

Is serum irisin level lower in neonates born to mothers with gestational diabetes?

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Abstract

Aim: Irisin is a newly identified myokine that is released from skeletal muscles after exercise and has a regulatory role on energy metabolism. Low serum irisin causes glucose metabolism disorder and metabolic syndrome. The aim of this study was to assess neonatal irisin levels in infants born to mothers with and without gestational diabetes mellitus (GDM).

Material and Methods: Hundred neonates born at gestational ages of 26-40 weeks were included in the study. Neonates born to mothers with GDM comprised one group; neonates born to mothers without GDM were evaluated in three groups: appropriate for gestational age (AGA), small for gestational age (SGA), and large for gestational age (LGA) infants. Peripheral blood samples were obtained at postnatal 48 hours and analyzed for serum irisin levels by ELISA.

Results: Serum irisin levels in infants born to GDM mothers were significantly lower (mean 0.81 ng/ml) than AGA newborns of healthy mothers (mean 1.21 ng/ml) ($p=0.017$). Serum irisin levels were not correlated with gestational age, birth weight, Z-score, or BMI ($p>0.05$).

Conclusion: This study show that serum irisin levels are lower in infants born to GDM. Lower irisin levels in the neonatal period may increase the risk of obesity, metabolic syndrome, and glucose metabolism disorder later in life.

Keywords: Irisin; newborn; gestational diabetes.

INTRODUCTION

Irisin is a myokine involved in energy metabolism through the transformation of white adipose tissue to brown adipose tissue (1,2). Skeletal muscles take up glucose in response to insulin release in the body, and thus are the most important organ in insulin resistance development. In recent years, it has been determined that skeletal myocytes produce certain hormones and peptides, the latter of which are called myokines (3).

Myokines act as endocrine hormones, regulating the function of both the synthesizing organs and distant organs (1). Exercise induces increased synthesis of the myokine irisin (4). Irisin triggers the transformation of white adipose tissue to brown adipose tissue and has a regulatory effect on energy metabolism (1). Animal studies have shown that irisin has an important role in the development of Type 2 DM in obese rats. In human studies, lower irisin levels have been detected in patients with Type 2 DM compared to healthy individuals (5,6). In contrast, adults with metabolic syndrome exhibit higher

irisin levels, which is thought to be a result of irisin resistance at the receptor level (7). Previous studies have also demonstrated lower serum irisin levels in women with GDM (8). However, there are no publications concerning serum irisin levels in neonates born to mothers with GDM.

Brown adipose tissue is very important for thermogenesis in the neonatal period and decreases in volume as the infant grows (9). Moreover, fat mass index is lower in infants that are small for gestational age (SGA) compared to their appropriate for gestational age (AGA) counterparts (10,11). Because low fat mass can cause lower serum irisin levels, this may be a factor in the development of metabolic syndrome and diabetes mellitus in these infants when they reach adulthood (12). However, despite all of these theories, the mechanisms leading to adult metabolic syndrome in SGA infants has not been definitively determined.

This study aimed to evaluate and compare the irisin levels of neonates born to mothers with GDM with those of SGA, AGA, and LGA neonates born to healthy mothers.

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MATERIAL and METHODS

Study population

This prospective study investigated serum irisin levels at postnatal 48 hours in 100 newborns who admission to the neonatal intensive care unit (NICU) of Hacettepe University Ihsan Dogramaci Children's Hospital between April and November 2016. Ethical approval was obtained from the Ethics Committee of Hacettepe University Faculty of Medicine in Ankara, Turkey. The study adhered to the Declaration of Helsinki and written informed consent was obtained from the families of newborns included in the study. Newborns with major congenital anomalies such as congenital heart disease and congenital kidney anomalies, and twins newborns, maternal chronic inflammatory disease such as Crohn's disease, ulcerative colitis, and collagen tissue disease, maternal preeclampsia, and placental developmental anomaly were excluded. Demographic characteristics, and maternal history were obtained from records.

The first three groups of newborns were formed based on intrauterine growth curves as follows: Group 1 included SGA (birth weight <10th percentile) infants; Group 2 included AGA (birth weight between 10th and 90th percentile) infants; and Group 3 included LGA (birth weight >90th percentile) infants (13). Group 4 included infants born to mothers with GDM. Maternal GDM was detected with 50-g glucose loading test and confirmed by subsequent diagnostic 100-g oral glucose tolerance test (OGTT). Gestational diabetes was diagnosed when two or more serum glucose results exceeded the following thresholds: >95 mg/dL fasting, >180 mg/dL at 1 hr post-glucose load, >155 mg/dL at 2 hr post-glucose load, or >140 mg/dL at 3 hr post-glucose load (14).

Collection of blood samples and measurement of serum irisin levels

Venous blood samples were collected at postnatal 48 hours. The samples were kept at room temperature for 30 min, then separated by centrifugation. The serum was divided into 0.5-ml aliquots and stored in Eppendorf tubes at -80°C until analysis. Serum irisin levels were measured

using commercial enzyme-linked immunosorbent assays (Human FNDC5/Irisin ELISA Kit [Sandwich ELISA], LifeSpan Biosciences Inc., North America). The assay had a sensitivity of 0.094 ng/mL, intra- and inter-assay variability was <10%, and range of detectable concentration was 0.156 - 10 ng/mL.

Statistical analysis

Data were analyzed using the Statistical Package for Social Sciences 21.0 for Windows (SPSS Inc., Chicago, IL, USA). Irisin values are not normally distributed (Kolmogorov-Smirnov test) and non-parametric tests were used to evaluate differences between groups. Descriptive analyses were presented using medians and interquartile range (IQR) for non-normally disturbed and ordinal variables. The Mann-Whitney U test was used to compare irisin values between the groups. Results with p values <0.05 were considered statistically significant.

Sample size

We consider a 60% difference in serum irisin levels between group-4 and other group. With $\alpha=0.05$ (one-tailed test) for type I error risk and study power of 0.80, the required sample size was 25 subjects per group. Therefore, a minimum of 25 patients was included in each group.

RESULTS

A total of 100 neonates were included in the study: 25 SGA infants in Group 1 (25%), 25 AGA infants in Group 2 (25%), 25 LGA infants in Group 3 (25%), and 25 infants of GDM mothers in Group 4 (25%). The demographic characteristics of the groups and their irisin values are summarized in Table 1. Median serum irisin levels were 0.624 (0.368 - 0.781) ng/mL in Group 1, 0.735 (0.544-0.877) ng/mL in Group 2, 0.609 (0.500 - 0.780) ng/mL in Group 3, and 0.355 (0.331 - 0.560) ng/mL in Group 4. (Figure 1). When the serum irisin levels were evaluated in the four groups, serum irisin levels were lower in group 4 and there was statistically significant difference in irisin levels between the group-4 and other groups (Group-1, 2 and 3) ($p<0.001$). However, there were no statistically significant differences in serum irisin levels between the groups 1,2 and 3 ($p>0.05$) (Table 1).

Table 1. Demographic features and irisin levels of the all groups

	SGA (n:25)		AGA (n:25)		LGA (n:25)		GDM (n:25)		p
	Median	IQR	Median	IQR	Median	IQR	Median	IQR	
GA ^a (week)	37.0	35.4-37.2	38.3	37.1-38.6	38.1	37.2-38.3	38.0	37.0-38.3	P<0.001
BW ^b (g)	2280	1850-2380	3200	2680-3670	4000	870-4110	3260	2940-3610	P.0.36
Male (%)	60	-	40	-	52	-	60	-d	-
BMI ^c	10.6	9.2-11.4	12.4	11.0-13.3	12.6	12.3-13.0	13.0	12.6-13.7	P<0.001
zskord	-1	-2/-1	0	0-1	3	3-4	0	0-1	P<0.001
irisin ^e (ng/ml)	0.624	0.368-0.781	0.735	0.544-0.877	0.609	0.500-0.786	0.385	0.331-0.560	P<0.001

Abbreviations: GA: gestational age, BW: Birth weight, BMI, body mass index, SGA: Small for gestational age, AGA: Appropriate gestational age, LGA: Large gestational age; Variables are presented with median (interquartile range), or n (%), *Mann Whitney U test (test p<0.05 significant)

^aSignificant difference between Group-1 and Group-2/ Group-3/ Group-4

^bNo significant difference between all groups

^cSignificant difference between Group-3 and Group-1/ Group-2/ Group-4

^dSignificant difference between Group-4 and Group-1/ Group-2/ Group-3

In correlation analysis, we found no significant correlation between serum irisin levels and gestational age, birth weight, BMI, Z-score (Table 2).

Table 2. Correlation analysis of irisin, sex, gestational age, birth weight Z-score, and BMI

	sex	Gestational age (weeks)	Birth weight (g)	Birth weight Z-core	BMI (Kg/m ²)
Irisin (ng/mL)	r: -0.045 p: 0.6	r: 0.029 p: 0.78	r: -0.007 p: 0.95	r: -0.01 p: 0.89	r: -0.121 p: 0.231

Spearman correlations (test p<0.05 significant)

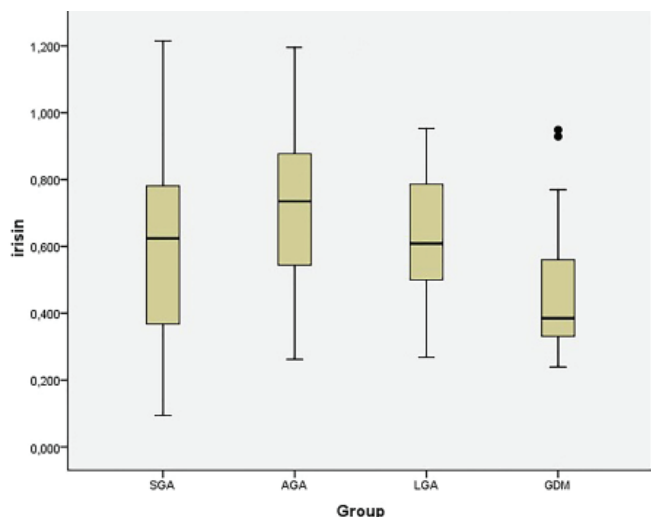


Figure 1. Distribution of iris levels in group-1, group-2, group-3, group-4

DISCUSSION

In this study, we showed that serum irisin levels were lower in infants of mothers with GDM compared to infants of healthy mothers, with a statistically significant difference between GDM infants and AGA infants of healthy mothers. To the best of our knowledge, this is the first study examining serum irisin levels in neonates born to mothers with GDM.

One of the few studies examining serum irisin levels in the neonatal period demonstrated low serum irisin in infants with intrauterine growth restriction (IUGR), and the authors suggested that low irisin was involved in the development of IUGR. Cord irisin levels and maternal serum irisin levels were also found to be correlated (15). In another study, Baka et al (16) showed that cord irisin level was lower in IUGR infants compared to AGA infants. They suggested that low irisin levels caused growth deficiency and would lead to insulin resistance later in life (16). Kyoung et al. found that cord irisin levels were correlated with Z-score, and serum irisin levels were low in SGA infants (17). In contrast, serum irisin levels were not correlated with gestational age, birth weight, or BMI in our study.

Our comparison of serum irisin levels in SGA, LGA, and AGA infants showed a tendency toward lower

serum irisin in SGA infants, but the difference between groups was not statistically significant. There are two possible explanations for this discrepancy. The first is that serum samples were obtained from umbilical cord blood samples in previous studies, whereas we analyzed peripheral blood samples collected at postnatal 48 hours, after metabolic adaptation. This eliminated maternal confounding factors such as preeclampsia and collagen tissue disorder that affect serum irisin level. A second possibility is that the release of irisin precursors from the decidua, cytotrophoblasts, and syncytiotrophoblasts, as demonstrated in a study by Garces et al (18), may be a confounding factor in cord blood analyses. The same study also showed that irisin levels were lower in umbilical cord blood samples in preeclamptic pregnancies compared to healthy pregnancies (18). This indicates that maternal factors influencing placental growth could affect irisin levels in umbilical cord blood. Moreover, it is not possible to determine the origin of irisin in samples taken from the cord (16).

Studies have shown that the incidence of obesity later in life is higher among infants born to mothers with GDM. Silverman et al. (19) followed the infants of mothers with GDM and pre-pregnancy diabetes until 8 years of age. At the end of the follow-up period, they determined that the infants gained 30% more weight than expected for their height. Infants born to diabetic mothers were found to have 20% more body fat regardless of birth weight compared to infants born to mothers with normal glucose tolerance test results, and the prevalence of childhood obesity was higher in infants born to mothers with GDM (19). In a study of adolescents born to diabetic mothers, it was reported that they had a higher rate of glucose intolerance compared to the control group, as well as a higher diabetes prevalence. These increases in obesity and diabetes prevalence were independent of maternal diabetes (19,20). Furthermore, all of these disorders were shown to result from glucose metabolism disorder starting in the neonatal period.

In our study, serum irisin levels of AGA babies born to GDM mothers were found to be significantly lower than AGA infants born to non-GDM mothers. Low serum irisin levels have been detected in patients with Type 2 diabetes and even implicated as a cause of insulin resistance. These studies demonstrated that the decrease in serum irisin levels occurred before the development of insulin resistance and may be used as an early marker in patients with Type 2 diabetes (5,6,22). Low serum irisin levels in neonates born to mothers with GDM may be an early marker of insulin resistance and later morbidities, some of which may start developing in the neonatal period.

CONCLUSION

Our findings suggest that serum irisin levels can be used as an early marker of insulin resistance and later morbidities in neonates born to mothers with GDM. Studies with larger groups and a longer follow-up period are required to support these findings.

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