Study on the correlation between the changes of TNFRI, TNF-α, and adiponectin in patients with gestational diabetes mellitus and insulin resistance

Jie Xie,1 Lan Dai1,∗ and Xiaolei Tang2

Abstract
Gestational diabetes mellitus (GDM) refers to pregnant women with impaired glucose tolerance, which could bring high risk to the mother and fetus. However, the early diagnosis and treatment of GDM remained unclear. In this study, 60 patients with GDM were selected as the research group and 50 healthy pregnant women as the control group. Tumor necrosis factor receptor 1 (TNFR1), tumor necrosis factor-α (TNF-α), and adiponectin (ADP) in the serum were measured by enzyme-linked immunosorbent assays (ELISAs). The levels of fasting blood glucose (FBG), fasting insulin (FINS), and glycosylated hemoglobin (HbA1c) were also detected to calculate homeostasis model assessment insulin resistance index (HOMA-IR) and pancreatic β-cell function index (HOMA-HBCI). Compared with the control group, the serum levels of TNFR1, TNF-α, and HbA1c in research group were significantly increased (P < 0.05), while ADP showed lower levels (P < 0.01). Furthermore, FBG, FINS, and HOMA-IR were evidently increased (P < 0.05), while homeostasis model assessment insulin secretion index (HOMA-β) and insulin sensitivity index (ISI) were decreased (P < 0.05) in research group. TNFR and TNF-α were positively correlated with FBG, FINS, and HOMA-IR (P < 0.05). In addition, there was a significant negative correlation between ADP and FINS and HOMA-IR (P < 0.01). From logistic regression analysis, age, gestational age, FBG, FINS, TNFR1, TNF-α, and ADP (P < 0.05) were shown to be risk factors to affect the function of islet β-cells. In conclusion, the high levels of TNFR1 and TNF-α and the low levels of ADP in the second trimester of pregnancy are the risk factors of GDM, which are related to the insulin resistance and impaired pancreatic β-cell function.

Keywords
adiponectin, gestational diabetes mellitus, insulin resistance, TNFRI, TNF-α

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Introduction
Gestational diabetes mellitus (GDM) refers to any degree of impaired glucose tolerance first discovered during pregnancy, excluding those known to be pre-pregnancy diabetic patients.1 In recent years, pregnant women with pregnancy risk of diabetes mellitus continue to increase. Untimely treatment of pregnancy with diabetes may lead to threatened epilepsy in pregnant women, and newborns appear huge, leading to prolonged labor, postpartum hemorrhage, and cesarean section. Therefore, its early diagnosis and treatment in clinic are of great significance.2 Some studies have found3 that GDM patients have insulin resistance (IR) more severe than normal pregnant
women, and the existence of pancreatic β-cell function is impaired. Related data show that GDM is not only a metabolic syndrome with elevated blood pressure, blood glucose, and lipid metabolism but also an inflammatory disease. Some inflammatory factors, such as C-reactive protein (CRP), were closely related to the occurrence and development of GDM. Adiponectin (ADP), a cytokine secreted by adipose tissue, is involved in the body fat and energy metabolism through autocrine or paracrine pathways and is closely related to obesity, IR, and type 2 diabetes. Previous studies have confirmed that the main mechanisms of ADP in diabetes are as follows: (1) acts on the human central nervous system to promote the decomposition and utilization of glucose, (2) inhibits hepatic gluconeogenesis and improves liver insulin sensitivity, and (3) prevents autoimmune destruction of insulin-secreting cells. Some studies have found that ADP levels in women with gestational diabetes were significantly lower than healthy pregnant women, indicating that plasma concentration of ADP in pregnant women is the risk of pregnancy-associated diabetes mellitus, an independent risk factor. However, there are few reports on the relationship between inflammatory factors such as tumor necrosis factor receptor 1 (TNFR1) and tumor necrosis factor-α (TNF-α) and GDM. This study was designed to investigate the relationship between TNFR1, TNF-α, ADP, and IR in serum of patients with GDM.

**Methods**

**Serum FBG, FINS, and HbA1c measurements**

Morning fasting blood was drawn from the pregnant matrix for direct inspection. Fasting blood glucose (FBG), fasting insulin (FINS), glycosylated hemoglobin (HbA1c), and other biochemical indicators were examined by a chemiluminescent immunoassay using Cobas E610 (Roche, Basel, Switzerland). Subsequently, the homeostasis model assessment insulin resistance index (U/mL) (HOMA-IR = FINS (µU/mL) × FBG (mmol/L)/22.5), insulin secretion index (HOMA-β = 20 × FINS (µU/mL)/FBG (mmol/L)–3.5), and insulin sensitivity index (ISI = 1/FBG (mmol/L) × FINS (U/mL)) were used to evaluate the β-cell function of the pregnant women.

**The concentrations of TNFR1, TNF-α, and ADP detected via enzyme-linked immunosorbent assay**

The morning fasting blood samples were collected into a serum separator tube. Until the clot formation, the blood samples were centrifuged at 2000 g for 10 min, and then, the serums were collected. Finally, the concentrations of TNFR1, TNF-α, and ADP in the serums were determined using the enzyme-linked immunosorbent assay (ELISA) kits (Nanjing Deheven Biological Technology Co. Ltd), following the manufacturer’s instructions.

**Statistical analysis**

SPSS 21.0 software was used to analyze the data, and the experimental data are expressed as mean ± standard deviation. The mean of each group was compared by t-test, and correlation analysis of groups was performed using Pearson’s test. The relationship between pancreatic β-cell function and each index of GDM patients was analyzed by multivariate linear stepwise regression analysis. P < 0.05 means a significant difference.

**Results**

**The general data of two groups**

As shown in the Table 1, there was no significant difference in the gestational weeks, pre-pregnancy body mass index (BMI), and age between the two groups (P > 0.05).
Compared with the control group, levels of TNFR1, TNF-\(\alpha\), and HbA1c in the serum in the research group were significantly increased (\(P<0.05\)). ADP level was evidently lower (\(P<0.01\)). The levels of FBG, FINS, and HOMA-IR were obviously increased (\(P<0.05\)). The levels of HOMA-\(\beta\) and ISI were significantly decreased (\(P<0.05\)), as shown in Table 2.

### Table 2. Comparison of biochemical indexes between two groups.

| Group         | n   | HbA1c (%) | TNFR1 (mg/L) | TNF-\(\alpha\) (mg/L) | ADP (ng/L) | FBG (mmol/L) | FINS (µU/L) | HOMA-IR | HOMA-\(\beta\) | ISI (×10^-2) |
|---------------|-----|-----------|--------------|------------------------|------------|--------------|-------------|---------|---------------|--------------|
| Research group| 60  | 15.12 ± 0.23 | 14.36 ± 2.94 | 15.67 ± 3.18 | 6.77 ± 1.45 | 7.83 ± 0.32 | 9.82 ± 0.33 | 3.42 ± 0.27 | 46.17 ± 3.94 | 1.43 ± 0.36 |
| Control group | 50  | 6.54 ± 0.67 | 7.23 ± 2.12  | 7.64 ± 2.25 | 11.93 ± 1.04 | 4.91 ± 0.17 | 6.42 ± 0.51 | 1.41 ± 0.18 | 96.03 ± 6.55 | 3.38 ± 0.27 |
| \(t\)         |     | <0.05      | <0.05        | <0.05       | <0.05       | <0.05        | <0.05       | <0.05       | <0.05         | <0.05        |
| \(P\)         |     | \(<0.05\)  | \(<0.05\)    | \(<0.05\)   | \(<0.05\)   | \(<0.05\)    | \(<0.05\)   | \(<0.05\)   | \(<0.05\)     | \(<0.05\)    |

HbA1c: glycosylated hemoglobin; TNFR1: tumor necrosis factor receptor 1; TNF-\(\alpha\): tumor necrosis factor-\(\alpha\); ADP: adiponectin; FBG: fasting blood glucose; FINS: fasting insulin; HOMA-IR: homeostasis model assessment insulin resistance index; ISI: insulin sensitivity index; HOMA-\(\beta\): homeostasis model assessment insulin secretion index.

### Multiple linear stepwise regression analysis

Logistic regression analysis was conducted to determine whether pancreatic \(\beta\)-cell function is impaired as a dependent variable, with age, pregnancy, pre-pregnancy BMI, FBG, FINS, TNFR1, TNF-\(\alpha\), and ADP as covariates. Regression analysis showed that the factors affecting the function of pancreatic \(\beta\)-cell were age, pregnancy (\(P<0.05\)), FBG, FINS, TNFR1, TNF-\(\alpha\), and ADP, as demonstrated in Table 4.

### Discussion

GDM is a very common disease throughout the world, and it will significantly interrupt the normal life activities, including decreasing the carbohydrate metabolism, increasing the fat metabolism, and inhibiting the decomposition of proteins. In this study, we found that compared with the control group, the levels of FBG, FINS, and HOMA-IR were obviously higher in the research group and the levels of HOMA-\(\beta\) and ISI were significantly downregulated. These results indicated that the IR and the dysfunction of pancreatic \(\beta\)-cell played an important role in the development of GDM.
Increasing studies demonstrated that GDM was an immunological disease, which was mainly induced by the inflammatory response mediated by cytokines, including the TNF-α, TNFR1, ADP, leptin, and resistin. TNF-α is a cytokine secreted by activated monocytes/macrophages. Some studies have found that the TNF-α levels and insulin sensitivity in the serum of GDM women was negatively correlated. Other studies have revealed that the expression of TNF-α was significantly increased in insulin-resistant mice, while the knockdown of TNF-α gene could obviously improve the insulin sensitivity of mice. Consistent with these previous studies, we discovered that the expression of TNFR1 and TNF-α in the research group was significantly higher than that in the control group, which were involved in the occurrence and development of GDM.

ADP is a cytokine secreted by white adipose tissue. Some studies have shown that the ADP level is closely related to the occurrence and development of obesity, type 2 diabetes, and cardiovascular disease. Weerakiet et al. revealed that the plasma ADP levels of pregnant women were negatively correlated to the pregnancy, after detecting the blood glucose levels through the oral glucose tolerance test (OGTT). Other studies have found that the ADP is an independent predictor of GDM incidence which can be used to exclude low-risk GDM population in GDM screening experiments. Moreover, the results in this study suggested that the ADP levels of the research group were significantly lower than the control group and that the ADP level was the main risk factor for GDM.

In summary, the cytokines associated with inflammatory response (such as TNFR1, TNF-α, and ADP) are significantly related to the occurrence and development of the GDM.

**Declaration of conflicting interests**

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**ORCID iD**

Lan Dai https://orcid.org/0000-0003-2707-8628

**References**

1. Ares J, Martín-Nieto A, Díaz-Naya L et al. (2017) Gestational diabetes mellitus (GDM): Relationship between higher cutoff values for 100 g oral glucose tolerance test (OGTT) and insulin requirement during pregnancy. *Maternal and Child Health Journal* 21(7): 1488–1492.
2. Leng J, Shao P, Zhang C et al. (2015) Prevalence of gestational diabetes mellitus and its risk factors in Chinese pregnant women: A prospective population-based study in Tianjin, China. *PLoS ONE* 10(3): e0121029.
3. Sharifi F, Nezamidiba M and Kamali K (2014) Thyroid function and its relation to insulin resistance in women with gestational diabetes mellitus (GDM) compared with healthy pregnant women. *Arthritis & Rheumatism* 22(94): 61–71.
4. Retnakaran R, Hanley AJ, Raif N et al. (2005) Adiponectin and beta cell dysfunction in gestational diabetes: Pathophysiological implications. *Diabetologia* 48(5): 993–1001.
5. Hoyda TD, Samson WK and Ferguson AV (2009) Adiponectin depolarizes parvocellular paraventricular nucleus neurons controlling neuroendocrine and autonomic function. *Endocrinology* 150(2): 832–840.
6. Worda C, Leipold H, Gruber C et al. (2004) Decreased plasma adiponectin concentrations in women with...
gestational diabetes mellitus. *American Journal of Obstetrics and Gynecology* 191(6): 2120–2124.

7. Guzmán-Flores JM, Escalante M, Sánchez-Corona J et al. (2013) Association analysis between -308G/A and -238G/A TNF-alpha gene promoter polymorphisms and insulin resistance in Mexican women with gestational diabetes mellitus. *Journal of Investigative Medicine* 61(2): 265–269.

8. Long Y, Su K, Zhou Y et al. (2009) Relationship between the adiponectin and TNF-α with insulin resistance in patients with gestational diabetes mellitus. *Shandong Medical Journal* 49(20): 26–28.

9. Gu Y, Wang G, Pan G et al. (2004) Transport and bioavailability studies of astragaloside IV, an active ingredient in Radix Astragali. *Basic & Clinical Pharmacology & Toxicology* 95(6): 295–298.

10. Plomgaard P, Penkowa M and Pedersen BK (2005) Fiber type specific expression of TNF-alpha, IL-6 and IL-18 in human skeletal muscles. *Exercise Immunology Review* 11(5): 53–63.

11. Weerakiet S, Lertnarkorn K, Panburana P et al. (2006) Can adiponectin predict gestational diabetes? *Gynecological Endocrinology* 22(7): 362–368.