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ORIGINAL ARTICLE

Serum Irisin Levels in Adult Type 2 Diabetic Patients with Microvascular Complications

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ABSTRACT

Background: Type 2 diabetes mellitus (T2DM) is a multisystem chronic disease that has attained an epidemic scale. The microvasculature is harmed by persistent hyperglycemia, which eventually results in diabetic nephropathy, neuropathy, and retinopathy. Irisin was identified as a myokine that can affect several metabolic pathways. The present study aimed to investigate the value of irisin measurement in early detection of microvascular complications in adult T2DM patients. **Methods:** This case-control study included 90 subjects divided into 3 equal groups: Group I of 30 healthy volunteers, group II of 30 adult T2DM patients without complications, and group III 30 adult T2DM patients with microvascular complications. All studied subjects were subjected to clinical assessment and lab investigations that included routine parameters, cystatin C, urine albumin creatinine ratio as well as irisin measurement. **Results:** Irisin was significantly lower in the patient groups. It showed moderate performance (AUC 0.674, p-value 0.007) with 70% sensitivity and 63.3% specificity for detection of microvascular complications. **Conclusions:** Irisin has a connection to T2DM, with moderate performance in detection of micro-vascular complications. Irisin could, therefore, be used to early of diabetic microvascular complications in adult T2DM patients. **Keywords:** Irisin, microvascular complications, type 2 diabetes.

INTRODUCTION

Type 2 diabetes mellitus (T2DM) has become a widespread worldwide epidemic of chronic endocrine and metabolic disorders, causing several acute and chronic consequences with fatal complications. [1]. Over 1 million deaths have been linked to the condition in 2017 alone, making it the tenth leading cause of death worldwide. Diabetes comes 7th regarding suffering, causing disability and shortened life span [2]. It was found that patients with T2DM for longer durations are more prone to microvascular complications, all of which have negative impact on quality of life and life expectancy as well [3]. Irisin is a myokine that was discovered in 2012. It can boost body use of energy, stimulate metabolism, and trigger conversion of energy-storing white fat into heat-producing brown fat. Irisin can thereby increase insulin sensitivity [1, 4]. The work of **Choi *et al*.** has shown that reduced irisin level is related to insulin resistance and T2DM occurrence [5]. The pleiotropic features of irisin have been extensively studied, indicating its role in the control of energy metabolism by interfering with many metabolic processes. Irisin has been suggested to have actions by way of alpha-5 (αV) integrin receptors [6,7]. Irisin is primarily synthesized by skeletal muscle, making up around two-thirds of total circulating irisin. However, investigations indicate that it can be generated by cellular islets in the pancreas [8]. There is a growing interest in irisin as a potential marker of diabetic profile and

complications in different subgroups**,** including elderly patients with T2DM [9], elderly patients with hypertension, patients with overweight and obesity, and pregnant women with gestational DM [7]. The present work aimed to investigate the value of serum Irisin level measurement in early detection of microvascular complications in adult T2DM patients.

METHODS

This is a case-control study, which was conducted on cases attending the clinical pathology department and outpatient clinics of internal medicine in Zagazig University hospitals during the period from March 2022 to September 2022. Verbal and written informed consents were obtained from all participants after an explanation of the procedure and medical research. The study was carried out after the approval of the Institutional Review Board (IRB), with approval number #8013-3108-2021. The research was conducted according to the World Medical Association's Code of Ethics (Helsinki Declaration) for human research.

Sample Size: Subjects enrolled included 90 subjects divided into 3 equal groups: Group I of 30 healthy volunteers, group II of 30 adult T2DM patients without complications, and group III 30 adult T2DM patients with microvascular complications.

Patients:

Patients with the following criteria were included; adult patients above 18 years old, clinical diagnosis with T2DM and its complications, approval for enrollment in the study, and Egyptian nationality. We excluded pediatric patients, patients with other types of diabetes rather than type 2, oncology patients, patients with autoimmune disorders, and patients refusing to enroll in study.

Methods:

Full clinical assessment which includes complete history taking, clinical examination (internal medicine, ophthalmology, neurology), and anthropometric measurements were performed for all diabetic patients. Laboratory tests were performed including complete blood count on Sysmex XN cell counter (*Sysmex corporation-Japan*), routine chemistry and diabetic profile (liver function tests, kidney function tests, lipid profile, fasting and postprandial blood glucose) on Roche Cobas 8000 modular (*Roche Diagnostics, Switzerland*), ESR by Westergren method, and HbA1c, Urinary albumin⁄creatinine ratio and Cystatin C on Roche Cobas 6000 modular (*Roche Diagnostics, Switzerland*).

The following parameters were calculated as follows:

- CKD-EPI Creatinine Equation (2021) for GFR estimation [10]

eGFRcr = 142 x min (Scr/κ, 1) α x max (Scr/κ, 1)-1.200 x 0.9938Age x 1.012 [if female]

where:

Scr = standardized serum creatinine in mg/dL

κ = 0.7 (females) or 0.9 (males)

α = -0.241 (female) or -0.302 (male)

min (Scr/κ, 1) is the minimum of Scr/κ or 1.0

max (Scr/κ, 1) is the maximum of Scr/κ or 1.0

Age (years)

- CKD-EPI Creatinine-Cystatin Equation (2021) [10]

eGFRcr-cys = 135 x min (Scr/κ, 1) α x max (Scr/κ, 1)-0.544 x min (Scys/0.8, 1)-0.323 x max (Scys/0.8, 1)-0.778 x 0.9961Age x 0.963 [if female]

where:

Scr = standardized serum creatinine in mg/dL

κ = 0.7 (females) or 0.9 (males)

α = -0.219 (female) or -0.144 (male)

min (Scr/κ, 1) is the minimum of Scr/κ or 1.0

max (Scr/κ, 1) is the maximum of Scr/κ or 1.0

Scys = standardized serum cystatin C in mg/L

Age (years)

- Triglycerides index (TyG) [11]

TyG index = ln [Fasting triglyceride (mg/dl) × fasting glucose (mg/dl)]/2

Irisin was measured in serum samples by *ELISA* according to the instruction of the manufacturer. Kit was provided by SunRed biotechnology company *(China)*, Catalogue No. 201-12-5328. Kit specifications as follows: Sensitivity: 0.157ng/ml, Assay range: 0.2ng/ml→60ng/ml. Data was analyzed statistically with IBM SPSS,

version 23.0 *(IBM Corporation, Armonk, New York)*.

RESULTS

There was a statistically significant increase in weight, height, waist circumference and BMI in patients' groups compared to control group (P < 0.005) (Table 1). The most common complication found was neurological complications (93.3 %), then nephropathy (73.3%), followed by retinopathy (56.6%).

Considering the three microvascular complications studied in this work (retinopathy, nephropathy and neuropathy) patients were distributed into 3 subgroups according to the number of microvascular complications as follows: having 1, 2 or 3 microvascular complications. There was no marked variation in the irisin level among the three subgroups (p>0.05) (Table 2).

There was a statistically significant increase in ESR, glucose, HbA1C, creatinine, urea, triglycerides levels, and urine albumin/creatinine ratio in the patients group compared with the control group (P<0.05). There was a statistically significant decrease in total protein, albumin, HDL, irisin, triglycerides index, and estimated GFR in the patients' groups as regard to the control group (Table 3).

There was a statistically significant increase in albumin, creatinine, HDL-c, GFR, urine albumin/creatinine ratio and cystatin C levels in patients with microvascular complications compared to control subjects (p <0.005) (Table 4).

There was no correlation between irisin and any of studied parameters (Table 5).

Irisin showed moderate performance (area under curve of 0.674, p-value 0.007), with 70% sensitivity and 63.3% specificity in detection of microvascular complications (Table 6).

Table 1: Demographic and anthropometric criteria of studied groups.

	Control	Patients	t	P
Age: **Mean ± SD** **Range**	 55.8 ± 5.65 48 - 70	 59.3 ± 11.13 28 – 82	1.617	0.109
Weight	80.2 ± 9.4	91.7 ± 8.7	3.9	< 0.005
Height	164.8 ± 8.2	167 ± 9.7		
Waist circumference	95.8 ± 5.3	104.3 ± 5.9		
BMI	29.7 ± 4	33.1 ± 3.8		
	N (%)	**N (%)**	**t value**	**P**
Gender: **Female** **Male**	 11 (36.7) 19 (63.3)	 27 (45) 33 (55)	1.794	0.180

Table 2: Comparison of Irisin values among patients in group III (n=30) distributed into groups according to number of complications.

Group	1 complication	2 complications	3 complications	F	P
No.	7	9	14	2.77959	0.79858
Irisin (ng/ml)	19.53471	6.781	10.12179		

Table 3: Laboratory data of studied patients.

Parameter	Control	Patients	t	P
TLC (10^3/cmm) Mean ± SD Range	7.24 ± 1.79 4.2 - 9.9	8.5 ± 2.8 5.9 - 11.5	1.71	0.08
Hemoglobin (g/dl) Mean ± SD Range	12.3 ± 2.2 10.0 - 14.6	12.1 ± 1.6 11.5 – 13.9	0.74	0.45
Platelet count (10^3/cmm) Mean ± SD Range	230 ± 90.4 155 - 331	230± 96.3 147 – 324	1.21	0.22
ESR (mm/hour) Mean ± SD Range	11.3 ± 7 3 – 36	32.4 ± 27 3 – 121	4.2	< 0.005
T. proteins (g/dl) Mean ± SD Range	7.7 ± 1.6 5.9 – 12.3	6.8 ± 1.1 0.3 – 8.5	3.06	<0.005
Albumin (g/dl) Mean ± SD Range	4.4 ± 0.4 3.8 – 5.6	3.8 ± 0.8 1.9 – 5.2	4.3	< 0.005
ALT (IU/l) Mean ± SD Range	17.8 ± 9 9.2 – 50.2	25.3 ± 33.4 6.2 – 200	1.20	0.23
AST (IU/l) Mean ± SD Range	17.1 ± 3.7 11.6 – 24.9	42.2 ± 86.4 6.9 – 595.0	1.58	0.116
Total bilirubin (mg/dl) Mean ± SD Range	0.3 ± 0.2 0.1 – 1	1.2 ± 2.5 0.2 – 13.6	1.8	0.07
Direct bilirubin (mg/dl) Mean ± SD Range	0.2 ± 0.1 0 – 0.5	0.7 ± 2.2 0.1 – 12.2	1.3	0.16
Creatinine (mg/dl) Mean ± SD Range	0.8 ± 0.2 0.5 – 1.1	1.6 ± 1.4 0.3 – 6.3	2.9	< 0.005
Urea (mg/dl) Mean ± SD Range	13.2 ± 4.7 6.5 – 24.5	33.9 ± 26 7.8 – 124.2	4.3	< 0.005
Cholesterol (mg / dl) Mean ± SD Range	164.5 ± 26.4 99.2 – 215.8	181.3 ± 47.4 82.5 – 340.3	1.8	0.07
Triglycerides (mg/dl) Mean ± SD Range	110.9 ± 33.2 47.1 – 203.3	139.1 ± 41.8 55 – 230	3.21	< 0.005
HDL (mg/dl) Mean ± SD Range	49.3 ± 12.2 22 – 70	40.3 ± 14.2 6 – 72	2.97	< 0.005

LDL (mg/dl) Mean ± SD Range	100.5 ± 24.8 11.3 – 143	117.7 ± 44.3 26.6 – 257.6	1.97	0.05
Fasting blood glucose (mg/dl) Mean ± SD Range	95.2 ± 5 82 – 103	177.2 ± 48.3 110 – 362	9.2	< 0.005
2hPP (mg/dl) Mean ± SD Range	108.8 ± 8.7 99 – 130	262.1 ± 61.8 181 – 462	13.49	< 0.005
HbA1c (%) Mean ± SD Range	5.5 ± 0.4 4.8 – 6.1	8.6 ± 1.4 6.7 – 12.7	11.96	< 0.005
Urine albumin/creatinine ratio Mean ± SD Range	14.3 ± 7.3 3 – 29	412.9 ± 636.1 6 – 2661.6	3.4	< 0.005
Cystatin C (mg/l) Mean ± SD Range	1 ± 0.2 0.7 – 1.4	1.6 ± 1.1 0.6 – 4.7	3.5	< 0.005
Irisin (ng/ml) Mean ± SD Range	11.9 ± 9.3 3.6 – 56.2	10.2 ± 10.2 3.1 – 58.1	0.74	0.45
TyG* Mean ± SD Range	8.5 ± 0.3 7.6 – 9.2	9.3 ± 0.4 8.3 – 10.1	9.27	< 0.005
GFR by cystatin** Mean ± SD Range	85±19.5 (49-113)	59.5±34.1 (9-142)	-3.7943	<0.005
GFR by creatinine Mean ± SD Range	96.6±16.8 (56-123)	70.1±36.7 (7 – 158)	-3.75916	<0.005

*TyG: triglyceride glucose index. **GFR: glomerular filtration rate.

Table (4): Routine laboratory data between patient's subgroups.

	Group II (non-complicated)	Group III (complicated)	t	P
T. proteins (g/dl) Mean ± SD Range	7.1 ± 0.7 5.9 – 8.5	6.7 ± 0.8 4.3 – 8.2	0.655	0.514
Albumin (g/dl) Mean ± SD Range	4.2 ± 0.5 3 – 5.2	3.4 ± 0.8 1.9 – 4.6	4.45	< 0.005*
Creatinine (mg/dl) Mean ± SD Range	0.8 ± 0.2 0.3 – 1.1	2.4 ± 1.7 0.9 – 6.3	5.21	< 0.005*
ESR (mm/hour) Mean ± SD Range	25.7 ± 22.5 5 -114	39 ± 29.7 3 – 121	1.96	0.054
Cholesterol (mg/dl) Mean ± SD Range	181.6 ± 28 124.9 – 240	181.1 ± 61.6 82.5 – 340.3	0.03	0.97

Triglycerides (mg/dl) Mean ± SD Range	131 ± 32.3 55 – 189	147.2 ± 48.7 56.4 – 230	1.51	0.13
HDL (mg/dl) Mean ± SD Range	47 ± 13.5 11 – 72	33.5 ± 11.5 6 – 57.8	4.18	< 0.005*
LDL (mg/dl) Mean ± SD Range	119.3 ± 35.7 61.7 – 211	116.1 ± 52.1 26.6 – 257.6	0.277	0.78
Fasting blood glucose (mg/dl) Mean ± SD Range	189.3 ± 55.3 119 – 362	165.2 ± 37.4 110 – 278	1.97	0.053
2hPP (mg/dl) Mean ± SD Range	269.6 ± 63.7 198 – 462	254.6 ± 59.9 181 – 391	0.937	0.352
HbA1c (%) Mean ± SD Range	8.1 ± 0.9 6.8 – 11.2	9 ± 1.6 6.7 – 12.7	2.4	0.018
Urine albumin/creatinine ratio Mean ± SD Range	29.8 ± 36 6 – 167.6	796 ± 719 6 – 2661.6	5.82	< 0.005*
Cystatin C (mg/L) Mean ± SD Range	1 ± 0.3 0.6 – 1.7	2.2 ± 1.2 0.7 – 4.7	5.219	< 0.005*
Irisin (ng/ml) Mean ± SD Range	9.1 ± 8.4 3.1 – 45.8	11.3 ± 11.7 3.7 – 58.1	0.832	0.408
****TyG** Mean ± SD Range	9.4 ± 0.4 8.5 – 10.1	9.3 ± 0.5 8.3 – 10.1	0.336	0.737
*****GFR by cystatin C** Mean ± SD Range	79.3±27.4 (37-142)	39.6±28.3 (9-111)	5.51253	<0.005*
GFR by creatinine Mean ± SD Range	98.8±20 (56-158)	41.4±25.1 (7-91)	-9.79218	<0.005*

*TyG: triglyceride glucose index. **GFR: glomerular filtration rate.

Table (5): Correlation between Irisin and Lab data (patients' group).

	R	P-value
BMI*	-0.103	0.431
Total protein*	0.097	0.461
Albumin*	0.067	0.612
A/C ratio *	0.063	0.630
GFR by cystatin C *	-0.027	0.838
GFR by creatinine *	-0.018	0.890
urea **	0.02	0.878
cystatin C*	-0.036	0.786
creatinine **	0.179	0.170
cholesterol*	0.059	0.652
Triglycerides*	0.017	0.900
HDL*	-0.036	0.782
LDL*	0.176	0.178
HbA1c*	-0.111	0.397
Fasting blood glucose*	-0.253	0.051
2hour Post Prandial*	-0.151	0.250
TyG *	-0.150	0.254
ESR **	-0.138	0.293

(r): * Pearson Correlation

** Spearman's rho Correlation. Correlation is significant at the 0.05 level (2-tailed).

A/C: urine albumin / creatinine ratio.

TyG: triglycerides glucose index. GFR: glomerular filtration rate.

Table (6): Details of irisin performance in detection of microvascular complications.

Area under the curve		Sd. Error	P value	Asymptotic 95% Confidence Interval	
				Lower Bound	Upper Bound
0.674		0.058	0.007*	0.562	0.787
Sensitivity	**Specificity**	**PPV**	**NPV**	**Overall accuracy**	**Cut off level of irisin**
70.0%	63.3%	79.2%	51.4%	67.77%	8.59

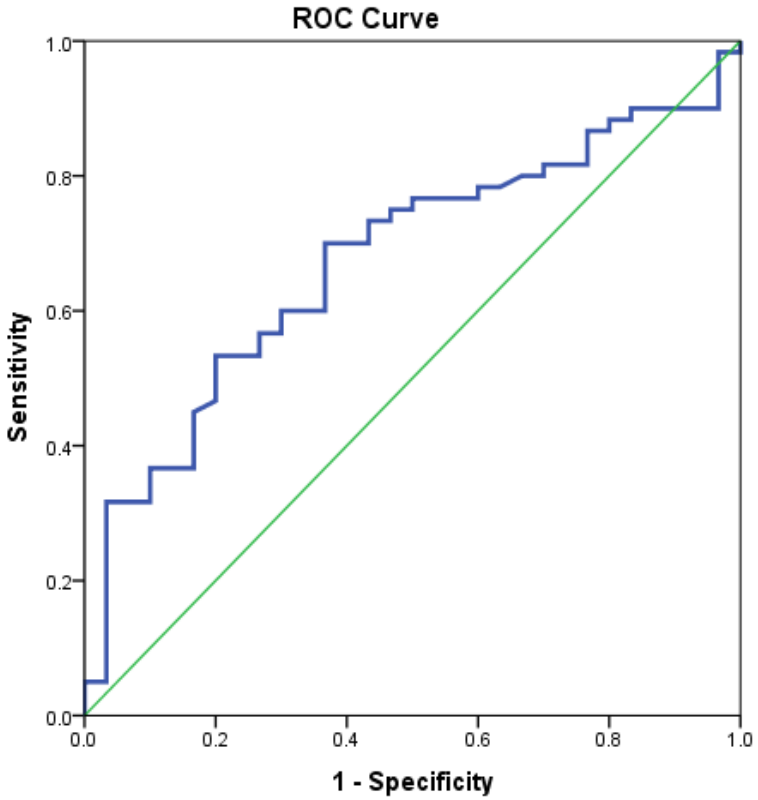

Figure 1: Receiver Operating Characteristics curve for irisin test in detecting microvascular complications.

DISCUSSION

Individual having T2DM were estimated to exceed 460 million in 2017. Annual deaths attributed to the disease are almost 1 million cases. Furthermore, it is anticipated that the prevalence of diabetes will keep increasing, especially in developed regions. These alarming figures imply that novel markers are needed in the field [12]. Our study aimed to investigate a potential role for irisin in early detection of microvascular complications in T2DM patients.

Regarding the demographic data in this study, a similar study was conducted by **Ahmed *et al.*** at a tertiary care hospital on 65 T2DM cases. In agreement with our findings, there was no marked variation between their studied groups regarding age. However, they found the same significant difference regarding BMI between patients and control subjects [13]. Another study by **Haddad *et al.*** that included 90 T2DM cases was in agreement with our results regarding microvascular complications of diabetes, where the most common complication found was diabetic neuropathy [14].

The laboratory data showed that there was statistically significant increase in ESR, creatinine, urea, triglycerides, fasting blood glucose, 2hPP as well as HbA1c in patients group compared to control group ($P < 0.005$). These results are aligned with that of **Liu *et al.*** [15]**, Xiang *et al.*** [16], **Yang *et al.*** [17]**, Huh *et al.*** [18] as well as with results of **Ahmed *et al.*** [13]. While these results were against results reported by **Tarboush *et al.*** [19]**.** In contrast, total protein, albumin &HDL in patient's group were significantly lower compared to control group. This is in agreement with findings of **Liu *et al.*** [15], and against those of **Strengel *et al.*** [20]**.**

As regard urine albumin/creatinine ratio and cystatin C , this study revealed significant increase in patient's group compared with

control group which get in accordance with that of **Liu *et al.*** [15]**, Wang *et al.*** [21] as well as **Ahmed *et al.*** [13]. For irisin level in this study, the patients' groups showed lower levels than that of control group with non-significant difference. This result agreed with that of **Liu *et al.*** [15]**, Xiang *et al.*** [16]**, Wang *et al.*** [21] **and Tarboush** [19]**.** In Contrast, **Huh *et al*** [18] stated that irisin was higher in the diabetic group. Also **Mehrabian *et al.*** [22] demonstrated similar results in obese patients compared to control subjects. **Ahmed *et al*** [13] also found a non-significant difference between control and patients with type 2 DM regarding serum irisin.

In contrast to the work of other investigators, we didn't find a correlation between serum irisin and any other studied parameters, possibly due to study limitations of sample size. **Ebert *et al.*** [23], however, found that irisin correlated with total cholesterol & LDL-c. In the same line **De Meneck *et al.*** [24] showed similar findings with triglycerides and total cholesterol. Against this study **Ahmed *et al.*** [13] reported that circulating levels of irisin were inversely correlated with levels of total cholesterol, LDL-C and triglycerides that were sensitive to high levels of irisin. **Park *et al.*** [25] found that irisin levels were negatively correlated with fasting glucose. **Liu *et al.*** [15] also reported an inverse correlation between hyperglycemia and serum irisin levels. **Mehrabian, Yan *et al.*** revealed that serum irisin was inversely correlated with both glucose and HbA1C in T2DM patients [22,26].

Also, **Liu *et al.*** [15] found that irisin level was positively correlated with blood glucose in non-diabetic subjects. **Huh *et al.*** [18] found that serum irisin was positively correlated with fat-free mass, and showed a positive correlation with BMI. Also, **Park *et al.*** [25] reported that circulating irisin levels were positively associated with body fat mass in the whole cohort and with BMI in the subgroup of obese individuals. The study by **Tarboush *et al.*** [19] revealed significant negative correlations between serum Irisin concentrations and HbA1c, TGs, and LDL, and positive correlation with HDL. No significant correlations were found with total cholesterol, triglycerides, age, gender, or BMI.

Our findings revealed that irisin showed 70% sensitivity and 63.3% specificity for detection of microvascular complications. However, there was no significant difference in irisin among our patient subgroups. **Ahmed *et al.*** [13] reported similar findings. However, **Xiang *et al.*** [16] reported lower levels of irisin in patients with a new onset T2DM. These controversies could be attributed to patterns of irisin release in different stages of disease, where it is earlier released in pre-diabetic phases, while there might be an exhaustion phenomenon leading to lower irisin later on. The negative correlation that **Huh *et al.*** [18] found between irisin level and diabetic illness duration might be a supporting theory.

CONCLUSIONS

Irisin has a connection to T2DM and its risk factors, suggesting increased sensitivity for spotting micro-vascular complications early. Irisin might therefore enable early detection of problems and therapeutic action. We recommend considering the serial assessment of irisin through the course of disease as a tool for earlier detection of T2DM complications. Future studies will be needed for further elucidation of the role of irisin in T2DM.

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