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Irisin in Adolescent Type 1 Diabetic Patients and its Relation to Diabetes Control and Atherosclerosis

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Abstract

AIM: The objective of this was to determine the role of irisin in adolescent type 1 diabetes (T1D) patients.

METHODS: This study was conducted on 65 patients with T1D and 50 healthy individuals as control group. Serum irisin, glycosylated hemoglobin (HbA1c), lipid profile, oxidized low-density lipoprotein (OxLDL), urinary albumin/creatinine ratio; carotid intimal medial thickness (cIMT), and aortic intimal medial thickness (aIMT) were evaluated for all participant.

RESULTS: HbA1c, lipid profile, albumin/creatinine ratio, OxLDL, irisin, aIMT and cIMT were significantly higher in diabetic patients. Irisin had a positive correlation with age of diabetic patients, onset of diabetes, mid arm circumference, waist/height ratio, body mass index, HbA1c, and cIMT.

CONCLUSION: Irisin is a marker for detection of diabetes control and early detection of subclinical atherosclerosis. Irisin had a relation with obesity.

Introduction

Irisin is a precious hormone-like myokine that plays a key role in energy expenditure and metabolic regulation. The main source is the heart, skeletal muscles, kidneys, liver, skin, and nerves [1]. It is an extracellular cleaved product of fibronectin type III domain-containing 5 (FDNC5) and is controlled by peroxisome proliferator-activated receptor gamma coactivator-1-alpha [2]. Overexpression FDNC5/irisin persuade activation of thermogenesis in white adipose tissue leading to improved glucose homeostasis and insulin resistance [3].

Irisin is associated with cardio metabolic risk as it had a role in atherogenic and pro-inflammatory pathways [4]. Relationship of circulating iris levels, endothelial dysfunctions, and subclinical atherosclerosis was reported in many previous studies in non-diabetic and is important.

Therefore, the aim of this work is to assess the levels of circulating serum irisin in type 1 diabetes (T1D) adolescent subjects and healthy controls and to reveal possible relationships of serum levels of irisin with anthropometric and metabolic parameters in the studied groups.

Methods

This cross-sectional study was done on 65 type of T1D patient and 50 healthy controls age- and sex-matched. The diabetic patients were selected from the endocrine clinic, Medical Center of Excellence, and National Research Centre (NRC). A written consent was obtained from the participants or their parents. The research protocol was approved through the NRC ethics committee, (registration number 19101). We selected diabetic patients (age > 14 and < 19 years) and duration of diabetes more than 5 years.

The exclusion criteria included; T2D, coronary artery disease, acute diabetic complications, cardiovascular disease, taking metformin or multivitamins, smoking or any other chronic disease, or malignancy.

All of the diabetics and controls underwent history taking, general, cardiac, chest and neurological physical examination, laboratory assessment, and carotid artery ultrasound examination. Blood pressure was assessed for all studied subjects. It was measured 3 times after 5-min rest in the sitting position using automatic manometer (Omron M4 Plus, Omron Health care Europe, Hoof drop, and Holland). The mean value of the second and the third measurement was calculated. Weight, height, waist circumference, and hip circumference were assessed for diabetics and controls. Weight (by Seca Scale Standing Balance) and height (by Holtain Portable anthropometer, Holtain, Ltd, Crymmych, Wales, U.K) were measured. Body mass index, waist/hip ratio, and waist/height ratio (cm/cm) were calculated [5], [6].

After an overnight fast of 12 h, venous blood was collected. Measurement of glycosylated hemoglobin (HbA1c) and lipid profile (total cholesterol [TC], high-density lipoprotein-cholesterol [HDL-C, mg/dL], and triglycerides [TGs, mg/dL]) was performed on automated clinical chemistry analyzer (OLYMPUS AU400). Low-density lipoprotein cholesterol (LDL-C) level was calculated using Friedewald formula: LDLc = TC – HDLc – TG/5 mg/dl [7].

Screening for microalbuminuria was assessed in fresh morning urine samples by measuring albumin/creatinine ratio. Microalbuminuria was measured 3 times (separated every 2 months), and it was considered positive if two from three samples were positive. If one sample was positive, urine analysis was done to exclude urinary tract infection.

Irisin and oxidized LDL (OxLDL) were measured by the ELISA method (quantitative sandwich enzyme linked immunosorbent assay technique) MyBioSource, Inc. P.O. Box 153308 San Diego, CA 7 92195-3308 USA.

Assessment of carotid intima-media thickness (cIMT) was done using General Electric medical ultrasonographic machine model: Vivid 7 Pro, GE Vingmed ultrasound AS-Nl90, and Horton-Norway equipped with 7.5–10 MHz linear-array transducer) [8]. Measurement of the aortic intimal medial thickness (aIMT) the transducer (7.5 MHz) was put in the upper abdomen for evaluation of abdominal aorta and aortic bifurcation. The aortic intima-media complex was assessed (10 MHz linear array transducer). For the assessment of aIMT, the image was focused on the far wall (dorsal arterial wall of the most distal 15 mm of the abdominal aorta), and gain settings were used to optimize image quality [9]. The average of three measurements of each patient was taken for evaluation of aIMT.

Statistical analysis

Statistical Package for the Social Science program version 20.0 (Chicago, Illinois, USA) was used. T-test for quantitative variables was done. We evaluate the correlation between irisin with demographics, laboratory data, anthropometric data, and image study of diabetic patients. Pearson's correlation, followed by stepwise multiple regression analysis, was also done. Receiver operating characteristic (ROC) curve was used for detecting sensitivity and specificity of irisin with cIMT and aIMT.

Results

In comparison to the control subjects, the values of TC, TG, HbA1c, LDL-C, urinary albumin/creatinine ratio, mid-arm circumference, aIMT, cIMT, OxLDL, and irisin were significantly increased ($p < 0.05$) (data not shown). A positive correlation was detected between Irisin and age of diabetic patients ($r = 0.25$, $p = 0.5$, onset of diabetes ($r = 0.33$, $p = 0.01$), mid arm circumference ($r = 0.3$, $p = 0.01$), body mass index ($r = 0.42$, $p = 0.0001$), waist/height ratio($r = 0.40$, $p = 0.0001$), HbA1c ($r = 0.39$, $p = 0.0001$), and cIMT ($r = 0.35$, $p = 0.0001$) (Table 1).

Table 1: Correlation analysis of demographic, laboratory data, carotid and aIMT with irisin in type 1 diabetes

Variables	Irisin	
	r	p-value
Age of diabetic patients (years)	0.25	0.05
Duration of diabetes (years)	–0.11	0.39
Onset of diabetes (years)	0.33	0.01
Insulin dose (U/kg)	0.10	0.45
Systolic blood pressure (mmHg)	0.21	0.10
Diastolic blood pressure (mmHg)	0.17	0.19
Midarm circumference (cm)	0.32	0.01
Body mass index (kg/m^2)	0.42	0.0001
Waist/hip ratio	0.22	0.09
Waist/height ratio	0.40	0.0001
TC (mg/dl)	0.01	0.9
TG (mg/dl)	0.13	0.38
HDL-C (mg/dl)	0.04	0.79
LDL-C (mg/dl)	0.19	0.19
OXLDL	0.23	0.07
HbA1c (%)	0.39	0.0001
Albumin/creatinine ratio (μg/g creatinine)	0.06	0.71
Both carotid intimal medial thickness (mm)	0.35	0.0001
aIMT (mm)	0.15	0.23

HDL-C: High-density lipoprotein cholesterol, LDL-C: Low-density lipoprotein cholesterol, TC: Total cholesterol, TG: Triglyceride, HbA1c: Glycated hemoglobin, OXLDL: Oxidized low-density lipoprotein, aIMT: Aortic intimal medial thickness.

Stepwise multiple regression analysis of irisin with all demographic data, anthropometric, laboratory, carotid, and aIMT revealed that irisin had a correlation with HbA1c, mid arm circumference, and cIMT (Table 2).

Table 2: Stepwise multiple regression analysis of irisin in relation to demographic, anthropometric data, laboratory data, and image study in type 1 diabetic patients

	Unstandardized coefficient		Standardized coefficient		P-value
	B	SE	Beta	t	
(Constant)	–47.4	18.2		–2.6	0.01
HbA1c (%)	1.8	0.7	0.4	2.5	0.02
Mid arm circumference (mm)	1.04	0.4	0.4	2.7	0.01
cIMT (mm)	61.6	24.4	0.3	2.5	0.02

Dependent variables is irisin, HbA1c: Glycosylated hemoglobin, cIMT: Carotid intimal medial thickness.

ROC curve of irisin with carotid and aIMT of adolescent T1D patients revealed that irisin had a higher sensitivity with cIMT (91.1%) and higher specificity with aIMT (81.8%) (Table 3).

Table 3: ROC curve of irisin for early detection of atherosclerosis of carotid and aIMT of adolescent type 1 diabetic patients

Variables	Cut off	AUC	SE	95% CI	Sensitivity	Specificity	+PV	–PV
cIMT	>20.2	0.8	0.05	0.7–0.9	91.1	66.7	92.7	61.5
aIMT	>22.1	0.9	0.04	0.8–0.9	81.7	81.8	96.1	

ROC: Receiver operating characteristic, aIMT: Aortic intimal medial thickness, cIMT: Carotid intimal medial thickness, AUC: area under the curve, SE: Standard error, CI: Confidence interval, +PV: Positive predictive value, –PV: Negative predictive value.

Discussion

T1D is a multifactorial disorder caused by destruction of pancreatic β cells and it involves a lot of genetic and environmental factors [10]. Available data about irisin serum concentration is still controversial.

In the present study, results showed that serum irisin levels were significantly higher in T1D adolescent group in comparison to controls. Our findings were similar to other studies conducted with type 1 diabetes mellitus (T1DM) patients [11], [12]. A study by Aydin *et al*. showed that irisin is present in pancreas [13]. This may indicate that irisin is synthesized in pancreas and and destruction of the pancreas can increase their level.

However, these data are not in accordance with Tentolouris *et al*. who reported that circulating irisin levels were lower in subjects with T1D than in controls [14].

Circulating irisin concentration was positively correlated with onset of diabetes, Body mass index, waist/height ratio, and cIMT. On the contrary, irisin has been negatively correlated with adverse metabolic parameters as waist-to-hip ratio [15]. Negative correlations between irisin levels and age presented at the onset of the T1DM were presented in other study [16].

In agreement with our results, Tang *et al*. also reported that irisin was not correlated with TC, LDL-C, and HDL-C and both systolic and diastolic blood pressure [15].

Stepwise multiple regression analysis of irisin in relation to demographic, anthropometric data, laboratory data, and image study in T1D revealed that irisin is correlated with glycosylated hemoglobin, mid arm circumference, and cIMT.

ROC curve of irisin with carotid and aIMT of adolescent T1D revealed that irisin had a higher sensitivity with cIMT (91.1%) and higher specificity with aIMT (81.8%).

Conclusion

Irisin is higher in diabetic patients and it is related to obesity, metabolic control, and subclinical atherosclerosis. We recommend using of irisin for determination of control of diabetes.

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