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ORIGINAL ARTICLE

Retrospective Study

Impact of different stereoisomers of inositol on insulin sensitivity of gestational diabetes mellitus patients

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Abstract

BACKGROUND

Inositol is a hexa-carbon polyol, a naturally soluble vitamin, often found in various foods.

AIM

To discuss the impact of different stereoisomers of inositol on insulin sensitivity of gestational diabetes mellitus (GDM) patients.

METHODS

Eighty GDM pregnant women were divided into four groups according to their treatment received: A group (placebo folic acid 400 μg/d), B group [myo-inositol (MI) 1500 mg, twice a day], C group [D-chiro-inositol (DCI) 250 mg, twice a day], and D group (inositol MI and inositol DCI 1500 mg/250 mg, twice a day). Each patient routinely used dietary guidance adjustments and did some safe and effective aerobic exercise in addition to receiving placebo or inositol from GDM diagnosis to delivery. Triglyceride, total cholesterol, fasting plasma glucose, oral glucose tolerance test postprandial glucose (2 h postprandial blood glucose), fasting insulin, fasting plasma glucose, and glycosylated hemoglobin levels and Homeostasis Model Assessment-insulin resistance (HOMA-IR) and Homeostasis Model Assessment-insulin sensitivity index (HOMA-ISI) scores were determined before treatment and 8 wk after treatment onset. Adverse maternal and infant outcomes, including hypoglycemia, excessive amniotic fluid, premature infants, macrosomia, fetal distress *etc.*, were also recorded.

RESULTS

There was no statistical difference in the baseline data of each group. The levels of 2 h blood glucose, glycosylated hemoglobin, fasting insulin, total cholesterol, and triglyceride in the B, C, and D groups were significantly lower than those in the control group (A group) after treatment ($P < 0.05$). Moreover, compared with the B group, the level of the above indexes in the C and D groups decreased more

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significantly, and the differences were statistically significant ($P < 0.05$). The HOMA-IR of B, C, and D groups decreased significantly, and the HOMA-ISI increased significantly compared with the A group, and the differences were statistically significant ($P < 0.05$), among which the decrease of HOMA-IR and the increase of HOMA-ISI were more significant in the C and D group compared with the B group ($P < 0.05$). The occurrence rate of adverse maternal and infant outcomes in the C and D group was significantly lower than that in the control group (A group), and the differences were statistically significant ($P < 0.05$).

CONCLUSION

Treatment with different inositol stereoisomers (inositol MI and inositol DCI) can improve insulin sensitivity and reduce insulin resistance in diabetic patients, and inositol DCI has a better curative effect than inositol MI.

Key Words: Gestational diabetes mellitus; Myo-inositol; Insulin resistance during pregnancy

Core Tip: We compared the impact of different stereoisomers of inositol on insulin sensitivity and prognosis of gestational diabetes mellitus patients.

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INTRODUCTION

Inositol, a hexa-carbon polyol, is a naturally soluble vitamin often found in various foods. It has been listed as an insulin sensitizer. There are nine different isomers of inositol, of which the most representative in the human body are myo-inositol (MI) and D-chiro-inositol (DCI). The occurrence of some effects of insulin may include the participation of small molecule inositol phosphate polymer conductors. The conductor is produced by hydrolysis of glycosylated phosphatidylinositol ester (GPIs) located on the outer layer of the cell membrane. As a result, the released inositol phosphoglycan enters the cell and affects the metabolic process inside the cell. Studies have shown that inositol and inositol glycan intake can have beneficial effects on metabolism, hormone levels, and ovarian function[1,2]. A recent study showed that the supplementation of inositol significantly improved insulin resistance (IR) in gestational diabetes mellitus (GDM) patients[3], but the effects of chiral inositol (DCI) on IR in GDM have not been reported.

In this cohort study, the impact of different stereoisomers of inositol on insulin sensitivity and prognosis of GDM patients were determined.

MATERIALS AND METHODS

Research subjects

All 80 GDM patients in our hospital were treated with diet guidance and safe and effective aerobic exercise. The selected cases all met the diagnostic standard of GDM in China. In the 24-28 wk of gestation, 75 g glucose loading was used for the oral glucose tolerance test (OGTT) for pregnant women. OGTT diagnostic thresholds were as follows: The blood glucose values of empty stomach, feeding 1 h, and feeding 2 h of 5.1, 10.0, and 8.5 mmol/L, respectively. Any blood sugar that reached or exceeded the above threshold was diagnosed as GDM. Patients were excluded if pregnancy complications were present or if there was a history of alcohol or tobacco use or other

bad habits prior to pregnancy.

Clusters and interventions

Eighty GDM pregnant women were divided into four groups according to their treatment received: A group (placebo folic acid 400 μg/d), B group (inositol MI 1500 mg, twice a day), C group (inositol DCI 250 mg, twice a day), and D group (inositol MI and inositol DCI 1500 mg/250 mg, twice a day). Each patient routinely used dietary guidance adjustments and did some safe and effective aerobic exercise in addition to receiving placebo or inositol from diagnostic GDM to delivery.

Mensuration of relevant indicators

After GDM diagnosis and 8 wk of treatment respectively measuring the Triglyceride, total cholesterol, fasting plasma glucose (FPG), OGTT postprandial glucose (2 h postprandial blood glucose), fasting insulin (FINS), FPG, and glycosylated hemoglobin levels were determined and the Homeostasis Model Assessment (HOMA)-IR index and HOMA-insulin sensitivity index (HOMA-ISI): HOMA-IR = FINS × FPG /22. 5, HOMA-ISI = 1/ FINS × FPG were calculated before treatment and 8 wk after treatment onset. Adverse maternal and infant outcomes, including hypoglycemia, hydramnion, premature infants, macrosomia, fetal distress, *etc*., were recorded.

Statistical methods

SPSS 22.0 software (Armonk, NY, United States) was used for statistical processing and adopting the analysis of variance. All information is expressed as mean ± standard deviation (x ± s). The logarithm of blood insulin was taken, accounting for the data. $P < 0.05$ was the standard of statistical significance.

RESULTS

Comparison of general material

All patients in the four groups had no previous history or family history of diabetes. There was no statistical difference when comparing age, gestational weeks, and blood pressure during pregnancy. There was no difference in body mass index among the A, B, C, and D groups ($P > 0.05$). Overall, there was no statistical difference in baseline data, and follow-up studies were able to continue (Table 1).

Comparison of metabolic parameters of glycolipid

The level of the 2 h postprandial glucose, glycosylated hemoglobin, fasting insulin level, total cholesterol, and triglyceride in the B, C, and D groups decreased significantly compared with those before treatment, and they were significantly lower than those of the control group (A group), indicating statistical difference ($P < 0.05$). Moreover, compared with the B group, the above index level of the C and D groups decreased more significantly, and the differences were statistically significant ($P < 0.05$) (Table 2).

Comparison of HOMA steady state model evaluation

HOMA model has been widely used to evaluate insulin sensitivity, IR level, and islet B cell function in diabetic patients. The difference between HOMA-IR and HOMA-ISI was determined. There was no significant difference in HOMA-IR and HOMA-ISI among the A, B, C, and D groups before treatment. After treatment, the HOMA-IR of B, C, and D groups was significantly lower than that of the A group ($P < 0.05$), and the HOMA-ISI was significantly higher ($P < 0.05$). Among these, the decrease of HOMA-IR and the increase of HOMA-ISI were more significant in the C and D groups compared with the MI treatment group (B group), and the differences were statistically significant ($P < 0.05$) (Table 3).

Comparison of the occurrence rate of adverse maternal and infant outcomes

Fisher accurate test results showed that the difference of the occurrence rate of adverse maternal and infant outcomes in the four groups was statistically significant. Comparing two by two, the results indicated that compared with the A group, there was a statistically significant difference of the occurrence rate of adverse event in the C and D groups ($P < 0.05$). The details are shown in Table 4 and Table 5.

Table 1 Comparison of each groups of general material

Group	A, *n* = 20	B, *n* = 20	C, *n* = 20	D, *n* = 20	*F*	*P* value
Age in yr	27.61 ± 2.23	27.37 ± 2.16	26.82 ± 2.33	27.14 ± 1.99	0.4766	0.6995
Wk of pregnancy	39.29 ± 1.58	39.45 ± 1.42	38.65 ± 1.53	39.32 ± 1.52	1.122	0.3457
BMI in kg/m^2	21.27 ± 2.63	21.36 ± 2.11	20.35 ± 1.53	20.69 ± 1.95	1.057	0.3727
Systolic pressure in mmHg	115 ± 10	111 ± 8	109 ± 6	110 ± 9	1.969	0.1257
Diastolic pressure in mmHg	71 ± 8	73 ± 8	72 ± 7	73 ± 9	0.2842	0.8366

Data are presented as mean ± standard deviation. A: Control group; B: Myo-inositol treatment group; C: D-chiro-inositol treatment group; D: Myo-inositol + D-chiro-inositol treatment group. BMI: Body mass index.

Table 2 Comparison of blood glucose indicators of patients in each group before treatment and after treatment

Group		A, *n* = 20	B, *n* = 20	C, *n* = 20	D, *n* = 20	*F*	*P* value
Fasting glucose in mmol/L	Before treatment	5.52 ± 1.27	5.26 ± 1.23	5.28 ± 1.23	5.25 ± 1.26	0. 2094	0.8896
	After treatment	4.94 ± 1.14	4.97 ± 1.20	4.88 ± 0.99	4.77 ± 1.11	0.1260	0.9444
Two h postprandial glucose in mmol/L	Before treatment	8.52 ± 2.57	8.61 ± 2.25	8.72 ± 2.38	8.89 ± 2.57	0.2764	0.8423
	After treatment	7.87 ± 1.12	5.13 ± 1.40	4.71 ± 1.24	4.69 ± 1.20	30.12	< 0.0001
Glycosylated hemoglobin, %	Before treatment	5.72 ± 2.63	5.63 ± 2.59	5.78 ± 2.53	5.55 ± 2.27	0.0324	0.9921
	After treatment	5.57 ± 1.77	4.93 ± 1.54	4.58 ± 1.44	4.47 ± 1.20	2.178	0.0475
FINS in mmol/L	Before treatment	12.76 ± 1.85	12.97 ± 2.01	12.63 ± 1.73	12.53 ± 1.75	0.2136	0.8867
	After treatment	12.35 ± 1.76	10.56 ± 1.12	9.45 ± 1.71	9.86 ± 0.96	3.154	0.0296
TC in mmol/L	Before treatment	7.26 ± 0.62	7.42 ± 0.71	7.35 ± 0.83	7.25 ± 0.67	0.2553	0.8573
	After treatment	7.12 ± 0.67	5.18 ± 0.45	5.26 ± 0.52	5.33 ± 0.55	56.96	< 0.0001
TG in mmol/L	Before treatment	3.43 ± 0.52	3.31 ± 0.55	3.52 ± 0.64	3.63 ± 0.55	1.147	0.3356
	After treatment	3.13 ± 0.46	2.48 ± 0.48	2.13 ± 0.50	2.39 ± 0.42	16.65	< 0.0001

Data are presented as mean ± standard deviation. FINS: Fasting insulin; TC: Total cholesterol; TG: Triglyceride.

Table 3 Comparison of homeostasis model assessment steady state model of each group

Group		A, *n* = 20	B, *n* = 20	C, *n* = 20	D, *n* = 20	*F*	*P* value
Before treatment	HOMA-IR	8.47 ± 0.99	8.32 ± 1.01	8.51 ± 0.95	8.44 ± 0.90	0.144	0.9330
	HOMA-ISI	-4.34 ± 0.47	-4.72 ± 0.52	-4.56 ± 0.55	-4.77 ± 0.56	2.708	0.0510
After treatment	HOMA-IR	3.78 ± 0.85	3.12 ± 0.69	2.92 ± 0.53	2.85 ± 0.77	6.942	0.003
	HOMA-ISI	-0.86 ± 0.32	-0.54 ± 0.26	-0.37 ± 0.38	-0.32 ± 0.29	7.844	0.002

Data are presented as mean ± standard deviation. A: Control group; B: Myo-inositol treatment group; C: D-chiro-inositol treatment group; D: Myo-inositol + D-chiro-inositol treatment group; HOMA-IR: Homeostasis model assessment insulin resistance; HOMA-ISI: Homeostasis model assessment insulin sensitivity index.

DISCUSSION

GDM refers to diabetes mellitus that occurs or is discovered during pregnancy, but glucose metabolism is normal or potential glucose tolerance is abnormal before pregnancy[4]. GDM can cause serious harm to pregnant women, fetuses, and newborns. It often causes pregnancy hypertension disease, excessive amniotic fluid, macrosomia, neonatal hypoglycemia, neonatal respiratory distress syndrome, and other maladies. GDM pregnant women and their offspring also have a significantly increased long-

Table 4 The occurrence rate of adverse maternal and infant outcomes in each group

Group	Hypoglycemia	Excessive amniotic fluid	Premature infants	Macrosomia	Fetal distress	Occurrence rate
A	1 (11)	1 (11)	1 (11)	3 (11)	1 (11)	7 (63.6)
B	0	1 (11)	0	1 (11)	0	2 (18.2)
C	0	1 (11)	0	0	0	1 (9.1)
D	0	0	1 (11)	0	0	1 (9.1)

Table 5 Comparison of adverse outcomes in different groups

Group	Occurrence rate	*P* value	[1]*P* value	[2]*P* value	[3]*P* value
A	7 (63.6)	0.045			
B	2 (18.2)		0.135		
C	1 (9.1)		0.047	1.000	
D	1 (9.1)		0.047	1.000	1.000

P: Overall comparison of four groups;
[1]*P*: A groups.
[2]*P*: B groups.
[3]*P*: C groups.

term risk of type 2 diabetes. The World Health Organization listed GDM as an independent type of diabetes in 1979. The incidence of GDM is not consistently reported around the world, but at 1%-5% in our country, it is increasing year by year.

Increased IR[5] during pregnancy is recognized as a major pathophysiological mechanism of GDM. Pregnancy leads to a decline in insulin sensitivity in the body, which is known as IR. Physiological IR[6] can provide more glucose to promote fetal growth and meet the maternal central nervous system's dependence on certain blood glucose levels. However, abnormal IR during pregnancy can lead to abnormal metabolism of blood sugar and blood lipids, which can lead to obesity, GDM, gestational hypertension, and fetal intrauterine growth and development disorders, which are also closely related to the occurrence of long-term metabolic diseases in both mother and child. GDM pregnant women have a weaker biological response to insulin than women with normal glucose tolerance[7]. IR is caused by many factors, mainly the blocking or weakening of insulin signal transduction[8]. Impairments in the insulin receptor, insulin receptor substrate, and phosphatidylinositol 3 kinase function are important mechanisms of IR. One study reported that a pregnancy supplement significantly improved IR in GDM patients[3]. In that study, pregnant women with GDM were given inositol (MI). This group had significantly improved glucose and lipid metabolism and IR compared with the control group, which fully demonstrated the clinical value of inositol in pregnant women with GDM.

DCI is one of the nine isomers of inositol with optical rotation. The DCI pure product is a white powder that is soluble in water. In nature, DCI occurs in the form of compounds in buckwheat, soybeans, and other plants and insects. Ortmeyer *et al*[7] observed the acute effects of chemically synthesized DCI on blood glucose in rats. They treated streptozotocin (STZ) rats with DCI (10 mg/kg, intragastric administration), which reduced blood glucose levels by 30%-40%. In another study, the treatment with DCI (15 mg/kg) reduced the 120 min blood glucose of diabetic rats. Kawa *et al*[8] treated STZ rats with buckwheat extract containing DCI and showed that after receiving 15-20 mg/kg DCI 90 min, blood glucose decreased by 12%-19%. At the same time, it was found that giving DCI to normal rats in advance could reduce the increase in glucose after a glucose load. However, the effect of DCI on insulin resistance in GDM has not been reported[9-11].

In this study, we investigated the effects of different inositol stereoisomers (MI and DCI) on insulin sensitivity in GDM patients[12]. We found that MI or DCI simultaneously improved glycolipid metabolism in the HOMA steady state model, which significantly reduced the HOMA-IR value and improved the HOMA-ISI value[13,14]. These findings show that different inositol stereoisomers can increase insulin sensitivity and reduce IR in patients with GDM, thus having a clear therapeutic

effect on GDM patients[15]. Further study found that compared with the effects in the MI treatment group, the decrease in HOMA-IR, the increase in HOMA-ISI, and the improvement of glucose metabolism in the DCI group were more significant and could lead to better maternal and infant outcomes. That is, DCI had a better curative effect on GDM pregnant women.

Sanchez-Arias *et al*[10] confirmed that the GPI-dependent insulin signaling pathway is impaired in STZ rats. The GPI level in hepatocytes isolated from STZ rats was lower than that in the GPI control group. STZ-induced diabetic rats[16-18] also blocked GPI hydrolysis of the insulin response, thus reducing the release of inositol phosphoglycan in the DCI group. Therefore, there is a defect in the reduction of inositol conversion to a differential isomer in insulin-sensitive tissues under type 2 diabetes mellitus. Moreover, Ostlund *et al*[11] found a certain concentration of DCI in normal human blood and urine, while almost no DCI was detected in the blood of type 2 diabetes patients. The content in their urine was many times higher than that of normal people. These results show that these patients may have metabolic disorders, resulting in overly fast DCI loss and blockage of insulin signaling[19]. Thus, DCI treatment can directly supplement its *in vivo* deficiencies. It can correct this deficiency through GPI-dependent insulin signaling pathways and increase the effectiveness of insulin, reducing blood sugar[20]. The purpose of this study was to explore new treatment methods that can reduce IR in patients with GDM. The specific reasons why these two stereoisomers of inositol affect insulin signaling need to be further explored.

CONCLUSION

In conclusion, treatment of different inositol stereoisomers (inositol MI and inositol DCI) can improve insulin sensitivity and reduce IR in diabetic patients. The inositol DCI was more effective in GDM than inositol MI.

ARTICLE HIGHLIGHTS

Research background

Inositol has nine different isomers, of which the most representative of the human body are myoinositol (MI) and D-chiro-inositol (DCI).

Research motivation

The supplementation of inositol significantly improved insulin resistance in gestational diabetes mellitus (GDM) patients, and the effects of DCI on insulin resistance in GDM have not been reported.

Research objectives

Discuss the impact of different stereoisomers of inositol on insulin sensitivity of GDM patients.

Research methods

Eighty GDM pregnant women were divided into four groups according to their specified treatment regimen.

Research results

There was no statistical difference in the baseline data of each group. The levels of 2 h blood glucose, glycosylated hemoglobin, fasting insulin, total cholesterol, and triglyceride in the B, C, and D groups were significantly lower than those in the control group (A group) after treatment ($P < 0.05$).

Research conclusions

Treatment of different inositol stereoisomers (inositol MI and inositol DCI) can improve insulin sensitivity and reduce insulin resistance in diabetic patients. The inositol DCI was more effective in treating GDM than inositol MI.

Research perspectives

The treatment of diabetes is diversified.

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