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Correlation of TNF-a, TNFR1 and adiponectin levels with HOMA-IR in patients with gestational diabetes mellitus.

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Abstract

Objective: To investigate the correlation of serum Tumor Necrosis Factor α (TNF-α), Tumor Necrosis Factor Receptor 1 (TNFR1) and Adiponectin (ADP) with insulin resistance index (HOMA-IR) in patients with Gestational Diabetes Mellitus (GDM) and to analyze the relationship between the levels of TNF-a, TNFR1 as well as ADP during pregnancy period and adverse pregnancy outcomes as well as postpartum progression to type 2 diabetes mellitus (T2DM).

Method: A total of 240 pregnant women who received regular prenatal examination in our hospital from January 2017 to September 2017 were selected as the research objects, among whom 180 patients diagnosed with gestational diabetes mellitus were set as patient group with other 60 normal pregnant women as control group. The selected patients were examined on Fasting Plasma Glucose (FPG), Fasting Serum Insulin (FINS), Glycosylated Hemoglobin (HbAlc), Total Cholesterol (TC), Three Glycerol (TG), High Density Lipoprotein (HDL), Low Density Lipoprotein (LDL), TNF-a, TNFR1 and ADP with HOMA-IR calculated by formula, which was followed by the analysis on the correlations of HOMA-IR with various indexes, of pregnancy outcome with serum index and of postpartum progression to T2DM with serum index.

Results: Compared with the control group, the levels of FPG, FINS, HbAlc, LDL, HOMA-IR, TNF-a and TNFR1 were significantly increased while ADP obviously decreased in patient group. Multivariate Logistic regression analysis showed: in patient group, the levels of FPG, FINS, HbAlc, TG, HDL, LDL, TNF-a and TNFR1 showed a positive correlation with HOMA-IR. ADP showed a significant negative correlation with HOMA-IR. The adverse pregnancy outcome was positively correlated with HOMA-IR, TNF-a and TNFR1 while negatively correlated with ADP. The postpartum progression to T2DM was positively correlated with HOMA-IR, TNF-a and TNFR1 while negatively correlated with ADP.

Conclusion: In patients with gestational diabetes the levels of TNF-a and TNFR1 are relatively high and ADP level moderately low, which is closely related with insulin resistance.

Keywords: Gestational diabetes mellitus, TNF-a, TNFR 1, Adiponectin, Insulin resistance.

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Introduction

Gestational diabetes mellitus (GDM), as a common complication in perinatal period, refers to the condition that abnormal glucose metabolism or impaired glucose tolerance is first detected in the women during pregnancy and its endocrine changes are absolute or relative deficiency of insulin secretion, mainly glucose metabolism disorder [1]. In recent years, GDM has attracted more and more attention from scholars and its incidence accounts for 3-14% in worldwide pregnant women [2]. The main harmfulness of GDM is the increased risk of such adverse perinatal outcomes as abortion, gestational hypertension, preeclampsia, intrauterine growth retardation, macrosomia, neonatal hypoglycemia, hyperinsulinemia and postnatal development of type 2 diabetes, seriously affecting the health of mother and baby [3]. At present, it is generally believed that gestational diabetes mellitus is connected with the increase of insulin resistance (IR) with the pathogenesis similar to type 2 diabetes, but the specific etiology is not clear yet with any unified understanding, and adipokine is a research hotspot in recent years [4,5]. Adipokines including leptin, adiponectin (ADP) and visfatin, are mainly secreted by placenta and play an important role in insulin resistance during pregnancy, they, regulated and affected by various factors, will give rise to abnormal glucose metabolism when serious, finally resulting in gestational diabetes [6]. Among many factors, tumor necrosis

factor (TNF)-a plays an extremely important role in the development of insulin resistance [7]. However, there are few reports about whether the expression of TNF-a and its tumor necrosis factor receptor (TNFR) 1 in the endometrium is related to insulin resistance in GDM patients. This study is to observe the changes and correlation of TNF-a, TNFR1, ADP and insulin resistance index (HOMA-IR) in patients with GDM to provide a theoretical basis for the pathogenesis of gestational diabetes, which, contributed to estimating pregnancy outcome and transiting trend to T2DM, has positive significance for prevention and treatment of diabetes as well as for complications, now the detail is reported as follows.

Materials and Methods

General information

A total of 240 pregnant women who received regular prenatal examination in our hospital from January 2017 to September 2017 were enrolled in this study. They with the gestational age of 24-28 weeks were all voluntary to participate in the study. All participants were given oral glucose tolerance test at 24 weeks of gestation, and 180 of them diagnosed with gestational diabetes mellitus due to abnormal glucose tolerance were selected as patient group with the rest of 60 normal pregnant women as control group. The diagnosis of gestational diabetes mellitus was conducted with reference to the diagnostic criteria established by the American Diabetes Association in 2011. Exclusion criteria: (1) Patients suffered from other acute or chronic infectious diseases before pregnancy; (2) Patients suffered from diabetes or chronic hypertension before pregnancy; (3) Women had a multiple pregnancy. All subjects signed informed consents form and approved by the ethics committee of our hospital. There were no significant differences between the two groups in age, gestational week, height, weight, Body Mass Index (BMI) and blood pressure (Table 1).

Table 1. Comparison of general data between two groups.

Group	n	Age (y)	Gestational week	Height (cm)	Weight (Kg)	BMI (Kg/m^2)	Systolic pressure (mmHg)	Diastolic pressure (mmHg)
Patient group	180	26.72 ± 2.14	27.84 ± 2.32	159.31 ± 3.76	67.05 ± 5.24	26.85 ± 2.17	114.68 ± 3.54	76.54 ± 3.12
Control group	60	26.52 ± 1.98	27.38 ± 2.57	159.05 ± 3.35	67.13 ± 5.07	26.94 ± 2.31	117.96 ± 3.62	74.61 ± 2.95
t		1.05	1.14	0.59	0.97	1.27	0.65	0.84
P		0.246	0.158	0.402	<0.05	0.255	0.381	0.357

Specimen collection and index

Fasting venous blood (8 mL) was collected from all subjects in the morning, which were divided into 2 parts. One part was placed in anticoagulation tube and the serum was isolated after standing followed by extraction within 30 min to detect the levels of Fasting Plasma Glucose (FPG), Fasting Serum Insulin (FINS), Glycosylated Hemoglobin (HbAlc), Total Cholesterol (TC three), Triglyceride (TG), High Density Lipoprotein (HDL) and Low-Density Lipoprotein (LDL) in serum. The other part was given separation of serum followed by being stored at -80 degrees in refrigerator for determination of TNF-a, TNFR1 and ADP levels.

Detection method

Blood glucose was determined by Glucose Oxidase method and the results were analyzed by American Beckman LX-20 fully automatic chemistry analyzer. HbAlc was determined by turbidimetric immunoassay method. FINS, TNF-a, TNFR1 and ADP were detected by enzyme linked immunosorbent assay (ELISA). The kit was produced by Beijing Equation Jiahong Technology Co., Ltd. and the detecting instrument was the automated enzyme immunoassay analyzer manufactured in Spain. The formula of HOMA-IR calculation was: HOMA-IR=FINS (μU/mL) × FPG (mmol/L/22.5).

Statistical analysis

SPSS 21.0 statistical software was used to analyze the data in which the measurement data were assessed by t test, Logistic regression was performed for multifactorial correlation analysis, $P<0.05$ suggests that the difference is statistically significant.

Results

Comparison of various indexes between two groups

There was no statistically significant difference in TC, TG and HDL between control group and patient group. Compared with the control group, the levels of FPG, FINS, HbAlc, LDL, HOMA-IR, TNF-a and TNFR1 were significantly increased while ADP obviously decreased in patient group (Table 2).

Table 2. Comparison of clinical indexes between two groups.

Group	n	HbA1c (%)	TNFR1 (mg/L)	TNF-α (mg/L)	ADP (ng/L)	FPG (mmol/L)	FINS (μU/L)	HOMA-IR	TC (mmol/L)	TG (mmol/L)	HDL (mmol/L)	LDL (mmol/L)
Patient group	180	16.34 ± 0.35	15.04 ± 2.76	16.65 ± 2.95	7.32 ± 1.06	8.02 ± 0.25	9.79 ± 0.35	3.52 ± 0.24	5.85 ± 0.78	3.63 ± 0.37	1.78 ± 0.25	3.61 ± 0.84
Control group	60	6.67 ± 0.42	7.13 ± 2.36	8.02 ± 2.14	11.45 ± 1.12	4.84 ± 0.14	6.37 ± 0.44	1.45 ± 0.17	5.82 ± 0.81	3.66 ± 0.45	1.82 ± 0.28	3.07 ± 0.52
t		7.14	7.09	6.35	6.08	5.71	7.15	5.87	0.65	0.9	0.73	5.58
P		0.016	0.017	0.022	0.031	0.036	0.031	0.038	0.124	0.165	0.178	0.029

Table 3. *Multivariate logistic regression analysis of HOMA-IR and various indexes in patient group.*

Independent variable	β	SE	Wald X^2	OR (95% CI)	P
TC	3.125	0.307	0.946	0.156 (0.141-0.973)	0.263
TG	0.224	0.539	2.314	1.305 (0.632-3.178)	0.014
FBG	0.451	0.209	2.477	1.726 (1.087-2.594)	0.012
FINS	0.312	0.165	2.311	1.689 (1.037-2.035)	0.015
TNFR1	0.875	0.493	2.765	2.608 (1.156-4.844)	0.011
TNF-α	0.654	0.387	2.208	2.606 (1.254-4.912)	0.019
ADP	-1.782	0.363	0.175	0.243 (0.072-0.416)	0.024
HDL	3.746	0.347	1.151	0.149 (0.132-0.985)	0.282
LDL	3.008	0.362	0.873	0.162 (0.156-0.998)	0.205
HbAlc	0.403	0.215	2.195	1.553 (0.177-3.762)	0.037

Table 4. *Multivariate Logistic regression analysis on pregnancy outcome and serum indexes.*

Independent variable	β	SE	Wald X^2	OR (95% CI)	P
HOMA-IR	0.167	0.617	1.998	1.236 (1.096-3.114)	0.021
TNF-a	0.295	0.601	2.462	1.674 (1.048-3.652)	0.018
TNFR1	0.377	0.515	2.503	1.693 (1.102-3.793)	0.015
ADP	-1.065	0.418	0.236	0.215 (0.015-0.873)	0.037

Table 5. *Multivariate Logistic regression analysis on postpartum progression to T2DM and serum indexes.*

Independent variable	β	SE	Wald X^2	OR (95% CI)	P
HOMA-IR	0.152	0.544	2.416	1.741 (1.107-3.652)	0.031
TNF-a	0.378	0.597	2.509	1.874 (1.156-3.793)	0.029
TNFR1	0.401	0.476	2.633	1.602 (1.169-3.984)	0.026
ADP	-1.295	0.392	0.317	0.228 (0.056-0.912)	0.041

Analysis on the correlation of HOMA-IR with various indexes in patient group

The multivariate Logistic regression analysis was conducted in patient group with HOMA-IR as the dependent variable and FPG, FINS, HbAlc, TC, TG, HDL, LDL, TNF-a, TNFR1 and ADP as independent variables, and the results indicated that levels of FPG, FINS, HbAlc, TG, HDL, LDL, TNF-a and TNFR1 showed a positive correlation with HOMA-IR, ADP showed a significant negative correlation with HOMA-IR with no significant correlation between TC, HDL as well as LDL and HOMA-IR (Table 3).

Analysis on the correlation of pregnancy outcome with serum indexes

Multivariate Logistic regression analysis was conducted with the presence/absence of adverse pregnancy outcomes (premature delivery, fetal distress, neonatal asphyxia, postpartum hemorrhage, preeclampsia) as the dependent variable and HOMA-IR, TNF-a, TNFR1 and ADP as the independent variables in patient group, and the results showed that the adverse pregnancy outcome was positively correlated with HOMA-IR, TNF-a and TNFR1, while negatively correlated with ADP (Table 4).

Analysis on the correlation of postpartum progression to T2DM with serum indexes

The multivariate Logistic regression analysis was conducted with the possibility of postpartum progression to T2DM as the dependent variable and HOMA-IR, TNF-a, TNFR1 and ADP as the independent variables in patient group, and the results showed that the postpartum progression to T2DM was positively correlated with HOMA-IR, TNF-a and TNFR1 while negatively correlated with ADP (Table 5).

Discussion

Gestational diabetes mellitus is the most common complication during pregnancy with moderately high incidence. The disease will cause serious harm to mother and fetus, resulting in adverse pregnancy outcomes like premature delivery, neonatal asphyxia, fetal distress and postpartum hemorrhage, on the other hand, it will cause long-term damage to pregnant women and lead to subsequent incidence of T2DM and cardiovascular diseases. There are many researches on the pathogenesis of gestational diabetes mellitus but with the lack of consistent conclusion. In recent years, some studies have found that the adipokines secreted by placenta such as leptin, adiponectin and visfatin play a key role in insulin resistance [8,9]. Adiponectin, secreted by adipocytes, is a protein with a molecular weight of 30 kDa and consisting of 244 amino acids, and the gene locus encoding adiponectin is associated with the susceptibility of diabetes and cardiovascular disease [10]. With development of the research, it is found that adiponectin, as an insulin sensitizer, can enhance the gluconeogenesis of insulin, inhibit the production of liver glycogen and reduce blood sugar, closely related to the incidence of obesity, IR and type 2 diabetes. Research shows that adiponectin reduction or deficiency is likely to cause IR and then lead to type 2 diabetes, Yamauchi et al. have found the level of adiponectin is reduced in patients with IR and clinical data further show that with the progression of GDM, the pancreatic beta cell is subjected to progressive failure with decreased adiponectin [11]. This study showed that the level of serum adiponectin in patients with gestational diabetes mellitus is lower than in normal pregnant women, and is closely related to adverse pregnancy outcomes as well as postpartum development to T2DM, suggesting that the adiponectin in serum can be used to predict outcome of pregnancy and postpartum glucose transferring in patients with gestational diabetes.

TNF-a is a cytokine secreted by activated monocyte/ macrophage, which, by binding to its receptor, mediates many biological effects such as inducing tumor cells apoptosis and inflammation. Recent studies have shown that TNF-a plays an important role in the pathogenesis of insulin resistance. Insulin is the only hormone in the body able to reduce blood sugar, by binding to its cell-membrane receptor activates the receptor-tyrosine kinase activity and through a series of signal transduction, ultimately stimulates the translocation of glucose transporter 4 (GLUT-4) from cytoplasm to cell membrane for glucose absorption [12]. The defect in any link of this process may lead to insulin resistance. The close relationship between TNF-a and insulin resistance has been confirmed in many studies. Some scholars have found that the level of serum TNF-a is negatively correlated with insulin sensitivity in women with GDM [13]. The expression of TNF-a in mouse fat and liver of insulin resistant is increased significantly, while TNF-a gene knockout enables to obviously raise insulin sensitivity in mice [14]. At present, it is believed that the mechanism of insulin resistance induced by TNF-a may be hindering normal tyrosine phosphorylation of Insulin Receptor Substrate (IRS) through the promotion of its serine phosphorylation and resulting in insulin signal transduction retardancy. TNF- a receptors include such two subtypes as TNFR1 and TNFR2, in which TNFR1 mediates the major biological effects of TNF-a. It is speculated that insulin resistance in the endometrium of rats with GDM might be related to the overexpression of TNF-a and its receptor [15]. And this study found that the levels of serum TNF-a and TNFR1 were significantly higher in pregnant women with gestational diabetes mellitus than in normal pregnant women, and that they were positively correlated with HOMA-IR, adverse pregnancy outcomes as well as postpartum progression to T2DM, suggesting that TNF-a and TNFR1 are closely related to the occurrence and development of gestational diabetes mellitus, which provides a new direction for the prevention and treatment of the disease.

To sum up, in patients with gestational diabetes the levels of TNF-a and TNFR1 are relatively high and ADP level moderately low, which is closely related with insulin resistance. The higher the antenatal levels of TNF-a and TNFR1 and the lower the level of ADP, the higher the risk of adverse pregnancy outcomes and postpartum progression toT2DM in patients.

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