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Original Article

Insulin aspart plus high-dose vitamin D supplementation for gestational diabetes mellitus: analysis of efficacy and risk factors for maternal and infant outcomes

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Abstract: Background: Gestational diabetes mellitus (GDM) presents not only immediate challenges affecting maternal and infant health but also long-term consequences. Effective prevention and treatment of GDM are crucial for minimizing the short- and long-term health impacts. Objectives: This retrospective study evaluated the effects of insulin aspart injection plus high-dose vitamin D (HD-VD) supplementation on treatment outcomes and maternal - infant outcomes in patients with GDM. Methods: A total of 129 GDM patients admitted to the Zhongshan Hospital Xiamen University from December 2021 to December 2023 were included in this study. According to the intervention regimen, the patients were divided into two groups: a control group of 59 patients receiving insulin aspart injection plus low-dose vitamin D (LD-VD) supplementation and a research group of 70 cases receiving insulin aspart injection plus HD-VD supplementation. The curative effect, blood glucose metabolism (fasting blood glucose [FPG], 2-hour postprandial blood glucose [2hPG], and glycosylated hemoglobin [HbA1c]), homocysteine (HCY), and cystatin C (Cys C), maternal and infant outcomes (maternal outcomes: hypoglycemia, cesarean section, polyhydramnios, and premature rupture of membranes; neonatal outcomes: stillbirth, macrosomia, neonatal respiratory distress syndrome, and Apgar score) were recorded and compared between the two groups. Risk factors affecting maternal and infant outcomes were analyzed. Results: The research group demonstrated a higher overall effective rate in compared to the control group ($P<0.05$). Post-treatment measurements of FPG, 2hPG, HbA1c, HCY, and Cys C in the research group were statistically lower than the pre-treatment levels and those in the control group (all $P<0.05$). Additionally, the research group showed better maternal and neonatal outcomes, with fewer adverse pregnancy-related conditions and better neonatal health indicators, including higher Apgar scores ($P<0.05$). Besides, insulin aspart injection plus high-dose vitamin D was a protective factor for maternal and infant outcomes ($P<0.05$). Conclusions: Insulin aspart injection plus HD-VD supplementation markedly enhances treatment efficacy and improves maternal and infant outcomes in GDM.

Keywords: Insulin aspart injection, high-dose vitamin D supplementation, gestational diabetes mellitus, therapeutic effect, maternal and infant outcomes

Introduction

Gestational diabetes mellitus (GDM) is a prevalent metabolic disorder during pregnancy, often triggered by vitamin D deficiency, increased fat consumption, excessive weight gain during pregnancy, and psychological stress including negative emotions [1]. According to statistics, the incidence of GDM in Asia was as high as 21.0% in 2017, with a 30-69% likelihood of recurrence in subsequent pregnancies [2-4]. GDM is mainly manifested by varying degrees of glucose intolerance during pregnancy, which can further lead to a decrease in insulin sensitivity in peripheral tissues and compensatory hyperinsulinemia [5]. This condition is associated with a range of adverse pregnancy outcomes, such as premature birth, cesarean section (CS), and premature rupture of membranes (PROM), as well as unfavorable neonatal outcomes such as stillbirth, macrosomia, and neonatal respiratory distress syndrome (NRDS) [6, 7]. Beyond immediate concerns, GDM can also bring long-term harm to maternal and infant outcomes like cardio-metabolic diseases [8]. Therefore, effective prevention and treatment

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of GDM are essential to mitigate its short- and long-term health impact.

Insulin aspart is a commonly used treatment for GDM, with a rapid onset, quick absorption, and rapid peak plasma concentrations, mirroring the activity of natural insulin [9, 10]. In the research of Mu et al. [11], insulin aspart plus exercise-diet therapy not only helped GDM patients stabilize their blood sugar levels effectively, but also reduced the risk of adverse pregnancies. According to Wang et al. [12], insulin aspart can be combined with metformin to help GDM patients with chronic hypertension to effectively control blood sugar and blood pressure, contributing to a reduction in unfavorable perinatal and neonatal outcomes. On the other hand, vitamin D deficiency has been linked to an increased risk of developing GDM [13]. Early intervention with vitamin D supplements has proven effective in slowing the progression of GDM in deficient pregnant women [14]. As indicated by Hosseinzadeh-Shamsi-Anar et al. [15], high-dose vitamin D (HD-VD) support for pregnant women with GDM helped to improve the condition of GDM rapidly, while maintaining safety.

Currently, research on the influence of insulin aspart injection plus HD-VD supplementation on GDM patients and maternal - infant outcomes is still limited. This study aims to fill that gap, offering insight into more effective treatment and enhanced outcomes for mothers with GDM and their babies.

Materials and methods

Patient information

This retrospective study selected 129 GDM mothers admitted in the Zhongshan Hospital, Xiamen University between December 2021 and December 2023. Among them, the control group (n=59) received insulin aspart plus low-dose vitamin D (LD-VD) treatment, and the research group (n=70) received insulin aspart plus HD-VD therapy. This research was conducted under the approval of the Zhongshan Hospital Xiamen University's Ethics Committee.

Inclusion and exclusion criteria

Inclusion criteria: Patients with singleton pregnancies and diagnosed with GDM (the criteria for GDM: oral glucose tolerance test (OGTT) at 25-29 weeks of pregnancy showing one or more of the following: fasting plasma glucose (FPG) >5.1 mmol/L, 1-hour postprandial blood glucose (1hPG) >10.0 mmol/L, and 2hPG >8.5 mmol/L [16]); Patients with serum 25(OH)D3 levels below 35 ng/ml; Patients with fasting blood glucose (FBG) over 13.9 mmol/L and the glycosylated hemoglobin (HbA1c) over 11%; Preference for intensive insulin treatment.

Exclusion criteria: History or family history of diabetes; Use of vitamin D and calcium in the past six months; History of medication that affected insulin secretion and sensitivity; Severe diseases of the heart, lungs, kidneys, or endocrine system; Mental illness or cognitive dysfunction.

Medication method

Insulin aspart plus LD-VD therapy was applied in the control group. Patients received subcutaneous injections of insulin aspart (ShenZhen ChemStrong Scientific Co., Ltd., EPY0000349). The dosage was adjusted according to the patient's glycemic index. In addition, the patients were given 400 units of vitamin D3 (Beijing Yita Biotechnology Co., Ltd., YT63592) orally once daily.

The research group received insulin aspart plus HD-VD. All patients received subcutaneous injections of insulin aspart (ShenZhen ChemStrong Scientific Co., Ltd., EPY0000349), with the injection dose appropriately adjusted according to the patient's blood sugar. The total daily dosage was calculated based on body weight, ranging from 0.5 to 1.0 U/kg. This included two-thirds as dietary insulin to manage postprandial glucose levels and one-third as basal insulin to maintain baseline insulin levels. Patients were given 800 units of vitamin D3 (Beijing Yita Biotechnology Co., Ltd., YT63592) orally once daily. Both groups were treated for 12 weeks.

Outcome measures

(1) Efficacy [17]. Efficacy evaluation criteria: Cure is defined as the disappearance of all clinical symptoms with FPG, 2hPG, and HbA1c returning to the normal range; Markedly effective is defined as near-complete resolution of symptoms, as with reductions in FPG and 2hPG

Table 1. General information of two groups

	Control group (n=59)	Research group (n=70)	t/χ^2	P
Age (years old)	30.00±4.51	31.61±5.10	1.882	0.062
Gestational weeks	27.95±3.06	28.13±3.22	0.324	0.747
Body mass index (kg/m^2)	23.90±4.11	24.01±3.85	0.157	0.876
Primipara			0.305	0.581
Yes	30 (50.85)	39 (55.71)		
No	29 (49.15)	31 (44.29)		
Family history			0.154	0.695
With	11 (18.64)	15 (21.43)		
Without	48 (81.39)	55 (78.57)		

Table 2. Comparison of treatment efficacy between the two groups

	Control group (n=59)	Research group (n=70)	χ^2	P
Cure	15 (25.42)	14 (20.00)	-	-
Markedly effective	18 (30.51)	23 (32.86)	-	-
Effective	15 (25.42)	28 (40.00)	-	-
Ineffective	11 (18.64)	5 (7.14)	-	-
Total effective rate	48 (81.36)	65 (92.86)	3.898	0.048

by more than 40% and HbA1c by more than 30%, although values may not be within the normal range; Effective corresponds to improvement in clinical symptoms and a 20%-40% reduction in FPG and 2hPG along with a 10%-30% decrease in HbA1c; Ineffective is defined as failure to meet the above criteria. The total effective rate = (cure cases + markedly effective cases + effective cases)/total cases * 100%. (2) Blood glucose metabolism [18]. 2 mL of fasting venous blood was collected before and after treatment. After centrifugation, the supernatant was analyzed using an automatic glycation analyzer for FPG and 2hPG, and high-performance liquid chromatography for HbA1c. (3) Homocysteine (HCY) and cystatin C (Cys C) [19]. HCY and Cys C levels in the supernatant samples collected before and after treatment were detected by immunoturbidimetry. (4) Maternal and infant outcomes [20]. Maternal outcomes: The perinatal complications such as hypoglycemia, cesarean section (CS), polyhydramnios, and premature rupture of membranes (PROM) were observed and recorded. Neonatal outcome: The number of adverse reactions such as stillbirth, macrosomia, and neonatal respiratory distress syndrome (NRDS) were observed and recorded. Meanwhile, neonatal Apgar scores were comparatively evaluated.

Statistical processing

SPSS21.0 was used for statistical analyses of the collected experimental data. The measured data were represented as $\bar{x}\pm s$; an independent sample t-test was used for between-group comparison while a paired t-tests was used for within-group comparison. The counted data were expressed as the rate [%], and χ^2 test was used to determine inter-group differences. Logistic regression analysis was performed to identify the risk factors affecting adverse maternal and infant outcome. Differences were significant when $P<0.05$.

Results

General information

No notable inter-group differences were observed in age, gestational weeks, body mass index, primipara, or family history between the two groups (all $P>0.05$), as shown in **Table 1**.

Comparison of curative effects between the two groups

The research group had an overall effective rate of 92.86%, which was significantly higher than the 81.36% in the control group ($P<0.05$), as shown in **Table 2**.

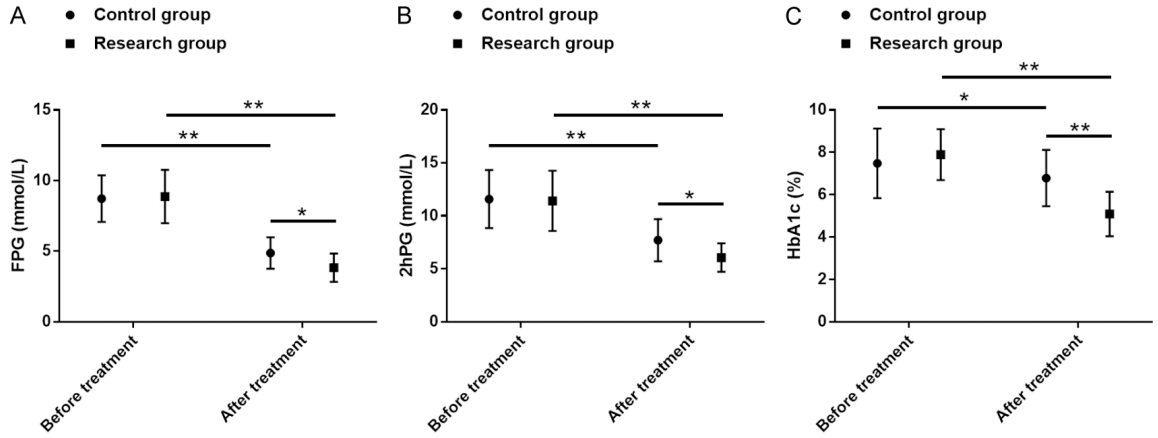

Figure 1. Comparison of blood glucose metabolism between the two groups. A. Changes in FPG before and after treatment. B. Changes in 2hPG before and after treatment. C. Changes in HbA1c levels before and after treatment. Note: ** and * represent P<0.01 and P<0.05, respectively. FPG, fasting blood glucose; 2hPG, 2-hour postprandial blood glucose; HbA1c, glycosylated hemoglobin.

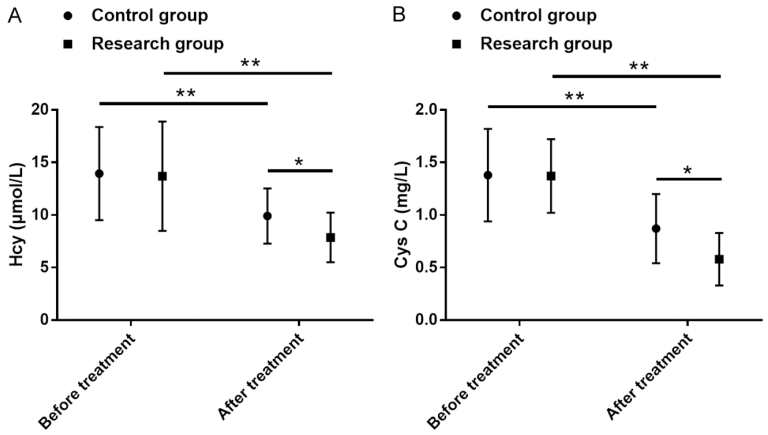

Figure 2. Comparison of HCY and Cys C levels between the two groups. A. Changes in HCY level before and after treatment. B. Changes in Cys C level before and after treatment. Note: ** and * represent P<0.01 and P<0.05, respectively. HCY, homocysteine; Cys C, cystatin C.

Comparison of blood glucose metabolism between the two groups

Initial testing showed no significant differences in FPG, 2hPG, or HbA1c levels between the groups (all P>0.05). Post-treatment, all indices significantly decreased in both groups (all P<0.05), with the research group exhibiting greater reductions than the control group (all P<0.05), as shown in **Figure 1**.

Comparative observation of HCY and Cys C

The research and control groups were similar in pre-treatment HCY and Cys C levels (all P>0.05). After treatment, an evident reduction in HCY and Cys C levels was identified in both groups (all P< 0.05), with significantly lower levels in the research group compared to the control group (all P<0.05), as shown in **Figure 2**.

Comparison of maternal and infant outcomes

Maternal outcomes, including hypoglycemia, CS, polyhydramnios, and PROM were assessed. The research group had significantly lower rates of hypoglycemia, CS, and PROM compared with the control group (all P<0.05), but with no significant difference in polyhydramnios (P>0.05), as shown in **Table 3**.

Neonatal outcomes focused on stillbirth, macrosomia, NRDS, and Apgar scores. The study group exhibited markedly lower incidences of macrosomia and NRDS than the control group (all P<0.05), with an equivalent incidence of stillbirth (P>0.05); in addition, the study group demonstrated higher neonatal Apgar than the control group (P<0.05), as shown in **Table 4**.

Logistic regression analysis of risk factors affecting maternal and infant outcomes

According to logistic regression analysis, age, gestational weeks, BMI, primipara, and family

Table 3. Comparison of maternal outcomes between the two groups

Maternal outcome	Control group (n=59)	Research group (n=70)	χ^2	P
Hypoglycemia	6 (10.17)	1 (1.43)	4.766	0.029
Cesarean section	12 (20.34)	5 (7.14)	4.873	0.027
Hydramnios	4 (6.78)	3 (4.29)	0.388	0.533
Premature rupture of membranes	7 (11.86)	2 (2.86)	4.002	0.045

Table 4. Comparison of neonatal outcomes between the two groups

Neonatal outcome	Control group (n=59)	Research group (n=70)	t/χ^2	P
Stillbirth	1 (1.69)	0 (0.00)	1.196	0.274
Macrosomia	6 (10.17)	1 (1.43)	4.766	0.029
Neonatal respiratory distress syndrome	5 (8.47)	0 (0.00)	6.171	0.013
Apgar score	6.88±1.15	7.37±1.49	2.061	0.041

Table 5. Assignment

Variable	Assignment
X1, age (years)	Age <30 = 0, ≥30 = 1
X2, gestational weeks	<28 = 0, ≥28 = 1
X3, body mass index (kg/m^2)	<24 = 0, ≥24 = 1
X4, primipara	Primipara = 0, multipara = 1
X5, family history	No = 0, yes = 1
X6, treatment mode	Insulin aspart plus high-dose vitamin D = 0, insulin aspart plus low-dose vitamin D = 1

Table 6. Analysis of risk factors affecting maternal and infant outcomes

Factor	β	S.E.	Wald	P	Exp (β)	95% CI
Age (years)	-0.538	0.410	1.724	0.189	0.584	0.261-1.304
Gestational weeks	0.398	0.412	0.935	0.334	1.489	0.664-3.337
Body mass index	-0.253	0.415	0.372	0.542	0.776	0.344-1.751
Primipara	-0.171	0.413	0.171	0.679	0.843	0.375-1.895
Family history	0.456	0.524	0.759	0.384	1.578	0.566-4.404
Treatment mode	-1.383	0.411	11.342	0.001	0.251	0.112-0.561

history were not risk factors for maternal and infant outcomes (all P>0.05); however, insulin aspart injection plus HD-VD supplementation was a protective factor (P=0.001; **Tables 5**, **6**).

Discussion

Gestational diabetes mellitus (GDM) is a prevalent complication during pregnancy, influenced by decreased insulin sensitivity caused by abnormal hormones such as estrogen, progesterone, and placental prolactin [21]. As pregnancy progresses, these hormonal changes complicate the maintenance of blood sugar balance, often leading to abnormal blood sugar elevation that trigger GDM. Common symptoms include polyphagia, polydipsia, and polyuria, which can lead to unfavorable outcomes like macrosomia, NRDS, fetal malformations, and neonatal jaundice [22]. Therefore, taking effective prevention and treatment measures for GDM is of great significance for improving neonatal and pregnancy outcomes.

This study identified an obviously higher overall efficacy in the research group compared to the control group (92.86% vs. 81.36%), indicating substantial benefits of combining insulin aspart with high-dose vitamin D (HD-VD) for treating GDM patients. A systematic review and meta-analysis indicated a significant inverse association between vitamin D and the risk of develop-

ing GDM, suggesting that vitamin D supplementation could help mitigate the development of GDM [23]. A study has demonstrated that low vitamin D level in the first trimester is a risk factor for GDM and closely related to insulin resistance in the second trimester [24]. Vestergaard et al. [25] also pointed out that HD-VD supplements not only helped improve placental function during pregnancy, but also benefited the brain development of newborns. A guinea pig experiment showed that dietary intake of vitamin D during pregnancy could improve the body's glucose tolerance to some extent, although it did not reduce the risk of GDM [26]. In our study, post-treatment measurements showed significant reductions in FPG, 2hPG, and HbA1c in the research group, significantly lower than the pre-treatment levels and the control group, indicating that insulin aspart injection and HD-VD can effectively restore normal glucose metabolism in GDM patients. Similarly, evidence has also shown that vitamin D supplementation during pregnancy can effectively alleviate maternal insulin resistance and improve fetal growth [27].

Both HCY and Cys C are associated with adverse maternal outcome. HCY is significantly associated with GDM in pregnant mothers, while Cys C correlates with adverse birth outcomes (macrosomia and large-for-gestational-age infants) in the third trimester, making them potential targets for GDM treatment [28-30]. Therefore, we assessed the changes in HCY and Cys C levels in this study. Post-treatment assessment showed that HCY and Cys C levels were significantly decreased as compared to the pre-treatment levels and those of the control group. This suggests that insulin aspart plus HD-VD can significantly inhibit HCY and Cys C in GDM patients, thereby potentially slowing disease progression. In the research by Wang Y et al. [31], insulin aspart plus metformin contributed to effective control of FPG, 2hPG, HbA1c, and other blood glucose metabolism-related indexes, as well as significant inhibition of Hcy, which is similar to our observations. As reported by Al-Bayyari et al. [32], HD-VD used in overweight female patients not only reduced HCY levels, but also improved liver function and helped prevent cardiovascular and liver diseases.

Furthermore, our evaluation of maternal and infant outcomes revealed lower incidence rates of hypoglycemia, CS, and PROM in the research group compared to the control group. In addition, the research group also reported statistically fewer cases of macrosomia and NRDS and higher neonatal Apgar scores than the control group, with a similar incidence of stillbirth. Supporting these findings, report by Wu et al. [33] demonstrated that vitamin D supplementation effectively regulated blood lipid metabolism in GDM patients and reduced adverse neonatal outcomes. In a meta-analysis [34], vitamin D supplementation in GDM pregnancies was associated with reduced adverse outcomes such as CS and postpartum hemorrhage, with a preventive effect on adverse complications such as neonatal hyperbilirubinemia, macrosomia, fetal distress, and preterm birth.

In addition, insulin aspart injection plus HD-VD supplementation was indicated as a protective factor for maternal and infant outcomes by logistic regression analysis, further demonstrating that this combination therapy may help improve maternal and infant outcomes in GDM patients. According to the logistic analysis by Cheng et al. [35], HD-VD supplementation significantly reduced the risk of GDM. In a logistic regression analysis by Wen et al. [36], low vitamin D level not only increased the risk of GDM, but also increased the risk of adverse pregnancy outcomes such as anemia, macrosomia, abnormal amniotic fluid, miscarriage, or stillbirth, which is similar to our study.

The innovation of this study lies in the comprehensive evaluation and confirmation of the clinical benefits of insulin aspart injection plus HD-VD supplementation in GDM patients from the perspective of efficacy, blood glucose metabolism, HCY, Cys C, as well as its effectiveness in controlling blood sugar and disease progression. In addition, it was confirmed that insulin aspart injection plus HD-VD supplementation has a positive impact on the improvement of maternal and infant outcomes in GDM patients. Moreover, this combined regimen was validated by logistic regression analysis to be a protective factor for improving maternal and infant outcomes in GDM patients.

Taken together, insulin aspart injection plus HD-VD supplementation is effective for treating GDM patients and helps stabilize patients' blood glucose metabolism and HCY and Cys C levels, which can effectively improve maternal

and infant outcomes, prevent hypoglycemia, CS, PROM, macrosomia, and NRDS.

Disclosure of conflict of interest

None.

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