

## Original Article

# Efficacy observation of metformin in the treatment of children with type II diabetes mellitus

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**Abstract:** Objective: To observe the effects of metformin on blood glucose levels and islet  $\beta$ -cell function of children with type II diabetes mellitus (T2DM). Methods: Sixty-five children with T2DM were enrolled and divided into a metformin group (Group A,  $n = 30$ ) and an insulin group (Group B,  $n = 35$ ). Outcome measures of children in the two groups were respectively recorded in terms of changes in body mass index (BMI), fasting blood glucose (FBG), 2-hour postprandial blood glucose (2hPBG), glycosylated hemoglobin (HbA1c), fasting insulin (FINS), 2-hour postprandial insulin (2hPINS), homeostasis model assessment of insulin resistance (HOMA-IR) index, insulin secretion (HOMA-IS) index, insulin sensitivity (HOMA-IAI) index, and adverse reactions before and 12 weeks after treatment. Results: Before treatment, there was no statistically significant difference between Group A and Group B in BMI, FBG, 2hPBG, HbA1c, FINS, 2hPINS, the HOMA-IR index, HOMA-IS index or the HOMA-IAI index ( $P > 0.05$ ). After treatment, these indicators in the two groups were significantly different from those before treatment (all  $P < 0.01$ ), but there was no significant difference in these indicators between Group A and Group B (all  $P > 0.05$ ). The incidence of gastrointestinal adverse reactions in Group A was significantly higher than it was in Group B ( $P < 0.05$ ). Conclusion: Metformin and insulin have the same hypoglycemic effect, so both can be used for the treatment of children with T2DM.

**Keywords:** Type II diabetes mellitus, children, metformin, insulin, insulin resistance

## Introduction

The main pathogenesis of type II diabetes mellitus (T2DM), which accounts for 90% of the types of diabetes, is that either the islet  $\beta$  cells cannot secrete insulin or the secreted insulin loses its physiological function. Therefore, T2DM is a kind of hyperglycemia disease caused by relative insulin deficiency, and chronic hyperglycemia for a long time leads to microangiopathy [1-3]. According to studies, the incidence of T2DM in children is 4.5% and gradually increases. Additionally, a high caloric diet for a long time, insufficient physical activity and hyperlipemia increase the risk of the disease [4, 5]. T2DM keeps the long-term hyperglycemia in the renal and fundus microvessels and increases the permeability and fragility of the microvessels [6-8]. Therefore, children with T2DM should be treated immediately.

Currently, T2DM is treated with various drugs which have their own advantages and disadvantages, but diabetes in children is mainly treated with metformin and insulin [9-12]. Metformin is recommended as a first-line hypoglycemic agent because of its stable hypoglycemic and cholesterol-lowering effects [13, 14]. As an analogue of endogenous hormones, insulin reduces blood glucose and lipid concentrations by regulating sugar, fat and protein metabolism, so it can be widely used in the treatment of diabetic patients of all ages [15, 16].

Metformin and insulin were studied in this research project. Insulin is a routine drug for the treatment of diabetes, but metformin has an unclear efficacy for the treatment of diabetes in children. Therefore, the effects of metformin on blood glucose levels and its efficacy for insulin resistance in children with T2DM were observed in order to define the role and signifi-

cance of metformin in children, so as to provide more choices for the treatment of diabetes in children.

## Materials and methods

### General information

Sixty-five children with T2DM admitted to the Department of Pediatrics, The First Affiliated Hospital of Wannan Medical College, Yijishan Hospital from January 2017 to December 2018 were enrolled and randomized into the metformin group (Group A, n = 30) and the insulin group (Group B, n = 35) according to the different drugs.

Inclusion criteria: Children met the *Standards of Medical Care in Diabetes 2018* [17]; children were initially diagnosed and not treated; children aged 12.3±2.4 years old; children had a body weight no more than 50 kg.

Exclusion criteria: Children complicated with severe cardiac, hepatic, and renal impairment; children unwilling to cooperate in the treatment; children with a contraindication to metformin or insulin.

### Therapeutic schemes

Children in Group A were orally administrated with metformin hydrochloride sustained-release tablets (Metformin, China), 0.25 g/time and 3 times/day. Their blood glucose was monitored during the medication. The dosage of metformin was adjusted according to fluctuations in blood glucose levels, and at least 250 mg of metformin was given to the children every day. The hypoglycemic effect of metformin was enhanced with the increased dosage. However, more than 2,000 mg daily did not enhance the hypoglycemic effect; it aggravated the burden of the liver and kidney instead. The children were followed up 12 weeks after treatment.

The children in Group B were subcutaneously injected with insulin (novorapid 30, China), 6 U/time and twice daily. Their blood glucose concentration was monitored during the treatment to prevent hypoglycemia. However, if the children had hypoglycemia, the dosage of insulin was reduced according to the blood glucose concentration. Daily insulin dosage (U) = (fasting blood glucose (FBG, mg/dL)-100)\*10\* body weight (kg)\*0.6/1,000/2. The children were followed up 12 weeks after treatment.

### Outcome measures

Body mass index (BMI) = body weight (kg)/height (m<sup>2</sup>).

FBG and fasting insulin (FINS): After fasting for 8-12 hours, the children were had venous blood extracted the next morning, to centrifuge and collect serum. Their blood glucose concentrations and insulin levels were measured in the Laboratory of The First Affiliated Hospital of Wannan Medical College, Yijishan Hospital. Two-hour postprandial blood glucose (2hPBG) and 2-hour postprandial insulin (2hPINS): Children's blood glucose concentration and insulin level were measured 2 hours after eating, with steps carried out as described above (A Biochemical Analyzer, Beckman Coulter, USA).

Insulin resistance (HOMA-IR) index = FPG\*FINS/22.5.

Insulin secretion (HOMA-IS) index: Rate of insulin secretion per unit time.

Insulin sensitivity (HOMA-IAI) index = 1/(FPG\*FINS).

Adverse reactions: Hypoglycemia: Children with general hypoglycemia were orally administrated glucose, but children with blood glucose concentration <2.8 mmol/L were intravenously injected with 2 mL of 50% glucose liquid.

Allergic reactions: Children with congestion, children who appeared red and swollen, or who felt pain and other symptoms in the whole body were additionally administrated with anti-allergic drugs such as H2 receptor blockers.

Edema: Pitting edema, which was localized redness, swelling, heat and pain caused by the long-term injection of insulin on the skin, could be eliminated using a local hot compress.

Nausea and vomiting: Children with nausea and vomiting were administrated aluminum sulfate and other drugs to protect the gastric mucosa.

### Statistical methods

SPSS 22.0 was used for the statistical analysis. Measurement data were expressed by the mean ± standard deviation ( $\bar{x} \pm sd$ ), and an independent t test was used for comparisons

**Table 1.** General information

	Group A (n = 30)	Group B (n = 35)	t/ $\chi^2$	P
Gender (male/female)	18/12	15/20		
Age (year)	12.3 $\pm$ 2.4	11.5 $\pm$ 3.1	1.899	0.255
BMI (kg/m <sup>2</sup> )	31.35 $\pm$ 2.31	30.39 $\pm$ 3.27	1.345	0.059
Total cholesterol (mmol/L)	9.93 $\pm$ 1.23	10.32 $\pm$ 1.48	1.144	0.257
Low-density lipoprotein ( $\mu$ mol/L)	23.42 $\pm$ 4.38	24.51 $\pm$ 2.29	1.283	0.204
Course of disease (month)	23.45 $\pm$ 4.37	24.59 $\pm$ 5.28	0.939	0.352
Family medical history (case)	6	8	0.078	0.780

Note: BMI, body mass index.

**Table 2.** Comparison of hypoglycemic effect

	Group A (n = 30)	Group B (n = 35)	t	P
BMI before treatment (kg/m <sup>2</sup> )	31.35 $\pm$ 2.31	30.39 $\pm$ 3.27	1.345	0.183
BMI after treatment (kg/m <sup>2</sup> )	24.52 $\pm$ 2.49**	23.49 $\pm$ 3.92##	1.240	0.219
FBG before treatment (mmol/L)	11.32 $\pm$ 2.34	12.37 $\pm$ 2.12	1.898	0.062
FBG after treatment (mmol/L)	4.57 $\pm$ 1.37**	4.61 $\pm$ 1.47##	0.113	0.911
2hPBG before treatment	15.34 $\pm$ 3.49	14.38 $\pm$ 4.38	0.966	0.338
2hPBG after treatment	7.54 $\pm$ 0.37**	7.37 $\pm$ 0.72##	1.167	0.248
HbA1c before treatment	8.92 $\pm$ 2.41	9.37 $\pm$ 1.47	0.923	0.360
HbA1c after treatment	5.28 $\pm$ 1.38**	5.62 $\pm$ 0.92##	1.183	0.241

Note: Compared with before treatment in Group A, \*\*P<0.01; compared with before treatment in Group B, ##P<0.01. BMI, body mass index; FBG, fasting blood glucose; 2hPBG, 2-hour postprandial blood glucose; HbA1c, glycosylated hemoglobin.

between groups, and a paired *t* test for comparison within groups. An  $\chi^2$  test or Fisher's exact test was used for count data. When *P*<0.05, the difference was statistically significant.

## Results

### Comparison of general information

There were no statistically significant differences between Group A and Group B in gender, age, body mass index (BMI), total cholesterol or low-density lipoprotein (*P*>0.05), which indicates that the two groups of children are comparable. See **Table 1**.

### Comparison of hypoglycemic effect

Before treatment, there were no significant differences between Group A and Group B in BMI, FBG, 2hPBG and HbA1c (all *P*>0.05). Twelve weeks after treatment, these indicators in the two groups were significantly lower than those before treatment (*P*<0.01), but there was no

significant difference between Group A and Group B (all *P*>0.05). See in **Table 2** and **Figure 1**.

### Comparison of insulin sensitivity

Before treatment, there were no significant differences between Group A and Group B in FINS, 2hPINS, the HOMA-IR index, HOMA-IS index, or the HOMA-IAI index (all *P*>0.05). Twelve weeks after treatment, these indicators in the two groups were significantly higher than they were before treatment (*P*<0.01), but there was no significant difference between Group A and Group B (all *P*>0.05). See **Table 3** and **Figure 2**.

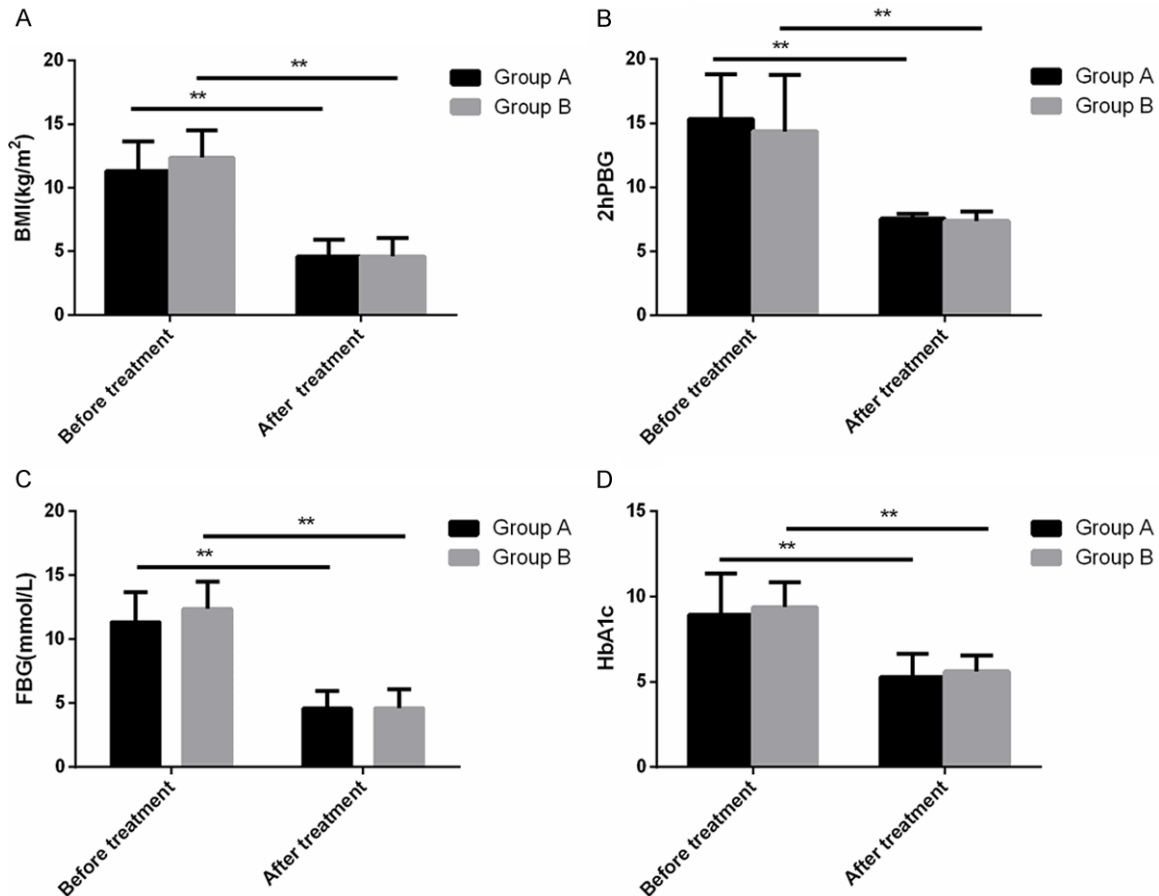
### Comparison of adverse reactions

After treatment, the incidence of gastrointestinal adverse reactions in Group A was significantly higher than it was in Group B (*P*<0.05), but there was no significant difference between the two groups in the incidence of hypoglycemia, allergic reactions, edema and local reactions (all *P*>0.05). See **Table 4**.

## Discussion

T2DM is mainly presented in children with obesity and a high-carbohydrate diet and in children whose parents have diabetes [2, 18]. Children gain weight and even obesity due to the disease. In this study, 65 children with T2DM were found to have a BMI more than 20 kg/m<sup>2</sup>. The loss of insulin function leads to a glycometabolism disorder and lipodystrophy in the body, and the long-term accumulation of sugar and fat causes weight gain. The main pathogenesis of T2DM is that either islet  $\beta$  cells cannot secrete insulin or the secreted insulin cannot reduce blood glucose [19, 20]. Most scholars believe that  $\beta$ -cell dysfunction in patients with T2DM mainly changes in the rapid phase of insulin secretion [21, 22]. Zhao

## Metformin in treatment of children with type II diabetes mellitus



**Figure 1.** Comparison of the hypoglycemic effect. A. BMI changes; B. 2hPBG changes; C. FBG changes; D. HbA1c changes. Compared with before treatment, \*\*P<0.01. BMI, body mass index; FBG, fasting blood glucose; 2hPBG, 2-hour postprandial blood glucose; HbA1c, glycosylated hemoglobin.

**Table 3.** Comparison of insulin sensitivity

	Group A (n = 30)	Group B (n = 35)	t	P
FINS before treatment	2.33±0.22	2.27±0.28	0.949	0.346
FINS after treatment	20.28±2.37**	19.34±2.87##	1.425	0.159
2hPINS before treatment	11.36±2.46	12.37±2.48	1.643	0.105
2hPINS after treatment	18.37±2.54**	19.44±1.38##	1.752	0.085
HOMA-IR before treatment	12.34±2.34	11.29±3.41	1.423	0.159
HOMA-IR after treatment	17.38±3.48**	18.36±2.39##	1.339	0.185
HOMA-IS before treatment	1.27±0.32	1.38±0.33	1.359	0.179
HOMA-IS after treatment	3.89±0.28**	3.87±0.82##	0.127	0.899
HOMA-IAI before treatment	3.28±0.37	3.48±0.73	1.358	0.179
HOMA-IAI after treatment	8.37±1.28**	8.39±1.22##	0.064	0.949

Note: Compared with before treatment in Group A, \*\*P<0.01; compared with before treatment in Group B, ##P<0.01. FINS, fasting insulin; 2hPINS, 2-hour postprandial insulin; HOMA-IR, homeostasis model assessment of insulin resistance; HOMA-IS, insulin secretion; HOMA-IAI, insulin sensitivity.

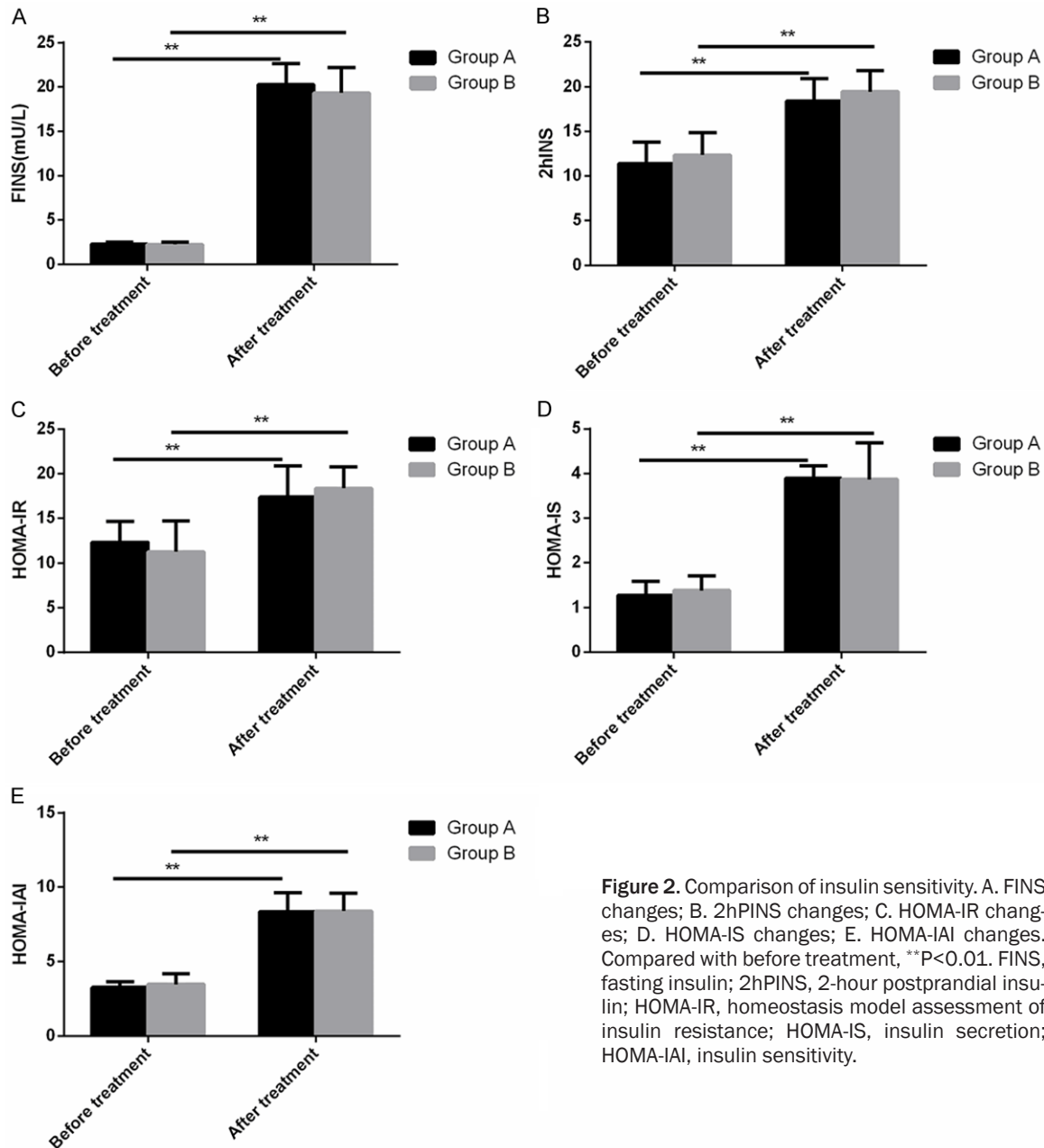
Patients with nausea, vomiting and other reactions can be alleviated by taking aluminum sulfate that can protect the gastric mucosa. Therefore, a timely correction of the first-phase insulin secretion defects and the improvement of insulin  $\beta$  cell function are essential for reducing the increase in postprandial blood glucose, maintaining glucostasis and reducing hyperinsulinemia.

In this study, the blood glucose of children with T2DM reduced to normal levels after a 12-week treatment with metformin and insulin, which indicates that metformin and insulin have the same hypoglycemic effect [22]. Metformin lowers

believes that FBG levels are directly related to the decompensation of insulin  $\beta$  cells [23].

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## Metformin in treatment of children with type II diabetes mellitus



**Figure 2.** Comparison of insulin sensitivity. A. FINS changes; B. 2hPINS changes; C. HOMA-IR changes; D. HOMA-IS changes; E. HOMA-IAI changes. Compared with before treatment, \*\*P<0.01. FINS, fasting insulin; 2hPINS, 2-hour postprandial insulin; HOMA-IR, homeostasis model assessment of insulin resistance; HOMA-IS, insulin secretion; HOMA-IAI, insulin sensitivity.

**Table 4.** Comparison of adverse reactions

	Group A (n = 30)	Group B (n = 35)	$\chi^2$	P
Hypoglycemia (%)	1	5		0.205
Allergic reactions (%)	1	3		0.618
Edema (%)	1	2		1.000
Local reactions (%)	2	7	1.149	0.121
Gastrointestinal adverse (%)	8	1		0.009

blood glucose mainly by promoting glucose absorption and inhibiting glycogen synthesis. It

can also be applied to the treatment of cardiovascular diseases, according to a recent research report. Moreover, metformin has hypoglycemic, cholesterol-lowering and antihypertensive effects, as well as anti-platelet aggregation, and the effect is even greater than the effects of aspirin. According to McIntyre, metformin not only enhances the sensitivity of the surrounding tissue to insulin and increases insulin-mediated glucose utilization, but it also eliminates the toxic effect of



diabetes and restores the damaged rapid phase of insulin secretion [24]. Therefore, metformin, which has been gradually used for first-line treatment, can be applied to the treatment of diabetes and cardiovascular diseases such as myocardial infarction and cerebral infarction.

The results of this study showed that after treatment, the incidence of gastrointestinal adverse reactions in Group A was significantly higher than it was in Group B. Children's livers are not fully developed, so it is easy to accumulate non-catabolic drugs and poisons whose long-term accumulation cause hepatic impairment. Insulin is a recognized drug for reducing blood glucose, but its long-term subcutaneous injection results in local edema and other adverse reactions on the skin [21]. Its damage to the liver is also significantly reduced without the first elimination by the liver. Therefore, insulin is significantly better than other oral hypoglycemic drugs. Metformin also reduces blood glucose, but it usually causes gastrointestinal adverse reactions such as nausea and vomiting and indigestion [22]. Both insulin and metformin can be used in the treatment of children with T2DM, but they should be properly chosen based on their different side effects. In a study by Sleiwah, nausea and vomiting during treatment with metformin are common, but the gastrointestinal discomfort can be significantly reduced by the protection of the gastric mucosa and the inhibition of gastric acid secretions [23]. In this study, nausea, vomiting and other adverse reactions in children were alleviated by taking aluminum sulfate and other drugs protecting the gastric mucosa.

In this study, the outcome measures were less, so the blood glucose levels, insulin and other indicators will be determined later to evaluate the effects of metformin on T2DM. The sample size is small and the children have individual differences, so the sample size will be enlarged to 200 cases in each group in the later stage, so as to further explore the mechanism of metformin in the treatment of children with T2DM. Diabetic microangiopathy is very common, of which the most common type is diabetic renal injury, so the effects of metformin on renal function changes in diabetic patients will be explored in subsequent research. Metformin combined with insulin has a better therapeutic

effect, so using them as a combined treatment for diabetic nephropathy will be investigated later.

In summary, metformin and insulin have the same hypoglycemic effect, so both of them can be used for the treatment of children with T2DM.

### Disclosure of conflict of interest

None.

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