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Cord blood irisin levels are positively correlated with birth weight in newborn infants

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ABSTRACT

Background. Irisin is a novel myokine, secreted from skeletal muscle after exercise. Irisin mediates exercise-related energy expenditure by turning white adipose tissue (WAT) into brown adipose tissue (BAT). Thus, irisin is considered as a potential biomarker for obesity and metabolic syndrome. Infants born small for gestational age (SGA) have increased risk for metabolic syndrome. However, the physiologic role of irisin in neonates remains to be studied.

Objective. To evaluate the association of umbilical cord blood irisin levels with gestational age and birth weight categories in neonates.

Methods. A cross-sectional study of 341 newborns, from 26 to 41 weeks' gestation. We collected umbilical cord blood and analyzed plasma for irisin by ELISA.

Results. Plasma irisin levels were positively correlated with gestational age ($r = 0.21$, $p < 0.001$), and birth weight Z-score ($r = 0.18$, $p < 0.001$). SGA infants had significantly lower irisin (median [interquartile range] 55.38 [46.56–65.72] ng/mL) compared to appropriate for gestational age infants (64.41 [53.87–76.76] ng/mL) and large for gestational age infants (68.70 [54.78–79.09] ng/mL, $p < 0.01$). The association between SGA and lower irisin remained significant in multivariate analysis independent of gestational age, maternal age, maternal BMI, and gestational diabetes ($p = 0.03$). In singleton infants, irisin was also significantly negatively associated with maternal preeclampsia ($p = 0.01$).

Conclusions. Our results support the notion that irisin may have a physiologic role in neonates. We speculate that decreased levels of irisin in SGA infants may contribute to the development of catch-up growth and metabolic syndrome later in life.

Abbreviations: PPARγ, peroxisome proliferator-activated receptor gamma; PGC-1α, PPARγ-coactivator 1 alpha; FNCD5, fibronectin type III domain containing 5; UCP1, uncoupling protein 1; BMI, body mass index; BAT, brown adipose tissue; GDM, gestational diabetes mellitus; HOMA-IR, homestasis model assessment-estimated insulin resistance.

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1. Introduction

Irisin, a novel regulator of metabolic function, is known for its role in exercise-induced energy expenditure and 'browning' of white adipose tissue [1]. Irisin is produced by cleavage of its precursor, fibronectin type III domain containing 5 (FNDC 5), in skeletal muscle after exercise-induced stimulation by peroxisome proliferator-activated receptor gamma (PPARγ) coactivator 1-alpha (PGC-1α) [1,2]. Circulating irisin acts on white adipose tissue, an energy-saving organ, and results in its 'conversion' to brown adipose tissue (BAT), which is an energy-producing organ. This is mediated by thermogenesis via the uncoupling protein 1 (UCP1) pathway. Animal studies showed that irisin improved glucose tolerance in obese, pre-diabetic mice [1]. In clinical settings, patients with type 2 diabetes mellitus have lower levels of irisin compared to healthy controls [3,4], and irisin's precursor, FNDC 5, is decreased in patients with obesity [5]. However, circulating irisin is reported to be paradoxically higher in adults with metabolic syndrome [6], which suggests that states of irisin resistance or tolerance may exist [7,8].

Newborn infants have predominantly high content of brown adipose tissue (BAT) for thermogenesis, and the content of brown fat decreases significantly after infancy [9]. Small for gestational age (SGA) infants have lower percentage of total body fat (% body fat) compared to appropriate for gestational age (AGA) infants [10–12], which may result in lower irisin levels. SGA and intrauterine growth restriction (IUGR) are known risk factors for metabolic syndrome in adult life [13]. However, the mechanism underlying the association between SGA and metabolic syndrome later in life is not fully understood. Thus, we examined the levels of irisin in the umbilical cord blood between different birth weight categories, and examined the association between cord blood irisin levels and birth weight Z-score and gestational age across a range of gestational ages from 26 to 41 weeks.

2. Methods

2.1. Study Population

This is a cross-sectional study of 341 neonates. Neonates included in the study were born at Brigham and Women's Hospital (BWH) from April 2010 to November 2013. Collection of umbilical cord blood was performed from all vaginal and cesarean deliveries when the research nurse or an investigator was available, and when the cord blood was not needed for another purpose such as cord blood banking. The study was reviewed and approved by the institutional review board (IRB) of Brigham and Women's Hospital (BWH). Analysis of discarded material (cord blood) and review of medical record do not require a written consent from the parents. The study adheres to the Declaration of Helsinki.

We excluded newborns with major congenital anomalies such as congenital heart and renal anomalies or maternal chronic inflammatory disease, such as Crohn's disease, ulcerative colitis, systemic lupus erythematosus (SLE) or cancer.

Among the 341 infants included in analysis, 217 were full term (≥37 weeks), and 124 were preterm (35–36 weeks: 51, 32–34 weeks: 29, 29–31 weeks: 26, 26–28 weeks: 18). Determination of gestational age was based on best obstetrical estimate from the medical record. Newborns were categorized as small for gestational age (SGA: birth weight <10th percentile), appropriate for gestational age (AGA: 10th percentile ≤ birth weight ≤ 90th percentile), and large for gestational age (LGA: birth weight > 90th percentile) groups based on the intrauterine growth curves [14].

2.2. Cord Blood Collection and Measurement of Plasma Irisin

Umbilical cord blood was collected from the umbilical vein attached to the placenta at the time of delivery. They were centrifuged and the plasma was divided into 0.5 milliliter aliquots, which were stored in Eppendorf tubes at −80 °C until analysis. Levels of irisin were measured by ELISA by commercial kits (EK 067–52, Phoenix Pharmaceutical, Burlingame, CA, USA) with 1:2 dilution of plasma sample (70 μL). Intra- and inter-assay variances were <4–6% and <8–10%, and the range of detectable concentration was 0.066–1024 ng/mL.

2.3. Clinical data of Newborn Infants and Mothers

We collected clinical information from the electronic medical records. Maternal data included age, race/ethnicity, marital status, parity, multiple gestation versus singleton, insurance, smoking status, pre-pregnancy body mass index (BMI), clinical chorioamnionitis, preeclampsia and gestational diabetes. Infant data included sex, gestational age, mode of delivery, birth weight, and 1 and 5 minute Apgar scores. Birth weight Z-scores were obtained using a reference by Fenton et al. [14]. Diagnosis of maternal preeclampsia was made by systolic blood pressure ≥ 140 mmHg and/or diastolic 90 mmHg after 20 weeks of gestation, and proteinuria ≥ 0.3 g protein in 24 hour urine or spot urine protein/creatinine ratio ≥ 0.3 mg/mg [15]. Diagnosis of gestational diabetes was made by glucose loading test with 50 g glucose, and confirmed by subsequent diagnostic oral glucose challenge test (OGTT) with 100 g glucose. Gestational diabetes was diagnosed when two or more of the following criteria were met: the glucose level at fasting was >95 mg/dL, 1 hour glucose >180 mg/dL, 2 hour >155 mg/dL, 3 hour >140 mg/dL [16].

Clinical chorioamnionitis was diagnosed with maternal fever > 100.4 °F, and two out of four additional findings (uterine tenderness, maternal tachycardia, fetal tachycardia, foul/purulent amniotic fluid) [17].

2.4. Statistical Analysis

Kruskal–Wallis test was used for continuous variables for comparison between the three different birth weight categories (SGA, AGA, and LGA). Post-hoc pairwise analyses between two groups were performed by Wilcoxon rank sum test with Bonferroni correction ($p < 0.017$ was considered significant in post-hoc analyses). Chi-square test and Fisher's exact tests were used for categorical variables. Normality of irisin was tested with Shapiro–Wilk test, and the data were transformed to logarithmic scale to obtain normality. Spearman