JDI Journal of Diabetes Investigation Open access
Official Journal of the Asian Association for the Study of Diabetes

ORIGINAL ARTICLE

Serum growth differentiation factor 15 is closely associated with metabolic abnormalities in Chinese pregnant women

Enhao Li[1,2], Peihong Chen[2], Jun Lu[2], Jiarong Dai[2,3], Jufen Yi[2], Shan Zhang[2], Hua Jin[2], Meixiang Guo[2], Hongtao Wang[2], Xuemei Yu[1,2]*

[1]The Third School of Clinical Medicine, Southern Medical University, Guangzhou, China, [2]Department of Endocrinology and Metabolism, Diabetes Ward, Fengxian Central Hospital Affiliated to the Southern Medical University, Shanghai, China, and [3]Department of Endocrinology, Endocrine and Diabetes Institute, Huashan Hospital Affiliated to Fudan University, Shanghai, China

Keywords
Gestational diabetes, Growth differentiation factor 15, Metabolic abnormalities

***Correspondence**
Xuemei Yu
Tel.: +86-21-5742-2963
Fax: +86-21-5742-2963
E-mail address:
xuemeiyu12@163.com

J Diabetes Investig 2021; 12: 1501–1507

doi: 10.1111/jdi.13488

ABSTRACT

Aims: To explore the relationship between serum growth differentiation factor 15 (GDF15) and metabolic abnormalities in Chinese pregnant women.

Materials and Methods: We recruited 200 patients with gestational diabetes mellitus (GDM) and 211 matched normal control within 24–28 weeks of pregnancy. Enzyme-linked immunosorbent assay (ELISA) was used to determine the serum GDF15 levels of all participants. Then we grouped participants according to the number of metabolic abnormalities (including blood glucose, blood lipids and blood pressure), divided them into a normal metabolic group, one metabolic abnormality group, two or more metabolic abnormalities group. Finally, multinomial logistic regression analysis was used to estimate the odds radio (OR) and 95% CIs expressing the association between GDF15 and metabolic abnormalities in pregnant women.

Results: Through bivariate correlation analysis, we found that serum GDF15 is linearly correlated with glucose metabolism indices, such as 1h-PG, 2h-PG, HbA1c (all $P < 0.05$). In addition, serum GDF15 and triglycerides were linearly correlated ($P < 0.05$). Grouping by the number of metabolic abnormalities, we found that as GDF15 levels increased, the risk of metabolic abnormalities also increased (OR > 1), and the risk of multiple metabolic abnormalities was higher. As the number of metabolic abnormalities increased, serum GDF15 levels also were elevated ($P < 0.001$).

Conclusions: The results suggest that serum GDF15 levels are closely associated with metabolic abnormalities in pregnant women and may be used as a predictor of metabolic abnormalities during pregnancy.

INTRODUCTION

The serum growth differentiation factor 15 (GDF15), also known as macrophage inhibitory cytokine-1 (MIC-1), placental bone morphogenetic protein, placental transforming growth factor-β and prostate-derived factor, is a member of the transforming growth factor beta (TGF-β) super-family[1–3]. GDF15 is secreted in the bladder, prostate, stomach and duodenum, especially in the placenta[4], and under pathological conditions, such as stress, inflammation and metabolic abnormalities, the secretion of GDF15 increases[5]. Growing evidence suggests that GDF15 is implicated in the pathogenesis of various metabolic disorders such as obesity, insulin resistance, myocardial infarction and atherosclerosis.

Type 2 diabetes mellitus (T2DM) causes an elevation of the blood glucose level and other components of the metabolic syndrome. The parameters of the metabolic syndrome are elevated blood pressure, elevated triglycerides, reduced high density lipoprotein levels and abdominal obesity. An increase in adipose tissue (abdomen obesity) results in elevation of adipokines, that is, free fatty acids (FFA), tumor necrosis factor (TNF), C-reactive protein (CRP), interleukin-6 (IL-6), plasminogen activator inhibitor-1 (PAI-1), adiponectin and leptin. Recently GDF15 was identified as one of the important plasma markers,

Received 17 September 2020; revised 26 November 2020; accepted 22 December 2020

which correlates with cardiometabolic syndrome. Recent studies have found that GDF15 is closely related to energy metabolism. In terms of glucose metabolism, Hellemons[6] found that in the diabetic population, compared with the normal glucose tolerance population, serum GDF15 levels were significantly increased[6]. There was also a report that in the hyperglycemic state, the amount of GDF15 secreted by endothelial cells was increased[7]. In terms of lipid metabolism, it was found that in mice GDF15 can regulate fat metabolism by suppressing appetite[8,9]. In human studies, it was found that with the increase of GDF15, serum triglycerides also increased. However, in some studies there were also cases of opposite findings[10].

The highest GDF15 expression is found in the placenta and the fetal membrane[4]. The hypothesis that GDF15 plays a role in feto-maternal immunotolerance was formulated in 1997[1]. Previous studies showed that GDF15 levels are increased in pregnant women at the onset of pregnancy and reach their highest concentration at the beginning of the third trimester[11]. In most people metabolic abnormalities during pregnancy are associated with pregnancy complications[12]. Therefore, it is very important to control metabolism during pregnancy.

A recent study found that serum GDF15 was significantly higher in GDM patients than in the normal pregnant population[10]. Therefore, in this study, we set out to explore whether GDF15 has a potential relationship with metabolic abnormalities in addition to hyperglycemia during pregnancy. We hypothesize that GDF15 may represent a predictor for the future development of type 2 diabetes and, possibly, disease severity in pregnant women.

METHODS

Ethical considerations

The study was approved by the Medical Ethics Committee of the Shanghai Fengxian District Central Hospital, in line with the Declaration of Helsinki (as revised in Fortaleza, Brazil, October 2013).

Participants

We recruited 200 pregnant women with GDM and 211 pregnant women with normal glucose tolerance as controls at Shanghai Fengxian District Central Hospital. This study obtained informed consent for all participants to conduct experiments, and we always abide by the privacy rights of participants. All participants underwent an oral glucose tolerance test (OGTT) at 24–28 weeks of gestation and blood tests for metabolic panel. The classification of GDM (fasting plasma glucose [FPG] $\geq$ 5.1 mmol/L or 1 h plasma glucose [1h-PG] $\geq$ 10.0 mmol/L, or 2 h plasma glucose [2h-PG] $\geq$ 8.5 mmol/L) was based on the World Health Organization guidelines published in 2013. Diagnosis of metabolic abnormalities includes a confirmed diagnosis of GDM, TG $\geqq$ 3.2 mmol/L, blood pressure higher than 140/90 mmHg. According to the number of metabolic abnormalities, patients were divided into a normal metabolic group, one metabolic abnormality group and two or more metabolic abnormalities group. All participants underwent routine blood metabolic analysis and physical examination. This study excluded participants with autoimmune disease, liver or kidney disease, blood system disease, thyroid disease, heart disease, tumor and other diseases known to affect glucose and lipid metabolism or serum GDF15 concentrations.

Clinical measurement

After an overnight fast of at least 8 h, blood samples were collected from the anterior elbow vein, centrifuged at a speed of 1,000 $\times$ g for 15 min to separate serum, then stored at –80°C until analysis of GDF15. The hemoglobin A1c level was determined by high pressure liquid chromatography (HLC-723G7; Tosoh, Tokyo, Japan). We used an automatic biochemical analyzer (DXC 800; Beckman Coulter, Brea, CA, USA) to measure triglycerides (TG), low-density lipoprotein cholesterol (LDL-c), blood total cholesterol (TC), high-density lipoprotein cholesterol (HDL-c). Fasting plasma insulin (FINS), 1 h postprandial insulin (1 h-INS) and 2 h postprandial insulin (2 h-INS) were determined by using a Roche Elecsys 1010 immunoassay analyzer and an electrochemiluminescence immunoassay kit (Roche Diagnostics, Germany). The area under the glucose–time curve from the 2-h OGTT (AUC for glucose) was calculated as (FPG (mmol/L) + 1 h-PG(mmol/L)) * 1 h/2 + (1 h-PG(mmol/L) + 2 h-PG(mmol/L)) * 1 h/2.

Serum GDF15 measurement

According to the manufacturer's instructions, the serum concentrations of GDF15 were quantified using an enzyme-linked immunosorbent assay (ELISA) kit (R&D Systems Inc, USA) (diluted 100 times). The assay has a high sensitivity, the minimum detectable dose of human GDF15 is 0.0–4.4 pg/mL, and the cross-reactivity or the interaction between the used GDF15 and the analog is negligible, so the detection of GDF15 has excellent specificity.

Statistical analysis

Normal distribution data were displayed as mean ± standard deviation. Non-normally distributed variables were log10 converted before analysis and expressed as the median of the quartile range. An independent-sample *t*-test was used to compare the differences between the two groups. The one-way ANOVA and rank sum test were used to compare the differences in the groups. Correlation between the blood GDF15 levels and clinical indicators was explored using Pearson's correlation analysis and linear regression analysis. The chi-square test was used for categorical variables, multiple stepwise regression analysis was used to analyze the relationship between GDF15 and related parameters. Multinomial logistic regression analysis was used to analyze the relationship between GDF15 and metabolic abnormalities. IBM SPSS (version 22.0; Armonk, NY, USA) was used for statistical analyses. GraphPad Prism software (version 6.02; La Jolla, CA, USA) was used to draw the figures. We considered all two-tailed P-values < 0.05 to be significant.

Table 1 | Anthropometric parameters and clinical characteristics of the participants

	Quartile 1 (<10885 pg/mL)	Quartile 2 (10885-15263 pg/mL)	Quartile 3 (15263-20192 pg/mL)	Quartile 4 (>20192 pg/mL)	*P* value
n	103	103	103	102	
Age (year)	29.38 ± 4.33	29.37 ± 4.41	29.69 ± 4.70	29.89 ± 3.89	0.789
SBP (mmHg)	112.33 ± 10.75	112.37 ± 10.88	110.42 ± 10.35	111.26 ± 9.90	0.478
DBP (mmHg)	71.10 ± 8.18	71.83 ± 8.09	69.44 ± 7.45	70.31 ± 7.43	0.146
FPG (mmol/L)	4.49 ± 0.82	4.48 ± 0.73	4.72 ± 1.11	4.57 ± 0.87	0.212
1h-PG (mmol/L)	7.70 ± 1.85	7.96 ± 1.95	8.46 ± 2.07	8.90 ± 2.04	<0.001
2h-PG (mmol/L)	6.76 ± 1.42	6.94 ± 1.53	7.45 ± 1.80	7.85 ± 1.73	<0.001
HbA1c (%)	4.85 ± 0.39	4.89 ± 0.39	4.92 ± 0.40	4.91 ± 0.35	0.557
AUC for glucose (mmol/L h)	13.29 ± 2.46	13.67 ± 2.55	14.41 ± 2.67	15.07 ± 2.69	<0.001
Triglycerides (mmol/L)	2.07(1.67,2.64)	2.18(1.74,2.61)	2.20(1.73,2.77)	2.39(1.88,3.24)	0.022
Total cholesterol (mmol/L)	6.11 ± 0.87	6.04 ± 1.14	6.19 ± 1.18	6.22 ± 1.04	0.603
HDL-c (mmol/L)	1.70 ± 0.26	1.67 ± 0.30	1.71 ± 0.31	1.71 ± 0.29	0.745
LDL-c (mmol/L)	2.89 ± 0.61	2.88 ± 0.86	2.97 ± 0.85	2.98 ± 0.79	0.699
GDM	37(35.9%)	38(36.9%)	56(54.4%)	69(67.6%)	<0.001

1h-PG, 1-h postprandial glucose; 2h-PG, 2-h postprandial glucose; AUC for glucose, area under the glucose-time curve from the 2h OGTT; DBP, diastolic blood pressure; FPG, fasting plasma glucose; HbA1c, hemoglobin A1c; HDL-c, high-density lipoprotein cholesterol; LDL-c, low-density lipoprotein cholesterol; SBP, systolic blood pressure. Data presented as the mean ± standard deviation or median (interquartile range).

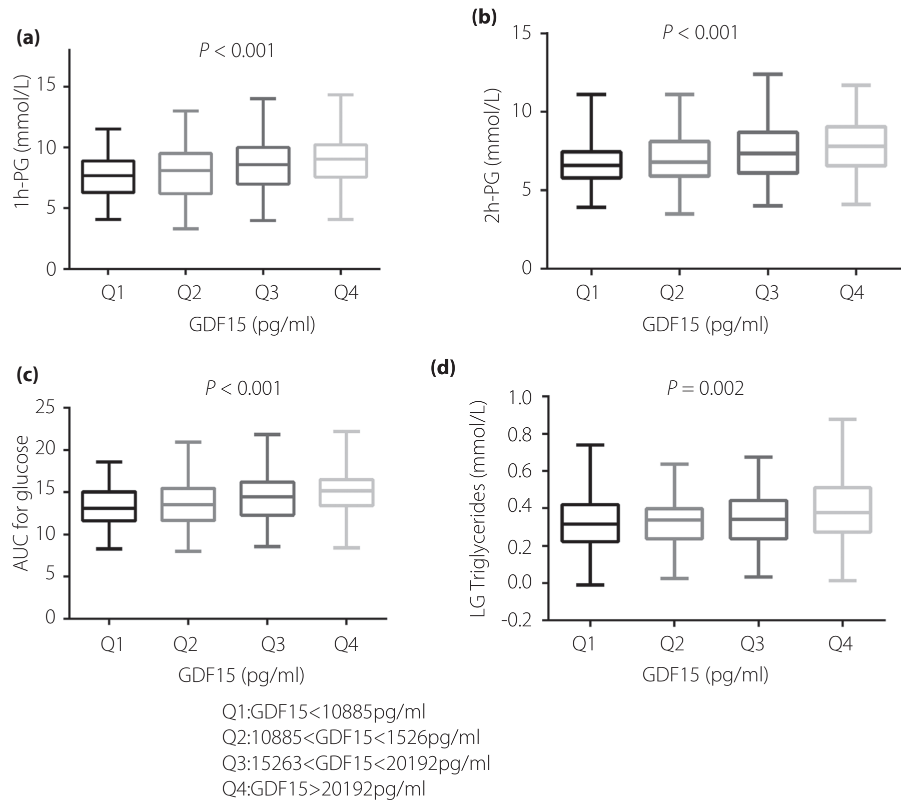

Figure 1 | (a-d) The relationship between GDF15 and 1h-PG, 2h-PG, AUC for glucose and LG triglycerides.

RESULTS

Relationship between serum GDF15 and glucose metabolism

As shown in Table 1, the anthropometric parameters and patient characteristics were described based on serum GDF15 levels (divided into four quartiles). One-way ANOVA analysis showed that with the rise of GDF15, there were significant differences in 1h-PG, 2h-PG and AUC for glucose between the groups, which in turn increased (all $P < 0.05$) (Figure 1).

Table 2 | Multiple stepwise regression analysis showing variables independently associated with the serum GDF15 levels

Independent variables	B	SE	Standardized β	*P* value
2h-PG (mmol/L)	826.976	279.087	0.182	0.003
Triglycerides (mmol/L)	6798.851	2395.221	0.146	0.005
1h-PG (mmol/L)	616.170	226.149	0.166	0.007
Gestational week (weeks)	759.353	287.144	0.128	0.009

The analysis also included age, total cholesterol, HDL-c, LDL-c and FPG, which were all excluded in the final model.

Table 3 | Characteristics of the NGT and GDM group

Variable	NGT (n = 211)	GDM (n = 200)	*P* value
Age (year)	29.35 ± 4.44	29.83 ± 4.22	0.258
FPG (mmol/L)	4.21 ± 0.35	4.94 ± 1.12	<0.001
1h-PG (mmol/L)	7.17 ± 1.47	9.39 ± 1.91	<0.001
2h-PG (mmol/L)	6.44 ± 0.99	8.11 ± 1.82	<0.001
HbA1c (%)	4.85 ± 0.35	4.94 ± 0.41	0.015
FINS (mU/L)	6.84 (4.74,10.30)	7.24 (5.01,10.77)	0.167
1h-INS (mU/L)	57.48 (42.66,86.59)	68.85 (45.87,96.58)	0.014
2h-INS (mU/L)	55.08 (37.08,82.24)	77.96 (50.53,125.10)	<0.001
Triglycerides (mmol/L)	2.15 (1.69,2.62)	2.27 (1.82,3.13)	0.002
Total cholesterol (mmol/L)	6.12 ± 1.06	6.16 ± 1.06	0.682
HDL-c (mmol/L)	1.70 ± 0.28	1.69 ± 0.30	0.585
LDL-c (mmol/L)	2.90 ± 0.77	2.97 ± 0.80	0.396
AUC for glucose (mmol/L h)	12.48 ± 1.84	15.82 ± 2.32	<0.001
GDF15 (pg/mL)	13941 ± 5567	18462 ± 8023	<0.001

Data presented as the mean ± standard deviation or median.

Through a bivariate correlation analysis, we tested the relationship between GDF15 levels and glucose metabolism-related indicators in pregnant women. GDF15 was positively correlated with 1h-PG (r = 0.267, P < 0.001), 2h-PG (r = 0.285, P < 0.001), HbA1c (r = 0.106, P = 0.031), AUC for glucose (r = 0.297, P < 0.001). In addition, after adjustment for age and gestational week, a partial correlation analysis showed GDF15 was still positively correlated with 1h-PG (r = 0.287, P < 0.001), 2h-PG (r = 0.297, P < 0.001), HbA1c (r = 0.117, P = 0.018), and AUC for glucose (r = 0.318, P < 0.001).

Relationship between serum GDF15 and lipid metabolism

One-way ANOVA analysis showed that, with the rise of GDF15, there were significant differences in triglycerides between the groups (P = 0.002) (Figure 1). Through a bivariate correlation analysis, we found a linear relationship between GDF15 and triglycerides (r = 0.203, P < 0.001). After adjustment for FPG, 1h-PG, 2h-PG, HbA1c, a partial correlation analysis showed GDF15 were still positively correlated with triglycerides (r = 0.129, P = 0.01). Furthermore, multiple stepwise regression analysis was carried out to determine variables with independent associations with serum GDF15 (Table 2). It was shown that GDF15 was independently corrected with 2h-PG, triglycerides, 1h-PG and gestational week (all P < 0.05). In addition, by chi-square test analysis, it was shown that the prevalence of GDM in each group was statistically different (x^2 = 25.910, P < 0.001). No significant differences were found with respect to age, SBP, DBP, FPG, HbA1c, total cholesterol, HDL-c and LDL-c.

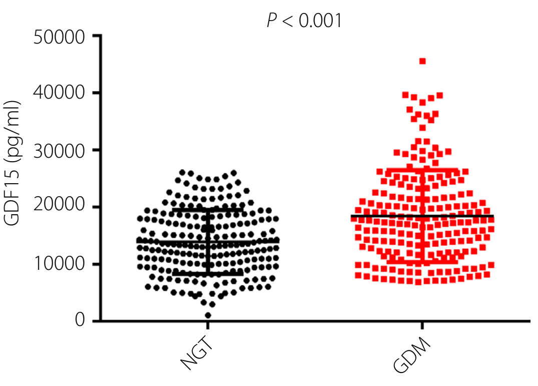

Figure 2 | GDF15 levels in NGT and GDM groups at 24–28 weeks of gestation. The GDF15 levels in the GDM group were significantly elevated than the NGT group.

Table 4 | Characteristics of metabolic groups

	G1	G2	G3	*P* value
n	188	171	48	
Age (year)	29.21 ± 4.33	29.71 ± 4.39	30.29 ± 4.08	0.246
SBP (mmHg)	111.69 ± 9.93	110.54 ± 10.39	115.21 ± 12.29	0.024
DBP (mmHg)	70.84 ± 7.07	69.70 ± 7.83	73.25 ± 9.96	0.019
FPG (mmol/L)	4.21 ± 0.33	4.86 ± 1.17	4.92 ± 0.80	<0.001
1h-PG (mmol/L)	7.11 ± 1.45	9.12 ± 2.00	9.72 ± 1.59	<0.001
2h-PG (mmol/L)	6.39 ± 1.00	7.77 ± 1.79	8.74 ± 1.54	<0.001
HbA1c (%)	4.82 ± 0.33	4.92 ± 0.42	5.05 ± 0.38	<0.001
AUC for glucose (mmol/L h)	12.39 ± 1.81	15.35 ± 2.44	16.46 ± 2.10	<0.001
Triglycerides (mmol/L)	2.03(1.64,2.40)	2.18(1.76,2.73)	3.68(3.39,4.59)	<0.001
Total cholesterol (mmol/L)	6.11 ± 1.05	6.20 ± 1.06	6.06 ± 1.13	0.639
HDL-c (mmol/L)	1.71 ± 0.28	1.72 ± 0.29	1.56 ± 0.29	0.003
LDL-c (mmol/L)	2.91 ± 0.75	3.03 ± 0.79	2.70 ± 0.85	0.030
GDF15 (pg/mL)	13762 ± 5288	17666 ± 7685	19890 ± 9138	<0.001

Grouped according to the number of metabolic abnormalities including blood sugar, triglycerides and blood pressure. G1: No metabolic abnormality; G2: One metabolic abnormality; G3: Two or more metabolic abnormalities.

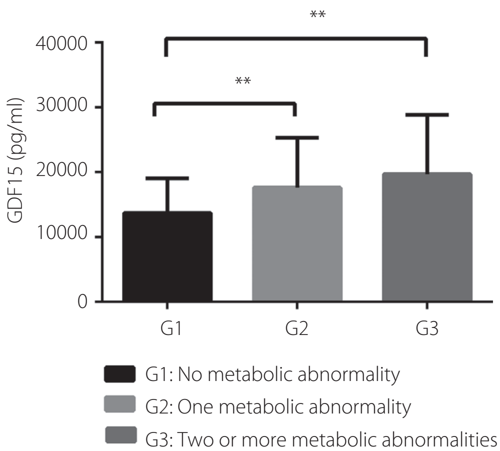

Figure 3 | GDF15 levels in no metabolic abnormality, one metabolic abnormality and two or more metabolic abnormalities groups. **Difference between groups at *P*.

Table 5 | Relationship between GDF15 and metabolic abnormalities

	n	OR (95% CI)	*P* value
G2 (one metabolic abnormality)			
Q1	103	Ref.	-
Q2	102	0.846 (0.467, 1.533)	0.581
Q3	101	1.919 (1.066, 3.454)	0.030
Q4	101	3.467 (1.857, 5.471)	<0.001
G3 (Two or more metabolic abnormalities)			
Q1	103	Ref.	-
Q2	102	0.952 (0.335, 2.700)	0.926
Q3	101	2.159 (0.811, 5.748)	0.124
Q4	101	5.673 (2.214, 14.535)	<0.001

The reference category is G1 (no metabolic abnormality), multinomial logistic regression analysis was used. Q: quarter. Four quarters according to the value of GDF15. Q1: GDF15 < 10885 pg/mL; Q2: 10885 < GDF15 < 15263 pg/mL; Q3: 15263 < GDF15 < 20192 pg/mL; Q4: GDF15 > 20192 pg/mL.

Comparison of GDF15 levels between GDM and NGT group

Basing on the World Health Organization guidelines published in 2013, we divided participants into a GDM group and a NGT group. Table 3 and Figure 2 show the concentration of GDF15 in the two groups. Compared with the level in the NGT group, the GDF15 levels in the GDM group were significantly elevated ($P < 0.001$).

Relationship between GDF15 and metabolic abnormalities

Table 4 shows the anthropometric parameters and clinical characteristics of each group according to the number of metabolic abnormalities in the participants. As shown in Figure 3, serum GDF15 levels in women with metabolic abnormalities increased significantly ($P < 0.001$). The level of GDF15 was highest in women with multiple metabolic abnormalities. We also performed multinomial logistic regression analysis, the results are shown in Table 5. Taking 'no metabolic abnormality' as the reference group, the occurrence of metabolic abnormalities in both the 'one metabolic abnormality' and the 'multiple metabolic abnormalities' is related to GDF15. We found that with the increase in the GDF15 level, the higher was the risk of metabolic abnormality in patients.

DISCUSSION

In previous studies on GDF15, most of them only focused on glucose metabolism or lipid metabolism. In the present study, we found that GDF15 is associated with metabolic abnormalities. High levels of serum GDF15 may predict the occurrence of metabolic abnormalities during pregnancy. By grouping abnormal conditions of metabolic status, we found that with multiple metabolic abnormalities, the level of serum GDF15 continued to rise. This finding suggested that GDF15 may play an important role in metabolism during pregnancy. Previous studies have found that the existence of high GDF15 may be a risk factor for some diseases, such as diabetes and its complications, obesity and cardiovascular disease [6,13,14]. In our study, we showed that as GDF15 levels increased, the risk of metabolic abnormalities also increased, especially the risk of two or more metabolic abnormalities. Therefore, we hypothesize that GDF15 is a potential risk factor in metabolic abnormalities during pregnancy.

We also found that in pregnant women, the GDF15 level was linearly correlated with 1h-PG, 2h-PG, HbA1c and AUC for glucose, even after controlling for age and gestational age. This is consistent with a previous study that showed similar findings in the third trimester general diabetes population[10]. When we divided the pregnant women into GDM and NGT groups according to the blood glucose situation for case–control analysis, we showed that in the GDM group, the level of GDF15 is significantly higher than that of the NGT group. In previous studies, the level of serum GDF15 in the diabetic population was significantly higher than that in the normal population[6,15]. This further confirms that the secretion of GDF15 is increased during hyperglycemia.

We also found that there is a linear positive correlation between GDF15 and triglycerides, even after controlling for indicators related to blood glucose metabolism. Although this result is inconsistent with previous results in pregnant women, which showed that in people with high GDF15, triglyceride levels were lower[10]. However, it has been found that triglycerides increase with the increase of GDF15 in both the general diabetic population and in mouse studies[8,9,16,17]. Moreover, it was found that increased GDF15 can suppress appetite and promote fat metabolism leading to weight loss[18]. Moreover, in the GDM population, serum triglyceride levels are significantly higher than in the normal glucose tolerance population[19], which is also in line with the results of our study. Therefore, we believe that in pregnant women, there is a linear positive correlation between serum GDF15 and triglycerides.

Our study showed that metabolic abnormalities may be more predictive than hyperglycemia alone in pregnant women when assessing the role of GDF15. We recognize certain limitations in our study. Although we found a relationship between GDF15 and metabolic abnormalities in pregnant women, the specific mechanism of their interaction has not been studied. The other limitation is that we did not measure BMI before pregnancy, as BMI is also important when assessing metabolic abnormalities in pregnancy.

In conclusion, our study found that GDF15 plays an important role in glucose metabolism, lipid metabolism and other metabolic abnormalities. GDF15 is a potential risk factor for metabolic abnormalities during pregnancy; a high concentration of serum GDF15 may indicate the future occurrence and severity of metabolic abnormalities in pregnant women. Therefore, the GDF15 level may usefully predict both insulin resistance and metabolic dysfunction.

ACKNOWLEDGMENTS

We thank all study participants. We also thank the nurses and doctors of the Department of Endocrinology and Metabolism of Fengxian Central Hospital for their contributions. This work was funded by a grant from the Shanghai Municipal Health Commission, China (No.202040182, No.KY201604).

DISCLOSURE

The authors declare that there are no conflicts of interest.

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