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The association of oxidative stress with serum irisin and betatrophin in pregnant women with gestational diabetes mellitus

ABSTRACT

Background. Irisin and betatrophin are polypeptide hormones implicated in glucose metabolism and insulin resistance (IR). Gestational diabetes mellitus (GDM) is accompanied by oxidative stress (OS) and the association between circulating irisin and betatrophin levels and GDM is controversial. The present study aimed to investigate the association of second-trimester irisin, betatrophin concentrations and their correlations between serum OS markers in GDM patients.

Methods. The study included 45 GDM patients and 45-age matched pregnant women as controls. Serum fasting glucose, HOMA-IR, ischemia modified albumin (IMA), total oxidative stress (TOS), total antioxidant status (TAS), oxidative stress index (OSI), irisin and betatrophin were measured.

Results. Serum irisin levels were decreased and TOS and OSI levels were found to be increased in the patient group. No significant difference was found with respect to serum betatrophin and IMA levels between study groups. A correlation analysis revealed no correlation between serum irisin and other assessed variables.

Conclusions. Gestational diabetes mellitus is an OS condition in addition to being a metabolic disease. Although not correlated with OS, irisin but not betatrophin may be a useful biomarker to predict GDM. (Clin Diabet 2020; 9; 5: 328–334)

Key words: irisin, betatrophin, oxidative stress, gestational diabetes mellitus

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Introduction

Gestational diabetes mellitus (GDM) defined as an impaired glucose tolerance of varying severity with onset or first recognition during pregnancy that may result in increased negative maternal and fetal outcomes [1]. It affects about nearly 15–20% of all pregnancies. Despite the increased rates of GDM detection with negative perinatal outcomes, the pathophysiologic mechanisms underlying GDM are still not fully understood. Recent studies suggest that oxidative stress (OS) and several polypeptide hormones apart from insulin could affect glucose metabolism and low-grade inflammation [2–4].

Irisin is a fragment of a cell membrane protein that is cleaved from the fibronectin type III domain-containing 5 (FNDC5) in skeletal muscles. Being a novel adipokine and myokine, it involves in exercise, total body energy expenditure and thermogenesis and contributes to the regulation of glucose and lipid metabolism in skeletal muscle and adipose tissue by improving insulin sensitivity [5]. Lower levels of irisin in DM patients supports the idea that irisin could be a protective response of organism to early glucose impairments by taking a crucial role in pancreatic β-cell function. Nevertheless, to date, there are only a paucity of data exists on irisin and human pregnancy including GDM [6, 7]. Since irisin could potentially counteract

impaired glucose control seen in GDM by improving β-cell function, our rationale was to investigate this polypeptide hormone and its potential associations with other metabolic markers and OS in GDM.

Betatrophin (also known as lipasin, Hepatocellular Carcinoma-Associated Gene TD26 or ANGPTL8) is a stress-response protein and has been introduced as a novel adipokine/hepatokine that down-regulates expression of adipocyte triglyceride lipase, improves glucose tolerance and promotes pancreatic β-cell proliferation [8]. Unfortunately accumulating data on betatrophin regulation in humans is partly limited to patients with adult obesity, fatty liver, diabetes mellitus (DM) and peripheral artery disease [9–12]. However, regulation of betatrophin as well as its association with irisin and other markers of OS have not been elucidated yet.

Oxidative stress is a major culprit in the pathogenesis of GDM. Enhanced oxidation products such as protein carbonyl, glutathione peroxidase and paraoxonase in GDM patients and reduced antioxidant capacity suggest that OS is a key factor in the development and progression of GDM [13]. It is believed that insulin resistance (IR) and glucose tolerance are strictly linked with OS levels and this leads to subclinical inflammation and altered biochemical pathways resulting in GDM-associated negative outcomes among pregnant women [14]. OS is a feature of normal pregnancy and partially produced in the placenta, and is heightened in pathological pregnancies including GDM. Although elevated levels of OS markers such as advanced glycated end products (AGEs), nitrotyrosine, malondialdehyde (MDA), and oxidized low-density lipoproteins (Ox-LDL) have been shown to be promising biomarkers for GDM, there are still debates on other markers including ischemia modified albumin (IMA) and total oxidant status (TOS) [2, 3, 15, 16].

Since GDM is regarded as an OS-related disorder and prediabetic condition with an enormous IR and inadequate insulin compensation, we hypothesized that betatrophin levels may be increased in women with GDM and these levels may be correlated with OS markers and circulating irisin levels.

Methods

Study design

This cross-sectional study was conducted in the Obstetrics and Gynecology department of Canakkale Onsekiz Mart University (COMU) Training and Research Hospital. Ethical board approval was obtained from COMU Faculty of Medicine Ethical Committee. Informed consent was provided by all study participants.

Subjects

From the population of 352 pregnant women routinely tested for GDM with a 75 g 2-hour oral glucose tolerance test (OGTT) between 24th and 28th weeks of gestation, 45 patients with GDM and 45 women with normal glucose tolerance (NGT), matched for age, gestational age and body mass index (BMI) were recruited for this study. GDM was diagnosed according to the criteria of The International Association of Diabetes and Pregnancy Study Groups on the basis of one or more of the following threshold glucose levels: fasting $\geq$ 92 mg/dL, 1 h $\geq$ 180 mg/dL and 2 h $\geq$ 153 mg/dL [17]. Pregnant women with conditions including obesity, multiple pregnancies, pre-existing glucose intolerance, vascular disease, having acute or chronic liver or renal disease, polycystic ovary disease, preeclampsia and acute or chronic inflammation were excluded from the current study. Maternal pregnancy characteristics including maternal age, BMI, smoking status, gestational weeks at sampling, history of spontaneous abortion, first-degree relative with diabetes and history of accompanying chronic disease were collected and recorded for each subject.

Biochemical analyses

After an overnight fasting, venous blood samples were obtained from each subject to assess study parameters on the day of OGTT screening. All samples were centrifuged within 30 min at 3000 rpm for 15 min to separate serum. Serum specimens were aliquoted and stored for analysis at –80°C until the biochemical estimation of irisin, betatrophin, TOS, TAS, and IMA. Insulin resistance was estimated by homeostasis model of assessment insulin resistance (HOMA-IR) as suggested by Matthews et al. [18] using serum glucose and insulin levels (HOMA-IR = fasting plasma insulin [mU/mL] × fasting plasma glucose [mg/dL]/405).

Measurement of TOS, TAS and IMA

Serum TAS and TOS levels were measured with spectrophotometric kits (Rel Assay Diagnostics, Gaziantep, Turkey) according to the method previously described by Jansen and Ruskovska [19]. The results for TAS and TOS are expressed as mmol Trolox equivalent/L and μmol H2O2 equivalent/L, respectively. IMA measurements were performed according to the colorimetric method described by Bar-Or et al. [20]. Results were reported in absorbance (ABSU) units.

Determination of the OSI and IMAR

The ratio percentage of TOS to TAS was used to calculate the OSI. Specifically, OSI (arbitrary unit)

Table 1. Demographic and laboratory characteristics of gestational diabetes mellitus (GDM) patients and controls

	GDM patients (n = 45)	Controls (n = 45)	P
Maternal age (years)	30.75 ± 4.99	28.17 ± 5.15	0.181
Gravidity [median (min-max)]	2 (1–5)	2 (1–5)	0.122
BMI at the time of OGTT [kg/m^2]	25.9 ± 3.9	24.0 ± 4.6	0.056
Fasting blood glucose [mg/dL]	94.48 ± 21.63	79.51 ± 6.76	0.001
OGTT-1st hour [mg/dL]	174.65 ± 32.47	128.35 ± 26.52	0.001
OGTT-2nd hour [mg/dL]	141.78 ± 30.53	106.17 ± 21.77	0.001
Insulin [μIU/mL]	14.35 ± 8.74	10.49 ± 7.00	0.023
HOMA-IR (%)	3.36 ± 2.19	2.07 ± 1.38	0.001
TSH [μIU/mL]	2.40 ± 1.65	2.44 ± 1.17	0.896
Total cholesterol [mg/dL]	217.9 ± 50.6	233.4 ± 37.5	0.102
Triglyceride [mg/dL]	223.0 ± 85.5	202.1 ± 64.6	0.195
Albumin [g/dL]	3.74 ± 0.23	3.90 ± 0.19	0.001
TOS [μmol H_2O_2 equivalent/L]	11.72 ± 2.48	7.19 ± 3.27	0.001
TAS [mmol Trolox equivalent/L]	0.71 ± 0.30	0.66 ± 0.32	0.501
OSI	21.83 ± 15.65	11.88 ± 9.32	0.002
IMA [ABSU]	0.44 ± 0.08	0.0047 ± 0.05	0.069
IMAR [ABSU/g]	0.12 ± 0.02	0.12 ± 0.01	0.595
Betatrophin [ng/mL]	218.1 ± 244.2	225.2 ± 200.7	0.881
Irisin [μg/mL]	2.62 ± 1.20	3.41 ± 2.22	0.038

¼ [(TOS, μmol H_2O_2 equivalent/L)/(TAS, mmol Trolox equivalent/L)].

After measuring serum albumin concentration with a standard commercial kit, IMAR levels were calculated as a ratio of IMA to albumin, and the results were expressed as ABSU/g (absolute unit/gram).

Irisin and betatrophin measurement

Serum irisin levels were measured using a commercially available enzyme-linked immunosorbent assay (ELISA) kit (Eastbiopharm, Hangzhou, China) and serum betatrophin concentration was determined using a commercially available human ELISA kit (USCN Life Science Inc., China) with both an intra- and an inter-assay coefficient of variation < 10%. Irisin and betatrophin results were expressed as μg/mL and ng/mL respectively.

Statistical analysis

Statistical analysis was performed using SPSS 19.0 (SPSS for Windows, SPSS, Chicago). Normally distributed data were expressed as mean ± standard deviation (SD) and non-normally distributed data were expressed as median and interquartile range. Depending on the distribution characteristics of the data parametric or non-parametric statistical tests were used. The differences among groups were analyzed using the Mann-Whitney U test. Bivariate correlations were assessed using standardized Pearson coefficients. Odds ratios (95% confidence intervals) of the independent clinical parameters were calculated with univariate and multiple logistic regression models to predict GDM. A multivariate logistic regression analysis was built by performing stepwise variable selection on those variables with a univariate P value < 0.25. The P values obtained of less than 0.05 was considered as statistically significant.

Results

The mean ages of the women in the GDM and control groups were 30.75 ± 4.99 and 28.17 ± 5.15 years respectively (P = 0.181). Clinical, metabolic and laboratory characteristics of patients in both groups are represented in Table 1. Blood glucose and OGTT measurements were found to be elevated in GDM women. HOMA-IR of GDM patients and controls were 3.36 ± 2.19 and 2.07 ± 1.38 respectively (P = 0.001). A statistically significant increase in terms of IMA and IMAR was observed in GDM patients (P = 0.001 and P = 0.002 respectively). Serum irisin levels were 2,62 ± 1,20 in GDM patients and 3.41 ± 2.22 in healthy pregnant women. This difference was found to be statistically significant between two groups (P = 0.038) (Fig. 1). Betatrophin levels were not found to be significant between study groups (P = 0.881).

Correlation analysis revealed a significant correlation between circulating irisin and IMAR (P = 0.012). No other significant correlations were found with other

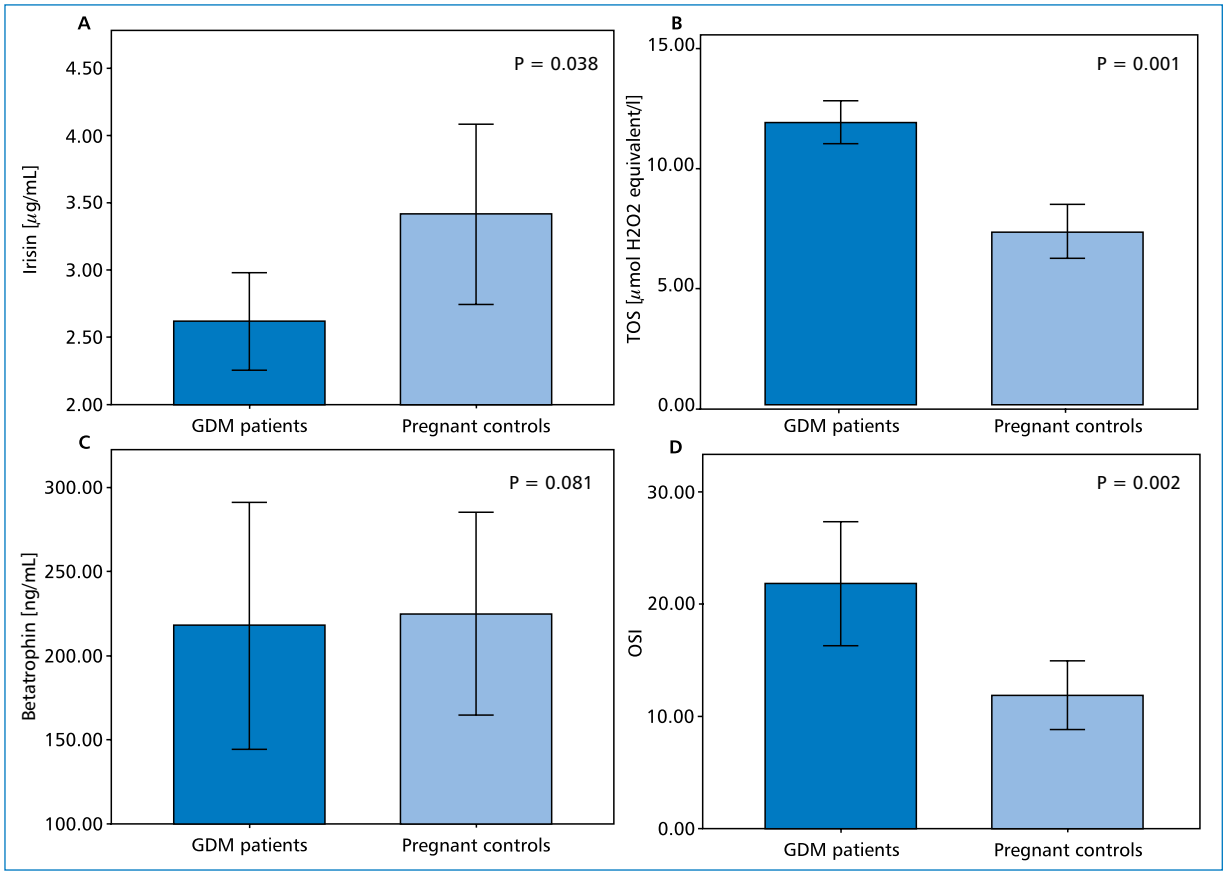

Figure 1. Box plot presentation of serum. **A** — irisin; **B** — TOS; **C** — betatrophin; **D** — OSI levels in study groups

Table 2. Correlations between serum TOS, OSI, irisin, and betatrophin with other demographic and laboratory parameters

	GDM patients (n = 45)							
	Betatrophin		Irisin		TOS		OSI	
	r	P	r	P	r	P	r	P
Maternal age (years)	–0.86	0.572	0.118	0.442	0.170	0.345	0.121	0.501
BMI at the time of OGTT	–0.195	0.200	0.079	0.604	0.156	0.386	0.094	0.601
HOMA-IR	0.022	0.886	0.147	0.335	0.092	0.299	0.162	0.368
TAS	0.013	0.945	–0.144	0.423	–0.117	0.517	–0.882	0.000
IMA	–0.144	0.346	0.209	0.168	–0.92	0.610	–0.087	0.629
IMAR	–0.101	0.510	0.371	0.012	0.120	0.507	0.094	0.603
OSI	–0.175	0.330	0.207	0.248	0.501	0.003		
TOS	–0.149	0.406	0.368	0.035				
Irisin	0.349	0.019						

study parameters in GDM patients (Table 2). A multivariable analysis revealed that TOS and OSI are significant predictors of GDM development (Table 3).

Discussion

Although the present study demonstrated that serum irisin levels were significantly lower in GDM patients, serum betatrophin levels were found to be similar in both study groups. Moreover, serum TOS levels and OSI were found to be increased in patients with GDM. Interestingly, no significant difference was observed between groups in respect to serum IMA levels and IMAR measurements.

Irisin is a recently discovered myokine that is encoded by the fibronectin type III domain-containing protein 5 (FNDC5) precursor gene. It has been sugges-

Table 3. Univariate and multivariate logistic regression analysis of study variables for the prediction of gestational diabetes mellitus

	Univariable analysis			Multivariable analysis		
	OR	95% CI	P value	OR	95% CI	P value
Age (years)	1.254	0.824–1.688	0.224			
Fasting glucose [mg/dL]	1.091	1.044–1.140	< 0.001	1.068	1.010–1.129	0.022
OGTT-1st hour [mg/dL]	1.053	1.031–1.075	< 0.001	1.039	1.013–1.065	0.002
OGTT-2nd hour [mg/dL]	1.058	1.032–1.084	< 0.001	1.043	1.013–1.075	0.005
Insulin [μIU/mL]	1.068	1.006–1.134	0.031			
HOMA-IR (%)	1.534	1.153–2.040	0.003			
Albumin [g/dL]	0.037	0.004–0.305	0.002			
TOS	1.827	1.277–2.614	0.001	1.762	1.236–2.512	0.002
TAS	0.798	0.168–3.780	0.776			
OSI	1.079	1.020–1.142	0.008			
IMA [ABSU]	0.742	0.134–2.944	0.083			
IMAR [ABSU/g]	0.841	0.234–3.981	0.591			
Betatrophin [ng/mL]	1.000	0.998–1.002	0.991			
Irisin [μg/mL]	0.992	0.892–1.102	0.878			

ted to be involved in mediating the favorable effects of exercise on the metabolism and its elevated levels induce browning of subcutaneous adipocytes and thermogenesis [21]. Moreover, accumulating evidence suggests that a decrease in circulating irisin levels may be linked with the development of impaired glucose metabolism and IR. Due to the vital impacts of irisin on body metabolism, several studies have been conducted to investigate the association between circulating irisin and metabolic disorders. In most of these studies, the variation of irisin levels was found to be affected by insulin metabolism. However, an association between irisin and IR, in particular during pregnancy, seems still controversial. In a study by Kuzmicki et al. [7] 130 women with GDM and 140 BMI-matched pregnant women with normal glucose tolerance were investigated. Mean irisin levels were found to be lower in patients with GDM compared to healthy pregnant women. Similarly, Yuksel et al. [6] reported that maternal serum irisin levels of patients with GDM were significantly lower compared with non-GDM controls. Contrary to these findings Ebert et al. [22] and Sancak et al. [23] demonstrated no significant difference in GDM patients. Therefore, the finding of lower levels of circulating irisin in the present study is noteworthy. Unfortunately, we didn't detect any correlation in GDM patients with respect to irisin and IR (measured as HOMA-IR). These discrepancies may be due to differences in the clinical characteristics of the subjects studied.

Betatrophin is a newly identified liver and adipose tissue-derived hormone with implications in the regulation of lipid metabolism, beta-cell replication and glucose homeostasis [24]. The scientific evidence linking betatrophin with obesity, peripheral artery disease and DM is enlarging, but data exploring the association between betatrophin status and GDM are still controversial [10, 25, 26]. In this regard, some studies reported higher betatrophin concentrations in GDM patients, while some studies showed the contrary [24, 27–30]. Wawrusiewicz-Kurylonek et al. [28] showed that circulating betatrophin levels are dramatically increased in pregnancy and are significantly elevated in GDM patients compared with healthy pregnants. Similarly, Pan et al. [31] found that betatrophin concentration was remarkably higher in patients with than without GDM. However, Huang et al. [27] demonstrated no significant difference between GDM and healthy pregnants with respect to circulating betatrophin levels. We also observed no significant difference between groups in terms of serum betatrophin levels.

Five oxidative stress parameters were analyzed in this study. But only TOS and OSI levels were found to be increased in GDM patients. Increased TOS levels and reduction in total TAS levels have been implicated in several disease states, such as DM, cancer and heart diseases [32–34]. But there are only a few studies in literature investigated the levels of TOS and TAS in GDM patients. Zhou et al. [35] demonstrated that total TOS and TAS levels were increased in GDM suggesting that increased OS and abnormalities in lipoproteins may be associated with the metabolic alterations in GDM. Usluoğulları et al. [36] not only reported elevated TOS and OSI levels but also decreased irisin levels in GDM patients. As being the first study to investigate the relation between serum

irisin levels and TOS, TAS, and OSI in patients with GDM, the authors demonstrated a strong correlation between TOS and irisin levels suggesting irisin as an OS marker and a metabolic protective hormone.

IMA is an "N-terminal modified" albumin which is generated immediately following ischemic conditions and IMAR is the percentage ratio of IMA to albumin that is used to eliminate the effect of reduced albumin concentrations. Studies showed that in certain conditions like cirrhosis and preeclampsia IMAR represents OS status more effectively [37, 38]. IMA was originally evaluated in patients with myocardial ischemia and later it has been identified to be helpful for evaluating patients with distinct disease conditions including type 2 DM, coronary ischemia, coronary bypass surgery, advanced cancer, systemic sclerosis, pulmonary embolism, liver cirrhosis, and metabolic syndrome [39–41]. Although, elevated IMA levels due to the physiologic OS state of pregnancy have been demonstrated previously, Ma et al. [2] was the first that evaluated IMA levels in GDM patients. The authors showed that IMA levels were elevated in GDM patients with a positive correlation with serum glucose levels. Furthermore, glycemic levels in GDM were correlated with concentrations of lipid peroxides and increased protein oxidation. In the present study, we did not find any significant difference between study groups in terms of IMA and IMAR. More importantly, there were no correlations between IMA and other maternal characteristics. This result can be interpreted as IMA was not influenced from other metabolic characteristics including IR and glucose metabolism.

A limitation of our study is the limited number of study participants. However, we must note that despite the relatively small sample sizes, the validity of our results is strengthened by the close matching of study groups including age, gestational weeks, gravidity and BMI, thus negating these parameters as confounders. Another limitation is the variety of physiological factors that can affect the levels of IMA in the body.

In conclusion, the present study confirmed lower levels of irisin and increased TOS and OSI as a marker of ongoing OS in GDM patients. However, the clinical significance of unaltered betatrophin levels demonstrated in this study remained unclear. Therefore, we believe that future large-scale prospective follow-up studies are essential for the standardization of irisin, betatrophin and OS measurements and also to clarify contradictory results.

Conflict of interest

The authors have no potential conflicts of interest or funding sources to declare.

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