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Association between circulating irisin and insulin resistance in non-diabetic adults: A meta-analysis

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ABSTRACT

Introduction. Exogenous administration of recombinant irisin improves glucose metabolism. However, the association of endogenous circulating (plasma/serum) irisin with insulin resistance remains poorly delineated. This study was aimed to examine this association by meta-analyzing the current evidence without study design restriction in non-diabetic adults.

Materials/Methods. Peer-reviewed studies written in English from 3 databases were searched to December 2015. Studies that reported the association between circulating irisin and insulin resistance (or its reverse, insulin sensitivity) in non-diabetic non-pregnant adults (mean ages ≥18 years) were included. The pooled correlation coefficient (*r*) and 95% confidence intervals (CIs) were calculated using a random-effects model. Subgroup analyses and meta-regression were performed to explore potential sources of heterogeneity.

Results. Of the 195 identified publications, 17 studies from 15 articles enrolling 1912 participants reported the association between circulating irisin and insulin resistance. The pooled effect size was 0.15 (95% CI: 0.07 to 0.22) with a substantial heterogeneity (I^2 = 55.5%). This association seemed to be modified by glycemic status (fasting blood glucose ≥6.1 mmol/L versus <6.1 mmol/L) and racial–ethnic difference (Asians versus Europeans versus Americans), but not by sex difference, sampling time-point, blood sample type, ELISA kits used, baseline age, or body mass index. Circulating irisin was inversely associated with insulin sensitivity (6 studies; r = −0.17, 95% CI: −0.25 to −0.09).

Conclusions. Circulating irisin is directly and positively associated with insulin resistance in non-diabetic adults. However, this association is rather small and requires further clarification, in particular by well-designed large epidemiological studies with overall, race-, and sex-specific analyses.

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Abbreviations: CIs, confidence intervals; FNDC5, fibronectin type-III domain containing protein 5; MOOSE, Meta-analysis of Observational Studies in Epidemiology; BMI, body mass index; STROBE, Strengthening the Reporting of Observational Studies in Epidemiology; Matsuda-ISI, Matsuda insulin sensitivity index; QUICKI, quantitative insulin sensitivity check index; FBG, fasting blood glucose; HOMA-IR, homeostasis model assessment for insulin resistance.

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1. Introduction

Induced by acute exercise training [1] and regulated by peroxisome proliferator-activated receptor γ coactivator-1α, irisin is produced primarily by skeletal muscle and adipose tissue, and released into the blood circulation upon the proteolytical cleavage of the membrane protein fibronectin type-III domain containing protein 5 (FNDC5) [2]. Despite a recent controversial debate regarding the existence of irisin due to its non-canonical start codon in humans [3] and the disputed effectiveness of distinct commercially available ELISA kits in detecting irisin [4], latest publications have questioned their methods used to judge irisin as a myth [5,6], and provided further convincing support for the presence of irisin in humans [6] as well as for the accuracy of irisin ELISA kits [7,8].

Upon its discovery in 2012, irisin has gained substantial interest as an appealing therapeutic target for metabolic disorders including obesity and diabetes, since in vivo studies have demonstrated that irisin reduces body weight and ameliorates insulin resistance in genetic mice models, which are highly prone to obesity and diabetes [2,9]. In addition to its therapeutic potential, there is now increasing evidence suggesting that irisin might be involved in the regulation of glucose homeostasis [10] and the pathogenesis of some metabolic disorders in non-diabetic populations — that is, elevated circulating (serum/plasma) irisin is associated with increased risk of metabolic syndrome and cardiovascular disease [11]. It is hypothesized that circulating irisin is increased in a compensatory manner to overcome or counteract the increasingly aggravated insulin resistance [11], a condition that is typically present in metabolic disorders such as polycystic ovary syndrome and pre-diabetes.

Although a growing body of evidence later on showed the positive association between circulating irisin and insulin resistance in non-diabetic populations [12–14], inconsistent findings were also reported in other studies [15–17]. The recent reviews by Chen et al. [18] and Hofmann et al. [19] have provided some insights into this ongoing debate, and both pointed out that the current discrepancy might be partly due to the differences in the enrolled populations (e.g., diabetic versus non-diabetic adults). However, their reviews were narrative (non-systematic) in nature, and importantly, failed to provide critical analyses on the association of circulating irisin with insulin resistance in specific populations (e.g., non-diabetic adults).

Therefore, the aim of this study was to assess the association between circulating irisin and insulin resistance in non-diabetic adults by meta-analyzing the available epidemiological studies without any study design restriction, attempting to sort out the potential source of heterogeneity that may lead to the discrepancies in the current literature with subgroup and meta-regression analyses.

2. Materials and Methods

2.1. Data Sources and Search Strategies

A comprehensive literature search of electronic databases including PubMed, the Cochrane Library, and Web of Science was conducted using text words of "irisin", "FNDC5" and "insulin" from January 1, 2012 [2] to December 25, 2015 (Table S1). Reference lists of relevant reviews and meta-analyses were manually checked to identify any additional studies. This meta-analysis is reported in adherence to the Meta-analysis of Observational Studies in Epidemiology (MOOSE) standards (Table S2), and a prospectively registered protocol (PROSPERO CRD42015017808).

2.2. Study Selection

English-language peer-reviewed studies that met the following criteria were included: (i) enrolled non-diabetic adults (mean ages ≥18 years); (ii) reported the association between circulating irisin (measured in plasma or serum) and insulin resistance (assessed by insulin resistance index) or its reverse — insulin sensitivity (evaluated by insulin sensitivity index) at baseline using correlation or simple linear regression analyses. Studies that were animal-based, had significant overlap in the study populations, or enrolled only children or patients with diabetes (or did not exclude patients with diabetes from the whole study populations) were excluded. There is no restriction to the study design, but reviews and posters were excluded. Studies were also excluded if the raw data of interest (correlation coefficients) could not be imputed or obtained after attempting to contact the corresponding authors via e-mails. Since pregnancy is a complex and heterogeneous state that involves various and significant metabolic changes during different gestational ages [20], this meta-analysis was therefore focused only on non-pregnant adults in order to minimize the heterogeneity in included populations.

2.3. Data Extraction and Quality Assessment

Titles and abstracts of retrieved publications were screened initially for potentially eligible studies, which were subsequently evaluated by full-text review. Data were collected by 2 authors (S.Q. and X.C.) in an unblinded manner using a pre-designed standardized data extraction form, which included: study population, study design, sample size, sex (proportion of men), country, baseline mean age, body mass index (BMI) and index of insulin resistance or insulin sensitivity, correlation or regression coefficients (along with the descriptions of confounders controlled for), and methods of irisin and insulin resistance measurement.

Study quality was assessed by the Cochrane Collaboration 'Risk of Bias' Tool [21,22] but with modifications according to the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement [23]. The quality criteria concerned in this modified 'Risk of Bias' Tool included selection, performance, attrition, detection, reporting and other bias. The risk of bias for each quality variable in each criterion (Table S3) was assessed by 2 authors (S.Q. and X.C.) in an independent manner, and judged as "low", "unclear", "high", or "not applicable" based on its description in each included study. Any disagreements in any phase were resolved by discussion until consensus was achieved.

2.4. Data Synthesis and Analysis

For studies having more than 1 measure of insulin resistance or insulin sensitivity index (e.g., insulin sensitivity was measured

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