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ORIGINAL ARTICLE

Comprehensive evaluation of irisin levels in fetomaternal circulation of pregnant women with obesity or gestational diabetes mellitus

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Abstract

Aim To evaluate maternal and cord blood irisin levels in pregnant women with gestational diabetes mellitus (GDM) and in obese pregnant women without GDM.

Methods The study included 109 patients, with 34 patients in the GDM group, 40 in the obese non-GDM group, and 35 in the control group. Maternal serum irisin levels at the time of delivery were measured by an enzyme-linked immunosorbent assay kit. The correlation of serum irisin levels with metabolic parameters and anthropometric measurements was analyzed.

Results There were significant differences between the study groups in terms of cord arterial, cord venous, and maternal serum irisin levels ($P < 0.001$, $P < 0.01$, $P < 0.001$, respectively). Cord arterial, cord venous, and maternal serum irisin levels were higher in the obese group compared to the control ($P < 0.01$, $P < 0.01$, $P < 0.01$, respectively) and the GDM group ($P < 0.001$, $P < 0.001$, $P < 0.001$, respectively).

Conclusion Elevation in irisin levels of women who have pregnancies complicated with obesity may be explained as part of the compensation mechanism against disturbed metabolic functions. Pregnant individuals with GDM have lower serum irisin levels in comparison to healthy pregnant women. In this regard, it is possible that the measurement of serum irisin levels may be utilized in the future for prediction, prevention, and treatment of GDM.

Keywords Gestational diabetes mellitus · Irisin · Obesity · Pregnancy

Introduction

Irisin, a recently discovered regulator of metabolic functions, plays roles in exercise-induced energy expenditure and the transformation of white adipose tissue to brown adipose tissue [1]. An adipokine consisting of 112 amino acid residues, its molecular weight is 12,587 kDa. Irisin is proteolytically processed from the product of the fibronectin type III domain containing 5 (FNDC5) gene in response to the activation of peroxisome proliferator-activated receptor γ (PPARγ) co-activator-1α (PGC-1α) [2, 3]. Previous animal studies showed that irisin can improve glucose tolerance in obese and pre-diabetic mice [2]. Clinical studies have found that circulating levels of irisin are lower in patients with type 2 diabetes mellitus (T2DM) and that obese patients have lower levels of FNDC5, the irisin's precursor [1, 4]. Paradoxically, patients with metabolic syndrome have been found to have higher levels of circulating irisin. It has been suggested that these patients might have developed resistance or tolerance against irisin [1, 5, 6].

The pathogenesis of GDM is not yet fully understood. Nevertheless, T2DM and GDM share common risk factors, and these two diseases are quite probably related to each other [7]. Some recent studies have found significantly lower irisin levels in T2DM patients compared to controls. Studies indicate a positive correlation between irisin levels

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and the well-known markers of insulin resistance in patients who have not been diagnosed with T2DM, suggesting a possible association of T2DM development with low irisin levels [8, 9]. Considering these results, the relationship between GDM and irisin levels has become an interesting subject of research [10, 11].

Obesity is a growing public health concern for the general population and for pregnant women, and the relationship between obesity and irisin has also been studied. After the discovery of irisin as a thermogenic agent, it has been thought to act to reduce the fat mass in an organism [3]. Stengel et al. found a positive correlation between body mass index (BMI) and irisin levels [12]. Our literature review has not yielded any study that examined irisin levels in obese pregnant women without GDM. In this context, the aim of the present study was to analyze serum irisin concentrations in pregnant women with GDM and in obese pregnant women without GDM, and additionally, to examine the association of maternal serum and fetal cord blood irisin levels in these patient groups with various indicators of impaired glucose tolerance and insulin level.

Materials and methods

Study design

This study was performed at the Obstetrics and Gynecology Department of Dumlupınar University Kutahya Evliya Celebi Training and Research Hospital, a tertiary care center affiliated with the Dumlupınar University School of Medicine, between September 2015 and July 2016. In all, 109 pregnant women were included in the study, 34 in the GDM group, 40 in the obese non-GDM group, and 35 in the control group. Participants in all groups were recruited from among pregnant women who presented to and delivered their babies in the department. To circumvent the metabolic effects of normal delivery, only patients who delivered via Cesarean section were included in the study. All pregnant women included in the study were screened for GDM with a 50-g glucose challenge test (GCT) at 24–28 weeks of gestation. The 50-g GCT was performed regardless of the time of day or any previous meals. Those who had a serum glucose level at the 60th minute of GCT ≥ 7.8 mmol/l (140 mg/dl) underwent an oral glucose tolerance test (OGTT) with 100-g glucose in order to diagnose GDM. Patients who had at least two of the following abnormal results above cutoff values in OGTT were diagnosed with GDM: fasting ≥ 5.3 mmol/l (95 mg/dl); 1 h, ≥ 10.0 mmol/l (180 mg/dl); 2 h, ≥ 8.6 mmol/l (155 mg/dl); and 3 h, ≥ 7.8 mmol/l (140 mg/dl) [13].

The control subjects had normal responses to GCT. The obese patient group had a body mass index (BMI) over 30 kg/m^2 and was not diagnosed with GDM. The control group consisted of healthy women with a BMI below 30 kg/m^2 and who underwent an elective cesarean section due to a previous cesarean section. Exclusion criteria were pre-term birth, multiple pregnancy, preexisting glucose intolerance or diabetes mellitus, acute or chronic inflammation, hypertension, pre-eclampsia, and smoking. The study was performed in accordance with the Declaration of Helsinki. Ethical committee approval was received from the local Human Research Ethics Committee (issue number: 2015-KAEK-86/10). Written informed consent was obtained from all volunteers.

Blood sample collection and biochemical analyses

All patients provided a venous blood sample just prior to the cesarean section operation, and during the operation, venous and arterial cord blood samples were obtained. The maternal fasting venous blood samples and cord arterial and cord venous samples were collected into aK3E 15% aprotinin 250 KIU vacuum tube (REF 361017, BD Vacutainer®, BD-Plymouth, UK) for biochemical analyses and into a dipotassium (K2) ethylene diamine tetra-acetic acid (EDTA) vacuum tube (BD Vacutainer®, BD-Plymouth, UK) for HbA1c measurements. Blood samples were centrifuged at 1500×*g* for 15 min within 1 h after collection to obtain serum samples. These samples were aliquoted into polystyrene tubes, and aliquots were stored at − 80 °C until the analysis time for irisin. The investigator executing the biochemical analyses was blinded to the randomization.

Irisin levels were measured in the umbilical cord arterial blood, umbilical cord venous blood, and maternal venous blood samples. Serum irisin levels were measured using commercial enzyme-linked immunosorbent assay (ELISA) kits (Cusabio Biotech Co., Ltd., Wuhan, Hubei Province, China; catalog number: CSB-EQ027943HU) on a microplate reader (BMG Labtech Spectrostar Nano, GmbH, Ortenberg, Germany), according to the manufacturer's protocol. Irisin levels were expressed as ng/ml.

After the blood samples were collected, fasting insulin (FI), fasting blood glucose (FBG), and HbA1c levels were measured immediately without storage. In healthy subjects, the reference range of insulin was accepted as 13.1–159.7 pmol/l. Insulin levels were measured based on the two-site immune-enzymatic (sandwich) chemiluminescent immunoassay method on a Beckman Coulter UniCel®DxI 800 immunoassay system (Beckman Coulter, Miami, FL, USA). Insulin levels were expressed as pmol/l. FBG levels were measured based on the hexokinase method on a Beckman Coulter AU680 instrument (Beckman Coulter, Miami, FL, USA), using the manufacturer's original reagents. Glucose levels were expressed as mmol/l. The measurement of HbA1c was performed based on the high-pressure liquid chromatography (HPLC) method on a Tosoh G8 HPLC Analyzer (Tosoh Bioscience, Inc., San Francisco, CA). HbA1c levels were expressed as NGSP (%) values. Insulin resistance was

calculated according to the homeostasis model assessment index (HOMA-IR) as follows: fasting glucose (mmol/l) × fasting insulin (pmol/l) / 405 [14].

Statistical analysis

Statistical analyses were performed using GraphPad Prism version 6.05 (GraphPadSoftware, Inc., CA, USA). All data sets were tested for normality using the Shapiro-Wilk test. Normally distributed data were expressed as mean ± standard deviation (SD). Non-normally distributed data were expressed as median and interquartile range (IQRs). Either parametric or non-parametric statistical tests were used depending on the distribution characteristics of the data. The differences among the multiple groups were analyzed with the one-way ANOVA or Kruskal-Wallis test. Differences between two groups were analyzed with the Holm-Sidak or Dunn's post hoc test. Correlation analyses were performed using Spearman's correlation test, since the data were not normally distributed. A P value < 0.05 was considered statistically significant.

Results

Demographic and clinical characteristics of the subjects are presented in Table 1. Differences among study groups for demographic and clinical parameters are also represented in Table 1. Differences among study groups for cord arterial, cord venous, and maternal serum irisin levels are presented in Table 2. Significant differences were found among the groups for cord arterial, cord venous, and maternal serum irisin levels ($P < 0.001$, $P < 0.01$, $P < 0.001$, respectively). Cord arterial, cord venous, and maternal serum irisin levels were higher in the obese group compared to the control ($P < 0.01$, $P < 0.01$, $P < 0.01$, respectively) and the GDM group ($P < 0.001$, $P < 0.001$, $P < 0.001$, respectively). However, cord arterial, cord venous, and maternal serum irisin levels were lower in the GDM group compared to the controls ($P < 0.05$, $P < 0.05$, $P < 0.01$, respectively).

Taking all study subjects as a whole, the relationships between maternal serum irisin levels and clinical and laboratory parameters are presented in Fig. 1. The Spearman's correlation analysis revealed that maternal serum irisin levels showed a significant positive correlation with BMI ($r = 0.252$, $P = 0.009$). On the other hand, the maternal serum irisin level was negatively correlated with newborn weight ($r = -0.244$, $P = 0.01$), FBG ($r = -0.202$, $P = 0.03$), FI ($r = -0.331$, $P < 0.001$), HbA1c ($r = -0.367$, $P < 0.001$), and HOMA-IR ($r = -0.318$, $P < 0.001$). Taking all study subjects as a whole, the relationships between fetal cord arterial and venous irisin levels and clinical and laboratory parameters are presented in Fig. 2. The Spearman's correlation analysis revealed that cord

Table 1 Differences among the study groups for demographic and clinical parameters

Parameters	Control ($n = 35$)	Obese ($n = 40$)	GDM ($n = 34$)	P
Maternal age (years)	28.4 ± 4.7	29.7 ± 5.7	30.6 ± 5.8	0.259
BMI (kg/m^2)	26.85 (25.28–28.15)	34.70[a] (32.40–42.20)	33.0[a] (28.85–38)	< 0.001*
Gestational age at delivery (week)	38.0 (37.0–39.0)	39.0 (37.0–40.0)	38.0 (37.0–39.0)	0.281
Newborn head circumference (cm)	34.0 (33.0–36.0)	35.5[a] (35.0–36.0)	35.0 (34.0–36.0)	0.01*
Newborn height (cm)	48.5 (48.0–50.0)	50.0[a] (48.0–51.0)	50.5[a] (50.0–51.0)	< 0.001*
Newborn weight (gram)	3065 (2903–3200)	3400[a] (3100–3730)	3495[a] (3198–3838)	< 0.001*
Fasting blood glucose (mmol/l)	4.2 (3.7–5.2)	4.6 (4.2–5.2)	5.3[ab] (4.8–6.1)	< 0.001*
Fasting insulin (pmol/l)	36.1 (29.1–90.2)	43.0 (27.0–75.0)	103.4[ab] (59.0–227.7)	< 0.001*
HbA1c (%)	5.1 (4.8–5.4)	5.3 (4.9–5.7)	5.7[a] (5.2–6.0)	0.001*
HOMA-IR	1.1 (0.6–2.9)	1.3 (0.8–2.5)	3.4[ab] (1.8–8.1)	< 0.001*

GDM, gestational diabetes mellitus; *BMI*, body mass index. Data are presented as median ± standard deviation (SD) or median and interquartile ranges (IQRs) depending on the distribution of data. P shows the differences among multiple groups (Kruskal-Wallis test or one-way ANOVA test depending on the distribution of data). $P^a < 0.05$, compared to the control group; $P^b < 0.05$, compared to the obese group (Holm-Sidak or Dunn's post hoc test). A P value < 0.05 was considered statistically significant

Table 2 Differences among study groups for cord arterial, cord venous, and maternal serum irisin levels

	Control ($n = 35$)	Obese ($n = 40$)	GDM ($n = 35$)	*P*
Cord arterial	260.8 (235.3–320.7)	334.5[a] (261.6–406.5)	240.8[ab] (186.1–257.9)	*< 0.001**
Cord venous	272.7 (248.5–328.8)	347.8[a] (272.4–412.8)	253.9[ab] (193.9–264.1)	*< 0.001**
Maternal serum	290.1 (268.9–353.1)	369.3[a] (286.3–438.8)	271.7[ab] (242.5–286.1)	*< 0.001**

GDM, gestational diabetes mellitus. Data are presented as median ± standard deviation (SD) or median and interquartile ranges (IQRs) depending on the distribution of data. *P* shows the differences among multiple groups (Kruskal-Wallis test or one-way ANOVA test depending on the distribution of data). $P^a < 0.05$, compared to the control group; $P^b < 0.05$, compared to the obese group (Holm-Sidak or Dunn's post hoc test). A *P* value < 0.05 was considered statistically significant

arterial and cord venous irisin levels showed significant negative correlation with newborn height ($r = -0.280$, $P = 0.005$, $r = -0.234$, $P = 0.02$ respectively), whereas there was no significant correlation of fetal cord arterial and venous irisin levels with other anthropometric measurements of the infants.

Discussion

Our results indicated that irisin levels in the fetomaternal circulation were lower in pregnant women with GDM compared with the control group and higher in obese pregnant women with no GDM compared with both the control and GDM groups. Our literature review revealed that the present study is the first that compares irisin levels between pregnant women with GDM and obese pregnant women without GDM. We also examined umbilical cord arterial and venous irisin levels separately, giving us the opportunity to evaluate irisin levels in fetomaternal circulation in more detail compared to many other studies.

Although many studies have evaluated irisin levels in the circulation, it was not possible to determine an accurate normal range for serum [15]. Circulating irisin levels have been found to be associated with age, BMI, renal function, and fatty tissue mass. We observe in the results of recent studies that irisin levels vary over a wide range [16]. Researchers have

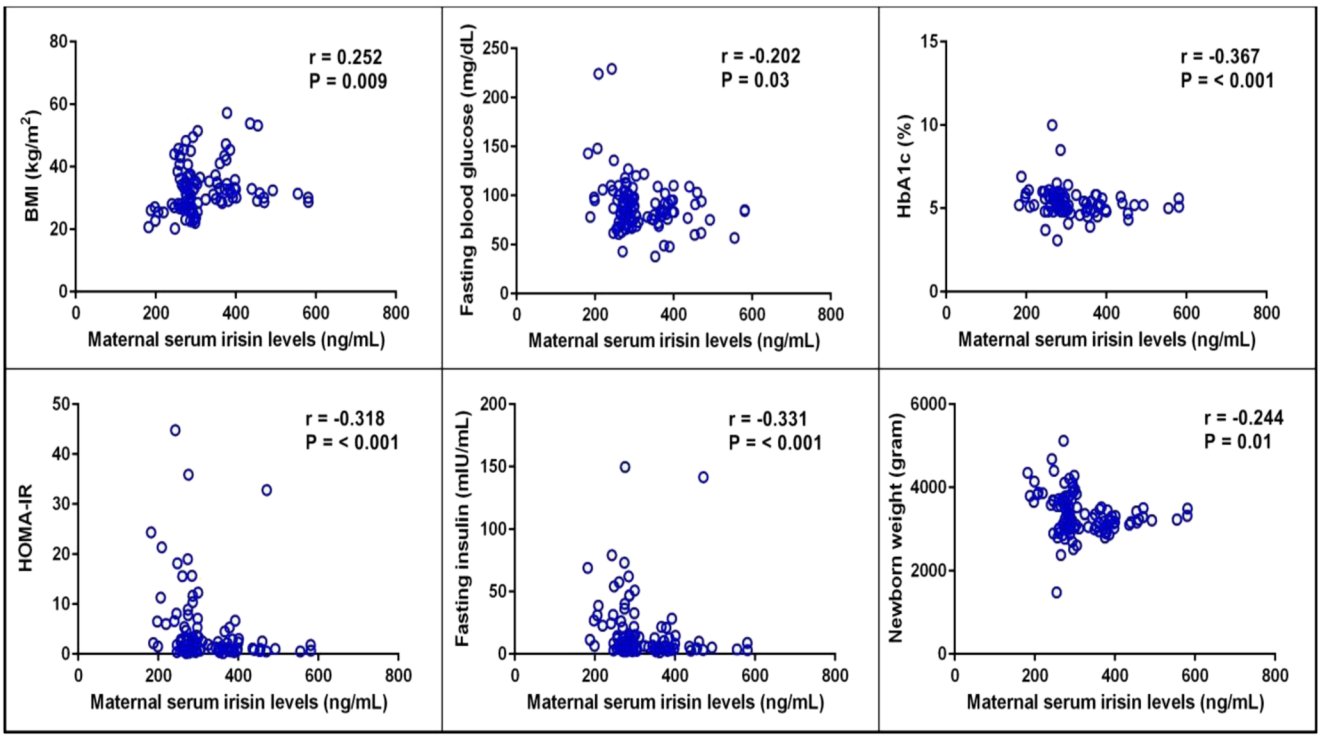

Fig. 1 Representative correlation graphs of variables showing relationships of maternal serum irisin levels with clinical characteristics of subjects in the whole study group. Data were tested using the Spearman's correlation analysis. A *P* value < 0.05 was considered statistically significant

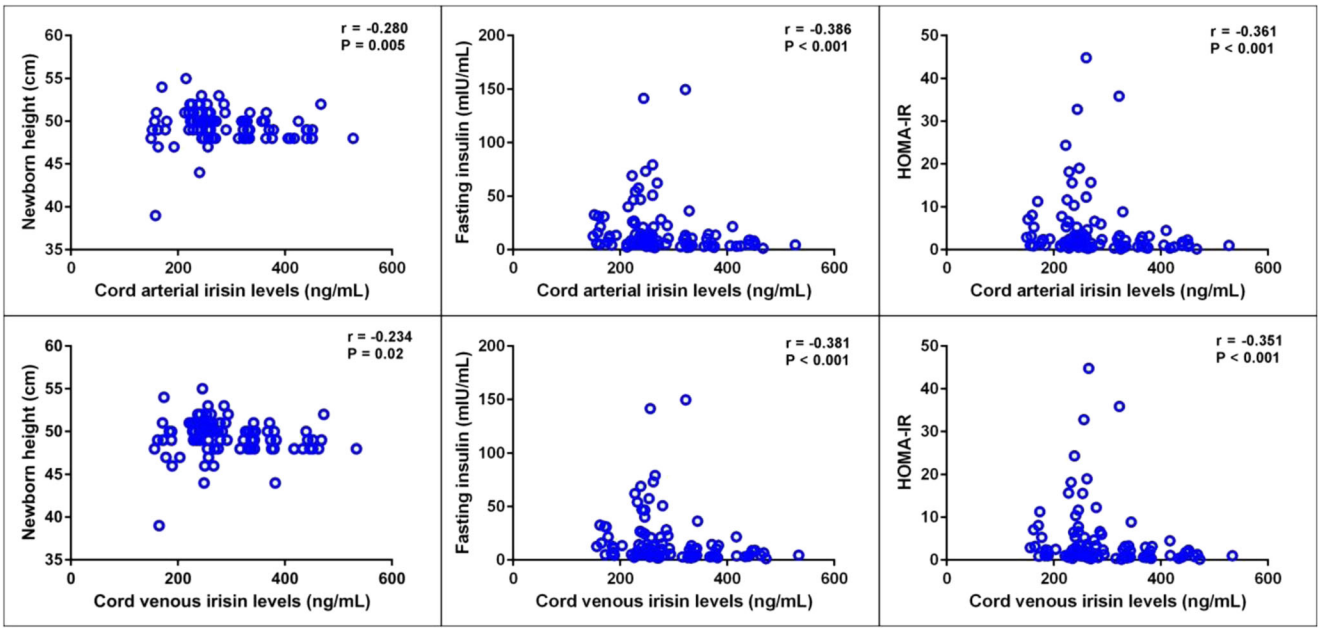

Fig. 2 Representative correlation graphs of variables showing relationships of cord arterial and venous irisin levels with clinical characteristics of subjects in the whole study group. Data were tested using the Spearman's correlation analysis. A P value < 0.05 was considered statistically significant

also determined various parameters showing a correlation with irisin levels. Choi et al. found a negative correlation between HbA1c and plasma irisin levels [9]. Stengel et al. reported that blood irisin levels showed a positive correlation with BMI and fasting insulin levels [12]; however, this finding has not been confirmed by all other studies [4]. According to our results, circulating irisin levels show a positive correlation with BMI and negative correlation with fasting blood glucose, fasting insulin, HbA1c, and HOMA-IR values, suggesting that irisin levels are elevated in obesity and that irisin levels decrease in the presence of GDM.

The relationship between irisin levels in the fetomaternal circulation and fetal anthropometric measurements has also been investigated. Various pathological conditions may result in fetal developmental disorders such as intrauterine growth restriction (IUGR) and fetal macrosomia. Additionally, these conditions have been associated with disturbances of fetal fatty tissue development, permanent changes in the regulation of hormonal functions, and a tendency towards the development of obesity and metabolic disorder in future life [17]. Çağlar et al. compared pregnant women with idiopathic IUGR to a control group in terms of maternal and umbilical cord irisin levels. They found significantly lower umbilical arterial irisin levels in pregnancies complicated with IUGR and found a positive correlation between umbilical artery irisin levels and fetal weight [18]. In their large-scale study, Joung et al. found significantly lower umbilical cord irisin levels in small for gestational age babies [1]. Authors of both studies stated that lower levels of irisin as a result of idiopathic IUGR might be associated with metabolic syndrome development in future life. Yuksel et al. did not find a correlation between maternal serum irisin levels and fetal weight in their study where they compared irisin levels of GDM and control groups [11]. In our study, we found a negative correlation between maternal serum irisin levels and neonatal weight. The reason may be that the GDM group had significantly lower irisin levels compared to other groups and significantly greater fetal weight compared to the control group. In our study, umbilical cord arterial and venous irisin levels did not show any correlation with fetal weight but showed a positive correlation with fetal height.

The role of irisin in obesity and glucose metabolism is not yet fully understood. While some researchers have observed increased levels of irisin in obesity [12, 19], others found the opposite [4, 20]. In one study, Stengel et al. compared irisin levels in anorexic and morbidly obese patients to controls, finding significantly higher irisin levels in obese patients compared to anorexic patients and controls. They also found a positive correlation between irisin levels and BMI, fatty tissue mass, and non-fatty tissue mass [12]. In a similar study, Pardo et al. analyzed irisin levels in patients with extreme BMI measurements, finding a positive correlation between irisin levels and body weight, BMI, and adipose tissue mass. They suggested that the most important determinant of plasma irisin levels was the fatty tissue mass [12, 21]. Increased irisin concentrations have been suggested as part of the compensation mechanism triggered in response to the metabolic disturbance associated with obesity [21]. Similar to the above results, we found that the serum irisin level was significantly higher in the obese patient group compared to both the GDM and control groups and that the levels were positively correlated with BMI. In their study including 97 overweight and obese

patients without diabetes mellitus, however, Huerta et al. found no significant association between fasting irisin levels and body weight, BMI, fatty tissue mass, or non-fatty tissue mass [22]. Thus, the relationship between obesity and irisin levels clearly remains controversial.

Prompt, accurate diagnosis of GDM, with its growing incidence rate, is of paramount significance in terms of the prevention of adverse outcomes that may occur in the mother and baby both during pregnancy and in the long term after pregnancy [23, 24]. Researchers have tried to find maternal and placental biomarkers to aid in predicting GDM before its development. These biomarkers have been defined from among various biological processes such as carbohydrate metabolism, insulin resistance, inflammation, and oxidative stress [25]. One of the first studies to investigate the relationship between GDM and irisin was conducted by Yuksel et al., and shortly afterward, Erol et al. put forward the proposition that irisin could be used in the early prediction of GDM [11, 26]. In their study, Yuksel et al. found that pregnant women with GDM had significantly lower levels of irisin compared to a control group [11]. Similarly, Kuzmicki et al. noted that irisin levels showed an increase in all pregnant women; however, this increase was significantly less in pregnant women with GDM compared to a control group [10]. In our study, serum irisin levels were significantly lower in pregnant women with GDM compared to both the control group and the obese non-GDM group. In contrast to our results and the general literature findings, Sanchis-Gomar et al. did not find a significant difference between the groups in their study where they compared irisin levels of both a T2DM patient group and an obese group to those of a control group [27]. Erol et al. found that pregnant women who later developed GDM had lower irisin levels in the first trimester when compared to controls; however, in the second trimester, the researchers did not find a significant difference between the GDM and control groups [26]. This contradictory result may possibly be explained by differences in the study design, the duration of T2DM, ethnicity, and fetal gender. The difference in the assay methods used to measure irisin levels should also be taken into consideration [26]. Furthermore, the high level of inconsistency between irisin levels measured in different studies has raised doubts concerning the accuracy of commercial antibody kits [15].

The potential limitations of the current study include a relatively small sample size and the absence of a GDM group without obesity. However, this is the first study in the literature evaluating the irisin levels in obese and overweight pregnant women with GDM and obese pregnant women without GDM compared to non-obese control pregnant women.

Women who have their pregnancies complicated with GDM have lower serum irisin levels in comparison to healthy pregnant women. In this regard, it is possible that measurements of serum irisin levels may be utilized in the future for the prediction, prevention, and treatment of GDM. Obesity-related elevation in irisin levels may be explained as part of the compensation mechanism against disturbed metabolic functions. Nevertheless, we believe that future large-scale prospective follow-up studies are necessary for the standardization of irisin measurements and also to clarify contradictory results.

Compliance with ethical standards

The study was performed in accordance with the Declaration of Helsinki. Ethical committee approval was received from the local Human Research Ethics Committee (issue number: 2015-KAEK-86/10). Written informed consent was obtained from all volunteers.

Conflict of interest The authors declare that they have no conflict of interest.

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