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Correlation of Fibroblast Growth Factor 21 (FGF-21) with Fetal and Maternal Complications in Patients with Gestational Diabetes Mellitus

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ABSTACT

Background: In the second or third trimester of pregnancy, gestational diabetes mellitus (GDM) can be characterized as glucose intolerance that was not overt prior to gestation. It can have long-term health effects, even if most GDMs go away on their own after delivery. It involves a higher risk for mothers to develop cardiovascular problems or type 2 diabetes mellitus (T2DM), and the child's propensity for obesity, cardiovascular disease, or T2DM. In addition to the liver, other metabolically active tissues such as fat, skeletal muscle, and the pancreas express the hepatokine FGF-21. T2DM can be predicted by a high level of FGF-21. T2DM and GDM are thought to share comparable pathogenesis, but the link between FGF-21 and GDM remains vague. The aim of the study to assess the correlation of FGF-21 with fetal and maternal complications among cases who had GDM.

Patients and methods: There were 50 women diagnosed with GDM at 24-28 weeks of gestation and 50 healthy women recruited from the Diabetes and Obstetrics outpatient clinic to participate in this case-control research.

Results: GDM patients had greater concentrations of FGF-21 compared to control group (p-value <0.01). Fasting blood glucose, 2-hour postprandial glucose, and haemoglobin A1C all had a significant correlation with serum FGF-21 in our research. Moreover, serum FGF-21 was correlated with the incidence of maternal hypertension in the studied groups (p-value 0.011), while the correlation of FGF-21 with the incidence of fetal complications whether fetal macrosomia, respiratory distress, or neonatal hypoglycemia was not significant.

Conclusion: : FGF-21 levels are elevated in patients with GDM. Pregnant women who had greater levels of FGF-21 in their blood were shown to have higher blood pressure readings in this study. Maternal and fetal outcomes should be better linked to FGF-21 levels during pregnancy through additional research.

Keywords: Fetal complications, Fibroblast growth factor 2, Gestational Diabetes mellitus, Maternal complications, Type 2 diabetes mellitus.

INTRODUCTION

It's not uncommon for pregnant women to suffer from gestational diabetes mellitus (GDM). Around 18 million babies are born each year to women with gestational diabetes, according to the International Diabetes Federation (IDF) [(1)].

Risk factors for GDM include a history of insulin resistance or diabetes in the mother's family, advanced maternal age, overweight/obesity, deficiencies in micronutrients, and a westernized diet. GDM is a common complication of pregnancy, but it can have long-term health consequences, involving a higher risk to mothers to develop heart problems or type 2 diabetes, and the child's propensity for obesity, cardiovascular disease, or type 2 diabetes mellitus (T2DM) [(2)]. Adding insulin to medical nutrition therapy and a change in lifestyle has most consistently been found to minimize fetal morbidities [(3)].

FGF-21 is a metabolic hormone synthesized by the liver, adipose tissue, skeletal muscle, and pancreas that is related to glucose metabolism and insulin resistance [(4)].

Several trials have established that FGF21 promotes fatty acids oxidation and ketone bodies production, and inhibits lipogenesis Therefore, FGF21regulates glucose-lipid metabolism. FGF21 is therefore a promising therapeutic target for metabolic illnesses because it has been discovered to influence glucose-lipid metabolism [(5,6)].

An increased level of FGF-21 has been reported in obesity and insulin resistance status [(7)]. Moreover, Placenta has appeared as an active endocrine organ expressing and secreting FGF-21[(8)]; however, its role in normal pregnancy and GDM is poorly understood

T2DM patients had significantly higher levels of circulating FGF-21, but FGF-21 levels are lower in those with type 1 diabetes and adults with latent autoimmune diabetes [(9,10)]. Unluckily, there is a lack of consensus on the level of FGF-21 circulating in GDM and its correlation with maternal and fetal outcomes.

The aim of the current study is to examine the link between FGF-21 and fetal and maternal problems in patients with GDM.

PATIENTS AND METHODS

The current cases-control study included 50 women with GDM and 50 pregnant normoglycemic (control) women of the same gestational age. Patients from Ain Sham University Hospitals were recruited between December 2020 and July 2021 to participate in the study.

Fasting blood glucose (FBG) had been obtained after 8 hours of fasting, for all participants at the first prenatal visit in the first trimester to exclude undiagnosed preexisting diabetes. Demographic

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characteristics were recorded in the first prenatal visit, and a number of other health-related measurements like height and weight as well as their respective BMI (body mass index) (BMI). Weight (kg)/height (m) was used to determine BMI (m2). At 24 to 28 weeks of pregnancy, a GTT was performed.

A 75-gram, two-hour oral glucose tolerance test (OGTT) was used to define GDM if at least one glucose level was above the following thresholds: 1 h 180 mg/dL, 2 h 153 mg/dL (based on a suggestion from the International Association of Diabetes and Pregnancy Study Groups) (IADPSG)(11). The FGF-21 Human ELISA Kit was used to test serum FGF-21 levels in fasting samples at the time of the OGTT.

Reporting maternal complication outcomes before, during, and after delivery (e.g.: hypertension, pre-eclampsia, cesarean section) and **fetal outcomes** before, during, and after delivery (e.g.: macrosomia, respiratory distress, fetal hypoglycemia) was carefully assessed.

Exclusion criteria: Women with a previous history of GDM, polycystic ovary syndrome, hypertension, preeclampsia, renal or liver disease, and who were taking drugs with effects on glucose metabolism were excluded from the study.

Laboratory data include: Analysis of maternal serum levels of FGF-21, (FBG), 2-hour postprandial (2hpp) blood glucose, HbA1C, Serum creatinine, and ALT.

Ethical consent:

Approval was received from our institution's Research Ethics Committee to conduct this study [FWA00017459]. All those who took part in our research gave us their full, clear, and informed consent. This work has been carried out in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki) for studies involving humans.

Statistical analysis

The collected data were coded, processed and analyzed using the SPSS (Statistical Package for Social Sciences) version 23 for Windows® (IBM SPSS Inc, Chicago, IL, USA). When assessing the distribution of some parameters, the quantitative data were provided as mean, standard deviations, and ranges when parametric, and median with inter-quartile range (IQR) when nonparametric. Qualitative data were represented as frequencies and relative percentages.

Qualitative data was compared between groups using Chi-square or Fisher exact tests where the expected number of cells was less than 5. An independent student's t-test was used to compare quantitative data with parametric distribution between two groups. Using the Mann-Whitney test, we compared quantitative data from two groups with nonparametric distributions.

Spearman coefficients were employed to determine whether two quantitative variables from the same group were related to one another. The margin of error acceptable was set at 5% with a confidence interval of 95%. In this case, the significance of the p-value was deemed to be as follows: >0.05: Non-significant (NS), ≤0.05: Significant (S), ≤0.01: high significant (HS).

RESULTS

For both the control group and the patients, maternal and gestational ages were matched to ensure that both groups were comparable.

There was no significant difference in gestational foetal weight between the two groups. As a result, BMI in the GDM group was considerably higher (p-value <0.01) **(Table 1).**

Table (1): Baseline characteristics for the studied cohort.

Variable		Control group	Patients group	Test value•	P-value
		No. = 50	No. = 50		
Age (years)	Mean ± SD	25.88 ± 4.23	26.98 ± 4.71	-1.229	0.222
Gestationalage (weeks)	Mean ± SD	25.74 ± 1.70	25.76 ± 1.96	-0.054	0.957
Fetal Weight (g)	Mean ± SD	834.40 ± 187.73	790.14 ± 167.58	0.707	0.481
BMI (Kg/m^2)	Mean ± SD	23.64 ± 3.28	27.06 ± 3.64	-4.944	**0.000***

Diabetes patients had greater LDL, FBG, 2 hours postprandial glucose, and HBA1C levels than their nondiabetic counterparts **(Table 2).**

GDM patients had a considerably greater concentration of FGF-21 compared to control groups **(Table 3).**

Table (2): Biochemical parameters for the studied cohort.

Variable		Controlgroup	Patientsgroup	Test value•	P-Value
		No. = 50	No. = 50		
T cholesterol (mg/dL)	Mean ± SD	186.84 ± 17.56	193.82 ± 4.68	-1.069	0.288
TG (ng/mL)	Mean ± SD	167.62 ± 20.83	172.58 ± 21.30	-1.177	0.242
LDL (mg/dL)	Mean ± SD	111.72 ± 13.51	122.40 ± 17.49	-3.417	**0.001***
HDL (mg/dL)	Mean ± SD	52.76 ± 8.05	55.94 ± 8.05	-1.975	0.051
Creatinine	Mean ± SD	0.86 ± 0.20	0.86 ± 0.21	0.000	1.000
ALT (mg/dL)	Mean ± SD	16.28 ± 3.16	15.56 ± 3.71	0.494	0.623
HbA1C	Mean ± SD	4.98 ± 0.46	7.37 ± 0.88	-17.017	**0.001***
FBG (mg/dL)	Mean ± SD	90.22 ± 8.11	112.78 ± 22.09	-6.778	**0.001***
2 hr post prandialglucose (mg/dL)	Mean ± SD	114.72 ± 11.31	179.56 ± 27.46	-15.442	**0.001***

GDM patients had a considerably greater concentration of FGF-21 compared to control groups **(Table 3).**

Table (3): Comparison between patients with GDM and healthy control pregnant ladies regarding FGF-21.

FGF-21	Control group	Patients group	Test value ǂ	P-value
	No. = 50	No. = 50		
Median (IQR)	47 (29 - 80)	258.50 (158 - 333)	-7.642	**0.001***

An outcome that is statistically significant BMI, FBS, fasting blood glucose levels, and haemoglobin A1C all show a connection to serum FGF-21 levels. Serum FGF 21 levels did not correlate significantly with any of the factors examined in this study: maternal age or pregnancy length or weight; lipid profile; serum creatinine; or alanine aminotransferase (ALT) **(Table 4).**

Table (4): Correlation between serum FGF-21 levels and demographic and laboratory data in both groups.

Variable	FGF-21	
	R	P-value
Age (years)	-0.069	0.635
BMI (kg/m^2)	**0.392**	**0.005***
Cr	-0.140	0.332
ALT (U/l)	-0.014	0.926
HbA1C	**0.460**	**0.001****
Fasting plasma glucose (mg/dL)	**0.330**	**0.019***
2 hr post prandial glucose (mg/dL)	**0.328**	**0.020***
T cholesterol (mg/dL)	-0.040	0.785
TG (ng/mL)	0.257	0.071
LDL (mg/dL)	-0.205	0.152
HDL (mg/dL)	0.101	0.485
Gestational age (week)	0.264	0.064
Fetal weight (g)	0.201	0.161

*: Significant relationship

Pre-eclampsia and hypertension rates were greater among GDM patients than in the control group, but the difference was not statistically significant (p-value >0.05), while patients with GDM had significantly more need for caesarean sections than the control group, (p-value <0.05). Furthermore, although the difference was not statistically significant, patients with GDM had a higher rate of foetal problems (hypoglycemia, macrosomia, and newborn respiratory distress) than those in the control group. (p-value >0.05) **(Table 5).**

Table (5): Maternal and fetal outcome in the studied cohort.

Maternal outcome		Control group		Patients group		Test value••	P-value
		No.	%	No.	%		
Pre-eclampsia	Negative	46	92.0%	45	90.0%	0.122	0.727
	Positive	4	8.0%	5	10.0%		
Hypertension	Negative	45	90.0%	41	82.0%	1.329	0.249
	Positive	5	10.0%	9	18.0%		
C-section	Negative	36	72.0%	23	46.0%	6.986	**0.008***
	Positive	14	28.0%	27	54.0%		
Fetal outcome							
Hypoglycemia	Negative	48	96.0%	43	86.0%	3.053	0.081
	Positive	2	4.0%	7	14.0%		
Macrosomia	Negative	45	90.0%	39	78.0%	2.679	0.102
	Positive	5	10.0%	11	22.0%		
Resp. Distress	Negative	45	90.0%	43	86.0%	0.379	0.538
	Positive	5	10.0%	7	14.0%		

Serum FGF-21 and the incidence of maternal hypertension were shown to be highly statistically significant in the study groups when it came to the complications for both the mother and the fetus.(p-value 0.011), FGF-21 levels and prenatal problems including macrosomia, respiratory distress, or newborn hypoglycemia were not statistically linked **(Table 6).**

Table (6): Correlation between serum FGF-21 levels and fetal and maternal outcomes in the studied cohort.

Variable		FGF-21		Test value ǂ	P-value
		Median (IQR)	Range		
Fetal outcome					
Hypoglycemia	Negative	233 (156 – 319)	38 – 635	1.943	0.052
	Positive	432 (277 – 504)	105 – 750		
Macrosomia	Negative	240 (144 – 344)	38 – 635	0.738	0.461
	Positive	277 (200 – 333)	126 – 750		
Resp. Distress	Negative	233 (156 – 333)	38 – 750	1.594	0.111
	Positive	319 (303 – 504)	105 – 635		
Maternal outcome					
Pre-eclampsia	Negative	240 (156 – 333)	38 – 750	1.472	0.141
	Positive	319 (304 – 330)	211 – 635		
Hypertension	Negative	226 (144 – 310)	38 – 620	2.551	**0.011***
	Positive	319 (308 – 455)	200 – 750		
C-section	Negative	226 (90 – 308)	38 – 620	1.879	0.060
	Positive	304 (200 – 432)	95 – 750		

DISCUSSION

Pregnant women with GDM are classified as having any degree of glucose intolerance that was not present prior to gestation. It is usually discovered between the 24th and the 28th week of pregnancy [12]. When gestational diabetes mellitus (GDM) occurs, it can have serious consequences for both the unborn child and its parents. GDM is primarily caused by insulin resistance and cell dysfunction [13].

FGF21 is a novel polypeptide adipokine that regulates metabolism and energy homeostasis. Several studies reported that FGF-21 is a strong independent predictor for T2DM [14].

During the study period, 50 pregnant ladies diagnosed with GDM were included and compared to 50 healthy pregnant controls. All subjects included in both groups were maternal and gestational age-matched and they have been closely observed for detection of antepartum, intrapartum, and postpartum complications.

The current study demonstrated that serum levels of FGF-21 were significantly increased in GDM compared with healthy pregnant women. This is agreed with several cross-sectional studies [7,8,15]. Similarly, a study by **Dekker *et al.*** [10] reported increased placental expression of FGF21 and its rise in GDM compared with healthy controls.

Moreover, in the present study, the circulating level of FGF-21 was significantly correlated with higher blood glucose levels including FBG, 2 hours postprandial blood glucose, and HbA1C. similarly, the association between FGF21 and diabetes was displayed in a large Chinese prospective study that recognized a progressive increase in circulating FGF-21 with hyperglycemia and supposed that FGF-21 could predict the development of diabetes [16].

FGF21 improves the pancreatic β cells' function and enhances glucose uptake in fat cells by acting as a mediator for the metabolic function of peroxisome proliferator-activated receptor α agonists [17,18]. These positive effects of FGF21 on glucose homeostasis and lipid metabolism propose that this adipokine might be a promising therapeutic agent for the management of T2DM and other obesity-associated metabolic conditions [17,18]. However, the paradoxical surge of circulating FGF-21 in GDM and insulin resistance states could be a defensive mechanism to counteract the metabolic disorders dictated by diabetes [19]. Additionally, resistance to FGF-21 actions in pancreatic β cells consequent to glucotoxicity and inflammation occurring in diabetes might lead to a compensatory increase in FGF-21 [7].

In the present study, the circulating level of FGF-21 was also significantly correlated with maternal BMI. Our data is consistent with **Zhang *et al.*** [20] study that demonstrated a positive correlation between FGF21 and BMI with a significantly increased serum level of FGF21 in obese persons and individuals with metabolic syndrome. The paradoxical increase in serum FGF-21 in insulin resistance-related disorders, for example, obesity, T2DM, and NAFLD [21] have raised concerns about whether this result is from resistance to its action [22] or might be a protective response to alleviate the metabolic stress imposed by obesity [23].

We observed a positive significant correlation between circulating FGF-21 levels and maternal blood pressure where higher FGF-21 levels were found in those with higher blood pressure values. This is consistent with **Bonakdaran *et al.*** [7] that showed a positive correlation between higher FGF 21 levels and higher maternal blood pressure values in patients with GDM. Similarly, **Semba *et al.*** [24] found an association between serum FGF21 levels and hypertension in adults. As an example, in an intervention research with 40 obese nondiabetic women, five days per week of supervised exercise training resulted in significantly lower blood pressure, FGF21 levels, and other markers of cardiovascular disease [25].

On the other hand, the current study failed to find a significant relation between FGF-21 and fetal complications whether fetal macrosomia, respiratory distress, or neonatal hypoglycemia. This agreed with **Megia *et al.*** [8] study which failed to find a correlation between FGF21 and birth weight.

CONCLUSION

FGF21 is increased in GDM. Higher serum FGF 21 levels were associated with higher blood pressure values in pregnant females included in this study.

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REFERENCES

1. **Ogurtsova K, da Rocha Fernandes J, Huang Y *et al.* (2017):** IDF Diabetes Atlas: Global estimates for the prevalence of diabetes for 2015 and 2040. Diabetes Research and Clinical Practice, 128:40-50.
2. **Plows J, Stanley J, Baker P *et al.* (2018):** The pathophysiology of gestational diabetes mellitus. International Journal of Molecular Sciences, 19(11): 3342.
3. **Gestational Diabetes Mellitus (2003):** American Diabetes Association. Diabetes Care, 1:103-105.
4. **Panahi Y, Bonakdaran S, Yaghoubi M *et al.* (2016):** Serum levels of fibroblast growth factor 21 in type 2 diabetic patients. Acta Endocrinologica, 12:257-261.
5. **Martin F, Maratos-Flier E (2016):** Understanding the physiology of FGF21. Annu Rev Physiol., 78: 223-241.
6. **Staiger H, Keuper M, Berti L *et al.* (2017):** Fibroblast Growth Factor 21-Metabolic Role in Mice and Men. Endocr Rev., 38:468-488.
7. **Bonakdaran S, Khorasani Z, Jafarzadeh F (2017):** Increased serum level of FGF21 in gestational diabetes mellitus. Acta Endocrinologica (Bucharest), 13: 278-281.
8. **Megia A, Gil-Lluis P, Näf S *et al.* (2015):** Cord blood FGF21 in gestational diabetes and its relationship with

postnatal growth. Acta Diabetologica, 52:693-700.

9. **Xiao Y, Xu A, Law L *et al.* (2012):** Distinct changes in serum fibroblast growth factor 21 levels in different subtypes of diabetes. The Journal of Clinical Endocrinology & Metabolism, 97:54-58.
10. **Nitert M, Barrett H, Kubala M *et al.* (2014):** Increased placental expression of fibroblast growth factor 21 in gestational diabetes mellitus. The Journal of Clinical Endocrinology & Metabolism, 99:591-598.
11. **Metzger B, Gabbe S, Persson B *et al.* (2010):** International association of diabetes and pregnancy study groups recommendations on the diagnosis and classification of hyperglycemia in pregnancy. Diabetes Care, 33(3):676-682.
12. **American Diabetes Association (2018):** Classification and diagnosis of diabetes: standards of medical care in diabetes -2018. Diabetes Care, 41:13-27.
13. **Jafari-Shobeiri M, Ghojazadeh M, Azami-Aghdash S *et al.* (2015):** Prevalence and Risk Factors of Gestational Diabetes in Iran: A Systematic Review and Meta-Analysis. Iran J Public Health, 44(8):1036-1044.
14. **Su S, Kuo C, Huang C *et al.* (2013):** Fibroblast growth factor 21 predicts type 2 diabetes in Taiwanese. The Changhua Journal of Medicine, 11:42-47.
15. **Li S, Wang W, Zhou L *et al.* (2015):** Fibroblast growth factor 21 expressions in white blood cells and sera of patients with gestational diabetes mellitus during gestation and postpartum. Endocrine, 48:519-527.
16. **Chen C, Cheung B, Tso A *et al.* (2011):** High plasma level of fibroblast growth factor 21 is an independent predictor of type 2 diabetes a 5.4-year population-based prospective study in Chinese subjects. Diabetes Care, 34(9):2113-2115.
17. **Liu J, Foo J, Liu S *et al.* (2015):** The role of fibroblast growth factor 21 in diabetes and its complications: a review from clinical perspective. Diabetes Res Clin Pract., 108(3):382-389.
18. **Ishida N (2009):** Role of PPAR in the Control of Torpor through FGF21-NPY Pathway: From Circadian Clock to Seasonal Change in Mammals. PPAR Res., 9:412949.
19. **Mraz M, Bartlova M, Lacinova Z *et al.* (2009):** Serum concentrations and tissue expression of a novel endocrine regulator fibroblast growth factor-21 in patients with type 2 diabetes and obesity. Clin Endocrinol., 71(3):369-375.
20. **Zhang X, Yeung D, Karpisek M *et al.* (2008):** Serum FGF21 levels are increased in obesity and are independently associated with the metabolic syndrome in humans. Diabetes, 57:1246-1253.
21. **Talukdar S, Zhou Y, Li D *et al.* (2016):** A long-acting FGF21 molecule, PF-05231023, decreases body weight and improves lipid profile in non-human primates and type 2 diabetic subjects. Cell Metabolism, 23:427-440.
22. **BonDurant L, Potthoff M (2018):** Fibroblast growth factor 21: a versatile regulator of metabolic homeostasis. Annual Review of Nutrition, 38:173-196.
23. **Fisher F, Chui P, Antonellis P *et al.* (2010):** Obesity is a fibroblast growth factor 21 (FGF21)-resistant state. Diabetes, 59:2781-2789.
24. **Semba R, Crasto C, Strait J *et al.* (2013):** Elevated serum fibroblast growth factor 21 is associated with hypertension in community-dwelling adults. J Hum Hypertens., 27(6):397-399.
25. **Yogev Y, Xenakis E, Langer O (2004):** The association between preeclampsia and the severity of gestational diabetes: The impact of glycemic control. Am J Obstet Gynecol., 191:1655-1660.