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Original Article

Correlation of serum PEDF concentration with blood lipid in pregnant women with gestational diabetes mellitus

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Abstract: Aims: The purpose of the study was to investigate the expression level of serum pigment epithelium derived factor (PEDF) and analyze the relationship of serum PEDF concentration with blood lipid in pregnant women with gestational diabetes mellitus (GDM). Methods: 40 GDM pregnant women (case group) in obstetrics clinic of Weifang Maternal and Child Health Hospital and 40 healthy pregnant women (control group) were enrolled into this study. Serum PEDF concentration, blood biochemistry, and clinical features were tested in 24-28 weeks of pregnancy. Results: Compared to the control group the following factors levels were all higher in GDM group, including serum PEDF, total cholesterol (TC), triglyceride (TG), low-density lipoprotein (LDL-C), fasting blood glucose (FBG), blood glucose 1 h after oral glucose tolerance test (OGTT), blood glucose 2 h after OGTT, and homeostasis model assessment of insulin resistance (HOMA-IR), and the differences were statistical significance ($P<0.01$). However, the serum high-density lipoprotein (HDL-C) and adiponectin levels were lower in GDM group than in control group ($P<0.05$). Moreover, the univariate analyses showed that serum PEDF level had positive correlation with FBG, TC, TG, LDL-C, and HOMA-IR levels but negative correlation with adiponectin. In multiple linear regression analysis, the serum PEDF level was independently associated with TG, FBG, and HOMA-IR ($P<0.05$). Conclusion: Serum PEDF concentration was higher in GDM pregnant women than in healthy pregnant women. Independent correlation existed between serum PEDF concentration and TG, FBG, and HOMA-IR levels, which indicated that serum PEDF could serve as a new marker for GDM.

Keywords: Gestational diabetes mellitus, serum PEDF, blood lipid

Introduction

Gestational diabetes mellitus (GDM), which refers to varying degrees of abnormal glucose tolerance during pregnancy for the first time, is a common pregnancy associated complication. GDM does not include the diabetes occurring before pregnancy, and its morbidity is rapidly increasing at present [1, 2]. GDM represents s heterogeneous group of metabolic disorders and is associated with an increased maternal incidence of type 2 diabetes mellitus, cardiovascular disease at follow up as well as various adverse acute and long-term outcomes among the offspring [3, 4]. What's more, GDM may cause macrosomia, stillborn foetus, polyhydramnios, abortion, and premature delivery in short term and even lead to insulin resistance or β-cell dysfunction in long term, which may further increase the risk of developing into type 2 diabetes mellitus of GDM patients in future [5].

Pigment epithelium derived factor (PEDF) is a naturally occurring neurotrophic factor found in the interphotoreceptor matrix surrounding the photoreceptor. The PEDF protein was encoded by the SERPINF1 gene which is expressed by retinal pigment epithelium [6, 7]. In recent years, researchers have found that pigment epithelium derived factor (PEDF) is related to insulin sensitivity and is involved in the occurrence of diabetes mellitus and various complications like diabetic nephropathy and diabetic retinopathy [8-10]. Patients with type 2 diabetes mellitus had higher PEDF level than healthy

Table 1. Clinical and biochemical features of GDM and control groups

Parameter	GDM (n=40)	Control group (n=40)	*P* value
Age (year)	29.15±5.35	28.87±4.17	0.794
Gestational weeks	25.93±1.49	26.23±1.31	0.505
Weight (kg)	61.88±5.7	60.75±4.8	0.340
Height (cm)	162.52±4.48	161.42±4.35	0.292
Progestational BMI (kg/m^2)	23.38±3.01	22.19±3.34	0.091
Heart rate (beat/min)	69.2±11.7	68.6±9.8	0.804
Systolic pressure (mmHg)	130.4±16.4	128.4±15.6	0.578
Diastolic pressure (mmHg)	76.8±8.9	75.6±7.9	0.526
TC (mmol/L)	4.74±0.55	3.9±0.60	<0.01
TG (mmol/L)*	2.03±0.78	0.95±0.50	<0.01
HDL-C (mmol/L)	1.10±0.21	1.35±0.23	<0.05
LDL-C (mmol/L)	2.47±0.53	2.80±0.56	<0.01
FBG (mmol/L)*	5.02±0.81	4.34±0.51	<0.01
1 h BG (mmol/L)*	10.1±1.09	8.47±0.98	<0.01
2 h BG (mmol/L)*	7.96±0.93	6.69±0.86	<0.01
FINS (pmol/L)*	15.54±6.87	13.92±4.42	0.030
HbA1c (%)	4.74±0.73	4.34±0.58	0.057
HOMA-IR	2.78±1.35	1.59±1.2	<0.01
Adiponectin (mg/l)*	13.04±5.75	22.87±6.84	<0.01
PEDF (μg/ml)*	5.45±2.79	3.23±1.37	<0.01

*: logarithmic transformation was conducted on the variables.

people [11]. However, fewer studies have investigated the correlation between PEDF and GDM.

In the present study, we attempted to investigate the serum expression level of PEDF in GDM patients and analyze the association of PEDF concentration with blood lipid in pregnant women with GDM.

Materials and methods

Study objects

40 GDM patients and 40 healthy pregnant women diagnosed in obstetrics clinic of Weifang Maternal and Child Health Hospital were respectively selected as cases and controls. 80 patients were all single pregnancy, and had no family history of diabetes mellitus, and no medical history of essential hypertension, kidney diseases, immune diseases, tumor, or acute inflammation. All study objects signed informed consents, and retrospective analysis of the collected information was conducted.

Definition of GDM and type 2 diabetes mellitus

The diagnoses of GDM and type 2 diabetes mellitus were in accordance with Diagnostic standards of gestational diabetes mellitus published by American Diabetes Association (ADA) in *Diabetes Care* in January, 2013 [12]. 1. In the first prenatal examination performed within the 12 weeks of pregnancy, patients with fasting blood glucose (FBG) ≥7.0 mmol/L, glycosylated hemoglobin (HbA1c) ≥ 6.5%, blood glucose (BG) ≥11.1 mmol/L 2 hours after 75 g oral glucose tolerance test (OGTT), or random BG ≥11.1 mmol/L and with typical symptoms of diabetes mellitus can be determined to have GDM. 2. If all indexes are normal during the first prenatal examination, a second examination should be performed during the 24-28 weeks of gestation. During the second examination, FBG, and BG 1 h and 2 h after 75 g OGGT are assessed. Patients satisfying FBG ≥5.1 mmol/L (92 mg/d1), BG ≥10.0 mmol/L (180 mg/d1) 1 h after 75 g OGGT, or BG ≥8.5 mmol/L (153 mg/d1) 2 h after 75 g OGG can be diagnosed with GDM.

Physical assessment

The weight and height were respectively measured by an electronic scale and a range finder. The body mass index (BMI) was calculated as follows: weight (kilo)/height (meter) × height (meter). Vigorous physical activity and smoking were avoided within the 30 minutes before blood pressure (BP) and resting heart rate was measured. Desk model sphygmomanometer was used to measure the sitting BP.

Detection of biochemical indexes

The objects were not allowed to eat for 12 hours at night before the blood collection day and elbow venous blood was extracted on the morning of the next day. BG, insulin, HbA1c, total cholesterol (TC), triglyceride (TG), low-density lipoprotein (LDL-C), and high-density lipoprotein (HDL-C) were measured and 75 g OGTT was also performed. Serum adiponectin and PEDF levels were determined by enzyme linked

Table 2. Univariate regression analysis of factors related to PEDF

Parameter	β	SE	*P* value
Age (year)	0.018	0.002	0.672
Gestational weeks	0.015	0.002	0.775
Progestational BMI	0.075	0.001	0.070
Heart rate (beat/min)	0.025	0.051	0.404
Systolic pressure (mmHg)	0.032	0.001	0.315
Diastolic pressure (mmHg)	0.041	0.002	0.211
TC (mmol/L)	0.142	0.001	<0.01
TG (mmol/L)*	0.308	0.044	<0.01
HDL-C (mmol/L)	-0.015	0.001	0.292
LDL-C (mmol/L)	0.131	0.003	<0.04
FBG (mmol/L)*	0.318	0.028	<0.01
FINS (pmol/L)*	0.042	0.035	0.09
HbA1c (%)	0.028	0.029	0.432
HOMA-IR*	0.422	0.055	<0.01
Adiponectin (mg/l)*	-0.181	0.038	<0.04

β: regression coefficient; SE: standard error; *: logarithmic transformation was performed on the variables.

immunosorbent assay (ELISA), and the operations were strictly conducted according to the instructions of the kit. The kit was purchased from R&D Systems China Co., Ltd. LTD.

Insulin resistance evaluated by HOMA-IR

The calculation formula of homeostasis model assessment of insulin resistance (HOMA-IR) was (blood glucose × insulin)/405.

Statistical analysis

SPSS 17.0 was applied to analyze the data. The data in abnormal distribution was analyzed after logarithmic transformation. All data were expressed as mean ± SD. Mean values of GDM group and control group were compared through independent sample t test. Pearson correlation coefficient was adopted to study the association of PEDF concentration with clinical features. Independent correlation factors of PEDF were determined through multiple linear regression analysis. P<0.05 was considered to be statistically significant.

Results

Characteristics of the study objects

Features of the study objects were shown in **Table 1**. The differences in age, gestational weeks, BMI, heart rate, systolic pressure, diastolic pressure, and HbA1c between GDM and control groups were not statistically significant (P>0.05). Apparent differences existed in TC, TG, HDL-C, LDL-C, fasting insulin (FINS), and HOMA-IR between the two groups (P<0.01). Meanwhile similar results were observed in BG levels in 0 hour, 1 hour, 2 hours after 75 g OGTT between the two groups (P<0.01). Furthermore, the GDM group had apparently lower serum adiponectin level and significantly higher PEDF concentration than the control group (all, P<0.01).

Single factor correlation analysis

As shown in **Table 2**, there were positive associations between serum PEDF concentration and TC, TG, LDL-C, FBG, and HOMA-IR (P<0.05), while there were negative relationships between serum adiponectin level and PEDF level. No apparent linkages of serum PEDF concentration with age, gestational weeks, BMI, heart rate, systolic pressure, diastolic pressure, FINS, and HbA1c were indicated. Multiple linear regression analysis showed independent correlation of PEDF with TG, FBG, and HOMA-IR (**Table 3**, P<0.05).

Discussion

PEDF was firstly purified and separated from the conditional medium culture of retinal pigment epithelium of fetuses in 1989 [13]. It belongs to the serine protease inhibitor family, and is a multifunctional protein which has roles of nurturing nerves, preventing tumors, angiogenesis, vasopermeability, and oxidation, as well as regulating the formation of adipocytes [14]. The PEDF in blood is mainly produced by liver and adipose tissues, and is now regarded as the most important inhibitor of angiogenesis. In the past few years, researchers have also reached a conclusion that PEDF is relevant to diabetes mellitus and its complications [15]. Moreover, increased PEDF level has been observed in patients with diabetes mellitus in previous studies [11]. In this study, the serum PEDF concentration of 80 objects was measured during their 24-32 weeks of pregnancy.

The results displayed that serum PEDF level was higher in GDM group than in the control group. The univariate analysis demonstrated that serum PEDF concentration had positive

Table 3. Multiple stepwise regression analysis of factors relevant to PEDF

Parameter	β	SE	*P*
TC (mmol/L)	0.094	0.011	0.067
TG (mmol/L)	0.130	0.031	<0.05
LDL-C (mmol/L)	0.058	0.001	0.289
FBG (mmol/L)	0.28	0.012	<0.01
HOMA-IR	0.150	0.026	<0.01
Adiponectin (mg/l)	-0.046	0.011	0.079

β: regression coefficient; SE: standard error; *: logarithmic transformation was conducted on the variables.

correlation with BG 1 h and 2 h after 75 g OGTT, and HOMA-IR. The multiple stepwise linear regression analysis reflected that serum PEDF concentration had independent association with FBG, BG 1 h and 2 h after 75 g OGTT, and HOMA-IR, which suggested that the serum PEDF concentration may be abnormal among GDM patients. HOMA-IR, which is a sign of insulin resistance in epidemiologic studies, has important value in determining the risk of diabetes mellitus and has been widely applied for clinically evaluating the insulin sensitivity of patients with diabetes mellitus. Tong-Huan Li et al. illustrates that serum PEDF level is enhanced in GDM patients and indicates that it may be used as an early detection marker of predicting the development of GDM to diabetes mellitus [16].

In the case of normal pregnancy, the blood lipid may be increased to meet the physiological changes required by the normal development of the fetus, which involves no pathological changes [17]. Increased fat storage in early and middle pregnancy is not a pathological phenomenon, but a physiologically adaptive measure which provides abundant materials for accelerated degradation of fat in late pregnancy, rapid growth and development of the fetus, and postpartum lactation. Nevertheless, lipid metabolism disorder is aggravated in GDM patients owing to disturbances of carbohydrate metabolism and insulin resistance. Kitajima et al. put forward that the rising lipid of patients with abnormal glucose metabolism in middle pregnancy is positively correlated with neonatal body weight [18]. Hormone secreted by placenta can greatly affect the insulin resistance feature of GDM patients, so glucose metabolism disorder is always accompanied by aggravated lipid metabolism disorder [19]. In the present study, there existed positive correlation between the serum PEDF concentration and TC, TG, LDL-C ($P<0.05$), while the multiple linear regression analysis illustrated independent correlation of serum PEDF concentration with TG ($P<0.05$) ($R_2=0.332$). TG level is high in pregnant women due to the increased secretion of estrogen and enhanced insulin resistance level in late pregnancy as well as the high protein diet of most pregnant women. Through comparing the blood lipid level of 178 normal pregnant women and 58 non-pregnant women, Mazurkiewicz et al. find that TG>6.5 mmol/L in 63% of the late pregnant women and LDL-C>4.0 mmol/L in 44% of the late pregnant women, and thus conclude that late pregnant women have hyper lipidaemia [20]. The above situation is especially prominent in GDM patients because the insulin resistance is greatly affected by placenta secreted hormones. Yamagishi et al. indicate that the rising of serum PEDF level is proportional to molecular constitution of metabolic syndromes [21]. Therefore, we consider that the increased PEDF can be used to counter metabolic disorders related to obesity. The increased serum PEDF level in GDM women may also contribute to the resistance to GDM metabolic disorders.

In summary, serum PEDF concentration was higher in GDM patients, and the PEDF had independent correlation with triglyceride. Thus we concluded that PEDF could be used as a marker of GDM diagnosis. Moreover the present study also provided bases for assistant diagnosis, monitoring, and prevention of GDM.

Disclosure of conflict of interest

None.

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