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Serum levels of irisin in gestational diabetes mellitus during pregnancy and after delivery

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ABSTRACT

Objective: Irisin has recently been introduced as a novel an exercise-inducible myokine which improves glucose metabolism in mice. However, regulation of circulating irisin in gestational diabetes mellitus (GDM) and in the peripartal period has not been assessed so far.
Methods: Circulating irisin was quantified in 74 GDM patients and in 74 healthy, pregnant, gestational age-matched controls. In a subset of these patients (44 GDM, 41 controls), postpartum follow-up data were also available. In a second study population of 40 healthy women with singleton pregnancies undergoing elective Cesarean section, irisin was assessed in maternal serum before and within 24 h after delivery, as well as in umbilical cord blood and in placental tissue.
Results: In the first study population, median [interquartile range] irisin levels were significantly higher in GDM patients as compared to controls after delivery (previous GDM: 446.3 [146.9] μg/l; controls: 378.0 [111.4] μg/l) but not during pregnancy (GDM: 482.1 [132.1] μg/l; controls: 466.6 [178.0] μg/l). Interestingly, fasting insulin (FI) was independently and positively associated with serum irisin in multivariate analysis during pregnancy. In agreement with these findings, relative changes (ratio) of FI independently and positively predicted relative changes of irisin (ratio) in the second study population.
Conclusions: The myokine irisin is independently associated with FI in pregnancy. The physiological significance of these findings needs to be assessed in future experiments.

1. Introduction

Gestational diabetes mellitus (GDM) is a metabolic disorder during pregnancy leading to acute and chronic complications in both mother and newborn. Thus, GDM patients have an increased risk of co-morbidities during pregnancy, e.g. preeclampsia, pregnancy-induced hypertension, and shoulder dystocia with impeded delivery [1]. Furthermore, chronic complications might occur after delivery including type 2 diabetes mellitus (T2DM) and cardiovascular disease [2,3]. Simultaneously, hyperinsulinemia frequently seen in GDM [1] can lead to large-for-gestational age-fetuses with subsequent birth traumata. Furthermore, offspring of diabetic women have an increased risk of childhood obesity [4] and impaired glucose tolerance [5] in later life.

The exact pathogenesis of GDM has not been fully understood, yet. However, since the disease shares risk factors with T2DM, a relationship between these two disease states is plausible. In the past few years, dysregulation of various adipocyte- and hepatocyte-derived factors including adiponectin, leptin, fibroblast growth factor (FGF)-21, and adipocyte fatty acid-binding protein (AFABP) has been reported to mediate insulin resistance and proinflammatory effects in both T2DM [6] and GDM [7,8]. Moreover, myocyte-secreted proteins in addition to adipokines and hepatokines generated renewed interest in the field of metabolic diseases most recently. In this context, the fundamental study of Boström and co-workers introduced the myokine irisin as an exercise-inducible secreted factor that improves glucose tolerance and increases energy expenditure in mice [9].

Abbreviations: AFABP, adipocyte fatty acid-binding protein; BMI, body mass-index; CRP, C reactive protein; ELISA, enzyme-linked immunosorbent assay; FFA, free fatty acids; FG, fasting glucose; FGF-21, fibroblast growth factor-21; FI, fasting insulin; GDM, gestational diabetes mellitus; HbA1c, glycosylated hemoglobin A1c; HDL, high density lipoprotein; HOMA-IR, homeostasis model assessment of insulin resistance; LDL, low density lipoprotein; OGTT, oral glucose tolerance test; T2DM, type 2 diabetes mellitus; TG, triglycerides; WHR, waist to hip-ratio.

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Whereas irisin has beneficial effects in rodents, data in humans are insufficient so far to evaluate its metabolic effects and association with metabolic disease. Thus, few data suggest that irisin is associated with insulin sensitivity and new-onset of T2DM [10,11]. Furthermore, irisin is dysregulated in patients on chronic hemodialysis [12]. However, no data on irisin regulation in GDM and pregnancy are available. Therefore, we quantified circulating irisin concentrations in 74 GDM patients and 74 healthy, gestational age-matched pregnant controls (study population 1). Furthermore, serum irisin was also quantified in a subset of this population after delivery. Moreover, irisin levels were assessed in maternal serum of 40 healthy women with singleton pregnancies in the immediate peripartal period, as well as in the placenta and in cord blood (study population 2). We hypothesized that GDM patients have lower irisin levels as compared to controls and that irisin is associated with a beneficial metabolic profile.

2. Research design and methods

2.1. Subjects

2.1.1. Study population 1 – Irisin in GDM

For the first part of the study, 148 patients during pregnancy were recruited from the outpatient care unit of the Department of Endocrinology and Nephrology, University of Leipzig between 2006 and 2011. Patients with severe conditions including generalized or other chronic inflammation, immunosuppressive treatment, preexisting diabetes, and/or end-stage malignant diseases were excluded from the study. GDM was diagnosed if one or more plasma glucose levels were elevated during a 75 g, 2 h oral glucose tolerance test (oGTT) according to the criteria of the American Diabetes Association [13]. The following threshold plasma glucose levels were used: fasting $\geqslant$ 5.1 mmol/l; 1 h $\geqslant$ 10.0 mmol/l; 2 h $\geqslant$ 8.5 mmol/l. Based on these thresholds, 74 pregnant subjects were classified as GDM patients. Furthermore, 74 pregnant women with normal glucose tolerance and matched for gestational age served as controls. In 2012, all patients were asked to take part in a follow-up examination. A total of 85 patients (41 previous controls, 44 previous GDM) were available for follow-up. Blood samples for irisin and laboratory analysis were taken after an overnight fast at both the pre- and postpartum assessment. During pregnancy, blood sampling was performed together with the 0 h oGTT time point. In the follow-up examination, median time after delivery was 1576 days.

2.1.2. Study population 2 – Irisin in the peripartal period and in the placenta

For the second part of the study, 40 healthy women with singleton pregnancies were consecutively recruited from the Department of Obstetrics, University of Leipzig. Patients with generalized or other chronic inflammation, liver diseases, and diabetes mellitus were excluded. In all patients, elective Cesarean section was performed for indications including breech presentation, previous Cesarean section, or prior surgery of the womb. On the day of delivery, a fasting blood specimen was obtained in the morning. Soon after delivery, umbilical cord blood was drawn. Furthermore, placenta was weighed and placental biopsies for later enzyme-linked immunosorbent assay (ELISA) analysis were obtained similar to [14]. Moreover, fasting blood samples were again obtained within 24 h after delivery.

2.2. Clinical assessment

All participants of study population 1 and 2 underwent a thorough clinical examination at both time points. Body mass-index (BMI) was determined as weight before gestation divided by squared height. At the follow-up examination of study population 1, BMI was assessed as weight divided by squared height. At this time point, also waist to hip-ratio (WHR) was calculated after waist and hip circumferences were assessed. In all patients, homeostasis model assessment of insulin resistance (HOMA-IR) was calculated as previously described [15]. Both studies were approved by the local Ethics Committee and all subjects gave written informed consent before taking part in the study.

2.3. Assays

In both studies, irisin serum concentrations were determined with an enzyme-linked immunosorbent assay (Phoenix Pharmaceuticals, Burlingame, CA, USA) according to the manufactureŕs instructions. Furthermore, fasting insulin (FI) was determined with a two-site chemiluminescent enzyme immunometric assay for the LIAISON automated analyzer (DiaSorin, Saluggia, Italy). Moreover, glycosylated hemoglobin A1c (HbA1c), glucose levels during oGTT, total cholesterol, high density lipoprotein (HDL) cholesterol, low density lipoprotein (LDL) cholesterol, triglycerides (TG), free fatty acids (FFA), creatinine, and C reactive protein (CRP) were measured by standard laboratory methods in a certified laboratory.

2.4. Statistical analysis

SPSS software version 20.0 (IBM, Armonk, NY, USA) was used in all statistical analyses. Differences between age- and BMI-adjusted parameters in GDM patients and controls during and after pregnancy were assessed by Mann–Whitney-U-test. In both study populations, longitudinal changes in anthropometric and biochemical parameters during pregnancy as compared to after delivery were analyzed by Wilcoxon signed rank test. For longitudinal data, relative changes (ratios) of postpartum to prepartal values were calculated as follows according to [16]: parameter (ratio) = $\text{parameter}_{\text{postpartum}}/\text{parameter}_{\text{during pregnancy}}$ (postpartum-to-prepartal ratio). Univariate correlations were performed using Spearman's rank correlation method. To adjust the effects of covariates and identify independent relationships, multivariate linear regression analyses were performed. Before multivariate correlation analyses were calculated, distribution was tested for normality using Shapiro–Wilk W test and non-normally distributed parameters were logarithmically transformed. A p-value of < 0.05 was considered as statistically significant in all analyses.

3. Results

3.1. Study population 1 – Irisin in GDM

3.1.1. Baseline characteristics

Median [interquartile range] serum irisin was 472.8 [159.4] μg/l in the total sample during pregnancy and 418.8 [123.8] μg/l in follow-up examination after delivery. Clinical characteristics of the subgroups studied (Controls, GDM) during pregnancy are shown in Table 1. Median serum irisin levels were not significantly different in pregnancy between GDM (482.1 [132.1] μg/l) and control (466.6 [178.0] μg/l) patients ($p = 0.616$) (Table 1). In contrast, postpartum irisin concentrations were significantly higher in subjects with prior GDM (446.3 [146.9] μg/l) as compared to the control group (378.0 [111.4] μg/l) ($p = 0.002$). Matched pre- and postpartum samples revealed that postpartum levels of irisin (418.8 [123.8] μg/l) were significantly lower as compared to irisin concentrations during pregnancy (483.1 [155.9] μg/l) ($p < 0.001$) (Fig. 1).