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Original Article

Relationship between serum irisin levels and renal function in patients with type 2 diabetes mellitus

Robab Aboutorabi (MD) [1#]
Golrokh Hariri (MD) [1, 2 #]
Zahra Mazloum Khorasani (MD)[1]
Hassan Mehrad-Majd (PhD) [3*]

1. Metabolic Syndrome Research Center, Mashhad University of Medical Sciences, Mashhad, Iran
2. Department of Internal Medicine, School of Medicine, Neyshabur University of Medical Sciences, Neyshabur, Iran
3. Cancer Molecular Pathology Research Center, Mashhad University of Medical Sciences, Mashhad, Iran

*** Correspondence:**
Hassan Mehrad-Majd, Clinical Research Development Unit, Ghaem Hospital, Faculty of Medicine, Mashhad University of Medical Sciences, P.O. Box: 9176699199, Mashhad, Iran

#These two authors contributed equally in this work.

E-mail:
Mehradmajd.h@gmail.com,
Mehradmajdh@mums.ac.ir
Tel: +98 511 8828574

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Abstract

Background: Irisin, a myokine implicated in metabolic hemostasis, have been investigated in relation to type 2 diabetes mellitus (T2DM), yet findings on its serum levels and association with diabetic complications such as nephropathy remain inconsistent. This study aimed to assess the relationship between serum irisin levels and renal function in T2DM patients.

Methods: A cross-sectional study was conducted involving 140 individuals diagnosed with T2DM. Demographic, anthropometric, and clinical data were recorded. Fasting blood samples were collected to determine serum irisin levels using the ELISA method. Additional biochemical measurements included fasting blood glucose, creatinine, HDL, LDL, triglycerides, HbA1c, and urinary albumin. Correlations between irisin levels and these parameters were analyzed. Patients were divided into two groups based on glomerular filtration rate (GFR) and albumin-to-creatinine ratio (ACR) to assess associations between irisin levels and renal function.

Results: No statistically significant difference in serum irisin levels was observed between patients with reduced renal function (GFR≤60) and those with GFR>60 (10.45±6.54 vs. 13.32±10.59 ng/ml, P=0.08). In stratified analysis by ACR, patients with nephropathy displayed a non-significantly lower irisin level than those without (11.70±8.18 vs. 13.38±11.51, P=0.33). Serum irisin showed no significant correlations with FBS (P=0.05), insulin (P=0.06), LDL (P=0.96), HDL (P=0.61), or BMI (P=0.42).

Conclusion: Lower irisin levels in T2DM patients with reduced renal function or nephropathy may indicate a potential role for irisin in diabetic renal disease progression. Serum irisin could serve as a prognostic biomarker for diabetic nephropathy pending further validation.

Keywords: Diabetes, Irisin, nephropathy, renal function, GFR, ACR.

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Diabetes is a chronic, metabolic disease characterized by abnormal glucose homeostasis, impaired lipid and protein metabolism (1). The chronic hyperglycemia in diabetic patients predisposes them to long-term complications such as cardiovascular disease, nerve damage, diabetic retinopathy, diabetic foot/lower limb amputation, diabetic nephropathy/kidney failure, and etc. (2, 3). Among these, diabetic nephropathy stands out as a common complication of T2DM and is the primary reason for end-stage renal disease (ESRD) (4). Early detection of diabetic nephropathy provides a unique opportunity for appropriate interventions to prevent or reduce further adverse outcomes. Diabetic nephropathy is routinely diagnosed by measuring the rates of albumin excretion (AER) and glomerular filtration (GFR). Although these two criteria are widely being used for detection and staging of nephropathy in diabetic patients, they have some limitations in accuracy (5).

Some patients with lack of albuminuria have been reported with some degrees of renal nephropathy, while some other cases with microalbuminuria have shown normal renal function. To overcome the incompatibility of conventional markers, ongoing efforts have been focused on the identification and potential application of novel biomarkers for the early detection and management of diabetic nephropathy (6). A growing body of evidence have reported various inflammatory, metabolic and/or oxidative biomarkers originated from urine or serum may be more accurate for evaluating the renal function in diabetic patients (7).

Among these metabolic factors, irisin as a novel polypeptide hormone secreted from muscle and adipose tissue, has been shown to be involved in energy homeostasis and insulin sensitivity (8). Animal interventional studies have reported a potential role for irisin in preventing obesity and diabetes in animal models (9, 10). Data regarding the serum irisin levels in T2DM patients are controversial. Some previous studies have reported elevated levels of irisin in T2DM patients than those in healthy controls (11-13) while, in other studies a significant reduction has been reported (14, 15). Although, many studies have well-established the altered levels of irisin in diabetes, few studies have assessed the relationship of serum irisin levels and nephropathy in patients with T2DM (13). In view of the above conditions, this study was conducted to compare the irisin concentration in T2DM patients with normal and abnormal renal function and also to explore the potential prognostic value of irisin in diabetic nephropathy.

Methods

Subjects: In this cross-sectional study conducted from 2018 to 2020, we enrolled 140 T2DM patients aged between 25 and 65 years, comprising 55 males and 85 females, from the endocrinology clinics of Mashhad University of Medical Sciences. All patients were diagnosed according to the American Diabetic Association criteria, which includes fasting plasma glucose (FBS) levels ≥126 mg/dL, HbA1c levels ≥6.5%, or random plasma glucose levels ≥200 mg/dL in a patients exhibiting symptoms of hyperglycemia (16). Patients with acute renal failure not caused by diabetes, end-stage renal disease, liver disease, a history of polycystic kidney disease, evidence of active infection and sepsis, as well as professional athletes and patients who have done heavy exercise during the 9 days before sampling were excluded from the study. The research protocol was approved by Research Ethics Committee of Mashhad University of Medical Sciences under the code IR.MUMS.fm.REC.1397.344. Following the signing of the informed consent form, each patient underwent a comprehensive clinical examination and fasting blood sampling. Using an appropriate checklist, all data including demographic characteristics (age, gender, education, occupation), past medical history (the age of diabetes, duration of disease), family history of diabetes, symptoms of cardiovascular disease (chest pain or shortness of breath during activity), and anthropometrics (height, weight, waist, systolic and diastolic blood pressure) were collected from each patient.

Biochemical measurements: A 5 mL venous blood sample was collected from each patient in the morning after fasting for at least 12 h. About 2 mL of whole blood was used to measure the glycosylated hemoglobin (HbA1c) levels using cation-exchange column chromatography on an automatic analyzer. Using centrifugation-based methods, serum was extracted from the rest of the whole blood and stored at −80 °C until analysis. Biochemical parameters including triglyceride (TG), total cholesterol (TC), high-density lipoprotein (HDL), low-density lipoprotein (LDL), serum creatinine and urea were measured according to international standard procedures. Glucose oxidase procedure was applied to measure fasting blood glucose (FBG). About 2 mL of random morning urine sample was used to estimate microalbuminuria by nephalometer.

Insulin levels were measured with a Siemens kit by quantitative luminescence method. Insulin resistance index (HOMA-IR) was calculated based on the following formula; HOMA-IR =INSULIN (μu/ml) × FBS mmol/l/22.5. Serum irisin levels of all patients were quantified in ng/ml by an enzyme-linked immunosorbent assay (ELISA) method based on the manufacturer's instructions (ELISA kit, Shanghai Crystal day Biotech Co., Ltd, China). Estimated glomerular filtration rate (eGFR), as a patient's renal function index, was estimated by MDRD formula, then all patients were categorized into two groups accordingly; 15<eGFR≤60 referred to individuals with reduced renal function and eGFR> 60 as their controls. Subjects were also divided into two groups based on the urine albumin to creatinine ratio (ACR). Accordingly, patients with ACR≥30mg/g were assigned as diabetic nephropathy and those with ACR<30mg/g were defined without nephropathy.

Statistical analysis: All statistical analyses were performed on IBM SPSS Statistics 22 software and a *p*- value less than 0.05 was set as significant level. Quantitative variables were expressed as mean±SD and frequency with percentage were used for qualitative ones. Between-group comparisons were performed using independent student's t test and ANOVA

(for normally distributed variables) or Mann-Whitney test and Kruskal-Wallis (if non-parametric variables) for quantitative variables while chi-square test was used for qualitative variables. Pearson's correlation coefficients were calculated to assess any significant correlation between serum irisin levels and metabolic parameters. Logistic regression was performed to assess the association of irisin with odds of reduced renal function and nephropathy. Receiver operating characteristic (ROC) curve was obtained to explore the area under curve (AUC) and optimum cut-off value for irisin concentration for distinguishing two groups of patients in each stratified model.

Results

Patients characteristics: Demographic, clinical, and laboratory characteristics of 140 T2DM patients stratified by renal function (54 cases with eGFR≤60 and 86 cases with eGFR>60) and diabetic nephropathy (43 cases with ACR≥30mg/g and 97 cases with ACR<30mg/g) are summarized in table 1. Subjects with reduced renal function were significantly older (56.79±6.81 vs. 53.89±8.34 years, P=0.03) and had lower values for waist circumference (99.76±9.8 vs. 102.02±9.82 cm, P=0.02) than their control group.

No significant difference was observed in gender distribution, BMI, weight, height, diabetes duration, and systolic and diastolic blood pressure in both groups. No significant differences were also found for FBS, HbA1c, HDL, LDL, TG, total cholesterol, albumin and insulin (P=0.07) concentration between two groups of patients. However, as expected blood urea (36.40±10.06 vs. 26.74±8.50, P=0.02), and creatinine (1.27±0.25 vs. 0.89±0.19, P=0.001) were significantly higher in patients with reduced renal function. Consistently, when the patients were stratified based on diabetic nephropathy, no significant differences were found in all aforementioned variables between diabetic patients with and without nephropathy.

Serum irisin concentration: The data regarding the serum irisin levels in four study groups of diabetic patients is listed in table 1 and figure 1. Mean irisin level was lower in patients with reduced renal function compared with their controls (10.45±6.54 vs 13.32±10.59 ng/ml). However, this difference was statistically non-significant (P=0.08) (figure 1a). In stratified analysis by nephropathy, diabetic patients with nephropathy showed a non-significant lower irisin level than those without (11.70±8.18 ng/ml vs 13.38±11.51, P=0.33) (figure 1b).

The association of serum irisin concentrations with renal function and diabetic nephropathy: The clinical value of serum irisin level in predicting the renal function and diabetic nephropathy was evaluated using logistic regression analysis both in crude and adjusted models for age and gender variables. The adjusted odds ratios (ORs) with associated 95% confidence intervals (CIs) revealed that serum irisin levels were not significantly associated with the risk of reduced renal function (OR = 1.04, 95% CI = 0.99-1.09, p =0.086), as well as diabetic nephropathy (OR = 1.02, 95% CI = 0.98-1.06, P =0.297).

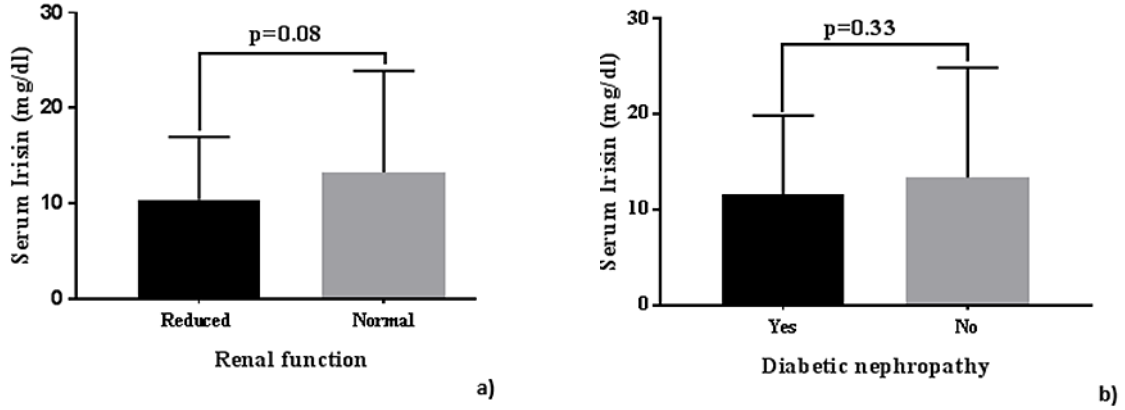

Figure 1. Serum irisin levels in diabetic patients; a) with and without reduced renal failure, and b) with and without nephropathy

Correlation between serum irisin levels and clinical parameters in diabetic patients: The data regarding the correlation analysis between serum Irisin levels and various demographic, metabolic parameters, as well as different indices of diabetic nephropathy such as age, BMI, insulin, duration of diabetes, albuminuria, HOMA-IR, creatinine, TG, TC, urea, HDL, LDL, HbA1c, FBS, systolic and diastolic blood pressure and GFR are summarized in table 2. As shown, no significant correlation was observed between serum irisin levels and all above mentioned variables (p>0.05).

ROC analyses of irisin levels: To assess whether irisin levels could be serve as a novel biomarker for distinguishing diabetic patients with reduced renal function/nephropathy form those without, a ROC analysis was performed.

The ROC analysis results revealed no evidence of significant predictive value of irisin levels for reduced renal function or diabetic nephropathy (AUC=0.568, 95% CI=0.47-0.68, P=0.173 & AUC=0.531, 95% CI=0.43-0.64, P=0.565 respectively).

Table 1. Demographic, clinical, and laboratory characteristics of T2DM patients stratified based on eGFR and ACR values.

Variables		Reduced renal function		P-value	Diabetic nephropathy		P-value
		Yes (n=54) (GFR≤60)	No (n=86) (GFR>60)		Yes (n=43) ACR≥30mg/g	No (n=97) ACR<30mg/g	
Gender*	Male	19 (35.2)	36 (41.9)	0.43	15 (34.9)	40 (41.2)	0.48
	Female	35 (64.8)	50 (58.1)		28 (65.1)	57 (58.8)	
Age (years)**		56.79±6.81	53.89±8.34	0.03	55.33±7.16	54.87±8.23	0.75
BMI (kg/m²)**		28.57±4.57	28.87±4.02	0.69	28.52±3.44	28.86±4.58	0.64
Waist (cm)**		99.76±9.8	102.02±9.82	0.02	99.62±10.27	101.76±9.65	0.28
Height (cm)**		160.44±9.77	159.52±22.26	0.81	160.81±8.55	159.41±21.94	0.65
Weight (kg)**		72.94±9.40	75.47±9.80	0.14	73.57±8.53	74.90±10.21	0.44
Duration of diabetes (years)**		10.48±6.98	8.49±6.80	0.10	9.93±6.33	8.97±7.17	0.44
Systolic blood pressure (mmHg)		123.84±17.39	123.71±15.96	0.96	126.15±15.11	122.75±17.02	0.26
Diastolic blood pressure (mmHg)		74.42±10.46	76.79±10.87	0.21	76.15±8.70	75.71±11.54	0.81
FBS (mg/dl)		158.35±56.17	171.22±64.52	0.23	177.79±64.03	160.84±60.24	0.15
HbA1c (%)		7.83±1.21	8.00±1.67	0.51	8.20±1.46	7.82±1.52	0.17
HDL (mg/dl)		46.74±10.60	43.53±9.16	0.06	46.60±9.63	43.89±9.86	0.14
LDL (mg/dl)		101.92±26.31	95.00±33.37	0.17	97.07±32.95	97.96±30.16	0.88
TG (mg/dl)		153.30±81.43	149.30±64.79	0.74	156.72±87.83	148.39±63.79	0.58
TC (mg/dl)		151.60±42.62	164.68±39.49	0.49	155.46±29.66	166.33±42.85	0.34
Cr (mg/dl)		1.27±0.25	0.89±0.19	0.001	1.09±0.35	1.02±.26	0.23
Albuminuria (mg/g)		91.68±248.56	34.44±82.25	0.11	165.36±288.76	12.45±7.68	0.002
Insulin (µIU/mL)		13.42±7.80	10.00±6.75	0.07	11.94±6.98	10.78±7.41	0.55
Urea (mg/dl)		36.40±10.06	26.74±8.50	0.02	30.42±9.32	26.92±9.15	0.30
eGFR		51.82±7.05	79.58±14.82	<0.0001	65.43±19.16	70.40±17.89	0.15
HOMA-IR		5.60±4.12	4.32±3.49	0.19	5.43±3.96	4.43±3.62	0.33
Irisin (ng/ml)		10.45±6.54	13.32±10.59	0.08	11.70±8.18	13.38±11.51	0.33

*Chi-square test was used for analysis. **T-test was used for analysis, eGFR is calculated by the abbreviated MDRD equation: 186 × (creatinine/88.4)−1.154 × (age)−0.203 × (0.742 if female) × (1.210 if black). Values are expressed as mean ± SD. BMI, Body mass index; FBS, fasting blood sugar; HbA1c, hemoglobin A1c; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; TG, triglycerides; TC, total cholesterol; Cr, creatinine; ACR, albumin to creatinine ratio; eGFR, estimated glomerular filtration rate.

Table 2. Correlation of irisin with demographic, laboratory and clinical data of patients included

	Variables	r	P-value
Irisin	BMI	0.07	0.42
	Age	0.02	0.73
	Insulin	-0.22	0.06
	Duration of diabetes	0.05	0.55
	Albuminuria	-0.05	0.55
	HOMA-IR	-0.38	0.76
	Cr	-0.10	0.21
	TG	-0.04	0.58
	TC	-0.02	0.87
	Urea	-0.18	0.29
	HDL	0.04	0.61
	LDL	0.003	0.96
	HBA1C	0.04	0.61
	FBS	0.16	0.05
	Systolic blood pressure	-0.15	0.08
	Diastolic blood pressure	-0.13	0.11
	eGFR	0.02	0.77

r, Correlation coefficient; MBI, Body mass index; Cr, creatinine; TG, triglycerides; TC, total cholesterol; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; HbA1c, hemoglobin A1c; FBS, fasting blood sugar; eGFR, estimated glomerular filtration rate.

Discussion

In the present study, serum levels of irisin were not significantly different between two groups of diabetic patients based on both eGFR and ACR classification. Also, no significant correlation was observed between serum irisin level and various demographic, anthropometric and metabolic related parameters including, age, BMI, insulin, duration of diabetes, albuminuria, HOMA-IR, creatinine, TG, TC, urea, HDL, LDL, HbA1c, FBS, Systolic and diastolic blood pressure and GFR. According to previous studies conflicting results from decreased (8, 17-20), unchanged (21-23), or increased (24-26) serum irisin levels have reported in patients with type 2 diabetes. These conflicting data could be attributed to the compensatory nature of irisin secretion mechanism in response to decreased energy expenditure and glucose metabolism that varies regarding the phenotypic features of diabetic patients. It was proposed that in prediabetes status an initial increase of irisin happened to regulate energy expenditure, but prolonged diabetic condition may lead to exhaustion or habituation in this compensatory mechanism and subsequent decrease in irisin expression and activity (21, 24). In one cross-sectional study by Magswari et al. it was shown that serum irisin levels were significantly different between diabetic patients with and without nephropathy (13). Irisin levels was significantly higher in diabetic patients with nephropathy indicating a potential indicator for assessing the severity of diabetic nephropathy. Recently, two studies have reported that irisin levels in diabetic nephropathy have decreased and also shown that there is a negative relationship between serum irisin and creatinine and the ratio of albumin to creatinine (19, 27). Our results were in contradiction with these studies as there is no significant correlation for irisin and serum creatinine. Besides, some studies have a negative correlation between the irisin levels and different stages of chronic kidney disease (28, 29).

The negative relationship between GFR and irisin levels indicated that high irisin levels were inversely related to the severity of diabetic nephropathy. In our study, no significant differences were observed for irisin levels based on GFR stratification. This result is in line with some previous studies. Hu et al. reported that diabetic patients with macroalbuminuria exhibited significantly lower serum irisin levels compared to those with normoalbuminuria and microalbuminuria (15). Although, a poor correlation was

found between serum irisin levels and FBS in our study, no significant relationship was seen between insulin and irisin. This discrepancy could be explained by the regulatory role of irisin in energy expenditure and glucose metabolism, as, increased levels of FBS induces initial irisin rises in diabetic patients to rectify blood sugar through reducing insulin resistance. In line with this finding, a meta-analysis by Ko et al. reported a positive correlation between irisin and insulin resistance in non-diabetic adults (30). However, similar to the findings of Magswari et al., our study failed to reveal this significant correlation in patients with diabetic nephropathy (13). In one study conducted by Mazloum-Khorasani et al. that examined the irisin levels in two groups of diabetic patients with and without coronary artery disease, serum irisin levels were significantly lower in diabetic patients with coronary artery disease (31). Also, a significant association was observed regarding the BMI, age and duration of diabetes, confirming this hypothesis that serum irisin may be determined by the degree of adiposity and the differences in irisin levels among similar studies may be at least partly related to participant's phenotypic variables (24).

It should be noted that the current study has some limitations; first, the relatively small sample size and subsequent reduced power analysis. Second, due to cross-sectional design of study, the causal relationship between irisin and renal function in diabetic patients remain to be cleared. Further prospective, and interventional studies are needed to shed light on this relationship. Second, irisn fluctuation over time was not considered as just fasting blood was collected. Finally, to avoid any bias in insulin measurements, patients undergoing insulin therapy and those with severe renal impairment were not included in this study. This may lead to an inappropriate assessment of the relationship between irisin and the various stages of renal dysfunction. In the present study, non-significant lower levels of irisin were observed in diabetic patients with reduced renal function or nephropathy and may be considered in the progression of diabetic nephropathy and kidney failure. Serum irisin concentration holds potential as a prognostic marker for diabetic nephropathy. However, further studies in different populations are needed to confirm the results.

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Ethics approval: Informed written consent was obtained from all subjects using approved protocols by Research Ethics Committee of Mashhad University of Medical Sciences.

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Authors' contribution: Study concept and design: Mazloum Khorasani Z, Aboutorabi R, Acquisition of data: Aboutorabi R, Harriri G, Statistical analysis: Mehrad-Majd H, Drafting of the manuscript: Harriri G, Mehrad-Majd H, Study supervision: Mazloum Khorasani Z.

Data availability: All data generated or analyzed during this study are included in this article. Further inquiries can be directed to the corresponding author.

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