Serum irisin with metabolic syndrome, type II diabetes, and insulin resistance

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Background
Obesity is the most significant problem nowadays and is concomitant with higher risk of insulin resistance, type II diabetes, and metabolic syndrome (MetS).

Aim
The aim of the study was to determine the possible association between serum irisin among obesity-associated MetS and type II diabetes mellitus patients and if there was a connection between serum irisin and insulin resistance.

Materials and methods
This study was directed on 60 patients '35 patients with MetS and 25 patients with type II diabetes' and 25 healthy controls. Serum irisin was measured by the enzyme-linked immunosorbent assay (ELISA) kits.

Results
Serum irisin was statistically significantly lower in the MetS group and the DM group in contrast to the control group and also there was significant reduction of the mean value of serum irisin of the MetS group when equated to the DM group.

Conclusion
In conclusion, this study has shown that there may be an association with decreased irisin level and obesity with insulin resistance.

Keywords:
Metabolic syndrome (MetS), Diabetes mellitus (DM), irisin

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Introduction

Obesity is considered a risk factor for diabetes, cardiovascular disease, and metabolic syndrome (MetS) [1]. Insulin resistance is one of the key influences of MetS. Adipose tissue releases chlorinated fatty acids and leads to insulin resistance [2]. Insulin resistance and obesity have long been the most principal constituents in causing MetS [3].

MetS is a group of metabolic abnormalities that often co-occur and leads to a marked upturn in the risk of cardiovascular disease and type 2 diabetes mellitus (T2DM), including obesity, hyperglycemia, and high blood pressure [4].

Adipose tissue is documented as a dynamic organ of the endocrine, and can regulate the metabolism, insulin resistance, and MetS by producing inflammatory adipokines [5].

The skeletal muscle tissue has been known as another endocrine manager of metabolism [6].

A recently determined hormone named irisin is derived from the fibronectin type III domain-containing protein 5 (FNDC5) gene that is released mostly from the skeletal muscle after exercise or exposure to cold [7]. Adipose tissue also discharges irisin [8].

Adipose tissue is described by the fat tissue either white fatty tissue (WAT) or brown tissue structure. WAT serves as the chief storage site for fat and energy, while brown tissue structure can disintegrate energy as heat due to the separate breathing of the mitochondria [9]. This process is achieved by a particular protein in the mitochondria called as uncoupling protein 1 (UCP1). The homogeneous activity of UCP1 is illuminated by its ability to pass protons through the mitochondrial inner membrane, shunning the synthesis of ATP and instead, scattering energy as heat [10].

Irisin transforms WAT-like brown fat by stimulating the UCP1 expression of white adipose cells. This transformation from white adipocytes to brown adipocytes and the resulting rise in heat generation stimulate improved glucose tolerance, amplified insulin sensitivity, reduced body weight, and squeezed fat mass [11].

Materials and methods

This study was directed on 60 patients '35 patients with MetS and 25 patients with type II diabetes' and 25 healthy controls. The patients were selected from the outpatient clinic of the Internal Medicine Department of Assiut University Hospital in a period between September 2017 and September 2018 and the study was performed in the Clinical Pathology Department.

The patients were identified as having MetS consistent with the National Heart, Lung, and Blood Institute/American Heart Association standards, which define the presence of MetS as presently having three or more of the following five cardiovascular risk factors: first, central obesity (waist circumference >102 cm for men and >88 cm for women); second, high triglycerides (TG >150 mg/dl) or specific treatment for this lipid anomaly; third, low high-density lipoprotein cholesterol (<40 mg/dl for men and <50 mg/dl for women) or specific drug for this lipid defect; fourth, systemic hypertension (blood pressure >130/85 mmHg) or antihypertensive treatment; and fifth, raised fasting serum glucose (FSG >5.5 mmol/l) or history of diabetes mellitus (DM) or taking antidiabetic therapy [12].

Sample collection, storage, and handling

A measure of 10 ml of fasting venous blood was reserved under complete aseptic conditions after fasting for 14 h; '7 ml of blood was collected into plain tubes without anticoagulants and 3 ml of blood was collected on an EDTA container for the estimation of blood count and HbA1C.'

Blood was permissible to clot for 20 min at 37°C and serum was detached by centrifugation at 3000 rpm for 10 min.

The separated serum was checked to ensure that it was clear and non-hemolyzed or lipemic.

Serum was allocated into three aliquots, one of them was used for routine laboratory investigations and the other two stored at −80°C till the time of assay of specific investigations.

Random urinary samples

Urine samples were collected at random for complete urine analysis and urinary albumin/creatinine ratio.

Routine investigations

Fasting and postprandial serum glucose concentration, urea, creatinine, liver function tests, lipid profile, glycosylated hemoglobin (HbA1c), and urinary protein/creatinine ratio were done on Cobas Integra 400 (Roche, Oststeinbek, Germany. SNIBE Co.,Ltd, China).

Complete blood count was estimated by Cell-DYN.

Special investigations

Fasting serum insulin

Fasting serum insulin analysis was done on Maglumi 'fully automated chemiluminescence immunoassay (CLIA) analyzer', Snibe, catalog number: 130205002M.

Homeostasis model assessment for insulin resistance

The above was assessed using the following method:

$$\text{HOMA-IR} = \left[\begin{array}{c}\text{fasting serum glucose } (\text{mmol}) / 1 \times \\ \text{fasting insulin } (\mu\text{U/ml})\end{array}\right] / 22.5$$

Serum irisin concentration

Serum irisin was measured by enzyme-linked immunosorbent assay (ELISA) kits: 'SinoGeneClon Biotech Co. Ltd., catalog number: SG-10179 (Hangzhou, China).

Principle of the test

Enzyme-linked immunosorbent assay was based on the formation of antibody–antigen–enzyme–antibody complex to identify human irisin. Absorbance is measured spectrophotometrically at a wavelength of 450 nm [13].

Statistical analysis

Information was collected and evaluated using SPSS (the Statistical Package for the Social Sciences, version 20; IBM, Armonk, New York, USA). Constant data were stated in the formula of mean ± SD or median (range) while nominal data were held in arrangement with rate (percentage).

The nominal data of different groups in the study were matched by χ^2-test, while Student's t-test was used to counterpart the mean of the different two groups. Pearson's connection was used to determine the association between serum irisin and other continuous variables. P value was significant if less than 0.05.

Ethical consideration

Prescribed written consent was obtained from patients and controls. The study was accepted by the Ethos Commission of Faculty of Medicine, Assiut University.

Results

Levels of BMI, serum irisin, fasting insulin, HOMA-IR, and HbA1C in patients and control groups

Irisin

Serum irisin was statistically significantly lower in both the MetS group and DM group compared with the control group with *P* values of less than 0.001 and less than 0.02, respectively and also there was significant reduction of mean value of serum irisin of the MetS group when compared with the DM group ($P = 0.03$) (Table 1).

BMI, Fasting insulin, HOMA-IR, and HbA1C

Patients with MetS had significantly higher BMI, fasting insulin, Homeostasis model assessment for insulin resistance (HOMA-IR), and HbA1C in comparison to those with DM and control group ($P < 0.001$).

Correlation of serum irisin with different laboratory data in the studied groups

The MetS group irisin had insignificant negative association with BMI but in the case of DM group serum irisin had significant positive correspondence with BMI ($P = 0.02$; $r = 0.46$); serum irisin had significant negative association with urinary albumin/creatinine ratio ($r = -0.29$; $P = 0.01$) and significant positive correlation with serum creatinine ($r = 0.30$; $P = 0.01$) and in the DM group, serum irisin shows significant negative association with HbA1 C ($r = -0.33$; $P = 0.01$) (Figs 1–4 and Table 2).

As regards serum irisin in obesity-related MetS patients, serum irisin in all MetS patients was less than 0.8 ng/ml with no major difference ($P = 0.65$) between obese and nonobese patients, while in obesity-related diabetic patients, serum irisin in all obese DM patients was less than 0.8 ng/ml while only 62.5% of nonobese patients had serum irisin less than 0.8 ng/ml with $P = 0.03$ when obese patients were compared with nonobese patients.

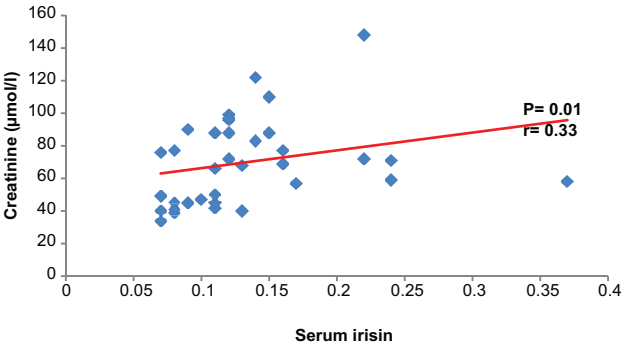
The obese MetS patient group had significantly increased percent of elevated HOMA-IR (100 vs 62.5% nonobese patients), increased fasting insulin (73.5 vs 37.5% nonobese patients), and increased FSG (100 vs 68.8% nonobese patients) with *P* values of 0.01, 0.03, 0.01, respectively.

The obese diabetic patient group had suggestively increased percent of elevated HOMA-IR (100 vs 50% nonobese patients) with a *P* value of 0.01 (Table 3)

Discussion

This study shown that serum irisin levels were reduced in patients with MetS and DM than controls. These

Figure 1



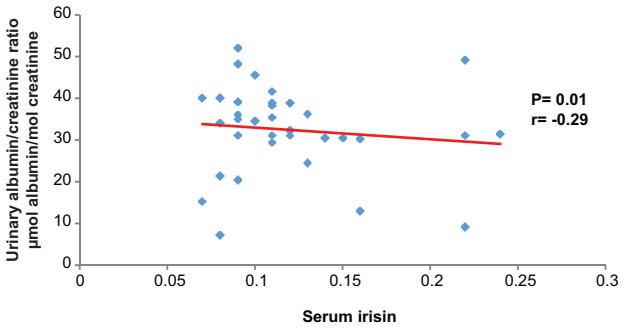
Correlation between serum irisin and creatinine in patients with metabolic syndrome.

Table 1 Levels of BMI, serum irisin, fasting insulin, HOMA-IR, and HbA1C in patients and control groups

	MetS group (*n*=35)	DM group (*n*=25)	Control group (*n*=25)	P_1	P_2	P_3
BMI (kg/m^2)						
Mean±SD	29.63±6.28	26.13±8.44	25.97±6.28	**<0.001**	0.10	**<0.001**
Median (range)	22.57-53.1	18.42-33.90	18.44-30			
Irisin (ng/ml)						
Mean±SD	0.13±0.06	0.46±0.22	0.80±0.47	0.03	**<0.001**	0.02
Median (range)	0.07-0.37	0.07-2.43	0.07-2.98			
Fasting insulin (mIU/l)						
Mean±SD	12.48±5.05	12.80±6.86	6.46±1.54	0.34	0.02	0.02
Median (range)	6.06-33.29	5.69-31.08	1.49-8			
HOMA-IR						
Mean±SD	5.86±3.57	6.16±4.68	0.83±0.67	0.45	0.02	0.01
Median (range)	1.66-18.49	1.59-21.96	0.27-1.5			
HbA1C (%)						
Mean±SD	7.91±1.94	7.68±1.08	4.18±0.81	0.45	0.03	0.02
Median (range)	5.24-11.81	5.41-9.71	2.99-5.00			

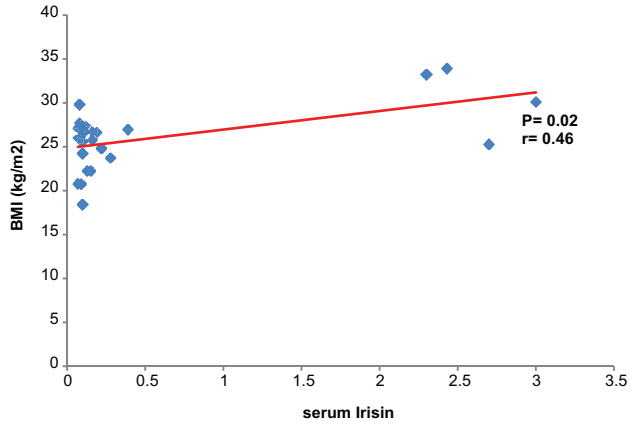
DM, diabetes mellitus; HbA1C, glycosylated hemoglobin; HOMA-IR, homeostasis model assessment for insulin resistance; MetS, metabolic syndrome.

Figure 2



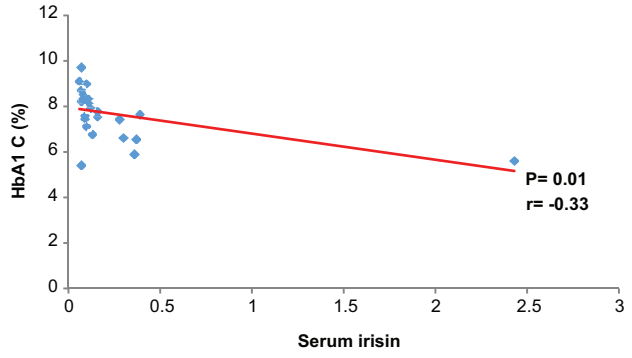
Correlation between serum irisin and urinary albumin/creatinine ratio in patients with metabolic syndrome.

Figure 3



Correlation between serum irisin and BMI in patients with diabetes mellitus.

Figure 4



Correlation between serum irisin and glycosylated hemoglobin in patients with diabetes mellitus.

results agree with those of Moreno-Navarrete *et al.*[14] and Huh *et al.* [15], who also found low serum irisin in link with type II diabetes and obesity. The study of Ebert *et al.*[16] exhibited that circulating irisin decreased during the oral glucose tolerance test in patients with MetS, insulin resistance, and type II diabetes mellitus (T2DM) and they recommended that irisin is expressively and extremely down regulated

Table 2 Correlation of serum irisin with different laboratory data in patient groups

Variables	Groups	
	MS group	DM group
BMI	−0.09 (0.61)	**0.46 (0.02)**
Waist circumference	−0.21 (0.21)	−0.13 (0.49)
Fasting serum glucose	Nil	Nil
2 h-postprandial glucose	Nil	Nil
Cholesterol	−0.41 (0.22)	0.24 (0.44)
Triglycerides	−0.19 (0.94)	−0.30 (0.09)
High-density lipoprotein	−0.23 (0.06)	Nil
Low-density lipoprotein	−0.25 (0.12)	0.15 (0.45)
Urea	0.22 (0.11)	Nil
Creatinine	**0.30 (0.01)**	0.28 (0.16)
HOMA-IR	−0.15 (0.41)	0.25 (0.23)
Fasting insulin	−0.01 (0.90)	Nil
Urinary albumin/creatinine ratio	**−0.29 (0.01)**	0.02 (0.85)
Glycosylated hemoglobin	Nil	**−0.33 (0.01)**

DM, diabetes mellitus; HOMA-IR, homeostasis model assessment for insulin resistance; MetS, metabolic syndrome.

by an acute glucose burden during the oral glucose tolerance test.

Also, regarding irisin, 100% of obese and nonobese MetS patients had decreased irisin level with no significant change ($P = 0.65$) between the two groups.

The results of irisin in the MetS group were consistent with that of Yan *et al.* [17], while the outcomes of Hee park *et al.*[18] showed high irisin levels in patients with MetS than participants without MetS. Chen *et al.*[19] concluded that variation of the results of these studies may be due to different populations recruited in these studies as the study of Hee park *et al.*[18] included patients with MetS with high BMI, making it the most important factor while a study from Yan *et al.*[17] included subjects with central obesity making glucose hemostasis and insulin resistance the major factors.

The results of the DM group of this study showed a positive correlation of irisin with BMI; the same finding was achieved by Liu *et al.*[19] and Crujeiras *et al.* [20], while Choi *et al.*[21] found a negative correlation between irisin and patients with new-onset type II diabetes. On the other hand, Sanchis-Gomar *et al.*[22] did not find a positive or negative association between circulating irisin levels and BMI. This study also found no positive or negative correspondence between irisin and BMI in the MetS patient group. Yan *et al.*[17] explained this finding that central obesity of MetS patients is linked to several metabolic disorders, making glucose hemostasis and insulin resistance, the major factors affecting irisin. The controversy of these data may be explained by the antiobesity effect of irisin which maybe acting as a physiological defensive factor against obesity mediated by the browning of WAT and is then increased in compensation for increasing

Table 3 Distribution of laboratory data in patients with metabolic syndrome and diabetes mellitus based on obesity

	Metabolic syndrome [*n* (%)]			Diabetes mellitus [*n* (%)]		
	Obese (*n*=19)	Nonobese (*n*=16)	*P*	Obese (*n*=17)	Nonobese (*n*=8)	*P*
Irisin	<0.8 ng/ml (100%)	<0.8 ng/ml (100%)	0.65	<0.8 ng/ml (100%)	<0.8 ng/ml: 5 (62.5%) >0.8 ng/ml: 3 (37.5%)	**0.03**
FSG						
Normal	0	5 (31.2)	**0.01**	0	2 (25)	0.09
Increased	19 (100)	11 (68.8)		17 (100)	6 (75)	
HbA1C						
Normal	1 (5.3)	2 (12.5)	0.43	0	2 (25)	0.09
Increased	18 (94.7)	14 (87.5)		17 (100)	6 (75)	
Fasting insulin						
Normal	5 (26.3)	10 (62.5)	**0.03**	6 (35.5)	6 (75)	0.07
Increased	14 (73.7)	6 (37.5)		11 (64.7)	2 (25)	
HOMA-IR						
Normal	0	6 (37.5)	**0.01**	0	4 (50)	**0.01**
Increased	19 (100)	10 (62.5)		17 (100)	4 (50)	

FSG, fasting serum glucose; HbA1C, glycosylated hemoglobin; HOMA-IR, homeostasis model assessment for insulin resistance.

body mass. In pathological states of morbid obesity, physiological irisin cannot maintain the equilibrium of energy storage and spending [19].

The reason of Fukushima *et al*.[23] was that peroxisome proliferator-activated receptor gamma coactivator 1α (PGC1α) supports irisin secretion, contributing to mitochondrial biogenesis and an advancement in oxidative metabolism and metabolic parameters, and a decrease in PGC1α expression of function induces marked insulin resistance, diabetes, and MetS along with decreased irisin.

Also, correlation studies have shown that irisin level was negatively correlated with HbA1C in the diabetic patients' group. These results were comparable with that of Choi *et al*. [24], Haddad *et al*. [25], and Yan *et al*. [17], who reported the same finding and they advised that irisin advances glucose hemostasis. In addition, Hee Park *et al*.[18] stated that irisin overexpression resulted in enhancement of hyperinsulinemia and glucose tolerance.

This study has shown that irisin level in the diabetic patient group was positively associated with fasting insulin and HOMA-IR; however, this association was statistically insignificant. The same results were also reported by Hee Park *et al*.[18] and Stengel *et al*. [26].

Hee Park *et al*.[18] concluded that irisin level is affected in response to the worsening of insulin sensitivity; and insulin resistance might also be correlated with irisin secretion, because irisin stimulates energy intake, which in turn causes weight loss, fat reduction, and improves insulin resistance [27].

In the MetS patient group, there was an insignificant negative association between serum irisin, HOMA-IR, and fasting insulin and this finding is reported by Moreno-Navarrete *et al*. [14], who found a negative relationship between irisin level and insulin resistance in men with obesity, while Fukushima *et al*.[23] stated a positive connection between irisin and HOMA-IR in untreated Japanese patients with obesity. In the MetS group, there was no association between irisin and HbA1C. Moreno-Navarrete *et al*.[14] have also found no association between irisin and HbA1C.

There was a significantly negative relationship between irisin and albumin/creatinine ratio and positive correlation with creatinine.

Ebert *et al*.[28] have studied a patient population with stage 1–5 chronic kidney disease (CKD) and found that irisin levels positively diminished with increasing CKD stage and are lowest in patients with stage 5 CKD. These results submit that irisin is considered as a marker of renal function as albumin in the urine is one of worthy indicators of MetS--related renal injury [2].

In the study of obesity-related metabolic disorders, 100% of obese MetS and 68.8% of nonobese MetS patients had increased FSG (P = 0.01). About fasting insulin, 73.7% of obese MetS patients and 37.5% of nonobese MetS patients had increased fasting insulin (P = 0.03). As regards HOMA-IR, 100% of obese MetS patients and 62.5% of nonobese MetS patients had increased HOMA-IR.

In the study of obesity-related-diabetic patients, 100% of obese diabetic patients and 62.5% of nonobese diabetic patients had a low irisin level with a significant change between the frequency of patients in the two groups (P = 0.03). Also, 100% of obese diabetic patients had high HOMA-IR and 50% of nonobese diabetic patients showed raised HOMA-IR with significant alteration (P = 0.01).

These results are in agreement with Elizondo-Montemayor *et al*. [13], who reported that irisin is positively accompanied with anthropometric

and metabolic markers of T2DM and irisin may play a part as a therapeutic prescription in obesity and T2DM.

Conclusion

In conclusion, this study has shown that there may be an association with decreased irisin level and obesity with insulin resistance.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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