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Original Article

Clinical efficacy of metformin combined with lifestyle intervention for treatment of childhood obesity with hyperinsulinemia

Wei Li[1], Min Li[1], Deqing Kong[2]

[1]*Sanquan College of Xinxiang Medical University, Xinxiang, Henan Province, China;* [2]*Department of Pediatrics, Army Eighty-three Group Army Hospital, Xinxiang, Henan Province, China*

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Abstract: Objective: The aim of the current study was to investigate the clinical effects of metformin combined with lifestyle intervention on childhood obesity with hyperinsulinemia. Methods: Obese children with hyperinsulinemia were randomly divided into the control group (n = 42) and treatment group (n = 42). Patients in the control group were given healthy lifestyle guidance, while those in the treatment group received metformin. Changes in body mass index (BMI) and related physical indexes (including waist circumference (WC), waist-to-hip ratio (WHR), and waist-to-height ratio (WHtR)) were observed before treatment and at 6 months after treatment. Blood glucose and insulin levels at fasting and at 1 hour and 2 hours after glucose loading were compared between the two groups. This study also compared insulin resistance indexes (HOMA-IR) and levels of total cholesterol (TC) and triglycerides (TG) in plasma, before and after treatment. Results: BMI decreased significantly after treatment. Differences were statistically significant, before and after treatment ($P<0.05$). WC, WHR, and WHtR levels in the treatment group were significantly lower than those in the control group after treatment (all $P<0.05$). After treatment, insulin levels at fasting and at 1 hour and 2 hours after glucose loading in the treatment group decreased significantly. Levels in the treatment group decreased more significantly at 2 hours than those in the control group (all $P<0.05$). Blood glucose levels at 1 hour after glucose loading (PG-1 h) and blood glucose levels at 2 hours after glucose loading (PG-2 h) in the treatment group, after treatment, were significantly lower than those before treatment. PG at 2 hours was lower than that in the control group. Differences were statistically significant (all $P<0.05$). HOMA-IR in the treatment group decreased significantly after treatment ($P<0.05$). TC and TG levels of children in the treatment group were lower than those in the control group, after treatment. Differences were statistically significant (both $P<0.05$). Conclusion: Metformin combined with lifestyle intervention can more effectively treat obese children with hyperinsulinemia, improving insulin resistance.

Keywords: Metformin combined with lifestyle intervention, childhood obesity, hyperinsulinemia, clinical effects

Introduction

Childhood obesity has become a major health problem, worldwide. Surveys have shown that prevalence of overweight children is on the rise in all countries. Nearly 43 million preschool children in developing countries are overweight and obese [1, 2]. With the continuous development of economic levels, dietary conditions of children in this country have gradually improved. At the same time, incidence of obesity in children has gradually increased. This may be due to insufficient exercise caused by various reasons, including excessive academic pressure [3]. Hyperinsulinemia is mainly caused by insulin resistance that can stimulate islet β cells to release insulin continuously, promoting lipid deposition in adipose tissue and aggravating obesity [4]. Childhood obesity can further aggravate the performance of insulin resistance, increase insulin resistance *in vivo,* and induce apoptosis of islet β cells. Therefore, hyperinsulinemia treatment and insulin resistance alleviation are important steps in treating childhood obesity.

Lifestyle intervention, drugs, and surgical methods are mainly used for childhood obesity in clinical practice [5, 6]. Lifestyle intervention, as the basis of treatment, can effectively reduce

body fat levels in obese children, improve insulin sensitivity, and reduce the risk of type 2 diabetes, increasing patient exercise and adjusting the diet structure. However, a lack of activity and low compliance, due to various reasons, make lifestyle changes difficult to maintain in children. This may easily lead to the recurrence of obesity. Clinical practice has found that lifestyle intervention combined with drug treatment can often achieve more significant therapeutic effects.

Metformin, a hypoglycemic drug and insulin sensitizer acting on the pancreas, plays an important role in the treatment of childhood obesity. Its application in the treatment of obesity and hyperinsulinemia has gradually received attention [7-9]. Studies have shown that metformin can effectively relieve symptoms in hyperinsulinemia patients [10]. It can also relieve symptoms related to insulin resistance, effectively treating hyperinsulinemia by combining with lifestyle improvements of obese adolescents. Therefore, metformin can be used as an optional drug, combining with lifestyle intervention, for treatment of obesity and hyperinsulinemia in children.

Materials and methods

General data

A total of 84 obese children with hyperinsulinemia, admitted to the Army Eighty-three Group Army Hospital, from January 2017 to June 2017, were selected for the current randomized controlled trial. They were divided into the control group and treatment group. Patients in the control group (n = 42) were treated with diet control and exercise guidance. Those in the treatment group (n = 42) received metformin in addition to the above methods. The control group included 28 males and 14 females, with an average age of (11.99±1.45) years. The treatment group included 26 males and 16 females, with an average age of (12.27±1.64) years. Guardians of all patients provided informed consent. The study was reviewed and approved by the Ethics Committee of Army Eighty-three Group Army Hospital.

Inclusion and exclusion criteria

Inclusion criteria: Children diagnosed with obesity unable to meet the diagnostic criteria for diabetes and BMI before treatment ≥25 kg/m^2 [11]; Fasting insulin (FINS) concentration >15 mU/L and insulin at 2 hours after glucose loading ≥75 mU/L [12]; Fasting plasma glucose (FPG) <7.0 mmol/L and 2-hour postprandial plasma glucose <11.1 mmol/L [11]. Exclusion criteria: Children with severe mental illness; Obesity caused by endocrine diseases, such as adrenal hyperplasia; Patients with liver and kidney dysfunction; Female children diagnosed with polycystic ovary syndrome via B-ultrasounds of the uterus and ovary; Patients that had intolerable side effects after taking metformin; Patients with poor compliance.

Treatment methods

The control group adopted the following diet control and exercise methods: (1) Children were advised to maintain a light diet and healthy recipes were formulated. Caloric intake of children aged 10-14 years was controlled at 1,000-1,200 kcal/d; (2) They were assisted in changing eating habits, including chewing carefully and slowly and avoiding distractions during eating; and (3) More than 30 minutes of exercise every day was prescribed. Patients in the treatment group were given metformin hydrochloride (Suzhou Sinochem Pharmaceutical Industry Co., Ltd.) half an hour before meals. Children aged 8 years and below took metformin at a dose of 0.25 g/time, while those over 8 years received a dose of 0.5 g/time. It was taken three times a day. Treatment lasted for 6 months. Various patient indicators were tested after treatment.

Outcome measures

Waist circumference (WC), waist-to-hip ratio (WHR), waist-to-height ratio (WHtR), and BMI index, as well as blood glucose and insulin levels at fasting, 1 hour, and 2 hours after glucose loading, were recorded. Changes in blood lipid indicators, including total cholesterol and triacylglycerol were also recorded.

Indicator detection

(1) BMI = weight/height^2 (kg/m^2); (2) WHR = WC (cm)/hip circumference (cm); (3) WHtR = WC (cm)/height (cm); (4) Fasting blood glucose and insulin levels: After 8 hours of fasting, 10 mL of venous blood was taken in the morning to detect FPG and insulin indexes; (5) Blood glucose and insulin levels after glucose loading: Anhydrous glucose was taken orally in 4 minutes with 2.5 mL of water per gram. Venous

Table 1. Comparison of physical parameters before and after treatment

	BMI (kg/m^2)	WC (cm)	WHR	WHtR
Before treatment				
Control group	30.76±2.45	90.78±10.97	1.09±0.24	0.61±0.03
Treatment group	31.76±2.46	90.19±8.77	1.07±0.24	0.60±0.03
t	1.871	0.271	0.246	0.815
P	0.065	0.787	0.806	0.417
After treatment				
Control group	27.72±3.00$^{\#\#\#}$	85.93±9.74$^{\#}$	0.92±0.15$^{\#\#\#}$	0.52±0.04$^{\#\#\#}$
Treatment group	26.44±2.18***	81.97±7.32***	0.80±0.09***	0.50±0.03***
t	1.953	2.636	4.498	2.338
P	0.055	0.010	<0.001	0.022

Note: BMI, body mass index; WC, waist circumference; WHR, waist-to-hip ratio; WHtR, waist-to-height ratio. Compared with before treatment in the control group, $^{\#\#\#}$P<0.001, $^{\#}$P<0.05; compared with before treatment in the treatment group, ***P<0.001.

Table 2. Comparison of insulin levels at fasting and at different time points after glucose loading (mU/L)

	FINS	INS-1 h	INS-2 h
Before treatment			
Control group	30.46±19.03	180.00±66.30	183.29±80.87
Treatment group	31.78±22.15	194.53±64.30	206.97±74.07
t	0.292	1.020	1.399
P	0.771	0.311	0.165
After treatment			
Control group	24.78±13.51	165.38±76.68	172.75±76.51
Treatment group	19.85±12.04*	132.33±85.18***	136.73±68.59***
t	1.765	1.868	2.272
P	0.081	0.065	0.026

Note: FINS, fasting insulin; INS-1 h, insulin at 1 h after glucose loading; INS-2 h, insulin at 2 h after glucose loading. Compared with before treatment in the treatment group, *P<0.05, ***P<0.001.

blood was collected for examination at 1 hours and 2 hours. Blood glucose was measured using the oxidase method. Insulin concentrations were measured via radioimmunoassay. Eating and strenuous exercising before the end of blood collection were avoided; (6) Determination of plasma total cholesterol and triacylglycerol: 10 mL of fasting venous blood was taken in the morning and measured using a full-automatic biochemical analyzer; and (7) Insulin resistance index was calculated using the HOMA formula: HOMA-IR = FPG (mmol/L) * FINS (mU/L)/22.5 [13].

Statistical methods

Data were statistically analyzed using SPSS 22.0 software. Measurement data are expressed as mean ± standard deviation (Mean ± SD), measured by t-tests, and expressed as t. Count data are expressed as cases or percentages, measured by χ^2 tests, and expressed by χ^2. All data conformed to normal distribution after Shapiro-Wilk W testing. P< 0.05 indicates that differences are statistically significant.

Results

Comparison of physical parameters before and after treatment

There were no significant differences in gender, age, and other general data between the two groups, suggesting that they were comparable. There were no significant differences in BMI between the two groups before treatment. However, after treatment, BMI was significantly lower than that before treatment. There were no significant differences between the groups. After treatment, WC, WHR, and WHtR levels decreased significantly, compared to those before treatment. Decreased levels in the treatment group were more significant than those in the control group. Differences were statistically significant (all P<0.05). See **Table 1**.

Comparison of insulin levels at fasting and different time points after glucose loading

There were no significant differences in FINS, insulin at 1 hour after glucose loading (INS-1 h), and insulin at 2 hours after glucose loading (INS-2 h) between the two groups before treatment. FINS, INS-1 h, and INS-2 h levels in the treatment group, after treatment, were significantly lower than those before treatment. Differences were statistically significant (all P< 0.05). In contrast, levels in the control group were not significantly lower than those before treatment. See **Table 2**, **Figure 1**.

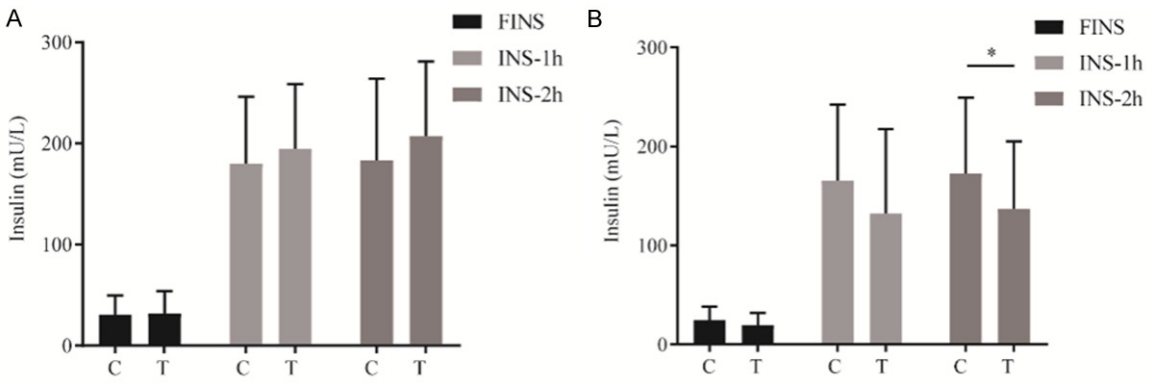

Figure 1. Comparison of insulin levels at fasting and at different time points after glucose loading. A: Before treatment; B: After treatment. FINS, fasting insulin; INS-1 h, insulin at 1 h after glucose loading; INS-2 h, insulin at 2 h after glucose loading. C: control group; T: treatment group. *P<0.05.

Table 3. Comparison of changes in blood glucose levels at fasting and after glucose loading (mmol/L)

	FPG	PG-1 h	PG-2 h
Before treatment			
Control group	5.44±2.64	7.39±1.05	7.34±0.97
Treatment group	4.72±2.36	7.55±1.14	7.31±0.82
t	1.325	0.666	0.151
P	0.189	0.507	0.880
After treatment			
Control group	4.75±2.04	7.27±1.31	7.02±0.23#
Treatment group	4.61±2.33	6.95±1.11*	6.50±0.25***
t	0.273	1.210	9.910
P	0.785	0.507	<0.001

Note: FPG, fasting plasma glucose; PG-1 h, blood glucose at 1 h after glucose loading; PG-2 h, blood glucose at 2 h after glucose loading. Compared with before treatment in the control group, #P<0.05; compared with before treatment in the treatment group, *P<0.05, ***P<0.001.

Comparison of changes in blood glucose levels at fasting and after glucose loading

There were no significant differences in FPG, blood glucose at 1 hour after glucose loading (PG-1 h), and blood glucose at 2 hours after glucose loading (PG-2 h) between the two groups before treatment. PG-1 h and PG-2 h levels in the treatment group decreased significantly after treatment (all P<0.05). PG-2 h levels in the control group, after treatment, were significantly lower than those before treatment. Levels in the treatment group were significantly lower than those in the control group, with statistically significant differences (P<0.05). See **Table 3**, **Figure 2**.

Analysis of insulin resistance and blood lipid indexes

Levels of insulin resistance (HOMA-IR) in the treatment group, after treatment, were significantly lower than those before treatment. Differences were statistically significant. After treatment, TC levels in the two groups and TG levels in the treatment group decreased significantly. Levels in the treatment group were significantly lower than those in the control group. Differences were statistically significant (all P<0.05). See **Table 4**.

Discussion

With continuous improvement in living standards, changes in dietary structure, and an apparent decrease in physical activity, incidence of childhood obesity has gradually increased [14]. Obesity increases risks of insulin resistance and is the main cause of insulin resistance in children and adults [15]. One study suggested that hyperinsulinemia is one of the clinical manifestations of insulin resistance. It is not only an important factor in the development of type 2 diabetes, but also causes different degrees of damage to the health of children [16]. Metformin, a biguanide hypoglycemic drug, acts on the process of glucose metabolism, inhibits the regeneration of hepatic glycogen, and reduces the output of hepatic glucose and intake of glucose in intestinal and peripheral tissues. Moreover, it can promote the anaerobic degradation of glucose, effectively reduce peripheral insulin resistance,

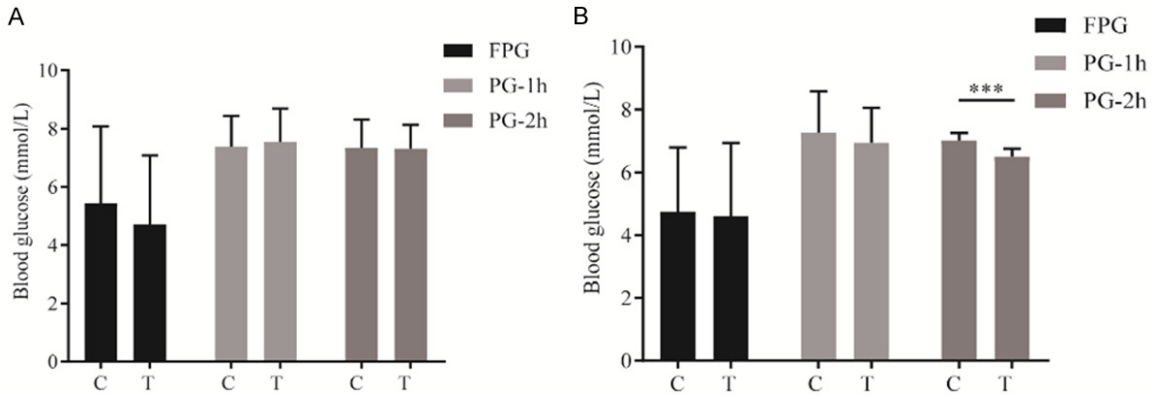

Figure 2. Comparison of changes in blood glucose levels at fasting and after glucose loading. A: Before treatment; B: After treatment. FPG, fasting plasma glucose; PG-1 h, blood glucose at 1 h after glucose loading; PG-2 h, blood glucose at 2 h after glucose loading. C: control group; T: treatment group. ***P<0.001.

Table 4. Comparison of HOMA-IR, TC, and TG between the two groups

	HOMA-IR	TC (mmol/L)	TG (mmol/L)
Before treatment			
Control group	7.15±6.03	3.96±0.23	1.57±0.32
Treatment group	6.80±5.99	3.94±0.22	1.54±0.31
t	0.268	0.489	0.379
P	0.790	0.626	0.706
After treatment			
Control group	5.25±4.08	3.43±0.32###	1.52±0.28
Treatment group	4.06±3.22*	3.2±0.32***	1.22±0.29***
t	1.495	2.578	4.861
P	0.139	0.012	<0.001

Note: HOMA-IR, insulin resistance index; TC, total cholesterol; TG, triglyceride. Compared with before treatment in the control group, ###P<0.001; compared with before treatment in the treatment group, *P<0.05, ***P<0.001.

and further protect islet β cells [17]. There have been reports of the use of metformin combined with lifestyle intervention on children with clinical characteristics of insulin resistance, showing very good efficacy. However, results concerning obese children with hyperinsulinemia are not uniform [18].

Freemark randomly divided adolescent obese patients receiving no lifestyle intervention into two groups [18]. Results showed that the BMI of patients taking metformin alone decreased by an average of 0.5 kg/m^2, while that in the placebo arm increased by 0.9 kg/m^2. Differences were statistically significant. Some studies have found that metformin combined with lifestyle treatment can significantly reduce the body weight of patients [19]. In the current study, using metformin combined with lifestyle treatment, BMI decreased significantly after 6 months of treatment, compared with that before treatment. These results are consistent with previous results. However, there were no significant differences between the treatment group and control group, indicating that both treatments could reduce body weight to some extent.

Freemark found that fasting insulin levels after metformin treatment were significantly lower than those before treatment. Results showed no significant changes in the control group, before and after treatment, suggesting that metformin reduces fasting insulin levels to a certain extent [18]. Another study showed that metformin can lower fasting insulin levels more effectively than lifestyle intervention alone. A combination of the two methods can achieve more significant effects [20]. The current study found that metformin combined with lifestyle intervention can significantly reduce fasting insulin levels. The decline was greater than that of lifestyle intervention alone. Differences were statistically significant. At the same time, the current study compared insulin levels at 1 hour and 2 hours after glucose loading. Results showed that FINS, INS-1 h, and INS-2 h levels in the treatment group were significantly reduced. INS-2 h levels in the treatment group decreased more significantly than those in the control group, with statistically significant dif-

ferences. The treatment group showed more significant effects concerning reduced insulin levels after glucose loading.

Glucose tolerance is the tolerance of human body to glucose. Impaired glucose tolerance (IGT) is an important stage in the occurrence and development of type 2 diabetes. One study showed that metformin can effectively inhibit the progression of IGT to type 2 diabetes [21]. The current study found that PG-1 h and PG-2 h in the treatment group and PG-2 h in the control group decreased significantly after treatment. In addition, the decrease of blood glucose levels was more significant in the treatment group at 2 hours after glucose loading. This may be related to the decrease of blood glucose of IGT at 2 hours.

Insulin resistance refers to the abnormal function of insulin, leading to blocked glucose utilization and increased compensatory insulin *in vivo*. This induces hyperinsulinemia to promote the balance of glucose utilization *in vivo*. One study showed that metformin can effectively improve insulin resistance, thereby treating hyperinsulinemia [22]. The current study found that insulin resistance levels in the treatment group decreased more significantly, after treatment, compared with those before treatment. Differences were statistically significant.

Hypercholesterolemia affects the secretory function of islet β cells and causes disorders of glucose metabolism *in vivo*. It can also cause insulin resistance, lead to insulin secretion disorder, and accelerate apoptosis of islet β cells. Some studies have shown that metformin regulates metabolic disorders of blood lipids *in vivo,* playing an important role in reducing TC, TG, and low-density lipoprotein [23]. The current study found that TC and TG levels in the two groups were significantly lower than those before treatment. Moreover, the decline in the treatment group was significantly greater than that in the control group, indicating that metformin combined with lifestyle changes can effectively regulate blood lipid metabolism *in vivo*.

In the current study, metformin combined with lifestyle intervention for treatment of childhood obesity and hyperinsulinemia was examined. However, there were still some limitations. For example, the small sample size might have led to biased results. Thus, sample sizes should be increased in future studies. In addition, this study did not analyze the adverse reactions of children, failing to effectively assess safety levels of metformin drugs. Therefore, related studies concerning drug safety should be carried out.

In summary, metformin combined with lifestyle intervention produces positive effects. It helps control body weight, improves insulin resistance, reduces blood lipid levels, and prevents glucose metabolic disorders in children. Therefore, this method is worthy of promotion in clinical treatment.

Disclosure of conflict of interest

None.

Address correspondence to: Deqing Kong, Department of Pediatrics, Army Eighty-three Group Army Hospital, No.210 Wenhua Road, Hongqi District, Xinxiang 453000, Henan Province, China. Tel: +86-0373-5193603; Fax: +86-0373-5193603; E-mail: kongdeqing17er@163.com

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