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The Potential Relationship Between Serum Irisin Concentration With Inflammatory Cytokines, Oxidative Stress Biomarkers, Glycemic Indices and Lipid Profiles in Obese Patients With Type 2 Diabetes Mellitus: A Pilot Study

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Abstract

Objectives. Diabetes mellitus is a serious health-treated problem identified by disorders such as insulin resistance, dyslipidemia, and inflammation. Irisin, a newly discovered myokine/adipokine, is involved in metabolic homeostasis. The present study was carried out to investigate the potential relationship between serum irisin with inflammatory cytokines, oxidative stress biomarkers, glycemic indices, and lipid profiles in obese patients with type 2 diabetes mellitus.

Methodology. This analytical cross-sectional study was conducted on 62 participants (n=32 obese participants with diabetes, n=30 participants with normal weight). The participants answered a demographic questionnaire. Serum irisin, glycemic indices, lipid profiles, inflammatory cytokines and oxidative stress biomarkers were measured using standard methods. The difference between groups was assessed by independent-sample t-test or by a non-parametric equivalent. For qualitative variables, the Chi-Square test was used. Pearson rho coefficient was used to determine the potential relationship between irisin and inflammatory cytokines, oxidative stress biomarkers, glycemic indices, and lipid profiles. A $p<0.05$ was defined as significant.

Results. The median (IQR) age of the obese participants with diabetes was 54.0 years (52.2-60.7) and in the normal weight group was 38.0 years (30.0-47.2) ($p<0.001$). About 78% and 60% of participants in the obese with diabetes and the normal weight groups were females ($p>0.05$), respectively. Significant differences were observed in serum irisin levels between the two groups, with lower levels (218.74 ng/mL, [144.98-269.26]) noted in the obese with diabetes group compared to the normal weight group (266.68 ng/mL, [200.64-336.57]) with a $p=0.024$. There was a substantial difference between the two groups regarding IL-6, TNF-α, and hs-CRP ($p<0.05$). IL-6 had a moderate negative correlation with irisin in obese patients with T2DM (r=-0.478, $p=0.006$).

Conclusion. Irisin concentration was detected to be lower in obese people with diabetes. A negative relationship was detected between irisin and IL-6. Considering emerging evidence about the beneficial functions of irisin in improving metabolic abnormalities, designing future studies with greater sample sizes that will validate these results is needed.

Key words: Irisin, inflammation, glycemic indices, lipid profile, obesity, type 2 diabetes

INTRODUCTION

Diabetes mellitus is a severe global health problem and is one of the ten causes of morbidity and mortality in the adult population.[1,2] The prevalence of diabetes mellitus has increased in the past decades. In 2021, diabetes prevalence in all adults aged 20-79 years was estimated to be 10.5% worldwide (about 537 million).[3] It is estimated that this rate will rise to 783 million by 2045.[4]

In people with diabetes, insulin secretion is impaired or decreased due to beta-cell dysfunction. Glucose intolerance, hyperglycemia, insulin resistance and diabetes-related conditions such as dyslipidemia and inflammation are

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the main drivers of diabetes.[5] Cytokines released by adipose tissue initiate the pro-inflammatory status. This contributes to the downregulation of insulin signaling receptors in β-cells and insulin resistance.[6] One of the common co-existing conditions with diabetes mellitus is dyslipidemia, seen in. approximately 50% of people with diabetes.[7] The perturbation in lipid metabolism interacts with insulin resistance which may become contributory to the development of cardiovascular complications in type 2 diabetes mellitus (T2DM).[8]

The various microvascular and macrovascular complications of diabetes annually impose huge costs on the healthcare system.[9] In the long term, the complications of diabetes affect the quality of life of people with diabetes and reduce their life expectancy.[10] Thus, it is necessary to identify novel diagnostic and therapeutic approaches to timely diagnose diabetes and its related comorbidities.

Irisin, a proliferator-activated receptor-γ coactivator-1α (PGC-1α)-dependent myokine, is mainly secreted by skeletal muscles and exerts beneficial functions in human health. The PGC-1α expression influences irisin secretion in skeletal muscle cells. The expression of the PGC-1α protein promotes the expression of the transmembrane protein fibronectin type III domain-containing protein 5 (FNDC5), the precursor of irisin.[11] Aside from skeletal muscles, adipose tissue, liver, heart, brain, tongue, rectum, subcutaneous glands, stomach, spleen, and testis secrete irisin slightly.[12] The expression of FNDC5 in skeletal muscle is 100–200 times higher than in adipose tissue.[13]

Irisin exerts crucial effects on metabolic processes,[14] it modulates glucose homeostasis by enhancing glucose uptake by target cells, inhibits gluconeogenesis, increases insulin sensitivity and induces glucose transporter four (GLUT4) expression. Also, irisin imposes anti-inflammatory effects on macrophages and adipocytes.[15] A high level of irisin controls the levels of inflammatory cytokines such as IL-1β and TNF-α.[16]

Irisin exerts anti-oxidative and anti-apoptotic properties in various pathological conditions by enhancing the production of antioxidant enzymes and decreasing the production of reactive oxygen species.[17] Irisin promotes fatty acid oxidation,[18] increases the release of glycerol molecules and inhibits lipid accumulation in adipocytes by up-regulation of the expression of genes involved in lipolysis such as hormone-sensitive lipase (HSL), adipose tissue triglyceride lipase (ATGL), and fatty acid binding protein 4 (FABP4).[19]

The results of studies regarding circulating irisin were inconsistent. Reports revealed that there was a low level of irisin in patients with breast cancer, chronic kidney disease, chronic obstructive pulmonary disease, Behcet's disease, early-stage of non-alcoholic fatty liver disease (NAFLD) and hypothyroidism.[20,21] In contrast, it was previously observed that circulating irisin was high in individuals with obesity, late-stage NAFLD, polycystic ovary syndrome, coronary artery diseases, metabolic syndrome and gastrointestinal system cancer.[22,23] Also, controversial results were reported regarding the relationship between irisin and biochemical parameters in individuals with diabetes. Some studies showed a positive correlation between biochemical and metabolic factors, such as glycemic indices and anthropometric measurements in patients with T2DM with irisin. In contrast, others revealed a negative or no correlation.[24,25] There are limited human studies that assessed the relationship of irisin with inflammatory cytokines, oxidative stress biomarkers and biochemical factors. Given that there is insufficient evidence regarding the beneficial aspects of irisin in inflammatory and metabolical pathways, the present study aimed to determine the relationship between irisin and inflammatory cytokines, oxidative stress biomarkers, glycemic indices and lipid profiles in obese patients with T2DM.

METHODOLOGY

Study design and enrollment of participants

This analytical cross-sectional study was carried out on 62 participants (n=32 obese participants with diabetes, n=30 participants with normal weight).

Participants with diabetes enrolled in the study were referred from the healthcare centers of Maragheh University of Medical Sciences between August 2020 and March 2021. The volunteer healthy normal-weight participants were enrolled through recruitment announcements.

The protocol of the study was approved by the Regional Ethics Committee of the Maragheh University of Medical Sciences (Registration Number: IR.MARAGHEHPHC.REC.1398.029). Upon enrolment, the participants filled out a written consent form.

Participants were not included if they fulfilled any of the following criteria: age more than 65 and below 18 years, duration of diabetes history more than 6 months, severe mental and physical disabilities, co-existing medical conditions such as chronic diseases such as chronic kidney disease, type 1 diabetes, cirrhosis, autoimmune diseases and heart failure, pregnancy, lactating mothers, and patients taking insulin, anti-inflammatory agents, multivitamins or weight loss drugs.

Procedures

Participants were asked to accomplish a demographic questionnaire. The body mass index was calculated using weight (kilogram) and height (meter). Blood samples (approximately 5 ml) were collected in a fasting state. After serum extraction, samples were kept and frozen at -80 °C.

Samples were then processed accordingly for biochemical parameters which included the following: serum irisin concentration via enzyme-linked immunosorbent assay

(ELISA) test (Zellbio GmbH, Ulm, Germany [Inter-Assay: CV<12%, Intra-Assay: CV<10%]); serum malondialdehyde (MDA) and the total antioxidant status (TAS) via spectrophotometer using a commercial kit (Merck chemicals and Randox Laboratories, Ltd, Crumlin, UK, respectively); serum level of TNF-α and IL-6 using the ELISA method (Zellbio GmbH, Ulm, Germany [Inter-Assay: CV<12%, Intra-Assay: CV<10%] and E0082Hu, Bioassay Technology Laboratory, Shanghai, China [Inter-Assay: CV<10%, Intra-Assay: CV<8%]); high sensitive-C reactive protein level via immunoturbidimetry assay (Biosystems, Barcelona Spain COD 31927); serum levels of fasting blood sugar (FBS), triglycerides (TG), high-density lipoprotein – cholesterol (HDL-C), low-density lipoprotein – cholesterol (LDL-C), and total cholesterol (TC) via photometric method (Pars Azmoun Company, Tehran, Iran [Inter-Assay: CV<3.6%, Intra-Assay: CV<1%]); HbA1c level via commercial kit using the immunoturbidometric assay (Autoanalyzer, BT 1500, Biotecnica Instruments, Italy. The insulin level was measured via chemiluminescence method (Abbott ARCHITECT i2000SR, Chicago, USA).

To evaluate insulin resistance, the homeostatic model assessment insulin resistance (HOMA-IR) was computed by dividing the product of fasting insulin (FI) level (μU/ml) and fasting serum glucose level (mmol/L) by a factor of 22.5. The quantitative insulin sensitivity check index (QUICKI) model assessed insulin sensitivity using the following formula: QUICKI = $1/[\log(I_0) + \log(G_0)]$, where I_0 is insulin (μIU/ml), and G_0 is fasting serum glucose (mg/dl).[26] Estimated average glucose (eAG) was calculated using the formula: eAG = 28.7 x A1c– 46.7.

Sample size estimation

The results of Shanaki et al.'s study[27] were used for computing sample size. Because the median and IQR (1st and 3rd quartile) of irisin among diabetics and the healthy group have been reported in the cited study, the median and IQR (1st and 3rd quartile) values were converted to the mean and SD by using the proposed formulas in Xiang Wan et al., study as:

$$\text{Mean} = \frac{(q1+\text{Median}+q3)}{3} \quad \text{and SD} = \frac{(q3-q1)}{1.35}$$

(Q1 = 1st quartile, Q3 = 3rd quartile, SD = Standard deviation)

The reported median and IQR (1st – 3rd quartile) of irisin among diabetes patients and healthy participants were 1.96 (1.32- 3.32) and 4.14 (2.7 – 6.34) which were then converted to mean (SD) of 2.2 (1.5) and 4.4 (2.7), respectively. The computed minimum sample size was 21 per group. This sample size was adjusted to at least 23 per group in consideration of a possible drop-out rate of 10%.

Statistical analysis

The normality of data was assessed by both Shapiro–Wilk and Kolmogorov-Smirnov tests. Normally distributed quantitative data were presented as means and standard deviations (SD) and non-normal distributed data were shown as medians (25 to 75 percentile). The qualitative data were presented as frequencies (percent). To evaluate the mean difference between both groups, the independent-sample t-test for normal variables and the Mann-Whitney U-test for non-normal variables was used. Qualitative variables between groups were examined by the Chi-square test. Pearson correlation coefficient (Pearson's r) was used to determine the potential relationship between irisin level with inflammatory biomarkers, glycemic indices and lipid profiles. A p<0.05 was defined as statistically significant.

Data were analyzed using Statistical Product and Service Solutions (SPSS) Version 21 (SPSS Inc., Chicago, IL).

RESULTS

The mean (SD) ages of participants in the obese diabetes group and the normal weight group were 54.0 years (52.2-60.7) and 38.0 years (30.0-47.2), respectively, with significant differences between the two groups (p <0.001). About 78% of participants in the obese-diabetes group and 60% in the normal weight group were females. The baseline characteristics of the participants are shown in Table 1.

The serum irisin level was significantly different between the two groups, with the obese diabetes group noted to be lower at 218.74 ng/mL (SD: 144.98-269.26]) compared to the normal weight group at 266.68 ng/mL (SD: 200.64-336.57) with a p=0.024. The FBS, HbA1c and eAG in the obese with diabetes group was 139.0 mg/dL (108.0-157.0), 7.4% (6.2-8.4) and 161 (131-193), respectively, and there were significant differences between the two groups for these variables. Moreover, there were also significant differences between groups for inflammatory biomarkers IL-6, TNF-α, and hs-CRP. The obese patients with T2DM had a higher level of TG than the normal weight group (p<0.001). The tabulated results of the biochemical parameters for both groups are shown in Table 2.

Table 1. The baseline characteristics of participants enrolled in the study (n=62)

Variables	Obese with diabetes (n=32)	Normal weight (n=30)	*p*
Age (year)[b]	54.0 (52.2-60.7)	38.0 (30.0-47.2)	<0.001
Educational level[c]			
Illiterate	22 (6.8)	2 (6.7)	<0.001
Diploma	9 (28.1)	4 (13.3)	
Bachelor's degree	1 (3.1)	24 (80.0)	
Occupation[c]			
Employee	5 (15.6)	25 (83.3)	<0.001
Housewife	27 (84.4)	5 (16.7)	
Sex[c]			
Male	7 (21.9)	12 (40.0)	0.122
Female	25 (78.1)	18 (60.0)	
BMI (kg/m^2)[a]	34.35 ± 4.07	24.33 ± 3.70	<0.001

[a] Data presented as mean (SD), Independent-samples t-test
[b] Data presented as Median (IQR), Mann-Whitney U-test
[c] Data presented as frequency (percent), Chi-Square test
p<0.05 was defined as significant

Table 2. The difference between biochemical parameters in obese participants with diabetes and normal-weight participants (n=62)

Variables	Obese with diabetes (n=32)	Normal weight (n=30)	*p* *
FBS (mg/dL)[b]	139.0 (108.0-157.0)	87.0 (83.0-89.0)	<0.001*
HbA1C (micro dL)[b]	7.4 (6.2-8.4)	5.3 (5.1-5.5)	<0.001*
eAG[b]	161.0 (131.0-193.0)	105.0 (102.2-111.0)	<0.001*
FI (μIU/mL)[b]	20.7 (9.9-28.8)	10.1 (7.1-14.4)	0.002*
HOMA-IR[b]	6.5 (3.0-9.7)	2.0 (1.7-3.0)	<0.001*
QUICKI[b]	0.29 (0.27-0.32)	0.33 (0.31-0.35)	<0.001*
IL-6 (ng/L)[a]	3.90 ± 1.44	2.27 ± 1.71	0.006*
TNF-α (ng/L)[a]	11.84 ± 3.26	9.85 ± 3.15	0.018*
hs-CRP (pm/mL)[b]	6.15 (3.50-9.45)	1.65 (1.20-2.20)	<0.001*
MDA (μmol/L)[a]	2.14 ± 0.78	1.88 ± 0.66	0.172
TAC (mmol/L)[a]	1.21 ± 0.31	1.14 ± 0.28	0.386
TG (mg/dL)[b]	157.0 (111.0-225.0)	92.0 (72.0-122.2)	<0.001*
TC (mg/dL)[b]	156.5 (139.7-182.7)	161.5 (138.2-184.2)	0.905
LDL-C (mg/dL)[b]	87.5 (73.2-108.5)	101.5 (82.2-118.0)	0.081
HDL-C (mg/dL)[b]	36.0 (36.0-41.5)	38.0 (35.7-44.2)	0.207

[a] Data presented as mean (SD), Independent-samples t-test.
[b] Data presented as Median (IQR), Mann-Whitney U-test
*p<0.05 was defined as significant
IL-6: Interleukin-6, TNF-α: Tumor necrosis factor alpha, hs-CRP: High-sensitivity C-reactive protein, MDA: Malondialdehyde, TAC: Total antioxidant capacity, FBS: Fasting Blood Sugar, eAG: estimated average glucose, FI: Fasting Insulin, HOMA-IR: Homeostatic Model Assessment for Insulin Resistance, QUICKI: Quantitative Insulin-Sensitivity Check Index, TG: Triglyceride, TC: Total Cholesterol, LDL-C: Low-Density Lipoprotein - Cholesterol, HDL-C: High-Density Lipoprotein - Cholesterol

Table 3 shows the relationship between irisin with inflammatory biomarkers, oxidative stress biomarkers, glycemic indices and lipid profiles between the two groups of participants. Assessing the relationship between irisin values and the different biochemical parameters, IL-6 showed a moderately negative correlation with irisin in obese patients with diabetes (r=-0.478, p=0.006, 95%CI [-0.749 to -0.185]). There was no significant correlation detected between irisin and other inflammatory biomarkers, oxidative stress, glycemic indices, and lipid profiles.

DISCUSSION

The present study demonstrated that the level of irisin in obese people with type 2 diabetes was significantly lower than in controls. A negative correlation was detected between irisin and IL-6 in obese patients with type 2 diabetes (r=-0.478, p=0.006). Previously published results regarding irisin's association with biochemical and metabolic biomarkers were inconsistent. In agreement with our study, Khorasani and company's study showed no significant correlation between irisin and FPG, HbA1C and HOMA-IR except for fasting insulin, TG, LDL-C, and HDL-C in 30 people with diabetes and CAD. On the other hand, the correlation between irisin and body mass index (BMI), age, and duration of disease was significant.[25] El Hadad et al., showed no significant difference in irisin levels in 60 patients with T2DM compared with 30 control patients. However, a substantial correlation was detected between irisin level and FBS, HbA1C, CRP, cholesterol, and TG.[28] He et al., demonstrated a significant correlation between irisin with HbA1C and LDL-C in 71 patients with T2DM and 40 normal control patients. Like our study, the irisin level was significantly lower in people with diabetes than in controls (p<0.001), and no significant correlation was observed between irisin and lipid parameters of TG and HDL-C.[29]

The low concentration of irisin in patients with T2DM could be attributed to the low level of PGC-1α expression.[30] Insulin resistance, inflammation via the induction of oxidative stress, and pro-inflammatory cytokines decrease the expression of FNDC5.[31,32] Oxidative stress, advanced glycated end-products and other toxins in chronic disorders also inhibit the secretion of irisin and irisin-related gene expression.[21] The different circulating concentrations of irisin in patients with T2DM, obese and normal weight subjects may be attributed to their body composition and abnormalities in their glucose and lipids.[33] In the absence of sufficient muscle mass in patients with abnormal blood glucose levels or T2DM, the expression of FNDC5/Irisin in skeletal muscles and adipose tissue is decreased.[24,34] The contradicting results between this study and that of others may be explained by the differences in the stage and duration of diabetes. In early diabetes, the elevated circulating irisin may constitute a compensatory response to decreased energy expenditure.[35] Other factors such as ethnicity, diet, genetic parameters, methodological variations, different assay kits used for irisin detection and differences in the studied population may influence irisin levels.[34]

Table 3. The relationship between Irisin level with inflammatory biomarkers, oxidative stress biomarkers, glycemic indices and lipid profiles in obese patients with diabetes and normal weights (n=62)

Variables	Groups		FBS	HBA1C	FI	eAG	HOMA-IR	QUICKI	IL-6	TNF-α	hs-CRP	MDA	TAC	TG	TC	LDL-C	HDL-C
Irisin (ng/mL)	Obese with diabetes	r	-0.192	-0.239	0.142	-0.240	0.087	-0.108	-0.478	-0.021	-0.309	-0.286	0.003	0.074	0.096	0.100	0.126
		p	0.292	0.187	0.438	0.186	0.635	0.555	0.006	0.910	0.085	0.113	0.988	0.688	0.688	0.587	0.493
		95% CI (Lower-Upper)	(-0.459 to 0.025)	(-0.486 to 0.031)	(-0.075 to 0.411)	(-0.486 to 0.032)	(-0.132 to 0.281)	(-0.344 to 0.269)	(-0.741 to -0.185)	(-0.365 to 0.313)	(0.587 to 0.027)	(-0.542 to -0.015)	(-0.340 to 0.336)	(-0.265 to 0.389)	(-0.288 to 0.440)	(-0.274 to 0.409)	(-0.254 to 0.443)
	Normal weight	r	-0.059	-0.144	0.108	-0.147	0.049	0.176	0.278	0.056	-0.140	0.028	-0.025	0.112	0.039	0.047	-0.178
		p	0.758	0.446	0.569	0.437	0.797	0.352	0.137	0.770	0.460	0.884	0.896	0.557	0.840	0.806	0.346
		95% CI (Lower-Upper)	(-0.395 to 0.310)	(-0.462 to 0.137)	(-0.192 to 0.454)	(-0.465 to 0.132)	(-0.262 to 0.388)	(-0.161 to 0.483)	(-0.271 to 0.651)	(-0.293 to 0.404)	(-0.390 to 0.198)	(-0.381 to 0.392)	(-0.365 to 0.380)	(-0.254 to 0.483)	(-0.417 to 0.440)	(-0.367 to 0.431)	(-0.501 to 0.206)

Pearson rho coefficients
** Correlation is significant at the 0.01 level
* Correlation is significant at the 0.05 level
FBS: Fasting Blood Sugar, eAG: estimated average glucose, FI: Fasting Insulin, HOMA-IR: Homeostatic Model Assessment for Insulin Resistance, QUICKI: Quantitative Insulin-Sensitivity Check Index, IL-6: Interleukin-6, TNF-α: Tumor Necrosis Factor - alpha, hs-CRP: High-sensitivity C-reactive protein, MDA: Malondialdehyde, TAC: Total antioxidant capacity, TG: Triglyceride, TC: Total Cholesterol, LDL-C: Low-Density Lipoprotein - Cholesterol, HDL-C: High-Density Lipoprotein - Cholesterol

In our study, there was a negative correlation between irisin and IL-6. Similar to irisin, IL-6 is a contraction-regulated myokine that is known to be a muscle-derived protein.[36] Limited human studies have assessed the relationship between irisin and inflammatory cytokines and oxidative stress. According to Liu et al., exposure of mice with type 1 diabetes to irisin at 0.5 to 1.5 μg/g body weight for 16 weeks remarkably decreased the production of ROS, MDA, IL-1β and IL-18.

Irisin exerts anti-inflammatory effects by suppressing the NLR family pyrin domain containing 3 (NLRP3) inflammasome, a mediator of cellular damage and inflammation. NLRP3 plays a critical role in the activation of caspase-1 that involves induction and secretion of pro-inflammatory cytokines such as pro-IL-18 and pro-IL-1β.[37,38] In the study of Shao et al., the lipopolysaccharide (LPS)-induced acute lung injury in a mice model that was treated with irisin revealed that irisin significantly decreased the production of the pro-inflammatory cytokines IL-6, MCP-1, IL-1β, and TNF-α. Irisin also reduced MAPK activation by LPS and nuclear factor (NF)-$_k$B signaling pathways in mice models and A549 cells.[39] Sanchis-Gomar noted that despite the lower level of irisin in obese patients with T2DM (n=34) than in controls (n=20), there was no significant difference between them. Moreover, a negative correlation between irisin and HbA1C (r=-0.401, *p*=0.025) and homocysteine (r=- 0.430, *p*=0.020) was noted in obese patients with T2DM.[40]

The primary mechanism attributed to the immune system boosting and anti-inflammatory properties of irisin is its role in decreasing the production of ROS and inhibiting the expression of inflammatory cytokines such as IL-6, TNF-α, and cyclooxygenase 2.[41] Irisin also inhibits the expression of toll-like receptor 4 (TLR4) and down-regulates the signaling pathway of mitogen-activated protein kinases (MAPK). Irisin suppresses the activation of NF-κB and IL-1β in the secretion of other pro-inflammatory cytokines, such as IL-8 and MCP-1, and causes the natural immune system to weaken.[42] It can also modulate inflammation by increasing the gene expression of CD206 and IL-10, which are the macrophage markers with anti-inflammatory properties, and upregulates NO synthesis.[43,44]

The other function of irisin is attributed to its anti-apoptotic effect. In people with diabetes, high glucose levels induce cell apoptosis, insulin insensitivity and impaired β-cell function.[45] Irisin downregulates the expression of apoptotic markers such as Bax, Bad, Caspase 9 and Caspase 3; in contrast, it enhances the expression and activity of anti-apoptotic markers such as Bcl-2 and Bcl-xl.[17] Irisin exerts anti-inflammatory effects indirectly via modulating the leptin level which is an insulin-sensitizing hormone.[13] It seems that the significant relationship between irisin and IL-6 compared with other inflammatory biomarkers can be attributed to the high sensitivity and rapid generation and response of IL-6, especially in the early phase of inflammation. As a pleiotropic cytokine, IL-6 exerts

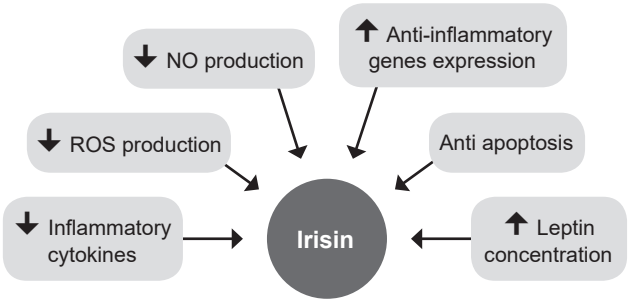

Figure 1. The potential anti-inflammatory role of Irisin in the management of chronic diseases.

fundamental functions in regeneration, immune system response and tissue repair.[46,47] Also, IL-6 is involved in the activation of other inflammatory signaling pathways such as CRP.[48] Figure 1 summarizes the potential anti-inflammatory role of irisin in the management of chronic diseases.

To the best of our knowledge, this study was the first to investigate the relationship between irisin concentration, inflammatory cytokines and oxidative stress biomarkers aside from glycemic indices and lipid profile parameters in patients with T2DM. However, this study had some limitations. Major limitations noted were the small sample size and the failure to measure other biomarkers and molecular pathways that may influence irisin levels in patients with diabetes. The lack of assessment of the participants' physical activity and body composition was considered another limitation. It is suggested that future studies be conducted to find the exact role of irisin in boosting the immune system and its anti-inflammatory properties to decrease the burden of disorders with low inflammation states.

CONCLUSION

In conclusion, the present study investigated the relationship between irisin and inflammatory biomarkers, glycemic indices and lipid profiles. The level of irisin was significantly lower in obese patients with T2DM than in healthy normal weight participants, and a significant negative correlation was detected between circulatory irisin and IL-6. Other biochemical factors did not show a substantial correlation with irisin. The potential protective functions of irisin in boosting the immune system and regulating metabolism in chronic disorders remains an open question that merits further investigations with a large-scale sample size to discover unknown mechanisms and other factors that affect circulating irisin in patients with T2DM.

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Statement of Authorship
The authors certified fulfillment of ICMJE authorship criteria.

CRediT Author Statement

YK: Conceptualization, Methodology, Writing – original draft preparation, Writing – review and editing, Supervision, Project administration; **AHF, SD:** Resources, Writing – original draft preparation; **AS:** Validation, Formal analysis, Data curation; **SI, SP:** Investigation, Resources; **LP:** Conceptualization, Methodology, Writing – review and editing, Supervision, Project administration, Funding acquisition.

Author Disclosure

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