Int J Clin Exp Med 2020;13(12):9699-9705
www.ijcem.com /ISSN:1940-5901/IJCEM0116728

Original Article

Expression of IGF-1 and GDF-15 in patients with gestational diabetes

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Received June 21, 2020; Accepted August 15, 2020; Epub December 15, 2020; Published December 30, 2020

Abstract: Objective: To evaluate the expression of IGF-1 and GDF-15 and the risk factors associated with the onset of gestational diabetes mellitus (GDM) in patients with gestational diabetes in the third trimester. Methods: 527 GDM patients and 527 healthy subjects admitted to our hospital from June 2017 to January 2020 were enrolled and divided into GDM group and normal glucose tolerance (NGT) group. The following parameters including baseline data, serum IGF-1 and GDF15 levels, maternal blood glucose-related biochemical indicators and their correlation with serum IGF-1 levels, the correlation between the blood glucose-related biochemical indices with serum GDF15 level, and the correlation between the expression levels of serum IGF-1 and serum GDF15 were analyzed. Results: In the third trimester of pregnancy, no significant difference was observed in age, gestational weeks, BMI, and blood lipid parameters between two groups. GDM group had higher BMI, fasting blood glucose, blood glucose level at 1 h, 2 h after meal, and AUCG than NGT group, but there was no significant difference on glycated hemoglobin. Serum IGF-1 and GDF15 levels of GDM group were higher than those of NGT group. IGF-1 levels were positively correlated with maternal FBG, while 1 h-PG, 2 h-PG, and AUCG were positively correlated with HbA1c. There was a positive correlation between GDF15 levels and maternal FBG as well as between 1 h-PG, 2 h-PG, AUCG and HbA1c. IGF-1 was positively correlated with GDF15. Conclusion: The main risk factors for GDM include low education level, increased fasting 1 h and 2 h postprandial blood glucose levels, and increased BMI and AUCG in late pregnancy. In the third trimester of pregnancy, the levels of IGF-1 and GDF15 are positively correlated with the glucose metabolism, which is an underlying protective factor for gestational diabetes, and IGF-1 is positively correlated with GDF15.

Keywords: Gestational diabetes, IGF-1, GDF-15, glucose metabolism, risk factors

Introduction

Gestational diabetes mellitus (GDM) refers to the onset or initial diagnosis of glucose intolerance during pregnancy, and it is one of the most common pregnancy complications, with the incidence of about 15% [1]. GDM is related to the increased risk of adverse perinatal outcomes [2]. The International Diabetes and Pregnancy Research Group established the diagnostic criteria for GDM in 2010 [3].

Insulin-like growth factor I (IGF-1) is involved in the occurrence of GDM [4]. Tsai and other scholars found that compared with non-diabetic pregnant women, IGF-I is remarkably higher in pregnant women [5]. Among patients with gestational diabetes, the levels of IGF-I were positively correlated with BMI, fasting insulin and insulin sensitivity before pregnancy [4]. A small clinical study showed that the levels of plasma IGF-I may be a predictor of GDM in early pregnancy [6].

A study has found that growth differentiation factor 15 (GDF15) is closely related to disorders of glucose metabolism [7]. Zhang and his colleagues have found that the serum GDF15 level of a pregnant woman is higher than the normal level at the beginning of pregnancy, and gradually increases with the progress of pregnancy, reaching the highest level in the third trimester [7]. Therefore, serum GDF15 levels may be related to pregnancy diseases, especially GDM. However, only a small sample research found that serum GDF15 levels have not changed significantly in the second trimester, while serum GDF15 levels increased in the third trimester [7]. Since IGF-1 and GDF15 levels are both involved in the metabolic regula-

tion of blood glucose during pregnancy, and both show an upward trend, whether there is a correlation between them remains to be further explored.

In this study, we recruited patients with gestational diabetes and pregnant women with normal glucose tolerance (NGT) strictly in accordance with the JSOG standard, and statistically analyzed the expression of IGF-1 and GDF-15 from pregnancy to the third trimester and risk factors for the occurrence of gestational diabetes.

Materials and methods

Subjects

Inclusion criteria: Patients (1) in the first trimester; (2) aged 25-35 years old; (3) received 75 g OGTT test in the second or third trimester, diagnosed with GDM with one of the following conditions: fasting blood glucose > 5.1 mmol/l or blood glucose > 10.0 mmol/l at 1 hour after meal, or more than 8.5 mmol/l at 2 hours after meal. Exclusion criteria: Patients (1) suffered from diabetes before pregnancy; (2) complicated by hypertension; (3) abnormal thyroid function or other complications during pregnancy; (4) abnormal liver and kidney function, heart and lung function; (5) abnormal lipid metabolism.

A total of 527 GDM subjects and 527 healthy controls were recruited and divided into GDM group and NGT group. All participants in this study fully understood the research procedures and related risks and have signed the written consent form. This study has been conducted with the approval of the Medical Ethics Committee of Affiliated Hospital of Gansu Medical College. The study was performed in accordance with the provisions of the Declaration of Helsinki.

Research design

Baseline data including age, gestational age, pre-pregnancy BMI index, late pregnancy BMI, history of smoking and drinking, and education level were recorded. Blood samples were taken from all subjects. The glucose level was measured on the Roche Cobas 701 analyzer (Roche, Ltd., Basel, Switzerland) using the hexokinase method. The area under the glucose curve of 75 g OGTT (AUCG) is counted as 1/2 × [FBG (mmol/L) + 1 h-PG (mmol/L)] 1 h + 1/2 × [1 h-PG (mmol/L) + 2 h-PG (mmol/L)]. Siemens automatic chemical analyzer (Siemens, Munich, Germany) was used to measure the lipid-related parameters. HbA1c was measured on Arkray HA-8160 analyzer (Arkray, Ltd. Kyoto, Japan) using high performance liquid chromatography.

Serum IGF-1 detection

According to the kit instructions, the free serum IGF-1 was measured with an ELISA kit (R&D Systems, Inc. Minneapolis, MN, USA). The lower limit was 0.015 ng/mL and the coefficient of variation was 6.2%.

Serum GDF15 detection

The level of serum GDF15 was measured with an ELISA kit (R&D Systems, Inc. Minneapolis, MN, USA) in strict accordance with the manufacturer's instructions. This assay is highly sensitive to GDF15, and the minimum detectable dose range for human GDF-15 is 0.0-4.4 pg/mL. The intra-assay coefficient of variation is 6.0%.

Statistical analysis

SPSS software (SPSS for Windows, Version 22; SPSS Inc., Chicago, IL, USA) was used for all analyses. Histograms and scatter plots were drawn using GraphPadPrism software (version 7.0). The normal distribution of experimental data was represented by mean ± standard derivation (mean ± SD) or the median within the quartile range and compared using paired t test or signed rank test. The chi-square test was used for the comparison of categorical variables. The difference between subgroups was analyzed by ANOVA or Kruskal-Wallis test. Correlation analysis was carried out using Spearman or Pearson. $P < 0.05$ was considered statistically significant.

Results

Baseline data

In the third trimester, no significant difference was observed in age, gestational week, BMI before pregnancy, and blood lipid parameters ($P > 0.05$). However, GDM group had fewer people with higher education level, higher BMI in late pregnancy ($P < 0.01$), higher fasting blood glucose, and higher blood glucose level and AUCG at 1 h and 2 h after meal than the NGT

Table 1. General baseline information

Variable	GDM group (n = 527)	NGT group (n = 527)	*P*
Age (years)	31.3±2.6	30.1±1.5	0.43
Gestational age (week)	25.6±3.5	25.3±3.2	0.47
Pregestational BMI (kg/m^2)	21.1±2.2	21.2±1.9	0.52
Second trimester BMI (kg/m^2)	26.3±1.8	25.8±2.4	< 0.01
Smoking	79	69	0.65
Drinking	94	71	0.68
Education level			
University and above	126	171	< 0.01
Middle school	77	50	0.43
Primary school	3	6	0.57
FBG	4.83±0.23	4.16±0.27	< 0.01
1 h-PG	9.73±0.29	7.08±0.28	< 0.01
2 h-PG	8.59±0.38	6.02±0.33	< 0.01
AUCG	16.49±0.27	12.32±0.31	< 0.01
Total cholesterol	6.62±0.23	6.71±0.24	0.34
LDL-C	3.62±0.22	3.87±0.32	0.37
HDL-C	1.88±0.38	1.79±0.26	0.57
Triglycerides	3.52±0.58	3.61±0.44	0.62
HbA1c	5.3±0.39	5.2±0.17	0.77

Data are expressed as mean ± SD or median (interquartile range).

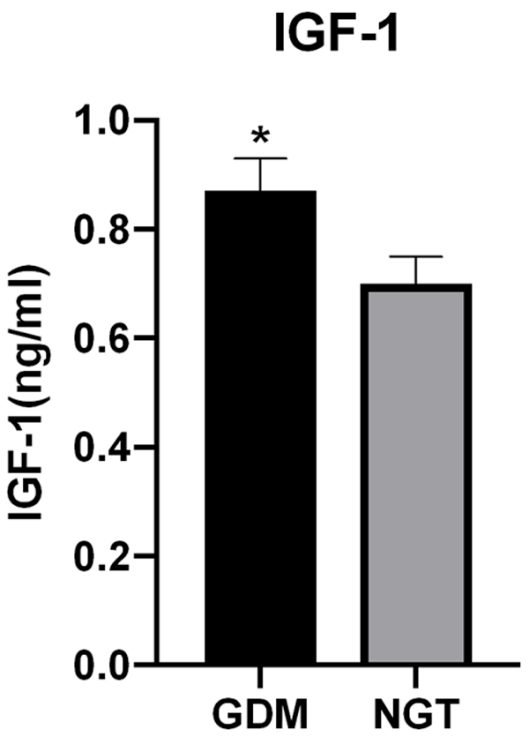

Figure 1. GDM (n = 527) and NGT (n = 527) serum IGF-1 levels in late pregnancy. *P < 0.005 compared with NGT group.

group (P < 0.01). No significant difference was found on glycated hemoglobin between the two groups (P = 0.77) (**Table 1**).

Serum IGF-1 and GDF15 levels in both groups

The GDM group showed higher serum level of IGF-1 than NGT group (0.87±0.06 vs 0.69±0.05 ng/ml) (**Figure 1**; **Table 2**). Besides, the level of GDF15 of the GDM group in the third trimester was also remarkably higher than that of the NGT group (137.3±28.31 ng/ml vs 84.22±14.02 ng/ml) (P < 0.001) (**Figure 2**; **Table 2**).

Correlation analysis of serum IGF-1 levels and maternal blood sugar related biochemical indicators in both groups

It was found that the maternal blood glucose-related biochemical indicators of the GDM group were higher than those of the NGT group, and the IGF-1 level also showed upward trend. Therefore, IGF-1 levels were associated with clinical indicators such as FBG, 1 h-PG, 2 h-PG, AUCG, and HbA1c. The results showed that IGF-1 levels had positive correlation with maternal FBG, 1 h-PG, 2 h-PG, AUCG and HbA1c (P < 0.05) (**Table 3**).

Correlation analysis of GDF15 serum levels and maternal blood glucose-related biochemical indicators in both groups

It was found that the maternal blood glucose-related biochemical indicators of the GDM group were higher than those of the NGT group, and the GDF15 level also gradually increased. Therefore, GDF15 levels were correlated with indicators such as FBG, 1 h-PG, 2 h-PG, AUCG, and HbA1c. The results implied that GDF15 levels had positive correlation with maternal FBG, 1 h-PG, 2 h-PG, AUCG and HbA1c (P < 0.05) (**Table 4**).

Correlation between serum levels of IGF-1 and GDF15 in both groups

The GDM group showed an upward trend in both IGF-1 and GDF15 levels compared with

Table 2. Serum IGF-1 and GDF15 levels in both groups

Variable	GDM group (n = 527)	NGT group (n = 527)	*P*
IGF-1 (ng/mL)	0.87±0.06	0.69±0.05	< 0.01
GDF15 (ng/mL)	137.3±28.31	84.22±14.02	< 0.01

Data are expressed as mean ± SD or median (interquartile range).

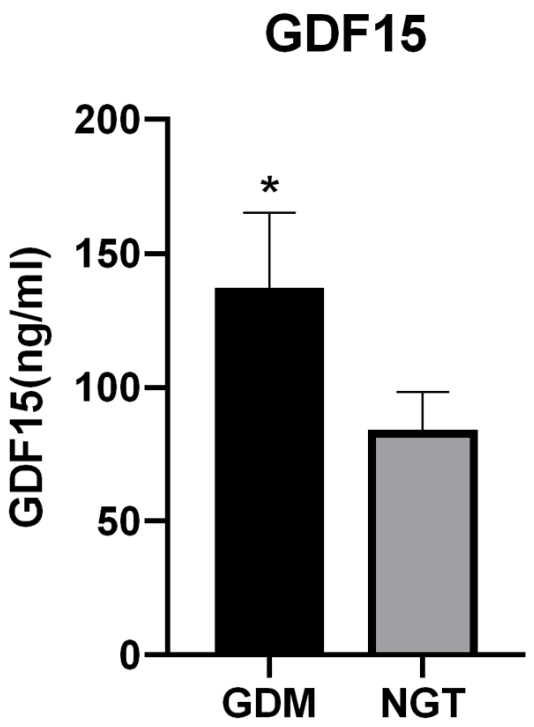

Figure 2. GDM (n = 527) and NGT (n = 527) serum GDF15 levels in late pregnancy. *P < 0.005 compared with NGT group.

Table 3. Correlation coefficient between serum IGF-1 and blood glucose-related biochemical indicators in the NGT and GDM groups

Variable	GDM group (n = 527)	r	*P*
FBG	4.83±0.23	0.067	< 0.01
1 h-PG	9.73±0.29	0.022	< 0.01
2 h-PG	8.59±0.38	0.046	< 0.01
AUCG	16.49±0.27	0.031	< 0.01
HbA1c	5.3±0.39	0.054	< 0.01

Data are expressed as mean ± SD or median (interquartile range).

the NGT group. Therefore, the correlation was analyzed between the two indicators. The results showed that IGF-1 was positively correlated with GDF15 (P < 0.05) (**Table 5**; **Figure 3**).

Table 4. Correlation coefficient between serum GDF15 and blood glucose-related biochemical indicators in the NGT and GDM groups

Variable	GDM group (n = 527)	r	*P*
FBG	4.83±0.23	0.047	< 0.01
1 h-PG	9.73±0.29	0.027	< 0.01
2 h-PG	8.59±0.38	0.034	< 0.01
AUCG	16.49±0.27	0.024	< 0.01
HbA1c	5.3±0.39	0.79	0.03

Data are expressed as mean ± SD or median (interquartile range).

Table 5. Correlation analysis between serum levels of IGF-1 and GDF15 in NGT and GDM groups

Group	r	*P*
GDM group (n = 527)	0.051	0.02
NGT group (n = 527)	0.108	0.47

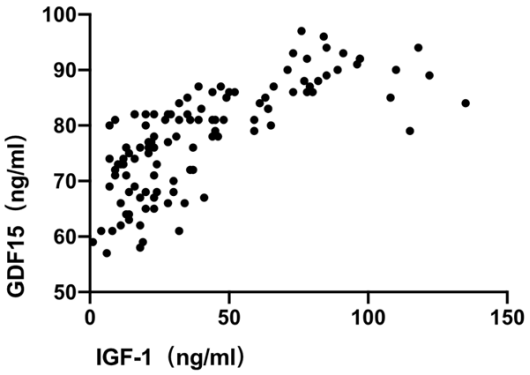

Figure 3. Correlations between GDF15 (log-transformed) and IGF-1 (log-transformed) serum levels in 527 pregnant women in the third trimester. Maternal age, BMI before pregnancy, changes of BMI until the third trimester, and gestational age of diabetes were adjusted.

Discussion

This study mainly draws the following conclusions: (1) In the third trimester, no significant difference was found in age, gestational weeks, BMI, and blood lipid parameters between the two groups; (2) BMI increased in the third trimester. The fasting blood glucose, 1 h-PG, 2 h-PG levels as well as AUCG in the GDM group were higher than those in the NGT group. No significant difference was observed between the two groups on glycated hemoglobin; (3) The serum levels of IGF-1 and GDF15 of the GDM group were higher than those of the NGT group;

(4) IGF-1 levels had positive correlation with maternal FBG, 1 h-PG, 2 h-PG, AUCG, and HbA1c; (5) GDF15 levels were positively correlated with maternal FBG, 1 h-PG, 2 h-PG, AUCG and HbA1c; (6) IGF-1 was positively correlated with GDF15.

A research found that the occurrence of gestational diabetes may be related to the patient's age, gestational age and other factors [8]. However, other scholars believed that the occurrence of gestational diabetes is not related to the patient's age and gestational age [9, 10]. The results of this study showed that no significant correlation was found between gestational age and age, which is consistent with the above conclusions. The reason may be that pregnant women included aged between 25-35 years with narrow distribution, so there is no significant difference. Two researches believed that the basal metabolic rate may affect the occurrence of GDM [11, 12]. However, the results of the present study indicated that there was no significant difference in pre-pregnancy BMI between the two groups, but the BMI had a significant difference in the third trimester. The reason may be that patients were of similar age, which indicated no significant difference in their basal metabolic rate, but in the third trimester, due to severe abnormalities in the blood glucose regulation system, the BMI of GDM patients increased significantly. In addition, this study analyzed other risk factors for patients with GDM, such as smoking, drinking, blood lipids and other indicators, and found that there is no significant relationship between these indicators and GDM levels. In addition, the influence of education level on the occurrence of GDM was also analyzed. Kanai and other scholars found that the number of patients with GDM above the university level is more [13]. Our research results are inconsistent with the above research results. Pregnant women considered to have a college education level or above have a higher education level and medical-related knowledge, and have a good level of diet and monitoring during pregnancy.

Some studies also suggested that there was no significant change in glycated hemoglobin in patients with GDM [14, 15]. The results are consistent with the findings of this study. Due to impaired islet function during pregnancy, the blood glucose regulation system was unbalanced, and blood glucose was increased in GDM patients. However, the combination of blood glucose and hemoglobin was not increased, thus the HbA1c levels were not affected.

Lappas and other scholars revealed that pregnant women in the GDM group had lower IGF levels than those in the non-GDM groups [16]. Dilli and Liao analyzed the relationship between the risk of gestational diabetes and the expression level of IGF-1 in pregnant women, and found that IGF-1 had a positive correlation with blood glucose levels in GDM patients [17, 18]. This study found that the IGF-1 level in the GDM group increased, consistent with the conclusion of the above study. In summary, GDM pathogenesis is mainly related to islet β cell damage and insulin resistance. In the third trimester, postprandial blood glucose level rises, and the required insulin also increases accordingly. Long-term large-volume secretion eventually damages islet β cells, resulting in a decrease in insulin levels. IGF-1 can play an insulin-related role, and its secretion level will increase accordingly to regulate blood sugar.

GDF15 is mainly expressed in placental trophoblasts and is a member of the transforming growth factor b superfamily [19]. Tang and other scholars found no significant difference in the serum GDF15 expression level between pregnant women and healthy controls. The concentration of GDF15 was positively associated with glucose metabolism in late pregnancy [20]. The findings of this study further suggested that the GDF15 levels of GDM patients in the third trimester were remarkably higher than those in the control group. At present, the mechanism of abnormal metabolism of GDF 15 in GDM is unclear. We consider that the mechanism may be related to abnormal glucose metabolism in GDM patients, leading to increased ROS production. Excessive ROS causes endothelial damage and lipid peroxidation, which in turn promotes the release of GDF15 from the damaged endothelium, leading to increased GDF15 levels in serum of GDM patients.

High sugar levels can induce the secretion and expression of IGF-1 and GDF15. The levels of IGF-1 and GDF15 had positive correlation with

blood glucose. Bozkurt and other scholars found that in people with impaired glucose tolerance, serum GDF15 levels had positive correlation with metformin dose, indicating that metformin can regulate the secretion and expression of GDF15 signaling pathways, thereby regulating glucose homeostasis [21]. GDF15 is a protective factor for glucose metabolism. IGF system exerts a crucial part in the process of glucose metabolism. A small sample of a clinical randomized study found that IGF-1 has a positive correlation with GDF15 [19]. This study further verified this view by a large sample of clinical randomized study. There is a positive association between IGF-1 and GDF15.

Our study has some shortcomings. First, this is a single-center study with certain regional limitations. Second, it was impossible to monitor the changes in serum IGF-1 and GDF15 levels throughout the pregnancy. Although the correlation between IGF-1 and GDF15 has been analyzed, the specific mechanism of the interaction between the two has not yet been clarified. Therefore, prospective large-sample multi-center clinical study is needed to clarify the effects of IGF-1 and GDF15 on GDM patients during the pregnancy.

In conclusion, it was found in our study that low education level, increased BMI in the third trimester, increased fasting blood glucose levels during pregnancy and 1 h, 2 h after meals and increased AUCG were risk factors for GDM. The levels of IGF-1 and GDF15 are positively correlated with glucose metabolism in late pregnancy, which may be potential protective factors for gestational diabetes, and IGF-1 is positively correlated with GDF15.

Disclosure of conflict of interest

None.

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