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Original article

# Association of serum irisin levels with anthropometric, biochemical, and atherogenic indices in healthy adults

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**Summary.** *Objective:* Irisin, a myokine mostly expressed by muscle, is proposed to increase energy expenditure and reduce obesity and metabolic disorders. So, we evaluated the association between serum irisin levels and various anthropometric, biochemical, and atherogenic indices. *Methods:* This cross-sectional study was conducted on 90 apparently healthy males and females, aged 20-55 years, selected with simple random sampling. Anthropometric and atherogenic indices, dietary intake, physical activity levels, serum irisin levels, lipid profile, and fasting blood sugar (FBS) of the subjects were measured. *Results:* Median Irisin level was 1200 (500-8600) pg/ml which was higher in women than men (1250.00 (800-8600) VS. 1050 (500-7700)). In multivariate linear regression analysis, after controlling for potential confounders (age, total energy intake and physical activity), irisin levels were significantly associated with BMI (r=-0.214; P=0.003), waist circumference (WC) (r=-0.002; P=0.004), hip circumference (HC) (r=-0.245; P=0.004), waist-to-height ratio (WHtR) (r=-0.223; P=0.005), Body Roundness Index (BRI) (r=-0.214; P=0.008), Abdominal Volume Index (AVI) (r=-0.189; P=0.009), and Body Adiposity Index (BAI) (r=-0.207; P=0.046). In male subjects, it was significantly associated with BMI (r=-0.182, P=0.049), HC (r=-0.295; P=0.005), waist-to-hip ratio (WHR) (r=0.279; P=0.038) and BAI (r=-0.418; P=0.001), while in females with BMI (r=-0.268; P=0.005), WC (r=-0.236; P=0.030), WHtR (r=-0.223; P=0.047), and AVI (r=-0.226; P=0.047). No significant association was observed between irisin and biochemical and atherogenic indices. *Conclusions:* In the present study, irisin level was significantly associated with BMI, WC, HC, WHtR, BRI, and BAI. However, further studies are needed to clarify the role of irisin in obesity and its comorbidities.

**Key words:** abdominal obesity, atherogenesis, gender, Irisin, myokine

## Introduction

The muscular tissue has recently emerged as an endocrine organ by releasing a variety of cytokines (termed as myokines) into the circulation. Myokines regulate physiological and metabolic pathways including energy metabolism and the underlying mechanisms of obesity, metabolic syndrome, and cardiovascular disease (CVD)(1, 2). A novel myokine, irisin, is the extracellular cleaved product of fibronectin type III domain containing 5 (FNDC5) gene prior to be released into the circulation and is regulated by the peroxisome proliferator-activated receptor-γ (PPAR-γ) coactivator-1-alpha (PGC-1-α). Irisin is mainly secreted during or after exercise and it is possibly responsible for the thermogenesis and many health benefits of physical-activity (3, 4). Moreover, irisin is able to stimulate brown-fat-like

development in white fat by increasing uncoupling protein 1 (UCP1) levels, and hence increase total energy expenditure (5, 6). Regarding to its modulatory effect in energy metabolism and thermogenesis, several studies have indicated a possible relationship between circulating irisin levels and diseases such as obesity, CVD, type 2 Diabetes (T2D), chronic kidney disease, nonalcoholic fatty liver disease, and cancer. Therefore, it has been suggested as a therapeutic agent against metabolic disorders (7-11). In rodents, irisin significantly increases total energy expenditure and reduces obesity and insulin resistance (12).

Human studies on the association between circulating irisin levels and anthropometric parameters are conflicting; some authors reported a negative correlation between circulating irisin levels and Body Mass Index (BMI) (13, 14), whereas others reported a positive correlation (15-17). Although limited human studies have examined the relationship between irisin and some abdominal obesity indices such as Waist Circumference (WC) and Waist-to-Hip Ratio (WHR) (18, 19), its association with other novel and more feasible indices such as Conicity Index (CI), A Body Shape Index (ABSI), and Abdominal Volume Index (AVI) has not yet been investigated. These indices evaluate body fat distribution effectively which is important in obesity-related co-morbidities. Body Roundness Index (BRI) is a new index to predict percentage of body fat and visceral adipose tissue (20, 21). Recent studies demonstrated a predictive ability of the BRI for predicting CVD and diabetes (22). Furthermore, Body Adiposity Index (BAI) has been proposed for estimating the percentage of body fat (23). Regarding the importance of abdominal obesity indices and body fat percentage indices in predicting obesity-related co-morbidities, exploring the association between different myokines and these indices seems valuable.

Studies on the association between circulating irisin levels and biochemical indices are conflicting, as well. Choi et al. (13) found that circulating irisin levels negatively correlated with oral glucose tolerance test (OGTT), glycated hemoglobin (HbA1C), and triglyceride (TG). However, Liu et al. (24) found that circulating irisin was positively correlated with total cholesterol (TC), TG, Low-density lipoprotein cholesterol (LDL-C) and fasting blood sugar (FBS). Although several studies have been carried out to determine the association between serum irisin levels and biochemical indices, no study have examined the relationship between irisin and atherogenic indices. Atherogenic indices such as atherogenic index of plasma (AIP), atherogenic coefficient (AC), castelli risk index I and II (CRI) and non-HDL Cholesterol (NHC) are derived from lipid profile and are better predictors of coronary heart diseases rather than the traditional lipid profile (25-27).

Controversial results were reported regarding the association of irisin and anthropometric and biochemical indices in previous studies. Moreover, the association of irisin with novel anthropometric and atherogenic indices has not yet been evaluated. Therefore, the aim of current study was to explore the association of serum irisin levels with abdominal and atherogenic indices along with body composition, lipid profile, total energy intake, and physical activity levels in healthy subjects.

## Materials and Methods

*Subjects*

The present cross sectional study was conducted on 90 apparently healthy volunteers of both sexes (% 50 male), aging between 20 and 55 years. Participants were selected by simple random sampling from an outpatient clinic belonging to Tabriz University of Medical Sciences between October 2016 and February 2017. Subjects were excluded if they were pregnant, lactating, menopause or cigarette smokers.

The study protocol was approved by the Ethics committee of Tabriz University of Medical Sciences, Tabriz, Iran (ethical code: TBZMED.REC.1395.685). All subjects were made aware of the content of the study and a written informed consent document was obtained.

*Anthropometric measurements*

Weight was measured to the nearest 0.1 kg using Seca scale in light outdoor closing without shoes. Height was measured to the nearest 0.5 cm using a portable stadiometer in subjects standing in standard

position. BMI was calculated by dividing weight in kilograms by the square of the height in meters. WC was measured at the midpoint between the lowest rib and the iliac crest with a flexible anthropometric tape on the midaxillary line (28). HC was measured over thin clothing at the level of the maximum circumference of the buttocks posteriorly in a horizontal plane, without compressing the skin. Waist-to-Hip Ratio was calculated as WC (cm) divided by HC (cm), WHtR was calculated as WC (cm) divided by height (cm) and WHHR was calculated as WHR divided by height (cm) (21, 29, 30).

All anthropometric indices were calculated according to the following formula (30-37):

$$ABSI = \frac{WC(m)}{BMI^{\frac{2}{3}}(kg/m^2) * height^{\frac{1}{2}}(m)}$$

$$AVI = [2\,(WC)^2(cm) + 0.7\,(WC - HC)^2(cm)]/1000$$

$$CI = \frac{WC(m)}{0.109\sqrt{\frac{weight(kg)}{Height(m)}}}$$

$$BAI = \frac{(HC)\,(Cm)}{Height^{1.5}(m)} - 18$$

$$BRI = 364.2 - 365.5 \times \sqrt{1 - \left(\frac{(WC\,(m)/(2\pi))^2}{(0.5\,Height)^2\,(m)}\right)}$$

*Dietary assessment and Physical activity*

Participants' dietary intake was assessed using a validated interviewer-administered semi-quantitative 79 item food frequency questionnaire (FFQ) (38), which included all of the major food groups. To assess physical activity (PA), validated International Physical Activity Questionnaire – short form (IPAQ-SF) (39) was used, in which individuals reported the number of days and the duration of the vigorous, moderate, and walking activities during one week. According to IPAQ's scoring protocol, each individual was categorized to one of "inactive", "minimally active", and "Health Enhancing Physical Activity (HEPA)" categories.

*Assessment of biomarkers*

Blood samples were taken in the morning (8:00 – 9:00 AM) after 12 h of fasting. Serum lipid profiles, including TG, TC and high-density lipoprotein cholesterol (HDL-C) were also measured using enzymatic methods. Low-density lipoprotein cholesterol was calculated using the Friedewald's formula (40). Fasting blood sugar was measured by the hexokinase method. Circulating irisin levels were quantified in serum samples using commercial ELISA kits (ZellBio GmbH, Germany) (Cat. No: ZB-13253S-H9648) (13).

Lipid indices were calculated according to the following formulas (25-27):

AIP = log (TG / HDL)
CRI-I = TC / HDL
CRI-II = LDL / HDL
AC = (TC – HDL) / HDL
NHC = TC – HDL

*Statistical analyses*

Statistical analysis was performed using Statistical Package for the Social Sciences (SPSS) software version 21 (SPSS Inc., Chicago, IL). Kolmogorov–Smirnov test was used to check the normality of distributions of continuous variables. Data were presented as mean ± standard deviation (SD) and median (maximum – minimum). The differences in mean between two groups were compared with independent samples t-tests or Mann–Whitney test. Chi-square test was used for between group comparisons, in case of categorical variables. Multiple linear regression analysis was used to identify variables independently associated with irisin levels. $P < 0.05$ was considered as statistically significant.

## Results

The mean age of all participants was 35.59 ± 9.73 years and the mean BMI (Kg/m$^2$) was 27.83 ± 5.18 Kg/m$^2$ (Table 1). There was no significant difference between the BMI levels of male (27.52 ± 4.82 Kg/m$^2$) and female subjects (28.14 ± 5.56 Kg/m$^2$) in this study. Male subjects had significantly higher levels of weight (Kg) than female subjects ($P < 0.05$). The daily energy intake of men (2984.13 ± 623.22 Kcal) was significantly higher than women (2591.61 ± 729.20 Kcal) ($P < 0.05$) (Table 1). Based on three categories of IPAQ-SF, 68.2, 22.7 and 9.1 percent of men and 54.5, 40.9 and 4.5 percent of women were categorized as inactive, minimally active and health enhancing physical activity.

Laboratory characteristics of all participants are detailed in Table 2. There was no significant difference in biochemical characteristics including TC, LDL-C

**Table 1.** Baseline anthropometric characteristics, dietary intake and physical activity of total, male and female subjects

| Variables | Total (n=90 | Male (n=45) | Female (n=45) | P-value |
|---|---|---|---|---|
| Age (years) † | 35.59± 9.73 | 37.47 ± 9.47 | 33.70 ± 9.73 | 0.069 |
| Weight (kg) † | 78.64 ± 15.92 | 83.20 ± 14.67 | 74.08 ± 15.97 | 0.006 |
| BMI ($Kg/m^2$) † | 27.83 ± 5.18 | 27.52 ± 4.82 | 28.14 ± 5.56 | 0.575 |
| WC (cm) † | 90.12 ± 13.94 | 93.88 ± 12.21 | 86.36 ± 14.67 | 0.011 |
| HC (cm) † | 105.09 ± 11.00 | 103.20 ± 9.09 | 106.97 ± 12.45 | 0.108 |
| WHR † (cm/cm) | 0.85 ± 0.08 | 0.90 ± 0.06 | 0.80 ± 0.07 | <0.001 |
| WHtR † (cm/cm) | 0.53 ± 0.08 | 0.54 ± 0.07 | 0.53 ± 0.09 | 0.679 |
| WHHR † (cm/cm/cm) | 0.50 ± 0.04 | 0.52 ± 0.04 | 0.49 ± 0.05 | 0.010 |
| CI † ($m^{2/3}/kg^{1/2}$) | 1.21 ± 0.10 | 1.24 ± 0.08 | 1.17 ± 0.10 | 0.001 |
| ABSI †($m^{11/6}\,kg^{-2/3}$) | 0.07 ± 0.00 | 0.07 ± 0.00 | 0.07 ± 0.00 | <0.001 |
| AVI † ($cm^2$) | 16.63 ± 4.99 | 17.92 ± 4.69 | 15.33 ± 5.00 | 0.014 |
| BRI † | 4.19 ± 1.64 | 4.24 ± 1.49 | 4.15 ± 1.79 | 0.796 |
| BAI † ($cm/m^{1.5}$–18) | 30.49 ± 6.45 | 27.08 ± 4.72 | 33.90 ± 6.18 | <0.001 |
| Total energy intake (kcal/d)† | 2787.87 ± 702.67 | 2984.13 ± 623.22 | 2591.61 ± 729.20 | 0.008 |
| Physical activity (Met-minutes/week) ‡ | 594 (0.00-23916) | 480 (0.00-23916) | 693 (0.00-3732) | 0.341 |

*bbreviations: BMI: Body mass index; WC: waist circumference; HC: Hip circumference; WHR: waist-to-hip ratio; WHtR: waist-to-height ratio; WHHR: waist-to-hip-to-height ratio; CI: Conicity Index; ABSI: A Body Shape Index; AVI: Abdominal Volume Index; BRI: Body Roundness Index; BAI: Body Adiposity Index. † The P value was obtained by independent samples t-test for normal distributed variables and represented as mean ± SD. ‡ The P value was obtained by Mann-Whitney test for non-normally distributed variables and represented as median (interquartile range). Bold values mean that the value is statistically significant, P < 0.05.*

**Table 2.** Laboratory characteristics of total, male and female subjects

| Variables | Total (n=90) | Male (n=45) | Female (n=45) | P value |
|---|---|---|---|---|
| FBS (mg/dl) † | 89.98 ± 8.16 | 92.75 ± 8.50 | 87.21 ± 6.85 | 0.001 |
| TG (mg/dl) ‡ | 133.50 (43-481) | 174.50 (43-481) | 114.50 (50-300) | <0.001 |
| TC (mg/dl) † | 181.62 ± 38.74 | 183.97 ± 35.07 | 179.26 ± 42.37 | 0.571 |
| HDL-C (mg/dl) † | 45.91 ± 8.34 | 43.20 ± 7.82 | 48.62 ± 8.05 | 0.002 |
| LDL-C (mg/dl) † | 93.13 ± 24.82 | 95.70 ± 28.16 | 90.56 ± 20.98 | 0.334 |
| Irisin (pg/ml) ‡ | 1200 (500-8600) | 1050 (500-7700) | 1250.00 (800-8600) | 0.086 |
| AIP‡ | 0.46 (- 0.2-1.16) | 0.62 (- 0.2-1.16) | 0.35 (- 0.1-0.83) | <0.001 |
| AC † | 3.09 ± 1.15 | 3.36 ± 1.00 | 2.81 ± 1.22 | 0.023 |
| CRI-I † | 4.09 ± 1.15 | 4.36 ± 1.00 | 3.81 ± 1.22 | 0.023 |
| CRI-II † | 2.07 ± 0.62 | 2.25 ± 0.66 | 1.90 ± 0.52 | 0.008 |
| NHC † | 135.70 ± 40.11 | 140.77 ± 34.93 | 130.64 ± 44.52 | 0.238 |

*Abbreviations: FBS: fasting blood sugar; TG: triglyceride; TC: total cholesterol; HDL-C: High-Density Lipoprotein Cholesterol; LDL-C: Low-Density Lipoprotein Cholesterol; AIP: Atherogenic Index of Plasma; AC: Atherogenic Coefficient; CRI-I: Castelli's Risk Index- I; CRI-II: Castelli's Risk Index- II; NHC: Non HDL Cholesterol. † The P value was obtained by independent samples t-test for normal distributed variables and represented as mean ± SD. ‡ The P value was obtained by Mann-Whitney test for non-normally distributed variables and represented as median (interquartile range).*
*Bold values mean that the value is statistically significant, P < 0.05*

and NHC between male and female participants (P > 0.05). However, the FBS, TG, AIP, AC, CRI-I and CRI-II were significantly higher in men than women (P < 0.05). There were no significant differences in the levels of irisin between the men and women (P > 0.05). The range of minimum and maximum values of irisin were 500 – 8600 pg/ml in total, 500 - 7700 pg/ml in men and 800 -8600 pg/ml in women.

**Table 3.** The association of anthropometric indices with irisin

| | BMI | | | | | | WC | | | | | | WHR | | | | | | WHtR | | | | | | WHHR | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Total | | Male | | Female | | Total | | Male | | Female | | Total | | Male | | Female | | Total | | Male | | Female | | Total | | Male | | Female | |
| | β | P* | β | P* | β | P* | β | P* | β | p | β | P* | β | p | β | P* | β | p | β | P* | β | p | β | P* | β | P* | β | P* | β | P* |
| Irisin | -.214 | .003 | -.182 | .049 | -.268 | .005 | -.200 | .004 | -.078 | .439 | -.236 | .030 | -.061 | .516 | .279 | .038 | -.195 | .169 | -.223 | .005 | -.169 | .126 | -.223 | .047 | -.103 | .296 | .052 | .728 | -.157 | .310 |
| Age | .041 | .549 | .172 | .066 | .013 | .878 | .164 | .014 | .017 | .864 | .250 | .013 | .248 | .007 | -.058 | .650 | .318 | .017 | .213 | .005 | .174 | .112 | .289 | .007 | .324 | .001 | .223 | .134 | .331 | .023 |
| Total Energy Intake | .703 | .000 | .785 | .000 | .738 | .000 | .697 | .000 | .784 | .000 | .620 | .000 | .491 | .000 | .585 | .000 | .338 | .013 | .602 | .000 | .704 | .000 | .589 | .000 | .341 | .001 | .396 | .010 | .256 | .079 |
| Physical Activity | .020 | .767 | .028 | .771 | -.030 | .705 | .029 | .655 | .194 | .063 | -.037 | .691 | -.096 | .276 | .233 | .086 | -.211 | .095 | .040 | .581 | .127 | .255 | -.018 | .857 | -.089 | .341 | .087 | .567 | -.170 | .216 |

*Abbreviations: BMI: Body mass index; WC: Waist circumference; WHR: waist-to-hip ratio; WHtR: waist-to-height ratio; WHHR: waist-to-hip-to-height ratio. P values are from linear regressions adjusted for age, total energy intake and physical activity. Bold values mean that the value is statistically significant, P < 0.05*

| | CI | | | | | | ABSI | | | | | | AVI | | | | | | BRI | | | | | | BAI | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Total | | Male | | Female | | Total | | Male | | Female | | Total | | Male | | Female | | Total | | Male | | Female | | Total | | Male | | Female | |
| | β | P | β | P | β | p | β | p | β | p | β | p | β | P* | β | p | β | P* | β | P* | β | p | β | P | β | P* | β | P* | β | p |
| Irisin | -.151 | .114 | -.001 | .997 | -.131 | .347 | -.078 | .472 | .086 | .591 | -.029 | .852 | -.189 | .009 | -.092 | .363 | -.226 | .047 | -.214 | .008 | -.174 | .116 | -.210 | .072 | -.207 | .046 | -.418 | .001 | -.178 | .191 |
| Age | .294 | .002 | -.030 | .836 | .474 | .001 | .304 | .004 | -.114 | .470 | .543 | .000 | .147 | .034 | .008 | .936 | .247 | .019 | .211 | .006 | .165 | .130 | .308 | .005 | .071 | .486 | .355 | .002 | .181 | .149 |
| Total Energy Intake | .407 | .000 | .425 | .005 | .337 | .012 | .166 | .120 | .085 | .592 | .088 | .539 | .692 | .000 | .778 | .000 | .609 | .000 | .593 | .000 | .705 | .000 | .575 | .000 | .273 | .011 | .487 | .000 | .560 | .000 |
| Physical Activity | .029 | .745 | .272 | .074 | -.036 | .768 | .018 | .858 | .275 | .097 | -.038 | .778 | .034 | .607 | .185 | .078 | -.035 | .718 | .049 | .507 | .125 | .263 | .000 | .998 | .127 | .209 | -.013 | .912 | .137 | .252 |

*Abbreviations: CI: Conicity Index; ABSI: A Body Shape Index; AVI: Abdominal Volume Index; BRI: Body Roundness Index; BAI: Body Adiposity Index. P values are from linear regressions adjusted for age, total energy intake and physical activity. Bold values mean that the value is statistically significant, P < 0.05*

**Table 4.** The association of biochemical indices with irisin

| | FBS | | | | | | TC | | | | | | HDL | | | | | | LDL | | | | | | TG | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Total | | Male | | Female | | Total | | Male | | Female | | Total | | Male | | Female | | Total | | Male | | Female | | Total | | Male | | Female | |
| | β | p | β | P | β | p | β | p | β | p | β | p | β | p | β | p | β | p | β | p | β | p | β | p | β | p | β | p | β | p |
| Irisin | .097 | .368 | .146 | .341 | -.061 | .723 | -.025 | .831 | -.272 | .087 | .142 | .408 | -.050 | .646 | .005 | .974 | -.165 | .321 | -.104 | .371 | .130 | .421 | -.328 | .070 | -.042 | .690 | -.050 | .742 | -.108 | .527 |
| Age | .236 | .025 | .294 | .048 | .061 | .696 | .104 | .349 | -.028 | .855 | .322 | .045 | -.241 | .022 | -.181 | .257 | -.250 | .104 | .007 | .948 | -.166 | .299 | .124 | .448 | .320 | .002 | .412 | .008 | .083 | .598 |
| Total Energy Intake | .245 | .023 | .181 | .235 | .109 | .492 | -.089 | .438 | -.219 | .158 | -.032 | .843 | -.276 | .011 | .002 | .990 | -.419 | .009 | .049 | .670 | .095 | .552 | -.113 | .494 | .261 | .013 | .123 | .409 | .337 | .039 |
| Physical Activity | .237 | .021 | .169 | .281 | .416 | .009 | .078 | .476 | -.217 | .176 | .324 | .037 | -.176 | .085 | -.152 | .357 | -.200 | .175 | .069 | .527 | .184 | .266 | .099 | .527 | -.016 | .871 | -.011 | .942 | -.099 | .512 |

*Abbreviations: FBS: fasting blood sugar; TC: total cholesterol; HDL-C: High-Density Lipoprotein Cholesterol; LDL-C: Low-Density Lipoprotein Cholesterol; TG: triglyceride*

*P values are from linear regressions adjusted for age, total energy intake and physical activity.*

*Bold values mean that the value is statistically significant, P < 0.05*

**Table 5 .** The association of atherogenic indices with irisin

| | AIP | | | | | | AC | | | | | | CRI-I | | | | | | CRI-II | | | | | | NHC | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Total | | Male | | Female | | Total | | Male | | Female | | Total | | Male | | Female | | Total | | Male | | Female | | Total | | Male | | Female | |
| | β | P | β | P | β | p | β | p | β | p | β | p | β | p | β | p | β | p | β | p | β | p | β | p | β | p | β | p | β | p |
| Irisin | -.017 | .869 | .019 | .898 | -.058 | .718 | .024 | .831 | -.134 | .406 | .135 | .412 | .024 | .831 | -.134 | .406 | .135 | .412 | -.060 | .588 | .131 | .418 | -.191 | .251 | -.014 | .906 | -.016 | .925 | .071 | .653 |
| Age | .336 | .001 | .378 | .015 | .190 | .204 | .276 | .011 | .196 | .217 | .379 | .015 | .087 | .427 | -.159 | .315 | .157 | .304 | .188 | .086 | .067 | .674 | .163 | .289 | -.028 | .804 | -.049 | .762 | -.056 | .733 |
| Total Energy Intake | .346 | .001 | .152 | .311 | .442 | .005 | .087 | .427 | -.159 | .315 | .157 | .304 | .087 | .427 | -.159 | .315 | .157 | .304 | .188 | .086 | .067 | .674 | .163 | .289 | -.028 | .804 | -.049 | .762 | -.056 | .733 |
| Physical Activity | .065 | .494 | .089 | .565 | .036 | .800 | .165 | .117 | -.069 | .672 | .373 | .013 | .165 | .117 | -.069 | .672 | .373 | .013 | .169 | .108 | .247 | .137 | .240 | .104 | .112 | .303 | .065 | .687 | .157 | .323 |

*Abbreviations: AIP: Atherogenic Index of Plasma; AC: Atherogenic Coefficient; CRI-I: Castelli's Risk Index- I; CRI-II: Castelli's Risk Index- II; NHC: Non HDL Cholesterol;*
*P values are from linear regressions adjusted for age, total energy intake and physical activity;*
*Bold values mean that the value is statistically significant, P < 0.05*

To adjust the potential confounders involved in the association of irisin with anthropometric indices, we performed multiple linear regression analysis. As shown in Table 3, irisin was negatively and significantly associated with BMI (β= - 0.214, P= 0.003), WC (β= - 0.200, P= 0.004), HC (β= - 0.245, P= 0.004), WHtR (β= - 0.223, P= 0.005), AVI (β= - 0.189, P= 0.009), BRI (β= - 0.214, P= 0.008), and BAI (β= - 0.207, P= 0.046) after adjusting for age, total energy intake and physical activity. In addition, irisin had a significant association with BMI (β= - 0.182, P= 0.049), HC (β= - 0.295, P= 0.049), WHR (β= 0.279, P= 0.038), and BAI (β= - 0.418, P= 0.001) in men and BMI (β= - 0.268, P= 0.005), WC (β= - 0.236, P= 0.030), WHtR (β= - 0.223, P= 0.047) and, AVI (β= - 0.226, P= 0.047) in women. According to table 4, irisin was positively associated with FBS and negatively associated with TC, HDL, LDL and TG which was not statistically significant. As presented in table 5, irisin was positively associated with AC and CRI-I and negatively associated with AIP, CRI-II and NHC; however, these differences were not statistically significant.

## Discussion

In this study, no significant difference was found between male and female subjects in circulating irisin levels , which was similar to Karan et al. study (41). On the other hand, some studies reported contradictory results. Al-Daghri and colleagues (42) observed higher irisin levels in girls compared with boys. While in another study, irisin levels were higher in men than women (43). This contradiction can be explained by the differences in characteristics of participants.

We also found a significant and negative association between serum irisin levels and BMI in total, male and female subjects. Existing evidence about association of irisin with BMI is controversial. Some studies reported a negative correlation between irisin and BMI (13, 14, 44, 45). Choi YK et al. (13) found that circulating irisin levels reduced in recently diagnosed T2D. In addition, in the study performed by Moreno-Navarrete et al. (14), serum irisin level was lower in obese patients compared with normal weight subjects. Reverse correlation between circulating irisin levels and BMI might

be due to a decreased expression of FNDC5 gene in adipose tissue, obesity-associated lower amounts of brown or beige adipocytes or impaired conversion of FNDC5 to irisin in obese patients. On the other hand, some studies reported a null or positive correlation. In a research performed in a relatively small sample size, Jameel et al. (18) reported that irisin was not associated with BMI. Whilst, Stengel et al. (16) reported that subjects with high degree of obesity (BMI > 35) had higher levels of serum irisin than those with normal weight. Also, Liu JJ et al. observed that in the healthy subjects, serum irisin levels had a positive correlation with BMI and metabolic factors. In another study performed by Park et al. (46), BMI was positively correlated with irisin. The controversial results in different studies along with different BMI levels, could be possibly due to methodological differences and variation in sensitivity and specificity of different kits used in different studies or other intervening variables such as age, gender, race and physical activity.

There is limited evidence about the association of irisin with abdominal obesity indices. In the present study, irisin was significantly associated with WC, HC, WHtR, and AVI in all study subjects. Also, it was associated with HC and WHR in male subjects and with WC, WHtR and AVI in female subjects, which indicates that irisin was significantly related to central obesity. Jameel et al. (18) reported that irisin was not associated with WHR. In a cross-sectional study conducted by Liu et al. (22) on more than 1000 Chinese adults with metabolic syndrome, irisin was associated with WC (an indicator of abdominal obesity). In addition, Moreno-Navarrete et al. (14) demonstrated that circulating irisin levels was negatively correlated with WHR. In contrast, Park et al. (47) showed that irisin levels were positively correlated with WC. In the current project, for the first time, we investigated the association of irisin with body fat percent indices including BRI and BAI. The results of our study showed a negative association in the total, male and female groups. In agreement with our results, Moreno-Navarrete et al. (14) reported that irisin was negatively correlated with percent fat mass. However, in the study performed by Jameel and co-workers (18), serum irisin levels inversely associated with percent body fat among men, but not women. In contrast, another study found that circulating irisin was positively correlated with body fat mass (47). Contradictory results may be due to the different experimental and physiological conditions, and the different health status of the participants.

In this study, no significant association was observed between circulating irisin levels and biochemical indices including FBS, TC, HDL, LDL and TG levels. Evidence indicating the association between irisin and biochemical indices are limited. Our results were similar to the Jameel et al. (18) findings who observed no significant relationship between serum irisin and glucose, TG, TC, HDL, and LDL levels. However, there are a number of studies which have reported significant relationships. Liu et al. (24) observed a positive correlation between serum irisin levels and TC, TG, LDL-C, and FBG. In contrary, Choi and colleagues (13) reported a negative correlation between irisin level and OGTT, HbA1c, and TG. The controversy over the associations between circulating irisin and glycaemic and lipid profile among different studies might be explained due to the variation in experimental design, differences in the biochemical analytical assays, different BMI levels, confounding variables such as age, race, sex, physical activity and the variation in health status of study participants.

In multivariate linear regression analysis, after controlling for potential confounders such as age, total energy intake, and physical activity, no significant associations between serum irisin levels and atherogenic indices were found.This result suggest that age, total energy intake, and physical activity are the main confounders.

In elderly subjects, the percentage of muscle tissue decreases, and subsequently the amount of irisin secretion decreases. Tanisawa et al. reported that serum irisin levels were significantly lower in elderly subjects than in young subjects (48). Scharf et al. reported that the endocrine release of myokines from skeletal muscle might be impaired in sarcopenia, and irisin is on the list of potential candidates in this regard (49).

This study had some strengths but also some limitations. The strengths included the homogeneity of the population in living conditions and health status, assessment of food intake and physical activity by validated questionnaires, consideration of the confounding factors such as smoking, age, total energy intake, and physical activity. This is also the first report that revealing the association between serum irisin levels

and new anthropometric and atherogenic indices. The limitations of this investigation were the low number of sample size and the cross-sectional design of the study that couldn't show the causality and provide information on a prospective manner.

In conclusion, our results indicated negative associations between serum irisin levels and various anthropometric measurements including BMI, WC, HC, WHtR, BRI, AVI and BAI in total healthy participants, without any associations with biochemical and atherogenic indices. The present research could raise credible hypotheses to be extended by future studies with prospective design, larger sample size and different BMI categories to clarify the role of irisin in obesity and its comorbidities.

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