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Irisin Has Evident Association With Insulin, HOMA-IR, and Glucagon In Obese Diabetic and Non-Diabetic Iraqi Women

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Abstract, *Objective : We aimed to explore that the association of irisin with various anthropometric and metabolic parameters in obese diabetics and non-diabetics Iraqi women. Methods: Eighty obese Iraqi women participated in this cross-sectional study grouped into 40 obese and 40 obese diabetics. The correlation coefficient between circulating irisin levels and metabolic parameters were performed. Results: Serum irisin levels in obese group showed highly significant positive correlations with body weight, WC, BMI, FPG, fasting insulin (FI), HOMA-IR and glucagon (r=0.8684, P <0.0001 ; r = 0.8104, P <0.0001; r = 0.8285, P <0.0001; r = 0.5876, P <0.0001; r = 0.5283, P <0.0005; r = 0.0005, P <0.0001; r = 0.5244, P <0.0005) respectively, and significant negative correlation with FPG, FI and HOMA-IR (r=-0.3246, P<0.041; r=-0.7903, P<0.0001; r=-0.6105, P<0.0001) respectively. Stepwise regression results showed that body weight, FPG, HOMA-IR and glucagon had significant independently related with irisin (β=2.3150, P<0.0001; β=-1.2200, P=0.0002; β=21.8760, P=0.02; β=-20.9800, P<0.005; β=0.0468, P=0.037) respectively. Conclusions: Irisin had a strong positive correlation with anthropometric parameters. Irisin independently associated with body weight, glucagon, HOMA-IR and FPG.*

Keywords: *Irisin, Glucagon, Type 2 Diabetes Mellitus, HOMA-β, HOMA-IR, Body Mass Index.*

1. INTRODUCTION

Irisin is a novel myokine and adipokine expressed in skeletal muscle; it exerts beneficial effects on metabolism by prompting the browning of subcutaneous white adipocytes. Irisin acts on white adipose cells in in vivo to stimulate uncoupling protein 1 (UCP1) expression and a broad program of brown-fat-like development. The expression of UCP1 is regulated by many transcriptional factors, including peroxisome proliferator-activated receptor γ coactivator-1 α (PGC-1α), which can be stimulated by exposure to cold temperatures. Similarly, the precursor of irisin, the fibronectin type III domain-containing protein 5 (FNDC5) and a type I transmembrane protein of skeletal muscle, is a PGC-1α-dependent myokine [2]. Circulating irisin elevated in some studies, decreased in others and persisted unchanged in others after exercise [4]. Circulating irisin is significantly decrease in individuals with diabetes compared with healthy [6]. In a study of non-diabetic subjects, results showed that an elevated irisin level is related to insulin resistance (IR) and vascular atherosclerosis in humans [7]. Similarly, irisin is correlated with increased risk of metabolic syndrome, systolic and diastolic blood pressure, fasting glucose, TGs and IR, and cardiovascular disease (CVD) in humans [8]. The correlation of PPARα with FGF-21, irisin may regulate intrahepatic triglycerides content through FGF-21

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[9]. The role of irisin in obesity and glucose metabolism has not been fully well-known yet. While some authors observed that plasma irisin concentrations are decreased in obesity [10]. The regulation of α-cell glucagon secretion by nutrients, hormones, neurotransmitters, and drugs is complex. It involves direct signalling of α-cells circulating glucagon activates hepatic glucagon receptors and protein kinase A (PKA) to increase hepatic glucose production (HGP) [15]. Puigserver 2005 demonstrated that positive signals such as glucagon activate via cAMP an important regulator of PGC-1 α gene expression 16.[

Aims of this study are to understand and find the relation of irisin in obese, diabetic and non-diabetic Iraqi women with assessment of irisin relation to insulin resistant, anthropometric and lipid profile.

2. SUBJECTS & METHODS

A cross-sectional study of eighty Iraqi women recruited consecutively during the period from April 2014 to February 2015 at the Obesity Research and Therapy Unit, Alkindy College of Medicine/ baghdad. Women classified according to obesity (BMI≥ 30 kg/m2) and type 2 diabetes presences into two groups (40 obese type 2 diabetics, and 40 non-diabetic). The exclusions criteria including; pregnant, lactating, menopause, smoker, alcohol, and any endocrine or genetic or drug causes of obesity, T1DM, cardiac, renal, hepatic diseases, anemia and hyperproteinemia are also excluded. Anthropometric measurements were obtained using standard protocols. The homoeostasis model assessment (HOMA) was applied to estimate degree of IR and β cells [20]. Sera of hormones levels were obtained and determined with human ELISA kits after addition of antiprotease.

The Statistical Analysis System- SAS (2012) was used to find the effects of different factors for study parameters. The least significant difference (LSD) test was used to significant compared between study groups. The estimation of correlation coefficients between irisin and all study variables are used. Univariable and stepwise multiple linear regression analysis was used to identify variables independently correlated with serum irisin levels. A P value of ≤ 0.01 and ≤ 0.05 was used as the level of significant differences.

3. RESULTS

The results showed highly significant differences in age, WC, BMI, TGs, HDL-C, FPG, FI, HOMA-IR, HOMA-β between groups. In addition, demonstrated there were no significant differences in glucagon, total protein, TSH, irisin, betatrophin (P> 0.05) between groups, table (1) illustrate these results.

Table 1. Descriptive data for obese diabetic and non-diabetic patients.

Variables	Obese N= 40	Obese diabetic N= 40	LSD value	P value
Age years	34.40 ± 7.62	41.42 ± 5.28	2.918 **	<0.0001
WC cm	93.35 ± 16.22	114.82 ± 11.15	6.195 **	<0.0001
BMI kg/m^2	30.55 ± 1.68	38.22 ± 5.85	3.039 **	<0.0001
FPG mg/dl	84.22 ± 7.46	175.15 ± 45.75	14.67**	<0.0001
TC mg/dl	169.95 ± 31.99	192.52 ± 33.67	14.621 **	<0.003
TGs mg/dl	108.42 ± 60.85	180.67 ± 69.56	29.092 **	<0.0001
HDL-C mg/dl	51.82 ± 11.57	41.05 ± 10.37	4.891 **	<0.0001
LDL-C mg/dl	102.52 ± 25.82	120.82 ± 30.75	12.640 **	<0.005
FI mU/ml	4.97 ± 1.45	16.38 ± 3.34	1.153 **	<0.0001
HOMA-IR	1.04 ± 0.33	7.21 ± 2.95	0.939 **	<0.0001
HOMA- β	92.26 ± 37.63	60.23 ± 25.51	14.38 **	<0.0001
Glucagon pg/ml	843.37 ± 230.35	808.83 ± 167.16	89.590	0.445
Irisin ng/ml	118.01 ± 76.74	91.35 ± 44.75	28.108	0.061

**Highly significant correlation (P <0.01)
Significant correlation (P <0.05)*

BMI: body mass index; WC: waist circumference; FPG: fasting plasma glucose; TC: total cholesterol; TGs: triglycerides; HDL-C: high density lipoprotein cholesterol; LDL-C: low density lipoprotein cholesterol; FI: fasting insulin; HOMA-IR: homeostasis model assessment-insulin resistance; HOMA-β: homeostasis model assessment-β cells.

Serum irisin levels showed highly significant positive correlations with body weight, WC, BMI, UA, total protein and glucagon as seen in the table. Also, serum irisin levels had statistically significant negative correlation with FPG, FI and HOMA-IR respectively. All other variables had no statistically significant negative or positive correlation with irisin. Table (2) showed correlation results' of irisin in all study population.

Table 2. The association between irisin and study variables.

Variables	All patients-r	P value	Obese -r	P value	Obese diabetic-r	P value
Age years	0.0442	0.6970	0.2223	0.1682	0.0358	0.8266

WC cm	0.4418**	<0.0001	0.8104**	<0.0001	-0.0797	0.6252
BMI kg/m²	0.2851**	0.0104	0.8285**	<0.0001	0.2105	0.1923
FPG mg/dl	0.0002	0.9985	0.5876**	<0.0001	-0.3246*	0.0410
TC mg/dl	-0.0063	0.9561	0.1132	0.4869	0.0210	0.8976
TGs mg/dl	-0.1807	0.1086	0.2660	0.0971	-0.1012	0.5345
HDL-C mg/dl	0.1208	0.2857	-0.4727**	<0.0020	-0.0272	0.8677
LDL-C mg/dl	-0.0063	0.9561	0.2578	0.1082	0.1474	0.3641
FI mU/ml	-0.2650*	0.0175	0.5283**	<0.0005	-0.7903**	<0.0001
HOMA-IR	-0.3075**	0.0060	0.0005**	<0.0001	-0.6105**	<0.0001
HOMA- β	-0.0045	0.9680	-0.0732	0.6536	-0.2166	0.1795
Glucagon pg/ml	0.3452**	0.0017	0.5244**	<0.0005	-0.1043	0.5218

Significant correlation (P <0.05)*
**Highly significant correlation (P <0.01)

BMI: body mass index; WC: waist circumference; FPG: fasting plasma glucose; TC: total cholesterol; TGs: triglycerides; HDL-C: high density lipoprotein cholesterol; LDL-C: low density lipoprotein cholesterol;: fasting insulin; HOMA-IR: homeostasis model assessment-insulin resistance ; HOMA-β: homeostasis model assessment-β cells.

Serum irisin levels in obese group showed highly significant positive correlations with body weight, WC, BMI, FPG, FI, HOMA-IR and glucagon . Also, serum irisin levels in obses group had statistically significant negative correlation with HDL-C . Irisin levels in obese diabetic group showed significant negative correlation with FPG, FI and HOMA-IR .

Multiple regression analysis of irisin as dependent variable

Results of stepwise regression showed that only, body weight, FPG, total protein, HOMA-IR and glucagon had significant independent relation with serum irisin, while FI had no significant independent relation.Table (3) showed this results.

Table 3. Stepwise multiple regression of irisin with study variables.

Variables	Univariable		Stepwise R^2= 0.694	
	Coefficient – r	P-value	Coefficient - β	P-value
Age years	0.3808	0.6970		---
WC cm	**1.0829****	**<0.007**	---	---
BMI kg/m^2	**3.5546****	**<0.0001**	---	---
FPG mg/dl	**-0.2460***	**<0.05**	**1.2200****	<0.0002
TC mg/dl	0.0003	0.9985	---	---
TGs mg/dl	-0.0054	0.9561	---	---
HDL-C mg/dl	-0.9466	0.1086	---	---
LDL-C mg/dl	0.2599	0.2857	---	---
FI mU/ml	**-2.6910***	**≤0.02**	**-4.2610**	0.08
HOMA-IR	**-5.2470****	**<0.006**	**-20.9800****	<0.005
HOMA- β	-0.0080	0.9680	**---**	---
Glucagon pg/ml	**0.1098****	**<0.002**	**0.0468***	0.037

**Highly significant regression (P <0.01)
Significant regression (P <0.05)*

BMI: body mass index; WC: waist circumference; FPG: fasting plasma glucose; TC: total cholesterol; TGs: triglycerides; HDL-C: high density lipoprotein cholesterol; LDL-C: low density lipoprotein cholesterol; FI: fasting insulin; HOMA-IR: homeostasis model assessment-insulin resistance ; HOMA-β: homeostasis model assessment-β cells.

4. DISCUSSIONS

This cross sectional study revealed a positive correlation between irisin and BMI. This is also has been found in several other studies [21] [25][12] , while Huerta *et al*, and Timmons *et al*. 2012 found no association [22] [24]. These differences may have been elucidating by alterations in their studies populations and sample characterstics. Available evidence about the influence of adiposity on irisin has been controversial. Liu and co-workers found a positive association of irisin with BMI in non-diabetics but not in diabetic patients [23]. In contrast, Moreno-Navarrete *et al*. 2013 found a negative association of circulating irisin with BMI [3]. The relationship between irisin and adiposity show that adipose tissue may be a main inducer of irisin secretion, especially in obesity. Muscle/adipose secretion ratio may vary and affected by the physiological situation; during exercise, muscle tissue powerfully contributes to the

FNDC5 circulating levels, while in obesity, the adipose tissue would actively increase the circulating FNDC5/irisin [25].

On the other hand, irisin showed significant inverse correlation with FPG, FI, and HOMA-IR in obese diabetic patients, where obese diabetic patients showed more increase in WC and BMI when compared with obese without diabetes. This indicate that irisin loses its correlation with anthropometric parameters in the presence of diabetes, also, the relation of irisin with FPG, FI and HOMA-IR was inverse in obese diabetic comparing with obese. Sanchis-Goma et. al suggested that irisin levels are not associated with BMI in obese and diabetic patients [26], while Moreno-Navarrete et. al. showed that circulating irisin levels were significantly decreased with obesity and T2DM [11]. The differences of previous studies may be due to different gender, race, and study design. Possibly the reduced irisin in muscle/adipose tissue with increasing of obesity could be the cause of obesity-associated lower amounts of brown or beige adipocytes in human. It was suggested that lack of association between irisin and anthropometric parameters in obese diabetics may be due to insulin resistance [29], or lower PGC-1α activity in skeletal muscles [30]. Additionally, an independent study revealed a significant positive association between baseline circulating irisin levels and HOMA-IR [8]. In fact, circulating irisin associated directly with most known markers of insulin resistance in non-diabetic individuals. Irisin level appears to be related to important metabolic factors in non-diabetic, but not in T2DM [23]. Altogether the current and previous studies results support the hypothesis that increased irisin is an adaptive response to compensate for the reducing insulin sensitivity and disturbances in metabolism associated with obesity [27].

The results of this study showed that the main predictors of circulating irisin consecutively were body weight, FPG, HOMA-IR, and glucagon. All these variable were significant independently related to irisin while fasting insulin is not. It appears that there were different predictor variables of irisin in a different status. Current study finding is consistent with findings of past study by Yang *et al*. 2014], which showed that irisin is closely related with glucose concentration, especially FPG. Another study that consistent with the current study which showed that HOMA-IR [37] independently related to irisin levels. A recent study by Li *et al*. 2015] show convincing evidence of a link between insulin resistance, T2DM and irisin. Stengel *et al*. 2013 suggested that the increase of irisin under situations of obesity may indicate a physiological function to mend glucose tolerance which is often decreased in obese subjects [12]. As irisin counteracts obesity and insulin resistance in animal experiments [2], it is tempting to speculate that the irisin upregulation might be a compensatory mechanism to limit metabolic and vascular consequences of various facets of the metabolic syndrome [36].

As shown in the results of regression that HOMA-IR was the independent negative predictor for irisin, this may indicate new pathway in insulin resistance [37].

Glucagon had significant correlation and independent positive predictor of irisin. Glucagon might be connected with HOMA-IR in predicting mechanism of irisin action, although, in current study further results corroborates the findings; irisin level were elevated in obesity, and a strong relation found between irisin and anthropometric parameters.

5. CONCLUSIONS

In this study circulating irisin has a strong positive relationship with anthropometric parameters (WC, and BMI,) and that serum irisin was correlated and independently associated with HOMA-IR, FI, FPG, and glucagon. Data of current study suggest that in non-diabetic women, fasting irisin levels had high positive significant relation with FPG, fasting insulin and HOMA-IR while there is a negative relationship with the diabetes.

6. DECLARATIONS

The study was approved by the scientific unit medical ethic committee of Alkindy College of Medicine / University of Baghdad, Bagdad, Iraq . This research is self-funding support.

7. COMPETING INTERESTS

The authors declare that there is no conflict of interest regarding the publication of this paper.

Authors' contributions

Athir Kadhim Mohammed and Faris Abdul Kareem Khazaal planned the design of the study and participated in the preparation of the manuscript, contributed to valuable and critical discussion, provided scientific input, coordinated the study, provided content checking and oversaw its performance. Athir Kadhim Mohammed collected data, carried out the biochemical and ELISA analysis, carried out the final data analysis and created tables and figures. By consulate of Faris Abdul Kareem Khazaal, this helps in selection and collected the clinic data. All authors read and approved the final manuscript.

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