Advances in Obstetrics and Gynecology Research, 2023, Volume 1, Issue 3
https://ojs.bbwpublisher.com/index.php/AOGR

Correlation of Serum Th1/Th2 Cytokines with Insulin Resistance in Gestational Diabetes Mellitus

Chenyuan Cao, Bei Wang, Rui Li, Yan An, Fang Wang, Yuxiang Huang, Jinjin Qin*

Department of Obstetrics, Affiliated Hospital of Hebei University, Baoding 071000, China

***Corresponding author:** Jinjin Qin, qinjinjin_1@163.com

Abstract: *Objective:* To investigate the correlation between serum Th1/Th2 cytokines and insulin resistance in gestational diabetes mellitus (GDM). *Methods:* A total of 50 cases of pregnant women diagnosed with GDM and 50 healthy pregnant women who visited the Affiliated Hospital of Hebei University from January 2019 to December 2022 were recruited and divided into the GDM group and control group. Serum Th1/Th2 cytokines were observed and analyzed. *Results:* In the GDM group, serum IFN-γ levels were significantly higher than in the control group ($P < 0.01$), while there was no statistically significant difference in IL-4 levels ($P > 0.05$). Within the GDM group, HOMA-IR showed a positive correlation with IFN-γ ($r = 0.67$, $P < 0.01$) and no correlation with IL-4 ($r = 0.19$, $P > 0.05$). Within the control group, HOMA-IR did not correlate with either IFN-γ or IL-4 ($r = 0.23$, $P > 0.05$; $r = 0.15$, $P > 0.05$). *Conclusion:* The study concludes that the serum Th1 cytokine IFN-γ is correlated with insulin resistance in GDM, providing a novel perspective on the pathogenesis of GDM. Future studies should further explore the mechanisms and interventions to offer improved treatment options for patients with GDM.

Keywords: Interferon-gamma (IFN-γ); Interleukin-4 (IL-4); Gestational diabetes mellitus (GDM); Insulin resistance

Online publication: December 26, 2023

1. Introduction

Gestational diabetes mellitus (GDM) manifests as an abnormality in glucose tolerance during pregnancy, with insulin resistance (IR) standing out as a prominent characteristic. IR denotes a reduction in insulin efficiency, hindering the facilitation of glucose uptake and utilization due to various factors. To counteract this inefficiency, the body increases insulin secretion to stabilize blood glucose levels. However, this compensatory mechanism can result in abnormal blood glucose levels in pregnant women, potentially impacting both maternal and fetal health adversely.

In recent years, a growing body of research has unveiled a close association between the immune system and insulin resistance. Within the context of insulin resistance, the equilibrium of Th1/Th2 cytokines assumes a crucial role. Type 1 T helper (Th1) and type 2 T helper (Th2) cells, integral components of the immune

system, secrete cytokines with distinct biological functions. Th1 cells predominantly engage in cellular immune response, releasing cytokines such as interferon-gamma (IFN-γ). Conversely, Th2 cells play a primary role in humoral immune responses, secreting cytokines such as interleukin-4 (IL-4). Understanding this interplay is essential in comprehending the pathogenesis of GDM, predicting disease progression, and identifying potential therapeutic targets. Therefore, exploring the correlation between serum Th1/Th2 cytokines and insulin resistance in GDM holds significant implications for advancing knowledge and improving clinical outcomes.

2. Materials and methods

2.1. General information

Fifty cases each of pregnant women diagnosed with GDM (GDM group) and healthy pregnant women (control group) at the Affiliated Hospital of Hebei University from January 2019 to December 2022 were selected. All study participants were devoid of other chronic diseases or immune system diseases.

(1) Inclusion criteria: Participants met the diagnostic criteria for GDM, as evidenced by abnormal results in the glucose tolerance test during pregnancy, where fasting glucose ≥ 5.1 mmol/L, or oral glucose tolerance test ≥ 10.0 mmol/L at 1 hour or ≥ 8.5 mmol/L at 2 hours. Additionally, they willingly agreed to participate in the study, signed an informed consent form, were aged between 18–45 years old, and had singleton pregnancies, with no other chronic diseases or immune system disorders.

(2) Exclusion criteria: Pregnant women with other pregnancy complications, such as gestational hypertension syndrome, cholestasis in pregnancy syndrome, etc., were excluded. Also excluded were pregnant women with other medical diseases, including thyroid function abnormalities, liver and kidney function abnormalities, etc. Additionally, those with immune system diseases or taking immunosuppressant drugs, experiencing adverse pregnancy outcomes (hemorrhage, infections, fetal abnormalities, etc.), or having other hereditary diseases or a family history were excluded.

2.2. Methods

2.2.1. Serum collection and processing

In the early morning during fasting, all study participants had 5 mL of venous blood drawn. The supernatant was then centrifuged to determine the concentration of Th1 and Th2 cytokines in serum, including IFN-γ and IL-4, using enzyme-linked immunosorbent assay (ELISA).

2.2.2. Insulin resistance assessment

The IR index was calculated using the homeostatic model assessment method (HOMA-IR):

HOMA-IR = fasting blood glucose (mmol/L) × fasting insulin (mU/L) ÷ 22.5

2.3. Statistical methods

Data analysis was performed using SPSS 24.0 statistical software. Measurement data were expressed as mean ± standard deviation (SD) and analyzed using the independent *t*-test, and count data were presented as percentages and analyzed using the χ^2 test. A significance level of $P < 0.05$ was regarded as a statistically significant difference.

3. Results

3.1. Th1/Th2 cytokine levels

Table 1 shows that the serum IFN-γ levels were significantly higher in the GDM group than in the control group ($P < 0.01$), while IL-4 levels were not statistically different between the two groups ($P > 0.05$).

Table 1. Serum Th1/Th2 cytokine levels in each group (pg/mL, mean ± SD)

Group	IFN-γ	IL-4
GDM group ($n = 50$)	3.81 ± 1.10	4.93 ± 1.31
Control group ($n = 50$)	2.64 ± 0.80	5.14 ± 1.22
t	6.08	0.83
P	0.00	0.41

3.2. Correlation between IR and Th1/Th2 cytokines

In the GDM group, HOMA-IR demonstrated a positive correlation with IFN-γ ($r = 0.67$, $P < 0.01$) and no correlation with IL-4 ($r = 0.19$, $P > 0.05$). Conversely, in the control group, HOMA-IR exhibited no correlation with either IFN-γ or IL-4 ($r = 0.23$, $P > 0.05$; $r = 0.15$, $P > 0.05$).

4. Discussion

Diabetes mellitus, a pervasive chronic disease, poses a substantial threat to public health, with type 2 diabetes mellitus (T2DM) being its primary manifestation, predominantly driven by IR. Recent insights suggest that Th1 cytokines may play a pivotal role in the development of insulin resistance [1-6]. This discussion explores the intricate relationship between serum Th1 cytokines and insulin resistance in diabetes.

Th1 cytokines, principally produced by $CD4^+$ T cells, encompass IFN-γ, IL-2, and tumor necrosis factor-alpha (TNF-α). Under normal physiological conditions, these cytokines contribute significantly to the immune response. However, in specific pathologies, such as T2DM, their impact on IR becomes apparent. A growing body of evidence indicates a positive correlation between serum Th1 cytokines and IR. For instance, one study revealed that elevated serum levels of IFN-γ and IL-2 in patients with type 2 diabetes correlated with increased severity of IR [7]. In another investigation, TNF-α was identified as a potential inducer of IR, possibly through the activation of the c-Jun N-terminal kinase (JNK) and inhibitor of nuclear factor-kappa B-alpha (IκBα) pathways in adipose tissue, resulting in impaired insulin signaling. The precise mechanism by which serum Th1 cytokines contribute to insulin resistance remains incompletely understood [8]. Nevertheless, multiple studies propose that these cytokines may influence the insulin sensitivity of adipose tissue by regulating the secretion of adipokines [9-11]. For instance, IFN-γ can stimulate adipocytes to release resistin, a recognized mediator of IR. Collectively, serum Th1 cytokines emerge as significant contributors to the development of IR in T2DM. Future research in this domain should strive to deepen our understanding of their mechanisms of action and explore potential interventions to enhance insulin sensitivity in diabetic patients. Strategies to address the effects of Th1 cytokines on IR may involve inhibiting their production or impeding their interaction with insulin signaling. Moreover, the modulation of adipokine secretion could offer novel therapeutic targets for alleviating IR. As research progresses, the development of drugs targeting these novel therapeutic avenues holds promise for improving IR in diabetic patients.

Th2 cytokines, primarily produced by $CD4^+$ T cells and including IL-4, IL-5, and IL-13, play a crucial role in the immune response under normal physiological conditions. However, in certain pathologies, such as

T2DM, these cytokines may exert an impact on IR. Studies have revealed a negative correlation between serum Th2 cytokines and IR [12-15]. Various investigations propose that Th2 cytokines may influence the sensitivity of adipose tissue to insulin by regulating the secretion of adipokines. For instance, IL-4 inhibits the secretion of resistin by adipocytes. IL-4 also stimulates adipocytes to secrete leptin, a known adipokine that increases insulin sensitivity. In addition, both IL-5 and IL-13 can enhance insulin sensitivity by modulating signaling pathways in adipose tissue. The precise mechanism through which serum Th2 cytokines contribute to insulin resistance has yet to be elucidated. In conclusion, serum Th2 cytokines may play a significant role in the development of IR in T2DM. Future research in this field should strive to gain a deeper understanding of their mechanisms of action and explore potential interventions to enhance insulin sensitivity in diabetic patients.

In this study, it was observed that the serum IFN-γ levels were elevated in patients with GDM, while the levels of IL-4 showed no significant change. IFN-γ, a Th1 cytokine known for its pro-inflammatory and IR-inducing effects, suggests the potential involvement of Th1 cells in the pathogenesis of GDM. On the other hand, IL-4, a Th2 cytokine, exhibited no significant impact on IR, indicating a potentially lesser influence of Th2 cells in the development and progression of gestational diabetes. Furthermore, the findings revealed a positive correlation between IR and IFN-γ levels, providing additional confirmation of IFN-γ's role in IR in GDM. However, no correlation was observed between IR and IL-4 levels, suggesting that IL-4 may not contribute significantly to the development of IR in GDM.

In the future, several advancements are anticipated in the treatment of insulin resistance in GDM [16-18]:

(1) Novel drug development: Currently, drugs addressing GDM IR primarily include insulin sensitizers such as metformin and rosiglitazone. However, their widespread application is limited due to side effects and clinical constraints. Future research aims to identify new drugs, potentially derived from natural plant extracts or microbial compounds, with fewer side effects. Meanwhile, novel drug targets for the pathogenesis of insulin resistance, such as JNK, IκBα, and adipokines, will be explored to enhance treatment options.

(2) Cell and gene therapy: Advancements in cell and gene therapy technologies may offer the potential to alleviate IR by modulating patients' immune responses. This includes regulating the balance of T-cell subpopulations (e.g., Th1/Th2) and modifying the expression of relevant genes. Genetic engineering technologies, such as silencing or overexpressing key genes associated with IR, could improve the overall IR status.

(3) Lifestyle intervention: Current studies underscore the positive impact of a healthy lifestyle, encompassing a balanced diet, regular exercise, and sufficient sleep, in mitigating IR. With the increasing prevalence of wearable devices such as smart bracelets and watches, individuals will have the ability to monitor real-time health data, facilitating scientific lifestyle interventions to improve GDM IR.

(4) Combination therapy: The future of GDM IR treatment is envisioned to involve a comprehensive approach, incorporating multiple drugs and therapeutic modalities. Combining drug therapy, lifestyle interventions, and cell/gene therapy is anticipated to yield more effective outcomes in addressing IR.

The present study has unveiled that the serum Th1 cytokine IFN-γ correlates with IR in GDM, offering novel insights into the pathogenesis of GDM. However, IL-4 did not exhibit a significant correlation with IR. Future investigations can delve deeper into the specific mechanisms underlying the roles of Th1/Th2 cytokines in the development of GDM, paving the way for further advancements in the understanding and treatment of this condition.

Funding

Baoding Science and Technology Program Project (2041ZF295); Hebei University Medical Discipline Cultivation Program (2022B03)

Disclosure statement

The authors declare no conflict of interest.

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