

Meta-analysis of Irisin Levels in Gestational Diabetes Mellitus

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Abstract

Background: Irisin is known as a miracle myo-adipokine that is secreted by skeletal muscle and fat tissue that increases insulin sensitivity. Current literature supports its role as a pathogenic agent in development of gestational diabetes; however, others have reported little or no difference between the two groups. Therefore, this meta-analysis aims to compare Irisin levels in gestational diabetes mellitus (GDM) pregnancies and non-GDM control pregnancies. A detailed literature search was carried via electronic databases, such as Medline, PubMed, and EMBase, for current related papers dating from January 1, 2017 over the last ten years. Only papers published in English were selected. Meta-analysis was preformed according to the Meta-analysis of Observational Studies in Epidemiology guidelines. Effect size and relative weights for each study were estimated and results of individual and combined effect size were plotted in the forest plots. p values <0.05 were regarded to be significant. In most studies, irisin levels in GDM were significantly lower, as compared to the control group. This level favored development of GDM in these subjects. This was confirmed by the forest plot report and contour-enhanced funnel plot of trials compared the GDM and Control group for effect estimates and standard error [I-V pooled SMD -0.482 (95%CI -0.610 to -0.353); Heterogeneity $\chi^2 = 54.53$ (d.f. = 7) $p = 0.000$; I^2 (variation in SMD attributable to heterogeneity) = 87.2%; Test of SMD = 0: $z = 7.32$ $p = 0.000$]. Lower circulating Irisin can contribute to hyperglycemic disorders such as GDM, through a collective loss of its normal anti-diabetic mechanisms. This revelation paves the way for research into the use of recombinant Irisin as treatment or prevention of GDM, so that the prevalence of GDM and its maternal and fetal consequences may be reduced.

Key words: Irisin, myokine, adipokine, GDM, obesity.

Introduction

Globally, up to 28% of women are affected by gestational diabetes mellitus (GDM), with low-income countries having a greater prevalence.¹ The importance in understanding GDM lies in its associations with numerous adverse outcomes. Women affected by GDM are at an increased risk for premature rupture of membranes, preterm delivery, cesarean section, and pre-eclampsia.² For

offspring, GDM also confers a greater risk of for development of metabolic syndrome, type 2 diabetes mellitus, and cardiovascular diseases.³ GDM is frequently linked with elevated levels of pregnancy-related hormones, including progesterone, estrogen, prolactin, human chorionic gonadotrophin and cortisol, which normally ensure adequate nutrition supply to the fetus. Higher levels of these hormones is associated with increase insulin resistance.⁴

Irisin is both an adipokine and a myokine, as it is released by both fat and muscle tissue.⁵ Irisin increases thermogenesis by inducing white adipose tissue (WAT) to convert to brown adipose tissue (BAT).⁶ Irisin is also proposed to increase insulin sensitivity,⁷ energy expenditure and glucose tolerance,⁸ and cause decrease in weight,⁹ body mass index, fat mass¹⁰ and hepatic triglyceride levels.¹¹ Furthermore, Irisin also inhibits hepatic gluconeogenesis and promotes glycogen synthesis.¹² Latest advances reveal that a lower Irisin level is representative of and might be a pathogenic link in causing GDM. However, others

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Authors Contribution

SSF conceptualized the project. SSF & RSM did the data collection. SSF, RSM & SAA performed the literature search. The statistical analysis was also done by SAA. The drafting, revision & writing of manuscript was done by SSF, RSM & SAA.

studies have shown lower levels in GDM versus non-GDM pregnancies or no difference between groups. Therefore, to clarify conflicting evidence on this topic, we aim to summarize and compare Irisin levels in GDM pregnancies with non-GDM pregnancies by means of a meta-analysis.

Methodology

The authors searched databases (PubMed, Medline and EMBase) for papers dating from up to ten years before January 1, 2017. The search terms 'GDM', 'myokines', 'betatrophin' and 'Irisin' were used as keywords to identify relevant published papers. Only papers published in English were selected. The entire search hits were scrutinized by the investigators and an initial set of 10 studies were identified and selected (Table). Studies were included in the final meta-analysis if they met all the following inclusion criteria: (1) manuscripts reporting the association between levels of circulating Irisin with GDM; (2) study design was cross-sectional or case-control for GDM; (3) both groups are described in the same paper (GDM vs. control group) (Figure-1). Two authors did the data extraction. Each of the following items had to be approved upon by agreement: authors name, country, publication time, data for case (GDM) and control groups, ethnicity, Irisin levels in serum or plasm, and numbers of cases and controls. To ensure minimal heterogeneity amongst included populations, this meta-analysis focused only on pregnant women. In order to assess the quality of the methodology of all studies included in the meta-analysis, the Newcastle-Ottawa Scale (NOS) for the evaluation of non-randomized studies and Agency for Healthcare Research and Quality (AHRQ) criteria was used. This scale comprises of three features measured using a star system (1-9 stars): study group selection, comparability between selected groups, and the ascertainment of the exposure.¹³ Controls patients without any previous history of DM were

reported in all studies. Studies received a three star for evaluation of exposure, and none discussed any missing data. Therefore, a hundred percent response rate was recorded. Similarly, in order to assess any publication bias, a sensitivity analysis using the Trim and Fill method was employed, which disclosed that irisin levels in GDM were consistent. Influence analysis revealed that circulating irisin levels were relatively consistent because the overall SMD in this meta-analysis was minimally affected by the omittance of any individual study (data not shown).

The Meta-analysis of Observational Studies in Epidemiology (MOOSE) guidelines¹⁴ was followed in this study. Using the command metan of Stata version 12.0 MP, Effect size and relative weights for each study were estimated and results of individual and combined effect size were plotted in the forest plots. $p < 0.05$ was considered significant for all analyses. To evaluate the link of Irisin level and GDM, fixed effect model using metan command was used to estimate the standardized mean difference (SMD), weight, and 95% confidence intervals (CI) for subjects with GDM and normoglycemia. Chi-square test was performed to assess heterogeneity amongst studies and the Higgins I^2 test (p value of more than 0.1 and I^2 less than 50 percent was considered as acceptable heterogeneity). Funnel plots using command confunnel were also generated.

Results

Results showed obvious heterogeneity, with the I^2 value for variation in SMD was 87.2% and the Chi2 test result $p = 0.000$. This heterogeneity was observed due to variability in the study designs, as well as differences in treatment of GDM and gestational dates of serum sampling across the subjects in these

Table: Features of included studies for meta-analysis.

S. No	Year	Author	Country	Type of Study	GDM (n)	Control (n)	Diagnostic Criteria for GDM
1	2016	Ural et al(24)	Turkey	Case-control	45	41	IDAPSG
2	2015	Zhao et al(15)	China	Cross Sectional	61	61	IDAPSG
3	2014	Kuzmicki et al(25)	Poland	Cross Sectional	130	140	IDAPSG
4	2015	Ebert et al(26)	Germany	Follow-up	74	74	ADA
5	2016	Erol et al(27)	Turkey	Prospective, nested case-controls	20	30	IADPSG
6	2013	Aydin et al(28)	Turkey	Case Control	15	15	WHO
7.	2014	Yuksel et al (20)	Turkey	Case Control	20	20	ADA
8.	2017	Usluogullari et al (29)	Turkey	Case Control	48	46	IADPSG

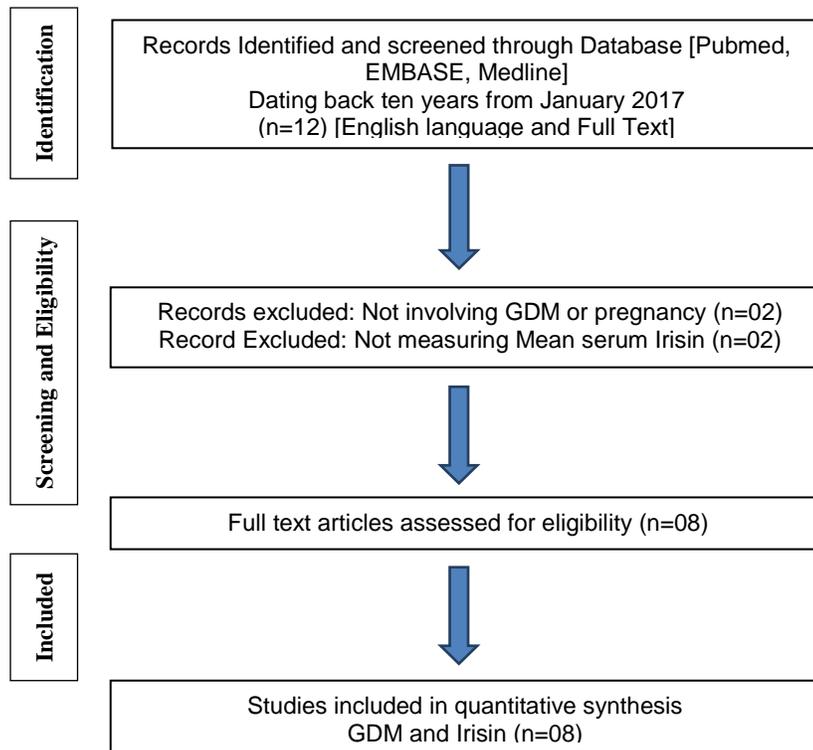


Figure 1: Flow diagram of selection method.

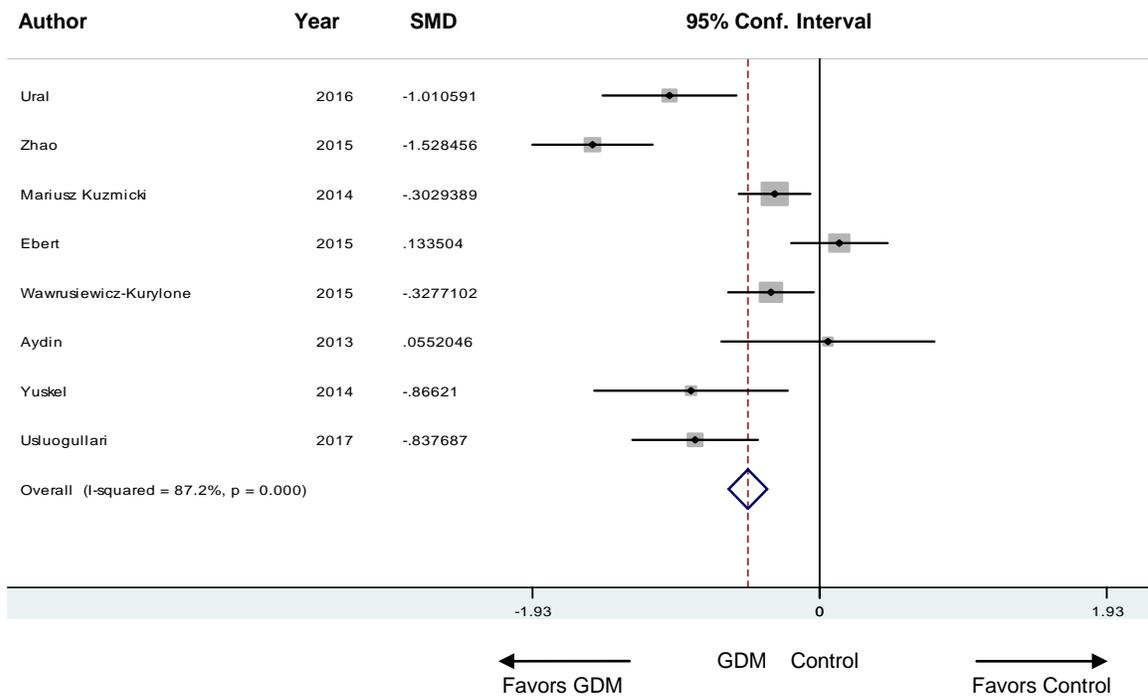


Figure 2: I-V pooled SMD -0.482 (95%CI -0.610 to -0.353); Heterogeneity $\chi^2 = 54.53$ (d.f. = 7) $p = 0.000$; I² (variation in SMD attributable to heterogeneity) = 87.2%; Test of SMD = 0: $z = 7.32$ $p = 0.000$

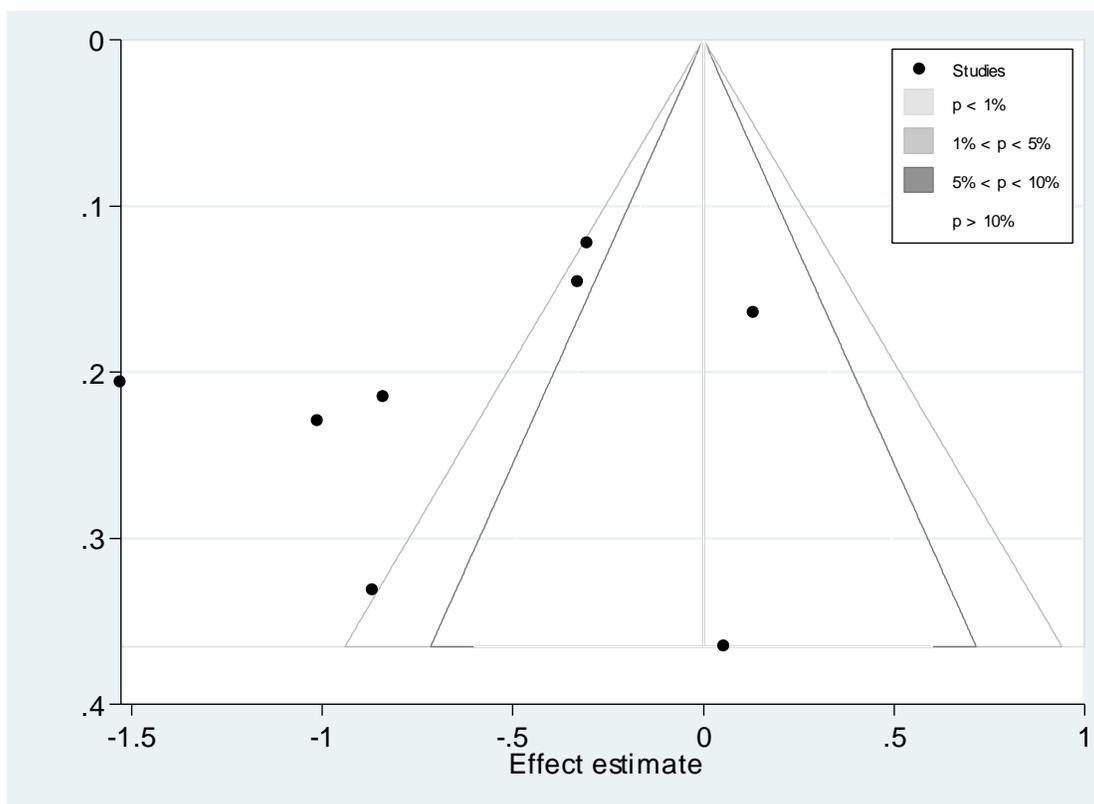


Figure 3: Effect estimate of studies in Meta-analysis.

different studies. However, the test of $SMD=0$ was rejected with p -value 0.00 showing that in most studies the levels of Irisin in subjects with GDM were significantly lower compared to control subjects. This level favored development of GDM in these subjects. The forest plot reports the relative risk for Irisin levels in GDM versus Control groups (Figure-2). The contour-enhanced funnel plot compared the GDM and Control group for effect estimates and standard error (Figure-3). The colored lines denote the level of statistical significance defined by the p -value of a z -test for the effect estimates [I-V pooled SMD -0.482 (95%CI - 0.610 to -0.353); Heterogeneity $\chi^2 = 54.53$ (d.f. =7) $p = 0.000$; I^2 (variation in SMD attributable to heterogeneity) = 87.2%; Test of SMD = 0: $z = 7.32$ $p = 0.000$].

Discussion

Irisin is involved in multiple metabolic processes in the body. Investigations into its role in the development of GDM have revealed slightly inconsistent results, necessitating a methodical analysis of printed literature. The findings of our meta-analysis reveal that Irisin levels are significantly lower in GDM. A previous meta-

analysis in 2015¹⁵ included 5 papers, and reported lower Irisin levels with a difference of -58.68 ng/mL in GDM [95% CI] (-113.42, -3.93, $p = 0.04$). Another meta-analysis in 2016 included 7 papers,¹⁶ and found similar results to ours ($\tau^2 = 0.45$, $\chi^2 = 76.32$; SMD = - 0.76, 95% CI: - 1.31, - 0.22; $p = 0.006$). These studies strengthen the credibility of our findings, which serve as an update to pre-existing information on the subject, since we included 8 studies in our meta-analysis.

The main mechanisms by which lower Irisin could precipitate hyperglycemic diseases such as GDM could be due to a disruption in its physiological roles of increasing insulin sensitivity and glucose tolerance. It also normally suppresses gluconeogenesis and promotes glycogen synthesis. Additionally, through its action on WAT, Irisin can also help reduce "high-fat-diet-induced insulin resistance".¹⁷⁻¹⁹ A study of mother's serum and cord blood Irisin at delivery showed an inverse relation with Irisin level and body mass index and homeostatic model assessment-insulin resistance ($r = -0.401$, $p = 0.010$; $r = -0.395$, $p = 0.012$, respectively), further demonstrating the link between low Irisin levels and GDM. It is due to increasingly strong evidence of Irisin's role in preventing against metabolic disorders such as T2DM, GDM and

Metabolic Syndrome that it has been suggested as an injectable therapeutic option in the management of such diseases.^{20,21} Recombinant Irisin injections in diabetic mice have been shown to result in significantly decreased blood glucose.²² Furthermore, another study used the locally administered Irisin and observed a decrease in arterial pressure in hypertensive animals,²³ elaborating on other potential pharmacological uses of Irisin in cardiometabolic disease.

It is being progressively established that lower circulating Irisin can contribute to hyperglycemic disorders such as gestational diabetes mellitus (GDM), through a collective loss of its normal anti-diabetic mechanisms. This revelation paves the way for research into the use of recombinant Irisin as a treatment or preventive modality for GDM, so that the burden of GDM and its maternal and fetal consequences may be reduced.

Conflict of interest: None declared.

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