

Expression and Significance of FABP4 and miRNA-182 in Plasma and Placental Tissues of Patients with Hypertensive Disorders During Pregnancy

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Abstract: *Objective:* To investigate the expression and significance of fatty acid binding protein 4 (FABP4) and microRNA-182 (miRNA-182) in the plasma and placental tissues of patients with hypertensive disorders in pregnancy (HDIP). *Methods:* 141 mothers admitted to The Affiliated Hospital of Hebei University between January 2019 and December 2022 were selected. The patients were divided into the observation group (61 HDIP patients) and control group (80 healthy pregnant women) based on the criteria for determining hypertensive diseases in pregnancy. The differences in the expression of FABP4 and miRNA-182 between the two groups were compared. *Results:* The expression levels of FABP4 in plasma and placental tissues of the observation group were significantly higher than those of the control group ($P < 0.05$). Conversely, the expression levels of miRNA-182 in the plasma and placental tissues of the observation group were significantly lower than those of the control group ($P < 0.05$). A negative correlation was observed between the plasma level of FABP4 and miRNA-182. However, there was no significant correlation between the expression levels of FABP4 and miRNA-182 in placental tissues. While plasma FABP4 levels exhibited a positive correlation with the severity of HDIP, miRNA-182 expression levels did not significantly correlate with the severity of HDIP. *Conclusion:* The expression of FABP4 and miRNA-182 in plasma and placental tissues of patients with HDIP differed significantly from that of healthy pregnant women. This observation may provide a new perspective on the pathogenesis of HDIP.

Keywords: Hypertensive disorders in pregnancy (HDIP); FABP4; miRNA-182

Online publication: December 26, 2023

1. Introduction

Hypertensive disorders in pregnancy (HDIP) represent conditions exclusive to the gestational period, encompassing chronic hypertension, gestational hypertension, preeclampsia/eclampsia, and chronic hypertension with superimposed preeclampsia/eclampsia. Clinical manifestations primarily involve

hypertension, edema, and proteinuria, among other factors^[1-6].

Fatty acid binding protein 4 (FABP4) is an intracellular protein responsible for binding and transporting fatty acids. It plays a crucial role in adipocyte differentiation, lipid metabolism, and inflammatory response. On the other hand, microRNA-281 (miRNA-182) serves as a significant microRNA with negative regulatory effects on cell growth, development, and differentiation. Moreover, it actively participates in various biological processes.

2. Materials and methods

2.1. General information

A total of 141 mothers admitted to The Affiliated Hospital of Hebei University between January 2019 and December 2022 were enrolled in this study. According to the criteria for diagnosing HDIP, the patients were categorized into two groups: an observation group (61 HDIP patients) and a control group (80 healthy pregnant women). Subsequently, plasma and placental tissue samples from both groups were collected.

Inclusion criteria included patients meeting the criteria for HDIP, including chronic hypertension, gestational hypertension, preeclampsia/eclampsia, and chronic hypertension with superimposed preeclampsia/eclampsia. Additionally, inclusion criteria encompassed pregnant women aged between 18 and 45 years, and patients who willingly agreed to participate in the study, providing their informed consent.

Exclusion criteria included patients with pre-existing pregnancy complications such as gestational diabetes mellitus or gestational heart disease, those who had undergone antihypertensive and anti-inflammatory treatments before the study, pregnant women with severe hepatic or renal insufficiency or other systemic diseases such as immune system disorders, and non-cooperative participants or those failing to adhere to the study protocols for relevant examinations and tests.

2.2. Judgment criteria for hypertension in pregnancy

- (1) Elevated blood pressure: The standard for HDIP is a systolic blood pressure ≥ 140 mmHg or diastolic blood pressure ≥ 90 mmHg. As blood pressure elevation varies in degree and duration, regular blood monitoring is crucial for detecting abnormalities promptly.
- (2) Proteinuria: In HDIP, criteria for proteinuria include random urinary protein \geq (++) or 24-hour urinary protein quantification ≥ 0.5 g/24 h. The presence of proteinuria indicates potential kidney damage, often accompanied by elevated blood pressure and edema.
- (3) Edema: Criteria for edema in HDIP involve a weight gain of ≥ 0.9 kg/week or lower extremity edema of ++ or more. Edema typically initiates at the ankles, progressing upwards, and severe cases may extend to the thighs and abdomen. Edema not only impacts the quality of life for pregnant women but can also affect kidney and liver function.
- (4) Vision changes: Standardized vision changes in HPID include blurred vision and eye pain. These symptoms may arise suddenly and intensify as the pregnancy advances. Immediate medical attention is advised when such symptoms occur.
- (5) Impaired kidney function: Criteria for impaired renal function in hypertensive disorders of pregnancy encompass blood urea nitrogen ≥ 7.14 mmol/L or creatinine ≥ 97.2 μ mol/L. Impaired renal function typically coexists with symptoms such as hypertension, proteinuria, and edema. Pregnant women should monitor protein and water intake, seeking prompt treatment to preserve renal function.
- (6) Low platelet count: The criterion for low platelet count in HPID is a platelet count $< 100 \times 10^9$ /L. A reduced platelet count may impact the coagulation function, potentially leading to postpartum

hemorrhage and other complications. Pregnant women are advised to prioritize warmth and rest, seeking timely medical intervention.

By adhering to these criteria, healthcare professionals can diagnose and treat HPID promptly. Pregnant women should remain vigilant regarding symptom changes, maintaining open communication with their healthcare providers to safeguard their health and that of the fetus.

2.3. Measurement of plasma FABP4 level and miRNA-182 level in embryos

Plasma FABP4 level:

- (1) Collect venous blood from pregnant women, separate the plasma, and store it in a -80°C cryogenic refrigerator for measurement.
- (2) Measure the concentration of FABP4 in plasma using enzyme-linked immunosorbent assay (ELISA).

miRNA-182 level in embryo:

- (1) Collect embryo tissue samples, quick-freeze them with liquid nitrogen, and then store them in a cryogenic refrigerator at -80°C for measurement.
- (2) Measure the expression level of miRNA-182 in embryonic tissues using reverse transcription polymerase chain reaction (RT-PCR) technology.

The differences in the expression of FABP4 and miRNA-182 were compared between the two groups and their relationship with HDIP was analyzed.

2.4. Statistical methods

Data analysis was performed using SPSS 18.0 statistical software. Measurement data were expressed as mean \pm standard deviation (SD), and the *t*-test was used, whereas count data were expressed as %, and the χ^2 test was used. $P < 0.05$ was regarded as a statistically significant difference.

3. Results

3.1. Expression of FABP4

Table 1 shows that the expression levels of FABP4 in plasma and placental tissues of the observation group were significantly higher than those of the control group ($P < 0.05$).

Table 1. Comparison of FABP4 expression in maternal serum and placenta (mean \pm SD)

Group	Number of cases	Blood serum	Placenta
Control group	80	1.29 \pm 0.23	0.63 \pm 0.07
Observation group	61	1.61 \pm 0.29	0.82 \pm 0.09
<i>t</i>		7.31	14.10
<i>P</i>		0.00	0.00

3.2. Expression of miRNA-182

Table 2 shows that the expression levels of miRNA-182 in plasma and placental tissues of the observation group were significantly lower than those of the control group ($P < 0.05$).

Table 2. Comparison of miRNA-182 expression in maternal serum and placenta (mean \pm SD)

Group	Number of cases	Blood serum	Placenta
Control group	80	1.51 \pm 0.29	0.91 \pm 0.09
Observation group	61	1.21 \pm 0.23	0.62 \pm 0.07
<i>t</i>		6.85	20.81
<i>P</i>		0.00	0.00

3.3. Correlation analysis

Plasma FABP4 levels were negatively correlated with miRNA-182 expression levels ($r = -0.78$, $P < 0.05$), while there was no significant correlation between FABP4 and miRNA-182 expression levels in placental tissues ($r = -0.32$, $P > 0.05$). In addition, plasma FABP4 levels were positively correlated with the severity of HDIP ($r = 0.67$, $P < 0.05$), while miRNA-182 expression levels were not significantly correlated with the severity of HDIP ($r = -0.23$, $P > 0.05$).

4. Discussion

Uteroplacental ischemia stands out as a pivotal factor contributing to hypertension in pregnancy. During early pregnancy, uteroplacental blood circulation intensifies to accommodate the demands of fetal growth and development. However, anomalies in the uteroplacental vasculature, such as vascular stenosis and embolism, can lead to uteroplacental ischemia. This condition is associated with complications including fetal growth restriction, hypertension, and proteinuria. HDIP exhibits familial tendencies, with certain studies suggesting a hereditary predisposition to preeclampsia. Although genetic factors are implicated in disease development, the mode of inheritance remains unclear. Maternal physical well-being significantly influences the onset of pregnancy-related hypertension. A history of maternal diseases such as obesity, diabetes, and chronic hypertension heightens the risk of gestational hypertension. Factors such as hypoalbuminemia and deficiencies in crucial nutrients such as calcium, magnesium, zinc, and selenium, coupled with a lack of moderate physical activity, can amplify the likelihood of HDIP. Aberrant activation of the immune system and inflammatory responses have also been linked to the development of gestational hypertension. The over-activation of the inflammatory immune response, coupled with reduced maternal immune tolerance to the embryo, manifests in symptoms such as pre-eclampsia. Inadequate remodeling of small uterine spiral arteries and diminished placental perfusion represent additional influential factors in pregnancy-related hypertension. This is primarily attributed to heightened uterine tension impacting uterine blood supply and the systemic blood circulation's inability to adapt to uterine-placental needs. These dynamics collectively contribute to the development of hypertension in pregnancy [7-14].

The connection between HDIP and FABP4 in the plasma and placental tissues of patients constitutes a complex and intriguing area of research. Some studies suggest that FABP4 may play a role in the pathogenesis of hypertensive disorders in pregnancy [15-17]. However, the precise nature of this relationship and how FABP4 influences the course and severity of HDIP necessitates further investigation. FABP4, classified as an adipocytokine, predominantly expresses itself in adipose tissue and the placenta. Functionally, it participates in fatty acid uptake, transportation, and metabolism, holding crucial roles in energy homeostasis and insulin resistance. In the context of HDIP, FABP4 may assume the following roles:

- (1) Vasoreactivity: FABP4 potentially influences the balance of vasoactive substances, fostering the

hypertrophy and proliferation of smooth muscle cells. This cascade effect contributes to manifestations such as vascular remodeling and elevated blood pressure.

- (2) Oxidative stress: FABP4 could be implicated in the development of HDIP by inducing vascular endothelial damage and dysfunction. This occurs through increased production of reactive oxygen species and oxidative stress.
- (3) Inflammatory response: FABP4 may play a role in promoting the release of inflammatory factors by activating signaling pathways such as nuclear factor- κ B (NF- κ B) and mitogen-activated protein kinase (MAPK). This, in turn, contributes to vascular inflammation and elevated blood pressure.

While some existing studies suggest a link between FABP4 and HDIP, some have failed to find a significant association, as the role of FABP4 is likely influenced by a variety of factors, including genetics, environment, and nutrition during pregnancy.

A significant association exists between HDIP and miRNA-182 in patients' plasma and placental tissues. miRNA-182, a non-coding RNA molecule, exerts its influence by binding to the 3' untranslated region of target genes, thereby regulating gene expression. Numerous studies have indicated the potential importance of miRNA-182 in HDIP [15-20]. There appears to be a correlation between plasma miRNA-182 expression levels and the onset of HDIP. Several studies have reported reduced miRNA-182 expression levels in the plasma of patients with gestational hypertension. This reduction might be linked to the regulation of its target genes, which, in turn, could be involved in signaling pathways related to blood pressure regulation, oxidative stress, and inflammatory response. For instance, miRNA-182 might contribute to the inflammatory response in HDIP by regulating inflammation-related genes such as toll-like receptor 4 (*TLR4*) and myeloid differentiation primary response 88 (*MYD88*). Within placental tissues, miRNA-182 expression levels may be associated with pathophysiological changes in HDIP. Elevated miRNA-182 expression levels were observed in placental tissues of patients with gestational hypertension, potentially linked to the regulation of its target genes. These genes could be implicated in signaling pathways related to placental vascular remodeling, oxidative stress, and apoptosis. For example, miRNA-182 might contribute to the process of placental tissue injury in HDIP by regulating apoptosis-related genes such as B-cell lymphoma 2 (*Bcl-2*).

In this study, a negative correlation was observed between plasma FABP4 levels and miRNA-182 expression level ($r = -0.78$, $P < 0.05$), highlighting a potential interplay between these factors. Conversely, no significant correlation was identified between the expression levels of FABP4 and miRNA-182 in placental tissues ($r = -0.32$, $P > 0.05$). Elevated FABP4 expression may be linked to inflammatory response and lipid metabolism disorders, while down-regulated miRNA-182 expression may be associated with abnormalities in cell growth and differentiation. Moreover, a positive correlation was found between plasma FABP4 levels and the severity of HDIP ($r = 0.67$, $P < 0.05$), suggesting a potential role for FABP4 as an indicator in the assessments of these disorders. However, miRNA-182 expression levels did not exhibit a significant correlation with the severity of HDIP ($r = -0.23$, $P > 0.05$). The expression patterns of FABP4 and miRNA-182 in plasma and placental tissues of patients with HDIP significantly differed from those of healthy pregnant women. This divergence could offer novel insights into the pathogenesis of HDIP. Despite these promising findings, further research is essential to elucidate the roles of FABP4 and miRNA-182 in the pathogenesis of HDIP and to identify potential therapeutic targets. This study lays a foundation for future investigations that could enhance the understanding of these intricate relationships and contribute to the development of effective therapeutic strategies for HDIP.

Funding

Hebei Provincial Health Commission (No. 20220634)

Disclosure statement

The authors declare no conflict of interest.

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