Clinical Trials Study

Association between plasma dipeptidyl peptidase-4 levels and cognitive function in perinatal pregnant women with gestational diabetes mellitus

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Abstract

BACKGROUND
Dipeptidyl peptidase-4 (DPP4) is associated with cognitive dysfunction in patients with type 2 diabetes.

AIM
To assess a possible relationship between serum DPP4 and cognitive function in perinatal pregnant women with gestational diabetes mellitus (GDM).

METHODS
The study subjects were divided into three groups: GDM group (n = 81), healthy pregnant (HP) group (n = 85), and control group (n = 51). The Montreal Cognitive Assessment (MoCA) was used to assess the cognitive status of each group. Venous blood samples were collected to measure blood lipids, glycated hemoglobin, and glucose levels. For each participant, a 3-mL blood sample was collected and centrifuged, and the serum was collected. Blood samples were stored at -80 °C, and DPP4, interleukin-6 (IL-6), and 8-iso-prostaglandin F2α (8-iso-PGF2α), and brain-derived neurotrophic factor (BDNF) were detected using ELISA.

RESULTS
The MoCA scores in the GDM and HP groups were significantly different from those in the control group in terms of visuospatial/executive function and attention (P < 0.05); however, the scores were not significantly different between the GDM and HP groups (P > 0.05). In terms of language, the GDM group had significantly different scores from those in the other two groups (P < 0.05). In
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INTRODUCTION

With the advent of the two-child policy in China, the number of elderly parturient women is increasing, which has led to a rise in many pregnancy-related complications, the most common of which is gestational diabetes mellitus (GDM). The global incidence of DM during pregnancy is 15%, of which, GDM comprises 87.5% of cases [1]. GDM causes serious adverse effects to the mother and fetus, and increases the risk of eclampsia, maternal metabolic disorders, miscarriage, premature birth, obstructed labor, macrosomia, fetal distress, neonatal pulmonary immaturity, and neonatal hypoglycemia[2]. Although the pathogenesis of GDM is poorly understood, it might be associated with insulin resistance, and may share similarities with the pathogenesis of type 2 DM (T2DM). Most of the women with GDM regain normal glucose metabolism after delivery but face a significantly higher risk of developing DM than healthy pregnancy women in the future[3].

Several recent studies have found that T2DM can lead to cognitive dysfunction[3], which mostly manifests as impairments in various abilities such as memory and orientation. Zheng et al[4] confirmed the correlation between cognitive dysfunction and serum dipeptidyl peptidase-4 (DPP4) activity in patients with T2DM; they also found that the underlying mechanism was related to DPP4-mediated activation of inflammatory responses and oxidative stress. Thus, they suggested that altered DPP4 activity could be a risk factor for cognitive dysfunction in T2DM. Other studies have also reported a decline in verbal memory, associative learning, reaction time, and verbal recall in healthy pregnant (HP) women[5-7]. However, only a few studies have examined the presence of altered cognitive function in patients with GDM. Therefore, this study aimed to determine whether having GDM for nearly 6 mo during the perinatal period, combined with the stress of anxiety during pregnancy, could cause mild cognitive impairment (MCI), and whether there are subsequent changes in serum terms of memory, a significant difference was found between the HP and control groups (P < 0.05), as well as between the GDM and HP groups. The levels of DPP4, IL-6, and 8-iso-PGF2α in the GDM group were significantly higher than those in the HP and control groups (P < 0.05); however, the differences between these levels in the HP and control groups were not significant (P > 0.05). The level of BDNF in the GDM group was significantly lower than that in the HP and control groups (P < 0.05), although the difference in this level between the HP and control groups was not significant (P > 0.05).

CONCLUSION

Cognitive dysfunction in perinatal pregnant women with GDM mainly manifested as memory loss, which might be associated with elevated DPP4 levels.

Key Words: Gestational diabetes mellitus; Dipeptidyl peptidase-4; Cognitive function; Oxidative stress; Perinatal pregnant women; Montreal cognitive assessment

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Core Tip: It is generally believed that diabetes can cause cognitive impairment, and even is an important cause of Alzheimer’s disease. This study investigated whether gestational diabetes mellitus (GDM) induced cognitive decline in perinatal pregnant women and assessed a possible relationship between serum dipeptidyl peptidase-4 (DPP4) levels and maternal cognitive function in perinatal pregnant women with GDM, and detected DPP4 levels in cord blood. DPP4 may cause cognitive impairment by aggravating inflammatory response and oxidative stress response.

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DPP4 levels.

MATERIALS AND METHODS

Subjects and protocols
Patients aged 18–35 years, with American Society of Anesthesiologists physical status I/II, were included in this study. A total of 100 consecutive perinatal pregnant women with GDM who were diagnosed, followed up, and treated at the First Affiliated Hospital of Harbin Medical University were included in the study (GDM group). One hundred age-matched perinatal pregnant women without DM comprised the HP group. The healthy control group included 51 nonpregnant female volunteers of similar age with normal blood glucose levels. All patients and volunteers read and signed informed consent forms before enrolment in the study. The study protocol was approved by the Ethics Committee of the First Affiliated Hospital of Harbin Medical University, and was registered with the Chinese Clinical Trial Register (registration number: ChiCTR2000038703).

GDM was diagnosed with at least one abnormal result during the oral glucose tolerance test: plasma glucose during fasting, ≥ 92 mg/dL (5.1 mmol/L); at 1 h, ≥ 180 mg/dL (10.0 mmol/L); or at 2 h, ≥ 153 mg/dL (8.5 mmol/L). Women with fasting plasma glucose ≥ 126 mg/dL (7.0 mmol/L), glycated hemoglobin (HbA1c) ≥ 6.5%, or random plasma glucose ≥ 200 mg/dL (11.1 mmol/L) were diagnosed with overt diabetes and excluded. Subjects on medications that affect cognitive function, including corticosteroids, antidepressants, and antiepileptics, were also excluded. In addition, all patients with other chronic diseases were excluded[8].

The Hamilton Depression Rating Scale was used to assess the psychological status of pregnant women; those with a score > 7, who might have depression, were excluded[9]. On the survey date, all enrolled patients underwent routine medical history inquiries, physical examinations, and laboratory measurements. Clinical research coordinators used a standard questionnaire to collect information on demographic characteristics and medical history. All pregnant women were instructed to maintain their usual physical activity and diet for at least 3 d before the survey. After an overnight fast of ≥ 10 h, venous blood samples were collected to measure blood lipid, HbA1c and glucose levels. For each participant, a 3-mL blood sample was collected and centrifuged, and the serum was collected. Blood samples were stored at -80 °C, and DPP4, interleukin-6 (IL-6), 8-iso-prostaglandinF2α (8-iso-PGF2α), and brain-derived neurotrophic factor (BDNF) were detected using ELISA (Mibio, Shanghai, China). All measurements were performed within 6 mo of sample collection.

Umbilical cord blood was collected at the time of delivery from participants in the GDM and HP groups. Serum DPP4 level was measured using ELISA in these groups as well.

Assessment of cognitive function
To assess cognitive function, the Montreal Cognitive Assessment (MoCA), which is a brief cognitive screen used in a variety of clinical settings to screen for MCI, was administered[10]. The cognitive assessment was conducted in a quiet room, without distractions, by a physical therapist trained in the administration of the MoCA. The maximum score for the MoCA is 30, and the assessment evaluates visuospatial/executive, naming, attention, language, abstraction, orientation, and delayed recall abilities, among others. A score of ≤ 25 indicates MCI[11,12].

Statistical analysis
The data were analyzed using SPSS 19.0. All data were tested for normality and homogeneity of variance. Normally distributed data were expressed as mean ± SD. Normally distributed continuous variables were compared using Student’s t test, while those with non-normal distributions were compared using the Mann–Whitney U test; multiple comparisons between groups were performed using the least significant difference method. Categorical data were presented as numbers and percentages, and comparisons between groups were performed using the two-sided χ² test. Correlations of DPP4 and BDNF levels with those of IL-6 and 8-iso-PGF2α, respectively, were performed using Pearson’s correlation coefficient, and P < 0.05 was considered statistically significant.
RESULTS

Demographic information
A total of 166 pregnant women and 51 nonpregnant healthy volunteers were enrolled in this study; they included 83 pregnant women with GDM in the GDM group, 85 HP women in the HP group, and 51 nonpregnant healthy volunteers in the control group (Figure 1). The weight, blood glucose level, and HbA1c level of the participants in the GDM group were significantly higher than those in the other two groups ($P < 0.05$) (Table 1).

MoCA scores
The MoCA scores in the GDM and HP groups were significantly different from those in the control group in terms of visuospatial/executive function and attention ($P < 0.05$); however, the scores were not different between the GDM and HP groups ($P > 0.05$). In terms of language, the GDM group had significantly different scores from those in the other two groups ($P < 0.05$). In terms of memory, a significant difference was found between the HP and control groups ($P < 0.05$), as well as between the GDM and HP groups ($P < 0.05$) (Table 2).

Expression of serum indicators
The levels of DPP4, IL-6, and 8-iso-PGF2α in the GDM group were significantly higher than those in the HP and control groups ($P < 0.05$); however, the differences between these levels in the HP and control groups were not significant ($P > 0.05$). The level of BDNF in the GDM group was significantly lower than that in the HP and control groups ($P < 0.05$), although the difference in this level between the HP and control groups was not significant ($P > 0.05$) (Figure 2 and Table 3). In the GDM group, the elevated DPP4 level significantly correlated with the elevated levels of IL-6 and 8-iso-PGF2α ($P < 0.05$). Moreover, the elevated IL-6 and 8-iso-PGF2α levels significantly correlated with decreased BDNF levels ($P < 0.05$) (Table 4). Cord blood DPP4 level in the GDM group was significantly higher than that in the HP group ($P < 0.05$) (Figure 2 and Table 3).

DISCUSSION

Although the viewpoint that pregnant women experience deficits in memory is widespread, evidence supporting this supposition is limited in the literature, especially in humans[13]. Based on the results of this study, the following conclusions can be drawn. (1) Perinatal pregnant women with GDM experience cognitive decline, which mainly involves memory loss; (2) Elevated serum DPP4 level is involved in the cognitive decline of perinatal pregnant women with GDM, and they are significantly correlated. Possible mechanisms underlying these findings may include the activation of inflammatory mediators and oxidative stress pathways due to elevated DPP4 level; and (3) DPP4 levels are significantly higher in the cord blood of women with GDM than those without GDM.

Our demographic results showed that pregnant women with GDM had significantly different body weight as well as blood glucose and HbA1c levels than those in the HP group. Although the blood glucose levels in the GDM group were maintained within the normal range, most patients had blood glucose or HbA1c levels near the upper limit, thus indicating the persistence of insulin resistance and metabolic disorders. Some studies suggest that women with GDM have a 20%–70% chance of developing T2DM within 10 years of delivery[14]. The pathogenesis of GDM is complex, involving beta-cell dysfunction, abnormal neuroendocrine function, and abnormal lipid metabolism[15]. Current treatments for GDM are limited to dietary interventions and insulin use, which often has unsatisfactory therapeutic efficacy due to the presence of insulin resistance. Therefore, an in-depth analysis on the etiology, mechanisms, and treatment strategies of GDM is of crucial significance for reducing complications during pregnancy and neonatal morbidity.

In this study, the MoCA scale, which is the most sensitive instrument for detecting cognitive decline, was used to assess cognitive function in perinatal pregnant women with GDM. Our results showed that the GDM and HP groups were significantly different from the control group in terms of executive function and attention, but there was no difference between the GDM and HP groups for these parameters. In addition, there was a significant difference in language scores between the GDM group and the other two groups. It is worth noting that in terms of memory, there was a significant...
The mild stress, anxiety, and depression surrounding childbirth during pregnancy could also affect the cognitive functions of women. As such, it is important to consider the impact of childbirth on women’s cognitive ability, especially for working women of childbearing age. The results of this study highlight the need for further research to understand the long-term effects of pregnancy on cognitive function, particularly in women with GDM.
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Table 3 Concentration of diabetes related factors of each group

|                | DPP4 (UCB) | BDNF      | IL-6      | 8-iso-PGF2α |
|----------------|------------|-----------|-----------|-------------|
| GDM (n = 81)   | 8.94 ± 8.50| 1.56 ± 0.18| 29.72 ± 7.14| 9.02 ± 1.50| 31.24 ± 15.78 |
| HP (n = 85)    | 2.87 ± 2.31| 0.18 ± 0.16| 51.72 ± 15.82| 8.10 ± 1.08| 24.81 ± 4.90  |
| CG (n = 51)    | 2.85 ± 1.76| /         | 43.53 ± 8.93| 8.11 ± 1.02| 24.88 ± 5.07  |
| P value (GDM vs HP) | < 0.001     | < 0.001   | < 0.001   | < 0.001     | < 0.001       |
| P value (GDM vs CG) | < 0.001     | /         | < 0.001   | < 0.001     | < 0.001       |
| P value (HP vs CG) | 0.98        | /         | 0.18      | 0.96        | 0.97          |

Data are expressed as means ± SD. UCB: Umbilical cord blood; GDM: Gestational diabetes mellitus; HP: Healthy pregnant group; CG: Control group; DPP4: Dipeptidyl peptidase-4; IL-6: Interleukin-6; 8-iso-PGF2α: 8-iso-prostaglandinF2α; BDNF: Brain-derived neurotrophic factor.

Table 4 Correlations of DPP4 and BDNF with IL-6 and 8-iso-PGF2α

|                | DPP4 Cor | P value | BDNF Cor | P value |
|----------------|----------|---------|----------|---------|
| IL-6           | 0.617    | 0.006   | -0.749   | 0.001   |
| 8-iso-PGF2α    | 0.547    | 0.019   | -0.349   | 0.029   |

DPP4: Dipeptidyl peptidase-4; IL-6: Interleukin-6; 8-iso-PGF2α: 8-iso-prostaglandinF2α; BDNF: Brain-derived neurotrophic factor.

Figure 1 Patient recruitment flowchart. GDM: Gestational diabetes mellitus; HP: Healthy pregnant group; CG: Control group.

cognitive function of pregnant women to a certain extent[18,19]. However, most of these negative emotions during pregnancy would resolve following childbirth. Conversely, the levels of DPP4 and BDNF were closer to those of healthy women; therefore, we believe that the decline of cognitive function in pregnant women is minimal.
Our focus in this study was on memory loss in perinatal pregnant women with GDM, which was pronounced when compared with that in the HP group. This may be a transient phenomenon, and its long-term effects are still unclear; however, its mechanisms might be similar to that of cognitive impairment in patients with T2DM. Several recent studies have shown that DPP4 is strongly associated with cognitive impairment in T2DM patients[4], which prompted us to examine DPP4 levels. DPP4 (also known as CD26) is an exopeptidase that cleaves peptides after the second position from the N terminus (NH2-Xaa-Pro)[20]. DPP4 is a widely expressed multifunctional enzyme that exists in two forms: one is a membrane-anchored cell surface protein, and the other is a soluble form present in the plasma[21,22]. DPP4 levels are higher in subjects who are obese and have T2DM, predisposing them to hyperglycemia, inflammation and oxidative stress[23,24]. DPP4 degrades glucagon-like peptide-1 (GLP-1), as well as several other peptides, including glucose-dependent insulinotropic polypeptide, brain natriuretic peptide, substance P, neuropeptide Y, and stromal-derived factor-1α[25]. More interestingly, there is a study showing that increased DPP4 activity is independently associated with MCI in elderly patients with T2DM[4]. Reports that DPP4 is associated with cognitive dysfunction are limited[26]. These reports have mainly been about the cognitive dysfunction in T2DM. DPP4 play crucial roles in GLP-1 degradation and in the development of inflammation and oxidative stress[27]. Inflammmation and oxidative stress have been widely demonstrated to be strongly associated with cognitive decline[28]. DPP4 inhibitors ameliorate cognitive impairment by suppressing inflammatory reactions, oxidative stress and GLP-1 degradation[29]. DPP4 inhibitors might have therapeutic potential for reducing amyloid-β-protein-induced impairment of insulin signaling and neurotoxicity in the pathogenesis of Alzheimer’s disease[30]. In this study, the results of the DPP4 assay showed that women in the GDM group had significantly higher expression levels than those in the HP group. We hypothesized that the high level of DPP4 expression may have contributed to the cognitive decline in patients with GDM. To investigate the reason for this, we further tested the patients’ level of inflammatory response and oxidative stress.

Systemic inflammation has been suggested to play an important pathogenic role in the late severe stages of cognitive decline, and inflammatory markers, such as IL-6, were only found to be elevated in patients with dementia but not in those with cognitive decline[31,32]. We propose that this discrepancy could be due in part to differences in the methods of detecting inflammatory cytokines and the diagnosis of cognitive dysfunction. The majority of the studies support the possibility that systemic inflammation could be a pathophysiological cascade response to cognitive decline, and do not explicitly exclude low-grade inflammatory diseases, such as T2DM, cardiovascular disease, and GDM. The present study showed that the serum IL-6 level in perinatal pregnant women with GDM is significantly elevated and correlates with the elevated DPP4 level. Therefore, we speculate that elevated serum DPP4 in perinatal...
Pregnant women with GDM might exacerbate the progression of cognitive dysfunction to some extent via its proinflammatory effects.

Besides systemic inflammation, oxidative stress has also been shown to cause cognitive decline. 8-iso-PGF2α is a biologically active prostaglandin-like substance and a specific product resulting from the oxygen free radical peroxidation of cellular membranes. This indicator can accurately reflect lipid peroxidation in patients with hypoxia–ischemia–reperfusion[33]. The production of 8-iso-PGF2α is not dependent on cyclooxygenase (COX), but on the damage caused by oxygen free radicals to polyunsaturated fatty acids (arachidonic acid) in lipid cell membranes. Thus, its expression levels in vivo are not affected by the use of nonsteroidal anti-inflammatory drugs, such as aspirin, which can alter COX activity. Therefore, 8-iso-PGF2α is an ideal biochemical indicator for the clinical determination of the degree of free radical oxidation in patients and the efficacy of antioxidant therapy. Furthermore, studies have shown that increased peripheral blood 8-iso-PGF2α levels in pregnant women positively correlate with disease severity[34]. One study confirmed that DPP4 increases the production of reactive oxygen species in endothelial cells in a dose-dependent manner[35]. Our data also suggest a positive correlation between 8-iso-PGF2α and DPP4 activity.

We also examined the serum levels of BDNF, which is a plasma marker associated with cognitive function. BDNF downregulation could lead to synaptic loss and neurodegeneration[36]. Our results indicate that patients in the GDM group had significantly lower expression levels. This suggests that patients in the GDM group not only experienced cognitive decline, but also showed changes in plasma marker levels, which is the greatest cause of our concern.

In this study, we found that DPP4, IL-6, and 8-iso-PGF2α levels were significantly higher and BDNF level was lower in pregnant women with GDM, and that these biomarkers were mutually correlated to a certain extent. Zheng et al[4] found that DPP4, IL-6 and 8-iso-PGF2α levels were elevated in patients with T2DM and associated with their cognitive dysfunction. Furthermore, the increased DPP4 levels correlated with increased IL-6 and 8-iso-PGF2α levels. In this study, we found that elevated serum DPP4 levels in perinatal pregnant women with GDM positively correlated with elevated serum IL-6 and 8-iso-PGF2α levels, while the latter was also correlated with decreased BDNF levels. Therefore, we speculate that elevated DPP4 levels might exacerbate the inflammatory response and oxidative stress in pregnant women with GDM. These inflammatory and oxidative stress factors can cross the blood–brain barrier and act on the nervous system to reduce BDNF levels, which will affect hippocampal function, thereby exacerbating memory loss. DPP4 might not only be involved in the process of cognitive dysfunction in pregnant women with GDM, but also in insulin resistance, lipid oxidative stress, and other pathophysiological processes. It may also serve as a potential target for GDM treatment, which is the next step in our research.

The limitations of this study were as follows: (1) the sample size was small; and (2) we observed the cognitive status of pregnant women with GDM and discussed the pathophysiological mechanisms associated with DPP4 from the perspective of inflammatory factors and oxidative stress. However, complex mechanisms may be involved in memory loss in pregnant women with GDM, not limited to the effects of DPP4 alone. Therefore, further elucidation of the underlying mechanisms is needed.

This study also found significantly elevated levels of DPP4 in the cord blood, suggesting that DPP4 could affect fetal development through the placental barrier. However, we did not examine the effect of this change on the fetus.

We believe that in addition to strict dietary control and glycemic control, it is also important to stabilize the moods of perinatal pregnant women with GDM to reduce inflammatory and stress responses. In particular, we should pay attention to methods of controlling intraoperative patient stress during anesthesia for painless natural delivery or caesarean delivery. This is not only crucial for the mother but also for the fetus.

**CONCLUSION**

Cognitive dysfunction in perinatal pregnant women with GDM mainly manifested as memory loss, which might be associated with elevated DPP4 levels.
ARTICLE HIGHLIGHTS

Research background
Studies have confirmed that type 2 diabetes mellitus (DM) can cause cognitive impairment. The mechanism is not clear. Dipeptidyl peptidase-4 (DPP4) may be involved in this process.

Research motivation
The main problem in this study is whether cognitive impairment exists in pregnant women with gestational DM (GDM) and whether it is related to DPP4. This has a great impact on the physical and mental health of pregnant women with perinatal GDM and the health of the fetus.

Research objectives
Objective to study the cognitive function of pregnant women with GDM, and to find out whether the pathway is related to DPP4.

Research methods
They were divided into three groups: GDM group, healthy pregnant group and control group. Women in the three groups were scored with Montreal Cognitive Assessment. Venous blood was collected from women in each group, serum was separated, and serum indexes such as DPP4, interleukin-6, and 8-iso-prostaglandin-F2 α, and brain-derived neurotrophic factor (BDNF) were detected by ELISA.

Research results
Compared with the other two groups, the GDM group had cognitive impairment, especially memory impairment. DPP4 may induce the change of BDNF by promoting oxidative stress and inflammatory response.

Research conclusions
GDM can lead to cognitive dysfunction in pregnant women, mainly manifested as memory loss. DPP4 may be involved in this process.

Research perspectives
Perinatal cognitive decline is worth our attention, especially in GDM pregnant women. How to prevent and treat is the key. Whether DPP4 can be used as a therapeutic target needs further study.

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