The relationship between serum adipokine fibroblast growth factor-21 and gestational diabetes mellitus

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ABSTRACT
Aims/Introduction: To explore the differences of serum fibroblast growth factor-21 (FGF-21) levels in pregnant women with normal glucose tolerance and gestational diabetes mellitus (GDM), and to analyze the relationship between FGF-21 and glucose and lipid metabolic indicators, leptin, retinol binding protein 4 (RBP-4) and adiponectin in GDM, in order to provide basis for the prevention and treatment of GDM.

Materials and Methods: Total of 120 women were included, and divided into normal glucose tolerance group (58 cases) and GDM group (62 cases) according to the 75 g oral glucose tolerance test results. General information were recorded; height, weight and blood pressure, blood glucose, lipids, insulin, FGF-21, leptin, RMP-4, and adiponectin were measured, and body mass index (BMI), homeostasis model assessment-IR, homeostasis model assessment-β and area under glucose curve were calculated. The t-test, Pearson analysis and multiple linear regression analysis were used to evaluate the differences and related factors of FGF-21 in GDM.

Results: The pre-pregnancy BMI, pregnancy BMI, weight gain during pregnancy and FGF-21 levels were higher in GDM group, whereas there were no statistically significant differences in leptin, RBP-4 and adiponectin. Correlation analysis suggested that FGF-21 level was correlated with age, pre-pregnancy BMI, weight gain during pregnancy, high-density lipoprotein cholesterol, leptin, RBP-4 and adiponectin, and the results of multiple linear regression showed that serum FGF-21 was related to pre-pregnancy BMI, weight gain during pregnancy, leptin, RBP-4 and adiponectin in GDM.

Conclusions: There were higher serum FGF-21 levels in GDM, which might be related to pre-pregnancy BMI, weight gain during pregnancy, leptin, RBP-4 and adiponectin.

INTRODUCTION
Gestational diabetes mellitus (GDM) is a serious pregnancy complication that occurs in women with previously undiagnosed diabetes who develop chronic hyperglycemia during pregnancy1. According to a 2017 International Diabetes Federation estimate, approximately 14% of pregnancies worldwide are affected by GDM2. In most cases, this hyperglycemia is the result of impaired glucose tolerance due to pancreatic β-cell dysfunction in the context of chronic insulin resistance34, which significantly increases the incidence of adverse perinatal maternal and infant outcomes, and maternal and infant mortality, seriously affecting maternal and infant health56. The pathogenesis of GDM is mainly considered to be due to the combination of the relative lack of insulin secretion and insulin resistance (IR) in pregnant women, but the specific mechanism is not clear. Recent studies have shown elevated levels of circulating FGF-21 in patients with insulin resistance, including obesity and type 2 diabetes mellitus7. Elevated levels of FGF-21 were also independent predictors of type 2 diabetes mellitus8. GDM and type 2 diabetes mellitus have a similar pathophysiological basis, which raises the question of whether there is a
similar relationship between FGF-21 and GDM. At present, some studies have pointed out that in diabetes mellitus animal models, long-time injection of FGF21 can control blood glucose at normal levels, and can significantly reduce the concentration of insulin in the blood, thereby improving the body’s sensitivity to insulin. The present study suggests that FGF21 may play a role in improving insulin resistance, but the specific mechanism is not clear. There are few studies on the causes of elevated circulating FGF-21 levels in GDM patients. In the present study, FGF-21 levels were compared between healthy people and pregnant women with GDM. The aim of this study was to explore the relationship between FGF-21 and glucose, and lipid metabolism indexes, leptin, retinol binding protein 4 (RBP-4) and adiponectin levels, and to detect the value of FGF21 in the early diagnosis of GDM patients.

MATERIALS AND METHODS

General information
A total of 120 pregnant women who underwent routine prenatal examinations in Qinhuangdao Maternal and Child Health Hospital from July 2017 to July 2018 were selected and underwent oral 75 g oral glucose tolerance test (OGTT) at the 24th to 28th week of pregnancy. The normal glucose test (NGT) group (n = 58) and the GDM group (n = 62) were determined according to the OGTT results. The diagnosis of GDM is based on the diagnostic criteria of the People’s Republic of China Health Industry Standards implemented since December 2011: fasting venous blood glucose ≥5.1 mmol/L or 1-h blood glucose ≥10.0 mmol/L or 2-h blood glucose ≥8.5 mmol/L after 75 g OGTT loading L.

Inclusion criteria were as follows: patients diagnosed with gestational diabetes mellitus; no diabetes mellitus before pregnancy; and family members and patients agreed to participate in the present study. Exclusion criteria were as follows: those with other diseases during pregnancy; those with hypertension and hyperglycemia; those with other complications and chronic diseases. This study was approved by the Ethics Committee of Qinhuangdao Maternal and Child Health Hospital, and all patients obtained informed consent and signed the informed consent form. The approval number of the ethics committee: 2021Q088.

Materials and Methods

Clinical data
All participants were asked about their medical history, recorded age, gestational weeks, pre-pregnancy weight, reproductive history, performed physical examination, measured height and weight; calculated pre-pregnancy and pregnancy BMI (BMI = weight/height² [kg/m²]); and calculated pregnancy gain. Weight gain during pregnancy = second trimester weight − pre-pregnancy weight. The right brachial artery blood pressure was measured by mercury sphygmomanometer in the quiet state, and the average value was recorded twice.

Detection of clinical biochemical indicators
All pregnant women (24–28 weeks of gestation) fasted for 8–10 h at night, and the venous blood was drawn the next morning, and the specimens were collected. The central laboratory automatic biochemical analyzer (Hitachi 7060 type, Ibaraki, Japan) was used to detect fasting plasma glucose (FPG), triglyceride, serum total cholesterol, high-density lipoprotein cholesterol (HDL-c), low-density lipoprotein cholesterol, creatinine, uric acid, blood urea nitrogen, alanine aminotransferase and aspartate aminotransferase. The methods used in an automatic biochemical analyzer include continuous monitoring method, turbidimetric method, ion selective electrode method and end-point analysis method. First, 5 mL venous blood of pregnant women was extracted, centrifuged for 10 min (3,130 g) and the supernatant was taken. Finally, the results of the above indexes can be obtained by adding the obtained plasma to the automatic biochemical analyzer. Fasting insulin (FINS) levels were detected by radioimmunoassay (Linco, San Francisco, CA, USA). Fasting serum FGF-21 (Czech Biovendor Company, San Francisco, CA, USA), RBP-4, Adiponectin and Leptin (all from American RD Company, San Francisco, CA, USA) were determined by enzyme-linked immunosorbent assay. The specific steps are as follows: 2,000, 1,000, 500, 250, 125, 62.5 and 31.2 pg/mL standard samples were added into a row of seven holes in turn, one hole only added sample diluent as zero hole. Human serum was directly added to 100 µL of the sample diluted with sample diluent. Enzymatic plate with sealing film, 37°C reaction 90 min. After the reaction, the liquid in the enzyme label plate was removed by the automatic plate washing machine, and then put on the absorbent pad. No washing. The prepared biotin anti-human FGF21 antibody working solution was added at 100 µL per well. Enzymatic plate with sealing film, 37°C reaction 60 min. Then, 1× washing buffer was washed three times, each time soaked for approximately 1 min. The prepared ABC working solution was added in order of 100 µL per well. Enzymatic plate with sealing film, 37°C reaction 30 min. Washed five times with 1× washing buffer, soaked 1–2 min each time. According to 90 µL per well, TMB chromogenic solution that had been balanced at 37°C for 30 min was added in turn, and the reaction was carried out in the dark at 37°C for 20–25 min. The termination solution was added at 100 µL per well, followed by TMB addition. At this time, blue turned yellow. The optical density value was measured at 450 nm by an enzyme-labeled instrument. The measured value can be obtained. The above adipokines samples were centrifuged for 10 min (3,130 g), and the serum was separated and stored in a −80°C refrigerator for the same batch of detection. The operation was carried out in strict accordance with the kit instructions. Serum levels of FGF-21, adiponectin, insulin and RBP-4 were measured using available kits: intra-assay CV(%) is <10% and inter-assay CV(%) is <15%.

The homeostasis model assessment method was used to evaluate the insulin resistance index (HOMA-IR) = FINS [mIU/L] ×
FPG [mmol/L]/22.5) and islet β-cell function ([HOMA-β] = 20 × FINS/[fasting blood glucose – 3.5]). The area under the OGTT blood glucose curve was calculated ([AUCG] = FPG2 + glycemic load 1 h blood glucose + glycemic load 2 h blood glucose).

Statistical methods
SPSS 22.0 software package was used for statistical analysis. All measurement data were consistent with normal distribution, expressed as $\bar{x} \pm s$. When the data were consistent with the homogeneity of variance, the independent samples $t$-test was used to compare the two independent samples. The univariate correlation was analyzed by Pearson correlation. Using FGF-21 as the dependent variable, meaningful variables in single-factor analysis: age, pre-pregnancy BMI, weight gain during pregnancy, HDL-c, leptin, RBP-4 and adiponectin as the independent variable, multiple linear regression analysis was used. Stepwise regression was used to eliminate the multicollinearity problem in independent variables. $P < 0.05$ was considered to be statistically significant.

RESULTS
Comparison of clinical data, indexes of glucose and lipid metabolism, and adipokines levels
There were no significant differences in age, systolic blood pressure, diastolic blood pressure, total cholesterol, HDL-c, low-density lipoprotein cholesterol and UA ($P > 0.05$), but there were differences in pre-pregnancy BMI, pregnancy BMI and weight gain during pregnancy ($P < 0.05$). The levels of fasting blood glucose, 1 h blood glucose, 2 h blood glucose, FINS, glycated hemoglobin, HOMA-IR, AUCG and triglyceride in the GDM group were higher than those in the control group, and HOMA-β was lower than that in the NGT group ($P < 0.05$). The comparison of adipokines levels showed that the levels of FGF-21 in the GDM group were higher than those in the NGT group ($P < 0.05$), whereas the levels of leptin, RBP-4 and adiponectin were not significantly different ($P > 0.05$; see Tables 1–3).

Univariate analysis results of FGF-21 level and each index in GMD group
FGF-21 level correlated with age ($r = −0.252, P = 0.050$), pre-pregnancy BMI ($r = −0.291, P = 0.01$), weight gain during pregnancy ($r = 0.441, P = 0.000$), HDL-c ($r = 0.276, P = 0.037$), Leptin ($r = 0.992, P = 0.000$), RBP-4 ($r = 0.983, P = 0.000$) and adiponectin ($r = −0.992, P = 0.000$).

It was negatively correlated with age, pre-pregnancy BMI, HDL-c and Adiponectin; while the correlation with HOMA-IR ($r = 0.169, P = 0.189$), HOMA-β ($r = −0.206, P = 0.108$), AUCG ($r = 0.163, P = 0.206$), were all not statistically significant. See Table 4.

Results of multiple linear regression analysis
In the GDM group, multiple linear regression analysis was carried out with serum FGF-21 as the dependent variable. The results showed that the level of FGF-21 was related to pre-pregnancy BMI, weight gain during pregnancy, leptin, RBP-4 and adiponectin (Table 5).

DISCUSSION
Patients with GDM have more severe IR than pregnant women with normal glucose tolerance, but the mechanism of IR is not very clear. Studies have shown that a variety of adipokines might regulate insulin sensitivity, are related to insulin sensitivity and glucose and lipid metabolism, and play an important role in the occurrence and development of IR and GDM characterized by IR. However, previous studies have suggested that there are a variety of adipokines secretion disorders in GDM patients. In addition, GDM significantly increases the risk of long-term adverse health problems for mothers and children, such as obesity, type 2 diabetes and cardiovascular disease. Some studies have pointed out that GDM and type 2 diabetes have similar potential pathophysiology, and FGF21 has a similar relationship with GDM and type 2 diabetes.

Through multiple linear regression analysis, the level of FGF-21 was related to pre-pregnancy BMI, weight gain during pregnancy, leptin, RBP-4 and adiponectin. The results suggest that with the continuous improvement of serum FGF21 level and the further aggravation of insulin resistance. The further weakening of cell function leads to the aggravation of impaired glucose tolerance. Analysis of the cause might be due to islets β-cell function cannot be compensated, resulting in the decrease of overall insulin secretion, which leads to the rise of blood glucose levels. With the further aggravation of abnormal glucose metabolism, the level of serum FGF21 in pregnant women increased gradually. It is speculated that it might be a protective role in the pathophysiology of GDM.

Table 1 | Comparison of general clinical data of the two groups of subjects ($\bar{x} \pm s$)

| Group | Case (n) | Age (years) | Systolic blood pressure (mmHg) | Diastolic blood pressure (mmHg) | BMI before pregnancy (kg/m²) | BMI during pregnancy (kg/m²) | Weight gain during pregnancy (kg) |
|-------|----------|-------------|-------------------------------|-------------------------------|-----------------------------|-------------------------------|---------------------------------|
| NGT   | 58       | 28.93 ± 3.31| 111.76 ± 8.97                | 68.89 ± 7.56                  | 20.67 ± 2.82                | 22.79 ± 2.93                  | 5.08 ± 3.17                     |
| GDM   | 62       | 29.38 ± 4.65| 114.43 ± 9.28                | 70.44 ± 7.44                  | 22.98 ± 3.31                | 25.80 ± 3.04                  | 7.43 ± 4.61                     |
| $t$   |          | 0.951       | −1.233                       | −1.547                        | −2.732                      | −2.698                       | −3.158                          |
| $P$   |          | 0.174       | 0.121                        | 0.113                         | 0.039                       | −0.041                       | 0.016                           |

BMI, body mass index; GDM, gestational diabetes mellitus; NGT, normal glucose tolerance.
compensatory mechanism of the body, which is similar to the mechanism of hyperinsulinemia. FGF-21 is an adipokine discovered in recent years, and believed to have potent hypoglycemic properties. It is mainly expressed in the liver, but also in other metabolically active tissues, such as the pancreas, skeletal muscle, adipose tissue and placenta. In GDM patients, systemic insulin-dependent glucose treatment is reduced by 40–60%, which requires a 200–250% increase in insulin secretion to maintain normal blood glucose. GDM occurs when pregnant women cannot produce enough insulin to maintain normal blood glucose levels.

Table 2 | Comparison of glucose metabolism indexes between the two groups of participants (x ± s)

| Group | FBG (mmol/L) | 1 h blood glucose (mmol/L) | 2 h blood glucose (mmol/L) | FINS (mIU/L) | HbA1c (%) | HOMA-IR | HOMA-β | AUCG |
|-------|--------------|---------------------------|---------------------------|--------------|-----------|---------|--------|------|
| NGT   | 4.61 ± 0.23  | 7.51 ± 1.00              | 6.35 ± 1.04              | 9.44 ± 3.65  | 4.87 ± 0.23 | 1.30 ± 0.23 | 173.44 ± 60.45 | 1.17 ± 1.98 |
| GDM   | 5.22 ± 0.44  | 9.54 ± 1.73              | 8.12 ± 1.49              | 12.47 ± 5.09 | 5.05 ± 0.30 | 1.89 ± 0.42 | 150.29 ± 58.41 | 20.33 ± 3.04 |
| t     | 9.307        | 7.801                    | 7.497                    | 3.734        | 2.853      | 9.488    | −2.314  | 8.802 |
| P     | 0.000        | 0.000                    | 0.000                    | 0.000        | 0.005      | 0.000    | 0.035   | 0.000 |

AUCG, area under the 75-g oral glucose tolerance test blood glucose curve; FBG, fasting blood glucose; FINS, fasting insulin; GDM, gestational diabetes mellitus; HbA1c, glycated hemoglobin; HOMA-β, homeostasis model assessment-β-cell function; HOMA-IR, homeostasis model assessment-insulin resistance; NGT, normal glucose tolerance.

Table 3 | Comparison of blood lipid metabolism and adipokines levels between the two groups of subjects (x ± s)

| Group | TG (mmol/L) | TC (mmol/L) | HDL-c (mmol/L) | LDL-c (mmol/L) | UA ([mol/L) | FGF-21 (pg/mL) | Leptin (ng/mL) | RBP-4 (g/mL) | Adiponectin (g/mL) |
|-------|-------------|-------------|----------------|----------------|-------------|----------------|----------------|--------------|-------------------|
| NGT   | 1.23 ± 0.34 | 4.48 ± 0.72 | 1.87 ± 0.56    | 195.55 ± 59.61 | 117.33 ± 33.80 | 7.57 ± 4.95 | 30.79 ± 21.51 | 20.80 ± 8.72 |
| GDM   | 1.75 ± 0.59 | 4.63 ± 0.83 | 1.88 ± 0.65    | 207.45 ± 46.43 | 192.07 ± 40.26 | 7.63 ± 6.19 | 33.08 ± 20.28 | 18.86 ± 8.78 |
| t     | 4.120       | 0.790       | −1.935         | 0.169          | 6.658       | 0.017         | 0.430         | −0.551       |
| P     | 0.000       | 0.000       | 0.000          | 0.000          | 0.000       | 0.000         | 0.000         | 0.000        |

FGF-21, fibroblast growth factor-21; GDM, gestational diabetes mellitus; HDL-c, high-density lipoprotein cholesterol; LDL-c, low-density lipoprotein cholesterol; NGT, normal glucose tolerance; RBP-4, retinol binding protein 4; TC, total cholesterol; TG, triglyceride; UA, uric acid.

Table 4 | Results of univariate correlation analysis between fibroblast growth factor-21 and age, body mass index and other adipokines in the gestational diabetes mellitus population

| Age       | BMI before pregnancy | Weight gain during pregnancy | HDL-c       | Leptin      | RBP-4       | Adiponectin  |
|-----------|----------------------|-----------------------------|-------------|-------------|-------------|--------------|
| r         | −0.252               | −0.291                      | 0.441       | −0.276      | 0.992       | −0.992       |
| P         | 0.050                | 0.01                        | 0.000       | 0.000       | 0.000       | 0.000        |

HDL-c, high-density lipoprotein cholesterol; RBP-4, retinol binding protein 4.

Table 5 | Results of multiple linear regression analysis with fibroblast growth factor-21 as the dependent variable in the gestational diabetes mellitus group

| Variables                      | B    | Standard error | β    | t    | P     | 95% CI for β |
|--------------------------------|------|----------------|------|------|-------|---------------|
| Constant                       | −7.207 | 30.390         | −    | −0.237 | −0.814 | −68.627 to 54.212 |
| Age                            | 3.146 | 1.433          | 0.052 | 1.081 | 0.079 | 0.710 to 6.484 |
| BMI before pregnancy           | −33.353 | 14.736       | −0.724 | −2.276 | 0.028 | −63.317 to −3.754 |
| Weight gain during pregnancy   | 13.822 | 5.535         | 0.372 | 2.497 | 0.017 | 2.635 to 25.010 |
| Leptin                         | 11.865 | 2.141         | 0.783 | 5.541 | 0.000 | 7.537 to 16.193 |
| RBP-4                          | 1.474 | 0.603          | 0.335 | 2.446 | 0.019 | 1.126 to 2.693 |
| Adiponectin                    | −3.610 | 0.801         | −0.551 | −4.506 | 0.000 | −5.229 to −1.990 |

B, body mass index; CI, confidence interval; RBP-4, retinol binding protein 4.
FGF-21 is a hormone mainly expressed in the liver, but it is also expressed in other metabolically active tissues, such as the pancreas, skeletal muscle, and adipose tissue. FGF-21 has emerged as an important regulator of energy metabolism with favorable effects on glucose and lipid homeostasis. There are many similarities between GDM and type 2 diabetes, and FGF21 might play a role in improving insulin resistance. Some studies believe that FGF-21 can regulate glucose uptake by adipocytes in an insulin-independent manner, improve glucose tolerance and islet cell function, and enhance insulin sensitivity. FGF-21 is associated with GDM and type 2 diabetes. Increased FGF-21 levels are an independent risk factor for type 2 diabetes. It was also found in the mouse model test that FGF-21 can regulate the secretion of glucagon in mouse pancreatic islets in vitro, and has a potential role in the treatment of diabetes. In addition, it was found in FGF-21 knockout rats, which resulted in a slight increase in bodyweight and impaired glucose tolerance. The results of the present study showed that the serum FGF-21 level in the GDM group was higher than that in the NGT group (P < 0.05). Univariate correlation analysis also showed that the FGF-21 level in the GDM group was positively correlated with pregnancy weight gain, leptin and RBP-4 levels. It was negatively correlated with age, pre-pregnancy BMI, HDL-c and adiponectin levels. After further adjusting for related influencing factors, it was still found that serum FGF-21 level was related to pre-pregnancy BMI, weight gain during pregnancy, HOMA-IR and AUCG. This result is consistent with some of the findings of Stein and Wang. To analyze the reasons, consider that FGF-21 is an important adipose factor regulating glucose and lipid metabolism, and its increase in the GDM population might be a compensatory mechanism for the body to improve this pathological state. FGF-21 might be involved in the pathophysiological process of GDM.

In conclusion, GDM is a complex disease with the interaction of environmental and genetic factors, and a variety of adipokines might be involved in the occurrence and development of GDM. FGF-21 is involved in a wide range of physiological processes, such as improving insulin resistance and regulating glucose and lipid metabolism, which might be related to the occurrence of GDM. However, the cases used in the present study cannot represent all the cases, and the controls often cannot represent the population to which they belong, which is prone to selection bias. Second, the sample size of the study was limited, which might lack strong convincing power. The relationship between FGF-21 and GDM, and its specific mechanism of action in GDM patients needs to be further verified by expanding the sample size and randomizing the multicenter in the future.

DISCLOSURE
The authors declare no conflict of interest.

Approval of the research protocol: This study was carried out in accordance with the declaration of Helsinki. This study was carried out with approval from the Ethics Committee of First Hospital of Qinhuangdao (NO.2021Q088). Approval date: 11
November 2021. Written informed consent was obtained from all participants.
Informed consent: N/A.
Registry and the registration no. of the study/trial: NO. 202101A211.
Animal studies: N/A.

**DATA AVAILABILITY STATEMENT**
All data generated or analyzed during this study are included in this article.

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