

Advanced glycation end products and adipocytokines and oxidative stress in placental tissues of pregnant women with gestational diabetes mellitus

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Abstract. Correlation between expression levels of advanced glycation end products (AGEs) and adipocytokines and oxidative stress index malondialdehyde (MDA) in placental tissues of pregnant women with gestational diabetes mellitus (GDM) was investigated. Seventy-two cases of GDM pregnant women who received routine prenatal examination and gave birth in the Department of Obstetrics, Binzhou City Center Hospital from March 2016 to May 2017 were collected as the observation group. Another 80 cases of normal pregnant women who gave birth at the same time were selected as the control group. Enzyme linked immunosorbent assay (ELISA) was used to detect the expression levels of AGEs, visfatin, APN and IL-6 in the lysate of placental tissues. MDA levels were measured by thiobarbituric acid method. Correlation of expression levels of AGEs, visfatin, APN, IL-6 and MDA were analyzed. The expression level of MDA in placental tissues of the observation group was significantly higher than that of the control group ($t=16.44$, $P<0.001$). The correlation of expression levels between AGEs, adipocytokines and MDA in placental tissues of the two groups was analyzed, and it was found that the expression levels of AGEs, visfatin and IL-6 in the two groups were positively correlated with MDA. There was a significantly negative correlation between APN and MDA in the two groups. The incidence of cesarean section, neonatal hypoglycemia, fetal distress and macrosomia in the observation group was significantly higher than that in the control group ($P<0.05$). There was no significant difference in the incidence of membrane rupture and premature birth between the two groups ($P>0.05$). In

conclusion, the expression levels of AGEs, visfatin and IL-6 in placental tissues of GDM pregnant women are positively correlated with MDA. There is a significant negative correlation between APN and MDA, and they play an important role in the pathogenesis of GDM.

Introduction

Gestational diabetes mellitus (GDM) is a common metabolic complication (1), which refers to the occurrence of symptoms such as abnormal glucose tolerance or glucose intolerance in different degrees during pregnancy, posing a great threat to the health of pregnant women and the fetus (2). In recent years, the incidence of GDM has gradually increased (3). GDM is a high-risk pregnancy, which will cause adverse effects on mother and baby. Before the treatment, the preperinatal mortality is approximately 40%, and the maternal mortality is up to 27-30% (4,5). Placenta is an essential organ for babies' growth and development. During normal and pathological pregnancy, placenta can adapt to changes in intrauterine environment (6).

The AGEs-RAGE signaling pathway, formed by advanced glycation end product receptor (RAGE) and its ligands, advanced glycation end products (AGEs), is closely related to the occurrence and development of glucose metabolism disorders, and can activate inflammatory reactions and oxidative stress (7). The AGEs accumulation caused by persistent hyperglycemia during gestation is one of the main factors leading to abnormal fetal development (8). Visfatin, a newly discovered adipocytokine, is mainly secreted by visceral fat cells and is related to insulin secretion, glucose uptake and abnormal glucose tolerance (9). Interleukin-6 (IL-6), an important chronic inflammatory cytokine secreted by adipose tissue, is an adipocytokine and is associated with states of various insulin resistance (IR) in the body and can be released from the placenta (10). Adiponectin (APN) is a biologically active peptide hormone secreted by fat cells, which can be used to enhance insulin sensitivity, it is anti-inflammatory, and maintains the body's glucose metabolism balance (11). Studies have shown that inflammatory factors and adipokines are significantly associated with IR formation (12).

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Oxidative stress plays an important role in GDM (13). It is caused by an imbalance between the oxidant and the antioxidant (14). Oxidative stress is considered to be a causative factor in human pregnancy-related diseases, such as fetal death, pre-eclampsia, and intrauterine growth restriction (15). Malondialdehyde (MDA) is a product of lipid peroxidation and is produced by the degradation of phospholipids induced by reactive oxygen species (ROS) under pathogenic conditions (16). Changes in MDA levels can be used to reflect the degree of oxidative damage in the body (17). At present, there are few studies on the correlation between adipokines and oxidative stress in GDM.

In this study, the correlation between AGEs, visfatin, APN, IL-6 and MDA was investigated by detecting the expression levels of AGEs and adipocytokines (visfatin, APN, IL-6) in placental tissues of pregnant women with GDM, to further improve the diagnosis and treatment of GDM and provide a reference for the pathogenesis of GDM.

Patients and methods

Methods. Seventy-two cases of GDM pregnant women who underwent routine prenatal examination and delivery in the Department of Obstetrics, Binzhou City Center Hospital (Binzhou, China) from March 2016 to May 2017 were enrolled as the observation group. Glucose tolerance test (OGTT) (75 g) was performed at 24–28 weeks of gestation. The diagnosis was made according to the International Association of Diabetes and Pregnancy Study Groups (IADPSG) standard (18). The mean age was 28.76 ± 4.58 years, the pre-pregnancy body mass index was 23.17 ± 3.16 kg/m², and the mean gestational age was 38.82 ± 1.18 weeks; another 80 cases of normal pregnant women who were delivered at the same time were selected as the control group, with an average age of 27.99 ± 5.82 years, a pre-pregnancy body mass index of 22.86 ± 2.66 kg/m², and an average gestational age of 39.11 ± 1.03 weeks.

Inclusion criteria were: Patients with singleton pregnancy, with no previous heart, liver and kidney disease, chronic hypertension and diabetes, and no dietary restrictions, with complete clinical data, without any smoking, drinking or other harmful habits.

Exclusion criteria were: Patients taking drugs affecting blood glucose metabolism three months before pregnancy, with premature rupture of the membranes, with a recent history of infection, with family hereditary mental illness, and with inactive cooperation with inspections.

The study was approved by the Ethics Committee of Binzhou City Center Hospital. Patients who participated in this research had complete clinical data. The signed informed consents were obtained from the patients or the guardians.

Specimen collection. Within 4 h after delivery of the placenta, 3 samples of placental tissue in sterile state were obtained from the center of the placenta maternal surface, each approximately 1x1x1 cm in size; avoiding the bleeding, infarct and calcification area. Tissue was washed repeatedly with sterilized physiological saline, and gauze used to remove water. Specimens under aseptic condition were cut up, RIPA lysate (Shanghai Yisheng Biological Technology Co., Ltd.) was used for pyrolysis, and then were ground into homogenate,

centrifuged at $10,000 \times g$ for 15 min at 4°C, finally the supernatant was taken into the trace centrifuge tube, stored at -80°C for later use.

Detection method. The expression levels of AGEs, visfatin, APN and IL-6 in the placental tissue lysate were detected by enzyme-linked immunosorbent assay (ELISA), and the standard well, the sample well and the blank well (no samples and enzyme-labeled reagents were added, and the other steps were the same) were set, respectively. First, 50 μ l of standard sample was added accurately on the enzyme-labeled coated plate, 40 μ l of diluent was added in the sample well, then 10 μ l of sample to be tested was added. Plate membrane was used to seal the plate, and incubated at 37°C for 30 min. Then the plate membrane was peeled off, the liquid was discarded, dried, and each well was filled with scrubbing liquid, discarded after standing, this was repeated five times, and then patted dry. In addition to blank wells, 50 μ l of enzyme-labeled reagent was added to each well for incubation and washing. After that, 50 μ l of chromogenic agent A and 50 μ l of chromogenic agent B were added to each well, shaken gently, and developed at 37°C for 15 min in the dark. Then 50 μ l of stopping solution was added to each well to immediately terminate the reaction when the blue turned yellow. The measurement was carried out within 15 min after the addition of the stopping solution, the blank well was used to adjust to zero and the absorbance (OD value) of each well was measured at the wavelength of 450 nm. ELISA kits of AGEs were provided by Wuhan Mossak Biotechnology Co., Ltd., while ELISA kits of visfatin, APN and IL-6 were from Shanghai Jining Industry Co., Ltd. SK201 microplate reader was from Shenzhen Shengxinkang Technology Co., Ltd.

Level of MDA was measured by thiobarbituric acid method. Samples were taken and added with trichloroacetic acid and a small amount of quartz sand to grind, and then trichloroacetic acid was added to fully grind them. After centrifugation at $3,680 \times g$ for 10 min at 20°C, 2 ml of supernates (sample suspension buffer) were taken and added with 2 ml of 0.6% thiobarbituric acid, mixed and heated in a boiling water bath for 10 min, cooled, and 2 ml of distilled water was used to replace the extract as a control, and the OD value was measured at 532, 450 and 600 nm. The kit provided was by Nanjing Jiancheng Biological Engineering Co., Ltd and it was performed in strict accordance with the instructions.

Observational indicators. Expression levels of AGEs, adipocytokines and MDA in placental tissues of the two groups were detected, and differences between two groups were compared. Correlation between MDA and expression levels of AGEs, visfatin, APN and IL-6 was analyzed.

Statistical processing. SPSS 19.0 software system (IBM Corp., Armonk, NY, USA) was used for statistical analysis of experimental data. Enumeration data were expressed as [n (%)], and Chi-square test was used for comparison between groups. Measurement data were expressed as (mean \pm SD), and independent sample t-test was used for comparison between groups. Pearson's correlation coefficients were used to analyze the correlation of bivariate normal distribution data. $P < 0.05$ was considered to indicate a statistically significant difference.

Table I. Comparison of general clinical data between the two groups (mean \pm SD)/[n (%)].

Factors	Observation group (n=72)	Control group (n=80)	χ^2/t value	P-value
Age (years)	28.76 \pm 4.58	27.99 \pm 5.82	0.900	0.370
Body mass index before pregnancy (kg/m ²)	23.17 \pm 3.16	22.86 \pm 2.66	0.656	0.513
History of childbirth				
Yes	16 (22.2)	20 (25.0)		
No	56 (77.8)	60 (75.0)		
History of hypertension				
Yes	8 (11.1)	12 (15.0)		
No	64 (88.9)	68 (85.0)		
Ethnicity				
Han	67 (93.1)	71 (88.8)		
Rest	5 (6.9)	9 (11.2)		
Gestational age (weeks)	38.82 \pm 1.18	39.11 \pm 1.03	1.618	0.108
Systolic blood pressure (mmHg)	117.37 \pm 12.87	118.28 \pm 12.76	0.437	0.663
Diastolic blood pressure (mmHg)	75.89 \pm 7.96	76.08 \pm 7.57	0.151	0.880
Fasting blood-glucose (mmol/l)	6.76 \pm 0.85	5.22 \pm 0.67	12.47	<0.001

SD, standard deviation.

Table II. Comparison of expression levels of AGEs, visfatin, APN and IL-6 in placental tissues between the two groups (mean \pm SD).

Group	No. of cases	AGEs (ng/ml)	Visfatin (ng/ml)	APN (mg/l)	IL-6 (ng/ml)
Observation group (n=72)	72	54.27 \pm 18.28	0.46 \pm 0.23	0.70 \pm 0.09	1.44 \pm 0.58
Control group (n=80)	80	32.18 \pm 12.12	0.52 \pm 0.25	1.29 \pm 0.14	0.78 \pm 0.39
t value		8.861	1.534	30.53	8.305
P-value		<0.001	0.127	<0.001	<0.001

AGEs, advanced glycation end products; APN, Adiponectin; IL-6, Interleukin-6.

Results

Comparison of general clinical data. General clinical data of the two groups were collected. Observation and control group showed no significant difference in age, body mass index before pregnancy, history of childbirth, history of hypertension, ethnicity, gestational age, systolic blood pressure, diastolic blood pressure and other aspects ($P>0.05$), which were comparable. Fasting blood-glucose of observation group was significantly higher than that of control group ($P<0.05$) (Table I).

Expression levels of AGEs and adipocytokines in placental tissues of the two groups. Expression levels of AGEs and adipocytokines in placental tissues of observation and control group were detected. Results showed that the expression levels of AGEs and IL-6 in placental tissues of observation group were significantly higher than those of control group ($t=8.861$, 8.305 , $P<0.001$). Expression level of APN in placental tissues of observation group was significantly lower than that of control

Table III. Expression levels of MDA in placental tissues of the two groups (mean \pm SD)

Groups	No. of cases	MDA (ng/ml)
Observation group (n=72)	72	6.21 \pm 1.03
Control group (n=80)	80	3.87 \pm 0.71
t value		16.44
P-value		<0.001

group, and difference was statistically significant ($t=30.53$, $P<0.001$). There was no significant difference in expression of visfatin between the two groups ($P>0.05$) (Table II).

Expression levels of MDA in placental tissues of the two groups. The expression level of oxidative stress MDA in placental tissues of observation and control group was detected, and

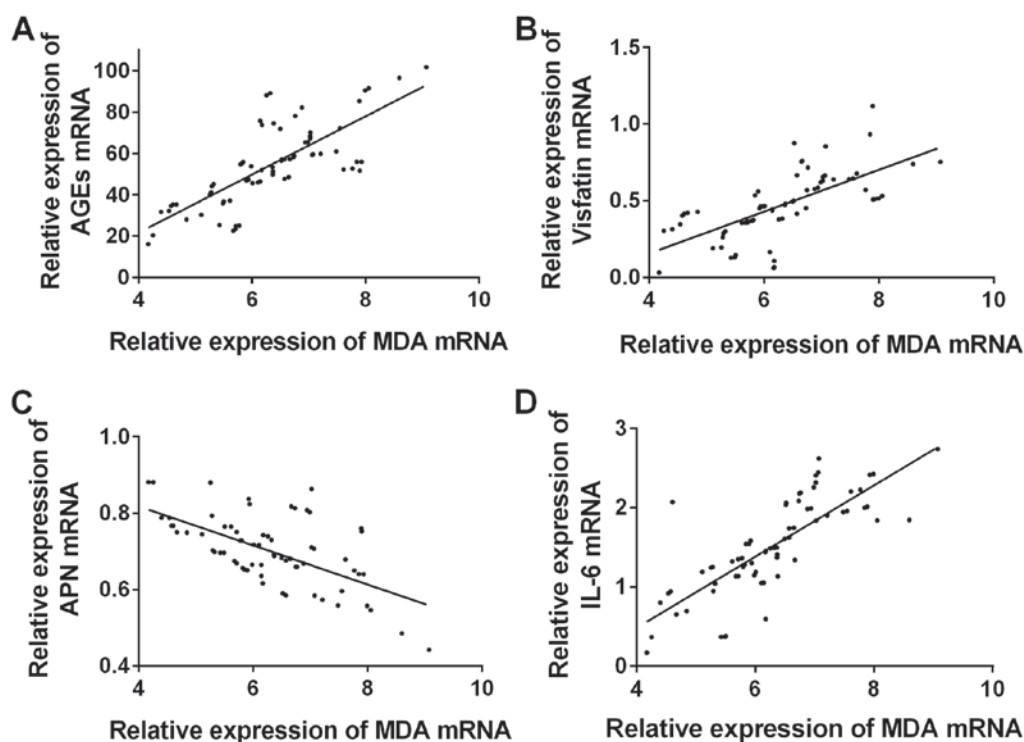


Figure 1. Pearson's correlation analysis of expression levels of AGEs, fat cytokines and MDA in the observation group showed that expression levels of (A) AGEs, (B) visfatin and (D) IL-6 were positively correlated with MDA ($r=0.757, 0.454, 0.792, P<0.001$). There was a significantly negative correlation between (C) APN and MDA in the two groups ($r=-0.602, P<0.001$).

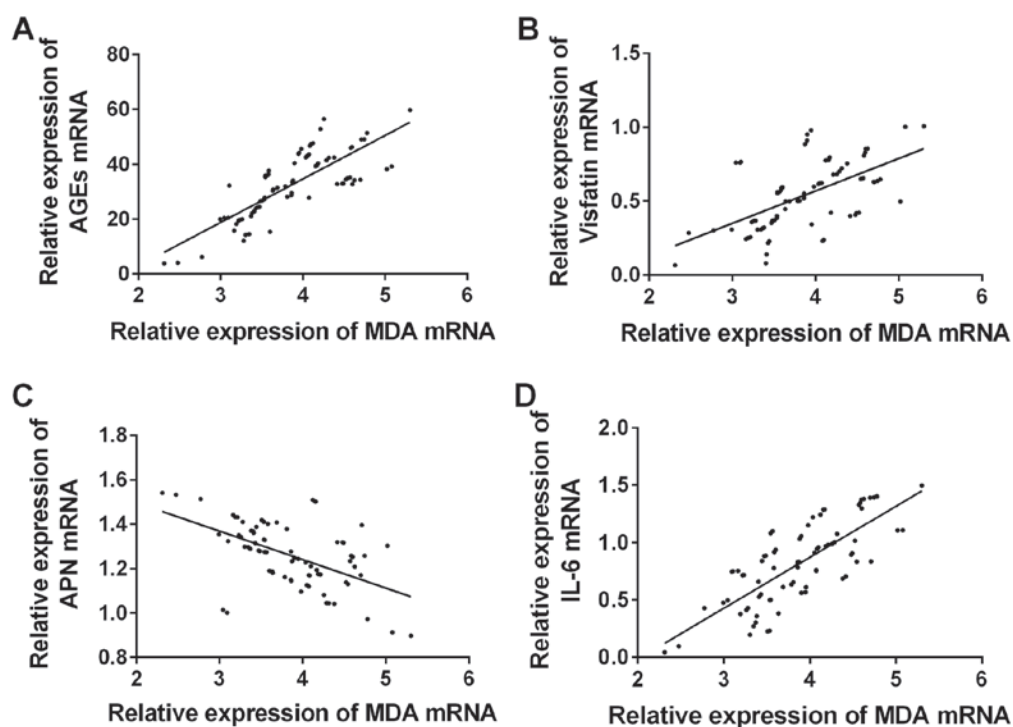


Figure 2. Pearson's correlation analysis of expression levels of AGEs, fat cytokines and MDA in the control group showed that the expression levels of (A) AGEs, (B) visfatin and (D) IL-6 were positively correlated with MDA ($r=0.794, 0.573, 0.763, P<0.001$). There was a significantly negative correlation between (C) APN and MDA in the two groups ($r=-0.544, P<0.001$).

results showed that the expression level of MDA in placental tissues of observation group was significantly higher than that of control group, and difference was statistically significant ($t=16.44, P<0.001$) (Table III).

Correlation analysis between AGEs, adipocytokines and expression of MDA. As shown in Figs. 1 and 2, the correlation between AGEs, adipocytokines and expression of MDA in placental tissues of the two groups was analyzed. The

Table IV. Correlation analysis between AGEs, visfatin, APN, IL-6 and expression of MDA.

Groups	AGEs		Visfatin		APN		IL-6	
	r	P-value	r	P-value	r	P-value	r	P-value
Observation (n=72)	0.757	<0.001	0.454	<0.001	-0.602	<0.001	0.792	<0.001
Control (n=80)	0.794	<0.001	0.573	<0.001	-0.544	<0.001	0.763	<0.001

Table V. Comparison of pregnancy outcomes between the two groups [n (%)].

Group	Cesarean section	Premature rupture of membranes	Premature birth	Neonatal hypoglycemia	Fetal distress	Macrosomia
Observation group (n=72)	34 (47.2)	8 (11.1)	18 (25.0)	9 (12.5)	6 (8.3)	14 (19.4)
Control group (n=80)	13 (16.3)	6 (7.5)	15 (18.6)	2 (2.5)	1 (1.3)	5 (6.3)
χ^2 value	17.020	0.591	0.871	5.645	4.328	6.032
P-value	<0.001	0.442	0.351	0.018	0.038	0.014

expression levels of AGEs, visfatin and IL-6 in the two groups were positively correlated with MDA. There was a significant negative correlation between APN and MDA in the two groups (Table IV).

Comparison of pregnancy outcomes between the two groups.

There was no neonatal malformation or perinatal death in the two groups. The incidence of cesarean section, neonatal hypoglycemia, fetal distress and macrosomia in the observation group was significantly higher than that in the control group ($P<0.05$). There was no significant difference in the incidence of membrane rupture and preterm birth between the two groups ($P>0.05$) (Table V).

Discussion

GDM not only leads to metabolic disorders in pregnant women, but may also lead to various early neonatal diseases (19). When the balance between the body's oxidative defense and free radical generation is broken, the target tissue will be damaged, thus forming oxidative stress (20). The function of tissue cells in GDM patients will be affected by the peroxidation state, and the function of islet β cells is most severely affected, so it is extremely easy to cause cell damage or apoptosis (21).

AGEs is a stable covalent compound produced by non-enzymatic glycation of proteins, lipids or nucleic acids in long-term hyperglycemia (22). AGEs can promote intracellular signal transduction and mediate diabetic renal dysfunction (23). Visfatin promotes the formation of fat, which is highly expressed in visceral adipose tissues (24), and can also upregulate the production of pro-inflammatory cytokines by monocytes (25). APN is a plasma protein (26), which can promote the proliferation of mesangial cells in high-glucose environment, delay their apoptosis, reduce cell damage, and have a protective effect on cells (27). IL-6 is overexpressed in obesity and inflammation (28). It has been reported that the increased level of IL-6 in the placenta of

GDM patients is caused by oxidative stress and inflammatory changes caused by hyperglycemia (24). MDA is one of the most reliable indicators of oxidative stress, and the increase of MDA level in diabetic patients is caused by the peroxidative decomposition of phospholipids caused by free oxygen radicals (29).

The expression levels of AGEs and adipocytokines in placental tissues of parturients in the observation group and the control group were detected. The results showed that the expression levels of AGEs and IL-6 in placental tissues of the observation group were significantly higher than those of the control group. The expression level of APN in placental tissues of the observation group was significantly lower than that of the control group. There was no significant difference in expression of visfatin in placental tissues between the two groups ($P>0.05$). It indicates that AGEs and IL-6 are highly expressed in placental tissues of GDM parturients, which is consistent with the studies of Voinov (30), and Wang *et al* (31). In this study, the expression of APN in placental tissues of GDM patients was low, indicating that there was abnormal regulation of adipokines in placenta. Studies have shown that compared with pregnant women with normal glucose tolerance, the expression of APN mRNA in GDM group was significantly decreased, and the expression change of APN in placental tissues was related to the expression of peroxisome proliferator activated receptor (PPAR- γ) and IL-6 (32). Relevant literature shows that the expression of visfatin in the female placental tissues of GDM was significantly higher than that in the normal control group, and the serum lipid concentration was positively correlated with the expression of visfatin in the placenta (33), and there are reports that the relative expression of visfatin mRNA in the placental tissues showed no statistically significant difference between the GDM group and the normal control group (34), and the results of this study are similar. It has been reported that GDM in pregnant women presents increased circulating oxidative stress hyperglycemia induction and decreased antioxidant

enzymes (35,36), suggesting that increased oxidative stress may have adverse effects on mother and fetus (37). In the present study, the expression level of MDA in placental tissues of the observation group and the control group was detected, and the results showed that the expression level of MDA in placental tissues of the observation group was significantly higher than that of the control group. In addition, studies have shown that MDA is highly expressed in the serum of pregnant women with GDM (16). This study showed that the expression levels of AGEs, visfatin and IL-6 in placental tissues of the two groups were positively correlated with MDA. There was a significantly negative correlation between APN and MDA in the two groups. The results suggested that AGEs, visfatin, IL-6 and APN might be related to oxidative stress in pregnant women with GDM. Bansal *et al* (38) indicated that AGEs and MDA in serum in type 2 diabetes mellitus patients with vascular complications were significantly positively correlated. Studies have reported that adipokines leptin and resistin are positively correlated with MDA in maternal blood of GDM pregnant women, and APN and oxidative stress are antagonistic to each other (39). However, whether there is interaction in placental tissues or not remains to be confirmed by further studies. There was no neonatal malformation or perinatal death in the two groups. The incidence of cesarean section, neonatal hypoglycemia, fetal distress and macrosomia in the observation group was significantly higher than that in the control group ($P < 0.05$). There was no significant difference in the incidence of membrane abruption and premature birth between the two groups ($P > 0.05$). The results of Dutta *et al* (40) showed that oxidative stress was associated with cell cycle arrest and fetal membrane oxidative injury, which jointly determined adverse pregnancy outcomes and were important factors for premature rupture of membranes and spontaneous premature birth. Studies on the relationship between AGE level and perinatal outcome in pregnant women with GDM have shown that high expression of AGEs is a risk factor for abnormal perinatal outcome in GDM (30). However, whether the AGEs, adipocytokines and oxidative stress levels can be used as important indicators to predict the pregnancy outcome with GDM requires further studies by expanding the number of samples.

This investigation studied the correlation between AGEs, adipocytokines and oxidative stress in pregnant women with GDM, but the specific mechanism still needs to be further studied to provide a clearer reference for the pathogenesis, clinical diagnosis and treatment of GDM.

In conclusion, the expression levels of AGEs, visfatin and IL-6 in placental tissues of GDM pregnant women were positively correlated with MDA. APN and MDA showed a significant negative correlation, which together played an important role in the pathogenesis of GDM.

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Availability of data and materials

The datasets used and/or analyzed during the present study are available from the corresponding author on reasonable request.

Authors' contributions

HL analyzed and interpreted the patients' data. AD was responsible for ELISA and thiobarbituric acid method. XL helped with statistical analysis. HL wrote the manuscript. All the authors read and approved the final manuscript.

Ethics approval and consent to participate

The study was approved by the Ethics Committee of Binzhou City Center Hospital (Binzhou, China). Patients who participated in this research had complete clinical data. The signed informed consents were obtained from the patients or the guardians.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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