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Irisin, a new envoy in newly diagnosed type 2 diabetes mellitus – A plausible association with insulin resistance

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Abstract

Background: Insulin resistance plays a significant role in the pathogenesis of type 2 diabetes mellitus (T2DM). Irisin, an adipo-myokine, is found to increase insulin sensitivity by adaptive thermogenesis. Various studies have found that endocrine and exocrine functions of the pancreas are affected in T2DM. This case-control study with 180 participants aimed to find any association of serum irisin with insulin resistance and pancreatic profile in newly diagnosed T2DM.

Methods: Fasting blood sugar (FBS) and pancreatic profile were measured by Auto Analyzer, serum insulin by chemiluminescence assay, serum irisin by Enzyme-Linked Immunoassay (ELISA) kit, and insulin resistance by Homeostatic Model Assessment of Insulin Resistance (HOMA-IR).

Results: Significantly lower irisin levels were observed in T2DM patients compared to healthy individuals (p =0.001*). A positive correlation was found between serum irisin and insulin resistance in T2DM patients, whereas a negative correlation was found in healthy controls. In some cases, serum amylase and lipase positively correlated with irisin, whereas a negative association was observed in controls.

Conclusion: This study concludes a protective role for irisin in combating insulin resistance and improving pancreatic function in T2DM, but more extensive studies are required to prove it.

Highlights:

What is current knowledge?

Many studies have been conducted on irisin, newly discovered in 2012. The therapeutic role of irisin in T2DM is a topic of recent research, as some studies have found lower irisin levels in diabetic cases (undergoing antidiabetic therapy), indicating an inverse relationship between irisin and insulin resistance. In contrast, others have found no relationship or a positive relationship.

What is new here?

This study was conducted for the first time in a population of the Eastern Indian state Odisha investigating newly diagnosed T2DM cases who have not been administered antidiabetic drugs. Lower serum irisin levels in cases than in controls indicate a protective role of irisin in combating insulin resistance.

Introduction

The ever-rising prevalence of type 2 diabetes mellitus (T2DM) and its complications have increased the economic burden on the general population (1). India ranks second after China in diabetes prevalence and is now referred to as the diabetic capital of the world. The prevalence of diabetes in adults aged twenty years or older in India has increased from 5.5% in 1990 to 7.7% in 2016 (2). Insulin resistance is the primary pathogenesis of T2DM. Insulin resistance is the hallmark of T2DM, where a greater-than-normal amount of insulin is required to obtain a quantitatively normal response (3).

Several factors have been proposed to explain the mechanism of insulin resistance. These include obesity, inflammation, mitochondrial dysfunction, hyperinsulinemia, hyperlipidemia, genetic background, endoplasmic reticulum stress, aging, oxidative stress, fatty liver, hypoxia, lipodystrophy and pregnancy (3).

Irisin, an adipo-myokine discovered in 2012 by Bostrom, is found to influence insulin resistance by adaptive thermogenesis (4,5). Irisin is a hormone-like polypeptide including 112 amino acids derived from proteolytic cleavage of the carboxy terminus of fibronectin type III domain-containing protein 5 (FNDC5) (5). Synthesis and secretion of irisin are induced by exercise and peroxisome proliferator-activated receptor-γ (PPAR-γ) coactivator 1-α (PGC1α). Insulin sensitivity and signaling in skeletal muscle are enhanced by increased expression of PGC1α after prolonged exercise (6). Proposedly, irisin is found to reduce insulin resistance in T2DM by increasing the sensitivity of insulin receptors in the skeletal muscles and heart, improving hepatic glucagon and lipid metabolism, promoting pancreatic cell function, and transforming white adipose tissue to brown adipose tissue (4-6).

Many studies have been carried out to explore the role of irisin in T2DM. In murine models, irisin increases glucose uptake in skeletal muscles by translocating Glucose transporter 4 (GLUT4) receptors via P38 mediated mitogen-activated pathway. Irisin is also found to be associated with pancreatic beta-cell regeneration (5).

Experimental animal studies have found irisin's beneficial role in decreasing insulin resistance, but human studies have shown mixed results regarding the correlation between irisin and insulin resistance (7,8). No studies have been conducted on irisin in this part of the country (Odisha, an eastern state of India). Hence, this study evaluated the correlation between serum irisin, insulin resistance, and pancreatic profile in newly diagnosed T2DM cases and healthy non-diabetic controls.

Methods

The Department of Biochemistry conducted this case-control study in collaboration with the General Medicine and Community Medicine departments at SCB medical college, Cuttack, Odisha, India.

- ***Recruitment of study subjects***

The cases were recruited from the Department of General Medicine at SCB Medical College—the cases comprised ninety newly diagnosed T2DM patients who were never on any oral hypoglycemic agent or insulin. Controls were non-diabetic healthy volunteers matched to T2DM patients by age and gender and

were not first-degree relatives of cases. T2DM was diagnosed based on the World Health Organization (WHO) criteria. People with fasting plasma glucose (FBS) values of ⩾ 7.0 mmol/L (126 mg/dl), two-hour post-load plasma glucose ⩾ 11.1 mmol/L (200 mg/dl), Glycated Hemoglobin (HbA1c) ⩾ 6.5% (48 mmol/mol), or a random blood glucose level ⩾ 11.1 mmol/L (200 mg/ dl) in the presence of signs and symptoms were considered to have diabetes (9). The FBS of subjects was compared. Subjects with a history of chronic diseases like hypertension, tuberculosis, chronic kidney disease, endocrine disorders (Addison's disease, Cushing's disease, thyroid disorders, and growth hormone disorders), autoimmune diseases (Rheumatoid arthritis), drug abuse, active hepatitis, steroid use, smoking, and pregnancy were excluded from the study. All subjects were recruited from October 2018 to September 2019.

All enrolled subjects had given written informed consent for participation in this study. The Institutional Ethics Committee approved the study protocol (Registered No ECR/84/Inst/OR/2013 issued under Rule 122DD of the Drugs and Cosmetics Rules 1945) SCB, MCH, Cuttack under the IEC/IRB No: 709/28.9.18.

The detailed history of all subjects was recorded, followed by anthropometric and biochemical measurements.

- ***Biochemical Measurements***

5ml fasting venous blood samples were obtained from all participants after a 12-hour overnight fast. 1.5ml was collected in two plain vials to analyze serum insulin and irisin. 2ml of the sample was collected in oxo-fluoride vials for plasma glucose. Serum samples were centrifuged at 3,000 rpm for 10-15 minutes at 4O C, and the clear supernatant was immediately aliquoted and stored at -80O C until measurements of irisin levels.

The biochemical parameters like fasting plasma glucose and serum Insulin were measured by the AutoAnalyzer using standard commercial kits adapted to the AutoAnalyzer in Regional Diagnostic Centre at SCB Medical College and Hospital. Insulin resistance was estimated by the homeostasis model assessment for insulin resistance (HOMA-IR), which was calculated as follows:

[fasting insulin (lU/mL) * fasting glucose (mg/dL)/405] 10

Fasting serum irisin was estimated by Enzyme-Linked Immunoassay (ELISA) kit (Bio codon) adapted to LISA-SCAN at the Postgraduate Laboratory of the Department of Biochemistry following the manufacturer's instructions. The sensitivity of the assay was 0.095 ng/mL. The assay detection range was 0.2-60 ng/mL. The intra- and inter-assay coefficients of variation (CV) were CV< 8% and CV< 10%, respectively.

- ***Anthropometric Measurements***

Patients' weight and height were measured according to WHO guidelines for physical measurement (11). BMI (kg/m^2) was calculated by dividing the weight (kg) by the height in meters squared (m^2).

Statistical analysis

Data was entered in MS Excel and analyzed using Statistical Package for Social Science (SPSS) version 22.0 (IBM, Armonk, NY: IBM Corp.). A baseline comparison of cases and controls was made, and quantitative variables were expressed as mean ± standard deviation, while categorical variables were expressed in percentages. All data in this study were subjected to tests for normality. Quantitative variables were compared using an unpaired t-test, and categorical variables were compared using the chi-square test. Pearson's correlation and linear regression were used to determine if the studied parameters were related to changes in other studied parameters in the same group. A p-value of ⩽ 0.05 was considered significant.

Results

- ***Anthropometric and clinical characteristics of subjects***

Table 1 shows the baseline comparison of anthropometric and biochemical parameters among cases and controls. Waist circumference was significantly higher among cases than controls (p=0.000). Other anthropometric parameters did not differ significantly. Among biochemical parameters, only serum lipase (p=0.037) was significantly higher among cases than controls. Serum insulin (p=0.004) and insulin resistance (p=0.000) were significantly higher among cases than controls. Serum irisin (p=0.001) was lower among newly diagnosed diabetic cases than non-diabetic controls.

- **Circulating *irisin levels and metabolic parameters***

Table 2 shows the correlation of serum irisin with anthropometric and biochemical parameters among cases and controls.

In the case group, weight, BMI, FBS, serum insulin, insulin resistance, amylase, and lipase had a positive correlation with irisin, whereas height had a negative correlation. In the case group, irisin significantly correlated with weight (p=0.015) and BMI (p=0.001).

In controls, weight, height, BMI, and serum insulin positively correlated with serum irisin, whereas FBS, insulin resistance, amylase, and lipase were negatively correlated. Among the controls, serum amylase (p=0.007) showed a significant positive correlation with serum irisin.

- ***Regression analysis of irisin with insulin resistance***

Table 3 shows the regression analysis of serum irisin and insulin resistance. With an increase in serum irisin levels, an increase was observed in insulin resistance among the cases (β coefficient = 0.180), whereas a decrease in insulin resistance was observed among controls (β coefficient = -0.004). Overall, there was a decrease in insulin resistance with increasing levels of serum irisin (β coefficient = -0.135).

Table 1. Comparison of bio-chemical and anthropometric parameter among studyparticipants

	Cases (n=90)	Controls (n=90)	p value
Age (years)	42.34±6.11	39.51±5.17	**0.43**
Anthropometry			
Weight (kg)	64.46±10.24	65±12.44	**0.190**
Height (meters)	1.56±0.10	1.57±0.09	**0.492**
BMI (kg/m^2)	25.28±4.48	26.21±4.32	**0.159**
Waist circumference (cm)	88.86±8.62	82.46±6.67	**0.000***
Biochemical			
FBS (mg/dL)	164± 24.32	97± 9.76	**0.000***
Lipid profile			
Cholesterol (mg/dL)	190.24±36.75	187.01±35.17	**0.547**
Triglyceride (mg/dL)	185.73±44.16	155.48±31.45	**0.050***
HDL (mg/dL)	45.20±7.26	50.53±8.29	**0.000***
LDL (mg/dL)	116.95±30.90	109.57±34.05	**0.190**
VLDL (mg/dL)	31.60±10.51	26.90±9.70	**0.021***
Pancreatic profile			
Serum Amylase (U/L)	52.71±17.63	54.32±16.62	**0.529**
Serum Lipase (U/L)	42.53±14.23	37.75±12.94	**0.037***
Serum Insulin (IU/mL)	14.89±5.15	11.62±4.49	**0.004***
HOMA-IR	5.59±2.26	2.86±1.34	**0.000***
Serum Irisin (ng/mL)	**2.39±1.21**	**3.47±1.58**	**0.001***

** p value ≤ 0.05: significant*

Table 2. Correlation of serum Irisin with anthropometric and biochemical parameters among cases and controls

	Cases (n=90)		Controls (n=90)	
	r	p value	r	p value
Anthropometric				
Weight (kg)	0.256	0.015*	0.136	**0.201**
Height (m)	-0.139	0.192	0.117	**0.273**
BMI (kg/m^2)	0.347	0.001*	0.086	**0.418**
Waist circumference (cm)	0.313	0.003*	0.074	**0.486**
Biochemical				
FBS (mg/dL)	0.078	0.467	-0.054	**0.612**
Serum Insulin (IU/mL)	0.119	0.262	0.035	**0.744**
HOMA-IR	0.067	0.530	-0.008	**0.944**
Pancreatic function test				
Amylase (U/L)	0.068	0.526	-0.282	**0.007***
Lipase (U/L)	0.021	0.844	-0.171	**0.106**
Lipid profile				
Cholesterol (mg/dL)	-0.068	0.524	-0.164	**0.122**
Triglyceride(mg/dL)	0.154	0.148	-0.129	**0.225**
HDL (mg/dL)	-0.315	0.002*	0.141	**0.186**
LDL (mg/dL)	-0.051	0.634	-0.155	**0.144**
VLDL (mg/dL)	**0.163**	**0.149**	**-0.131**	**0.217**

** p value ≤ 0.05: significant*

Table 3. Regression analysis of serum Irisin with HOMA-IR among cases and controls

Serum Irisin (ng/m)	Cases (n=9)	p value (95 % CI)	Controls (n=90)	p value (95 % CI)	Total subjects	p value (95 % CI)
βcoefficient	0.18	0.567 (-0.387-0.748)	-0.004	0.113 (-0.118 – 0.110)	-0.135	0.345 (-0.331 – 0.061)

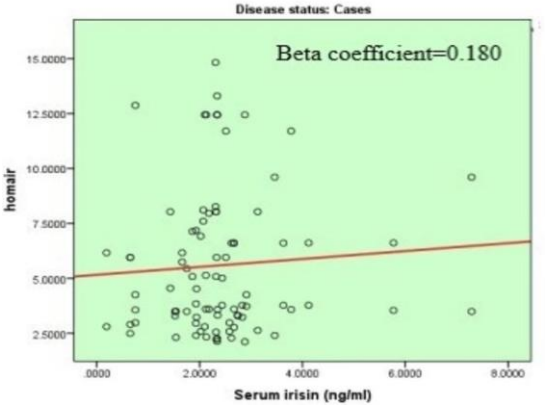

Figure 1. Scatter plot showing relationship between insulin resistance and irisin in cases, where insulin resistance increases by 0.180 units with every one-unit increase in serum irisin

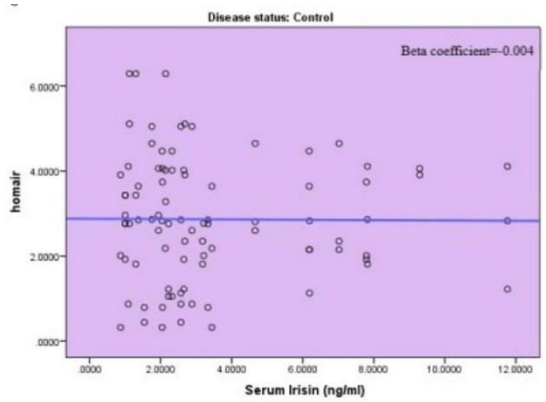

Figure 2. Scatter plot showing relationship between insulin resistance and irisin in controls, where insulin resistance decreases by 0.004 units with every one-unit increase in serum irisin.

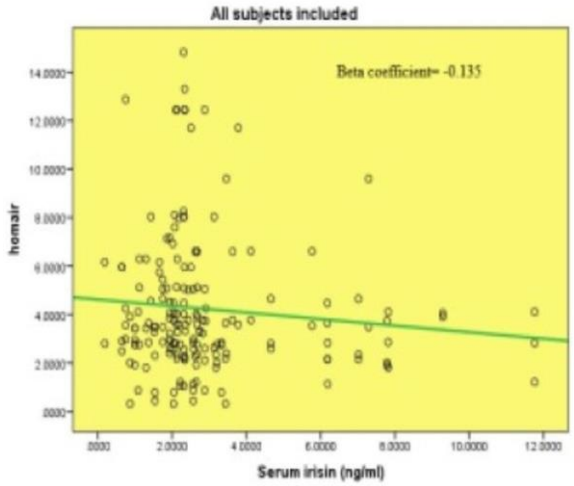

Figure 3. Scatter plot showing relationship between insulin resistance and irisin in all subjects, where insulin resistance decreases by 0.135 units with every one-unit increase in serum irisin

Discussion

This study showed a significantly lower serum irisin level in newly diagnosed T2DM cases than in non-diabetic controls. Studies by Choi et al., Xiang et al., and Kurdiova et al. support these findings (7,12). Systematic review by Alencar et al. supports this study's findings of decreased irisin levels in diabetic patients. According to them, decreased expression of PGC-1α in diabetic patients resulted in decreased irisin levels. Studies by Tang et al. and Xie et al. found no significant differences in irisin levels of newly diagnosed T2DM cases and those of healthy controls. It may be attributed to inflammation, stress hormones, and genetic factors affecting serum irisin levels (7).

A significant positive correlation was found between serum irisin levels, weight, and BMI in the cases. The controls also showed a positive correlation, but the co-efficient value was insignificant. Studies by Kyung Hee and Park found a positive correlation between serum irisin and BMI. They suggest that increased irisin levels in patients with high BMIs may be irisin's compensatory role in combatting obesity. Irisin causes more browning of white adipocytes in obese individuals (8). Contrary to the present study's findings, Choi et al. found a negative association between serum irisin and the above anthropometric parameters (12).

The present study found a positive correlation between serum insulin and irisin among the cases but a negative correlation in controls. A negative correlation was observed by including both cases and control groups as a single group. These associations did not have a significant p-value.

In the case group, a positive correlation between serum irisin, BMI, and insulin resistance may suggest a compensatory increase of irisin to combat insulin resistance (7). Experimental studies in mice and humans by Bostrom et al. revealed that irisin improves insulin resistance by increasing sensitization of the insulin receptor in the skeletal muscles and heart, improving hepatic glucose and lipid metabolism and pancreatic β cell functions, and transforming white adipose tissue to brown adipose tissue. However, evidence of this association in human studies is still controversial (8,12).

Recent studies by Liu JJ et al., Zhang Y et al., and Liu S et al. showed a negative correlation between irisin and insulin resistance. In contrast, Shoukry et al. and Park et al. found a positive correlation in newly diagnosed T2DM. The hypothesis suggested by both authors was that irisin increased to overcome insulin resistance, which may be caused by an insulin-resistant state (8, 12-14). Conversely, in controls, irisin and insulin resistance had a negative correlation in the present study, which is supported by many studies like Xiulin Shi et al., Huth C et al., and Moreno et al.' study (15-17). This observation differs from the meta-analysis by ShanhuQiu, which suggests that irisin levels are positively associated with insulin resistance in non-diabetics. They suggested that increased levels of inflammatory markers like tumor necrosis factor-α, interleukin-6, and C-reactive protein, sedentary lifestyle, physical inactivity, and obesity may affect the correlation between irisin and insulin resistance (18) The overall negative correlation between serum irisin levels and insulin resistance in the present study is supported by the findings of Bostrom et al (5).

Dyslipidaemia following diabetes results in uncontrolled triglyceride hydrolysis and increased free fatty acid (FFA) levels caused by the lipase enzyme in the pancreas. The increasing FFA concentration reduces the inhibiting effect of insulin on gluconeogenesis and glycogenolysis, thus increasing the blood glucose level (19,20). So, high serum lipase activity in diabetes and prediabetes groups depends on impaired insulin function due to insulin resistance and inadequate insulin secretion, which interferes with pancreatic exocrine-endocrine interactions (20,21). Positive correlation of irisin with the pancreatic profile in the case group may suggest the compensatory response of irisin in T2DM, and a negative correlation in controls may account for the irisin beneficiary impact on the pancreas (6,22).

This study is the first to be conducted in Eastern India to evaluate the association between serum irisin and insulin resistance. It was limited by the fact that only a small sample size had been studied. A larger sample size could have provided conclusive evidence.

Conclusion

The present study's key results showed significantly higher serum irisin levels in healthy volunteers than in newly diagnosed T2DM patients. Serum irisin positively correlated with insulin resistance in newly diagnosed T2DM patients and negatively correlated with insulin resistance in healthy volunteers. Associations between high irisin levels and insulin resistance could be elucidated by a physiological compensatory mechanism that would increase irisin levels due to an underlying decreased sensitivity to irisin's effects (obesity and irisin-resistant state, similar to insulin resistance). Another probable hypothesis is that increased muscle and fat tissue in obese patients releases more irisin than in healthy individuals. Further studies with larger samples should explore the possible pathways supporting these facts. The causality of the observed associations between the study parameters should be more comprehensively studied in prospective cohort and interventional studies to clarify irisin's role in T2DM.

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Ethical statement

All enrolled subjects had given written informed consent for participating in

this study. The Institutional Ethics Committee approved the study protocol (Registered No ECR/84/Inst/OR/2013 issued under Rule 122DD of the Drugs and Cosmetics Rules 1945) SCB, MCH, Cuttack under the IEC/IRB No: 709/28.9.18.

Conflict of interest

The authors declare that there is no conflict of interest regarding the publication of this article.

Author contributions

Saffalya Nayak collected data and performed the biochemical tests of the newly diagnosed T2DM cases. Debjyoti Mohapatra analyzed and interpreted the patient data and significantly contributed to writing the manuscript. All authors read and approved the final manuscript."

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