

Effects of insulin combined with metformin on serum cystatin C, homocysteine and maternal and neonatal outcomes in pregnant women with gestational diabetes mellitus

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Abstract. Effects of insulin combined with metformin on serum cystatin C (Cys C), homocysteine (Hcy) and maternal and neonatal outcomes in pregnant women with gestational diabetes mellitus (GDM) were investigated. In total, 80 cases of pregnant women diagnosed with GDM in the Department of Obstetrics and Gynecology of Liaocheng Third People's Hospital from July 2015 to July 2017 were selected and divided into a study group (42 cases) and a control group (38 cases). The study group was treated with insulin combined with metformin, and the control group was treated with insulin. Fasting blood glucose (FBG) and postprandial blood glucose after 2 h (2hPG) of the two groups were compared before and after treatment. Levels of serum Cys C, Hcy, urinary protein (UmAlb), postpartum maternal outcomes and adverse reactions during pregnancy were compared in the two groups before and after treatment. After treatment, the level of FBG and 2hPG in the control group was higher than that in the treatment group ($P < 0.05$). After treatment, the level of serum Cys C and Hcy in both groups were lower than that before the treatment, and the level in the study group was lower than that in the control group ($P < 0.05$). The total incidence of neonatal adverse outcomes and the number of adverse pregnancies in GDM patients in the study group were significantly lower than those in the control group ($P < 0.05$). There were no significant differences in adverse reactions during pregnancy between the two groups ($P > 0.05$). In conclusion, insulin combined with metformin is more effective than insulin alone in reducing serum Cys C and Hcy levels, with significant effect on the improvement of maternal and neonatal outcomes.

Introduction

Gestational diabetes mellitus (GDM) (1,2) is a disease that occurs during pregnancy, and its incidence rate has gradually increased. Lack of pregnancy knowledge, along with unreasonable diet, glycemic control and pregnancy weight gain lead to GDM in pregnant women (3). These are important factors in becoming a high-risk pregnant woman. If not controlled in time, the disease may have a severe impact on mothers and infants.

Most pregnant women with GDM cannot control their blood glucose effectively through diet control and exercise therapy (4). Consequently, they are often dependent on drug therapy to control their blood glucose level. Insulin is often selected for the treatment of diabetes as it can reduce blood glucose levels (5). However, it has no obvious effect on the treatment of insulin resistance in patients with GDM; thus, there are still some deficiencies in its efficacy. Metformin is an insulin sensitizer that adjusts glucose metabolism by adjusting insulin sensitivity (6). This constitutes an important reason for improving insulin sensitivity *in vivo*.

Increasing insulin resistance in GDM patients is the result of increased secretion of progesterone, estrogen and other substances in the middle and late stages of gestation, resulting in decreased insulin sensitivity, unstable blood glucose level, and abnormal glucose metabolism and various complications (7). Diabetic nephropathy is easy to occur during the treatment of GDM (8). Due to the inconspicuous early symptoms, diabetic nephropathy is not easy to detect, and develops to the point of severe damage when identified at late stage. While cystatin C (Cys C) is a sensitive indicator for early diagnosis of damage to glomerular filtration function, it can reflect the damage degree of patients with GDM complicated with renal disease (9). In addition, when the body's blood glucose level is at a high concentration, patients may lose excessive amounts of fluid (10,11). The level of homocysteine (Hcy) also increases, accelerating the pathological changes of small blood vessels and aggravating the course of GDM (10,11). Therefore, the monitoring of the two serum factors is conducive to the prevention and timely detection of some related complications.

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Previous findings have shown that insulin combined with metformin have an effect of declining the levels of blood sugar (12). However, few studies on the joint treatment of the two concerning the detection of serum Cys C and Hcy levels in patients with GDM and their effects on mothers and infants are currently available. In the present study, we explored the effect of the combined therapy of insulin and metformin on serum Cys C and Hcy levels, and the maternal and neonatal outcomes in GDM patients.

Patients and methods

General data. A total of 80 cases of GDM patients admitted to the department of obstetrics and gynecology of Liaocheng Third People's Hospital (Liaocheng, China) from July 2015 to July 2017 were selected, 42 cases of patients treated with insulin combined with metformin were included in the study group, and 38 cases of patients treated with insulin alone were included in the control group. There were no significant differences in age, BMI and gestational weeks ($P>0.05$). Patients who met one of the diagnostic criteria for GDM were included in the study: fasting blood glucose (FPG) ≥ 5.1 mmol/l, blood glucose after 1 h (1hPG) ≥ 10.0 mmol/l, and postprandial blood glucose after 2 h (2hPG) ≥ 8.5 mmol/l (13). Exclusion criteria were: patients who had gestational diabetes during previous pregnancy; patients with liver and kidney dysfunction; patients with communication and cognitive dysfunction; patients who did not cooperate with the study requirements.

All the patients and their families agreed to participate in the experiment and signed an informed consent. The present study was approved by the Ethics Committee of the Liaocheng Third People's Hospital.

Therapeutic schedule. Regular exercise and diet management were adopted in both groups. Patients in the control group received insulin treatment [import drug registration certificate no. X19990279[96], medicine authorized number: J-70[2]; Novo Nordisk (China) Pharmaceuticals Co., Ltd.], at the dose of 0.2-0.25 U/(kg·day). Patients in the study group received treatment of insulin combined with metformin. The insulin dose was 0.2-0.25 U/(kg·day), and the metformin was given orally at 0.5 g/time twice a day. The dosage could be increased or decreased according to the patient's blood glucose level, and the highest dose could not exceed 3 g/day. The treatment continued until the birth of the newborn.

Observational indexes. Blood glucose levels of GDM patients in both groups were observed before and after treatment, and FBG and 2hPG levels were measured and recorded in all patients before and after treatment.

Venous blood (5 ml) of the pregnant women was extracted before and after treatment and centrifuged at $2,600 \times g$ for 10 min at 4°C . Then, the serum was placed in the refrigerator (AU5800 automatic biochemical analyzer; Beckmen Coulter). ELISA was used to detect the level of Hcy in serum (EY-elisa2279; Shanghai Yiyuan Biological Technology Co., Ltd.). Immunoturbidimetry was used to detect the serum Cys C level (59400368211; Hangzhou Deangel Biological Engineering Co., Ltd.).

Maternal and neonatal outcomes between the two groups were compared, including maternal delivery methods: Cesarean section, preterm delivery and labor induction. The number of newborns with hypoglycemia, macrosomia, neonatal jaundice, and fetal malformation was recorded.

UmAlb levels of pregnant women in the two groups were compared, special protein immunoturbidimetry was used in the detection. The detection instrument was Beckman DXC600 automatic biochemical detector (Beckmen Coulter).

The incidence of adverse reactions was compared between the two groups, including nausea, vomiting, hypertension and diarrhea.

Statistical analysis. In this study, SPSS 20.0 [Boyi zhixun (Beijing) Information Technology Co., Ltd.] was used for statistical analysis of experimental data. Chi-square test was used for enumeration data. Mean \pm standard deviation was used for measurement data. The t-test was used for comparison between the two groups, and paired t-test was used for comparison before and after treatment of the two groups. GraphPad Prism 6 software was used to draw the experimental illustrations. $P<0.05$ was considered a statistically significant difference.

Results

Comparison of general data of the two groups. There were no significant differences in general data such as age, BMI and gestational weeks ($P>0.05$) (Table I).

Comparison of FBG and 2hPG levels before and after treatment in the two groups. The FBG content in the study group and the control group before treatment was 6.75 ± 0.68 and 6.72 ± 0.67 mmol·l⁻¹, and the 2hPG content was 10.34 ± 2.45 and 10.27 ± 2.23 mmol·l⁻¹, respectively. After treatment, the content of FBG was 5.13 ± 0.46 and 5.67 ± 0.52 mmol·l⁻¹, respectively. The 2hPG content was 5.24 ± 2.56 and 6.12 ± 2.67 mmol·l⁻¹, respectively. There were no significant differences between the study and control groups before treatment ($P>0.05$), and the levels of FBG and 2hPG in the study group after treatment were lower than those in the control group ($P<0.05$) (Fig. 1).

Content of serum Cys C and Hcy of patients in the two groups before and after treatment. Serum Cys C contents in the study group and control group before treatment were 1.480.56 and 1.460.45 mg/l, respectively. The contents of serum Hcy were 14.25 and 14.285.34 $\mu\text{mol/l}$, respectively. There were no significant differences between the two groups ($P>0.05$). After treatment, serum Cys C levels in the study group and control group were 0.780.34 and 1.210.25 mg/l, respectively. The serum Hcy levels were 7.212.67 and 103.48 $\mu\text{mol/l}$, respectively. After treatment, the levels of both groups were lower than those before treatment, but the serum levels of Cys C and Hcy in the study group were significantly lower than those in the control group, with statistically significant differences ($P<0.05$) (Fig. 2).

Comparison of urinary protein levels before and after treatment in the two groups. Urine protein levels in the study group and control group before treatment were 17.271.68 and 17.451.64 mg/mmol, respectively, and there were no significant

Table I. Comparison of general data of the two groups.

Factors	Research group (n=42)	Control group (n=38)	t/ χ^2 value	P-value
Age (years)			0.179	0.673
≤26	28 (66.67)	27 (71.05)		
>26	14 (33.33)	11 (28.94)		
Family history			0.038	0.846
With	5 (11.90)	4 (10.52)		
Without	37 (88.10)	34 (89.47)		
Embryo number			0.011	0.918
Single birth	40 (95.24)	36 (94.74)		
Twins	2 (4.76)	3 (7.89)		
History of abortion			0.506	0.613
With	8 (19.05)	9 (23.68)		
Without	34 (80.95)	29 (76.32)		
BMI before pregnancy (kg/m ²)	21.45±0.38	21.83±0.26	0.111	0.739
Body growth during gestation (kg)	16.24±0.27	16.34±0.34	0.128	0.617
Gravidity	1.67±0.38	1.58±0.25	0.220	1.237
Parity	1.35±0.26	1.46±0.37	0.125	1.550
Gestational weeks	27.47±2.27	27.42±1.82	0.108	0.914

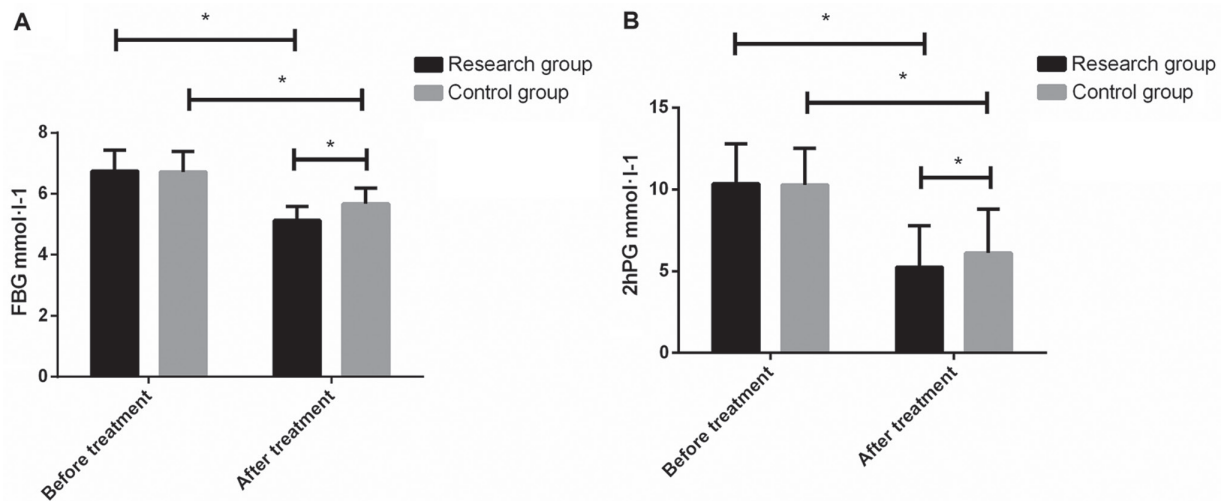


Figure 1. Comparison of FBG and 2hPG levels before and after treatment in the two groups. (A) FBG levels in both the study and control groups were significantly reduced after treatment, but the reduction level in the study group was higher than that in the control group. (B) The 2hPG level in both the study and control groups was significantly reduced after treatment, but the reduction level in the study group was higher than that in the control group. *P<0.05. FBG, fasting blood glucose; 2hPG, postprandial blood glucose after 2 h.

differences between the two groups (P>0.05). After treatment, the urine protein levels of the study group and the control group were 9.781.21 and 12.861.45 mg/mmol, respectively. After treatment, the urine protein levels of both groups were lower than those before treatment, and the level in the study group was significantly lower than that in the control group, with statistically significant differences (P<0.05) (Fig. 3).

Comparison of adverse reactions during pregnancy between the two groups. The number of patients with nausea and vomiting, dizziness, diarrhea and hypertension in the study group were 2, 1, 2 and 1, respectively. The number of patients with nausea and

vomiting, dizziness, diarrhea and hypertension in the control group were 1, 1, 0 and 1, respectively. There were no significant differences in the total number of adverse reactions between the two groups (P>0.05) (Table II). All adverse reactions were relieved after symptomatic treatment.

Comparison of neonatal outcomes between the two groups. When pregnancy ended, the number of neonates with hypoglycemia, neonatal jaundice, macrosomia and fetal abnormalities in the study group were 1, 2, 2 and 1, respectively. The number of the neonates with those symptoms in the control group were 3, 5, 3 and 2, respectively. The incidence of neonatal adverse

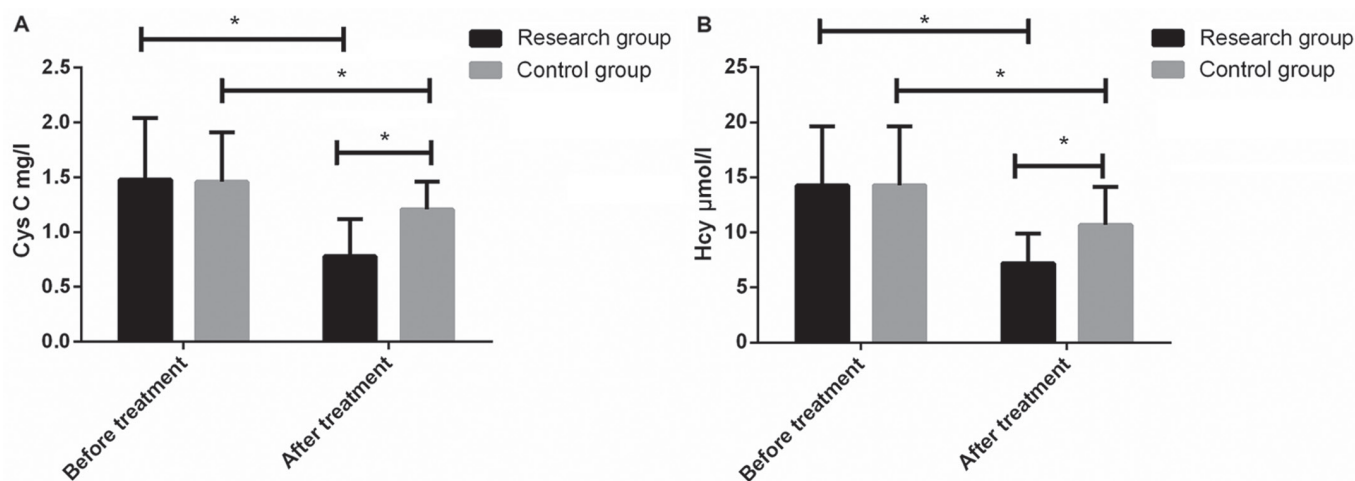


Figure 2. Content of serum Cys C and Hcy of patients in the two groups before and after treatment. (A) Serum Cys C levels in both the study and control groups were significantly reduced after treatment, but the reduction level in the study group was higher than that in the control group. (B) Serum Hcy levels in both the study and control groups were significantly reduced after treatment, but the reduction level in the study group was greater than that in the control group. * $P < 0.05$. Cys C, cystatin C; Hcy, homocysteine.

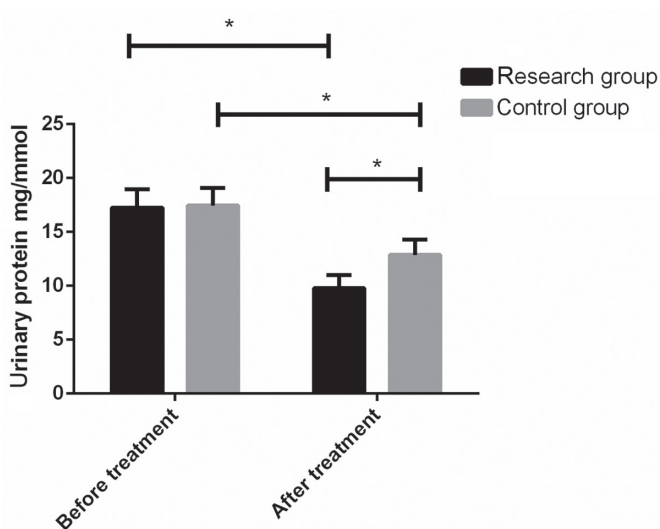


Figure 3. Comparison of urinary protein levels before and after treatment between the two groups. The urine protein levels of both the study group and the control group were significantly reduced after treatment, but the decrease level of the study group was greater than that of the control group. * $P < 0.05$.

outcomes in the study group were significantly lower than those in the control group ($P < 0.05$) (Table III).

Comparison of adverse pregnancy outcomes in the two groups. The number of adverse pregnancies in the study group was 10, and the number of adverse pregnancies in the control group was 17. The number of adverse pregnancies in the study group was significantly lower than that in the control group ($P < 0.05$) (Table IV).

Discussion

With the development of the society, people's quality of life has improved, and the incidence of GDM (14) has increased with the constant change of dietary forms. A high proportion of the incidence among young people has led to an impact

on human health. However, the pathogenesis of GDM is still unknown. GDM is known to cause great harm to pregnant women and infants (15). Thus, the primary principle of GDM treatment is to control the blood glucose level of GDM patients to a normal level, so as to reduce the occurrence of related complications of pregnant women and infants.

Metformin is the primary choice for the treatment of type 2 diabetes for its significant efficacy in controlling blood glucose level, with low incidence of hypoglycemia and protective effect on cardiovascular system (16). It is therefore widely used in clinical practice. In addition, metformin is often used alone or in combination with other drugs in clinical practice (17). Therefore, in the present study, we used insulin combined with metformin to treat GDM patients. Comparisons of the levels of FBG and 2hPG before and after treatment in the study group and the control group showed reduced level in the study group treated with insulin combined with metformin was greater than that in the control group treated with insulin alone. There were no significant differences in adverse reactions during pregnancy in the two groups, suggesting that insulin combined with metformin was more effective in lowering blood sugar levels and did not increase the incidence of adverse reactions during pregnancy. It confirmed the safety of the two drugs. Studies have also confirmed that insulin combined with insulin sensitizers has a relatively significant effect on the control of blood glucose level in the body, and can also reduce the incidence of maternal and neonatal complications (18). Other studies have shown that insulin and metformin are safe and effective during pregnancy (19). Those findings are consistent with our results.

Cys C is mainly filtered and cleared in the kidneys (20,21). If the glomerulus of the body is damaged, its level will increase rapidly and be positively correlated with the degree of injury (20,21). Hcy is one of the risk factors of vasculopathy (22). When vascular endothelial injury occurs, the risk of diabetic nephropathy increases. Studies have shown that serum levels of Cys C and Hcy are somewhat correlated with disease progression and maternal and neonatal complications (23). Therefore,

Table II. Comparison of adverse reactions during pregnancy in the two groups.

Adverse reactions	Research group (n=42)	Control group (n=38)	χ^2 value	P-value
Nausea and vomiting	2 (4.76)	1 (2.63)	0.251	0.617
Dizziness	1 (2.38)	1 (2.63)	0.005	0.942
Diarrhea	2 (4.76)	0 (0)	1.856	0.173
Hypertension	1 (2.38)	2 (5.36)	0.459	0.498
Total number	6 (14.27)	4 (10.53)	0.612	0.258

Table III. Comparison of neonatal outcomes between the two groups.

Groups	Research group (n=42)	Control group (n=38)	χ^2 value	P-value
Hypoglycemia	1 (2.08)	3 (6.25)	1.277	0.259
Neonatal jaundice	2 (4.16)	3 (7.89)	1.761	0.185
Macrosomia	3 (7.14)	5 (13.15)	0.334	0.563
Fetal abnormalities	1 (2.08)	2 (5.26)	0.459	0.498
Total number	7 (16.67)	13 (34.21)	4.373	0.037

Table IV. Comparison of adverse pregnancy outcomes in the two groups.

Groups	Research group (n=42)	Control group (n=38)	χ^2 value	P-value
Cesarean section	2 (4.76)	4 (10.53)	0.956	0.328
Premature birth	4 (9.52)	5 (13.16)	0.264	0.608
Polyhydramnios	2 (4.76)	4 (10.53)	0.956	0.328
Premature rupture of membrane	1 (2.38)	2 (5.23)	0.460	0.498
Postpartum hemorrhage	1 (2.38)	2 (5.23)	0.460	0.498
Total number	10 (23.81)	17 (44.73)	3.908	0.048

we compared the levels of the patients in the study and control groups before and after treatment. The results showed that there were no significant differences in serum Cys C and Hcy levels between the two groups before treatment, and the levels of patients in the study group after treatment were lower than those in the control group. At the same time, in order to study its correlation with renal injury, we also compared the urine protein levels of the two groups before and after treatment. It was found that there were no significant differences between the urine protein levels of the two groups before treatment. However, the urine protein levels of the treatment group were significantly lower than those of the control group. Therefore, it was speculated that the increase of serum Cys C and Hcy levels would lead to an increase of urinary protein levels, which may affect the kidneys of GMD pregnant women to some extent. The above results suggest that insulin combined with metformin can effectively reduce the serum Cys C and Hcy levels of patients, thus improving the patient's condition. Previous findings have indicated that the therapeutic effect and complications of patients with GDM could be predicted by monitoring factors in serum of patients with GDM (24).

GDM not only affects the normal development of infants, but also greatly increases the incidence of adverse pregnancy

outcomes (25). In addition, maternal and neonatal outcomes of GDM depend on blood glucose control, and good blood glucose control can reduce the incidence of maternal and neonatal complications (26). Therefore, we compared the number of neonatal hypoglycemia, neonatal jaundice, macrosomia and fetal malformation in the two groups, and found that the total number of adverse outcomes in the study group was lower than that in the control group, and the total number of adverse pregnancies in the GDM patients in the study group was significantly lower than that in the control group. This finding indicated that insulin combined with metformin had a significant effect on reducing blood glucose level in GDM patients, which could reduce adverse pregnancy and fetal outcomes in pregnant women, and it was conducive to improving maternal and neonatal quality of life. Therefore, effective control of blood glucose level is necessary in GDM.

In conclusion, the use of insulin combined with metformin can effectively reduce the levels of FBG, 2hPG and serum Cys C and Hcy in GDM patients, and can effectively improve maternal and neonatal outcomes without increasing adverse reactions during pregnancy. However, the current study did not make a comparison, for example, with other types of insulin, making further studies necessary.

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Availability of data and materials

The datasets used and/or analyzed during the present study are available from the corresponding author on reasonable request.

Authors' contributions

JZ and JX conceived and designed the study, and drafted the manuscript. JZ, JX, YZ and NZ collected, analyzed and interpreted the experimental data. JZ revised the manuscript for important intellectual content. JZ wrote the manuscript. All the authors read and approved the final manuscript.

Ethics approval and consent to participate

The study was approved by the Ethics Committee of Liaocheng Third People's Hospital (Liaocheng, China). Signed informed consents were obtained from the patients and their guardians.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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