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Fibroblast Growth Factor 21 and Metabolic Dysfunction in Women with a Prior Glucose-Intolerant Pregnancy

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Conflict of Interest

None declared.

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Abstract

Objective—We sought to determine if there is an association between fibroblast growth factor 21 (FGF21) levels and a history of gestational diabetes mellitus (GDM) in women with and without metabolic dysfunction, defined as a diagnosis of metabolic syndrome or type 2 diabetes (T2DM), 5 to 10 years following participation in a multiple cohort GDM study.

Study Design—At 5 to 10 years after index pregnancy, women underwent a follow-up visit and were categorized as having no metabolic syndrome, metabolic syndrome, or T2DM. FGF21 levels were compared between women who did and did not have a history of GDM using multivariable linear regression.

Results—Among 1,889 women, 950 underwent follow-up and 796 had plasma samples analyzed (413 GDM and 383 non-GDM). Total 30.7% of women had been diagnosed with T2DM or metabolic syndrome. Overall, there was no difference in median FGF21 levels in pg/mL between the prior GDM and non-GDM groups ($p = 0.12$), and the lack of association was observed across all three metabolic categories at follow-up (p for interaction = 0.70).

Conclusion—There was no association between FGF21 levels and prior history of mild GDM in women with and without metabolic dysfunction 5 to 10 years after the index pregnancy ([ClinicalTrials.gov](https://clinicaltrials.gov/ct2/show/study/NCT00069576) number, [NCT00069576](https://clinicaltrials.gov/ct2/show/study/NCT00069576), original trial).

Keywords

fibroblast growth factor; gestational diabetes; glucose intolerance; metabolic syndrome

Women with a history of gestational diabetes mellitus (GDM) are at increased risk for the development of type 2 diabetes mellitus (T2DM) and the metabolic syndrome. Approximately one half of these women develop diabetes in the first 5 to 10 years after the index pregnancy.¹ However, the rate of conversion to T2DM can vary widely, with ranges reported from 2.6 to 70% over a period from 6 weeks to 26 years from the index pregnancy.² A history of GDM is also a risk factor for cardiovascular disease, such as dyslipidemia and coronary artery disease later in life.^{3,4} Fibroblast growth factor 21 (FGF21) is a recognized metabolic regulator of glucose and lipid metabolism. Elevated levels of FGF21 have been identified in individuals with T2DM, atherosclerosis, coronary artery disease, and acute myocardial infarction. FGF21 holds promise as a potential biomarker not only for the development of T2DM, but also for the vascular complications associated with diabetes.⁵ Because the pathophysiology of GDM and T2DM is similar, both involving insulin resistance and impaired β cell function—the relationship between FGF21 and GDM—has been explored.⁶ Small studies have shown that second and third trimester FGF21 levels are higher in GDM women compared with women with normal glucose tolerance.^{7–9} Although the exact mechanism of elevations in FGF21 is unknown, there is speculation that the upregulation of FGF21 may be a compensatory response in an attempt to improve glucose metabolism when insulin resistance is high. In two 5-year prospective studies, elevations in FGF21 have also been shown to predict the development of metabolic

syndrome and T2DM.^{10,11} Given that elevations in FGF21 have been shown to predict varying degrees of glucose intolerance, it is plausible that FGF21 could be used to identify a subset of women with a history of prior GDM who may be at risk for the development of metabolic disorders long term. Therefore, our objective was to determine if there is an association between FGF21 levels and a prior GDM pregnancy in women with and without metabolic dysfunction (a diagnosis of metabolic syndrome or T2DM) 5 to 10 years, including metabolic syndrome and T2DM, following participation in a multiple cohort GDM study.

Study Design

This is a secondary analysis of women enrolled during pregnancy with and without mild GDM in a multicenter trial in the Eunice Kennedy Shriver National Institute of Child Health and Human Development Maternal Fetal Medicine Units Network GDM follow-up study who were evaluated 5 to 10 years after their index pregnancy. Details regarding the original trial have been previously described.¹² Mild GDM was defined with a 3-hour, 100-g oral glucose tolerance test (OGTT) with a fasting glucose of less than 95 mg/dL, but at least two of the 1-, 2-, or 3-hour determinations that exceeded established thresholds of 1 hour >180 mg/dL, 2 hours >155 mg/dL, and 3 hours >140 - mg/dL satisfying the criteria for a positive result. Non-GDM women were defined as women with a 50-g, 1-hour screening test between 135 and 200 mg/dL who underwent a 100-g, 3-hour OGTT with normal results and matched by race/ethnicity and body mass index (BMI) to the women with mild GDM. Women did not have a history of pregestational or GDM, renal or cardiovascular disease, or chronic hypertension at the time of enrollment in the original study. Once GDM women were consented, women were randomly assigned to receive either formal nutritional counseling and diet therapy, along with insulin if needed (treated) or usual prenatal care (untreated). The parent mild GDM Trial and the follow-up study were approved by the institutional review board of all participating centers. The follow-up study has been previously described.¹³ At the 5 to 10 year follow-up, women underwent anthropometric and blood pressure measurements and completed a 75-g, 2-hour OGTT. Additional fasting blood was obtained and saved for future analysis. Women were then categorized as having no metabolic syndrome (0–2 components of the formal diagnosis of metabolic syndrome), metabolic syndrome or T2DM at follow-up. Metabolic syndrome was defined per the American Heart Association and National Heart Lung and Blood Institute Scientific Statement including three or greater of the following: waist circumference >88 cm, triglyceride level ≥150 mg/dL, high-density lipoprotein <50 mg/dL, blood pressure ≥130/85 mm Hg, or fasting glucose ≥100 mg/dL.¹⁴ Diabetes was defined as a fasting glucose ≥126 mg/dL and/or 2-hour glucose ≥200 - mg/dL after a 75-g load or if a woman was currently undergoing treatment for a prior diagnosis of T2DM.¹⁵ Women with no metabolic syndrome had 0 to 2 components of the criteria for the metabolic syndrome defined above.

Women were excluded from the current study if they did not fast for at least 6 hours prior to the fasting blood draw or if they had incomplete study visit data (no waist circumference measurement, no fasting lipid profile, no BP measurement, or no 2-hour OGTT). Women

with no fasting aliquot sample available or if there was inadequate amount of protein to run the FGF21 assay once the sample was thawed were also excluded.

FGF21 levels were assayed using the Quantikine ELISA Human FGF21 Immunoassay kit (R&D Systems, Minneapolis, MN). The sensitivity of the Human FGF-21 Quantikine Elisa assay range from 1.61 to 8.69 pg/mL. The mean of the minimum detectable dose is 4.67 pg/mL. Three samples of known concentration were tested 20 times on one plate to assess intra-assay precision. Three samples of known concentration were tested in 40 separate assays to assess inter-assay precision. Assays were performed by at least three technicians using two lots of components. To determine if the detection of FGF-21 protein was in the standard curve range, undiluted samples and a series of dilutions from three random plasma samples from women enrolled in a different study were run. Undiluted sample results were in the standard curve range. A human FGF-21 standard curve was generated for each plate. Samples were thawed on ice and assayed in duplicate following assay procedure. Optical density was determined using a microplate reader set to 450 nm. FGF21 levels were analyzed as a continuous variable.

Baseline characteristics were compared between women who did and did not have a history of GDM. The Chi-square test and, in the case of small numbers, Fisher's exact test were used to examine categorical variables and the Wilcoxon's rank sum test was used to examine continuous variables. Univariate analysis comparing FGF21 levels between two groups (e.g., GDM and non-GDM groups) was undertaken using the Wilcoxon's rank sum test and for more than two groups using the Kruskal–Wallis test (e.g., GDM treated, untreated, and non-GDM groups). Multivariable analysis was performed using multivariable linear regression models adjusting for possible confounders and included maternal age, maternal BMI, and time interval in years between the original trial and the follow-up visit. Since the distribution of FGF21 values showed a right skewed distribution, FGF21 values were log-transformed in the regression analysis to approximate normality. Interaction between the original diagnosis of GDM and current metabolic status on FGF21 levels was also examined in regression models.

Additional regression models were run, separately, based on current metabolic status, categorized as no metabolic dysfunction, metabolic syndrome, and T2DM. Imputation for missing data was not performed. Nominal *p* values of less than 0.05 were considered to indicate statistical significance. No adjustments were made for multiple comparisons. Statistical analysis was performed using SAS 9.4 statistical software (SAS Institute Inc., Cary, NC).

Results

Among 1,889 women enrolled in the original trial, 950 (50%) completed a study visit for the GDM follow-up study. Of these women, 796 (83.8%) had plasma samples available for analysis. A total of 154 women were excluded for the following: 62 currently pregnant, 62 no fasting blood draw/missing metabolic syndrome data, 29 no sample, and 1 sample had inadequate amount of protein to run the FGF21 assay. Of the women included, 413 were diagnosed with GDM during the index pregnancy, 220 of whom underwent treatment

for GDM, and 193 had untreated GDM. Additionally, there were 383 non-GDM women (elevated 1-hour glucose challenge test [GCT], normal 3-hour OGTT). The mean duration from study index pregnancy delivery to follow-up was 6.9 ± 1.4 years.

Maternal clinical characteristics of women at follow-up study visit based on mild GDM status in the original trial are listed in ► Table 1. GDM and non-GDM women were similar except for maternal age, insulin therapy during the index pregnancy, and number of GDM pregnancies since the index pregnancy, all significantly higher in GDM women. At the time of the follow-up study visit, 200 women (58 prior treated GDM, 56 untreated GDM, and 86 non-GDM) were diagnosed with metabolic syndrome, 44 had T2DM (18 prior treated GDM, 14 untreated GDM, and 12 non-GDM) and 552 women (144 treated GDM, 123 untreated GDM, and 285 non-GDM) did not meet criteria for metabolic syndrome. Of the 552 women without metabolic syndrome, 245 had two criteria of the metabolic syndrome, 173 had one criterion, and 134 had none.

Overall, in univariate analysis, there was no difference in median FGF21 levels in pg/mL between the prior GDM and non-GDM groups (169.3 [interquartile range {QR}: 98.4–261.6] vs. 153.4 [IQR: 84.4–241.1], respectively, $p = 0.08$ [Wilcoxon's test]). In adjusted analyses utilizing linear regression modeling, there was also no association observed between prior GDM and non-GDM groups and log-transformed FGF21 values, after adjusting for maternal age, maternal BMI, and time interval between the original trial and the follow-up visit ($p = 0.12$). Additionally, there was no significant interaction between GDM group and metabolic category at follow-up with FGF21 levels (p for interaction = 0.70; ► Table 2). Similarly, there were no significant differences in FGF21 levels when the GDM group was analyzed according to whether or not their prior GDM was treated (► Table 3).

In a cross-sectional analysis, median FGF21 levels were significantly higher in women with a diagnosis of T2DM (235.8 [IQR: 155.8–411.4]) and metabolic syndrome (202.3 [IQR: 129.0–308.6]) compared with no metabolic syndrome (140.3 [IQR: 80.1–226.4]), ($p < 0.001$ [Kruskal–Wallis test]).

Of the 552 women without a formal diagnosis of metabolic syndrome, there were significant differences in FGF21 levels based on the number of components of metabolic syndrome they experienced from no components to two components ($p < 0.001$ [Kruskal–Wallis test]).

Conclusion

In a follow-up of a multiple cohort GDM study, we did not find an association between FGF21 levels measured 5 to 10 years postdelivery and a history of a GDM pregnancy.

We were able to demonstrate that FGF21 levels were significantly different among the groups based on their current metabolic status. Specifically, women with a diagnosis of T2DM, either prior to the study visit or at the time of the study visit had the highest levels of FGF21 and women with no metabolic syndrome having the lowest FGF21 levels. Women with a diagnosis of metabolic syndrome, as defined by the AHA/NHLBI, had higher FGF21 levels compared with women who were not diagnosed with metabolic syndrome, but lower

levels than those with T2DM. Our findings are consistent with prior reports demonstrating that FGF21 levels are elevated in individuals with both metabolic syndrome and T2DM.⁷ We were unable to demonstrate additional influence of a history of GDM in prior pregnancy on FGF21 levels.

Fibroblast growth factor is an important metabolic regulator with a significant effect on glucose homeostasis. Increased levels have been identified in individuals with varying degrees of insulin resistance including obesity and T2DM.^{16,17} In the GDM pregnancy, insulin resistance is mainly related to circulating placental hormones, although baseline maternal obesity may also play a role. Elevations in FGF21 have also been reported in women with GDM during pregnancy compared with women with normal glucose tolerance.^{7,8} In two studies of predominantly Chinese women, circulating FGF21 levels were higher among GDM women compared with those with normal glucose tolerance.^{7,8} Similarly, in a small group of Caucasian women, the association between elevations in FGF21 levels in those with GDM remained even when matched for maternal age and BMI.⁹ These findings were also confirmed in a larger population of women of European–Mediterranean descent.¹⁸ Whether elevations in FGF21 persist after delivery in GDM women known to be at increased risk for long-term metabolic and vascular dysfunction has not been well studied.

As clinicians, we are in search of biomarkers that may aid in identifying women at risk for disease as a point of intervention that may alter progression to that particular disease. GDM is no exception, especially when follow-up rates of postpartum screening are low.^{19,20} Women with a history of GDM possess higher levels of inflammation which may result in changes in inflammatory and metabolic markers years prior to a formal diagnosis of T2DM.²¹ Therefore, identifying a subset of prior GDM women who have not yet developed metabolic syndrome or T2DM in the 5 to 8 years following the index pregnancy, but who are still at risk for metabolic disorders long term could provide an intermediate window for interventions such as pharmacologic therapy and lifestyle interventions. Previous studies have focused on adiponectin and high sensitivity C-reactive protein as potential biomarkers in GDM women and risk of progression to T2DM with mixed results.²² In non-GDM studies, FGF21 has been shown to be superior to adiponectin in predicting future diabetes.²³ Elevated levels of FGF21 prior to a formal diagnosis of T2DM have been confirmed in mixed populations. In a 5-year prospective study of Chinese subjects, plasma FGF21 levels progressively increased through the continuum of glucose tolerance from normal glucose tolerance to diabetes.¹⁰ Similarly, in a Caucasian population of men and women, FGF21 levels drawn 5 years earlier were independently associated with the development of both T2DM and metabolic syndrome, with a twofold increased risk of metabolic dysfunction compared with normal glucose tolerant individuals.¹¹ In the Fenofibrate Intervention and Event Lowering in Diabetes (FIELD) study, elevations in FGF21 were also associated with a higher risk of cardiovascular events in participants with T2DM.²⁴ Higher levels of FGF21 were associated with both the baseline presence of microvascular complications (nephropathy, retinopathy, and neuropathy), and also with development of microvascular complications in T2DM without preexisting vascular complications in a sub-analysis of the FIELD study.⁵

Since women with GDM are at increased risk for metabolic syndrome and T2DM later in life, FGF21 may be an ideal biomarker to identify women who are predisposed to impaired glucose tolerance but whose glucose levels are below current diagnostic thresholds for either metabolic syndrome or T2DM.^{25,26} Animal models show promise for using FGF21 as a potential therapeutic target to increase insulin sensitivity and decrease blood glucose concentrations.^{25,26} If these results can be replicated in human studies, clinical development of FGF21 therapies could be used in the treatment of obesity and T2DM. Despite prior findings, we were unable to identify an independent association between FGF21 levels 5 and 10 years after exposure to a glucose intolerant pregnancy and a prior diagnosis of GDM. The lack of association was seen in all three metabolic categories, including the 69.3% of women who still had no evidence of metabolic syndrome.

Our study has several limitations. Women with normal 1-hour GCT were not included in the GDM follow-up study. Therefore, we were unable to evaluate whether differences in FGF21 levels might have been detected between women with mild GDM and women with normal 1-hour GCT results. In our study, women had a mild phenotype of GDM with a normal fasting glucose on the 3-hour OGTT and only 39 women in the original trial required insulin therapy to achieve adequate glucose control. Although we did not find an association between FGF21 levels and women with a history of mild GDM, it is plausible that an association may exist between FGF21 levels and women with a history of more severe phenotypes of GDM.

In summary, we were unable to demonstrate an association between FGF21 levels and prior history of a GDM pregnancy in women with and without metabolic syndrome or T2DM 5 to 10 years after the index pregnancy. Our results are consistent with prior studies showing a strong association between FGF21 levels and current metabolic status. Research efforts should continue to focus on approaches to improve intermediate and long-term follow-up of women with a history of GDM to identify points of intervention to prevent or delay progression to long term metabolic and vascular dysfunction in this at risk group of women.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Table 1

Clinical characteristics of the women at study follow-up based on mild gestational diabetes mellitus status in the original trial

	Prior GDM <i>n</i> = 413	Prior non-GDM <i>n</i> = 383
Maternal age (y)	36.4 ± 5.4	34.6 ± 5.6
BMI (kg/m ²)		
Normal	97 (23.5)	91 (23.8)
Overweight	150 (36.3)	138 (36.0)
Obese	166 (40.2)	154 (40.2)
Race/ethnicity		
White	131 (31.7)	116 (30.3)
Black	39 (9.4)	42 (11.0)
Hispanic	231 (55.9)	217 (56.7)
Other	12 (2.9)	8 (2.1)
Insurance status		
Private	142 (34.4)	121 (31.6)
Government	130 (31.5)	124 (32.4)
Self pay	141 (34.1)	138 (36.0)
Time since index GDM pregnancy (y)	7.0 ± 1.4	6.8 ± 1.4
Insulin therapy in index pregnancy, <i>n</i> (%)	18 (4.4)	0
Preeclampsia in index pregnancy, <i>n</i> (%)	15 (3.6)	15 (3.9)
Subsequent pregnancy since GDM trial	205 (49.6)	210 (54.8)
Pregnancies with GDM since index pregnancy		
None	351 (85.0)	355 (92.7)
1	54 (13.1)	25 (6.5)
2+	8 (1.9)	3 (0.8)
Years since last pregnancy (y)	3.0 ± 2.1	2.9 ± 2.0
Weight gain since GDM index pregnancy (kg)	7.3 ± 10.0	7.2 ± 9.8
Chronic hypertension, <i>n</i> (%)	27 (7.5)	24 (7.4)
Hypercholesterolemia, <i>n</i> (%)	51 (21.2)	38 (19.0)

Abbreviations: BMI, Body mass index; GDM, gestational diabetes mellitus. Note: Data expressed as *n* (%) or mean ± standard deviation.

Table 2

Fibroblast growth factor 21 levels measured 5 to 10 years after the index delivery in women with and without a history of gestational diabetes mellitus, overall and by current metabolic status

	Prior GDM <i>n</i> = 413	Prior non-GDM <i>n</i> = 383	<i>p</i>-value
All women	169.3 (98.4–261.6)	153.4 (84.4–241.1)	0.12 ^a
No metabolic dysfunction (<i>n</i> = 552)	144.9 (81.6–237.7)	131.4 (79.9–213.9)	0.24 ^a
Metabolic syndrome (<i>n</i> = 200)	194.0 (128.9–293.6)	210.4 (129.4–315.7)	0.69 ^a
Type 2 DM (<i>n</i> = 44)	225.9 (155.8–415.5)	247.6 (146.4–364.6)	0.60 ^a

Abbreviation: GDM, gestational diabetes mellitus.

Note: Data are presented as median (interquartile range). Units are pg/mL.

^a *p*-values were based on multiple linear regression models of log-transformed fibroblast growth factor 21 values adjusted for maternal age, maternal body mass index, and years since delivery. Separate models were generated overall and separately for each current metabolic status category.

Table 3

Fibroblast growth factor 21 levels measured 5 to 10 years after delivery in women with prior treated gestational diabetes mellitus, prior untreated gestational diabetes mellitus, and prior nongestational diabetes mellitus, overall and by current metabolic status

	Treated <i>n</i> = 220	Untreated <i>n</i> = 193	Normal OGTT <i>n</i> = 383	<i>p</i>-value
All women	181.1 (96.4–270.2)	168.9 (102.1–254.2)	153.4 (84.4–241.1)	0.30 ^a
No metabolic dysfunction (<i>n</i> = 552)	139.8 (71.7–249.9)	146.7 (84.3–233.2)	131.4 (79.9–213.9)	0.44 ^a
Metabolic syndrome (<i>n</i> = 200)	198.6 (125.7–327.8)	191.7 (129.0–272.5)	210.4 (129.4–315.7)	0.68 ^a
Type 2 DM (<i>n</i> = 44)	237.4 (149.1–537.6)	223.5 (162.4–313.3)	247.6 (146.4–364.6)	0.70 ^a

Abbreviations: DM, diabetes mellitus; OGTT, oral glucose tolerance test. Note: Data are presented as median (interquartile range). Units are pg/mL.

^a *p*-values were based on multiple linear regression models of log-transformed fibroblast growth factor 21 values, adjusted for maternal age, maternal body mass index, and years since delivery. Models were generated overall and separately for each current metabolic status category.