



Serum irisin levels in metabolically healthy versus metabolically unhealthy obesity: A case-control study

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Abstract

Background: Metabolically healthy obese (MHO) individuals appear to be protected or more resistant to the progression of obesity-related metabolic disorders. Hormonal regulation associated with adipose or muscular tissues such as irisin and leptin may facilitate the healthy metabolic profile of MHO cases. In this case-control study, the differences between serum level of irisin was investigated in metabolically unhealthy obese (MUO) and metabolically healthy obese (MHO) individuals.

Methods: The study participants included obese individuals with metabolic syndrome (MetS) (n=51) and 2 control groups that included weight matched cases without MetS (n=51) and normal weight cases without MetS (n=51). Diagnosis of MetS was made based on the Adult Treatment Panel III (ATPIII) criteria. Serum levels of leptin and irisin were determined by enzyme-linked immune-sorbent assay (ELISA) kit. Receiver Operator Characteristic (ROC) curve, multiple linear regression, and one-way ANOVA analysis were used in SPSS 16 software. Significant level was set at 0.05.

Results: Based on the statistical analysis, serum levels of irisin were 2.91±1.6, 3.14±1.4, and 4.47±3.23 (ng/mL) in MUO, MHO, and nonobese metabolically healthy participants, respectively (P = 0.001). Also, serum levels of leptin were 14.06±12.4, 11.2±9.3, and 7.09±7.1 (ng/mL) in MUO, MHO, and nonobese metabolically healthy cases, respectively (p=0.002). After adjusting for demographic variables, a significant association was found between irisin and study groups ($\beta = 0.77$, P = 0.001), weight ($\beta = -0.03$, p=0.014), BMI ($\beta = -0.11$, p=0.006), TG ($\beta = -0.003$, p=0.025), fat mass ($\beta = -0.04$, p=0.046), and fat free mass ($\beta = 0.08$, p=0.014).

Conclusion: Obese patients with/without MetS had lower level of irisin than normal weight participants.

Keywords: Irisin, Obesity, Metabolic syndrome, Leptin

Conflicts of Interest: None declared

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Introduction

Management of obesity, as the sixth most important risk factor for global health, is a puzzling issue for nutritionists

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↑What is “already known” in this topic:

Irisin is a novel exercise-induced adipo-myokine, and it has been proposed that this myokine is involved in various procedures such as obesity, glucose hemostasis, and insulin secretion.

→What this article adds:

This study revealed a meaningful difference between the serum levels of irisin in MHO and MUO cases and nonobese metabolically healthy individuals (Nonobese metabolically healthy participants had the highest irisin levels.). Obese patients with/without MetS had higher levels of leptin than normal weight individuals. The elevated irisin level may decrease the risk of MetS development by reducing TG levels.

(1). Based on the BMI criteria, the aforementioned condition affects more than 600 million people worldwide (2). Obesity is often associated with an increased risk of metabolic syndrome (MetS), type 2 diabetes mellitus (T2DM), beta cell dysfunction, and cardiovascular diseases (CVD) (3). Recently, it has been observed that a subset of obese cases appears to be protected or more resistant to the progression of obesity-related metabolic disorders (4-6). These individuals, known as metabolically healthy obese (MHO), are considered by having excessive body fat, while presenting a favorable metabolic profile such as sufficient insulin action, normal levels of liver enzyme function, no sign of dyslipidemia or hypertension as well as high level of cardiorespiratory fitness compared to the metabolically unhealthy obese (MUO) (5-7). The prevalence of the MHO phenotype varies largely depending on ethnicity, age, physical activity, life style, etc. (8, 9). Numerous investigations have been conducted to determine the underlying mechanism for the aforementioned protection in MHO individuals. It has been proposed that some cytokines secreted from adipose and muscular tissues play a crucial role in MHO cases. Leptin and irisin are 2 cytokines that interact with other parameters to facilitate the healthy metabolic profile of MHO (10).

Leptin, as an important anti-obesity adipocytokine, plays a key role in regulation of energy homeostasis, obesity, diabetes mellitus, and other metabolic condition (11). Despite the unclear mechanism of leptin action in metabolic condition, some new investigations demonstrated a relationship between leptin and MHO phenotype. Irisin, as a novel exercise-induced adipo-myokine, is involved in the fat burning and inhibiting weight gain and glucose/lipid metabolism (12). Based on the aforementioned characteristics, irisin may serve as an attractive candidate for prevention and treatment of obesity and its associated problems (12, 13). The present study aimed to investigate the differences in the serum levels of irisin and leptin between MHO, MUO, and nonobese metabolically healthy individuals. Moreover, this study aimed to determine the suitable cutoff and associated sensitivity and specificity of serum irisin to predict metabolic syndrome.

Methods

Participants and study design

This matched case-control study was conducted after being approved by the Ethics Committee of TUMS (code No: 26402-93-02-161). The case/control ratio was 1:2. Participants were 51 overweight/obese patients with newly diagnosed MetS (MUO) and 2 control groups age- and gender-matched with MetS patients, including 51 MHO and 51 nonobese metabolically healthy participants. All cases were recruited from the Endocrinology Center of Tehran University of Medical Sciences (TUMS). Based on the body mass index (BMI), non-MetS control participants were classified into 2 groups: lean (BMI 18.5–24.9 kg/m²); overweight/obese (BMI ≥ 25kg/m²). All participants received an explanation of the study purpose and signed a written informed consent for participation in the study.

Those with a history of coronary artery disease, acute or chronic renal failure, acute infection within the last week,

acute or chronic hepatic failure, uncontrolled thyroid disorder, use of medications for dyslipidemia or hypertension, presence of any chronic inflammatory and autoimmune disease, and any known malignancies were excluded from this study. Other nonpathological exclusion criteria included pregnancy, breast feeding, post menopause, smoking, being a professional athlete, or having a special diet for any reason provided by a qualified dietitian. MetS was diagnosed according to the National Cholesterol Education Program – Adult Treatment Panel III criteria (NCEP- ATP_{III}) (14).

Body composition and anthropometrics measurement

Body composition was measured by bioelectrical impedance analysis (BIA) (model TANITA BC-418), which records body water content, fat mass (FM), and fat free mass (FFM). Height, weight, BMI, and waist circumference (WC) were calculated in all participants. Anthropometric measurements were obtained using standard protocols (15). WC was measured in the midline between the costal margin and the iliac crest of hip, and the aforementioned measuring was done after normal expiration.

Clinical parameters measurement

All blood samples were obtained from all participants after a 12-hour fasting and immediately centrifuged. Triglycerides (TG) and HDL-C were measured using spectrophotometry kit (Pars Azmun, Iran). Fasting blood sugar (FBS) was measured by a glucose oxidase procedure. Serum levels of leptin and irisin were measured by ELISA kit (Reutlingen / Germany). Also, blood pressure was measured on the nondominant upper extremity in the cases in a sitting position after they rested at least for 10 minutes.

Statistical analysis

SPSS 16.0 software (SPSS Inc., Chicago, IL, USA) was used for basic statistical analysis. Continuous variables were described as mean ± SD. One-way analysis of variance was used to assess comparisons between the 3 groups. When the output of the ANOVA statistical test was meaningful, LSD test was done to find which means differed. Also, the analysis of covariance (ANCOVA) was used to adjust body fat components related to estimated irisin level among the various study groups. Receiver Operator Characteristic (ROC) curve was used to determine the suitable cutoff point and related irisin sensitivity and specificity for predicting metabolic syndrome. Multiple linear regression analysis was used to assess the relationships between irisin and other examined parameters. A p value < 0.05 was considered as statistically significant.

Results

The characteristics and MetS components of the cases in various groups were presented in Table 1. Blood pressure, FBS, TG, HDL-c, and number of MetS components were not significantly different between the MHO and nonobese metabolically healthy participants (p>0.05). Compared to participants without MetS (MHO and nonobese metabolically healthy participants), MUO had significantly higher level of WC, BMI, blood pressure, FBS, TG, and number

Table 1. Anthropometrics, MetS parameters, body composition, and serum leptin and irisin of participants based on study groups

Variable	MUO (n=51)	MHO (n=51)	Nonobese metabolically healthy (n=51)	Total (n=153)	p*
	Mean ± SD	Mean ± SD	Mean ± SD	Mean ± SD	
Age (year)	37.5±6.5	36.9±6.4	35.9±6.3	36.8±6.4	0.473
Sex**					0.944
Male	43(84.3)	43(84.3)	44 (86.3)	130(85)	
Female	8 (15.7)	8 (15.7)	7(13.7)	23(15)	
Weight(Kg)	92.5±13.3 ^a	89.1±13.7 ^a	69.1±6.8 ^b	83.6±15.6	<0.001
Height (cm)	171.5±7.7	172.2±7.0	171.1±6.8	171.6±7.1	0.742
WC (cm)*	105.1±8.1 ^a	100.2±11.3 ^b	87.02±7 ^c	97.4±11.8	<0.001
BMI(kg/m ²)*	31.4±3.7 ^a	29.9±3.6 ^b	23.6±1.4 ^c	28.3±4.5	<0.001
WHR*	97±0.1 ^a	93±0.1 ^b	0.9±0.1 ^c	0.93±0.1	<0.001
Fat index	8.6±2.8 ^a	7.8±2.6 ^a	4.6±1.7 ^b	7.0±2.9	<0.001
SBP*	121.2±11.7 ^a	113.8±8.6 ^b	111.3±12.2 ^b	115.4±11.6	<0.001
DBP*	80.8±9.1 ^a	75.7±6.6 ^b	74.1±8.3 ^b	76.8±8.5	<0.001
FBS*	116.2±37.3 ^a	97.8±20.4 ^b	95.2±7.6 ^b	103.1±26.4	<0.001
TG*	266.3±203.6 ^a	131.0±87.4 ^b	117.5±67.8 ^b	171.6±149.0	<0.001
HDL*	50.3±8.3 ^a	54.3±5.6 ^b	55.1±9.2 ^b	53.2±8.1	0.006
MetS* components	3.3±0.6 ^a	1.0±0.7 ^b	0.8±0.6 ^b	1.7±1.3	<0.001
Fat free mass (%)	72.9±6.2 ^a	74±6.6 ^a	80.6±6 ^b	75.8±7.1	<0.001
Fat mass (%)	27.1±6.2 ^a	25.9±6.6 ^a	19.4±6.1 ^b	24.1±7.1	<0.001
Trunk fat (%)	28.9±5.4 ^a	27.9±6.4 ^a	20.6±6 ^b	25.8±7	<0.001
Right hand (%)	26.1±8.4 ^a	25.2±7.7 ^a	18.5±6.2 ^b	23.3±8.2	0.001
Left hand (%)	26.9±8.5 ^a	26.2±7.9 ^a	19.1±6.6 ^b	24.06±8.4	<0.001
Right leg (%)	24.2±7.9 ^a	22.7±7.9 ^a	17.4±7.2 ^b	21.4±8.2	<0.001
Left leg (%)	24.7±8.9 ^a	22.9±7.7 ^a	17.6±7 ^b	21.7±8.4	<0.001
Leptin(ng/ml)	14.0±12.4 ^a	11.2±9.3 ^a	7.1±7.1 ^b	10.8±10.2	0.002
Irisin (ng/ml)	2.9±1.6 ^a	3.1±1.4 ^a	4.5±3.2 ^b	3.5±2.3	0.001

Values are analyzed by one-way ANOVA, values are mean ± SD.

Dissimilar values (a, b, c) of each row are significantly different.

** Value are N (%)

* WC: Waist Circumference, BMI: Body Mass Index, WHR: Waist to Hip Ratio, SBP: Systolic Blood Pressure, DBP: Diastolic Blood Pressure, FBS: Fasting Blood Sugar, TG: Triglyceride, HDL: High Density Lipoprotein, MetS: Metabolic Syndrome.

of MetS components ($p < 0.001$). MUO patients showed significant lower HDL-c ($p = 0.006$).

Based on the results of the statistical analysis, leptin was meaningfully different between MHO and MUO and nonobese metabolically healthy participants (Table 1). Also, nonobese metabolically healthy participants had lower levels of leptin (7.1 ± 7.1) compared to the obese with/without Mets (MHO and MUO) (11.2 ± 9.3 and 14.06 ± 12.4 , respectively) ($p = 0.002$) (Table 1). Based on ANCOVA results, there is still a considerable relationship between leptin and study groups ($p = 0.015$) (Table 2).

Also, serum irisin level was significantly different between obese participants with/without Mets (MHO and MUO) and nonobese metabolically healthy participants

(Table 1). Nonobese metabolically healthy cases had higher levels of irisin (4.5 ± 3.23) compared to the obese with/without Mets (MHO and MUO) (3.14 ± 1.40 and 2.91 ± 1.60 , respectively) ($p = 0.001$) (Table 1). Also, after adjustment for fat mass, there was still a significant association between irisin and study groups (ANCOVA: $p = 0.002$), so the mean of irisin in MUO and MHO patients was significantly lower compared to average concentrations in the nonobese metabolically healthy cases (Tables 2 and 3).

A ROC curve was used to identify the ability of irisin levels to predict the MUO phenotype. Area under the curve (AUC) and ROC curves for the ability of irisin levels to predict MUO phenotype are shown in Figure 1. It can be seen that the cut off for irisin were 5.5 (ng/ml), with the

Table 2. ANCOVA for highlighting the association between irisin and leptin with study groups

	Source	Sum of squares	df	Mean square	F	p
Leptin	Intercept	3382.31	1	3382.31	90.43	<0.001
	Fat mass	8949.26	1	8949.26	239.28	<0.001
	Study groups	325.48	2	162.74	4.35	0.015
	Error	5497.85	147	37.40		
	Total	33446.96	151			
Irisin	Intercept	81.58	1	81.58	16.23	<0.001
	Fat mass	3.06	1	3.06	0.61	0.437
	Study groups	67.12	2	33.56	6.68	0.002
	Error	728.64	145	5.02		
	Total	2640.96	149			

Table 3. Estimated marginal means of irisin and leptin among MUO, MHO, and nonobese metabolically healthy participants

	MUO* (n=51)	MHO* (n=51)	Nonobese metabolically healthy (n=51)	p*
	SD± mean	SD± mean	SD± mean	
Leptin	10.5±0.9 ^a	9.1±0.7 ^a	13.0±0.9 ^b	0.011
Irisin	2.8±0.3 ^a	3.1±0.3 ^a	4.6±0.3 ^b	0.022

Values are analyzed by ANCOVA, values are mean ± SE.

Dissimilar values (a, b, c) of each row are meaningfully different.

*MUO: Metabolic Unhealthy Obese. MHO: Metabolic Healthy Obese

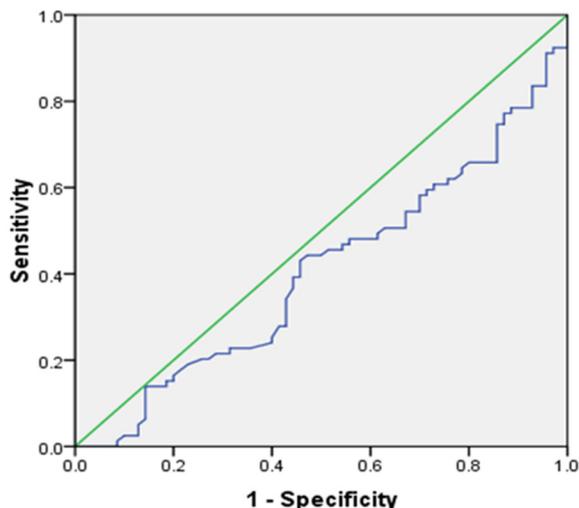


Fig. 1. The ROC curve for determining the irisin cutoff point in diagnosing MetS

area under the Receiver Operator Characteristic curve was 0.40 (95%CI for AUC: 0.31-0.49, $p < 0.04$).

Analysis of linear regression was used to quantifying the possible relation between irisin and other study parameters (Table 4). Based on linear regression analyzing with crude model (model 1), there was a significant association between irisin and study groups ($\beta = 0.78$, $p = 0.001$), weight ($\beta = -0.02$, $p = 0.021$), BMI ($\beta = -0.11$, $p < 0.001$), TG ($\beta = -0.003$, $p = 0.013$) and fat free mass ($\beta = 0.06$, $p = 0.012$). Also, in model 2, with adjusting for demographic variables, there was a considerable meaningful association between irisin and study groups ($\beta = 0.77$, $p = 0.001$), weight ($\beta = -0.03$, $P = 0.014$), BMI ($\beta = -0.11$, $p = 0.006$), TG ($\beta = -0.003$, $p = 0.025$), fat mass ($\beta = -0.04$, $p = 0.046$), and fat free mass ($\beta = 0.08$, $P = 0.014$), fat index ($\beta = -0.15$, $p = 0.034$). In model 3, with adjustment for all variables with p -value < 0.2 , there was still a significant association between irisin and the

study group ($\beta = 0.99$, $p = 0.042$). With increasing one unit in the study group, from MetS to healthy obese group and healthy obese to the normal weight group, the adjusted serum level of irisin was increased by on average 0.99 ng/mL.

In multiple linear regression analysis with backward method (model 4), there was a significant association between irisin and study groups ($\beta = 0.75$, $p = 0.001$).

In study groups, non-obese metabolically healthy subjects group have more serum irisin in compare with MHO and MUO groups so that there is an increasing trend of irisin level in study groups. In multiple linear regression analysis with backward method, there was a meaningful association between irisin and study groups ($\beta = 0.99$, $p = 0.042$). In study groups, non-obese metabolically healthy subjects group have more serum irisin in compare with MHO and MUO groups. It means that the MUO group of study meaningfully has a low level of irisin compared to other individuals in other groups (Fig. 2).

Also, there is significant association between irisin and number of MetS components ($\beta = -0.27$, $p = 0.053$) and study groups ($\beta = 0.78$, $p = 0.001$). With increasing one unit in number of MetS components, the irisin were decreased by 0.27, so that there is a decreasing trend of irisin according to number of MetS components (Fig. 3).

Discussion

In the present study, a meaningful difference was found between the serum levels of irisin in MHO and MUO patients and nonobese metabolically healthy participants. The results are in agreement with several studies that evaluated the possible role of irisin in the initiation and progression of obesity and MetS. Some studies reported that serum levels of irisin were decreased in obese adults (16-18). Irisin is one of the crucial secreted myokines and it has been proposed that this myokine is involved in various procedures such as energy balance, glucose hemostasis, insulin secretion, and action (13, 19).

Table 4. Multiple linear regression for estimating the relation between irisin and related factors

Variables	Model 1 ^a		Model 2 ^b		Model 3 ^c		Model 4 ^d	
	β	p	β	p	β	P value	β	p
Leptin	-0.01	0.471	-0.02	0.292	-	-	-	-
Age (years)	-0.01	0.536	-	-	-	-	-	-
Gender	0.05	0.927	-	-	-	-	-	-
Groups ^e	0.78	0.001*	0.77	0.001*	0.99	0.042*	0.75	0.001*
weight	-0.02	0.021*	-0.03	0.014*	0.07	0.493	-	-
WC ^f	-0.02	0.083	-0.02	0.084	0.04	0.265	-	-
BMI ^f	-0.11	<0.001*	-0.11	0.006*	-0.36	0.241	-	-
SBP ^f	0.001	0.962	0.002	0.925	-	-	-	-
FBS ^f	-0.09	0.198	-0.009	0.247	-0.001	0.983	-	-
TG ^f	-0.003	0.013*	-0.003	0.025*	-0.002	0.206	-	-
HDL ^f	0.001	0.954	0.001	0.962	-	-	-	-
MetS component	-0.27	0.053	-0.26	0.073	0.35	0.178	-	-
Fat mass	-0.04	0.055	-0.04	0.046*	-0.18	0.604	-	-
Fat free mass	0.06	0.012*	0.08	0.014*	0.3	0.402	-	-
Trunk fat	-0.03	0.238	-0.03	0.219	-	-	-	-
Fat index	-0.12	0.061	-0.15	0.034*	0.61	0.549	-	-

^a Crude model

^b Adjusted for demographic variables such as sex and age

^c Adjusted model (all variables with p -value < 0.2 entered the model such as sex, groups, weight, WC, BMI, SBP, TG, HDL, MetS component, BMR, fat mass, fat free mass, trunk fat).

^d Multivariate backward linear regression model.

^e: study groups including; 1: MetS patient, 2: healthy obese, 3: normal weight without MetS

^fWC: Waist Circumference, BMI: Body Mass Index, SBP: Systolic Blood Pressure, FBS: Fasting Blood Sugar, TG: Triglyceride, HDL: High Density Lipoprotein

*Significant at p value < 0.05 .

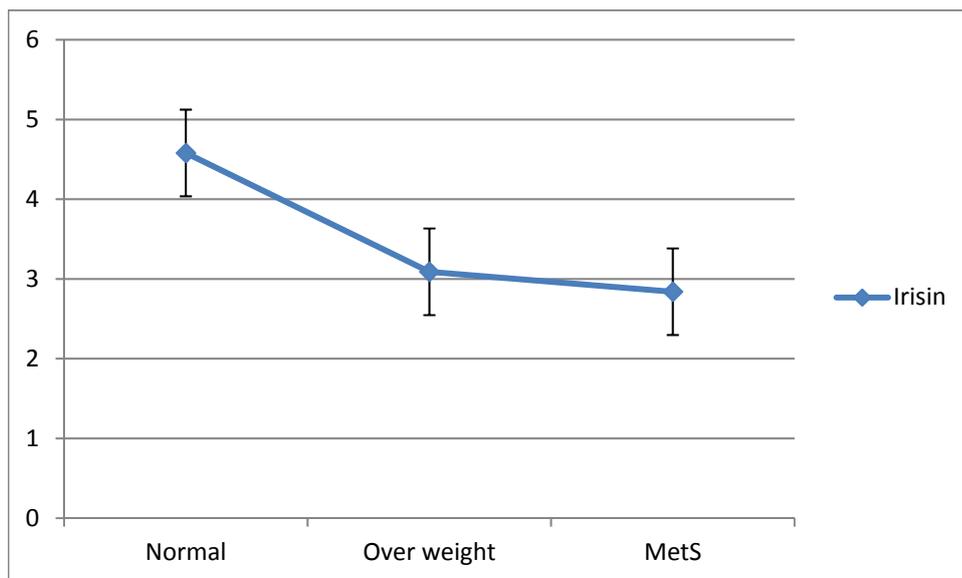


Fig. 2. Trend of irisin (ng/mL) according to study groups

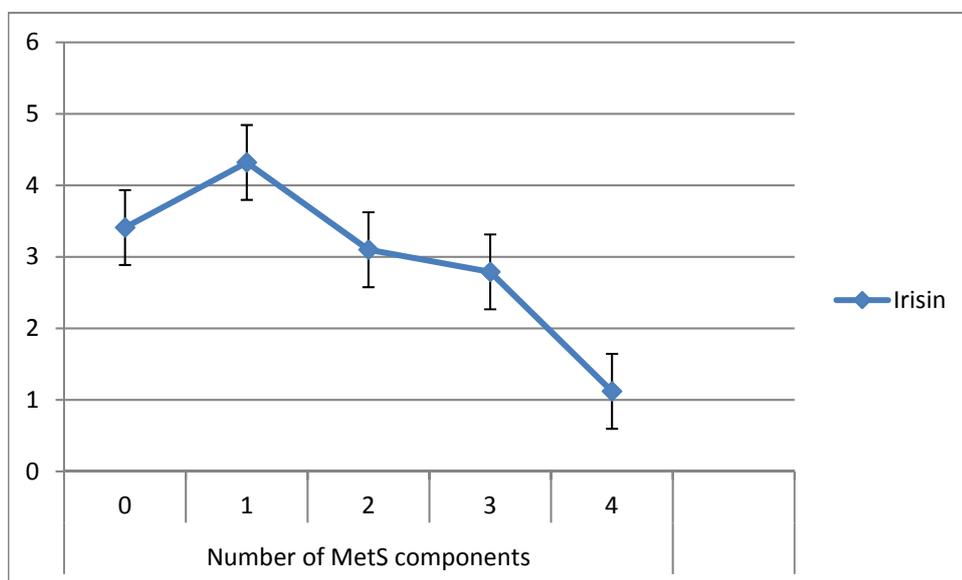


Fig. 3. Trend of irisin (ng/mL) according to number of MetS components

Previous studies reported contradictory results about the possible relationship between irisin levels and MetS. Hee Park et al reported increased serum level of irisin in participants with MetS (20). Furthermore, a positive relationship was found between serum levels of irisin and body weight in some studies (21-24). However, the precise basis for aforementioned discrepancy is unclear (21). However, the present study proposed lower irisin levels in MHO and MUO compared with nonobese metabolically healthy individuals.

The relationship between fat/muscle mass, MetS components, and circulating irisin levels remains a puzzling issue. This study revealed that serum irisin concentrations were negatively correlated with weight, BMI, TG, percent of fatty mass, and number of MetS components in all participants. Also, a positive correlation was found between irisin and percent of fat free mass. Moreover, it seems that high-

fat free mass and low-fat mass promote irisin secretion. Our findings are consistent with the results of Moreno-Navarrete and Choi's studies that demonstrated a significant negative correlation between circulating irisin and BMI (13, 25) as well as percentage of fatty mass in nondiabetic individuals (13). Another considerable result of this study was the positive correlation of serum irisin with percent of fat free mass. This part of our results was supported by Fukushima Y et al (2016) who reported positive relations between percent lean body mass and serum irisin level (21). However, contradictory effects of body composition (percent of fatty mass/ fat free mass) on serum irisin levels have been reported (13, 24-26). Several studies have proposed a positive correlation between serum irisin levels and BMI (20, 27) and fatty mass (24).

In accordance with our findings, some researches reflected fat free mass as the main predictor of serum irisin

(27). Based on some experimental investigations, an increase in muscle mass was accompanied by increased FNDC5 gene expression and PGC_{1-α} and other mitochondrial genes in muscle (28). Activated PGC_{1-α} and increased expression of FNDC5 gene act as a precursor of irisin and give rise to increasing irisin secretion into blood circulation (21). As previously mentioned, increased circulating irisin was associated with better energy expenditure, fat metabolism, insulin sensitivity, and MetS prevention (13). One of the other crucial consequences of higher irisin level is more browning of white fat performed by increasing uncoupling protein 1 (UCP1) gene expression (29). However, the effect of irisin on lipid profile and glucose concentration remains unclear. Some surveys have reported conflicting results regarding the association between serum level of irisin and lipid/glucose determinants and the issue is open to discussion (22, 24, 25, 27). In the present study, serum irisin concentrations were negatively correlated with TG ($p < 0.05$). Furthermore, cellular and molecular investigations are needed to determine the possible relations between irisin and TG levels.

In the present survey, no association was found between serum irisin and some clinical parameters such as fasting glucose, BP, and HDL-c. Some studies presented that circulating irisin levels were correlated with FBS (30), BP (20), and HDL-c (31). However, in this study, no correlation was found between serum irisin and HDL-c, FBS, and BP, which is consistent with many previous studies (13, 27).

In agreement with our findings, one study showed that circulating irisin levels were negatively correlated with TG (25). Furthermore, some studies reported that FBS (25, 32) and lipid profile (25) were not correlated with irisin levels.

This study had several limitations. First, this was a case-control study, so the causal relationship between metabolic and serum levels was not definitive. Another limitation was the small number of females compared to male participants; thus, it was not possible to examine the possible effect of sex. Finally, insulin resistance was not evaluated in the present study. Further study, especially by prospective cohort designs in different populations, are needed to confirm the precise estimation of the causal effect of this study's findings.

Conclusion

This study reported that the serum level of irisin was associated with TG level negatively and percent of fatty mass, while it was positively correlated with percent of fat free mass. Obese patients with/without MetS had lower irisin level than normal weight participants.

Acknowledgments

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Conflict of Interests

The authors declare that they have no competing interests.

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