Relationship between serum Nrf2 and FGF21 levels and insulin resistance and pregnancy outcomes in patients with GDM

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Introduction. To explore the relationship of serum levels of nuclear factor E2-related factor 2 (Nrf2) and fibroblast growth factor 21 (FGF21) with insulin resistance (IR) and pregnancy outcomes in patients with gestational diabetes mellitus (GDM).

Methods. 187 patients with GDM diagnosed by 75g-OGTT in the hospital were selected as the study subjects, and the physical examination data of 120 healthy pregnant women during the same period were included in control group. General clinical data of patients were collected after admission, and serum Nrf2 and FGF21 levels were determined by enzyme-linked immunosorbent assay, and IR was calculated. The general clinical data, serum Nrf2 and FGF21 levels and IR were compared between the two groups. Pearson correlation coefficient analysis was used to analyze the relationship between serum Nrf2 and FGF21 levels and IR in patients with GDM. All patients were followed up until delivery and pregnancy outcomes were counted. Serum Nrf2 and FGF21 levels and IR were compared among GDM patients with different pregnancy outcomes, and the predictive value of serum Nrf2 and FGF21 levels on pregnancy outcomes in patients with GDM was analyzed by receiver operating characteristic (ROC) curve.

Results The levels of FPG and FINS in GDM group were significantly higher than those in healthy group (P<0.05), but there were no statistically significant differences in age, gestational week and parity between the two groups (P>0.05). Serum Nrf2 level in GDM group was significantly lower than that in healthy group (P<0.05) while FGF21 level and

HOMA-IR were significantly higher than that in healthy group (P<0.05). Pearson correlation coefficient showed that serum Nrf2 level was significantly negatively correlated with HOMA-IR (P<0.05), and serum FGF21 level was significantly positively correlated with HOMA-IR (P<0.05). Among 187 pregnant women with GDM, there were 41 cases of poor pregnancy outcomes and 146 cases of good pregnancy outcomes. Serum Nrf2 level in the poor pregnancy group was significantly lower than that in good pregnancy group (P<0.05) while FGF21 level and HOMA-IR were significantly higher than those in good pregnancy group (P<0.05). ROC curve analysis showed that the sensitivities of serum Nrf2 and FGF21 alone and in combination in the diagnosis of adverse pregnancy outcomes in patients with GDM were 82.93%, 87.80% and 90.24%, and the specificities were 61.64%, 63.70% and 61.64%, and the AUCs were 0.761, 0.823 and 0.881, and combined diagnosis had higher value.

Conclusion. Serum Nrf2 and FGF21 levels in patients with GDM are significantly correlated with IR, and can be used as biological potential diagnostic indicators of pregnancy outcomes.

Keywords. Gestational diabetes mellitus; Nuclear factor E2-related factor 2; Fibroblast growth factor 21; Insulin resistance; Pregnancy outcomes

INTRODUCTION

Gestational diabetes mellitus (GDM) is defined as abnormal glucose metabolism in pregnant women due to obesity or older age after pregnancy with normal glucose metabolism or potential impaired glucose tolerance before pregnancy [1] . The prevalence of GDM is 9.3% ~ 25.5% in the world and 14.8% in our country. In recent years, with the development of economy and the reform of birth policy, the incidence of GDM in our country is on the rise [3] . Multiple studies have shown that GDM pregnant women have a significantly increased risk of adverse pregnancy outcomes such as preterm birth, gestational hypertension, postpartum hemorrhage, and neonatal hypoglycemia compared with normal pregnant women [4] . Insulin resistance (IR) in pregnant women with GDM can aggravate abnormal glucose metabolism and affect the growth and development of pregnant women and their fetuses, exploring the

factors that influence IR in patients with GDM is of great significance in predicting pregnancy outcomes [5] . Nuclear Factor E2-related factor 2(Nrf2) is a major regulator of cellular redox and can maintain the balance of oxidative stress in vivo and in vivo [6] . Up-regulation of Nrf2 was found to significantly inhibit the generation of advanced glycation end products (AGEs) , which in turn ameliorates glycotoxic injury in diabetic nephropathy patients. Fibroblast growth factor 21(FGF21) is a Fibroblast growth factor regulator that, like insulin, regulates cellular glucose and lipid metabolism. FGF21 has been found to modulate insulin sensitivity and improve IR to a certain extent [9] . At present, there are few studies on Nrf2 and FGF21 in GDM, so this study aims to explore the relationship between Nrf2, Fgf21 and IR and pregnancy outcome in GDM patients.

1. DATA AND METHODS

1.1 General information

A total of 187 GDM patients were selected from February 2020 to April 2022 were selected. Inclusion criteria: (1) meet the American College of Obstetricians and Gynecologists (american college of obstetricians and gynecologists, ACOG) GDM diagnostic criteria [10]: ① fasting blood glucose (FBG) 5.1 mmol/L; 10.0mmol/L 1h ②, ③ 2h 8.5 mmol/L, any of the three conditions break. Inclusion criteria: (1) non-existence of diabetes and family history before pregnancy; (2) age 20-39 years; (3) singleton pregnancy; (4) complete birth examination and delivery data. Exclusion criteria: (1) patients with severe abnormal liver and kidney function; (2) patients with abnormal immune and coagulation function and malignant tumors; and (3) patients with severe infection, inflammation and other diseases.187 patients aged 21 to 39 years, mean (30.04 ± 4.62) years, 41 had adverse pregnancy outcome and 146 had no adverse pregnancy outcome.

1.2 Methods

Serum Nrf 2 and FGF21 levels: Fasting venous blood was collected after admission, serum was isolated by centrifugation at 3500r, and serum levels of Nrf 2

and FGF21 were measured by enzyme-linked immunosorbent assay. All test kits were purchased from Shanghai Renjie Biotechnology Co., Ltd.

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1.3 Observing indicators

(1) Comparison of general clinical data between GDM and healthy groups; (2) comparison of serum Nrf 2, FGF21 levels and IR values between GDM and healthy groups; (3) analysis of the relationship between serum Nrf 2 and FGF21 levels and IR; (4) comparison of serum Nrf 2, FGF21 levels and IR values in pregnant women with different pregnancy outcomes; and (5) analysis of the value of serum Nrf 2 and FGF21 in predicting adverse pregnancy outcomes in patients with GDM。

1.4 Statistical methods

The SPSS 25.0 statistical software was selected, and the measurement data were recorded by normal distribution test in (± s), with independent sample t-test; the count data were recorded in n (%), and (2 test, the relationship between serum Nrf 2 and FGF21 levels and HOMA-IR was analyzed by Pearson correlation; serum Nrf 2 and FGF21 in GDM by the receiver operating characteristic curve (ROC), test level α =0.05.

2 RESULTS

2.1 Comparison of general clinical data between GDM and healthy groups

The FPG and FINS levels of the GDM group were significantly higher than those of the healthy group (P <0.05), and the difference between age, gestational age and parity between the two groups was not statistical significant (P> 0.05), as shown in Table 1

Table 1 Comparison of general clinical data of pregnant women in GDM and healthy groups [n (%) and ± s]

group	Example number	age	gestational weeks	parity	FPG（mmol/L）	FINs（U/L）
GDMgroup	187	30.22±4.23	26.78±1.86	2.06±0.47	6.78±0.72	13.68±2.16

Health group	120	29.76±4.46	27.13±1.73	2.12±0.43	4.42±0.53	10.87±2.04
t/χ^2price		0.910	1.653	1.128	30.923	11.364
P price		0.364	0.099	0.260	<0.001	<0.001

2.2 Comparison of serum Nrf 2, FGF21 levels and IR values between the GDM and healthy groups

Serum Nrf 2 levels were significantly lower in the GDM group than in the healthy group (P <0.05), and FGF21 levels and HOMA-IR were significantly higher than in the healthy group (P <0.05). See Table 2.

Table 2 Comparison of serum Nrf 2, FGF21 levels and IR values between GDM and healthy groups (± s)

group	Example number	Nrf2（ng/L）	FGF21（ng/mL）	HOMA-IR
GDM group	187	1.38±0.36	308.82±34.49	4.12±0.53
Health group	120	1.67±0.43	265.44±30.17	2.14±0.41
T price		6.377	11.282	34.780
P price		<0.001	<0.001	<0.001

2.3 Association between serum Nrf 2 and FGF21 levels and IR in the GDM group

Pearson Corcorrelation coefficient showed a significant negative correlation between serum Nrf 2 levels and HOMA-IR (P <0.05), and serum FGF21 levels with HOMA-IR (P <0.05). See Table 3.

Table 3 Association between serum levels of Nrf 2 and FGF21 and IR in the GDM group

project		Nrf2	FGF21
HOMA-IR	*r*	-0.576	0.633
	P	0.013	0.006

2.4 Comparison of serum Nrf 2, FGF21 levels and IR values in pregnant women with different pregnancy outcomes

Among 187 pregnant women with GDM, 41 had poor pregnancy outcomes, 146 had good pregnancy outcomes, serum Nrf 2 level in the poor pregnancy group was significantly lower than the good pregnancy group (P <0.05), and FGF21 levels and HOMA-IR were significantly higher than the good pregnancy group (P <0.05). See

Table 4. Table 4 Comparison of serum Nrf 2, FGF21 levels and IR values in pregnant women with different pregnancy outcomes (± s)

group	Example number	Nrf2（ng/L）	FGF21（ng/mL）	HOMA-IR
Poor pregnancy group	41	1.07±0.27	344.50±35.13	4.33±0.44
Good pregnancy group	146	1.47±0.45	298.80±33.89	4.06±0.48
T price		9.733	11.275	5.06
P price		<0.001	<0.001	<0.001

2.5 Value analysis of serum Nrf 2 and FGF21 in predicting adverse pregnancy outcomes in patients with GDM

ROC curve analysis showed that the sensitivity of adverse pregnancy outcomes in serum Nrf 2, FGF21 alone and combined GDM was 82.93%, 87.80%, 90.24%, specificity was 61.64%, 63.70%, 61.64%, and AUC was 0.761,0.823,0.881 respectively, with higher combined diagnostic value. See Table Table 5. The ROC curves are shown in Figure 1.

Table 5 Value analysis of serum Nrf 2 and FGF21 levels in predicting adverse pregnancy outcomes in patients with GDM

metric	Cut-off price	sensitivity (%)	specificity (%)	Youden	AUC	95% CI

				index		
Serum Nrf2	1.29 ng/L	82.93	61.64	0.446	0.761	0.689-0.832
Serum FGF21	310.08 ng/mL	87.80	63.70	0.515	0.823	0.758-0.888
Joint diagnosis	-	90.24	61.64	-	0.881	0.831-0.932

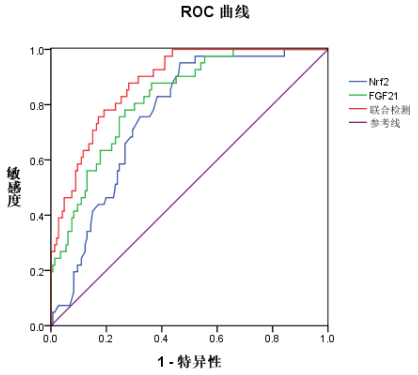

Figure 1 ROC curves of serum Nrf 2 and FGF21 for predicting adverse pregnancy in patients with GDM

3 DISCUSSION

GDM is a common metabolic symptoms of pregnancy disorders, its pathogenesis is similar to type 2 diabetes, it is generally believed that the precursor of pregnancy quality, pregnancy age, eating habits, environmental factors, etc, genetic factors, abnormal sugar tolerance during pregnancy, liver, adipose tissue sensitivity to insulin reduced, the body antioxidant capacity is weakened, is not conducive to pregnant women and the normal development of [11]. Several studies have shown that the onset of GDM is closely related to adverse maternal and infant outcomes, and understanding the related factors affecting adverse pregnancy outcomes in GDM patients and conducting targeted prevention is currently the key [12] to improve the quality of pregnancy in GDM patients.

Previous studies have shown that obesity is an important factor causing the pathogenesis of GDM, and pregnant women with overweight obesity and higher

weight gain before pregnancy have significantly increased the risk of GDM [13]. Glucose management during pregnancy is an important way to control the condition of GDM. Blood glucose management usually includes scientific diet, maintaining a balanced intake of energy and nutrition, avoiding overeating, anemia or hypoproteinemia caused by blind diet. IR is a phenomenon that the body decreases its sensitivity to insulin. The decrease of insulin sensitivity makes the body compensate to secrete too much insulin to maintain blood glucose stability. Therefore, GDM patients increase HOMA-IR value and FPG , The FINs values were also significantly elevated in [14]. In the results of this study, FPG, FINS, and HOMA-IR values in the GDM group were significantly higher than those in the healthy group ($P < 0.05$), which is consistent with the above findings.

Studies have shown that a variety of biological reactions in IR, including oxidative stress play an important role, when the body is in a state of high blood sugar time oxygen radical increased, aggravating oxidative stress level, oxidative stress can cause islet B cell damage and the loss of function, and cause insulin secretion decline, cause the body hypoglycemic ability decreased [15]. Nrf 2 is a sensitive factor against oxidative stress, which is widely expressed in various cells and tissues of the body. It can maintain the balance of oxidative stress and stabilize the REDOX steady state. When the body is in a state of high sugar, the production of reactive oxygen species increases, and the peroxidation state can aggravate the body Inflammatory damage, while Nrf 2 expression could contribute to upregulate reductase activity and avoid peroxidation damage [16]. Pharmacological studies have found that activation of the Nrf 2 / HO-1 pathway attenuates oxidative stress and ultrastructural abnormalities [17] in skeletal muscle of type 2 diabetic rats. Zhou Fenmei et al. [18] showed that serum Nrf 2 level was a significant influencing factor of HOMA-IR in diabetic patients, and it was significantly negatively associated with HOMA-IR. In addition, Nrf 2 is also associated with various adverse pregnancy outcomes such as recurrent abortion and preterm birth, and upregulation of Nrf 2 can reduce the incidence of oxidative stress-induced abortion.FGF 21 is a metabolic regulator, first isolated in murine

embryonic tissue, and has various effects of promoting fatty acid oxidation in liver, reducing ER stress, and enhancing glucose uptake capacity of adipocytes [19]. It was found that the effect of FGF21 focuses on the regulation of glucose and lipid metabolism and islet B cell function, and that serum FGF21 levels were significantly increased in diabetic patients with [20]. Li Yanrong et al. [21] found that serum F GF 21 levels, and they corcorassociated with glucose and lipid metabolism and IR. Yang Cai et al. [22] study showed that hypothyroidism was combined with GD M has increased serum FGF21 and is an independent risk factor for pregnancy outcome. The above studies suggest that both Nrf 2 and FGF21 are associated with GDM occurrence and IR

The results of this study showed that compared with the pregnant women in the healthy group, serum Nrf 2 level in GDM women significantly decreased, FGF21 level significantly increased, and serum Nrf 2 level in adverse pregnancy group was significantly lower than the pregnancy outcome group, FGF21 level was significantly higher than that of Nrf 2, FGF21 likely affected the body metabolism, through the oxidative stress pathway Nrf 2 expression is downregulated, the oxidative stress is weakened, the body metabolic disorder, and oxidative stress stimulates the expression of FGF21, improve the intake of sugar, and then aggravate the hair of IR give birth to. Pearson Correlation analysis showed that serum Nrf 2 levels were significantly negatively correlated with HOMA-IR in GDM patients, and a significant positive correlation with serum FGF21 levels was consistent with the above findings. ROC curve analysis showed that the AUC of serum Nrf 2, FGF21 alone and in combination were 0.761,0.823 and 0.881, which could be used for clinical auxiliary testing of IR during pregnancy in GDM patients during pregnancy.

In conclusion, the serum levels of Nrf 2 and FGF21 in GDM patients were significantly correlated with IR, and can be used as biological potential diagnostic indicators of pregnancy outcome in patients.

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