Research Article

Irisin as a Biomarker for Insulin Resistance in Polycystic Ovary Syndrome: a Meta-analysis

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Received on October 31, 2019; Accepted on December 15, 2019; Published on December 30, 2020

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Abstract

Background: Irisin has attracted growing interest as a potential novel biomarker of polycystic ovary syndrome (PCOS). Aim: A meta-analysis was performed to compare circulating irisin concentrations between PCOS and control women, and to explore the possible relation of irisin and insulin resistance, by associating this hormone with the homeostatic model assessment for insulin resistance (HOMA-IR). Methods: An extended search of the PubMed/Medline, Google Scholar, and Web of Science databases (last updated on 9 March 2019) was performed to identify all articles published in the English language pertaining to circulating irisin in women with PCOS and control women. Results: Eleven studies that involved 1,017 PCOS patients and 669 controls were included. A random effects model revealed a moderate estimate of effect size (SMD: 0.27, 95% CI: -0.13 to 0.67), indicating that circulating irisin concentrations did not differ significantly between PCOS women and controls. Another random effects model (four studies) revealed a moderate estimate of correlation and a statistically significant positive correlation between circulating irisin concentrations and HOMA-IR (Correlation: 0.372, 95% CI: 0.0843 to 0.603, p = 0.012). Irisin may play an important role in PCOS in relation to the inherent insulin resistance of the syndrome. This association requires further clarification in well-designed large-scale studies in women with PCOS.

Introduction

In modern societies, there is a great unmet need for the management of adiposity-associated health problems that result from excess energy intake relative to energy expenditure. As such, insulin resistance (IR), type 2 diabetes mellitus (T2DM) and polycystic ovary syndrome (PCOS) are increasing globally, without optimal medical care (Tate 2018, Lizneva *et al*. 2016). Recently, attention has been paid to irisin, a newly discovered myokine/adipokine implicated in the expenditure of energy and reduction of weight by generating browning of the white adipose tissue and hence, by increasing "beiging" (Boström *et al*. 2012, Zhang *et al*. 2014).

Since irisin's discovery, a number of studies of its circulating levels have been published in patients with PCOS, T2DM and IR. Polycystic ovary syndrome is a very common endocrinopathy with an estimated prevalence varying from 4% to 21%, depending on the population studied and the criteria used for diagnosis (Lizneva *et al*. 2016). Hyperandrogenism and anovulation are the core features of the syndrome, which is also associated with adiposity, IR and T2DM. Although it is not considered a diagnostic criterion, IR is a hallmark of the syndrome, as the majority of obese women with PCOS and almost 30% of lean PCOS women are insulin resistant (Kandaraki *et*

al. 2011). Irisin, which ameliorates IR in mice (Boström *et al*. 2012), may have a role in the development and expression of PCOS.

Studies of circulating irisin in adult and adolescent women with PCOS have reported discrepant results (Bostancı *et al*. 2015, Gao *et al*. 2016, Chang *et al*. 2014, Adamska *et al*. 2016, Abali *et al*. 2016, Li *et al*. 2016, Pukajło *et al*. 2015, Li *et al*. 2015, Bacopoulou *et al*. 2018, Wang W *et al*. 2018, Zhang *et al*. 2018). In most studies, women with PCOS have significantly higher irisin concentrations than controls (Bostancı *et al*. 2015, Chang *et al*. 2014, Adamska *et al*. 2016, Li *et al*. 2015, Bacopoulou *et al*. 2018, Zhang *et al*. 2018), whereas in others, patients with PCOS have significantly lower mean circulating irisin levels than non-PCOS controls (Abali *et al*. 2016, Wang W *et al*. 2018) or similar levels (Gao *et al*. 2016). Two previous meta-analyses (Cai *et al*. 2018, Wang C *et al*. 2018) summarized evidence of eight studies (Bostancı *et al*. 2015, Gao *et al*. 2016, Chang *et al*. 2014, Adamska *et al*. 2016, Abali *et al*. 2016, Li *et al*. 2016, Pukajło *et al*. 2015, Li *et al*. 2015) involving 918 patients with PCOS and 528 controls; for the same population both meta-analyses demonstrated significantly higher circulating irisin concentrations in women with PCOS than in healthy controls. However, further subgroup analysis by Cai *et al*. (Cai *et al*. 2018) demonstrated similar irisin concentrations in patients with PCOS and controls, when controlling for body mass index (BMI). In the same meta -analysis (Cai *et al*. 2018), fasting blood glucose, hemoglobin A1c or the homeostatic model assessment for insulin resistance (HOMA-IR), could not explain the differences in irisin levels between patients with PCOS and controls. Similarly, Wang *et al*. (Wang C *et al*. 2018) did not find a significant correlation between irisin concentrations and IR in the same population, however, the authors of the meta-analysis questioned the reliability of these findings because of sample size restrictions and inconsistent representation of IR in the individual studies. In the meta-analysis of Cai *et al*. (Cai *et al*. 2018), circulating irisin variations following euglycemic hyperinsulinemia were further assessed based on two individual studies that demonstrated a greater decline in circulating irisin 2 hours after the euglycemic hyperinsulinemic clamp in women with PCOS than in controls (Adamska *et al*. 2016, Li *et al*. 2015).

There is increasing scientific interest in searching for circulating novel biomarkers of the syndrome, yet the role of irisin in PCOS is still ambiguous. Therefore, the purpose of this meta-analysis was to compare circulating irisin concentrations between PCOS and control women and explore the potential association of irisin with HOMA-IR, the preferred method for IR measurement in most studies (Matthews *et al*. 1985).

Materials & Methods

Search Strategy

Following the PRISMA guidelines (Moher *et al*. 2010), an extended search of the PubMed/ Medline, Google Scholar, and Web of Science databases (last updated on 9 March 2019) was performed to identify all articles published in English language pertaining to circulating irisin in women with PCOS. In addition, the references of selected papers were searched manually. Search terms were "irisin" and "PCOS" or "irisin" and "polycystic ovary syndrome".

Inclusion and Exclusion Criteria

Retrieved articles were eligible for inclusion in this meta-analysis if they included (i) women with PCOS and control women, pooled from the general population and (ii) measurements of circulating (plasma or serum) irisin concentrations in women with and without PCOS. Articles were excluded if (i) published repeatedly or (ii) data were incomplete.

Data Extraction

Full articles derived from this search were screened by the author (F.B.) based on the inclusion and exclusion criteria. The flow diagram of article selection is shown in Figure 1.

For each included study, data were extracted regarding the general features, i.e. first author, year of publication, and the characteristics by study group (PCOS and control groups), such as (i) population and anthropometric characteristics, i.e. sample size, mean age, mean BMI, (ii) circulating (plasma/serum) concentrations of irisin (Table 1) and (iii) correlations of circulating irisin concentrations with HOMA-IR, where applicable.

Statistical Analysis

Statistical analysis was conducted with the use of the Review Manager software (Version 5.2, the Nordic Cochrane Centre, Copenhagen, Denmark). The differences of circulating irisin concentrations between women with PCOS and control women were evaluated by the standardized mean difference (SMD) with a 95% confidence interval (CI).

Table 1. Characteristics of studies included in the meta-analysis.

Author, year	**Country**	**PCOS** (n)	**Controls (n)**	**Age, years (mean ± SD) PCOS**	**Age, years (mean ± SD) Controls**	**BMI, kg/m^2 (mean ± SD) PCOS**	**BMI, kg/m^2 (mean ± SD) Controls**	**Irisin, ng/ml (mean ± SD) PCOS**	**Irisin, ng/ml (mean ± SD) Controls**
Abali et al. 2016 [a,b]	Turkey	49	39	23.5 ± 55	25.6 ± 7.2	25.2 ± 5.4	25.6 ± 6.1	158.5 ± 123.3	222.9 ± 152.2
Adamska et al. 2016 [a,b]	Poland	57	20	26.0 ± 5.7	27.3 ± 7.1	26.7 ± 6.4	27.3 ± 7.0	11.1 ± 4.8	8.3 ± 3.0
Bacopoulou et al. 2018 [a,b]	Greece	23	16	16.9 ± 2.1	17.9 ± 2.2	20.9 ± 1.2	20.3 ± 1.3	1,700 ± 1,000	1,000 ± 400
Bostanci et al. 2015 [a]	Turkey	35	35	24.51 ± 5.29	26.83 ± 7.02	26.74 ± 3.40	22.79 ± 2.64	491 ± 145	281 ± 138
Chang et al. 2014	Taiwan	202	47	25.25 ± 5.0	27.3 ± 4.9	24.73 ± 5.7	21.54 ± 3.6	975.7 ± 418.1	669.8 ± 244.1
Gao et al. 2016	China	52	39			22.9 ± 5.2	22.9 ± 3.5	470.6 ± 141.5	505.6 ± 274.6
Li et al. 2015 [a]	China	178	123	26.1 ± 4.5	25.7 ± 2.3	24.8 ± 4.4	20.5 ± 2.6	194.7 ± 90.0	168.6 ± 70.4
Li et al. 2016 [a]	China	166	103	25.8 ± 4.2	25.8 ± 2.3	24.3 ± 4.2	20.3 ± 2.5	193.2 ± 77.7	157.0 ± 58.8
Pukajlo et al. 2015 [a]	Poland	179	122	(range) 20-35	(range) 25-35			544 ± 767	508 ± 522
Wang W et al. 2018	China	40	30					678.8 ± 234.3	1,333.3 ± 358.1
Zhang et al., 2018 a	China	36	95	25.6 ± 4.3	25.7 ± 2.3	26.7 ± 4.3	20.4 ± 2.5	259.8 ± 93.6	176.9 ± 69.7

PCOS, polycystic ovary syndrome; BMI, body mass index; SD, standard deviation
a Age-matched; b BMI-matched

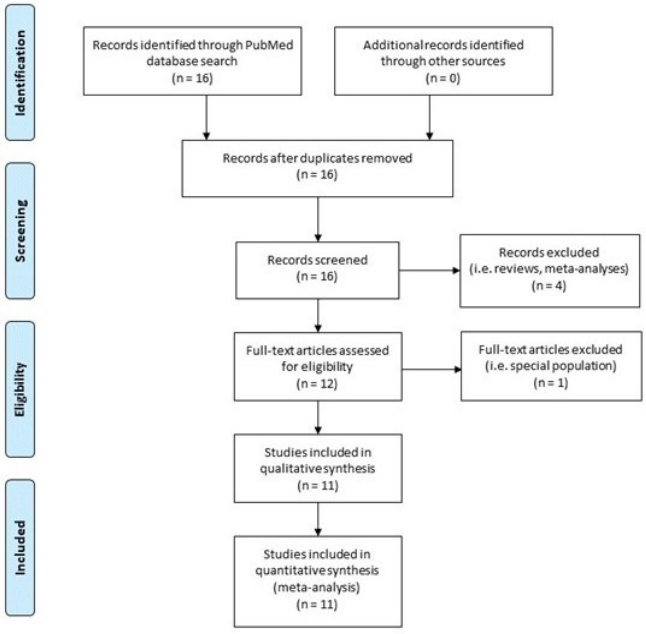

Figure 1. Flow diagram of article extraction for the meta-analysis.

The Z-test was applied to determine the significance of the pooled SMD. A random-effect model was used for heterogeneous data, by performing Cochran's Q-statistic ($P < 0.05$ for significant) and I2 test (100%, maximal heterogeneity) to evaluate heterogeneity among studies. Sensitivity analysis was conducted by removing studies one by one to assess the influence of each single study on the overall result. Publication bias was estimated with the use of funnel plot and Egger's test. Meta-analysis for correlation was conducted with the use of MedCalc for Windows, version 18.5 (MedCalc Software, Ostend, Belgium).

Results

Differences in Circulating Irisin Concentrations between PCOS patients and Controls

Eleven studies (Bostancı *et al*. 2015, Gao *et al*. 2016, Chang *et al*. 2014, Adamska *et al*. 2016, Abali *et al*. 2016, Li *et al*. 2016, Pukajło *et al*. 2015, Li *et al*. 2015, Bacopoulou *et al*. 2018, Wang W *et al*. 2018, Zhang *et al*. 2018), out of 16 extracted studies, were included in the meta-analysis and involved in total 1,686 women: 1,017 PCOS patients and 669 non-PCOS controls. In these studies, exercise was not reported as a factor for the management of PCOS. Among the 11 studies, three displayed stratified statistics according to BMI (Gao *et al*. 2016, Chang *et al*. 2014) or androgen (Li *et al*. 2016) values. Subgroups were combined into one using formulas recommended by Cochrane (Higgins *et al*. 2008). A random effects model demonstrated a moderate estimate of effect size (SMD: 0.27, 95% CI: -0.13 to 0.67) (Figure 2), indicating that circulating irisin concentrations were not significantly higher in PCOS patients than non-PCOS controls.

Significant heterogeneity was revealed for the included studies ($P < 0.001$, $I2 = 93.0\%$). There was no significant publication bias over the included studies, as shown by the Egger's test ($P=0.125$) and the visual examination of funnel plots.

Correlation between Circulating Irisin Concentrations and HOMA-IR

Meta-analysis of correlation comprised the four studies listed in Table 2. A statistically significant

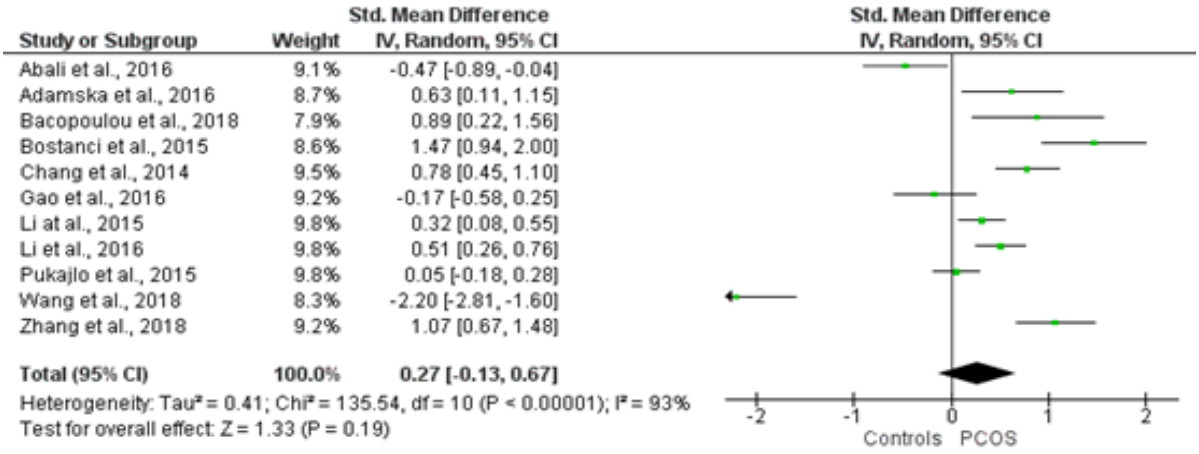

Figure 2. Forest plot demonstrating the meta-analysis results on the basis of standardized mean differences (SMDs) for the effect of irisin.

Table 2. Correlation of circulating irisin concentrations and HOMA-IR.

Author, year	**Country**	**PCOS** (n)	**Controls (n)**	**Correlation coefficient**	**P**
Abali et al. 2016	Turkey	49	39	-0.110	0.350
Bacopoulou et al. 2018	Greece	23	16	0.422	0.007
Li et al. 2015 [a]	China	178	123	0.188	0.001
Wang W et al. 2018 (PCOS)	China	40	30	0.685	0.013
Wang W et al. 2018 (Controls)	China	40	30	0.619	0.028

PCOS, polycystic ovary syndrome; HOMA-IR, homeostatic model assessment for insulin resistance
[a]HOMA2-IR Log transformed before analysis

positive correlation was observed between circulating irisin concentrations and HOMA-IR (Figure 3). A random effects model detected a moderate estimate of correlation (Correlation: 0.372, 95% CI: 0.0843 to 0.603, P = 0.012) with heterogeneity (P < 0.0001, I2 = 87.6%).

Discussion

Human research supports the role of several tissues in the biological regulation and secretion of irisin that seems to be connected with IR. The IR state of polycystic ovary syndrome has attracted growing interest in exploring novel biomarkers, as much remains unknown regarding its underlying pathophysiology and pertinent treatment. Since the late 1980s (Ibáñez *et al*. 2017), IR has been described in women with PCOS but it is not comprised in the diagnostic criteria of the syndrome (Azziz *et al*. 2009, Legro *et al*. 2013). Yet, IR is inherent to the syndrome; it can only partially be explained by obesity, as it is evident even in normal weight women with PCOS vs. controls (Dunaif *et al*. 1989). Amato *et al*. (Amato *et al*. 2015) demonstrated similar peripheral insulin sensitivity in normoglycemic women with the syndrome and prediabetic women. Furthermore, Lewy *et al*. (Lewy *et al*. 2001) found that obese adolescent girls at risk for developing PCOS had peripheral insulin sensitivity (assessed by the hyperinsulinemic-euglycemic clamp) that was reduced by 50% compared to

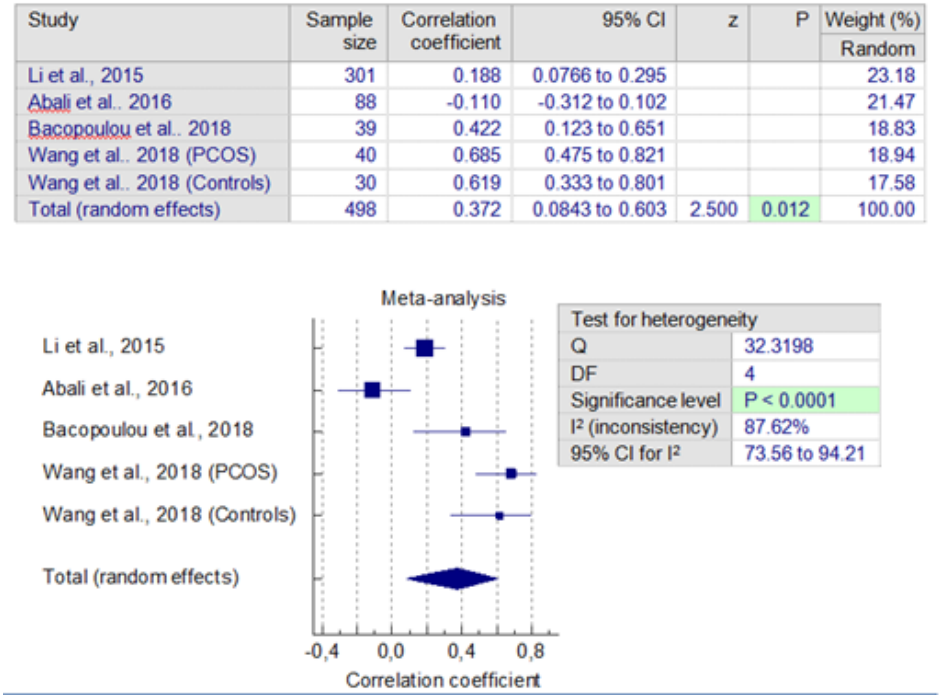

Figure 3. Forest plot demonstrating the meta-analysis of correlation between circulating irisin and HOMA-IR.

their obese peers (matched for BMI, body composition and central adiposity).

Insulin resistance is critical not only for the evolution and establishment of the syndrome (Amato *et al*. 2015, Salley *et al*. 2007), but also for the development of its metabolic complications, i.e. impaired glucose tolerance (IGT), metabolic syndrome, and T2DM, which confer a high risk of subsequent cardiovascular disease (Ducluzeau *et al*. 2003). Therefore, lifestyle (healthy diet, weight loss, exercise) and medical interventions (insulin-sensitizing medications and bariatric surgery) that decrease IR have the potential to alleviate its metabolic disturbances and complications (Spritzer 2014). Although the syndrome confers a high metabolic burden due to IR, the majority of PCOS women with IGT have normal fasting glucose levels, resulting in more missed diagnoses of IGT and T2DM in women with PCOS than in the general population (Legro *et al*. 1999).

As early identification of IGT in PCOS women and institution of lifestyle changes or pharmacologic interventions may halt progression to T2DM (Salley *et al*. 2007), new biomarkers are needed as warnings for affected women. Circulating biomarkers related to IR in PCOS would be of particular value in cases where the definition of PCOS is controversial, i.e. in adults with mild phenotypes of the syndrome, or in adolescents, in whom the diagnosis of PCOS is confounded by normal pubertal physiologic events (Witchel *et al*. 2015). In such cases, biomarkers could assist in identifying the subset of adult and adolescent women with PCOS who are the most insulin resistant and hence, at increased risk for adverse metabolic manifestations in future life.

Circulating irisin has been recently studied as a potential new biomarker of IR in PCOS (Polak *et al*. 2017). This meta-analysis demonstrated a statistically significant positive correlation of circulating irisin concentrations with HOMA-IR; nevertheless, irisin levels did not differ significantly between PCOS patients and controls. Zhang *et al*. (Zhang *et al*. 2018), in a study of 117 women with PCOS and 95 healthy control women, demonstrated differential circulating irisin concentrations for the PCOS phenotypes with distinct degrees of IR (assessed by the HOMA-IR and the gold standard euglycemic-hyperinsulinemic clamp). Interestingly, statistically significant positive correlations between circulating irisin and glucose homeostasis indices, i.e. fasting blood glucose (Park *et al*. 2013, Liu *et al*. 2013), insulin levels (Sesti *et al*. 2014, Stengel *et al*. 2013) and HOMA-IR (Park *et al*. 2013), have been found in other non-PCOS adult populations.

It has been speculated that irisin is upregulated in insulin resistance representing a physiological "effort" to combat the signaling changes, maintain homeostasis and increase insulin sensitivity. The term "irisin resistance", similarly to "insulin resistance" has been previously used to explain this upregulation of irisin in glucose intolerance states (Adamska *et al*. 2016, Polyzos *et al*. 2013). However this hypothesis needs to be further studied.

The results of the current meta-analysis, along with the aforementioned evidence, underline a potential role of irisin in PCOS and in association with the IR of the syndrome. Thus, circulating irisin may be regarded as a preliminary indicator of IR in PCOS that may predict the metabolic burden of the different phenotypes of PCOS, as they evolve with the advancement of age, from adolescence to adulthood.

Limitations of this meta-analysis include the small number of included studies, the language restriction and the small sample sizes, as well as the lack of uniform methodology for the detection of circulating irisin. Although the measurement of HOMA-IR used in some study populations suffices to establish IR (Gungor *et al*. 2004), it is not the gold standard for accurate evaluation of IR.

In conclusion this meta-analysis shows no evidence of differential irisin levels in PCOS and control women, but suggests a biologically plausible association between circulating irisin and IR. As PCOS constitutes an independent risk factor for glucose intolerance conditions, circulating irisin could be considered a potential surrogate marker of IR, allowing physicians to establish which women with PCOS merit full and regular lifelong metabolic investigation for timely management of related comorbidities.

Conflicts of Interest

The author has no conflicts of interest.

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