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Sex-dependent association between circulating irisin levels and insulin resistance in healthy adults

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ABSTRACT

Background: Irisin, a myokine, expressed by muscle and adipose tissue, has been reported to stimulate conversion of white into brown adipose tissue. The beneficial health effects of exercise are thought to be mediated in part, via increased production of irisin.
Objective: The primary aim of this study was to assess the association between plasma irisin levels glycaemic indices in healthy adults. Associations between irisin and lipid levels, CRP and body composition were explored as secondary outcomes.
Methods: A cross-sectional sample of forty nine (n = 49) free living healthy males (n = 28) and females (n = 21), between the ages of 18 and 65, with body mass index (BMI) within the healthy range, were recruited. Body weight, height, and body composition measurements were taken. Fasting blood samples were collected for the analysis of glucose, insulin and irisin levels. Insulin resistance score, HOMA-IR, was calculated using fasting blood glucose and insulin values. The relationship between plasma irisin levels and anthropometric measurements, glucose, insulin and HOMA-IR was determined using Spearman's bivariate correlation test.
Results: A significant inverse relationship was found between plasma irisin levels and insulin($r = -0.380$; $P = 0.007$) and HOMA-IR($r = -0.362$; $P = 0.011$). This relation was further strengthened in males when the data was stratified by gender. Circulating irisin levels were positively correlated with HDL-C ($r = 0.39$; $P = 0.05$) in male participants. Additionally, there was a significant negative correlation between percent body fat ($r = -0.43$, $P < 0.05$) and body fat mass ($r = -0.47$, $P < 0.05$) and circulating irisin levels in male participants.
Conclusions: This study reports a sex-dependent inverse relationship between plasma irisin levels and insulin resistance in healthy subjects.

1. Introduction

Insulin resistance is the pathological constellation of metabolic abnormalities such as impaired glucose uptake, increased hepatic glucose output and subclinical inflammation, often allied with physical inactivity [1]. The escalating prevalence of insulin resistance worldwide has greatly increased the interest in the metabolic and physiological role of hormones secreted by muscle [2]. Insulin resistance, being a component of metabolic syndrome, is a trigger for pathological conditions like type 2 diabetes and cardiovascular abnormalities [3,4]. Sedentary lifestyle is a major contributor for the development of insulin resistance, obesity and type 2 diabetes. Transient changes in physical inactivity tend to modulate the hormones associated with the metabolic processes leading to the accumulation of visceral adipose tissue and loss of muscle mass [5,6]. Scientific literature in recent years cites skeletal muscle as a key organ playing an important role in exhibiting resistance or sensitivity to insulin [2,7]. Advances in research examining the role of skeletal muscle in insulin resistance has highlighted the secretory function of skeletal muscle, releasing myokines during or post

Abbreviations: BMI, Body Mass Index; CRP, c-Reactive Protein; FFM, Fat Free Mass; FNDC5, Fibronectin type III Domain Containing protein 5; HDL-C, High Density Lipoprotein cholesterol; HOMA –IR, Homeostatic Model Assessment for Insulin Resistance; IPAQ, International Physical Activity Questionnaire; LDL-C, Low Density Lipoprotein cholesterol; PBF, Percentage Body Fat; PGC1α, Proliferator activated receptor-γ Co-activator 1; SMM, Skeletal Muscle Mass.

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muscular activity. The depiction of skeletal muscle as an endocrine organ suggests it may modify insulin resistance by modulation of myokines [2,8].

In 2012, Bostrom et al. discovered a novel myokine, irisin, modulated by peroxisome proliferator activated receptor-γ co-activator 1 (PGC1α) and released upon proteolytic cleavage from fibronectin type III domain containing protein 5 (FNDC5) [9]. Irisin is believed to be involved in browning of white adipose tissue and salutary effects of physical activity [10]. Since the discovery of irisin, a large volume of literature relating its physiological effects, browning effect and metabolic function [9,11,12] has been published. Administration of irisin through adenoviral delivery system exhibited browning of white adipose tissue at specific points associated with modest but significant weight loss [10]. The lower levels of circulatory irisin have been reported in type 2 diabetes individuals and positively correlated with age, BMI, cholesterol and blood pressure in individuals without diabetes [13,14].

Although several studies have been carried out in mice and humans to determine the therapeutic efficacy of irisin in obesity and diabetes, there is a need for further research to identify the role of irisin as a biomarker to predict metabolic disease in healthy individuals.

The aim of this study was to examine the association between the plasma irisin levels and glycaemic indices (fasting blood glucose and insulin levels) along with other metabolic markers, including lipid levels, CRP, physical activity and body composition in healthy adults.

2.. Subjects and methods

2.1. Subjects

his was a cross-sectional pilot study including 49 healthy adults (28 male and 21 female) between the ages of 18–65 years who were enrolled for an ongoing study. Participants were also asked to complete a medical questionnaire, International Physical Activity Questionnaire (IPAQ) and a 3 day food diary. Written consent was obtained from all the participants. Subjects with diagnosed hyperlipidaemia, diabetes mellitus, gastrointestinal disorders, currently on fructose/sugar restricted diet, vegan diet or weight loss program, who had undergone any surgical procedure for obesity, pregnant or lactating mothers, currently taking lipid-lowering drugs, anti-inflammatory drugs and BMI >30 kg/m^2 were excluded from the study. Fasting blood samples obtained from the participants were used to analyse the associations between circulating irisin levels and physical activity, body weight, height and body composition, blood lipids (triglyceride, LDL-C, HDL-C, Total/HDL-C), inflammation (CRP) and nutrient intake data. The study protocol was approved by the University of Newcastle Human Research Ethics Committee.

2.2. Methods

2.2.1. Anthropometry, body composition and nutrient intake

Standing height was measured to the nearest 0.1 cm using a stadiometer. Body weight, BMI, waist: hip ratio, body fat mass (BFM) and muscle mass (MM) in the fasting state were measured using direct segmental multi-frequency bioelectrical impedance (InBody 230, Biospace Co., Ltd. Seoul, Korea). Participants were asked to refrain from physical exertion and alcohol consumption for 24 h prior to testing. Physical activity (metabolic equivalent/week) was calculated from the International Physical Activity Questionnaire (IPAQ). 3 day food records were collected. Food records collected from participants were entered into FoodWorks Version 7.0.291 database (Xyris Software Pty Ltd, Queensland, Australia) to analyse daily energy and nutrient intake of participants.

2.2.2. Biochemical analysis

Blood samples were collected into tubes pre-coated with EDTA, lithium heparin and sodium fluoride by venipuncture. EDTA blood tubes were centrifuged for 10 min at 3000 g at 4 °C for separation of plasma and stored at −80 °C for further use. The lithium heparin tubes for CRP and blood lipids; sodium fluoride tubes for blood glucose and insulin measurement were analysed by the accredited Hunter New England Area Pathology Services.

Homeostatic model assessment for insulin resistance (HOMA-IR), an index of insulin resistance was calculated by using fasting blood glucose and insulin values as follows: HOMA-IR = (FBG × Insulin)/22.5, where insulin is in lU/mL and fasting blood glucose is in (mmol/L).

2.2.3. Hormone assays

Irisin levels were measured by competitive Enzyme Linked-Immunosorbent Assay (ELISA) for quantitative determination of irisin in human plasma (obtained from centrifugation of EDTA blood tubes) (Adipogen; Liestal, Switzerland, detection limit 1 ng/ml). Serum insulin levels were analysed by Hunter New England Area Pathology services.

2.2.4. Statistical analysis

All data are presented as mean ± SEM. The relationship between plasma irisin levels and anthropometric measurements, body composition, glucose, insulin and HOMA-IR was determined using Spearman's bivariate correlation test. All statistical analyses were carried out with SPSS software (version 21.0; SPSS Inc., Chicago, IL, USA). A probability level of $p < 0.05$ was adopted throughout to determine statistical significance unless otherwise mentioned.

3. Results

3.1. Participant anthropometric characteristics and nutrient intake

The mean age of the all participants was 36.0 ± 1.7 and the mean BMI (kg/m^2) was 24.3 ± 0.5 (Table 1). There was no significant difference between the BMI levels of males (25.0 ± 0.57) and females (23.5 ± 0.8) in this study group. Males had significantly higher levels of skeletal muscle mass (kg) (29.8 ± 1.1 vs 24.5 ± 1.5), fat free mass (kg) (59.5 ± 1.8 vs 42.1 ± 1.4), but lower levels of percent body fat (21.1 ± 1.4 vs 30.7 ± 1.8) and body fat mass (kg) (16.1 ± 1.2 vs 19.0 ± 1.5) than females. The daily energy intake of males (2121.6 ± 127.0 kcal) was significantly higher than females (1813.4 ± 65.7 kcal). Males consumed significantly higher levels of protein and fat (monounsaturated fat) when compared with the intake of females (Table 2). Physical activity of the participants was measured using IPAQ questionnaire. The mean physical activity of all participants was 1083.8 ± 116.4 MET minutes/week with females (1198.7 ± 199.7 MET minutes/week) slightly more physically active than males (997.7 ± 139.0 MET minutes/week).

3.2. Clinical and hormonal characteristics

There were no significant differences in clinical characteristics (Table 1) including glucose (4.8 ± 0.06 vs 4.9 ± 0.08 mmol/L), cholesterol (5.1 ± 0.18 vs 4.6 ± 0.19 mmol/L), and triglycerides (1.12 ± 0.11 vs 0.94 ± 0.01 mmol/L) between the male and female participants. But the LDL-C and total/HDL ratio was significantly higher in male participants (3.23 ± 0.17; 4.2 ± 0.24) than female participants (2.71 ± 0.18; 3.3 ± 0.22). There were no noteworthy differences in the levels of irisin and insulin between the males