Circulating levels of fibroblast growth factor 21 in gestational diabetes mellitus: a meta-analysis

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Abstract. In recent times, the role of fibroblast growth factor 21 (FGF21) in patients with gestational diabetes mellitus (GDM) has been increasingly investigated. However, to our knowledge, no systematic analysis has been conducted yet to evaluate the relationship between FGF21 levels and GDM. Confirmed studies related to circulating FGF21 levels and GDM were searched from the databases of PubMed, ISI Web of Science, MEDLINE and EMBASE. Data were reported as standard mean difference (SMD) and associated 95% confidence intervals (CIs). Analysis were performed with Review Manager 5.2 and Stata version 11.0. A total of 392 cases and 435 controls in nine articles were included in this meta-analysis. The circulating FGF21 levels in pregnant women with GDM was higher than that in controls (random effects MD [95% CI] = 0.46, [0.07–0.86], \( p = 0.02 \)). The result of multivariate meta-regression showed that sample size and point of sample collection contributed to heterogeneity (\( p = 0.033 \) and \( p = 0.047 \), respectively). Additionally, the results showed that there was no publication bias in this meta-analysis (\( Z = 1.36, \ p = 0.175; \ t = 1.24, \ p = 0.256, \) respectively). To conclude, this meta-analysis provides evidence that circulating FGF21 levels are higher in GDM subjects than controls, and it is important to clarify the relationship between circulating FGF21 levels and pregnant women with GDM in accurate prediction of GDM.

Key words: Fibroblast growth factor 21 (FGF21), Gestational diabetes mellitus (GDM), Cytokines, Body mass index

GESTATIONAL DIABETES MELLITUS (GDM) is the most common metabolic disorder of pregnancy, with an increasing worldwide prevalence; accordingly, it has garnered significant attention in recent years [1, 2]. Recent studies show that the prevalence of GDM is over 9% in the USA, while it ranges from 3.0 to 21.2% in Asian countries [3]. Women with GDM have an increased risk of obesity, type 2 diabetes mellitus (T2DM), and cardiovascular disease (CVD), along with their children [1-3]. The state of insulin resistance will gradually increase throughout the pregnancy, which involves changes in metabolism, nutrition status, and inflammation. This pathological condition can progress to GDM when the increased insulin resistance cannot be overcome by the enhancement of islet β-cell function [2, 4]. The pathophysiology of GDM is characterized by β-cell dysfunction, chronic insulin resistance, β-cell impairment, and tissue insulin resistance [2].

Fibroblast growth factor 21 (FGF21) is a hormone-like FGF, which is expressed in the liver, adipose tissue, and pancreas [5]. The involvement of FGF21 has been recognized in many metabolic processes such as insulin sensitivity, glucose and lipid metabolism, and energy homeostasis [6, 7]. A previous study showed that FGF21 could decrease glucose levels independent of insulin, by improving insulin resistance in peripheral tissues of patients with T2DM [8]. Other studies have explored the FGF21 levels in GDM patients. Some reported a difference in circulating FGF21 levels between pregnant women with GDM and those without, while other studies failed to identify a significant difference in FGF21 levels between GDM patients and pregnant women with...
normal glucose tolerance (NGT). Yuan et al. performed a mini-review to evaluate the role of FGF21 in GDM, but they were unable to provide further clarification [9]. To investigate the relationship between FGF21 levels and GDM, we performed a meta-analysis.

Materials and Methods

Search strategy
We searched all the clinical studies on the relationship between circulating FGF21 levels and GDM by using the databases of PubMed, ISI Web of Science, MEDLINE and EMBASE. All literatures related to both FGF21 and GDM published in English up to March 1, 2020 were searched. The search terms were fibroblast growth factor 21 or FGF21 AND gestational diabetes mellitus or GDM or (diabetes and pregnancy). In addition, the reference lists of identified articles and previous mini-review were also screened for more studies.

Inclusion and exclusion criteria
For this meta-analysis, the relevant articles had to be case-control or cohort studies, which reported circulating FGF21 levels in women with GDM compared with pregnant women with NGT. Articles defining GDM according to the GDM diagnosis criteria were included. Study sample size and geographical location were not restricted. Duplicated articles were excluded. Literature reviews, articles on research on other diabetes mellitus, studies comparing with non-gestational pregnant women, and articles with unavailable/incomplete data after contacting the corresponding authors were excluded.

Data extraction
According to the meta-analysis of Observational Studies in Epidemiology (MOOSE) guidelines, two qualified investigators independently searched the titles, abstracts, and full texts of all identified citations. If there were any disagreements, a third investigator intervened to resolve conflicts through group discussions. The following information was extracted from each article: (1) the first author’s name and publication year; (2) the country where the study was conducted; (3) study size, including number of cases and controls; (4) GDM diagnosis criteria; (5) age of patients; (6) BMI of patients; (7) time points of sample collection; (8) circulating levels of FGF21 (means and SD); (9) glucose levels of patients; (10) source of blood sample; (11) ELISA kit brands.

Statistical analysis
The circulating FGF21 levels in the cases with and without GDM were reported as standardized mean difference (SMD) and associated 95% confidence intervals (CIs). This primary variables were used to assess the relationship between circulating FGF21 levels and GDM. Chi-square tests and $F$ tests were used to estimate the heterogeneity among studies. $F$ values <25% represent insignificant heterogeneity, while those >50% show significant heterogeneity. According to the $F$ value, a random-effect model or a fixed-effect model was applied for pooling SMD (95% CI). To evaluate the possible sources of heterogeneity, we used subgroup analysis by publication year, sample size, source of blood sample, study region, ELISA kit manufacturer, oral glucose tolerance test (OGTT) criteria, and time point of sample collection. Further, to explore the possible sources of heterogeneity, univariate and multivariate meta-regression were conducted. A sensitivity analysis was performed to assess the stability of the results by excluding one study at a time. Both Begg’s funnel plot and Egger’s test were conducted to evaluate publication bias [10, 11]. All statistical analyses were performed with Review Manager 5.2 and Stata version 11.0. All tests were two sided with a significance level of 0.05.

Results

Study description
Overall, 79 potentially relevant articles were identified from the electronic databases, of which 51 were duplicates and 10 were excluded for obvious irrelevance after reading the titles or abstracts. Of the remaining 18 potentially relevant articles for full-text evaluation, three were excluded on account of being reviews. One study on FGF-21 mRNA expression and one without an NGT control group were also excluded. Another four articles were excluded because they lacked detailed data. Finally, 827 participants from nine included studies were used to investigate the FGF-21 levels in pregnant women with GDM and NGT controls during pregnancy. The process of study inclusion/exclusion is displayed in a flow chart (Fig. 1). The main characteristics of the included studies are presented in Table 1.

Results
A meta-analysis of the nine articles was performed [12-20]. Data were all extracted as means ± SD, and significant heterogeneity existed in the studies ($I^2 = 85\%$, $p < 0.001$, Fig. 2). Hence, the random effects model was used for the statistical analysis. Compared with the control group, the FGF-21 levels were significantly higher in pregnant women with GDM (random effects [MD], 95%CI = 80.46, [0.07–0.86], $p = 0.02$).

To detect the possible source of heterogeneity, subgroup analysis were conducted by publication year,
sample size, source of blood sample, study region, ELISA kit manufacturer, OGTT criteria, and time points of sample collection, respectively. In the subgroup analysis, when stratified by adjustment for variables such as sample size ≥100, the heterogeneity significantly reduced in the study for sample size <100 ($I^2 = 20\%, p = 0.29$). European studies were another variable that significantly decreased the heterogeneity ($I^2 = 50\%, p = 0.13$). ELISA kits manufactured in Europe were another variable that caused significant reduction in heterogeneity ($I^2 = 26\%, p = 0.26$). The variable of time points of sample collection ≥38 weeks of pregnancy in the study had no effect on heterogeneity ($I^2 = 0\%, p = 0.4$). Other factors such as publication year, source of blood sample, and OGTT criteria did not obviously affect the heterogeneity. The results of subgroup analysis are shown in Table 2.

Next, to further identify sources of heterogeneity, univariate and multivariate meta-regression analysis were performed. The results of univariate meta-regression showed that only sample size had a significant effect on heterogeneity ($p = 0.01$). In multivariate meta-regression, sample size and time point of sample collection contributed to heterogeneity ($p = 0.033$ and $p = 0.047$, respectively) (Table 3).

Furthermore, sensitivity analysis was performed to investigate whether the pooled SMD (95% CI) for FGF21 levels during pregnancy was affected by omitting one study at a time. The result showed that no one single study significantly changed the course of the effect (Fig. 3). Both Begg’s test and Egger’s test were performed to explore whether publication bias existed. No publication bias was observed in this meta-analysis ($Z = 1.36, p = 0.175; t = 1.24, p = 0.256$, respectively).

**Discussion**

Gestational DM is currently the most common complication of pregnancy, and the prevalence of undiagnosed hyperglycemia and even overt diabetes in young women is markedly increasing. The pathophysiology of GDM is complex. The major risk factors of GDM include maternal overweight and obesity, advanced age at childbearing, previous history of GDM, family history of T2DM, and ethnicity [21]. Thus far, no single diagnostic protocol or diagnostic criteria for GDM has gained universal acceptance; hence, the prevalence of GDM varies...
Table 1  Characteristics of the studies included in meta-analysis

| Study                  | Country | Number of case/ control | GDM diagnosis criteria | Age (year) | BMI (kg/m²) | Time points of sample collection | Circulating levels of FGF 21 (pg/mL) | Glucose 0 h (mmol/L) | Glucose 1 h (mmol/L) | Glucose 2 h (mmol/L) | Blood sample | ELISA kit brands |
|------------------------|---------|-------------------------|------------------------|------------|-------------|-----------------------------------|--------------------------------------|---------------------|---------------------|---------------------|--------------|------------------|
| Bonakdaran et al. 2017 | Iran    | 30/60                   | IADPSG                 | 26.8 ± 6.3 / 24.8 ± 4.3 | 26.0 ± 5.9 / 23.9 ± 4.3 | 24–28 weeks of gestation | 264.5 ± 196.2 / 59.1 ± 36.5 | 5 ± 0.06 / 4.01 ± 0.38 | 8.81 ± 1.87 / 6.41 ± 1.11 | 7.94 ± 2.07 / 5.31 ± 0.82 | serum        | ab125966, Abcam   |
| Li et al. 2015         | China   | 51/50                   | IADPSG                 | 30.53 ± 20.78 / 29.42 ± 18.38 | 38.20 ± 36.71 / 26.37 ± 27.15 | 28 weeks of gestation | 400.04 ± 914.46 / 247.62 ± 757.31 | 5.08 ± 4.21 / 3.49 ± 2.76 | 10.20 ± 9.86 / 7.03 ± 8.27 | 8.11 ± 9.36 / 5.51 ± 7.0 | serum        | R&D Systems, UK   |
| Megia et al. 2015      | Spain   | 79/78                   | Spanish diabetes in pregnancy guidelines | 32.15 ± 5.09 / 30.82 ± 4.78 | 25.6 ± 4.80 / 24.88 ± 5.17 | 26–30 weeks of gestation | 107.89 ± 77.40 / 85.62 ± 80.39 | 4.76 ± 0.67 / 4.51 ± 0.41 | 11.74 ± 1.66 / 8.45 ± 1.43 | 10.24 ± 1.30 / 14.95 ± 1.29 | serum        | BioVendor, Czech, Republic |
| Niert et al. 2014      | Australia | 10/10                  | Australasian Diabetes In Pregnancy guidelines | — / — | — / — | 38–39 weeks of gestation | 452.33 ± 729.31 / 358.42 ± 587.93 | — / — | — / — | — / — | serum        | ab125966, Abcam   |
| Stein et al. 2010      | Germany | 40/80                   | Austrian Diabetes Association | 33 ± 10 / 28 ± 5 | Pre-BMI: 24.9 ± 4.9 / 22.3 ± 7.0 | 205 ± 30 / 198 ± 39 days of gestation | 97.5 ± 166.1 / 102.9 ± 144.9 | 4.5 ± 0.9 / 4.2 ± 0.4 | 10.3 ± 1.6 / 7.5 ± 1.6 | 9.0 ± 2.3 / 6.2 ± 1.8 | serum        | BioVendor, Czech, Republic |
| Tan et al. 2013        | Spain   | 12/12                   | WHO                     | 34.42 ± 7.08 / 32.17 ± 5 | 31.75 ± 6.33 / 31.15 ± 1.67 | 39–40 weeks of gestation | 246.86 ± 168.75 / 122.17 ± 106.83 | 4.5 ± 0.5 / 4.34 ± 0.8 | 10.03 ± 1.15 / 8.45 ± 1.43 | 14.95 ± 1.29 / 19.65 ± 1.29 | plasma       | BioVendor, Oxford, UK |
| Wang et al. 2013       | China   | 30/60                   | MOH China               | 29.33 ± 3.29 / 28.95 ± 3.14 | 21.80 ± 3.06 / 20.36 ± 3.37 | 26–30 weeks of gestation | 132.77 ± 83.42 / 71.82 ± 36.57 | 5.01 ± 0.64 / 4.24 ± 0.32 | 10.13 ± 1.27 / 7.23 ± 1.34 | 8.70 ± 0.96 / 6.35 ± 1.01 | serum        | R&D Systems, Minneapolis, MN, USA |
| Wang et al. 2019       | China   | 20/25                   | MOH China               | 29.16 ± 3.43 / 28.72 ± 3.11 | 22.02 ± 3.03 / 20.03 ± 2.68 | 38–40 weeks of gestation | 199.31 ± 224.65 / 156.81 ± 186.11 | 4.66 ± 0.53 / 4.29 ± 0.41 | 10.03 ± 1.33 / 7.13 ± 1.32 | 8.93 ± 1.25 / 6.63 ± 1.12 | serum        | R&D Systems, Minneapolis, MN, USA |
| Xu et al. 2013         | China   | 120/60                  | ADA                     | 31.65 ± 3.73 / 31.21 ± 5.30 | 21.43 ± 2.39 / 20.54 ± 2.12 | 24–28 weeks of gestation | 375.8 ± 522.4 / 441.3 ± 606.1 | 4.8 ± 0.45 / 4.5 ± 0.45 | 10.17 ± 1.34 / 8.04 ± 1.29 | 8.89 ± 1.42 / 7.09 ± 0.83 | plasma       | Phoenix Pharmaceuticals, Burlingame, CA, USA |

GDM, Gestational Diabetes Mellitus; Control, pregnant women without GDM; BMI, body mass index; ELISA, enzyme-linked immunosorbent assay; Pre-BMI, body mass index of before pregnancy; IADPSG, International association of the diabetes and pregnancy study groups; WHO, World Health Organization; MOH, Ministry of Health; ADA, American Diabetes Association. The number on the left side of a slash is referring to cases with GDM, and the number on the right side is referring to cases without GDM. And in the columns of ‘Age’, ‘BMI’, ‘Time point of sample collection’, ‘Circulating levels of FGF21’, and ‘Glucose 0, 1, 2 h’, the data is presented as the means ± SD.
according to different diagnostic criteria [22].

Recently, growing evidence has supported the key role of adipokines played in the crosstalk between adiposity and decreased insulin sensitivity during pregnancy [23]. As a cytokine, FGF21 was initially isolated from the liver in 2000, and it has since been reported to be widely expressed in metabolic organs such as adipose tissue, pancreas, and the gastrointestinal tract [6]. FGF21 is an important factor in the homeostatic mechanisms with positive effects on glucose and lipid metabolism. It has been shown to promote insulin sensitization and enhance β-cell function [19]. Increased FGF21 levels were observed in patients with obesity and T2DM [24]. Chen et al. found that FGF21 levels increased progressively

![Fig. 2 Forest plot of meta-analysis of the association between FGF21 levels and GDM.](image)

| Subgroup                        | No. of Studies | No. of participants | SMD (95%CI) | p for Test | Heterogeneity Test |
|---------------------------------|----------------|---------------------|-------------|------------|--------------------|
| Overall                         | 9              | 827                 | 0.46 (0.08, 0.86) | 0.02       | 53.45              |
|                                 |                |                     |             |            | F (%) | <0.001 |
| Publish year                    |                |                     |             |            | Chi-square | 85% |
| ≤2015                           | 7              | 692                 | 0.29 (-0.02, 0.61) | 0.07       | 21.44              |
| >2015                           | 2              | 135                 | 0.98 (-0.53, 2.50) | 0.20       | 15.04              |
|                                 |                |                     |             |            | F (%) | <0.001 |
| Sample size                     |                |                     |             |            | Chi-square | 85% |
| <100                            | 5              | 269                 | 0.84 (0.23, 1.45) | 0.007      | 19.12              |
| ≥100                            | 4              | 558                 | 0.07 (-0.10, 0.25) | 0.39       | 3.74               |
|                                 |                |                     |             |            | F (%) | 20% |
| Blood sample                    |                |                     |             |            | Chi-square | 86% |
| serum                           | 7              | 623                 | 0.52 (0.06, 0.98) | 0.03       | 2.48               |
| plasma                          | 2              | 204                 | 0.28 (-0.65, 1.22) | 0.55       | 2.48               |
|                                 |                |                     |             |            | F (%) | 86% |
| Study region                    |                |                     |             |            | Chi-square | 87% |
| Asia                            | 5              | 506                 | 0.61 (-0.06, 1.27) | 0.08       | 47.05              |
| Europe                          | 3              | 301                 | 0.21 (-0.03, 0.44) | 0.08       | 4.03               |
|                                 |                |                     |             |            | F (%) | 50% |
| Australia                       | 1              | 20                  | —           | —          | —                  |
|                                 |                |                     |             |            | —                  |
| Elisa kit manufacturer          |                |                     |             |            | Chi-square | 84% |
| European                        | 4              | 402                 | 0.20 (-0.00, 0.40) | 0.05       | 4.04               |
| North America                   | 3              | 315                 | 0.38 (-0.38, 1.13) | 0.33       | 17.34              |
|                                 |                |                     |             |            | F (%) | 88% |
| Not recorded                    | 2              | 110                 | 0.98 (-0.59, 2.56) | 0.22       | 2.28               |
|                                 |                |                     |             |            | F (%) | 90% |
| OGGTT Criteria                  |                |                     |             |            | Chi-square | 85% |
| 75 g OGGTT criteria             | 7              | 490                 | 0.60 (0.07, 1.12) | 0.03       | 41.14              |
| 100 g OGGTT criteria            | 2              | 337                 | 0.08 (-0.31, 0.47) | 0.69       | 3.16               |
|                                 |                |                     |             |            | F (%) | 68% |
| Time point of sample collection |                |                     |             |            | Chi-square | 90% |
| <38 weeks of pregnancy          | 6              | 738                 | 0.50 (-0.00, 1.00) | 0.05       | 51.62              |
| ≥38 weeks of pregnancy          | 3              | 89                  | 0.35 (-0.07, 0.78) | 0.10       | 1.83               |

0.4%
with dysglycemia and concluded that FGF21 could predict the development of diabetes in a large Chinese prospective study [25].

To our knowledge, ours is the first meta-analysis of the relationship between circulating FGF21 levels and GDM although previously, systematic reviews have been published by Yuan et al. and Bellos et al. [9, 26]. In both reviews of Yuan et al. and Bellos et al., statistical analysis was not performed to draw an exact conclusion between circulating FGF21 levels and GDM. Based on our meta-analysis of nine observational studies, higher circulating FGF21 levels in pregnant women with GDM than in controls during pregnancy was noted. While the exact mechanism has not been clearly clarified, the results suggested that higher FGF21 levels likely contribute to the pathophysiology of GDM. One possible reason is that the higher levels of circulating FGF21 in pregnant women with GDM could be a compensatory response to the underlying differences in maternal physiology such as higher insulin resistance at the start of the pregnancy, poor reserve in insulin secretion capacity, and low-level inflammation in GDM subjects [27-29]. Additionally, circulating FGF21 levels are associated with overeating [30]; hence, increased food intake during pregnancy might also contribute to higher FGF21 levels in GDM subjects. Besides, increased FGF21 levels could reduce the appetite for sugar and preference for carbohydrate, thereby ensuring the supply of sufficient essential nutrients during pregnancy.

Table 3  Univariate and multivariate meta-regression analysis for circulating FGF21 levels

| Variables                | Univariate | Multivariate |
|--------------------------|------------|--------------|
|                          | t  | p  | 95% CI       | t  | p  | 95% CI       |
| Publsih year             | 1.46 | 0.145 | –0.24, 1.62 | 0.90 | 0.369 | –0.80, 2.17 |
| Sample size              | 2.57 | 0.010 | 0.19, 1.43  | 2.14 | 0.033 | 0.13, 3.11  |
| Blood sample             | –0.41 | 0.680 | –1.28, 0.84 | 0.65 | 0.519 | –0.84, 1.66 |
| Study region             | –0.75 | 0.454 | –0.91, 0.41 | 0.74 | 0.459 | –0.56, 1.23 |
| Elisa kit manufacturer   | 1.38 | 0.168 | –0.15, 0.86 | –0.79 | 0.428 | –1.04, 0.44 |
| OGTT criteria            | –1.09 | 0.277 | –1.46, 0.42 | –0.07 | 0.940 | –1.25, 1.16 |
| Time point of sample collection | –0.20 | 0.838 | –1.08, 0.88 | –1.99 | 0.047 | –3.05, –0.02 |

Fig. 3  Sensitivity analysis to evaluate the stability of the results during pregnancy.
who were matched for gestational age and fasting insulin, they showed that serum FGF21 concentrations showed a strong and positive relationship with metabolic and vascular risk factors including insulin resistance (e.g., increased homeostatic model assessment of insulin resistance (HOMA-IR) and decreased adiponectin) and adverse lipid profile (such as increased triglyceride and decreased HDL cholesterol) by univariate and multivariate analysis. Consistent with these findings, circulating FGF21 is significantly higher in patients in the second and third tertiles of HOMA-IR than in those in the first tertile. The results of their study indicate that FGF21 is related to metabolic and vascular risk factors in pregnant women but is perhaps not a causal factor in the pathogenesis of GDM independent of insulin resistance [18]. Additionally, compensatory increase of circulating FGF21 levels might aim to reduce microvascular damage [33].

Given that there was obvious heterogeneity in this meta-analysis, we performed subgroup and sensitivity analyses to investigate the underlying causes as to why the results varied among different studies. Our analysis showed that variables such as sample size, study region, ELISA kit manufacturer, and time point of sample collection affected the heterogeneity. In the subgroup analysis by sample size, our results suggested that FGF21 levels were higher in studies with sample size <100 GDM patients than in healthy pregnant controls, but not in those with sample size ≥100 GDM patients than in healthy pregnant controls. In the subgroup analysis by source of blood sample, our results suggested that FGF21 levels were higher in the serum samples but not plasma samples, of GDM patients than healthy pregnant controls. A possible explanation of this difference between serum and plasma samples may be owing to the composition of plasma samples being more complex than serum samples, and the interference of anticoagulation factors. In the subgroup by OGTT criteria, the FGF21 level was higher in the 75-g OGTT criteria for GDM patients than in healthy pregnant controls, but this difference was not observed in the 100-g OGTT criteria. According to multivariate meta-regression analysis, the sample size and time point of sample collection may be the sources of heterogeneity.

This meta-analysis has some methodological limitations despite the several advantages over individual studies. First, the diagnostic criteria of GDM is not uniform. Second, the small sample sizes in some subgroup analysis may limit the statistical power to estimate the FGF21 level in GDM patients. Third, the association between FGF21 levels and other parameters in GDM patients was not explored in the current meta-analysis because of unavailability of sufficiently detailed data in the original studies. Last, the relationship between FGF21 levels and postnatal outcomes was not studied.

In conclusion, FGF21 levels were higher in GDM patients, and the sample size, study region, ELISA kit manufacturer, and time point of sample collection could affect the heterogeneity among studies. However, the exact mechanism requires further investigation in future studies.

Acknowledgements

Not applicable.

Author Contributions

JJ, HW Z and GY Y conceived and designed the study; JJ, RZ, and RS L searched the related articles; JJ, WP W, FY, and YR S analyzed the data; and JJ, FY, and WP W wrote the manuscript. All authors read and approved the final manuscript.

Funding

This meta-analysis was supported by the National Natural Science Foundation of China (81500351), the Youth Medical Talent Project of Jiangsu Province (QNRC2016842), the Jiangsu University Affiliated Hospital “5123” Talent Plan (51232017305) and the 169 Talent Project of Zhenjiang.

Conflict of Interest Statement

The authors report no conflicts of interest.

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