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The Relationship between Serum Levels of Irisin with Cardiometabolic Biomarkers in Patients with Type 2 Diabetes

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ABSTRACT

Background: Diabetes and obesity are associated with an increased risk of cardiovascular disease. Irisin is a newly recognized peptidic myokine with anti-obesity and anti-diabetic properties. This study aims to investigate the relationship between serum irisin levels with cardiometabolic biomarkers in patients with type 2 diabetes mellitus (T2DM). M**ethods:** In this comparative cross- sectional study, 80 T2DM patients and 80 control participants (adjusted by age, body mass index (BMI), and physical activity) referring to Bou Ali Hospital in Zahedan, Iran, were enrolled. Serum irisin concentrations, anthropometric, and biochemical parameters were assessed. **Results:** Serum irisin level was significantly lower in T2DM patients compared to control group. Multiple linear regression analysis revealed that after adjustment for age, irisin was negatively associated with waist circumference (WC, $P < 0.01$) and waist to height ratio (WHtR, $P < 0.01$), homeostasis model assessment insulin resistance (HOMA-IR, $P = 0.009$), triglycerides (TG, $P = 0.016$), and positively associated with high density lipoprotein cholesterol (HDL-c, $P = 0.03$) in diabetic patients. **Conclusion:** The findings suggest that irisin can be used as a marker for predicting of obesity-related cardiometabolic biomarkers, insulin resistance, and incident T2DM.

Keywords: *Irisin; Insulin Rrsistance; Obesity; Cardiometabolic Risk factors; Type 2 diabetes mellitus*

Introduction

Obesity and diabetes have been recognized as one the most important health-threatening factors worldwide (Taghian, 2018). Some anthropometric markers are used to define obesity, including body mass index (BMI), which is the most common tool for diagnosis of general obesity and waist circumference (WC), a useful surrogate marker commonly used for indirect assessment of central adiposity (Esmaeil Motlagh *et al.*, 2017). There is a link between the visceral (Amato *et al.*, 2010) and central obesity (Engin, 2017) with insulin resistance, dyslipidemia, diabetes and the

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resulting pathogenesis of cardiovascular disease (CD) and metabolic syndrome (Esmaeil Motlagh *et al.*, 2017). WC, BMI, triglycerides (TG) , and high density lipoprotein cholesterol (HDL-c), indirectly express visceral fat function associated with cardiometabolic risk (Amato *et al.*, 2010). The interaction between myokines and adipokines, hormones produced by adipose and skeletal muscle tissues can potentially modulate metabolic processes (Hee Park *et al.*, 2013, Martinez Munoz *et al.*, 2018).

Irisin, a newly recognized peptidic myokine, is secreted by muscle tissue (Rana *et al.*, 2017, Schnyder and Handschin, 2015). It can improve metabolic abnormalities and increase thermogenesis by altering the brown adipose tissue (BAT) phenotype in white adipose tissue (WAT) (Boström *et al.*, 2012). Although the mechanism of the irisin effect has not been precisely defined, this hormone is secreted in response to the peroxisome proliferator-activated receptor-gamma co-activator-1 alpha (PGC-1α). Exercise induces uncoupling protein mRNA1 (UCP1) expression (a major component of β-adrenergically thermogenesis control in BAT) and converts subcutaneous and visceral fat into brown adipocytes, which in turn increases energy expenditure, weight loss, and reduces insulin resistance (Boström *et al.*, 2012, Martinez Munoz *et al.*, 2018).

There is controversial evidence regarding the role of irisin on glucose homeostasis (Alis *et al.*, 2014, Huh *et al.*, 2012, Liu *et al.*, 2013), obesity (Hee Park *et al.*, 2013, Sanchis-Gomar *et al.*, 2014b), and high risk of metabolic syndrome and CD in humans (Liu *et al.*, 2013, Zhang *et al.*, 2016). Given the contradictory results reported on irisin, this study aims to evaluate the relationship between serum irisin levels with cardiometabolic biomarkers in patients with type 2 diabetes mellitus (T2DM).

Materials and Methods

Design and participants: In this comparative cross-sectional study, 80 T2DM patients from outpatient diabetic patients referring to Bou Ali Hospital in Zahedan, Iran, from October 2018 to January 2019 were assessed. Eighty healthy non-diabetic individuals who accompanied the patients were evaluated as the control group. The participants were selected by convenience sampling method. The inclusion criteria included age of 30 and 65 years, diagnosed T2DM in the last 5 years based on fasting blood glucose ≥ 126 mg/dl, HbA1c ≥ 6.5% (Ta, 2014), taking oral hypoglycemic drugs and, BMI < 30 kg/m² in diabetic patients.

The exclusion criteria consisted of the history of CD (over the past three months), kidney and liver disease, hypo/hyperthyroidism, consuming NSAIDs and anti-depression drugs or insulin, taking supplements or food regimens for obesity or weight loss, and also pregnant and breast feeding women. The participants were matched in terms of age and BMI.

Measurements: Anthropometric parameters, including weight, height, BMI, WC, and waist to height ratio (WHtR) were evaluated. Weight and height were measured with light clothing without shoes. BMI was calculated as weight (kg) divided by the square of height (m^2) (kg/m^2). WC was measured with a non-elastic tape at the narrowest circumference, midway between the top of iliac crest and the lowest rib margin. Overnight fasting blood sample were taken from all participants. Serum levels of total cholesterol (TC), triglyceride (TG), low density lipoprotein cholesterol (LDL-c), and HDL-c, fasting blood sugar (FBS) were evaluated using standard biochemical kits (Pars Azmoon Kit, Tehran, Iran) with the colorimetric method by Auto-analyzer machine (Technical Publication No, UBA-7638-00/USA). Glycated hemoglobin (HbA1C) and insulin levels were measured using enzyme-linked immunoassay kits (ELIZA) (Randox kit, Co.Antrim, U.K) and (Mono bind Inc. Lake forest, CA 92630, USA, No: 5825-300), respectively. Insulin resistance was calculated using the homeostasis model assessment insulin resistance (HOMA-IR): fasting insulin ((µU/ml)/FBS (mmol/l) / 22.5 (Ioannou *et al.*, 2007). Iresin was measured by ELIZA (Bioassay Technology lab, Code No: E3253hU). Serum

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samples were stored at -70 °C for measurement of irisin.

Ethical considerations: The protocol of study was approved by the Medical Ethics Committee of Zahedan University of Medical Sciences, Zahedan, Iran (Ethical code IR.ZAUMS.REC.1398.125; Approval date: 2019.06.23). An informed consent was also obtained from the participants.

Data analysis: Statistical analysis was performed using SPSS version 21 (SPSS, Inc., Chicago, IL, USA). Data were expressed as Mean± SD or Mean± SEM with range, as appropriate. The student's *t-test* or Mann-Whitney *U* test was used to compare clinical characteristics between T2DM and control group. Normality of distribution was assessed using Kolmogorov-Smirnov test. One-way ANOVA was used to compare the mean values among groups. Age and BMI were considered as confounding factors. Pearson correlation coefficient was used to evaluate the relationship between irisin and anthropometric/biochemical markers. To evaluate the most significant associations between serum level of irisin and cardiometabolic risk factors in T2DM, multivariate regression analysis was performed. P-value < 0.05 was considered statistically significant.

Results

Demographic, anthropometric, and biochemical characteristics of the participants are presented in **Table 1**. The mean age and BMI of the participants were not significantly different between the two groups. Anthropometric measures showed that diabetic patients had significantly higher WC and WHtR compared to the control group (both $P < 0.0001$).

Comparisons between the two groups demonstrated a significant increase for FBS, insulin, HOMA-IR ($P < 0.0001$ for all), TG ($P < 0.01$), TG/ HDL-c, and TC/ HDL-c (both $P = 0.04$) and a significant decrease for HDL-c ($P = 0.05$) in T2DM compared to the control group. No significant difference was found in serum TC and LDL-c levels between the two groups. Serum levels of irisin were significantly lower in diabetes patients compared to the control group ($P < 0.0001$).

Based on **Table 2**, Pearson correlation analysis demonstrated that serum levels of irisin were negatively correlated with BMI, WC, WHtR ($P < 0.0001$), TG ($P = 0.008$), LDL-c, HOMA-IR ($P = 0.040$), and HbA1c ($P = 0.008$). It was positively correlated with HDL-c ($P = 0.038$) in diabetic patients. A significant negative correlation was found between WC with TC ($P = 0.03$), LDL-c, HOMA-IR ($P = 0.002$), and HbA1c ($P = 0.004$).

Table 3 represents associations between serum irisin concentration and cardiometabolic biomarkers by multivariate regression analyses. After adjustment for age, irisin was negatively associated with WC ($P = 0.002$), WHtR ($P = 0.005$), HOMA-IR ($P = 0.009$), and TG ($P = 0.016$), and was positively associated with HDL-c ($P = 0.03$). These associations remained significant even after adjustment for BMI.

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Table 1. Demographic characteristics in T2DM patients and control group

Variables	Diabetic group (n=40)	Control group (n=40)	P-value[a]
Age (year)	55.1±8.9[b]	52.8±8.8	0.27
Weight (kg)	74.60 ± 15.00	72.30 ± 11.80	0.45
Body mass index (kg/m^2)	28.40 ± 4.00	26.60 ± 5.00	0.07
Waist circumference (cm)	102.20 ± 14.10	90.10 ± 13.00	0.0001
WHtR	0.62 ± 0.09	0.49 ± 0.08	0.0001
Fasting blood sugar (mg/dl)	178.60 ± 47.60	85.60 ± 11.10	0.0001
Hemoglobin A1c (%)	7.75 ± 1.70	1.80 ± 0.14	0.0001
Serum insulin (ml/µIU)	7.40 ± 3.50	4.60 ± 1.10	0.0001
HOMA-IR	3.30 ± 2.00	0.96 ± 0.20	0.0001
Triglyceride (mg/dl)	168.00 ± 54.10	129.20 ± 28.00	0.01
Total cholesterol (mg/dl)	184.50 ± 73.30	170.70 ± 66.70	0.39
LDL-c (mg/dl)	98.80 ± 31.00	92.60 ± 32.50	0.60
HDl-c (mg/dl)	46.20 ± 9.00	57.30 ± 11.10	0.05
LDL-c/HDL-c	2.10 ± 0.84	1.62 ± 0.78	0.62
TG/ HDL-c	3.64 ± 1.50	2.25 ± 1.00	0.04
TC/ HDL-c	4.10 ± 1.80	2.98 ± 1.60	0.04
Irisin (ng/ml)[c]	152.5 ± 13.4	294.60 ± 36.00	0.0001

[a]: Student t-*test*; [b]: Mean ± SD; [c]: Mean ± SEM; WHtR: Waist to height circumference; HOMA-IR: Homeostatic Model Assessment for Insulin Resistance**;** LDL-c: Low density lipoprotein cholesterol; HDL-c: High density lipoprotein cholesterol.

Table 2. Correlation between Irisin and anthropometric/cardiometabolic biomarkers in two groups.

Variables		Diabetic group	Control group
Age (year)	r	0.299	0.111
	P -value	0.064	0.473
Weight (kg)	r	-0.04	-0.242
	P -value	.787	0.134
Body mass index (kg/m^2)	r	-0.632	-0.185
	P -value	0.0001	0.114
Waist circumference (cm)	r	-0.633	-0.154
	P -value	0.0001	0.11
Waist to height circumference (cm)	r	-0.665	-0.158
	P -value	0.0001	0.21
Fasting blood sugar (mg/dl)	r	-0.201	0.09
	P -value	0.220	0.57
Hemoglobin A1c (%)	r	-0.420	0.12
	P -value	0.008	0.98
Serum insulin (ml/µIU)	r	-0.220	0.09
	P -value	0.235	0.57
Homeostatic Model Assessment for Insulin Resistance	r	-0.435	0.07
	P -value	0. 040	0.63
Triglyceride (mg/dl)	r	-0.437	-0.13
	P -value	0.01	0.41
Total cholesterol (mg/dl)	r	-0.249	-0.28
	P -value	0.066	0.07
Low density lipoprotein cholesterol (mg/dl)	r	-0.326	-0.004
	P -value	0.040	0.18
High density lipoprotein cholesterol (mg/dl)	r	0.344	0.22
	P -value	0.038	0.89

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Table 3. Multiple linear regression analysis for the relationship between irisin and anthropometric /cardiometabolic biomarkers in diabetic group.

Variables	Unstandardized coefficients B	Unstandardized coefficients SE	Standardized coefficients Beta	P-value
Body mass index (kg/m^2)	-0.183	0.102	--0.266	0.047
Waist circumference (cm)	-0.421	0.060	-0.612	0.01
Waist to height circumference (cm)	-0.536	0.305	--0.632	0.01
Fasting blood sugar (mg/dl)	-0.026	0.006	--0.100	0.821
Hemoglobin A1c (%)	-0.199	0.096	-0.120	0.620
Serum insulin (ml/µIU)	-0.105	0.002	-0.006	0.992
Homeostatic Model Assessment for Insulin Resistance	-0.277	0.046	-0.109	0.009
Triglyceride (mg/dl)	-0.312	0.009	-0.228	0.016
Total cholesterol (mg/dl)	-0.101	0.007	-0.031	0.860
Low density lipoprotein cholesterol (mg/dl)	-0.034	0.018	-0.375	0.052
High density lipoprotein cholesterol (mg/dl)	0.207	0.005	0.022	0. 03

Discussion

This study revealed that serum irisin levels were significantly lower in diabetic patients and were negatively correlated with obesity-related anthropometric measurements, insulin resistance, HbA1c, LDL-c, and TG, which are the main CVD risk factors. Irisin was also positively associated with HDL-c.

Irisin is an adipomyokine secreted by skeletal muscles that increases total energy expenditure and improves glucose homeostasis through browning and thermogenesis of WAT. As a result, it reduces obesity and insulin resistance (Huh *et al.*, 2012, Sanchis-Gomar *et al.*, 2014b, Schnyder and Handschin, 2015). However, there are limited and contradictory studies of irisin in humans. Several studies have reported a significantly lower level of irisin in T2DM patients compared to non-diabetic controls (Alis *et al.*, 2014, Liu *et al.*, 2013, Shelbaya *et al.*, 2018). Some studies have indicated that irisin levels were significantly higher in diabetes patients (Huh *et al.*, 2016, Sanchis-Gomar *et al.*, 2014b) and individuals with metabolic abnormalities (Hee Park *et al.*, 2013). Several previous studies have reported conflicting results on the association between irisin levels and anthropometric parameters (Hee Park *et al.*, 2013, Huh *et al.*, 2016, Sanchis-Gomar *et al.*, 2014a), glucose levels, insulin levels, insulin resistance (Choi *et al.*, 2013, Huh *et al.*, 2016, Moreno-Navarrete *et al.*, 2013), HbA1c (Huh *et al.*, 2016), and lipid profile (Huh *et al.*, 2012, Liu *et al.*, 2013) in patients with T2DM**.**

Interestingly, the results of the present study showed that irisin was inversely associated with the adiposity indices (BMI, WC, WHtR) and some main CVD risk factors (such as LDL–c, TG, insulin resistance and HbA1c), and was positively correlated with HDL-c.

The indicated associations between lower irisin levels and the incidence of DM may be the result of compensatory decreases in irisin levels in response to insulin resistance, obesity, and metabolic disorders.

Similarly, some studies have found a negative correlation between irisin with BMI (Sanchis-Gomar *et al.*, 2014a), HbA1c, and insulin resistance (Hee Park *et al.*, 2013, Shelbaya *et al.*, 2018). Other studies have shown contradictory effects, including a positive correlation between irisin and BMI (Liu *et al.*, 2013, Rana *et al.*, 2017), FBS (Huh *et al.*, 2016, Liu *et al.*, 2013), HbA1c (Huh *et al.*, 2016, Rana *et al.*, 2017), and TG (Liu *et al.*, 2013), and a negative correlation between irisin and circulating HDL-c (Liu *et al.*, 2013). Some cross sectional studies have reported that T2DM patients did not reveal significant association between serum irisin with major markers of metabolic markers and body composition indices, such as BMI, WC (Huh *et al.*, 2016, Rana *et al.*, 2017), skeletal muscle index, and total fat mass (Huh *et al.*, 2016). WC is a reliable

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marker for central adiposity especially in adult**.** In addition, WHtR is also a relatively new indicator for measuring central obesity and predicting metabolic disorders (Esmaeil Motlagh *et al.*, 2017). Given the importance of body fat distribution and the strong association of excess abdominal fat with insulin resistance, dyslipidemia, and the pathogenesis of CD, these correlations suggest that irisin is inversely associated with insulin resistance and obese-dependent variables.

On the other hand, in multiple linear regression analysis after adjustment for confounders, a negative correlation was found between serum levels of irisin with WC, WHtR, HOMA-IR, and TG, and a positive correlation to HDL-c, This result suggests that increased irisin level was associated with improved obesity-related cardiometabolic biomarkers.

This study investigated the association between irisin and insulin resistance in humans as well as more detailed of some cardiometabolic risk factors by regression models adjusted for various anthropometric measurements (such as BMI, WC, and WHtR) and lipid profile, which provides more credibility for the study.

The study had some limitations. The study did not measure dietary intake, physical activity, body composition, and hypertension. This study was performed based on a cross-sectional design, thus the authors could not indicate a cause-effect association between irisin and T2DM.

Conclusion

The findings indicate that increased levels of irisin appear to be associated with decreased risk of insulin resistance, weight loss, and improvement in dyslipidemia, suggesting an inverse relationship between irisin and cardiometabolic risk factors in patients with T2DM. The results indicate that irisin can be used as a marker for predicting of obesity-related cardiometabolic biomarkers, insulin resistance, and incident DM. However, further studies are required to evaluate the potential mechanisms supporting these correlations.

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Authors' contributions

Montazerifar F and Karajibani M designed the research. Sedaghat G, Shourestani SH, and Azar Nour F conducted data collection. Montazerifar F wrote the paper and analyzed the data. Montazerifar F, Karajibani M, and Bolouri A reviewed and edited the manuscript. Montazerifar F had primary responsibility for final content. All authors read and approved the final manuscript.

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Conflict of interest

The authors declare that there is no conflict of interest.

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