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Circulating irisin in patients with polycystic ovary syndrome: a meta-analysis

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KEY MESSAGE

Circulating irisin in polycystic ovary syndrome (PCOS) patients seems comparable to healthy controls when controlling for body mass index. Despite this, irisin response to euglycemic hyperinsulinemia in PCOS patients appears to be impaired compared with healthy controls.

A B S T R A C T

There is growing interest in exploring circulating (plasma/serum) irisin in polycystic ovary syndrome (PCOS) patients. This meta-analysis aimed to summarize the evidence assessing circulating irisin changes in this population. A systematic search was conducted in three databases: PubMed, Cochrane Library and Web of Science, for studies reporting irisin in PCOS patients compared with healthy controls or stratified by body mass index (BMI), or assessing irisin response to hyperinsulinemia. Effect sizes (Cohen's *d* with 95% confidence intervals [CI]) were calculated using random-effects models. Eight studies with 918 PCOS patients and 528 healthy controls were included. Results showed that circulating irisin was higher in PCOS patients than in overall healthy controls (d = 0.37, 95% CI 0.05 to 0.70), but not compared with BMI-matched or age- and BMI-matched controls. Circulating irisin was higher in PCOS patients with higher BMI than lower (d = 0.36, 95% CI 0.16 to 0.56). Circulating irisin decreased 2 h later in response to euglycemic hyperinsulinemia in PCOS patients with a larger magnitude than healthy controls (d = −0.32, 95% CI −0.53 to −0.11). In summary, with adjustment for BMI, circulating irisin in PCOS patients seems comparable to healthy controls, but its response to hyperinsulinemia might be impaired.

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Introduction

Polycystic ovary syndrome (PCOS) is a prevalent heterogeneous endocrine disorder that affects approximately 10% of women during reproductive age (Bozdag et al., 2016), and is characterized by features of biochemical and/or clinical hyperandrogenism, oligo- or anovulation and polycystic ovaries (Legro et al., 2013). Accumulating evidence suggests that PCOS might be the leading cause of anovulatory infertility (Legro et al., 2013), and could predispose affected women to increased risks of cardiometabolic comorbidities including type 2 diabetes, metabolic syndrome and cardiovascular disease (Bond et al., 2017; Celik et al., 2014; Kyrkou et al., 2016; Zhao et al., 2016), subsequently leading to a negative impact on health-related quality of life for patients with PCOS and a significant burden on the healthcare system (Barry et al., 2011). As a result, specific intervention with a target in the aetiology of PCOS is crucial and strongly recommended. However, its aetiology remains not fully understood to date.

Insulin resistance, although not necessarily required for the diagnosis of PCOS, occurs in around 50–80% of women with this syndrome (Legro et al., 2004), and is considered to be an important contributor to its aetiology, in addition to hyperandrogenism (Cassar et al., 2016; Rotterdam ESHRE/ASRM-Sponsored PCOS Consensus Workshop Group, 2004; Teede et al., 2010). Irisin, an exercise-induced hormone that is produced primarily by skeletal muscle and adipose tissue upon proteolytical cleavage of protein fibronectin type-III domain containing protein 5 (FNDC-5) (Boström et al., 2012), is suggested to contribute to the development of PCOS because of its close relationship with insulin resistance (Polak et al., 2017; Qiu et al., 2016). Recently there has been a growing interest in investigating the alternations of circulating irisin from plasma or serum among patients with PCOS (Abali et al., 2016; Acet et al., 2016; Adamska et al., 2016; Bostanci et al., 2015; Chang et al., 2014; Gao et al., 2016; Li et al., 2015, 2016a; Pukajlo et al., 2015); however, conflicting rather than conclusive results have been reported when comparing with healthy controls. Some studies observed that patients with PCOS had higher circulating irisin than healthy controls, yet others argued that there was no significant difference between them (Gao et al., 2016; Pukajlo et al., 2015) or their association may even act in an opposite manner (Abali et al., 2016). Moreover, for patients with PCOS stratified by weight status (e.g. overweight or obese versus normal weight), individual results regarding circulating irisin were also inconsistent (Chang et al., 2014; Gao et al., 2016).

Therefore, the primary aims of this meta-analysis of observational studies were to assess the association of circulating irisin with PCOS and to identify the potential moderators. Moreover, in order to enrich our understanding of the pathophysiological characteristics of irisin in patients with PCOS, the secondary aim was to evaluate the changes of irisin in response to euglycemic hyperinsulinemia via metabolic clamp.

Materials and methods

Data sources and search strategies

This meta-analysis is reported following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement in general (Moher *et al*, 2009), and adheres to an unpublished protocol.

Databases including PubMed, the Cochrane Library and Web of Science were searched by two authors (X.C. and S.Q.) for studies published up to 23 May 2017. Text words or terms related to 'irisin' (i.e. irisin and FNDC-5) and 'PCOS' (i.e. polycystic ovary syndrome and PCOS) were used for the literature search, which were adjusted to fit for each database (**Supplementary Table S1**). A manual search of reference lists of retrieved reviews and included studies was performed to identify additional studies.

Study selection

Studies were included if they: (i) reported circulating irisin levels in PCOS patients compared with healthy controls or stratified by body mass index [BMI] (or weight status); (ii) had any study designs; and (iii) were published in English. Studies were also included that observed circulating irisin changes in response to euglycemic hyperinsulinemia in PCOS patients and healthy controls. PCOS had to be diagnosed based on well-defined criteria [e.g. the revised 2003 Rotterdam criteria (Rotterdam ESHRE/ASRM-Sponsored PCOS Consensus Workshop Group, 2004)]. Studies were excluded if they enrolled mixed populations other than solely PCOS patients, or were reviews, letters to editors or posters. Studies that had insufficient data of interest were excluded from the primary meta-analysis but were systematically reviewed if the missing information could not be obtained after contacting the authors via e-mails.

Data extraction and quality assessment

Data from eligible studies were extracted by one author (S.Q.) using an Excel form, which were later cross-checked by another author (X.C.) with reference to the original studies. Disagreements were resolved by referring back to the original studies or discussing with a third author (U.S.). The following information was collected: first author, publication year, study location, study design, numbers of cases and controls (non-cases), assays for irisin measurement, types of blood sample, circulating irisin levels (means and standard deviations), the means of age and BMI, fasting blood glucose, glycated haemoglobin A1c, and insulin resistance index assessed by using the homeostasis model assessment for insulin resistance (HOMA-IR). Study quality was assessed by two authors (X.C. and S.Q.) according to the Newcastle–Ottawa Scale (NOS) (Stang, 2010), which contains nine items, and scores range from 0 to 9.

Data synthesis and analysis

For studies reporting the standard errors of means (Chang et al., 2014), the corresponding standard deviations (SD) were calculated by multiplying by the square root of the respective sample size. For studies providing the medians together with the interquartile ranges (Adamska et al., 2016; Pukajlo et al., 2015), means were imputed using the medians directly while the SDs were calculated by dividing the widths of the interquartile ranges by 1.35 (Higgins *et al*, 2008). Studies reporting separate results from subpopulations (Gao et al., 2016) were combined to get the overall data with references to the following formulas as recommended (Higgins *et al*, 2008):

$$M = \frac{N_1 M_1 + N_2 M_2}{N_1 + N_2};$$

$$SD = \sqrt{\frac{(N_1 - 1)SD_1^2 + (N_2 - 1)SD_2^2 + \frac{N_1 N_2}{N_1 + N_2}\left(M_1^2 + M_2^2 - 2M_1 M_2\right)}{N_1 + N_2 - 1}}$$

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