig. 2. ROC curve of irisin's predictive effect on cardiovascular involvement in diabetes.

fragment of FNDC5 and can be released into circulation [17,21]. Irisin has a potential effect in converting brown adipose tissue into white adipose tissue by stimulating the expression of thermogenic genes including uncoupling protein 1 [6,7].

Studies that have been done to compare the levels of circulating irisin with the control group have shown a protective effect of irisin against the development of cardiovascular diseases [14–17]. Several potential mechanisms have been proposed for this issue. Irisin plays a key role in the preservation of endothelial cell function, and the low levels of the irisin lead to endothelial dysfunction and increase the incidence of atherosclerosis [21,22]. In addition, irisin reduces endothelial damage by inhibiting inflammation and oxidative stress [23,24]. Hyperhomocysteinemia (which increases the risk of heart disease) has an inverse correlation with the irisin levels [25]. The levels of circulating irisin can be a marker of cardiac muscle damage that increases in the patients with myocardial lesions [26]. Also, lower circulating irisin levels can increase the accumulation of AGEs (one of the causes of vascular complications in diabetic patients) [22]. In previous studies, serum levels of irisin were reported to be inversely correlated with the BMI of the humans [24,27]. Also, irisin plays an important role in lipid metabolism and decreased irisin levels can lead to hyperlipidemia in coronary artery disease patients [24]. Despite all of the above, the function and mechanism of irisin in cardiovascular disease are not fully understood.

In the studies conducted thus far, no cut-off point was reported for serum irsisin to predict cardiovascular involvement in diabetic subjects. As previously stated, the current research determined a cut-off point of 3.5 ng/mL with a sensitivity and specificity of 90% and 53.3%, respectively. Based on the ROC model, 64.8% accuracy was calculated for serum levels of irisin in the identification of the diabetic patients with cardiovascular involvement.

The Results of the study by Tang et al. Indicated that irisin inhibited the synthesis of liver cholesterol by AMPK-SREBP2 signaling mechanisms [28]. 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase is a rate-limiting enzyme in cholesterol synthesis that is regulated by AMPK [12]. HMG-CoA reductase inhibitors such as atorvastatin reduce the synthesis of cholesterol in the liver and also increase the expression of LDL receptors on the membrane of hepatocytes and stimulate LDL catabolism [29]. In our study, 70% of patients in both groups used atorvastatin, though higher doses of atorvastatin were used in the iabetic group having CAD. This could have affected the irisin levels and is a limitations of our study. Among other limitations, the relatively small population size should be considered. In addition, in our study, the mechanisms involved in the relationship between the levels of irisin and cardiovascular involvement in diabetic patients were not investigated. As another limitation, the design of our study precluded assessment of the association between serum irisin levels and hard outcomes in CAD patients. Nevertheless, our study had several strengths, including being the first to investigate the association between circulating irisin levels and cardiovascular involvement in diabetic patients. Moreover, diabetic patients in the two groups of patients with and without cardiovascular involvement in this study were similar in terms of sex, age, BMI, duration of the disease. Finally, the laboratory personnel were blind to the hypothesis and aim of the study.

5. Conclusion

To sum up, serum irisin levels were significantly lower in the diabetic patients with CAD compared with the uncomplicated diabetic patients. In the diabetic patients, serum irisin levels increased with increasing BMI and dropped with increasing duration of diabetes and patient's age. Our Results also indicated that serum irisin levels were positively related to serum insulin levels and negatively associated with LDL-C in diabetic patients. Further studies are required to clarify if serum irisin levels are also affected in acute coronary events and if altered levels of irisin could be of predictive value for hard coronary outcomes. The potential value of irisin as a treatment target is also another open question that merits further investigations.

Conflicts of interest

None.

Acknowledgments

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