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Cord blood and maternal serum preptin and irisin concentrations are regulated independently in GDM

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Abstract. – OBJECTIVE: The aim of this study is to examine the maternal serum and cord blood irisin and preptin levels in gestational diabetes mellitus (GDM) and correlate their levels with demographic and biochemical parameters.

PATIENTS AND METHODS: A total of 21 pregnant women with GDM and 21 BMI and age-matched pregnant women without GDM were included in the study. They underwent 50 g glucose challenge test (GCT) between 24-28th gestational weeks. Women with a GCT result higher than 140 mg/dl received 100 g oral glucose tolerance test (OGTT). Detection of one of the following criteria after OGTT was accepted as GDM: fasting plasma glucose level 92 mg/dL; 1-h plasma glucose level 180 mg/dL; and 2-h plasma glucose 153 mg/dL. Correlation between metabolic parameters and cord blood and maternal serum preptin and irisin levels in GDM and non-GDM subjects were analyzed.

RESULTS: Maternal serum preptin values of GDM subjects were similar to the serum preptin values of non-GDM control subjects (123.12±34.3 pg/mL *vs.* 112.02±12.0 pg/mL, $p<0.23$). Cord blood preptin levels of GDM (64.3±1.09 pg/mL *vs.* 123.12±34.3 pg/mL, $p<0.03$) and non-GDM subjects (59.2±021 pg/mL *vs.* 112.02±12.0 pg/mL, $p<0.02$) were significantly lower than the maternal serum preptin values. Serum preptin levels of GDM group were positively correlated with HOMA-IR (r=0.33, $p<0.04$), but not with other parameters. Maternal serum irisin levels in the GDM group were lower than the non-GDM control group (5.32±0.44 μg/mL *vs.* 7.74±4.52 μg/mL, $p<0.01$). Cord blood irisin concentrations were found similar in women with GDM and non-GDM subjects (4.91±3.12 μg/mL *vs.* 5.01±2.14 μg/mL, $p<0.14$). Cord blood irisin levels of GDM subjects were similar to maternal serum irisin levels (4.91±3.12 μg/mL *vs.* 5.32±0.44 μg/mL, $p<0.57$). We found positive correlation between irisin concentration and fasting insulin, HOMA-IR, and BMI in women with GDM. In subgroup analysis of 6 patients using insulin treatment, serum and cord blood irisin and preptin levels were similar to those that did not use insulin.

CONCLUSIONS: Maternal serum and cord blood preptin and irisin concentrations are regulated independently in women with GDM.

Key Words:
GDM, Irisin, Preptin, Cord blood, Maternal serum, HOMA-IR.

Introduction

Gestational diabetes mellitus (GDM) is a pregnancy-specific endocrine disease accompanied by impaired synthesis and release of many peptide hormones and cytokines. Both irisin and preptin levels in maternal serum and cord blood in GDM cases were evaluated in previous studies[1,2]. However, there is no study evaluating irisin and preptin together in GDM cases. The tight connection between these two peptides and insulin resistance is important in revealing the etiology of GDM[1]. Preptin is a proinsulin-like growth factor II E-peptide. It presents in islet beta-cells and is co-secreted with insulin in response to glucose. Preptin also stimulates insulin secretion in experimental animals. It has been reported that there is a strong link between circulating preptin levels and insulin resistance. So far, isolated studies have been conducted investigating serum and cord blood preptin levels in pregnant women with metabolic disorders including GDM[1,2].

Muscle tissue-derived irisin is a newly discovered myokin and there are studies showing that it plays an important role in metabolic homeostasis in nonpregnant and pregnant women[3,4]. Irisin involved in the circulation mediates the transfor-

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mation between normal adipose tissue and brown adipose tissue. Increased levels of circulating irisin is detected during exercise and pregnancy[3-5]. However, the main reason for this increase in irisin during normal pregnancy is unknown. It is thought that its synthesis is increased due to change in the production of placental or fat tissue. Similarly, the metabolism and function of the irisin in the fetus are not clearly known. It is known fact that labor increases the serum and cord blood irisin levels significantly[3-5].

The relationship between irisin, glucose and insulin levels is clearly known. However, the results of studies in terms of serum and cord blood irisin levels in gestational diabetes (GDM) occurring during pregnancy are not very compatible[1-4]. One of the possible causes of these incompatibilities are the measurement of irisin at 24-28th week in some women and at the birth others. Another reason is that some of the patients receive insulin therapy and some do not. The preconception age and body mass index (BMI) of patients with GDM and control group is another factor affecting the results. Since most of the patients included in these studies were on different age and BMI values, this discordance may be important causes of bias[6,7]. This study was, therefore, planned to investigate maternal serum and cord blood preptin and irisin levels at the time of cesarean delivery in age and BMI matched pregnant women with and without GDM and correlate their levels with demographic and laboratory parameters.

Patients and Methods

A total of 21 pregnant women with GDM and 21 BMI and age-matched pregnant women without GDM were included the study. Participants in each group were selected from patients who were admitted to our Obstetrics and Gynecology Departments between January 2018 and December 2018. Patients with chronic hypertension, pregnant women with preeclampsia, patients having preexisting diabetes mellitus and smokers were excluded from the study. GDM diagnosis was made according to the HAPO criteria[8]. The presence of one of the following criteria after oral glucose tolerance test (OGTT) was accepted as GDM: fasting plasma glucose level 92 mg/dL; 1-h plasma glucose level 180 mg/dL; and 2-h plasma glucose 153 mg/dL. Correlation between metabolic parameters and cord blood and maternal serum preptin and irisin levels in GDM and non-GDM subjects were analyzed. Homeostatic model assessment [HOMA-IR] Formula was used for calculating insulin resistance[9].

The venous blood samples were collected from each group of subject at the time of cesarean section delivery. Cord blood samples were obtained from umbilical cord vessels immediately after birth. Following centrifugation of maternal blood and cord blood samples (3000 g x 10 minute) serum levels of preptin and irisin were measured with a commercially available enzyme immuno assay kit according to the manufacturer's instructions. The minimum detectable concentration of irisin was 0.05 µg/mL. The intra and inter-assay variations were below 10% and 15%, respectively. Maternal serum and cord blood samples were diluted two-fold before performing the measurement with assay buffer and were measured in duplicate. The minimum detectable concentration of preptin was 25 pg/mL while assay range was 57-1000 pg/mL. The intra and inter-assay variations were below 8% and 12%, respectively. This study was conducted in accordance with the Declaration of Helsinki and Instutional Review Board (IRB) approval was obtained from Memorial Hospital, Kayseri.

Statistical Analysis

The Statistical Package for Social Sciences was used for statistical analysis version 21 (IBM, Armonk, NY, USA). The normal distribution of variables was tested using Shapiro-Wilk test. Variables with normal distribution were compared between GDM and non-GDM control groups using parametric *t*-test. Otherwise, nonparametric Mann Whitney U test was used. Pearson correlation analysis was used to detect relationship between circulating preptin, irisin levels and other parameters. Data are presented as mean±standard deviation (SD). $p < .05$ was accepted as statistically significant.

Results

The mean age of patients in GDM and control groups was 29.3±0.3 and 30.2±4.9, respectively. While preconception BMI of GDM cases was 23.6±1.9, BMI of control group was 24.1±3.7. BMI at birth was 27.6±4.4 in GDM group and 28.3±6.1 in non-GDM control group. All patients in GDM and control groups gave birth by cesare-

an section. Six of 21 GDM cases received insulin therapy. While the gestational age of GDM cases at the time of delivery was 37.4±1.2 weeks, the control group was found to be 38.1±2.3 weeks. Maternal serum preptin values of GDM subjects were similar to the serum preptin values of non-GDM control subjects (123.12±34.3 pg/mL *vs.* 112.02±12.0 pg/mL, $p<0.23$). Preptin levels of cord blood of women with GDM (64.3±1.09 pg/mL*vs.* 123.12±34.3 pg/mL, $p<0.03$) and non-GDM subjects (59.2±021 pg/mL *vs.* 112.02±12.0 pg/mL, $p<0.02$) were significantly lower than the maternal serum preptin values. Preptin levels obtained from the cord blood of GDM patients were higher than the cord blood preptin values of control group (64.3±1.09 pg/mL *vs.* 59.2±021 pg/mL, $p<0.52$). But the difference failed to show statistically significant. Serum preptin levels of GDM group were positively correlated with HOMA-IR ($r=0.33$, $p<0.04$), but not with other clinical and laboratory parameters. In subgroup analysis of six patients using insulin treatment, the concentrations of serum and cord blood preptin were similar to those that did not use insulin.

Maternal serum irisin levels in the GDM group were lower than non-GDM control group (5.32±0.44 µg/mL *vs.* 7.74±4.52 µg/mL, $p<0.01$). There are no significant differences between GDM and non-GDM groups in terms of cord blood irisin concentrations (4.91±3.12 µg/mL *vs.* 5.01±2.14 µg/mL, $p<0.14$). Cord blood irisin levels of GDM patients were similar to maternal serum irisin levels (4.91±3.12 µg/mL *vs.* 5.32±0.44 µg/mL, $p<0.57$). On the other hand, cord blood irisin levels of women with non-GDM subjects were lower than that of the maternal serum irisin levels (5.01±2.14 µg/mL *vs.* 7.74±4.52 µg/mL, $p<0.001$). We found positive correlation between irisin concentration and fasting insulin, HOMA-IR, and BMI in women with GDM. We did not find any correlation between maternal serum irisin levels and cord blood irisin levels in GDM group. Birth weights of babies born with GDM were approximately 3106±320 g and birth weight of control subjects was 3257±520 g. There was no correlation between birth weight and serum irisin levels inGDM group. Similarly, there was no significant relationship between cord blood irisin levels and birth weights. In subgroup analysis of 6 patients using insulin treatment, the concentrations of serum and cord blood irisin were similar to those that did not use insulin. However, it is a handicap that the insulin dosages used, insulin start times and treatment duration, are not taken into account. Neither positive nor negative correlation were found between maternal serum, cord blood irisin concentrations and other parameters in non-GDM subjects.

Discussion

Preptin is a peptide that stimulates insulin secretion and it is secreated in response to glucose release. There is a tight relationship between preptin levels and insulin resistance. In line with this, the link between preptin levels and insulin resistance in both diabetic patients and other metabolic conditions, such as PCOS, has been clearly demonstrated[1,2]. In the present study, we could not find any difference in maternal serum preptin levels between GDM patients and non-GDM controls. However, cord blood preptin levels of GDM subjects were found to be significantly lower than serum levels. Moreover, maternal serum preptin levels of GDM group were positively correlated with HOMA-IR but not with other parameters. Due to the difference in cord blood and maternal serum preptin levels in GDM women, it is logical to think that there is a preptin resistance between two compartments. In view of these findings, we can propose that the main production site of preptin is maternal site. Cord blood preptin is most likely local production from fetus that excluding transport of preptin from maternal serum to the cord blood. In contrast to our findings, Aslan et al[2]reported that serum and cord blood preptin levels of GDM women were higher than those in the non-GDM pregnant women. They also reported that maternal serum preptin concentration was positively correlated with maternal age, fasting insulin levels, 1-h blood glucose levels following glucose load and cord blood preptin concentrations at birth. Although preptin levels give different results in different studies, the correlation between preptin and HOMA-IR is remarkable in all studies.

A normal pregnancy causes insulin resistance and deviations in blood glucose levels. Serum irisin levels play a role in pregnancy-related glucose homeostasis and regulation of energy pathways. When we compared to maternal serum irisin concentrations between women with GDM and BMI-age-matched non-GDM pregnant women, we found that irisin levels in the GDM group were lower than that of non-GDM control group. However, we did not find significant difference between groups in terms of cord blood irisin levels. In line with our results, Cui et al[10] showed that

serum irisin levels of GDM patients were significantly lower than that of non-GDM control group during pregnancy. A meta-analysis also reported that there was no significant difference between GDM and non-GDM subjects in terms of cord blood irisin levels[10].

Based on the current study, maternal serum irisin levels do not seem to be related with the cord blood irisin levels. It has been reported that maternal serum irisin levels increase up to 20% during pregnancy[7]. The reason for this increase may be the change in the rate of placental production or pregnancy-related adipose tissue alteration. On the other hand, the presence of endocrine disease or placental development defects that may disrupt metabolism during pregnancy, may lead to a decrease in irisin production[4,5]. Because GDM changes serum insulin levels and oil composition, irisin production may decrease. Similarly, vascular pathologies related to GDM can disrupt the synthesis of irisin by disrupting placental development. Low serum irisin levels in preeclamptic patients also supports a link between vascular pathologies and the synthesis and release of irisin[4,5].

The main source of cord blood irisin levels is not clearly known. Since there is no correlation between maternal serum irisin levels and cord blood irisin levels, the main source of fetal irisin is placenta or fetal muscle tissues. Since the fetal fat tissue is mostly brown, the contribution of this tissue to cord blood irisin levels can be neglected. The beginning of labor is the most important process that significantly increases irisinlevels in both mother and fetus[4,5]. However, since all of the cases in our study delivered by cesarean section, no irisin increase due to labor was detected. For these reasons, normal irisin levels in cord blood suggest that metabolic change in fetuses and placenta of patients with GDM is close to normal. The reason for decreased levels of irisin in maternal blood may be due to deterioration in GDM-related metabolism, change in adipose tissue content and increased insulin resistance. Concordantly, Huh et al[11] reported that irisin concentrations were positively associated with BMI and fasting levels of glucose. Kuzmicki et al[6] showed that while serum irisin levels increased in healthy pregnant women, change in irisin levels in GDM subjects is less clear. Likewise, Shoukry et al[12] showed that circulating irisin levels were associated with BMI, HOMA-IR and fasting insulin levels. Finally, Löffler et al[13] showed that serum levels of irisin associated positively with HOMA-IR. In summary, a positive correlation was found between both irisin and preptin levels and insulin resistance in GDM cases. Interestingly, there was no significant change in preptin and irisin levels in patients who were given insulin therapy in GDM cases. These data show that there is no change in the synthesis and release of these two peptides with insulin administration. In addition, we thought that these two peptides were regulated independently from each other, since there was no significant relationship between serum and cord blood levels.

Conclusions

With this study, serum and cord blood preptin and irisin levels were investigated for the first time in patients with GDM and the correlation between insulin resistance and these peptides was revealed. Although maternal serum preptin and irisin concentrations were not associated with cord blood irisin and preptin levels in GDM subjects, presence of strong positive correlation between these peptides and insülin resistance was remarkable. Since the main function of cord blood irisin and preptin on fetal growth and metabolism has not been specified yet, further clinical studies are needed to clarify their role in fetal energy homeostasis during pregnancy and metabolic disorders.

Conflict of Interest

The Authors declare that they have no conflict of interests.

Informed Consent

Infromed consent was received from all participants.

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