Expression and correlation of Chemerin and FABP4 in peripheral blood of gestational diabetes mellitus patients

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Abstract. Expression and correlation of Chemerin and fatty acid-binding protein 4 (FABP4) in peripheral blood of gestational diabetes mellitus (GDM) patients were investigated. Sixty patients with GDM from March 2018 to March 2019 in the People's Hospital of Zhangqiu Area were selected as the study group (SG) and another 50 healthy pregnant women corresponding to their age and pregnancy were selected as the control group (CG). Enzyme linked immunosorbent assay (ELISA) was used to detect the expression of Chemerin and FABP4 in serum. Receiver operating characteristic (ROC) curve was used to evaluate the diagnostic value of Chemerin and FABP4 in peripheral blood for GDM patients. Pearson's correlation coefficient was used to analyze the correlation between Chemerin and FABP4 and the correlation between Chemerin and inflammatory factors such as interleukin-6 (IL-6) and tumor necrosis factor-α (TNF-α). Expression of Chemerin and FABP4 in peripheral blood of GDM patients were significantly higher than those in CG. The AUC of GDM patients diagnosed with Chemerin and FABP4 in peripheral blood was 0.820 and 0.814, while the AUC of GDM patients diagnosed with Chemerin combined with FABP4 in peripheral blood was 0.904. Expression of inflammatory factors IL-6 and TNF-α in the SG were significantly higher than those in the CG. Chemerin in the SG was positively correlated with FABP4 and positively correlated with inflammatory factors IL-6 and TNF-α. Patients with advanced age (≥35 years), family history of diabetes, hyperlipidemia, high pre-pregnancy BMI, high fasting blood glucose, high Chemerin and high FABP4 expression have high risk of GDM. In conclusion, Chemerin and FABP4 were upregulated in the peripheral blood of GDM patients. There was a positive correlation between the two and a positive correlation with the inflammatory factors IL-6 and TNF-α.

Introduction

Gestational diabetes mellitus (GDM) is a temporary diabetes mellitus with glucose intolerance during pregnancy. The difference between GDM and diabetes mellitus is sex specificity and temporality, while insulin resistance (IR) is a similar feature between GDM and diabetes mellitus (1,2). According to statistics, GDM accounts for ~2-6% of the total pregnancies in Europe and nearly half of GDM patients are highly likely to develop diabetes within 10 years (3). In recent years, the methods of early diagnosis and treatment of GDM have been continuously optimized, but early GDM may still lead to poor pregnancy outcomes (4). The pathophysiological mechanism of GDM involves chronic low-grade inflammation, insulin secretion deficiency and abnormal glucose and lipid metabolism caused by obesity (5-7). Therefore, we can explore new early diagnostic tools and potential therapeutic targets for GDM from three angles of improving chronic inflammatory response, increasing insulin sensitivity and maintaining glucose and lipid metabolism balance, which is of great significance for improving pregnancy outcomes of GDM patients.

Chemerin is an inflammatory adipocyte factor and chemoattractant protein secreted by adipocytes. Chemerin has regulatory functions on inflammatory state, fat formation and glycolipid homeostasis and is closely related to IR (8-10). Studies have shown that high levels of Chemerin are associated with poor prognosis of preeclampsia, polycystic ovary syndrome, GDM and other pregnancy diseases (11-13). In the studies of Yang *et al* (14), serum Chemerin level was upregulated in GDM patients. The higher the Chemerin level of GDM patients in early pregnancy, the greater the risk of GDM development. It suggested that Chemerin can be used as a predictive marker of GDM development risk. The fatty acid-binding protein (FABP) family is a group of small molecular proteins that act as fatty acid transporters in cells, while FABP4

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plays a key role in lipid metabolism as a member of FABP family (15). Studies have shown that FABP4 can enhance insulin sensitivity and reduce atherosclerosis. Knockdown of FABP4 gene can reduce the expression of inflammation-driven macrophage receptor (16). Ning et al (17), reported that FABP4 was overexpressed in GDM patients and has a significant positive correlation with IR and inflammatory factor TNF-α, suggesting that FABP4 can be used as a new biomarker for GDM. Chemerin and FABP4 are both inflammatory adipocyte factors expressed in adipocytes, both of which are related to the development and progression of GDM (18).

At present, there are few reports on the expression and correlation of Chemerin and FABP4 in the peripheral blood of GDM patients. Therefore, we explored the diagnostic value and potential therapeutic methods of Chemerin and FABP4 in GDM patients by detecting the expression of Chemerin and FABP4 in the peripheral blood of GDM patients.

Patients and methods

Baseline data. Sixty patients with GDM admitted to the People's Hospital of Zhangqiu Area (Jinan, China) from March 2018 to March 2019 were selected as the SG and another 50 healthy pregnant women corresponding in age and pregnancy were selected as the CG. In the SG, the age was 20-35 years with an average age of 27.33±4.75 years. In the CG, the age was 20-35 years with an average age of 27.80±5.27 years. The study was approved by the Ethics Committee of the People's Hospital of Zhangqiu Area. The subjects and family members signed an informed consent form.

Inclusion and exclusion criteria. Inclusion criteria: Patients who met the standards formulated by the American Diabetes Association (19) in 2012. After 75 g glucose tolerance test at 24-28 weeks of gestation, GDM was diagnosed if any one of following was present: fasting blood glucose over 5.1 mmol/l, blood glucose over 10.0 mmol/l for 1 h, blood glucose over 8.5 mmol/l for 2 h. The age range was 20-35 years. The patient was informed and agreed to cooperate with the study.

Exclusion criteria: Patients with communication barrier or severe mental disorder; patients comorbid with malignant tumor or serious cardiac, lung, liver, kidney and other dysfunction; pregnant women; patients with hypertension or endocrine and metabolic diseases before pregnancy.

Detection methods. Elbow venous blood (5 ml) was extracted from subjects on an empty stomach in the morning and then placed in a vacuum tube without anticoagulant and centrifuged at 2,600 x g for 10 min at 4°C. The serum was stored in EP tube for later use and placed in a low temperature refrigerator at -75°C. The serum was taken from the freezer, placed it in a refrigerator at 4°C for dissolution, and then placed it at room temperature for complete dissolution. Enzyme linked immunosorbent assay (ELISA) (20) was used to detect the expression of Chemerin, FABP4, interleukin-6 (IL-6) and tumor necrosis factor-α (TNF-α) in serum. The tests were carried out in strict accordance with the specifications of human Chemerin ELISA kit, human FABP4 ELISA kit, human IL-6 ELISA kit and human TNF-α ELISA kit (Shanghai Zhenyu Biotechnology Co., Ltd.; CSB-E10398h, CSB-E12995h, E-EL-H0102km,

E-EL-H0109km). The sample well, standard sample well and blank well were set up. Sample (50 μl) to be tested was added to the sample well. The standard sample (50 μl) was added to the standard sample well. No reagent was added to blank well. Horseradish peroxidase labeled detection antibody (100 μl) was added to the sample well and the standard sample well, then the plate was sealed and incubated at 37°C for 60 min. The liquid was discarded, shaken off and repeatedly washed 5 times. The substrates A and B were fully mixed to volume of 1:1. Then (100 μl) of substrate mixed solution was added to each well. The plates were sealed and incubated at 37°C for 15 min. Terminal liquid (50 μl) was added to each well. The absorbance (OD value) at 450 nm of each well was read by a fully-automatic enzyme-labeled analyzer (M15; Shanghai Chenlian Biotechnology Development Co., Ltd.). The expression of Chemerin, FABP4, IL-6 and TNF-α were calculated.

Statistical analysis. SPSS 19.0 (IBM Corp.) statistical data software was used for statistical analysis. GraphPad Prism6 (GraphPad Software) was used to draw the data. Enumeration data was expressed by the number of samples/percentage [n(%)]. The Chi-square test was used for comparison of enumeration data between groups. The measurement data were expressed as mean number ± standard deviation (mean ± SD). The independent-sample t-test was used to compare the measurement data between groups. Receiver operating characteristic (ROC) curve was used to evaluate the diagnostic value of peripheral blood Chemerin and FABP4 in GDM patients. Pearson's correlation coefficient was used to analyze the correlation between Chemerin and FABP4 as well as the correlation with inflammatory factors IL-6 and TNF-α. Logistic multivariate regression analysis was used to analyze the independent risk factors affecting GDN. P<0.05 was considered statistically significant.

Results

Baseline data. There was no significant difference between the two groups in baseline data of height, gestational age, abdominal circumference, systolic blood pressure, diastolic blood pressure, postprandial insulin for 0.5 h, postprandial insulin for 1 h, postprandial insulin for 2 h, total cholesterol (P>0.05), but there was a significant difference in baseline data of age, diabetes history, hyperlipidemia, pre-pregnancy BMI, increase of body mass during pregnancy, fasting blood glucose, fasting insulin, IR index (HOMA-IR), Chemerin or FABP4 (P<0.05) (Table I).

Expression of Chemerin and FABP4 of patients in the two groups. Expression of Chemerin was 5.78±1.35 and 7.71±2.23 μg/l in CG and SG, respectively, while expression of FABP4 was 21.53±8.89 and 35.14±11.39 μg/l in CG and SG, respectively. Expression of Chemerin in CG was significantly lower than that in SG (P<0.001). The expression of FABP4 in CG was significantly lower than that in SG (P<0.001) (Fig. 1).

Diagnostic value of Chemerin and FABP4 in GDM patients. The ROC curve of peripheral blood of Chemerin in the diagnosis of GDM patients was plotted and it was found that the AUC of peripheral blood of Chemerin in the diagnosis of GDM patients was 0.820 (95% CI, 0.744-0.896), the cut-off

Table I. Comparison of baseline data of patients between the two groups [n(%), mean ± SD].

Category	CG (n=50)	SG (n=60)	χ^2/t value	P-value
Age/years			3.976	0.046
≥35	7 (14.00)	18 (28.33)		
<35	43 (86.00)	42 (71.67)		
Diabetes history			13.943	0.002
Yes	8 (16.00)	30 (50.00)		
No	42 (84.00)	30 (50.00)		
Hyperlipidemia			4.125	0.042
Yes	5 (10.00)	15 (25.00)		
No	45 (90.00)	45 (75.00)		
Height (cm)	161.54±5.23	162.01±5.12	0.637	0.526
Pre-pregnancy BMI (kg/m^2)			4.073	0.044
≥23	11 (26.00)	24 (35.00)		
<23	39 (74.00)	36 (65.00)		
Increase of body mass during pregnancy (kg)	13.52±4.26	15.61±4.53	2.475	0.015
Gestational age (week)	23.85±1.85	24.45±1.55	1.851	0.067
Abdominal circumference (cm)	99.98±6.36	101.87±6.65	1.514	0.133
Systolic blood pressure (mmHg)	114.12±9.06	115.59±8.99	0.851	0.397
Diastolic blood pressure (mmHg)	72.98±7.16	75.04±6.88	1.535	0.128
Fasting blood glucose (mmol/l)	4.58±0.35	6.13±0.89	11.580	<0.001
Fasting insulin (mU/l)	9.12±4.67	13.19±5.15	4.304	<0.001
Postprandial insulin for 0.5 h (mU/l)	71.39±37.85	67.88±24.05	0.590	0.557
Postprandial insulin for 1 h (mU/l)	90.87±34.58	83.81±23.66	1.266	0.208
Postprandial insulin for 2 h (mU/l)	70.27±22.64	80.85±36.09	1.798	0.075
HOMA-IR	6.42±1.81	22.35±13.88	8.053	<0.001
Total cholesterol (mmol/l)	5.92±1.43	6.03±1.28	0.426	0.671
Chemerin (μg/l)	5.78±1.35	7.71±2.23	5.354	<0.001
FABP4 (μg/l)	21.53±8.89	35.14±11.39	6.880	<0.001

FABP4, fatty acid-binding protein 4; SG, study group; CG, control group.

Table II. ROC parameters of Chemerin and FABP4 in diagnosis of GDM patients.

Grouping	AUC	95% CI	SE	Cut-off	Sensitivity (%)	Specificity (%)
Chemerin	0.820	0.744-0.896	0.039	6.78	73.33	76.00
FABP4	0.814	0.733-0.895	0.041	27.64	75.00	80.00
Chemerin + FABP4	0.904	0.837-0.952	0.029	0.71	80.00	96.00

FABP4, fatty acid-binding protein 4; GDM, gestational diabetes mellitus; ROC, receiver operating characteristic.

value was 6.78, the sensitivity was 73.33% and the specificity was 76.00%. AUC of peripheral blood FABP4 in the diagnosis of GDM patients was 0.814 (95% CI, 0.733-0.895), the cut-off value was 27.64, the sensitivity was 75.00% and the specificity was 80.00%. Then, the two single factors, Chemerin and FABP4, were used as independent variables to conduct binomial Logistic regression analysis. Logistic regression model was obtained: Logit (p) =-8.73+1.663 chemerin+27.574

FABP4. The AUC of the model for diagnosis of GDM patients was 0.904 (95% CI, 0.837-0.952), the cut-off value was 0.71, the sensitivity was 80.00% and the specificity was 96.00% (Fig. 2 and Table II).

Expression of inflammatory factors IL-6 and TNF-α of patients in the two groups and the correlation with Chemerin and FABP4. The expression of inflammatory factor IL-6 in
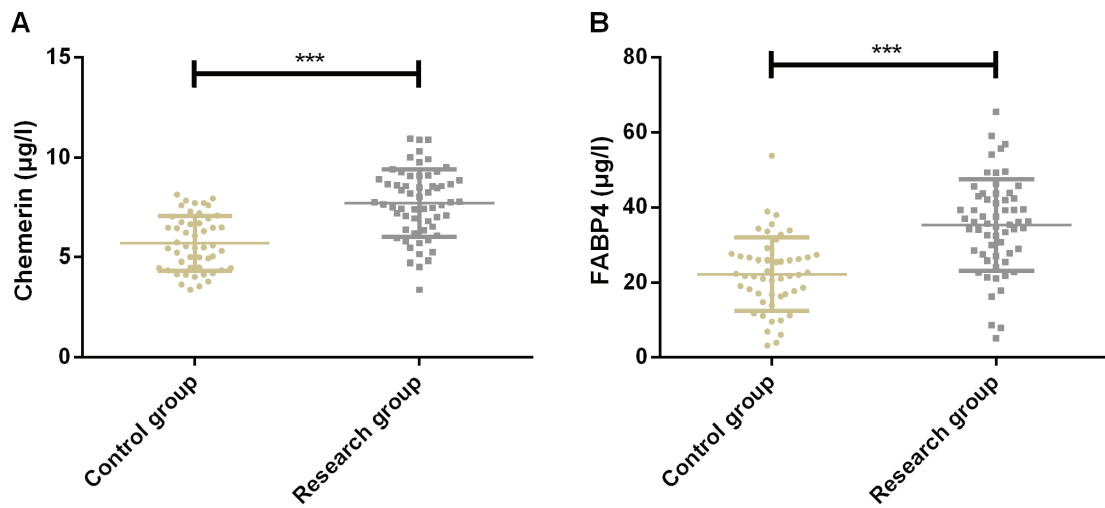
Figure 1. Expression results of Chemerin and FABP4 of patients in the two groups. (A) The expression of Chemorin in SG was significantly higher than that in CG. (B) The expression of FABP4 in SG was significantly higher than that in CG. ***P<0.001 compared with the control group. FABP4, fatty acid-binding protein 4; SG, study group; CG, control group.
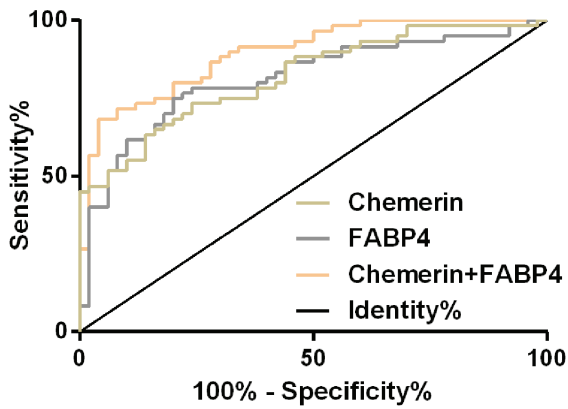

Figure 2. ROC curve of Chemerin and FABP4 in diagnosis of GDM patients. ROC, receiver operating characteristic; FABP4, fatty acid-binding protein 4; GDM, gestational diabetes mellitus.

Table III. Assignment of logistic multivariate regression analysis.

Factors	Variables	Assignment
Age	X1	<35=0, ≥35=1
Family history of diabetes	X2	No=0; Yes=1
Hyperlipidemia	X3	No=0; Yes=1
Pre-pregnancy BMI	X4	Continuous variables
Increase of body mass during pregnancy	X5	Continuous variables
Fasting blood glucose	X6	Continuous variables
Fasting insulin	X7	Continuous variables
HOMA-IR	X8	Continuous variables
Chemerin	X9	Continuous variables
FABP4	X10	Continuous variables

FABP4, fatty acid-binding protein 4.

CG and SG was 83.89±5.74 and 98.34±8.98, respectively. The expression of inflammatory factor TNF-α in CG and SG were 84.58±7.38 and 130.24±12.02, respectively. The expression of inflammatory factors IL-6 and TNF-α in CG was significantly lower than that in SG (P<0.001). Pearson correlation coefficient was used to analyze the correlation between chemerin, FABP4 and inflammatory factors IL-6, TNF-α. The results showed that chemerin and FABP4 were positively correlated with inflammatory factors IL-6 and TNF-α (r=0.658, P<0.001; r=0.672, P<0.001; r=0.648, P<0.001; r=0.649, P<0.001) (Fig. 3).

Multiple Logistic regression analysis of GDM. Multivariate Logistic regression analysis was conducted on the factors with differences. The results showed that age (P=0.002), diabetes history (P=0.007), hyperlipidemia (P=0.021), pre-pregnancy BMI (P=0.010), fasting blood glucose (P=0.002), Chemerin (P=0.004) and FABP4 (P=0.001) were independent risk factors for affecting GDM. Patients with advanced age (≥35 years), family history of diabetes, hyperlipidemia, high pre-pregnancy BMI, high fasting blood glucose, high

Chemerin and high FABP4 expression have increased risk of GDM (Tables III and IV).

Correlation analysis of Chemerin and FABP4. The correlation between Chemerin and FABP4 was analyzed by Pearson's correlation coefficient. The results showed that peripheral blood of Chemerin was positively correlated with FABP4 in SG (r=0.712, P<0.001) (Fig. 4).

Discussion

GDM is a heterogeneous multivariate pregnancy disease with complicated pathological mechanism. In addition to inflammatory reaction, IR and abnormality of lipid and glucose metabolism, GDM also involves DNA methylation and oxidative stress signal transduction that affect cardiac function (21). Statistics showed that the increase in the prevalence of GDM is global and 33.33% of GDM pregnant women will suffer from
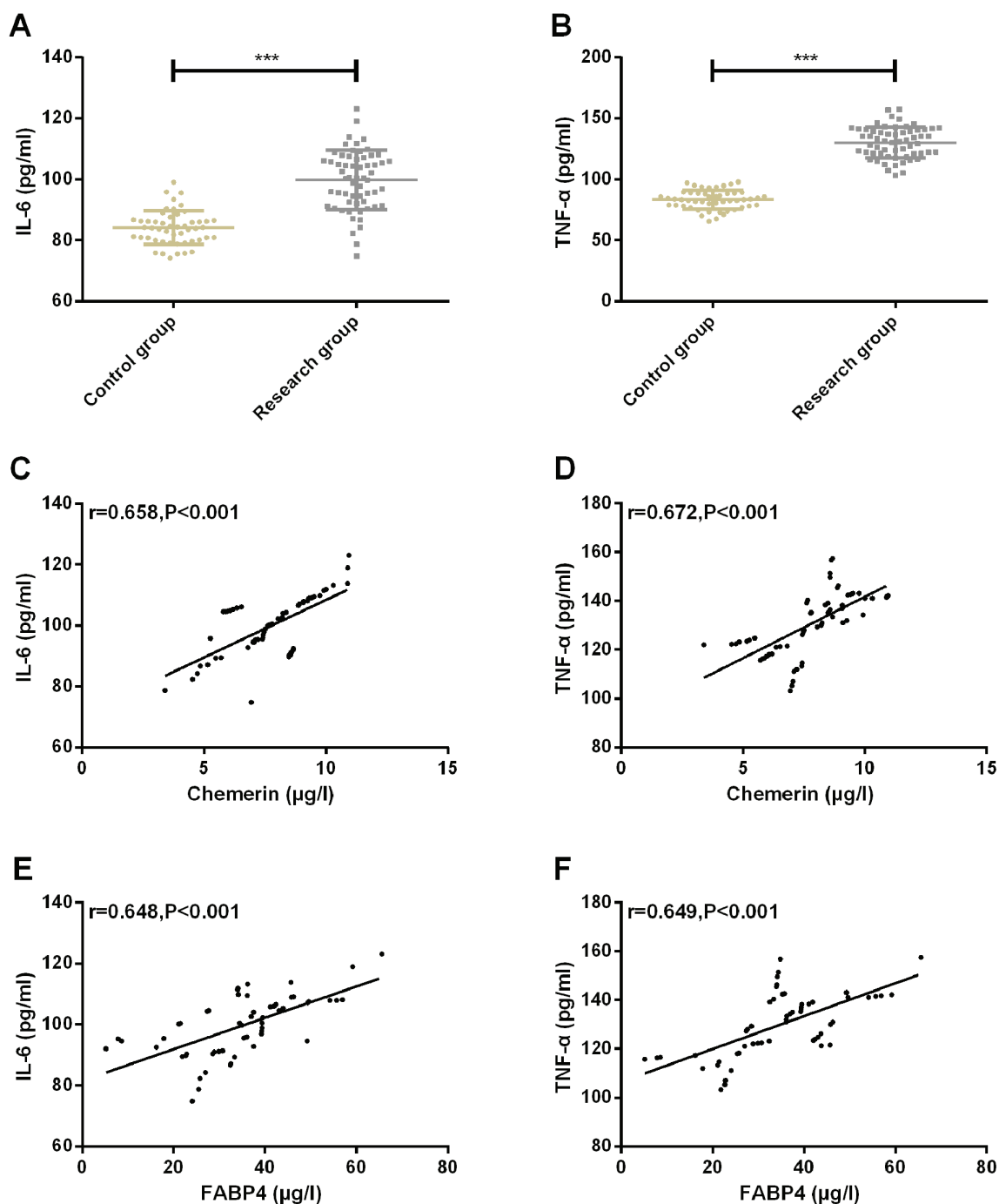
Figure 3. Expression of IL-6 and TNF-α of patients in two groups and their correlation results with Chemerin and FABP4. (A) The expression of inflammatory factor IL-6 in SG was significantly higher than that in CG. (B) The expression of inflammatory factor TNF-α in SG was significantly higher than that in CG. (C) Chemerin was positively correlated with inflammatory factor IL-6 (r=0.658, P<0.001). (D) Chemerin was positively correlated with inflammatory factor TNF-α (r=0.672, P<0.001). (E) FABP4 was positively correlated with inflammatory factor IL-6 (r=0.648, P<0.001). (F) FABP4 was positively correlated with inflammatory factor TNF-α (r=0.649, P<0.001). ***P<0.001 compared with the control group. FABP4, fatty acid-binding protein 4; SG, study group; CG, control group; IL-6, interleukin-6; TNF-α, tumor necrosis factor-α.

postpartum depression (22,23). In order to avoid the possible serious impact of GDM on the health of pregnant women and newborns, we advocate healthy diet and reasonable physical exercise for women during pregnancy. Some studies have shown that this has preventive effect on GDM (24).

In this study, the expression of peripheral blood of Chemerin and FABP4 in GDM patients was significantly upregulated compared with the CG. The AUC of peripheral blood of Chemerin and FABP4 for diagnosis of GDM patients was 0.820

and 0.814, while the AUC of peripheral blood of Chemerin combined with FABP4 for diagnosis of GDM patients was 0.904, indicating that peripheral blood of Chemerin combined with FABP4 has excellent diagnostic value for diagnosis of GDM patients and can be used as biomarker for prediction of GDM. In the study of Francis et al (25) on adipocyte factors and GDM risks, the concentrations of chemerin and FABP4 in GDM patients were significantly higher than those in CG and both were significantly positively correlated with GDM risks,

Table IV. Multiple Logistic regression analysis of GDM.

Variables	B	SE	Wals	P-value	OR	95% CI
Age	0.143	0.048	9.394	0.002	1.153	1.054-1.619
Family history of diabetes	0.579	0.192	7.040	0.007	1.784	1.165-2.751
Hyperlipidemia	0.174	0.080	5.001	0.021	1.897	1.003-1.343
Pre-pregnancy BMI	0.742	0.305	6.622	0.010	2.118	1.189-3.734
Increase of body mass during pregnancy	0.101	0.473	0.045	0.829	1.106	0.429-2.819
Fasting blood glucose	0.338	0.108	9.935	0.002	1.399	1.137-1.736
Fasting insulin	0.634	0.599	1.145	0.280	1.901	0.571-6.152
HOMA-IR	0.945	0.703	1.732	0.179	2.563	0.624-10.105
Chemerin	1.345	0.475	8.617	0.004	4.029	1.598-10.217
FABP4	1.612	0.471	11.658	0.001	5.005	1.942-12.618

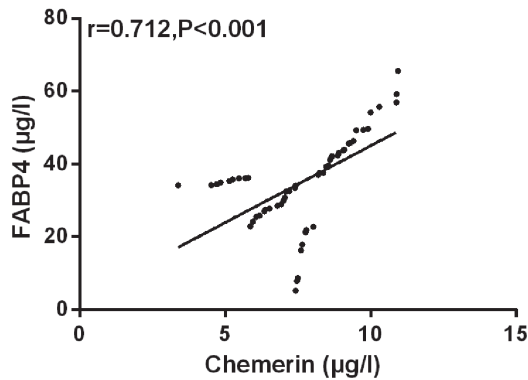FABP4, fatty acid-binding protein 4; GDM, gestational diabetes mellitus.

Figure 4. Chemerin is positively correlated with FABP4 (r=0.712, P<0.001). FABP4, fatty acid-binding protein 4.

indicating that Chemerin and FABP4 have certain diagnostic value for GDM and are important risk factors for GDM development. This is similar to the results of the present study. In the study of Zhang et al (26) on inflammation and metabolism of GDM patients in Inner Mongolia, the distribution frequency of inflammatory factors IL-6 and TNF-α in placenta in GDM women was significantly higher than that in healthy pregnant women and IL-6 was significantly correlated with GDM disease, suggesting that overexpression of these two inflammatory mediators may aggravate the progression of GDM disease by activating inflammatory cascade reaction in placenta. Other studies have shown that elevated levels of IL-6 and TNF-α in amniotic fluid of GDM patients may play an important role in the process of GDM (27). The results of this study on inflammatory factors showed that the expression of inflammatory factors IL-6 and TNF-α in SG was significantly higher than those in CG. Chemerin and FABP4 were significantly positively correlated with inflammatory factors IL-6 and TNF-α, suggesting that the high expression of Chemerin and FABP4 in inflammatory environment may be related to the development and progression of GDM. In studies of Feng et al (28) on risk factors of GDM, advanced age, hepatitis B virus, family history of diabetes, high BMI before pregnancy and a large increase of weight before 24 weeks of pregnancy may all increase the risk of GDM. In this study, the results of Logistic multivariate

regression analysis of affecting GDM showed that advanced age (≥35 years), family history of diabetes, hyperlipidemia, high pre-pregnancy BMI, high fasting blood glucose, high Chemerin and high FABP4 expression are risk factors of GDM patients. Among them, high Chemerin and high FABP4 expression have the greatest risk multiple, indicating that knockdown of Chemerin and FABP4 expression may reduce the onset risk of GDM patients. In the report of Chung et al (29), a CRISPR system of interfering with FABP4 expression was directionally transmitted to white adipocytes, which showed improvement effect on obesity, inflammation and IR. In studies of Josephrajan et al (30) on the secretion mechanism of FABP4, the main secretion of FABP4 is the selective secretion mediated by autophagy, suggesting inhibition of the secretion of FABP4 by autophagy inhibitor to reduce the influence of FABP4 expression on IR in GDM patients. Chemerin and FABP4 in SG have significant positive correlation, which indicated that Chemerin and FABP4 may play a synergistic role in GDM, but the specific regulatory mechanism needs to be further determined by cytological function research.

This study confirmed the positive correlation between Chemerin and FABP4, both of which are overexpressed in GDM patients and have positive correlation with inflammatory factors IL-6 and TNF-α.

In conclusion, Chemerin and FABP4 have satisfactory diagnostic value for GDM patients and inhibition of chemerin and FABP4 expression can be used as potential therapeutic targets for GDM patients.

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

XW, JL, DW and JJ led the conception and design of this study. XW, JL, DW, HZ and LK were responsible for the data collection and analysis. XW, JL and JJ were in charge of interpreting the data and drafting the manuscript. HZ and LK made revision from critical perspective for important intellectual content. The final version was read and adopted by all the authors.

Ethics approval and consent to participate

The study was approved by the Ethics Committee of the People's Hospital of Zhangqiu Area (Jinan, China). Signed informed consents were obtained from the patients and/or guardians.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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