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Serum Irisin levels as a predictor of presence of diabetic retinopathy: A case-control study

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Abstract

Background: Diabetic Retinopathy (DR) is a major microvascular complication of diabetes mellitus. Chronic hyperglycemia can damage the small blood vessels in the retina, leading to blindness. Novel marker could help us better understand the pathogenesis of DR. In 2012, Boström *et al.* discovered irisin, a new myokine generated by skeletal muscle in response to exercise. Irisin improves insulin sensitivity, glucose homeostasis, and lipid metabolism and modulates inflammatory processes.

Objective: This study aims to measure serum irisin levels in patients with DR, patients without DR, and a control group. Also, measure irisin levels across clinical stages of DR. Additionally, to evaluate the relationship between serum irisin levels and the presence of diabetic retinopathy.

Methods: The study includes 240 individuals. Participants were divided into three groups: 80 patients with DR, 80 patients without DR, and 80 subjects in the control group. The subdivided DR group was divided into four stages ($n = 20$ per stage). Standard procedures and techniques were used to assess serum irisin, lipid profile, fasting blood sugar (FBS), and glycated hemoglobin (HbA1c), and the results were analyzed statistically.

Results: The primary result serum irisin levels were significantly lower (69.68 ± 19.77 ng/ml) in patients with DR than in patients without DR and in the control group (82.17 ± 9.24 ng/ml) (120.66 ± 24.07 ng/ml), respectively, with a highly significant difference ($p < 0.001$). The study's further subgroup analysis within the DR group shows that irisin levels highly significant differences ($p < 0.001$), with a gradual decline across the clinical stages of DR with the lowest levels observed in the advanced stage (proliferative diabetic retinopathy). Irisin showed negative correlations with FBS, HbA1c, Triglyceride, Very Low-Density Lipoprotein, and duration of diabetes mellitus. Furthermore, logistic regression analysis confirmed that decreased serum irisin levels are independently associated with the presence of diabetic retinopathy.

Conclusion: The present study found that irisin levels were significantly lower in patients with DR. Additionally, a progressive decline in irisin levels was observed across the advancing clinical stages of diabetic retinopathy. Irisin is associated with disease presence and may serve as an independent predictor of the presence and progression of disease.

Keywords: Irisin, type 2 diabetes mellitus, diabetic retinopathy

Introduction

Diabetes Mellitus (DM) is a group of metabolic diseases characterized by disturbances in glucose metabolism that lead to chronic hyperglycemia due to impaired insulin secretion, insulin resistance, or both ^[1]. Long-term diabetes causes a number of complications, including microvascular and macrovascular ^[2].

Diabetic retinopathy (DR) is the most prevalent microvascular complication of diabetes ^[3]. Characterized by damage to the retina's tiny blood vessels caused by chronic hyperglycemia ^[4]. This can result in irreversible visual loss and blindness ^[5]. Therefore, early detection and treatment are critical to preventing vision loss from DR in patients with diabetes ^[6].

According to recent epidemic estimates for 2030, DR prevalence rates are expected to rise in low- to middle-income regions such as the Middle East, North Africa, and Africa, from 20.6% to 47.2%, significantly higher than in high-income regions such as Europe and North America ^[7]. Therefore, DR will become one of the world's most critical health issues ^[8].

Novel markers could help us understand the pathogenesis of DR. In 2012, Boström *et al.* discovered irisin, a novel myokine produced by skeletal muscle in response to physical activity ^[9]. This activity increases peroxisome-proliferator-activated receptor gamma coactivator 1-alpha (PGC1- α), which stimulates expression of the fibronectin type III

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Domain-containing protein 5 (FNDC5) gene, thereby increasing FNDC5, a membrane cell protein that when cleaved, generates irisin^[10]. Irisin plays an important role in converting white to brown adipose tissue, thereby reducing lipid accumulation^[11], regulates blood glucose by improving insulin sensitivity and reducing insulin resistance^[12], reduces oxidative stress effects induced by diabetes mellitus^[13], and reduces pro-inflammatory cytokines and increases the release of anti-inflammatory cytokines. This helps protect tissues from chronic inflammation^[14].

Materials and Methods

This case-control study was conducted from January to December 2025 at Basrah Teaching Hospital in Basrah Governorate, Iraq. The study comprised 240 participants, including 80 patients with T2DM and DR. Diabetic retinopathy cases were graded according to the International Clinical Diabetic Retinopathy (ICDR) Severity Scale into four stages: mild, moderate, severe NPDR, and PDR (20 in each stage). There were 80 individuals with T2DM who did not have DR. The study also included 80 control subjects who had no history of diabetes and appeared good healthy. Each group had 40 men and 40 females. Participants aged 30 to ≥ 70 years were recruited consecutively from the ophthalmology clinic at Basrah Teaching Hospital in Basrah Governorate, Iraq.

Inclusion Criteria:

1. Diabetic patients with diabetic retinopathy
2. Diabetic patients without diabetic retinopathy

Exclusion Criteria:

1. Cardiovascular disease, Chronic kidney disease
2. Chronic inflammatory diseases
3. Recent exercise regimen
4. Active infections
5. Pregnancy and lactation

Anthropometric measurements

Anthropometric measurements were taken of all study participants, including their height, weight, systolic blood pressure (SBP), and diastolic blood pressure (DBP). BMI is calculated by dividing weight in kilograms by height in meters squared (kg/m^2).

Collection and processing of samples

Blood samples were collected from all participants. A part of each obtained blood sample was placed in an anticoagulant tube for HbA1c testing. The remaining blood was deposited in sterile gel test tubes, left at room temperature for 30 minutes, and then centrifuged at 3000 rpm for 5 minutes to obtain serum. The divided serum parts were used for biochemical testing, including FBS and lipid profiling. The remaining portion is stored at -20°C for subsequent ELISA analysis of irisin levels.

Statistical analysis

Normality of continuous variables was assessed with the Shapiro-Wilk test. Normally distributed variables are presented as mean $\pm$ SD and compared using ANOVA; non-normal variables are summarized as median (IQR) and compared using the Kruskal-Wallis test. Multivariable logistic regression was used to assess the independent association between serum irisin and the presence of diabetic retinopathy, after adjustment for potential confounders. $p < 0.05$ was considered statistically significant.

Results

Table 1: The data for groups of patients with DR, patients without DR, and the control group were distributed by demographic characteristics, including age, sex, and BMI. There were no significant differences between study groups ($p > 0.05$). In contrast, there are significant differences between patients with DR, patients without DR, and controls in SBP and DBP ($p < 0.001$).

Table 1: Demographic characteristics of participants

Characteristic		Patient with DR (n=80)	patient without DR (n=80)	Control group (n=80)	P. value
Age (years)		53.44 $\pm$ 10.16	52.34 $\pm$ 10.70	49.58 $\pm$ 8.29	0.10 ^{NS*}
Sex	Male	40 (50.0%)	40 (50.0%)	40 (50.0%)	1.0 ^{NS**}
	Female	40 (50.0%)	40 (50.0%)	40 (50.0%)	
BMI (kg/m^2)		30.31 $\pm$ 4.19	29.63 $\pm$ 4.09	28.57 $\pm$ 6.52	0.15 ^{NS}
SBP (mmHg)		137.93 $\pm$ 11.21	130.04 $\pm$ 12.56	121.36 $\pm$ 2.50	<0.001
DBP (mmHg)		98.15 $\pm$ 8.56	91.16 $\pm$ 6.20	80.27 $\pm$ 6.13	<0.001

NS: non-significant at $p > 0.05$

*One-way ANOVA test, **Chi-square test.

Table 2: The results indicate that FBS and HbA1c in patients with DR were higher than in both patients without DR and controls ($p < 0.001$). Additionally, the study found highly significant differences between study groups in TC, TG, VLDL, and LDL levels ($p < 0.001$). For HDL levels, a significant difference was observed ($P = 0.02$).

Regarding irisin, the study found that the mean serum irisin level was lower in patients with DR (69.68 ± 19.77 ng/ml) compared to patients without DR and controls (82.17 ± 9.24 ng/ml) and (120.66 ± 24.07 ng/ml), respectively, with a highly significant difference ($p < 0.001$).

Table 2: Comparison of biochemical parameters among study groups

Parameters	Patient with DR (n=80) Mean ± SD	Patient without DR (n=80) Mean ± SD	Control group (n=80) Mean ± SD	P. value
FBS (mg/dl)	228.41 ± 93.84	218.26 ± 86.97	97.12 ± 13.23	<0.001
HbA1c (%)	8.75 ± 1.38	7.98 ± 1.21	4.85 ± 0.54	<0.001
T.C (mg/dl)	195.90 ± 48.24	188.15 ± 48.03	165.43 ± 27.88	<0.001
TG (mg/dl)	173.28 ± 81.72	169.92 ± 69.23	110.65 ± 26.82	<0.001
HDL (mg/dl)	41.91 ± 13.78	42.69 ± 12.60	46.73 ± 7.73	0.02
LDL (mg/dl)	117.38 ± 38.39	86.92 ± 33.13	73.50 ± 14.24	<0.001
VLDL (mg/dl)	34.25 ± 16.61	33.98 ± 13.83	22.12 ± 5.36	<0.001
Irisin (ng/ml)	69.68 ± 19.77	82.17 ± 9.24	120.66 ± 24.07	<0.001

One-way ANOVA test.

Table 3: presents the data for the clinical stages of diabetic retinopathy. The study found no significant differences in FBS, TC, and HDL levels among the mild, moderate, severe NPDR, and PDR stages of diabetic retinopathy ($p>0.05$). Regarding HbA1c and irisin, the study revealed highly

Significant differences ($p<0.001$), with a gradual decrease in irisin levels across the stages of diabetic retinopathy, with the lowest levels observed in the advanced stage (PDR). Additionally, TG and VLDL were significantly different ($p<0.01$) across the stages of DR.

Table 3: Comparison of biochemical parameters among clinical stages of Diabetic Retinopathy

Parameters	Mild NPDR n=20 Mean ± SD	Moderate NPDR n=20 Mean ± SD	Severe NPDR n=20 Mean ± SD	PDR n=20 Mean ± SD	P. value
FBS (mg/dl)	205.50 ± 45.53	201.14 ± 74.20	259.04 ± 130.10	209.40 ± 72.21	0.13 ^{NS}
HbA1c (%)	6.71 ± 0.38	7.31 ± 0.82	7.94 ± 1.51	9.05 ± 1.29	<0.001
T.C (mg/dl)	190.77 ± 48.01	206.24 ± 53.64	196.91 ± 56.89	189.69 ± 32.80	0.69 ^{NS}
TG (mg/dl)	135.76 ± 30.20	156.90 ± 59.34	180.26 ± 98.45	206.76 ± 53.46	<0.01
HDL (mg/dl)	44.12 ± 11.86	43.94 ± 12.26	40.00 ± 12.99	39.57 ± 17.62	0.60 ^{NS}
LDL (mg/dl)	97.06 ± 31.27	113.41 ± 36.44	122.41 ± 35.50	136.65 ± 41.14	<0.01
VLDL (mg/dl)	27.15 ± 5.95	31.39 ± 11.87	36.05 ± 19.69	41.35 ± 10.69	<0.01
Irisin (ng/ml)	87.79 ± 8.07	82.34 ± 5.97	60.99 ± 16.95	46.44 ± 9.37	<0.001

One-way ANOVA test.

Table 5: The study found that irisin correlates negatively and significantly with disease duration, HbA1c, TG, and VLDL. At the same time, a negative but non-significant correlation was observed between irisin and FBS ($p>0.05$).

retinopathy, whereas age, sex, BMI, SBP, and DBP were not statistically significant in the adjusted model.

Table 5: Pearson Correlation of Irisin Levels with Biochemical and Clinical Characteristics in Patients with Diabetic Retinopathy

Biomarkers	Pearson Correlation	P. value
Age (years)	.084	.464
BMI (kg/m ²)	.091	.426
Duration of DM (years)	-.257*	.022
FBS (mg/dl)	-.188	.100
HbA1c (%)	-.728**	.000
TC (mg/dl)	.079	.491
TG (mg/dl)	-.376**	.001
HDL (mg/dl)	.087	.443
LDL (mg/dl)	.202	.075
VLDL (mg/dl)	-.376**	.001

**. Correlation is significant at the 0.01 level (2-tailed).

*. Correlation is significant at the 0.05 level (2-tailed).

Table 5: Multivariable Logistic regression analysis

Variable	Adjusted OR	95% CI	P value
Irisin (ng/ml)	0.93	0.90 – 0.96	<0.001
Age (years)	1.03	0.99 – 1.06	0.102
Sex (males vs females)	1.08	1.37 – 0.85	0.190
BMI (kg/m ²)	1.10	1.02 – 1.19	0.015
HbA1c (%)	1.45	1.12 – 1.89	0.004
FBG (mg/dl)	1.01	1.00 – 1.02	0.033
TC (mg/dl)	1.01	1.00 – 1.02	0.041
LDL (mg/dl)	1.04	1.06 – 1.01	0.006
HDL (mg/dl)	0.96	0.93 – 0.99	0.018
TG (mg/dl)	1.01	1.00 – 1.02	0.021
VLDL (mg/dl)	1.02	1.01 – 1.03	0.008
Duration of DM (years)	1.18	1.08 – 1.29	<0.001
SBP (mmHg)	1.01	0.99 – 1.03	0.267
DBP (mmHg)	1.02	1.03 – 0.98	0.120

Discussion

The results of the study demonstrated that patients with DR had significantly lower serum irisin levels than patients without DR or the control group. Our findings are supported by previous studies by Hou *et al.* [15] and Hu *et al.* [16], which examined the relationship between irisin concentrations and DR and found that patients with PDR had lower irisin concentrations than patients without PDR or the control group. Despite being focused on PDR, these findings confirmed our finding that irisin levels decline with occurrence and progression of disease.

Table 5: A multivariable logistic regression analysis was performed to evaluate the independent association between serum irisin levels and DR. After adjusting for age, sex, BMI, FBG, HbA1c, lipid profile, duration of DM, SBP, and DBP, serum irisin remained a significant independent predictor of DR. Lower irisin levels were significantly associated with higher odds of DR (adjusted OR = 0.94, 95% CI: 0.91–0.97, $p<0.001$). All lipid profile parameters (TC, LDL, HDL, TG, and VLDL), FBG, HbA1c, and duration of DM were independently associated with diabetic

This decrease in serum irisin levels in patients with DR could be attributed to the negative effects of T2DM on blood components, in which increased glycated molecules lead to increased oxidative stress across a variety of organs, including skeletal muscle^[17]. Skeletal muscle is the primary source of irisin. Impaired skeletal muscle function inhibits PGC-1 α activation in muscle tissue. This reduces FNDC5 gene expression, thereby decreasing irisin production^[18].

The study's additional subgroup analysis of the DR group reveals that serum irisin levels gradually decrease across the clinical stages of DR, with the lowest levels observed in the advanced stage (PDR). This finding is consistent with a previous study by Abu-Yaghi *et al.*^[19]. Inflammation plays a significant role in the pathogenesis of DR^[20]. Irisin modulates inflammation by promoting anti-inflammatory cytokines, such as IL-10, and inhibiting the release of pro-inflammatory cytokines, such as TNF- α ^[21]. This may indirectly contribute to the progression of DR^[16]. This supports the hypothesis that low irisin levels indicate a loss of protective effects against retinal inflammation, leading to retinal damage and increased disease severity.

Regarding the lipid profile, the study found that TC, TG, LDL, and VLDL levels were elevated in patients with DR. In contrast, HDL levels were lower in patients with DR compared to patients without DR and the control group. Furthermore, a significant negative correlation was found between irisin and both TG and VLDL. These results align with the findings of Abu Tarboush *et al.*^[17], who reported a significant negative correlation between irisin and TG levels. No significant correlation was observed in our study between irisin and TC, HDL, and LDL.

Furthermore, lipid profiles across clinical stages of DR differ significantly in TG, VLDL, and LDL levels. At the same time, TC and HDL showed no significant differences across clinical stages. These results were consistent with the findings of a previous study by Alattas *et al.*^[22].

According to these results, patients with DR have increased lipid levels. This may damage the retinal microvasculature by forming lipid particles within capillaries. Additionally, dyslipidemia damages mitochondria, which may accelerate retinal neuronal apoptosis and retinal destruction^[23]. Irisin is involved in regulating lipid metabolism. Irisin activates the expression of uncoupling protein-1 (UCP-1), thereby accelerating the conversion of white adipose tissue to brown adipose tissue and enhancing lipid utilization^[24]. Therefore, decreased irisin levels may impair lipid control, leading to elevated blood lipid levels, which contribute to retinal damage and the progression of diabetic retinopathy.

In the correlation analysis, irisin was negatively correlated with FBG; however, this association was not statistically significant in our study. While the correlation of HbA1c was negative and statistically significant. These findings are in line with Wang *et al.*^[25], who observed increased irisin levels associated with decreased FBG and HbA1c levels. Supporting the role of irisin in maintaining glucose homeostasis by enhancing insulin sensitivity, facilitating glucose uptake in skeletal muscles, and improving hepatic glucose metabolism^[26]. Furthermore, a significant negative correlation between irisin levels and the duration of DM was observed in patients with DR. This finding is consistent with a previous study by Ali *et al.*^[27], which suggested that prolonged hyperglycemia may further suppress irisin secretion.

In logistic regression analysis, irisin is an independent predictor of diabetic retinopathy, remaining significant even after adjustment for major confounders. These findings suggest that irisin may have a beneficial effect on the retina and that lower irisin levels may be associated with increased severity of diabetic retinopathy.

In summary, our study found that circulating irisin levels were significantly reduced in diabetic retinopathy and decreased progressively across clinical disease stages. Irisin showed a significant association with disease presence and may act as an independent predictor of disease presence and progression.

Conclusions

This study discovered that patients with DR had significantly lower irisin levels than patients without DR or the control group. It also demonstrated that irisin levels decreased throughout the clinical stages of DR. Lower irisin levels are associated with the presence and severity of diabetic retinopathy in our study groups.

Study Limitations

This study has some limitations. It was conducted at a single center with a moderate sample size; therefore, the findings may not be generalizable outside Basrah. Variability in ELISA kits and serum storage time could also affect measurements. Further studies with multi-center recruitment and larger samples are needed to confirm these findings. In addition, future studies are required to investigate the potential therapeutic effects of irisin in diabetic retinopathy.

List of Abbreviations

T2DM: Type 2 Diabetes Mellitus, FBG: Fasting Blood Glucose, PGC1- α : Peroxisome proliferator-activated receptor Gamma coactivator 1-alpha, FNDC5: Fibronectin type III Domain-Containing 5, DR: Diabetic Retinopathy; NPDR: Nonproliferative Diabetic Retinopathy, PDR: Proliferative Diabetic Retinopathy, HbA1c: Glycated Hemoglobin, TG: Triglyceride, VLDL: Very Low-Density Lipoprotein, LDL: Low-Density Lipoprotein, HDL: High-Density Lipoprotein, TC: Total Cholesterol, SBP: Systolic Blood Pressure, DBP: Diastolic Blood Pressure.

Ethics Approval and Consent to Participate

The study was approved by the Research Ethics Committee of the College of Medicine, University of Basrah, Basrah, Iraq, under approval number 6395, Dated 9 December 2024, to conduct the study and collect data. In addition, an official letter dated 29 December 2024 confirms that the Basrah Health Directorate/Training and Human Development Center approval number 856 granted legal permission to access the Basrah Teaching Hospital for the research. Written informed consent was obtained from all participants before enrollment in the study.

Data Availability

The datasets generated and analyzed during the current study are available from the corresponding author on reasonable request.

Conflict of Interest

The author confirms they have no competing interests.

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