Growth differentiation factor-15 in patients with gestational diabetes mellitus and its relationship with microalbuminuria

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Abstract. Gestational diabetes mellitus (GDM) is a common pregnancy-related complication and growth differentiation factor-15 (GDF-15) is involved in a number of diseases; therefore, the aim of the present study was to investigate the level and clinical significance of serum GDF-15 levels in patients with GDM. A total of 237 pregnant women at 20-24 weeks of gestation were selected and assigned to a normal pregnancy group (70 patients) and a GDM group (167 patients) according to the presence or absence of GDM. The general clinical data of the two groups were collected. Fasting plasma glucose, 1-h plasma glucose, 2-h plasma glucose, glycated hemoglobin, fasting insulin, 24-h urinary albumin and serum GDF-15 levels were measured. The results showed that the body mass index (BMI) of the GDM group was higher than that of the normal pregnancy group. Fasting plasma glucose, 1-h plasma glucose, 2-h plasma glucose, fasting insulin, glycated hemoglobin and GDF-15 levels and the positive rate of microalbuminuria were significantly higher in the GDM group compared with the normal pregnancy group. GDF-15 levels were positively correlated with BMI, fasting plasma glucose, glycated hemoglobin, homeostasis model assessment-insulin resistance and fasting insulin levels. Logistic regression analysis suggested that elevated GDF-15 levels are an independent risk factor for microalbuminuria. In conclusion, serum GDF-15 levels are strongly associated with GDM and elevated GDF-15 levels are an independent risk factor for microalbuminuria. Serum GDF-15 may act as a novel biomarker for predicting microalbuminuria in GDM patients.

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Introduction

Gestational diabetes mellitus (GDM) is a significant pregnancy complication that is defined as glucose intolerance occurring in the second and third trimester of pregnancy with no preexisting diabetes diagnosis (1), which poses a great risk to the mother and fetus. Although most of these patients have normal glucose metabolism after childbirth, they are at higher risk for type 2 diabetes mellitus (T2DM) (2). The pathogenesis of GDM includes genetic factors and pancreatic β cell failure due to placental factors and common risk factors for GDM include metabolic inflammation, increased adipose tissue mass, a family history of diabetes mellitus, advanced maternal age, a lack of nutritional intake, a lack of physical activity, polycystic ovary syndrome and oxidative stress (3-5). Nevertheless, the molecular pathways of GDM are not clearly understood.

Growth differentiation factor-15 (GDF-15), which is also known as macrophage-inhibiting cytokine-1, is a member of the TGF-β superfamily and is present in a wide variety of cells and tissues (6,7). The level of GDF-15 in the circulation is closely related to the progression of a number of diseases (8). GDF-15 expression is increased in various acute and chronic inflammatory states, including tissue injury, cancer, cardiovascular disease and diabetes (9-12). Various animal and human studies have shown the association of GDF-15 and glycometabolic disorders (13,14). High plasma glucose levels and hyperinsulinemia significantly increase GDF-15 levels in humans (15). Furthermore, the expression level of serum GDF-15 increases with older age and higher body mass index (BMI) (16-18). Studies have shown that GDF-15 levels are higher in patients diagnosed with GDM at 24-28 weeks of gestation than in nondiabetic pregnant women (19,20). However, there are few relevant studies regarding the expression level of GDF-15 before 24 weeks of gestation.

The present study measured serum GDF-15 levels in pregnant women with GDM and healthy pregnant women at 20-24 weeks of gestation, as well as their relationship with various traditional indicators of diabetes mellitus and explored the risk factors for microalbuminuria in patients with GDM.

Materials and methods

Ethical considerations. The present study was approved by the Medical Ethics Committee of the Nantong Haimen People's Hospital (approval no. C20131102) and carried out in accordance with the Declaration of Helsinki.

Participant population. The present study recruited 237 pregnant women at 20-24 weeks gestation at Nantong Haimen People's Hospital between January 2014 and December 2020. The criteria for inclusion in the study were an uncomplicated pregnancy and good health, judged from the medical history. At entry, all subjects were nonsmokers and did not consume alcohol. The exclusion criteria were a history of anemia, hypertension, diabetes mellitus, or chronic kidney disease before pregnancy. When participants were enrolled in this study, an oral glucose tolerance test (OGTT) was performed according to a previous study (21). The classification of GDM was based on the World Health Organization guidelines published in 2013 (22), which was consistent with International Association of the Diabetes and Pregnancy Study Groups (IADPSG) diagnostic criteria: A fasting plasma glucose (FPG) level ≥5.1 mmol/l, 1-h plasma glucose (1-h PG) level ≥10.0 mmol/l, or 2-h plasma glucose (2-h PG) level ≥8.5 mmol/l (23). All 237 women were classified into either the GDM group (n=167) or normal glucose tolerance group (n=70) (non-GDM) according to plasma glucose levels. A urinary microalbumin level >30 mg/24 h and <300 mg/24 h was defined as positive for microalbuminuria based on the description in a previous study (24).

Clinical and serum GDF-15 measurement methods. Fasting venous blood was collected. Urine was collected for 24 h and sent to the clinical laboratory centre of Nantong Haimen People's Hospital. FPG, 1-h PG and 2-h PG levels were measured using the glucose oxidase method and glycated hemoglobin and urinary microalbumin levels were measured using the immunoturbidimetric method. Fasting insulin was measured by the chemiluminescence method. Homeostasis model assessment-insulin resistance (HOMA-IR) indexes were calculated as HOMA-IR=FPG x fasting insulin/22.5.

The levels of serum GDF-15 were determined by ELISA kit (Abcam; cat. no. ab155432) according to the manufacturer's instructions. Briefly, 100 μl of standard and sample were added into appropriate wells and incubated for 2.5 h at room temperature. After discarding the solution and washing three times with phosphate buffer solution, 100 μl of prepared biotinylated antibody was added to each well before incubation for 1 h at room temperature with gentle shaking. After the plate was washed three times, 100 μl of Streptavidin solution was added to each well. Following incubation for 45 min at room temperature, the plate was again washed three times with phosphate buffer solution. Then, 100 μl of TMB One-Step Substrate Reagent was added to each well, followed by the addition of stop solution. The absorbance at 450 nm was measured using an ELISA plate reader (Bio-Rad Laboratories, Inc.).

Statistical analysis. The Shapiro-Wilk test was used to check the normality of the distribution of continuous variables. The averages of the variables are expressed as the mean ± standard deviation (normally distributed data) or the median (interquartile range) (nonnormally distributed data). An independent-sample t test was used to compare differences between the two groups for the normally distributed parameters, whereas the Mann-Whitney U test was used for the nonnormally distributed parameters. Comparisons between proportions were performed with the chi-square test. The strength and direction of the relationships between continuous variables were analyzed by Pearson's analysis as applicable. Logistic regression was used to identify risks associated with elevated urinary microalbumin levels. Statistical analyses were performed using SPSS 20.0 software (IBM Corp.). GraphPad Prism 8.0 software (Dotmatics) was used for plotting.

Results

Basic clinical characteristics of the normal pregnancy and GDM groups. A total of 237 pregnant women participated in the present study. The two groups were matched by age. There was no significant difference in gestational age between the GDM and normal pregnancy groups (22.04±1.35 vs. 21.98±1.27; P=0.767). The BMI of the GDM group was higher than that of the normal pregnancy group (24.72±1.86 vs. 22.82±0.74; P<0.001). FPG (7.77±1.45 vs. 5.11±0.31; P<0.001), 1-h PG (9.81±1.53 vs. 5.79±0.52; P<0.001), 2-h PG (12.33±1.49 vs. 7.41±1.17; P<0.001), fasting insulin (8.45±1.05 vs. 6.08±0.50; P<0.001), HOMA-IR (1.38±0.21 vs. 2.94±0.77; P<0.001) and glycated hemoglobin (7.63±1.20 vs. 5.61±0.40; P<0.001) levels were significantly higher in the GDM group than in the normal pregnancy group. Microalbuminuria was significantly more common in the GDM group than in the normal pregnancy group (36.52% vs. 0%; P<0.001; Table I).

Comparison of serum GDF-15 levels between the normal pregnancy and GDM groups. Based on the World Health Organization guidelines published in 2013, participants were divided into a GDM group and a normal pregnancy group. Fig. 1 shows the concentration of serum GDF-15 in the two groups. Compared with the levels in the normal pregnancy group, the GDF-15 levels in the GDM group were significantly elevated (P<0.001; Fig. 1).

Correlations between serum GDF-15 levels and clinical characteristics and indicators in the GDM group. Through a Pearson correlation analysis, the relationship between serum GDF-15 levels and glucose metabolism-related indicators in pregnant women was analyzed. GDF-15 levels were positively correlated with BMI (r=0.223; P=0.004), FPG (r=0.401, P<0.001), glycosylated hemoglobin (r=0.339; P<0.001), HOMA-IR (r=0.474; P<0.001) and fasting insulin levels (r=0.375; P=0.000; Fig. 2).

Table I. Clinical characteristics and biochemical parameters of the participants.

Characteristic or parameter	Normal pregnancy group (n=70)	Gestational diabetes mellitus group (n=167)	$t/\chi^2/Z$	P-value
Age, median year[a] (lower, upper quartile)	28 (27, 29)	28 (24, 29)	-1.788	0.074
BMI, kg/m^2	22.82±0.74	24.72±1.86	-11.202	0.000
Gestational age, weeks	21.98±1.27	22.04±1.35	-0.297	0.767
Fasting plasma glucose, mmol/l	5.11±0.31	7.77±1.45	-22.311	<0.001
1-h plasma glucose, mmol/l	5.79±0.52	9.81±1.53	-30.008	<0.001
2-h plasma glucose, mmol/l	7.41±1.17	12.33±1.49	-115.27	<0.001
Fasting insulin, IU/ml	6.08±0.50	8.45±1.05	-23.272	<0.001
Homeostasis model assessment-insulin resistance	1.38±0.21	2.94±0.77	16.653	<0.001
Glycosylated haemoglobin, %	5.61±0.40	7.63±1.20	-90.194	<0.001
positive urinary microalbumin	0 (0%)	61 (36.52%)	34.431	<0.001

Clinical and biochemical parameters: expressed as mean ± standard deviation except that marked.

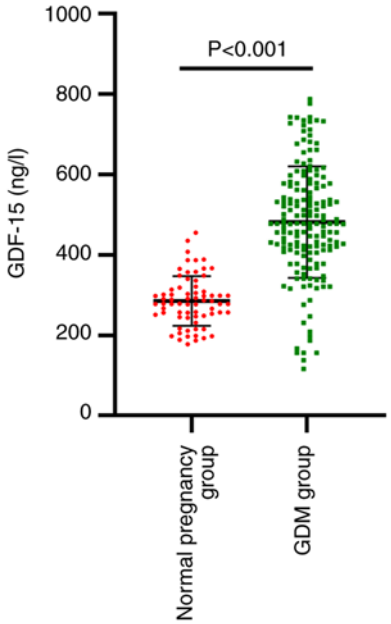

Figure 1. Comparison of serum GDF-15 levels between the normal pregnancy and GDM groups. GDF-15, growth differentiation factor-15; GDM, gestational diabetes mellitus.

Analysis of risk factors for microalbuminuria in the GDM group. As a result of the univariate logistic regression analysis, older age [odds ratio (OR)=1.101, 95% confidence interval (CI) 1.001-1.211] and FPG (OR=6.564, 95% CI 3.840-1.222), 1-h PG (OR=1.451, 95% CI 1.162-1.812), fasting insulin (OR=2.237, 95% CI 1.534-3.262), glycosylated hemoglobin (OR=1.521, 95% CI 1.100-2.103) and GDF-15 levels (OR=1.011, 95% CI 1.007-1.015) were related to elevated urinary microalbumin levels. Factors such as FPG, 1-h PG, fasting insulin, glycosylated hemoglobin and GDF-15 were included in the multivariable logistic regression analysis. In the multivariate logistic regression analysis, elevated GDF-15 (OR 1.013, 1.006-1.020) and FPG levels (OR 6.069, 3.130-11.874) were independent risk factors for microalbuminuria (Table II).

Discussion

GDM is defined as diabetes diagnosed in the second or third trimester of pregnancy without overt diabetes prior to gestation (25). GDM increases the risk of adverse pregnancy outcomes and causes adverse effects on both the mother and fetus. GDM often leads to diabetic nephropathy, retinopathy, fetal macrosomia and unexplained fetal death and increases the risk of neonatal hypoglycemia, hypocalcemia, jaundice, acute respiratory distress syndrome and cardiomyopathy (26). Women with GDM are also prone to postpartum obesity, metabolic syndrome and T2DM (27,28). In addition, the risk of long-term cardiovascular disease is significantly increased in women with GDM (29). The incidence of GDM varies among different races and populations, with incidence rates of 2-6% in European countries, 1-14% in the United States, 9.6-13.9% in the developing countries of South Asia and 14.8% in China (30).

The pathogenesis of GDM is not fully known. In pregnancy, the levels of estrogen, progesterone, placental lactogen, human placental growth hormone and cortisol in the placenta significantly increase, which promotes the aggravation of insulin resistance. With the gradual decrease in insulin sensitivity, insulin secretion gradually increases to keep blood glucose at a normal level. Therefore, pregnancy itself is a state of hyperinsulinemia (31). If pancreatic islet β-cells cannot secrete enough insulin to compensate for pregnancy-related insulin resistance, GDM may occur. Most women with GDM are overweight or obese, with the clinical features of metabolic syndrome (31). Yarsilikal Guleroglu *et al* (32) reported that FPG and HbA1c levels in women with GDM and obesity were higher than those in normal pregnant women. The present study found that the incidence of obesity in the GDM group was significantly higher than that in the normal pregnancy group and the mean BMI was also significantly higher. In addition, FPG, 1-h PG, 2-h PG, fasting insulin and glycated

Table II. Risk factors significantly correlated with urinary microalbumin in gestational diabetes mellitus group.

Risk factor	Odds ratio	95% confidence interval	P-value	Odds ratio	95% confidence interval	P-value
Age	1.101	1.001-1.211	0.048	1.197	0.983-1.457	0.074
Fasting plasma glucose	6.564	3.840-1.222	0.000	6.069	3.130-11.874	<0.001
1-h plasma glucose	1.451	1.162-1.812	0.013	1.371	0.835-2.249	0.212
2-h plasma glucose	0.854	0.674-1.081	0.189	-	-	-
Fasting insulin	2.237	1.534-3.262	0.000	0.777	0.361-0.975	0.518
Glycosylated haemoglobin	1.521	1.100-2.103	0.011	0.566	0.235-1.361	0.204
growth differentiation factor-15	1.011	1.007-1.015	0.000	1.013	1.006-1.020	<0.001

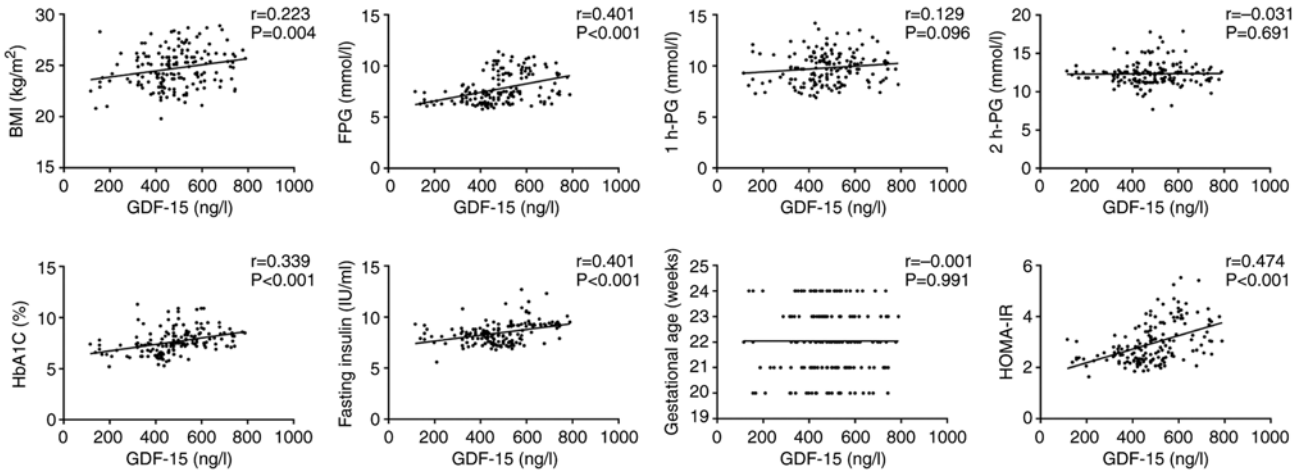

Figure 2. Correlations of GDF-15 levels with BMI, gestational age, FPG levels, 1-h PG levels, 2-h PG levels, glycosylated haemoglobin levels, HOMA-IR levels and fasting insulin levels in the GDM group. GDF-15, growth differentiation factor-15; BMI, body mass index; FPG, fasting plasma glucose; PG, plasma glucose; HOMA-IR, homeostasis model assessment-insulin resistance; GDM, gestational diabetes mellitus.

hemoglobin levels were significantly higher in the GDM group than in the normal pregnancy group. Furthermore, the positive rate of microalbuminuria in the GDM group was significantly higher than that in the normal pregnancy group.

GDF-15 widely expressed in various cells and tissues and plays an important role in inflammatory response regulation and cell growth and differentiation (33). Biomechanical stress, local ischemia, hypoxia and inflammatory cytokine stimulation can lead to increased GDF-15 expression (33). Hyperglycemia or obesity can promote GDF-15 expression through the reactive oxygen species-p53 pathway (33). In the adipose tissue of patients with GDM, GDF-15 expression is significantly elevated, which is the main source of abnormally elevated GDF-15 in the maternal circulatory system (34). Banerjee *et al* (20) found that the mean serum GDF-15 level was significantly higher in subjects with GDM at 24-28 weeks of gestation than in nondiabetic pregnant women. Li *et al* (19) reported that GDF-15 was significantly elevated in the GDM group compared with that in the group with normal glucose tolerance at 24-28 weeks of gestation. Yakut *et al* (35) found that serum GDF-15 levels were higher in patients with GDM than in non-GDM pregnant women at 24-28 weeks of gestation. Lu *et al* (36) reported that the expression levels of GDF-15 mRNA and GDF-15 protein in late pregnancy were significantly higher in GDM patients than in non-GDM pregnant women. Andersson-Hall *et al* (37) demonstrated that GDF-15 levels significantly increased in each trimester in pregnant women with normal weight and obesity. Notably, they also found that GDF-15 levels were increased in cerebrospinal fluid during pregnancy compared with those after pregnancy (38). Banerjee *et al* (20) reported that serum GDF-15 levels were higher in GDM patients in comparison to age-matched pregnant subjects without GDM in the early third trimester of pregnancy in Indian women. Moreover, in the third trimester, GDF-15 levels increased with increases in plasma glucose and insulin resistance. However, there are few reports on serum GDF-15 levels in GDM patients before 24 weeks of gestation. Berkowitz *et al* reported that 28.8% of cases of GDM were diagnosed before 24 weeks of gestation in 354 GDM patients (39). Therefore, it is important to explore the expression of GDF-15 in GDM patients before 24 weeks of gestation. In the present study, the serum GDF-15 level in the GDM group was significantly higher than that in the normal pregnancy group at 20-24 weeks of gestation.

In patients with T2DM, GDF-15 is positively correlated with BMI, body fat, FPG, glycated hemoglobin, insulin resistance, arterial blood pressure, triglycerides and the incidence of diabetic nephropathy and is negatively correlated with the degree of anemia (40). Elevated GDF-15 levels can be used as a predictor of diabetic cardiomyopathy in patients with

T2DM (31). GDF-15 elevation has good predictive value for all-cause mortality and cardiovascular death in patients with diabetes mellitus, cardiovascular disease, kidney disease, or rheumatic disease (23). Shin *et al* (40) reported that serum GDF-15 levels were independently correlated with cardiovascular risk scores in patients with new-onset T2DM. Yarsilikal Guleroglu *et al* (32) found that the serum GDF-15 level was higher in GDM patients with obesity than in healthy pregnant women, indicating that GDF-15 is not only associated with gestational hypertension but may also be associated with obesity. Banerjee *et al* (20) showed that GDF-15 had a significant positive correlation with fasting serum insulin, HOMA-IR and FPG at 24-28 weeks of gestation in subjects with GDM. However, the relationship between GDF-15 and fasting serum insulin, HOMA-IR and FPG in GDM patients at 20-24 weeks of gestation has not been reported. The present study found that serum GDF-15 was positively correlated with BMI, FPG, glycosylated hemoglobin, fasting insulin and HOMA-IR at 20-24 weeks of gestation in subjects with GDM. Compared with traditional indicators, GDF-15 has a superior predictive value for the transition from microalbuminuria to macroalbuminuria in patients with T2DM (40). In type 1 diabetes mellitus patients with macroalbuminuria, elevated GDF-15 levels were closely associated with decreased renal function and increased risk of progression to end-stage renal disease (28,41). In the present study, multivariate logistic regression analysis revealed that GDF-15 was an independent risk factor for microalbuminuria in women with gestational diabetes at 20-24 weeks of gestation.

There were a number of limitations in this study. First, this was a cross-sectional study; therefore, any change in GDF-15 levels over time could not be documented. Second, this was a single-centre study and the sample size was relatively small. Third, because some patients did not deliver in Nantong Haimen People's Hospital, pregnancy outcomes were not fully recorded. Further research is needed to determine the exact role and mechanisms of GDF-15 in the process of the disease.

In conclusion, serum GDF-15 levels in GDM patients have good correlations with traditional indicators of diabetes mellitus, such as FPG, glycosylated hemoglobin and fasting insulin levels. Serum GDF-15 levels are also an independent risk factor for microalbuminuria. The results suggested that GDF-15 could serve as a biomarker of GDM at 20-24 weeks of gestation. Nevertheless, whether GDF-15 plays a causal role in the pathogenesis of GDM or is just a bystander requires further investigation.

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Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Authors' contributions

YG conceived and designed the present study. JS and YG performed data collection. JL and LL analyzed the data. LL and JS confirm the authenticity of all the raw data. YG wrote the original draft, which LL reviewed and edited. All authors read and approved the final manuscript.

Ethics approval and consent to participate

The present study was approved by the Medical Ethics Committee of the Nantong Haimen People's Hospital (approval no. C20131102) and carried out in accordance with the Declaration of Helsinki.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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