Study on the Correlation Between SFRP-5 Expression Level, Insulin Resistance, and Glycolipid Metabolism in Gestational Diabetes Mellitus

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Abstract: *Objective:* To investigate the correlation between serum secretory frizzled-related protein 5 (SFRP-5) expression levels and insulin resistance and glucolipid metabolism in patients with gestational diabetes mellitus (GDM). *Methods:* Baseline data were collected from 58 patients with GDM and 51 healthy controls who were admitted Affiliated Hospital of Hebei University from May 2020 to June 2022. sSTRA5 concentrations in peripheral blood of pregnant women were measured, and SFRP-5 levels in patients with different GDM types and normal controls were analyzed by logistic regression models. *Results:* The levels of triglyceride (TG), total cholesterol (TC), low-density lipoprotein cholesterol (LDL-C), fasting blood glucose (FBG), fasting insulin (FINS), hemoglobin A1c (HbA1c), and homeostasis model assessment-estimated insulin resistance (HOMA-IR) were higher in the observation group than in the control group, with statistically significant differences ($P < 0.05$), while the expression levels of high-density lipoprotein cholesterol (HDL-C) and serum SFRP-5 were lower than in the control group, with statistically significant differences ($P < 0.05$); serum SFRP-5, TG, TC, FBG, and HOMA-IR were all risk factors for GDM ($P < 0.05$). *Conclusion:* Elevated serum sSTRA5 may be involved in the regulation of insulin resistance in the body and the regulation of blood glucose in the body by affecting lipid metabolism and inflammatory response.

Keywords: Gestational diabetes mellitus; Secretory frizzled-related protein 5; Insulin resistance; Glucolipid metabolism

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1. Introduction

The etiology and pathogenesis of gestational diabetes mellitus (GDM) are increasingly understood with the increased prevalence of GDM, and its causes include both genetic and environmental factors. Among the genetic factors, the adverse effects of pregnancy outcome in GDM patients are mainly due to genetic mutations in their mothers and therefore may lead to the development of diabetes and obesity-related disease manifestations in the offspring. Studies have shown that approximately 40% to 50% of pregnant women with diabetes have a higher risk of insulin resistance compared to non-diabetic pregnant women. In addition, environmental factors have been associated with GDM, including dietary structure, lifestyle, body mass index (BMI), and age at pregnancy and BMI. However, for these reasons, higher levels of insulin resistance, adipocyte dysfunction, and metabolic syndrome-related disorders have been found in pregnant women with GDM. Therefore, there is a need for early screening and intervention in patients with GDM,

which has a prevalence of approximately 1% to 5%; the prevalence in pregnant women is approximately 1 in 2500. In recent years, secretory frizzled-related protein 5 (SFRP-5) has been shown to be associated with a variety of pregnancy-related disorders and may have an impact on clinical outcomes, with no clear relationship to pregnancy outcomes. It has been shown that SFRP-5 levels can regulate glucolipid metabolism and affect several pathophysiological processes such as obesity, metabolic syndrome, inflammatory response, and apoptosis through its induced downstream signaling pathways. SFRP-5 can act directly on adipocytes and produce several effectors such as norepinephrine and enkephalin in adipocytes. It can also induce phosphorylation and dephosphorylation of various effector factors such as insulin receptor substrates and G protein-coupled receptor ligands. In addition, it can also induce a decrease in the expression level of some important genes in the insulin signaling pathway such as AMPK/mTOR/AKT and PI3K/Akt pathways and factors related to the mitochondrial apoptosis pathway (mediated by Caspase3/9) such as Bcl-2 and Bax; In addition, SFRP-5 is involved in several important signaling pathways in the process of apoptosis mediated by its signal transduction pathway. In this study, we analyzed the levels of soluble SFRP-5 in the serum of patients with different types of GDM, aiming to investigate the effects of the expression levels of soluble SFRP-5 in the serum of patients with gestational diabetes on glucolipid metabolism.

2. Materials and methodology

2.1. General materials

Baseline data were collected from 58 patients with gestational diabetes mellitus (GDM) and 51 healthy controls who received diagnosis and treatment in Affiliated Hospital of Hebei University from May 2020 to June 2022, and SFRP-5 concentration in peripheral blood of pregnant women was determined.

2.2. Methods

(1) Measurement of SFRP-5

   Peripheral blood was collected from pregnant women and the concentration of SFRP-5 in serum was determined by enzyme-linked immunosorbent assay (ELISA). Venous blood was collected from the subjects and their SFRP-5 levels were measured by double antibody sandwich ELISA. The quantitative assay was also performed using an enzyme marker.

(2) Measurement of insulin resistance-related indexes

   Pregnant women who met the inclusion criteria were numbered in the order of random sampling at admission, and then fasting blood glucose and glucose tolerance tests were performed. Fasting blood glucose ≥ 6.1 mmol/L and fasting insulin ≥ 300 IU (IU is glucose unit) were graded as the diagnostic criteria of insulin resistance. Pregnant women meeting the inclusion criteria were randomly selected. Venous blood was collected from all pregnant women in the control group and experimental group. All samples were tested by an automatic chemiluminescence analyzer, and pre-treatment and sample storage were performed according to the kit instructions.

(3) Logistic regression analysis

   The data were divided into four groups according to the sample size, and multi-factor logistic regression analysis models were used for each group: the relationship between serum SFRP-5 level and fasting blood glucose, glycated hemoglobin concentration, insulin resistance index and blood lipid level were analyzed separately. Logistic equation models were established for each group of data, and Pearson correlation coefficient analysis was used to test the statistical differences.

2.3. Statistical method

All data in this study were processed by SPSS 22.0 statistical software, the measurement data was expressed

as mean ± standard deviation, underwent t test, and the counting data was expressed by rate (%) and tested by χ^2.

3. Results

3.1. Levels of insulin resistance (IR), glycolipid metabolism and SFRP-5

The levels of levels of triglyceride (TG), total cholesterol (TC), low-density lipoprotein cholesterol (LDL-C), fasting blood glucose (FBG), fasting insulin (FINS), hemoglobin A1c (HbA1c), and homeostasis model assessment-estimated insulin resistance (HOMA-IR) in the observation group were higher than those in the control group, with statistical significance (P < 0.05); while the levels of high-density lipoprotein cholesterol (HDL-C) and SFRP-5 of the observation group were lower than those in the control group, with statistical significance ($P < 0.05$), as shown in **Table 1**.

Table 1. Comparison of IR, glycolipid metabolism indexes and serum levels of FRP-5 between the two groups

Group	Control group ($n = 51$)	Observation group ($n = 58$)	t	P
TG (mmol/L)	3.67 ± 0.82	4.92 ± 1.05	3.669	< 0.05
TC (mmol/L)	5.73 ± 0.96	6.61 ± 1.08	2.984	< 0.05
LDL-C (mmol/L)	2.33 ± 0.30	2.86 ± 0.43	3.694	< 0.05
HDL-C (mmol/L)	1.97 ± 0.39	1.72 ± 0.32	4.013	< 0.05
FBG (mmol/L)	5.07 ± 0.65	8.43 ± 1.51	5.694	< 0.05
FINS (mU/L)	14.15 ± 2.53	18.63 ± 2.92	4.366	< 0.05
HbA1c (%)	4.36 ± 0.92	5.75 ± 1.31	6.364	< 0.05
HOMA-IR	1.11 ± 0.37	2.85 ± 0.68	5.215	< 0.05
SFRP-5 (ng/mL)	12.35 ± 3.28	5.72 ± 1.16	6.321	< 0.05

3.2. Risk factors analysis of GDM

Unconditional logistic multiple regression analysis found that SFRP-5, TG, TC, FBG and HOMA-IR were all risk factors for GDM ($P < 0.05$), as shown in **Table 2**.

Table 2. Risk factors of GDM

Indicators	β	SE	Wald χ^2 value	P	OR	95% CI
Age	0.301	0.374	0.839	0.172	1.127	0.843–2.582
BMI	0.359	0.417	1.091	0.169	1.563	0.924–2.703
TG	1.367	0.385	6.328	0.021	1.783	1.360–6.115
TC	1.097	0.393	8.107	0.036	2.694	1.177–5.062
LDL-C	0.520	0.465	1.573	0.120	1.886	0.976–3.106
HDL-C	0.679	0.427	2.094	0.098	1.369	0.716–2.590
FBG	1.286	0.362	5.035	0.021	3.123	2.103–7.921
FINS	0.921	0.576	2.811	0.076	1.364	0.865–2.675
HbA1c	0.602	0.482	1.835	0.078	1.259	0.812–2.741
HOMA-IR	1.593	0.402	13.938	0.000	3.554	2.756–8.954
SFRP-5	1.639	0.598	15.069	0.000	3.887	2.915–10.017

4. Discussion

SFRP-5 (also known as frizzled-related protein 5) is a glycoprotein that is mainly expressed in adipocytes and adipose tissue. Members of the SFRP family include STAP and STAR3 or STAR4, among which two members play important roles in the regulation of glucolipid metabolism: STAP and StAR. STAP is widely distributed in human tissues and organs, and it plays an important role in glucose metabolism and lipid synthesis, with the function of regulating blood glucose concentration. SASP2 is a glycogen protein synthesized by the liver, which can inhibit insulin release and participate in glucose-lowering therapy; and SASP2 inhibits insulin secretion by binding to the SASP2 receptor, thereby reducing glucose uptake and utilization. In adipocytes, SFRP-5 can inhibit triglyceride synthesis by stimulating fibroblasts to secrete the adipokine FGF-2. SFRP-5 can also activate the heparin-like growth factor β receptor-mediated signal transduction pathway in cells. SFRP-5 can act as an adipokine in adipocytes. According to the study, the elevated level of sSTRA5 expression in insulin resistance state may be associated with the enhanced response of the organism to stimulation of high insulin levels. Therefore, SFRP-5 is considered as a potential target for effective treatment of type 2 diabetes and diseases such as obesity and fatty liver [1-9].

4.1. Pathogenesis of insulin resistance and disorders of glucolipid metabolism in gestational diabetic patients

Insulin resistance exists in gestational diabetic patients, and the mechanism of its occurrence is more complex compared with non-insulin resistant diabetes, and some scholars believe that it is related to obesity, disorders of lipid metabolism, genetic factors, and poor lifestyle. Studies have shown that obesity is higher in diabetic patients and regardless of age or race, while there is no significant difference between non-diabetic pregnant women and normal gestational weight women. In addition, TBG, TG, and TC were higher in the obese group than in normal weight pregnant women. There was no statistically significant difference in the prevalence of insulin resistance between the two groups, indicating that the islet function status of the patients in the two groups was basically similar. It was also found that insulin resistance in non-diabetic gestational diabetic patients may be due to disturbances in lipid metabolism induced by a high-fat diet. In addition, studies have shown that abnormal blood glucose regulation is one of the pathogeneses of fatty liver [10]. SFRP-5 plays an important role in the immune function of the body. Therefore, SFRP-5 is one of the important mechanisms of anti-insulin resistance and regulation of glucose metabolism homeostasis in the body, and may be correlated with insulin resistance and disorders of glucolipid metabolism.

4.2. The role of OSTN in glucose control during pregnancy and its correlation with metabolic and cardiovascular diseases

OSTN expression are positively correlated with fasting glucose, glycated hemoglobin and lipid levels, suggesting that OSTN expression levels are associated with gestational diabetes and pregnancy outcomes. Pregnancy OSTN plays an important role in the occurrence and development of insulin resistance and type 2 diabetes. High levels of OSTN inhibit fatty acid synthesis and increase the intracellular transport of triglycerides by up-regulating the key enzyme LKM-1 in liver gluconeogenesis and the key enzyme 2-1 in liver fat transport, thus promoting the occurrence and development of diabetes. The expression level of obesity-related genes is positively correlated with the degree of insulin resistance, which suggests that excessive weight gain during pregnancy may increase the risk of obesity due to the increase in the expression of peroxisome proliferators–activated receptor γ (PPARγ). A hyperglycemic response was observed in hyperlipidemic patients with type 2 diabetes, which was associated with elevated levels of serum OSTN mRNA expression [10-15].

In this study, SFRP-5 was shown to be negatively correlated with its level of glycemic control, insulin resistance, and disorders of glucolipid metabolism in patients with gestational diabetes, suggesting that

sSTRA5 may be involved in the regulation of insulin resistance and glucolipid metabolism. In this study, there was no statistical difference in SFRP-5 between gestational diabetes patients compared to healthy pregnant women. Therefore, a few conclusions can be made. (i) There is a negative correlation between SFRP-5 levels and glucose control levels by comparing with SASP and SLC20A1 assay values. (ii) The higher the serum sSTRa5 level associated with insulin resistance, the lower the insulin sensitivity. (iii) Due to the small sample size of this study, it is not yet possible to further investigate the specific mechanism by which SFRP-5 affects insulin sensitivity.

In conclusion, the results of this study suggest that elevated serum SFRP-5 may be involved in the regulation of insulin resistance and blood glucose in the body by affecting lipid metabolism and inflammatory response.

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Disclosure statement

The author declares no conflict of interest.

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