INCREASED SERUM LEVEL OF FGF21 IN GESTATIONAL DIABETES MELLITUS

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Abstract

Objective. Gestational diabetes mellitus (GDM) is a common endocrine complication in pregnancy. There are few risk factors that clearly correlate with GDM. Fibroblast growth factor 21 (FGF21) is a metabolic hormone that can regulate glucose metabolism. It has been recognized that serum levels of FGF21 are significantly increased in diabetes and insulin resistance states. The objective of this study was to determine the serum FGF21 levels in women with GDM compared with non-GDM women and its correlation with insulin resistance.

Methods. Thirty GDM patients and 60 healthy pregnant controls that matched for maternal and gestational age were selected. Women with previous history of GDM, hypertension, polycystic ovary syndrome, renal or liver failure and drug consumption with effects on glucose or insulin levels were excluded. FGF21 was determined and correlated with biochemical parameters of glucose metabolism and insulin resistance.

Results. FGF21 concentration was significantly higher in GDM (264.5±196.2 ng/L) as compared with control groups (59.1±36.5ng/L). Correlation of FGF21 with insulin resistance was not significant. A cut-off 82.07 ng/L of FGF21 had sensitivity of 100% and specificity of 85% for prediction of GDM.

Conclusion. FGF21 is increased in GDM and it is independent of insulin resistance. We suggest that FGF21 resistance could be directly involved in pathophysiology of GDM.

Key words: GDM, FGF21, pregnancy, insulin resistance.

BACKGROUND

Gestational diabetes mellitus (GDM) is one of the most common endocrine complications during pregnancy, resulting in perinatal and neonatal problems (1). GDM is a known predisposing factor for future type 2 diabetes and obesity for both mother and child (2). According to a meta- analysis in 2015, the prevalence of GDM in IRAN was 3.41% (lowest and highest rates were 1.3, 18.6% respectively) (3) and it has markedly been increasing in recent years (4). Insulin resistance and reduction in the pancreatic beta cell reserve for insulin secretion contribute to the development of GDM (3, 5). Fibroblast growth factor 21 (FGF21) is a metabolic hormone produced by the liver, adipose tissue, skeletal muscle, and pancreas that is related to glucose metabolism and insulin resistance (6-7). It has been recently reported that serum level of FGF21 is higher in insulin resistance status and obesity (FGF21 resistance) (8-9). Several studies reported that FGF21 is a strong independent predictor for type 2 diabetes (10-11). Association of FGF21with GDM has not been evaluated so far. As we reviewed the literature, there was no similar study in Iran and this study is performed the first time. In this study, we aimed to evaluate whether maternal FGF21 is altered in GDM compared to non-GDM women.

METHODS AND MATERIALS

Thirty women with GDM diagnosis (18 of GDM patients controlled with diet and 12 of them underwent insulin therapy) and 60 normoglycemic (control) women matched for gestational age were recruited for this 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. Women with 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. After a complete explanation of the project, demographic characteristics were recorded in first prenatal visit, including age, height, weight, blood pressure and body mass index (BMI). BMI was calculated according to the formula: Weight (kg)/height (m²). Blood pressure of the right arm was taken in a sitting position after resting for ten minutes. OGTT was done at 24-28 weeks of gestation.

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GDM was defined as at least one glucose level greater than following thresholds during 75 gram, 2 hour oral glucose tolerance test (OGTT): fasting≥ 92 mg/dL (5.1 mmol/L), 1 h≥ 180 mg /dL (1 0. 0 mmol/L), 2 h≥ 153 mg /dL (8.5 mmol/L) (on a recommendation of the international Association of the Diabetes and Pregnancy Study Groups (IADPSG). Serum FGF21 levels were measured in fasting samples at the time of OGTT by FGF-21 Human ELISA Kit (ab125966). Insulin level was assessed by immunoradiometric assay and Insulin resistance was estimated with the homeostasis model assessment-insulin resistance (HOMA-IR) index (fasting blood sugar (mmol/lit) * insulin (mIU/L)/22.5). Clinical and laboratory variables of patients were classified into two categories according to results of OGTT and then these groups were compared together.

Statistical analysis

Statistical analysis was done by using SPSS version 11.5. Data was expressed as mean ± SD. Student t. test or ANOVA was used for variables with normal distribution and quantitative variables with non-normal distribution were compared with Mann-Withney. Qualitative variables between the groups were analyzed by chi-square. Based on quartiles of FGF21 concentration participants were divided into 4 groups and GDM prevalence compared between groups. Receiver operating characteristic (ROC) curves were used to investigate FGF21 cut-off points to identify GDM. Sensitivity, specificity, positive predictive value and negative predictive value of FGF21 were calculated for estimation of GDM development.

Ethical statement

The study protocol was approved by the local Ethics Committee (The research ethics committee of Mashhad University of Medical Sciences), and was conducted according to the principles of Helsinki Declaration. Written informed consent was obtained from all patients.

RESULTS

Baseline clinical and paraclinical characteristics of 90 patients are shown in Table 1.

Comparison of laboratory and clinical parameters between GDM and non- GDM is shown in Table 2. Mean FGF21 level was significantly higher in patients with GDM and subjects without GDM. Correlation between FGF21 level with blood pressure and BMI was not significant. We divided FGF21 level into quartiles: 29.1% of all subjects had FGF21 level ≤42.69 (quartile 1), 20.9% of patients had FGF21 level between 42.7-83.44 ng/L (quartile 2), in 25.6 % of patients FGF21 level was between 83.45-154.1 ng/L (quartile 3) and 24.4 % of patients were in quartile 4 with FGF21 more than 154.1 ng/L. Figure 1 shows the distribution of GDM in FGF21 quartile.

Table 1. Baseline characteristics of patients (n= 90)

Characteristics	Mean± SD
Age (years)	25.4±5.1
Body mass index (kg/m²)	24.6± 4.9
Systolic blood pressure(mm Hg)	110.2 ± 14.5
Diastolic blood pressure(mm Hg)	67.2± 8.3
FGF21(ng/L)	130.8±153.9

Data are expressed as means ± SD.

Table 2. Comparison of clinical and paraclinical characteristics between GDM and non-GDM

Variable	GDM	Non-GDM	P
Age (year)	26.8±6.3	24.8±4.3	0.08
Body mass index(kg/m²)	26.0 ±5.9	23.9±4.3	0.07
Systolic blood pressure (mm Hg)	120.9±11.4	104.4±12.6	<0.001
Diastolic blood pressure (mm Hg)	72.9±6.8	64.1±7.4	<0.001
FBG (mg/dL)	90.0±13.3	72.1±6.8	<0.001
1 hour after 75 g glucose (mg/dL)	158.6±33.7	115.4±20.0	<0.001
2 hours after 75 g glucose (mg/dL)	142.9±37.3	95.5±14.8	<0.001
Insulin (m IU/L)	11.8±5.8	10.7±4.2	0.27
HOMA-IR	2.6±1.3	2.3±1.2	0.32
FGF21(ng/L)	189.2(110.5-1087.7)	54.9(3.12-166.0)	<0.001

FBS, fasting blood glucose;HOMA-IR, homeostasis model assessment-insulin resistance FGF21, Fibroblast growth factor 21:
- Data are expressed as means ± SD and median;
- P value <0.05 is considered significant;
- T. test was used for analysis of normal distribution variable and Kruskal Wallis for non normal distribution variable.
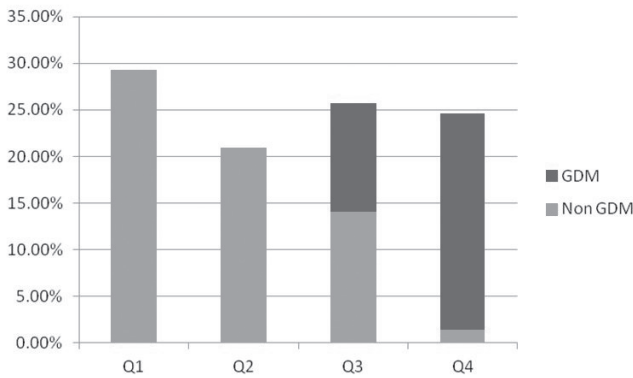
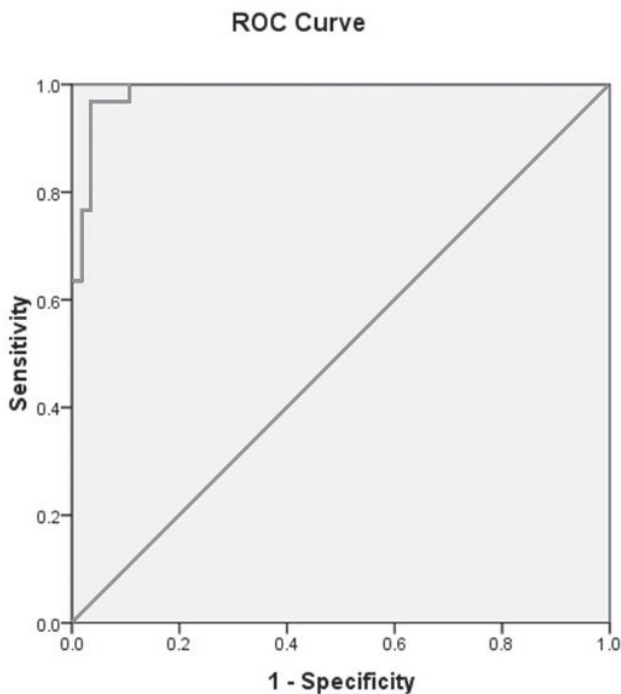**Figure 1.** Prevalence of GDM by FGF21 quartile.

Figure 2. ROC curves for the prediction of GDM based on the FGF21 concentration.

According to this figure, patients with higher level of FGF21 had a significant higher rate of GDM. A ROC curve for the prediction of GDM is based on the FGF21 (Fig. 2). Cut-off point of 82.07 had C statics of 0.95 (95% CI: 0.96-1.005, P<0.001). Sensitivity of this parameter was 100% and specificity was 75%. Positive predictive value of this test and negative predictive value were 68.2% and 100% respectively.

DISCUSSION

In this study, serum level of FGF21 is determined for the first time in pregnant patients in Iran, to our knowledge. Our results showed that serum FGF21 level is significantly higher in GDM patients as compared with healthy pregnant controls. There was not any significant difference in maternal and gestational ages between two groups and we excluded pregnant women with risk factors for GDM. Our results are consistent with some previous studies. Wang *et al.* in 30 patients with GDM and 60 healthy control groups found that FGF21 levels were significantly higher in GDM patients (12). Dekker Nitert *et al.* showed that FGF21 is expressed in placenta and is increased in GDM compared with healthy pregnant subjects (13). There are several studies that showed association between FGF21 and diabetes. In a large Chinese prospective by Chen *et al.*, FGF21 levels increased progressively with dysglycemia and this author concluded that FGF21 predicted the development of diabetes (14).FGF21 improves the function of pancreatic beta cell and induces glucose uptake in fat cells (15). It is suggested that FGF21 is a mediator for metabolic function of peroxisome proliferator –activated receptor α agonists (6, 16). It seems that in metabolic imbalance states, FGF21 resistance and compensatory up-regulation of this growth factor has occurred. Inflammation, metabolic dysregulation and hyperglycemia may cause defective FGF21 signaling. Glucotoxicity impairs FGF21 actions in pancreatic islet cells (17). High blood pressure is a component of metabolic syndrome. In our study, blood pressure was significantly higher in GDM patients compared with non-GDM women. This difference may be related to changes in FGF21 level in two groups. Semba *et al.* showed that serum FGF21 levels are independently associated with hypertension in community-dwelling adults (18).

In the current study, insulin resistance is not significantly different between GDM subjects with control groups and we failed to find a significant relation between FGFG21 and insulin resistance. This finding is in contrast to several previous studies indicating that FGF21 correlated positively with insulin resistance (19). On the other hand this finding is in accordance with a previous study by Chen *et al.* that found FGF21 is an independent predictor for type 2 diabetes after adjustment for insulin levels. It seems that FGF21 is an independent causal factor for GDM.

There are several limitations in our study. Cross sectional design of this study, low sample size and not considering other known biomarkers for GDM are limitations of this study.

In conclusion, we demonstrated that serum levels of FGF21 were significantly increased in GDM compared with healthy pregnant women and FGF21 is not correlated with insulin resistance. Clearly,

prospective large studies are needed to better elucidate this association and pathophysiological significance of FGF21 in GDM.

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