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Research Article

Influence of obesity on circulating irisin levels: results of a cross-sectional study

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Abstract. Objective: Evidence for the role of irisin, a newly discovered molecule, in insulin resistance and inflammation, is limited and controversial, and the pathways between them remain unknown. The objective of this research was to assess whether irisin levels are associated with total adiposity, subclinical inflammation, insulin resistance, and adiponectin levels in women with and without obesity. Material and methods: 42 adult women with normal body weight (BMI 18.5–24.9 kg/m²) or obesity (BMI ≥30.0 kg/m²) were enrolled in this cross-sectional study. The body composition analysis was performed by bioelectric impedance using an InBody 720 device (Biospace Co., South Korea). Fasting blood samples were collected to assess insulinemia, hsCRP, irisin and adiponectin levels. Insulin resistance was assessed using the homeostatic model assessment for insulin resistance (HOMA-IR) calculated as fasting insulin x fasting glycemia/405.Results Participants with obesity had significantly higher irisin levels as compared to those with normal BMI (21017.7 vs. 383.8357.3 ng/ml, p <0.001). In the univariate linear regression serum irisin was significantly associated with body adiposity (β=0.765, p-value <0.001), trunk fat (β=0.788; p-value <0.001) and limb fat (β=0.729; p-value <0.001). Irisin was also associated with hsCRP levels (β=0.378, p-value=0.002) independent of body fat mass and age. Although in the unadjusted linear regression the irisin was significantly associated with HOMA-IR, after adjustment for body fat the association lost its statistical significance (β=0.070, p-value=0.507). No association of irisin with adiponectin was found.Conclusions: We found that circulating irisin levels were higher in women with obesity as compared to normal body weight healthy controls and were positively predicted by total adiposity. Higher irisin levels were associated with systemic subclinical inflammation suggesting a role for irisin in the regulation of obesity-associated inflammation. In our samples, the relationship between circulating irisin levels and insulin resistance was mediated by visceral adiposity.

Key Words: irisin; obesity; visceral obesity; systemic inflammation; insulin resistance

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Introduction

Irisin is a thermogenic adipomyokine produced mainly by skeletal muscle and adipose tissue through the cleavage of fibronectin type III domain (Arhire et al 2019; Bostrom et al 2012). It plays a key role in glucose homeostasis, has anti-inflammatory properties, and is involved in thermogenesis by stimulating the conversion of white fat to brown fat and thus increasing energy expenditure (Chen et al 2015; Mazur-Bialy et al 2017). Two types of adipose tissues are described in humans: brown fat and white fat. The white fat, which represents the main type of fat, stores mainly triglycerides and fatty acids, and contains adipocytes with few mitochondria and a single lipid droplet (Arhire et al 2019). Apart from being the main lipid depot, it also has endocrine activity, and it is also involved in inflammatory and metabolic responses through the secretion of adipokines (Conde et al 2011). As opposed to white adipose tissue, the brown one consists of adipocytes with a large number of mitochondria and multilocular lipid droplets (Lidell et al 2010; Enerback 2010). The large number of mitochondria suggest its involvement in energy expenditure. Indeed, in newborns in whom the brown adipose tissue is better represented than in adults, the brown tissue is involved in body temperature regulation through heat release at mitochondrial level (Jastroch et al 2010; Affourtit et al 2012). Given irisin's effects, it has been recently regarded as an interesting target for the prevention and control of metabolic disease, and especially of obesity.

Correlations between circulating irisin and metabolic phenotypes have been assessed with conflicting results. Studies reported positive or negative associations or the lack of any relationship between irisin and markers of adiposity such as BMI, total body fat mass (Tang et al 2019; Huh et al 2012; Stengel et al 2013) or between irisin levels and abdominal distribution of adiposity (Moreno et al 2015; Shi et al 2016). Irisin has been studied in relation to concerning insulin resistance and inflammation as well. The studies reported either a positive association of higher irisin levels (Buscemi et al 2018; Qiu et al 2016; Moreno-Navarrete et al 2013) with higher levels of high sensitivity C-reactive protein (hsCRP) and lower insulin resistance, or lack of association (Eslampour et al 2019; Anastasilakis et al 2014).

The objective of this analysis was to assess whether irisin levels are associated with total adiposity, subclinical inflammation,

insulin resistance, and adiponectin levels in women with and without obesity.

Materials and methods

Study design and participants

This was a cross-sectional study performed in the Diabetes and Nutrition Department of the "Iuliu Hatieganu" University of Medicine and Pharmacy and "Regina Maria" Clinic Cluj-Napoca, Romania. The study included 42 adult women with a normal weight (BMI 18.5–24.9 kg/m²) or obesity (BMI ≥30 kg/m²) who agreed to participate. The enrollment period was between May 2017 and April 2021. Exclusion criteria were male sex, any chronic medical condition (including polycystic ovary syndrome, hypertension, thyroid dysfunction, diabetes mellitus), pregnancy and/or lactation and menopause.

The study was approved by the Ethics Committee of the "Iuliu Hatieganu" University of Medicine and Pharmacy Cluj-Napoca, Romania and was conducted according to the International Conference on Harmonization's Good Clinical Practice Guidelines and the Declaration of Helsinki. All study participants provided a written informed consent before any study-related procedure.

Study assessments

The study visit was performed in the morning, in fasting conditions. Data on age, gender, and medical history were collected by physical exam and interview. Height, weight, waist circumference, and hip circumference were determined by a standardized protocol. Waist circumference was measured halfway between the lower border of the last rib and the upper border of the iliac crest at the end of a normal expiration, using a non-stretchable tape measure. Hip circumferences were measured at the level of the anterior superior iliac spine, when it could be, otherwise at the broadest circumference below the waist. Bodyweight and height were measured while the subjects were wearing light clothes and no shoes. The body mass index (BMI) was calculated as weight (kg)/ square of height (m). Blood pressure was measured after 5 minutes of rest in a sitting position. The body composition analysis was performed by bioelectric impedance using an InBody 720 device (Biospace Co., South Korea). Parameters evaluated by bioelectric impedance analysis were visceral fat area (cm²), trunk fat (kg), body fat mass (kg), skeletal muscle mass (kg), and percentage of body fat (%). Upper and lower limbs fat was calculated as body fat mass (kg) – trunk fat (kg). InBody 720 device (Biospace Co., South Korea) is a multifrequency impedance plethysmograph body composition analyzer, which takes readings from the body using an eight-point tactile electrode method, measuring resistance at five specific frequencies (1 kHz, 50 kHz, 250 kHz, 500 kHz, and 1 MHz) and reactance at three specific frequencies (5 kHz, 50 kHz, and 250 kHz) which were pre-set by the manufacturer. Following the manufacturer's guidelines, participants wiped the bottom of their feet with a proprietary electrolyte tissue before standing on the electrodes embedded in the scale platform of the respective analyzers. The participants were instructed to stand upright and to grasp the handles of the analyzer, thereby providing contact with a total of 8 electrodes (2 for each foot and hand).

Blood samples were collected in the morning after at least 8 h of overnight fasting. These were used to assess biochemical parameters (fasting plasma glucose, lipid profile, creatinine, alanine aminotransferase, aspartate aminotransferase), insulinemia, hsCRP, irisin and adiponectin levels. All samples for the biochemical parameters were analyzed on the day of collection using commercially available enzymatic methods. Blood samples for insulinemia, hsCRP, irisin and adiponectin were frozen until the assessment by commercially available ELISA sandwich test, according to manufacturers' instructions (DIAsource ImmunoAssays S.A., Louvain-la-Neuve, Belgium; MyBioSource, California, SUA; R&D Systems, Inc. SUA & Canada).

Insulin resistance was assessed using homeostatic model assessment for insulin resistance (HOMA-IR) calculated as fasting insulin x fasting glycemia/405 (Matthews et al 1985).

Statistical analysis

Statistical analysis was performed using SPSS-PC SPSS-PC 20.0 (SPSS Inc., Chicago, IL, USA). The distribution of variables was tested with Shapiro-Wilk test. Data were presented as mean ± standard deviation (SD) for variables with normal distribution, median (1st quartile; 3rd quartile) for variables with non-normal distribution and percentage for categorical variables. Continuous variables were compared using student t-test and Mann-Whitney test, while categorical variables using chi-square test. The association between irisin and body fat mass, trunk fat, limb fat, HOMA-IR, hsCRP, and adiponectin was tested by Spearman correlation coefficients and univariate linear regression analysis. For the univariate linear regression analysis, irisin was used as the dependent variable and body fat mass, trunk fat, limb fat, hsCRP, HOMA-IR and adiponectin were used as independent predictors. Due to the small sample size, irisin was transformed logarithmically to achieve a distribution as close as possible to normal. Also, to achieve a normal distribution of HOMA-IR residuals, and thus fulfill the requirements of linear regression, a log transformation of this parameter was applied. A p-value <0.05 was considered statistically significant.

Results

This analysis included a total of 42 women, of which 20 with a normal BMI and 22 with obesity. Participants with obesity had significantly higher irisin levels as compared to those with normal BMI (1017.7 vs. 357.3 ng/ml, p <0.001). Also, all parameters related to body composition, hsCRP, and HOMA-IR were significantly higher in participants with obesity than in those with normal BMI. No difference between study groups was observed for age, total cholesterol, triglycerides, liver transaminase levels, creatine, and adiponectin (p-value >0.05 for all these parameters; Table 1).

Correlation of irisin with adiposity, adiposity distribution, inflammation, insulin resistance and adiponectin

Irisin was significantly correlated with BMI, body fat mass, trunk fat, limb fat, hsCRP and HOMA-IR (p <0.001). All Spearman correlation coefficients are presented in Table 2.

Association of irisin with adiposity, adiposity distribution, inflammation, insulin resistance and adiponectin

In the unadjusted univariate linear regression analysis Lg irisin was associated with BMI (β=0.771, p <0.001), body fat mass

Table 1. Characteristics of participants enrolled according to their BMI(Masson trichrome staining).

Variable	Total N=42	Normal weight N=20	Obesity N=22	p-value
Age, years	35.3±7.3	33.9±6.4	36.6±7.9	0.229
BMI, kg/m²	22.7 (21.1; 33.3)	21.3 (20.6; 22.5)	35.3 (32.3; 40.1)	<0.001
Waist, cm	86.0 (76.0; 101.5)	77.0 (74.0; 80.0)	102.0 (98.0; 115.0)	<0.001
Hip circumference, cm	103.0 (97.0; 115.0)	97.5 (94.5; 100.0)	117.0 (110.0; 120.0)	<0.001
SBP, mmHg	112.5±10.2	111.7±9.0	114.1±12.7	0.565
DBP, mmHg	76.2±7.1	74.5±6.7	79.7±7.0	0.067
FPG, mg/dl	91.0±8.3	91.4±8.6	90.5±8.0	0.735
Total cholesterol, mg/dl	172.0 (155.5; 191.0)	164.0 (154.0; 180.0)	183.0 (161.0; 193.0)	0.134
HDL-cholesterol, mg/dl	57.1±12.2	61.9±10.1	52.2±12.3	0.011
LDL-cholesterol, mg/dl	113.0±29.9	98.7±19.7	127.2±31.9	0.002
Triglycerides, mg/dl	76.0 (51.0; 112.5)	65.5 (48.0; 110.5)	84.0 (64.0; 112.5)	0.081
Creatinine, mg/dl	0.7 (0.6; 0.7)	0.7 (0.6; 0.7)	0.7 (0.6; 0.8)	0.331
ASAT	16.3±2.7	16.7±2.9	15.7±2.4	0.245
ALAT	14.1±4.8	14.8±4.8	13.2±4.7	0.33
hsCRP, ng/ml	86820.0 (38420.0; 135020.0)	52320.0 (19720.0; 85520.0)	130820.0 (100820.0; 155620.0)	<0.001
Irisin, ng/ml	489.9 (336.7; 918.9)	357.3 (307.8; 433.6)	1017.7 (840.8; 1083.4)	<0.001
Adiponectin, ng/ml	7945.0 (4870.0; 13545.0)	8945.0 (4845.0; 15170.0)	7945.0 (4895.0; 12770.0)	0.757
HOMA-IR	2.7 (2.4; 3.6)	2.5 (2.3; 2.7)	3.2 (2.6; 3.7)	0.002
Trunk fat, kg	10.6 (7.3; 20.3)	7.3 (6.6; 10.2)	21.0 (19.3; 24.4)	<0.001
Limb fat, kg	10.0 (7.5; 19.2)	7.6 (7.2; 9.7)	19.7 (17.6; 27.1)	<0.001
Body fat mass, kg	20.6 (14.7; 39.7)	15.0 (13.6; 20.1)	40.2 (36.3; 51.5)	<0.001
Visceral fat area, cm²	95.4 (66.3; 165.1)	70.7 (55.5; 93.0)	166.6 (157.2; 196.9)	<0.001
PBF, %	34.3 (25.8; 43.3)	26.8 (24.2; 31.9)	44.3 (42.6; 49.6)	<0.001
SMM, kg	26.8±4.9	23.2±2.6	30.0±4.2	<0.001

N/n (%), number (percentage) of participants; BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; FPG, fasting blood glucose; ASAT, aspartate aminotransferase; ALAT, Alanine aminotransferase; hsCRP, high sensitivity C-reactive protein; HOMA-IR, homeostatic model assessment for insulin resistance; PBF, percent body fat; SMM, skeletal muscle mass

Table 2. Correlation of irisin with adiposity, trunk fat, limb fat, hsCRP, adiponectin and HOMA-IR (whole sample)

	Correlation coefficient (p-value)
BMI	0.806 (<0.001)
BFM	0.803 (<0.001)
Trunk fat	0.813 (<0.001)
Limb fat	0.832 (<0.001)
hsCRP	0.706 (<0.001)
Adiponectin	-0.129 (0.415)
HOMA-IR	0.547 (<0.001)

BMI, body mass index; BFM, body fat mass; hsCRP, high sensitivity C-reactive protein; HOMA-IR, homeostatic model assessment for insulin resistance

(β=0.765, p <0.001), trunk fat (β=0.788, p <0.001), limb fat (β=0.729, p <0.001), hsCRP (β=0.683, p <0.001), and HOMA-IR (β=0.325, p=0.040; Table 3). After adjustment for body fat mass and age, irisin remained associated with hsCRP (β=0.378, p=0.002). No association was observed after adjustment with adiponectin and HOMA-IR (β=-0.162, p=0.119 and β=0.070; p=0.507, respectively).

Table 3. Unadjusted univariate linear regression analysis of the association of irisin levels with adiposity, adiposity distribution, inflammation, insulin resistance and adiponectin

	Standardized β-estimates	p-value
BMI	0.771	<0.001
BFM	0.765	<0.001
Trunk fat	0.788	<0.001
Limb fat	0.729	<0.001
hsCRP	0.683	<0.001
Adiponectin	-0.178	0.259
Lg HOMA-IR	0.325	0.04

BMI, body mass index; BFM, body fat mass; hsCRP, high sensitivity C-reactive protein; HOMA-IR, homeostatic model assessment for insulin resistance

Discussion

The main finding of this research is the demonstration that total adiposity contributed to the variability of the serum irisin levels. In our sample serum, irisin levels were significantly higher in women with obesity as compared to lean women. More

important we showed that both trunk fat, a marker of visceral adipose tissue, and limb fat, a marker of subcutaneous adipose tissue, were predictors of irisin levels.

The studies evaluating the association of irisin levels with adiposity in humans have been conflicting. Several have reported a positive correlation between serum irisin levels, adiposity and BMI (Park et al 2013; Liu et al 2013), while others found negative correlations of irisin with these parameters (Grygiel-Gorniak et al 2017) or no correlation (Gouni-Berthold et al 2013; Huh et al 2012). In rodents, irisin is secreted mainly by subcutaneous adipose tissue and to a lesser amount by visceral adipose tissue (Roca-Rivada et al 2013). In humans, visceral adipose tissue is also a source of irisin, although in a lower amount as compared to skeletal muscles (Perakakis et al 2017) and thus a larger amount of adipose tissue and visceral fat is associated with higher circulating irisin levels. It has also been hypothesized that signals originating from adipose tissue may contribute to increased muscle production of irisin and thus will determine higher irisin levels observed in persons with obesity (Crujeiras et al 2015). Both mechanisms may explain the positive strong association of irisin with body fat mass, trunk fat and limb fat observed in our sample, thus irisin is reflecting both subcutaneous and visceral adiposity.

In addition to its role in metabolism, several studies showed that irisin plays a role in inflammation and has anti-inflammatory properties (Mazur-Bialy et al 2017). We showed that irisin level is positively associated with subclinical inflammation as assessed by hsCRP levels, independent of body adiposity. A limited number of studies on the association of irisin levels with hsCRP are available and their results have also been conflicting (Eslampour et al 2019). Similar to our results, in 858 consecutive persons included in the ABCD (Alimentazione, Benessere Cardiovascolare e Diabete) prospective observational study, Buscemi et al showed a positive association of irisin with hsCRP levels (Buscemi et al 2018). Conversely, Hou et al (2015) showed a negative association of irisin with hsCRP in nonhypertensive nondiabetic persons with or without obesity. More recently, a meta-analysis including 14 studies and aiming to clarify the relationship between irisin and hsCRP showed no association. However, this meta-analysis showed an important heterogeneity of the studies included, with the study design, sample size, male-to-female ratio and medical history of the participants as the main source of heterogeneity. In the subgroup analysis, in healthy participants, with a larger sample size and a higher proportion of women among participants, a positive correlation of irisin with hsCRP was found (Eslampour et al 2019). Thus, the inclusion of women without any associated pathology may explain the positive association found in our research.

As studies in rodents showed its potential to ameliorate insulin resistance and were regarded as a potential therapeutic target for type 2 diabetes (Zhang et al 2014; Jeong et al 2015), the association of irisin with insulin resistance was extensively studied in humans. A growing number of studies have reported a positive relationship between irisin levels and insulin resistance (Li et al 2015; Moreno et al 2015), with higher irisin levels in those with higher insulin resistance. In the correlation analysis and unadjusted linear regression, we also found a positive association of irisin with insulin resistance as assessed by higher HOMA-IR. However, after adjustment for body fat mass, the association lost its significance, suggesting that the relationship of irisin with insulin resistance is mediated by body adiposity. This study has limitations. First, due to the cross-sectional design, we cannot infer the causality for the associations observed. Second, the small sample size and the inclusion of women only, limits the strength of the conclusions which cannot be generalized to men. Third, we did not assess the physical activity level which is known to influence the irisin levels.

Conclusion

In conclusion, circulating irisin levels were higher in women with obesity as compared to normal-weight healthy controls and were positively predicted by total adiposity. In our sample, the relationship between circulating irisin levels and insulin resistance was mediated by body adiposity. Also, higher irisin levels were associated with systemic subclinical inflammation suggesting that irisin levels may play a role in the regulation of obesity-associated inflammation. Given the controversies in the relationship of irisin with adipose tissue and our results showing that the association of irisin with insulin resistance was mediated by the body adiposity, future prospective studies aiming to clarify irisin secretion and metabolism are warranted.

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