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Irisin and Subclinical Atherosclerosis in Individuals with Overweight/Obesity with and Without Newly Diagnosed Type 2 Diabetes Mellitus

ABSTRACT

Objective: Irisin, a myokine involved in metabolism and glucose regulation, has been associated with obesity, type 2 diabetes mellitus (T2DM), and cardiovascular disease, with inconsistent findings. This study assessed irisin levels in individuals with overweight/obesity with and without newly diagnosed diabetes and examined its association with subclinical atherosclerosis.

Methods: Ninety participants were divided into 3 groups: 30 individuals with newly diagnosed T2DM and overweight/obesity (Group 1), 30 individuals with overweight/obesity without diabetes (Group 2), and 30 controls (Group 3). Anthropometrics, glycemic markers, lipid profile, serum irisin, high-sensitive C-reactive protein (hs-CRP), and carotid intimal-media thickness (CIMT) were measured. Spearman's correlation and logistic regression were applied.

Results: Serum irisin levels were higher in groups with overweight/obesity than in controls ($P = .002$) but did not differ by diabetic status. In subgroup analyses, irisin correlated positively with glycated hemoglobin ($r = 0.56$, $P = .001$), low-density lipoproteins (LDL-C) ($r = 0.50$, $P = .005$), hs-CRP ($r = 0.38$, $P = .038$), and CIMT ($r = 0.63$, $P < .001$) in Group 1 and with LDL-C ($r = 0.37$, $P = .042$) and CIMT ($r = 0.40$, $P = .030$) in Group 2. In multivariate regression, irisin remained independently associated with increased CIMT in individuals with T2DM and overweight/obesity (adjusted odds ratios (aOR) = 2.03 (95% CI = 1.04-3.94)) and in the overall cohort with overweight/obesity (aOR = 1.98 (95% CI = 1.15-3.42)).

Conclusions: Serum irisin is elevated in obesity, irrespective of diabetic status, and is independently associated with subclinical atherosclerosis, suggesting its potential role as an early biomarker of cardiovascular risk.

Keywords: CIMT, diabetes mellitus, hs-CRP, irisin, obesity

Introduction

Type 2 diabetes mellitus (T2DM) is a chronic illness characterized by aberrant pancreatic beta-cell function and insulin resistance in target organs.[1]

It is coupled with several health-related complications, where atherosclerotic cardiovascular disease (ASCVD) has been identified as the principal foundation of related death and morbidity.[2] Consequently, it is advisable to recognize patients at risk of developing ASCVD for their effective management. Both circulating and imaging biomarkers have been utilized for this purpose.[3,4]

Obesity is a chronic, progressive, and relapsing condition characterized by numerous metabolic, physical, and psychosocial complications, notably an elevated risk for T2DM and cardiovascular disease.[5]

Irisin is an adipo-myokine derived from fibronectin type III domain-containing protein 5 (FNDC5).[6] It is believed to communicate the beneficial impact of skeletal muscle-induced exercise on metabolic and vascular diseases through enhancing glucose homeostasis and suppressing endothelial injury, inflammation, and oxidative stress in atherosclerotic vasculature.[7,8] Moreover, irisin has been implicated in the beneficial browning of white adipose tissue, promoting the inhibition of fat deposition and subsequent obesity. However, different studies have reported mixed, inconsistent results regarding alterations in circulating irisin in obesity and T2DM, especially with respect to disease onset.[7]

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To current knowledge, few studies have examined irisin's utility as an independent predictor of carotid intimal-media thickness (CIMT) in patients with overweight/obesity and newly diagnosed T2DM. This study aimed to investigate the relationship between serum irisin and early markers of ASCVD in individuals with overweight/obesity and newly diagnosed T2DM, using CIMT as an indicator.

Methods

Study Design and Population

This cross-sectional study was conducted at the Internal Medicine Department (Endocrine Unit), Alexandria Main University Hospital Faculty of Medicine between August 2023 and February 2024 and enrolled 90 individuals aged 18-60 years. Participants were stratified into 3 equal groups (n = 30 each):

- Group 1: Individuals with overweight/obesity (body mass index (BMI) ≥ 27 kg/m^2) with newly diagnosed T2DM, defined according to ADA criteria in patients diagnosed within the previous 6 months, with no prior use of antidiabetic medications or insulin therapy.[9]
- Group 2: Individuals with overweight/obesity (BMI ≥ 27 kg/m^2) without diabetes.
- Group 3: Non-obese individuals with normal glucose tolerance (control group).

Although World Health Organization defines overweight as a BMI of 25 kg/m^2, a cutoff of 27 kg/m^2 was used to better select individuals with high metabolic and cardiovascular phenotypes, consistent with previous research and treatment eligibility guidelines.[10,11]

A post hoc power analysis (pwr package, R) confirmed adequate statistical power. For group comparisons of serum irisin (Kruskal–Wallis), the effect size ($\varepsilon^2 = 0.12$) yielded 88% power at $\alpha = 0.05$. Correlation analyses showed achieved powers of 95% in Group 1 and 72% in Group 2, indicating sufficient sensitivity to detect the observed relationships.

Ethics Committee of the Faculty of Medicine, Alexandria University validated the study (IRB: 0107806, Date: July 9, 2023). All participants provided written informed consent.

Recruitment and Setting

Groups 1 and 2 were recruited from the endocrinology outpatient clinic and the inpatient endocrinology, mainly presenting with obesity or newly diagnosed T2DM. Those reporting cardiovascular symptoms received a standard clinical evaluation. Group 3 participants were healthy volunteers enrolled from hospital staff and relatives.

Exclusion Criteria

Included established cardiovascular disease (prior myocardial infarction, angina, or stroke, as well as chronic heart failure), pregnancy or lactation, use of agents that can influence insulin sensitivity or glucose metabolism (oral antidiabetic drugs, Glucagon-like peptide-1 (GLP-1) receptor agonists, corticosteroids, or anti-obesity agents).

Because several comorbid and lifestyle factors can affect irisin levels, data on hypertension, dyslipidemia, use of antihypertensives or statins, smoking status, and sex distribution were collected to account for potential confounders.

Demographic and clinical data were collected, with a particular focus on symptoms suggestive of underlying cardiac disease. Symptoms were defined clinically: dyspnea as shortness of breath at rest or on exertion; orthopnea as breathlessness when lying flat with improvement on upright; angina as exertional retrosternal chest discomfort relieved by rest or nitroglycerin; and chest pain as any non-anginal pain localized to the chest.[12]

Weight and height were measured with participants barefoot and in light clothing, and BMI was calculated as weight (kg)/height (m^2). Waist circumference (WC) was measured midway between the last rib and iliac crest, and hip circumference at the widest buttock area; waist-hip ratio (WHR) was then calculated. Blood pressure was recorded using a calibrated sphygmomanometer after 5 minutes of rest, using the mean of 2 right-arm readings.[13]

Laboratory Investigations

Fasting and 2-hour postprandial plasma glucose (FPG, 2HPP), along with serum lipid profiles, total cholesterol, high-density lipoproteins (HDL-C), low-density lipoproteins (LDL-C), and triglycerides (TG), were estimated utilizing a fully automated chemistry analyzer, Advia1800 (Siemens, USA). The enzyme-linked immunosorbent assay technique (ELISA) was used to measure fasting plasma insulin (FPI) (Cat No. 10801, Chemux Bioscience, USA) and serum irisin (Aviscera Biosciences, Santa Clara, CA). Standard range: 0.066-1024 ng/mL. Homeostatic model assessment of insulin resistance (HOMA-IR) was estimated using the equation [fasting glucose (mg/dL)/fasting insulin (mU/mL)/405].[14]

Resting Electrocardiogram

All participants underwent a resting 12-lead electrocardiogram (Meditech EKG-6012, Meditech, Hungary) to assess baseline cardiac rate and rhythm and detect possible underlying ischemic changes.

Doppler Ultrasound of the Carotid Arteries

Carotid intima-media thickness (CIMT) of the common carotid arteries was assessed on both sides by the same trained sonographer using a high-resolution Doppler ultrasound system (Hitachi Arietta 850 SE, Hitachi Ltd., Japan) with a 7.5-12 MHz linear transducer. Carotid intima-media thickness was assessed bilaterally using the far wall of the common carotid artery ~10 mm proximal to the bulb, with participants in the supine position. Three measurements were obtained on each side from plaque-free segments and averaged for analysis. Increased CIMT was defined as ≥0.9 mm.[15]

Statistical Analysis of the Data

Data were analyzed using IBM SPSS software version 20.0 (IBM SPSS Corp.; Armonk, NY, USA) and R software version 4.3.3 (R Foundation for Statistical Computing, Vienna, Austria).

Descriptive Analysis: Categorical variables are presented as counts and percentages. Quantitative variables are summarized as the mean ± standard deviation (SD) for normally distributed data and as the median with interquartile range (IQR) for non-normally distributed

MAIN POINTS

- Serum irisin levels are elevated in individuals with obesity, irrespective of diabetic status.
- A direct correlation exists between serum irisin levels and markers of subclinical atherosclerosis, both biochemical and radiological.
- Irisin might act as a biomarker for cardiovascular risk in people with overweight/obesity.

data. The normality of quantitative data was assessed using the Shapiro–Wilk test. Statistical significance was set at a 2-tailed $\alpha = 0.05$.

Group Comparative Analysis: The chi-square test was used for categorical data, with a Monte Carlo correction applied when the expected cell counts were less than 5. Normally distributed quantitative variables were compared using 1-way analysis of variance, whereas non-normally distributed data were compared using the Kruskal–Wallis test.

Correlation Analyses: Associations between serum irisin and metabolic or vascular parameters were evaluated using Spearman's rank correlation coefficients.

Logistic Regression Modelling

Univariate logistic regression identified candidate variables for CIMT ≥ 0.9 mm. To limit overfitting, only 4 clinically relevant variables (glycated hemoglobin (HbA1c), LDL-C, high-sensitive C-reactive protein (hs-CRP), and irisin) were entered into the multivariable model based on univariate significance. Multicollinearity was checked using the variance inflation coefficient >5 for exclusion, and adjusted odds ratios (aOR) with 95% CIs were reported.

Results

Baseline Demographic, Clinical, and Laboratory Data for the Studied Cohort

The cohort consisted of 3 groups: individuals with newly diagnosed T2DM and overweight/obesity (Group 1), individuals with overweight/obesity without diabetes (Group 2), and healthy controls (Group 3). Mean age did not differ significantly among groups ($P = .436$). Although sex distribution varied across groups, the difference was not statistically significant (Table 1).

Regarding cardiovascular manifestations (Figure 1), angina was reported in 5 individuals (16.7%) of Group I only. Dyspnea was present in 8 individuals (26.6%) of Group I and in 3 individuals (10%) of Group II. Orthopnea and chest pain were reported exclusively in Group I in 2 (6.7%) and 3 (10%) individuals, respectively. Ischemic changes on ECG were detected in 47% of Group II and in 33% of Group I, whereas all controls (Group III) showed normal ECG findings. Additionally, a significantly higher proportion of patients in the control group reported no history of cardiovascular medications compared to Groups I and II ($P = 0.033$).

Anthropometric parameters: Among the 60 individuals with overweight/obesity (Groups 1 and 2), 11 (18.3%) were overweight (BMI: 27-29.9 kg/m^2), and 49 (81.7%) were obese (BMI: ≥ 30 kg/m^2). Anthropometric measurements (weight, height, BMI, waist circumference, and waist–hip ratio) were significantly elevated in groups 1 and 2 vs. controls ($P < .001$). Median BMI was 34.05 ± 4.26 kg/m^2 in group 1 and 33.67 ± 3.21 kg/m^2 in group 2 versus 23.66 ± 3.42 kg/m^2 in controls. Systolic Blood pressure (BP) was marginally higher in Group 1 ($P = .051$), while diastolic BP did not differ significantly.

Group 1 showed significantly higher glycemic indices (fasting blood glucose (FBG), 2HPP, HbA1c, FPI, and HOMA-IR). Total cholesterol and LDL-C in individuals with overweight/obesity, particularly in group 1, while HDL-C was reduced compared with controls ($P < .001$). Triglycerides were also higher in group 1 [median 156 mg/dL (140-180)] compared with group 2 [120 mg/dL (102.5-133.8)] and healthy groups [110 mg/dL (110-120)].

High-sensitive C-reactive protein showed no significant difference among the 3 groups ($P = .982$). Serum irisin levels were significantly lower in controls [median 3.3 ng/mL (2.4-4.2)] compared with individuals with overweight/obesity with and without T2DM [4.7 ng/mL (3.2-6.4)] and [4.7 ng/mL (3.4-6.5) respectively ($P = .002$)]. Carotid intimal-media thickness was higher in individuals with newly diagnosed T2DM (0.8 mm) compared with individuals with overweight/obesity without diabetes (0.7 mm) and the healthy controls (0.6 mm), with CIMT ≥ 0.9 mm observed in 9/30 (30%) of Group 1 and 3/30 (10%) of Group 2 ($P < .001$).

Correlation Between Serum Irisin and Different Parameters Studied by Spearman's Rank Correlation Coefficient

In the total sample (n = 90), serum irisin demonstrated significant positive correlations with several clinical and biochemical parameters (Figure 2). Serum irisin showed significant positive correlations with anthropometric measures, including BMI ($r = 0.341$, $P = .001$), WC ($r = 0.337$, $P = .001$), and WHR ($r = 0.362$, $P < .001$). Among lipid parameters, irisin showed significant positive correlations with LDL ($r = 0.458$, $P < .001$) and TG ($r = 0.213$, $P = .044$), but not HDL ($r = 0.021$, $P = .844$). Regarding glycemic and metabolic markers, serum irisin correlated positively with HbA1c ($r = 0.236$, $P = .025$), hs-CRP ($r = 0.228$, $P = .031$), and CIMT ($r = 0.537$, $P < .001$). However, no significant correlations were noted with FPI ($r = 0.043$, $P = .690$), HOMA-IR ($r = 0.096$, $P = .368$), or FPG ($r = 0.198$, $P = .062$).

Within subgroup analyses (Table 2), serum irisin demonstrated weak, non-significant correlations with BMI, WC, and WHR in both groups with overweight/obesity. Regarding glycemic parameters, only HbA1c was significant, correlating positively in Group 1 ($r = 0.564$, $P = .001$), whereas no significant correlations were observed with FBG or 2HPP in either subgroup.

A significant positive correlation was also noted between serum irisin and LDL-C in group 1 ($r = 0.500$, $P = .005$) and group 2 ($r = 0.373$, $P = .042$). Conversely, HDL-C correlated negatively with serum irisin in group 1 only, but this did not reach statistical significance ($r = -0.281$, $P = .133$). Markers of inflammation and vascular risk also showed notable relationships. Serum irisin correlated positively with hs-CRP in group 1 ($r = 0.380$, $P = .038$); in group 2, the correlation was weaker and did not reach significance ($r = 0.338$, $P = .068$). Notably, a strong positive correlation was observed between serum irisin and CIMT in group 1 ($r = 0.631$, $P < .001$) and a moderate correlation in group 2 ($r = 0.397$, $P = .030$).

Univariate and Multivariate Regression Analysis to Assess Different Variables Associated with CIMT ≥ 0.9 mm

Univariate analysis showed that HbA1c, hs-CRP, and serum irisin were associated with CIMT ≥ 0.9 mm in individuals with newly diagnosed T2DM and overweight/obesity (ORs: 3.18, 1.39, and 2.17, respectively). In the overall cohort with overweight/obesity, significant factors included HbA1c (OR: 1.77), LDL-C (OR: 1.07), hs-CRP (OR: 1.48), and irisin (OR: 2.30). In multivariable analysis, serum irisin remained independently associated with CIMT ≥ 0.9 mm in both the group with diabetes (aOR: 2.03) and the total group with overweight/obesity (aOR: 1.98) (Table 3).

Discussion

This study provides a comprehensive analysis of serum irisin levels and their relationship with metabolic parameters, inflammation, and subclinical atherosclerosis in individuals with overweight/obesity

Table 1. Demographic, Anthropometric, Clinical, and Biochemical Characteristics Among Individuals with and Without Newly Diagnosed T2DM and Overweight/Obesity Compared with Healthy Controls

	Individuals with T2DM and Overweight/Obesity, Group 1 (n = 30)	Individuals with Overweight/Obesity Without Diabetes, Group 2 (n = 30)	Healthy Controls, Group 3 (n = 30)	*P*
Age (years), mean ± SD	42.60 ± 8.59	41.43 ± 10.35	39.70 ± 6.92	.436
Gender, n (%)				.311
Female	20 (66.7)	20 (66.7)	15 (50.0)	
Male	10 (33.3)	10 (33.3)	15 (50.0)	
Smoker (yes), n (%)	1 (3.3)	3 (10.0)	4 (13.3)	.383
Medication history, n (%)				.033*
No	23 (76.7)	27 (90.0)	30 (100.0)	
ACEI	2 (6.7)	0 (0.0)	0 (0.0)	
ARBS	3 (10.0)	0 (0.0)	0 (0.0)	
BB	2 (6.7)	3 (10.0)	0 (0.0)	
Weight (kg), mean ± SD	91.60 ± 14.15	89.90 ± 11.65	71.50 ± 13.04	<.001*
Height (cm), mean ± SD	163.8 ± 6.72	163.2 ± 6.01	172.2 ± 10.06	<.001*
BMI (kg/m^2), mean ± SD	34.05 ± 4.26	33.67 ± 3.21	23.66 ± 3.42	<.001*
WC (cm), median (IQR)	93.0 (89.2, 98.8)	93.5 (89.0, 98.0)	77.5 (75.0, 88.0)	<.001*
WHR, median (IQR)	0.9 (0.9, 0.9)	0.9 (0.9, 0.9)	0.8 (0.7, 0.8)	<.001*
Systolic (mmHg), median (IQR)	120.0 (110.0, 120.0)	110.0 (110.0, 120.0)	110.0 (110.0, 120.0)	.051
Diastolic (mmHg), median (IQR)	80.0 (71.2, 80.0)	77.5 (70.0, 80.0)	77.5 (70.0, 80.0)	.565
FBG (mg/dL), median (IQR)	139.0 (131.0, 165.5)	95.0 (90.0, 95.0)	89.0 (86.0, 90.0)	<.001*
2HPP (mg/dL), median (IQR)	210.0 (190.0, 237.5)	131.0 (128.0, 134.8)	124.0 (119.2, 129.8)	<.001*
HbA1c, median (IQR)	8.0 (7.5, 8.5)	5.2 (4.9, 5.4)	4.9 (4.3, 5.2)	<.001*
FPI, median (IQR)	9.2 (7.7, 11.5)	6.7 (5.8, 7.6)	7.0 (6.3, 8.5)	<.001*
HOMA-IR, median (IQR)	3.6 (2.7, 4.5)	1.5 (1.3, 1.8)	1.5 (1.4, 1.8)	<.001*
Total serum cholesterol (mg/dL), mean ± SD	226.5 ± 33.20	204.2 ± 30.15	158.8 ± 18.32	<.001*
LDL cholesterol (mg/dL), median (IQR)	160.0 (150.0, 167.5)	140.0 (120.0, 170.0)	115.0 (111.2, 120.0)	<.001*
HDL cholesterol (mg/dL), median (IQR)	40.0 (40.0, 50.0)	40.0 (35.0, 45.0)	45.0 (45.0, 55.0)	<.001*
TG (mg/dL), median (IQR)	156.0 (140.0, 180.0)	120.0 (102.5, 133.8)	110.0 (110.0, 120.0)	<.001*
hs-CRP (mg/L), median (IQR)	5.0 (3.0, 6.0)	5.0 (4.0, 5.0)	5.0 (4.0, 5.0)	.982
Irisin (ng/mL), median (IQR)	4.7 (3.2, 6.4)	4.7 (3.4, 6.5)	3.3 (2.4, 4.2)	.002*
CIMT (mm), median (IQR)	0.8 (0.7, 0.9)	0.7 (0.6, 0.8)	0.6 (0.5, 0.7)	<.001*
<0.9, n (%)	21 (70.0)	27 (90.0)	30 (100.0)	.002*
≥0.9, n (%)	9 (30.0)	3 (10.0)	0 (0.0)	

Quantitative data with normal distribution are presented as mean ± SD and compared using one-way analysis of variance. Non-normally distributed quantitative data are presented as median (IQR) and compared using the Kruskal–Wallis test. Categorical variables are analyzed using the chi-square test or the Monte Carlo test. $P \leq .05$ was considered statistically significant.

2HPP, 2-hour postprandial blood glucose; ACEI, angiotensin-converting enzyme inhibitors; ARB, angiotensin II receptor blocker; BB, beta blocker; BMI, body mass index; CIMT, carotid intima–media thickness; ECG, electrocardiogram; FBG, fasting blood glucose; FPI, fasting plasma insulin; HbA1c, glycated hemoglobin; HDL, high-density lipoprotein cholesterol; HOMA-IR, homeostatic model assessment for insulin resistance; hs-CRP, high-sensitivity C-reactive protein; IQR, interquartile range; LDL, low-density lipoprotein cholesterol; n, number; SD, standard deviation; T2DM, type 2 diabetes mellitus; TG, triglycerides; WC, waist circumference; WHR, waist–hip ratio.

with and without newly diagnosed T2DM. The main findings reveal a complex, paradoxical role for irisin. While it was elevated in overweight/obesity states, its strong positive correlation with markers of atherosclerosis (CIMT, LDL-C) and its independent association with increased CIMT suggest a possible compensatory but ultimately maladaptive response in the context of obesity and early-stage dysglycemia.

In this study, symptoms suggestive of ASCVD, chest pain, and dyspnea were more prevalent in individuals with newly diagnosed diabetes and overweight/obesity, compared with those with normal glucose tolerance. Ischemic changes were observed in almost one-third of individuals with newly diagnosed diabetes and nearly half of nondiabetic individuals with overweight/obesity. Similarly, Bedane et al[16] reported positive ischemic ECG findings in two-thirds of apparently healthy individuals with T2DM, especially those with a longer duration of diabetes and a BMI of ≥ 25 kg/m^2.[16] A meta-analysis of 1.4 million obese individuals showed that obesity is linked to a high risk of developing cardiovascular disease (CVD) and even sudden cardiac death, through both indirect metabolic mechanisms and direct effects on cardiac structure and hemodynamics.[17]

A positive correlation was observed between irisin and glycemic indices in individuals with diabetes and overweight/obesity, although only HbA1c was significant. The link between irisin and glycemic parameters has been previously studied, yielding contradictory

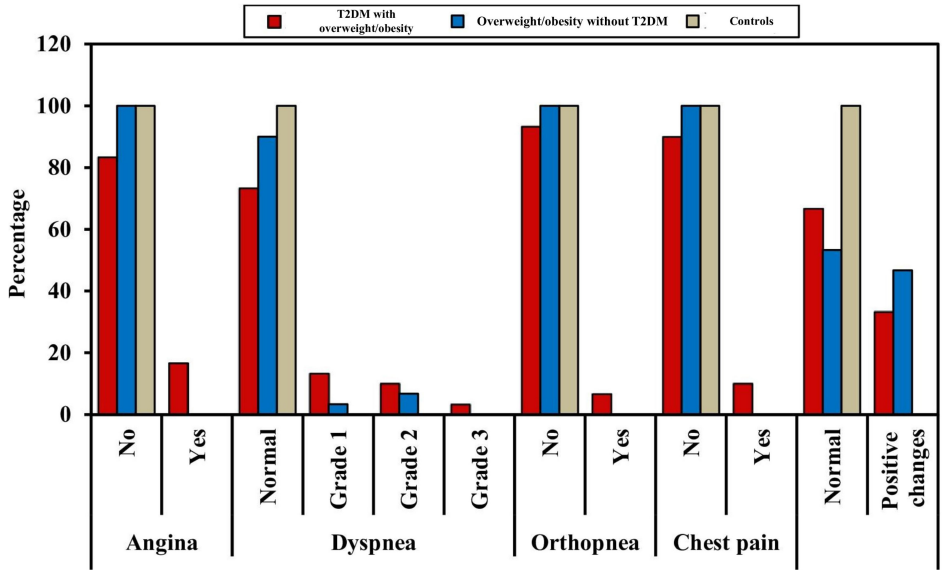

Figure 1. Cardiovascular manifestations across study groups. Distribution of angina, dyspnea, orthopnea, chest pain, and ischemic ECG changes in individuals with T2DM and overweight/obesity (Group 1, n = 30), individuals with overweight/obesity without diabetes (Group 2, n = 30), and healthy controls (Group 3, n = 30). ECG, electrocardiogram; T2DM, type 2 diabetes mellitus.

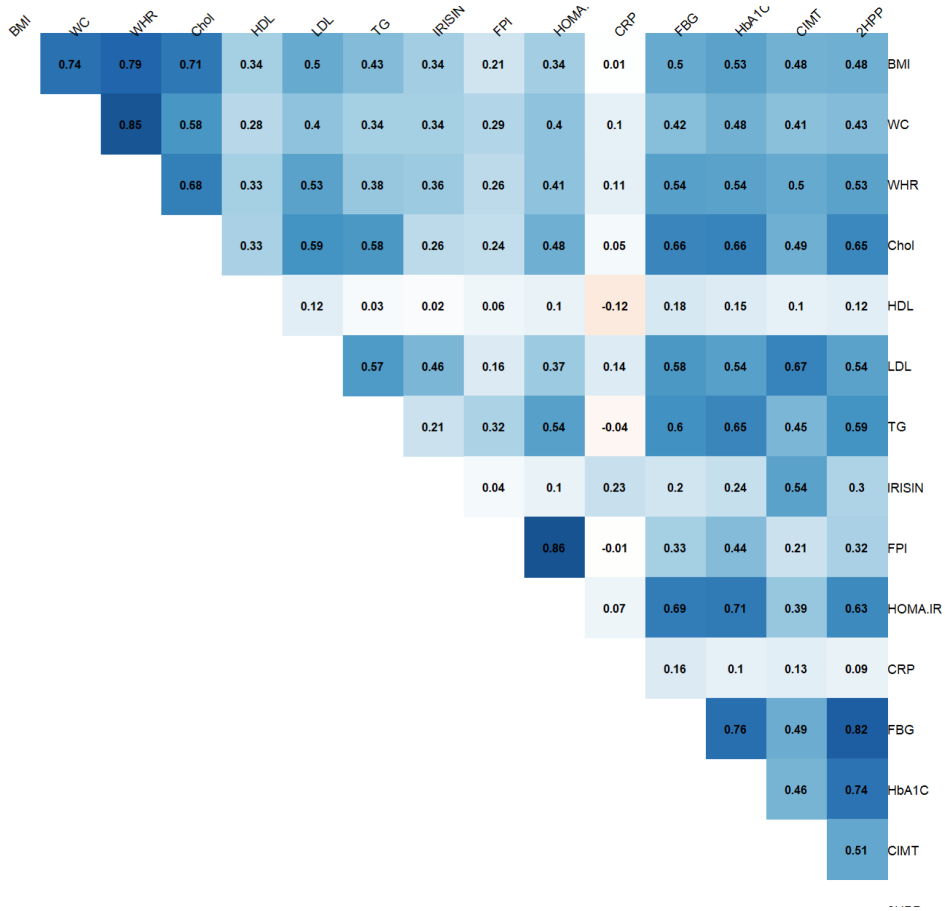

Figure 2. Spearman's correlations between serum irisin and anthropometric, metabolic, and vascular parameters in the total study population (n = 90). Darker colors represent stronger correlations; only significant correlations are detailed in the text. BMI, body mass index; WC, waist circumference; WHR, waist-to-hip ratio; Chol, total cholesterol; HDL, high-density lipoprotein cholesterol; LDL, low-density lipoprotein cholesterol; TG, triglycerides; IRISIN, serum irisin; FPI, fasting plasma insulin; HOMA-IR, homeostasis model assessment of insulin resistance; CRP, C-reactive protein; FBG, fasting blood glucose; HbA1c, glycated hemoglobin; CIMT, carotid intima–media thickness; 2HPP, 2-hour postprandial plasma glucose.

Table 2. Spearman's Correlation Between Serum Irisin and Metabolic, Inflammatory, and Vascular Parameters in Individuals with and Without Diabetes and Overweight/Obesity

	Individuals with T2DM and Overweight/Obesity Group 1 (n = 30)		Individuals with Overweight/Obesity Without Diabetes Group 2 (n = 30)	
Irisin	***r***	***P***	***r***	***P***
BMI (kg/m^2)	0.061	.751	0.115	.545
WC (cm)	0.084	.661	0.143	.452
WHR	0.140	.460	0.160	.398
hs-CRP (mg/L)	**0.380***	**.038**	0.338	.068
FBG (mg/dL)	0.194	.305	−0.065	.733
2HPP (mg/dL)	0.331	.074	0.088	.643
HbA1c	**0.564***	**.001**	0.098	.605
FPI	0.102	.593	−0.103	.588
HOMA-IR	0.176	.352	−0.116	.543
Total serum cholesterol (mg/dL)	0.127	.503	−0.137	.470
LDL cholesterol (mg/dL)	**0.500***	**.005**	**0.373***	**.042**
HDL cholesterol (mg/dL)	−0.281	.133	−0.033	.864
TG (mg/dL)	−0.125	.511	0.339	.067
CIMT (mm)	**0.631***	**<.001**	**0.397***	**.030**

r, Spearman's rank correlation coefficient.
2HPP, 2 hours postprandial blood glucose; BMI, body mass index; CIMT, carotid intima–media thickness; FBG, fasting blood glucose; FPI, fasting plasma insulin; HbA1C, glycated hemoglobin; HDL, high-density lipoproteins; HOMA-IR, homeostatic model assessment for insulin resistance; hs-CRP, high sensitive C-reactive protein; LDL, low-density lipoproteins; T2DM, type 2 diabetes mellitus; TG, triglycerides; WC, waist circumference; WHR, waist hip ratio.
*Statistically significant at $P \leq .05$.
Bold values indicate statistically significant correlations ($P \leq 0.05$).

results. Supporting the findings, Huh et al[18] observed higher irisin in individuals who later developed diabetes, indicating an early compensatory rise to enhance its beneficial metabolic effects or overcome its resistance. Similarly, Kopuz et al[19]found elevated irisin in newly diagnosed T2DM, proposing a diagnostic cutoff level of 2.195 ng/mL (79% sensitivity and 71% specificity). On the other hand, 2 meta-analyses have shown downregulated irisin expression in patients with established T2DM,[20] as well as in diabetes-related complications.[21]

Diminished serum levels of irisin in patients with diabetes can be attributed to diabetes-related sarcopenia, reduced muscular PGC-1α activity, and a consequent reduction in FNDC5 and irisin expression. Moreover, the widespread inflammatory process and oxidative stress may further suppress FNDC5/irisin gene expression.[22]It has been postulated that serum irisin levels may initially increase in the stages of prediabetes and new-onset diabetes, perpetuating their positive effects on glucose homeostasis, followed by a gradual decline proportionate to diabetes duration.[21]

In this study, higher irisin levels were observed in individuals with overweight/obesity compared to the controls. However, the correlation between irisin and clinical indicators of obesity, including BMI, WC, and WHR, was weak and insignificant. Studies have shown that irisin activates UCP-1, promoting thermogenesis and inhibiting adipogenesis. Its role in adipose browning further supports a contribution to obesity-related metabolic regulation.[6-8]

Nevertheless, the relationship between serum irisin and obesity-related parameters is contradictory. A meta-analysis by Jia et al[23] reported inconsistent findings: some studies observed high irisin levels in individuals with obesity, others reported a negative association, and others found no relationship. A proposed explanation is irisin resistance, analogous to insulin and leptin resistance, or increased release from abundant adipose tissue.[23,24] The latter hypothesis was supported by Huh et al[24], who showed that FNDC5 expression and circulating irisin levels decreased after bariatric surgery, parallel with fat mass loss, despite preserved lean mass. Notably, the muscle-to-fat ratio is the primary determinant of irisin levels, and serum irisin originating from muscle is 100 times higher than that released from adipose tissue. Moreover, circulating irisin levels are influenced by physical exercise, age, gender, ethnicity, and concomitant cardiometabolic phenotypes.[22-24]

Atherosclerotic cardiovascular disease is the principal cause of death in patients with T2DM. Studies have shown that irisin, by modulating the Adenosine monophosphate-activated protein kinase (AMPK) pathway, can play a beneficial role in lipid and glucose metabolism due to its inherent anti-inflammatory and antioxidative properties. Moreover, pretreatment with irisin in diabetic mice is coupled with a substantial improvement in lipid profile, resulting in meaningful cardiovascular protection.[25]

In this work, mean serum irisin was found to be positively correlated with mean serum total cholesterol, triglycerides, and LDL-C, and negatively correlated with high-density lipoproteins, showing significant positive correlation with LDL-C in individuals with overweight/obesity with and without diabetes and a significant negative correlation with HDL-C only with diabetes and overweight/obesity.

Park et al[26] found that patients with elevated irisin levels have a higher risk of developing metabolic syndrome, showing positive correlations with glycemic parameters, insulin sensitivity, and a negative correlation with adiponectin levels. They also found that patients with the highest irisin levels are tightly linked with individual components of metabolic syndrome. On the other hand, Khorasani et al[14]observed that patients with T2DM and CVD had lower irisin levels than those without, suggesting that low irisin levels may serve as a surrogate marker for early disease monitoring and management.

Vascular endothelial dysfunction underlies atherosclerosis, driven largely by oxidative stress and endothelial cell death. Irisin was found in diabetic mice to attenuate hyperglycemia and advanced glycated end products-induced oxidative stress. Moreover, it enhances endothelial repair and proliferation and inhibits apoptosis caused by oxidized LDL-C. Additionally, irisin exerts its anti-inflammatory effects by inhibiting inflammatory cell recruitment and suppressing the Reactive oxygen species ROS–p38 MAPK–NF-κB pathway, hence reducing inflammatory mediator expression.[27]

C-reactive protein has been identified as a distinct indicator of insulin resistance, T2DM, and increased cardiovascular risk. In this work, CRP showed a direct correlation with irisin levels in individuals with and without diabetes and in those with overweight/obesity. Several mechanisms elucidate this relationship.[28] Initially, following skeletal muscle contraction, both serum irisin and Interleukin-6 (IL-6) levels tend to increase; Tumor necrosis factor-alpha (TNF-α) and IL-6

Table 3. Univariate and Multivariate Logistic Regression Analysis for the Parameters Affecting Carotid Intima Media Thickness (CIMT ≥ 0.9)

	Individuals with T2DM and Overweight/Obesity (No. CIMT ≥ 0.9 = 9 vs. 21)				Total Group with Overweight/Obesity (No. CIMT ≥ 0.9 = 12 vs. 48)			
	Univariate		#Multivariate		Univariate		#Multivariate	
	P	OR (95% CI)	*P*	OR (95% CI)	*P*	OR (95% CI)	*P*	OR (95% CI)
Age (years)	.092	0.913 (0.821-1.015)			.804	0.991 (0.927-1.061)		
Female	.404	0.464 (0.077-2.813)			.496	0.608 (0.145-2.551)		
Smoker	1.000	NA			.796	1.364 (0.129-14.402)		
Angina	.596	1.714 (0.234-12.551)			.261	3.000 (0.442-20.379)		
Orthopnea	.999	NA			.999	NA		
Chest pain	.999	NA			.999	NA		
ECG	.402	2.000 (0.396-10.108)			.599	0.700 (0.185-2.648)		
Weight (kg)	.345	1.028 (0.971-1.088)			.614	1.013 (0.964-1.063)		
Height (cm)	.928	1.005 (0.893-1.132)			.992	0.999 (0.904-1.106)		
BMI (kg/m^2)	.344	1.095 (0.907-1.321)			.631	1.042 (0.881-1.234)		
WC (cm)	.625	1.027 (0.923-1.142)			.698	1.017 (0.935-1.106)		
WHR	.751	1.455 (0.144-14.697)			.987	0.986 (0.190-5.114)		
Systolic (mmHg)	.953	1.002 (0.928-1.082)			.757	1.010 (0.947-1.078)		
Diastolic (mmHg)	.869	0.989 (0.868-1.127)			.794	0.986 (0.889-1.094)		
FBG (mg/dL)	.696	1.004 (0.985-1.023)			.099	1.012 (0.998-1.026)		
2HPP (mg/dL)	.517	1.005 (0.989-1.022)			.054	1.011 (0.999-1.022)		
HbA1c	.043*	3.182 (1.039-9.746)	.933	1.076 (0.194-5.957)	.013*	1.768 (1.127-2.772)	.149	1.524 (0.860-2.701)
FPI	.375	0.871 (0.642-1.182)			.847	0.977 (0.773-1.235)		
HOMA IR	.809	0.917 (0.454-1.851)			.254	1.296 (0.830-2.026)		
Total serum cholesterol (mg/dL)	.944	0.999 (0.976-1.023)			.217	1.012 (0.993-1.031)		
LDL cholesterol (mg/dL)	.060	1.053 (0.998-1.111)			.004*	1.067 (1.021-1.115)	.187	1.037 (0.983-1.094)
HDL cholesterol (mg/dL)	.139	0.930 (0.846-1.024)			.079	0.933 (0.863-1.008)		
TG (mg/dL)	.751	0.998 (0.983-1.012)			.328	1.005 (0.995-1.016)		
Hs-CRP (mg/L)	.038*	1.394 (1.019-1.908)	.622	1.116 (0.721-1.727)	.008*	1.476 (1.108-1.967)	.841	1.041 (0.705-1.537)
Irisin (ng/mL)	.006*	2.170 (1.243-3.788)	.038*	2.026 (1.041-3.944)	<.001*	2.301 (1.457-3.635)	.014*	1.979 (1.146-3.417)

CIMT is taken as the mean of 3 readings on both sides.

2HPP, 2 hours postprandial blood glucose; BMI, body mass index; CIMT, carotid intima–media thickness; ECG, electrocardiogram; FBG, fasting blood glucose; FPI, fasting plasma insulin; HbA1c, glycated hemoglobin; HDL, high-density lipoproteins; HOMA-IR, homeostatic model assessment for insulin resistance; hs-CRP, high sensitive C-reactive protein; LDL, low-density lipoproteins; OR, odds ratio; T2DM, type 2 diabetes mellitus; TG, triglycerides; WC, waist circumference; WHR, waist hip ratio.

*Variables with $P < .05$ in univariate analysis were entered into the multivariate model. $P \leq .05$ was considered statistically significant.

*Statistically significant at $P \leq .05$.

#Variables with $P < 0.05$ in univariate analysis were entered into the multivariate model.OR: odds ratio; CI: confidence interval.

stimulate hepatic CRP production. Second, irisin is positively correlated with abdominal adiposity, which is associated with low-grade inflammation, leading to enhanced release of pro-inflammatory cytokines, such as IL-6 and TNF-α, and subsequently increasing CRP production. In contrast to the results, an inverse relationship was found between the CRP and serum irisin in the study performed by Ahmed et al,[29]while Eslampour et al[28] failed to find an association between serum irisin and CRP, except for a weak positive association in studies enrolling obese patients and those with female predominance.[28]

Carotid intima-media thickness is an early marker of subclinical atherosclerosis and can predict cardiovascular risk. Results adopted from a pooled analysis of 21 studies concluded a significantly higher CIMT in patients with prediabetes and diabetes vs. healthy controls, translated into a 40% increased risk of ASCVD.[30] Both groups with overweight/obesity had higher CIMT levels than healthy controls, and serum irisin exhibited a strong positive correlation with CIMT. Multivariable regression confirmed that higher irisin levels were independently associated with CIMT ≥ 0.9 mm in both overweight/obese groups.

In line with the findings, Sesti et al[31] demonstrated a positive correlation between mean serum irisin and body fat mass, fasting insulin, and CIMT, and an inverse relationship with Matsuda Index and insulin clearance. Despite that, most of the enrolled participants in their research were overweight/obese, and only one-quarter had impaired glucose tolerance. Conversely, El Haddad et al,[32] found an inverse relationship between serum irisin and BMI, HbA1c, urinary albumin, CRP, and CIMT in T2DM, with an inverse relationship with T2DM duration, suggesting that irisin varies across diabetes stages.[32]Furthermore, an indirect relationship between serum irisin and CIMT has been elicited in patients with Behçet's disease[33]and rheumatoid arthritis, especially in those with high disease activity.[34]These discrepancies likely reflect differences in study populations and patients' profiles.

Strengths and Limitations

Strengths include a well-defined cohort of individuals with overweight/obesity with and without newly diagnosed T2DM, standardized measurements, the use of CIMT as a validated marker of subclinical atherosclerosis, and appropriate modeling with acceptable predictive power and collinearity checks. On the other hand, this cross-sectional, single-center study cannot establish causality, and the modest sample size, particularly the small number of events of CIMT ≥ 0.9 mm, may reduce the power of subgroup analyses, including BMI-stratification and multivariable analyses. Although age or sex was not formally matched, the baseline distributions were not statistically different; however, residual confounding cannot be entirely excluded. All participants were recruited during diabetes/obesity management visits; individuals exhibiting cardiovascular-related symptoms underwent clinical evaluation, and although not targeted toward CVD, some referral bias toward higher-risk individuals remains possible. To minimize overfitting, a concise logistic model incorporating 4 clinically relevant variables was employed, with accepted collinearity (VIF ≤ 5); yet the findings should be regarded as exploratory. Moreover, irisin was quantified once using a single ELISA platform, and unassessed factors, such as physical activity, dietary habits, and lean mass, were not quantified. Despite these constraints, the consistent association between irisin and CIMT across analyses supports the validity of the observed relationship.

Serum irisin is elevated in obesity and independently associated with subclinical atherosclerosis (increased CIMT), irrespective of diabetic status. The findings suggest that irisin may act as a biomarker for cardiovascular risk in these populations.

Recommendations

More longitudinal observational studies are advised to track irisin changes from prediabetes to overt diabetes, across various stages of dysglycemia in both individuals with overweight/obesity and non-overweight/obese individuals, while controlling confounding factors such as physical activity and metabolic profiles.

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