Research Paper

Effects of Metformin Treatment on Metabolic Indices and Serum Lipid-Derived Sex Hormones in Obese Children with Hyperinsulinemia

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The main objective of this study is to investigate the effects of metformin on metabolic indices and serum adiponectin, resistin and leptin levels in obese children with hyperinsulinemia. 90 obese children with hyperinsulinemia admitted to Shenzhen Maternity and Child Healthcare Hospital from March 2021 to March 2023 were divided into two groups, in which the control group was given exercise and diet control, while the research group was given metformin treatment based on the control group. The metabolic indices, serum adiponectin, resistin and leptin levels of the two groups were compared. The effective rate of the study group (95.56 %) was significantly higher than that of the control group (80.00 %). After treatment, the fasting blood glucose, fasting insulin, insulin resistance index (i.e., homeostatic model assessment for insulin resistance) and body mass index in the study group were significantly lower than those in the control group. After treatment, resistin and leptin levels in the study group decreased significantly compared with the control group, and adiponectin increased significantly. The incidence of adverse reactions in the study group was significantly lower than that in the control group. Metformin treatment for obese children with hyperinsulinemia can stabilize their metabolic function, improve serum lipid-derived sex hormones, improve the treatment efficiency and reduce the incidence of adverse reactions, which has high practical value.

Key words: Hyperinsulinemia, obesity, metformin, metabolic index, serum adiponectin

Studies have shown that insulin resistance is directly related to obesity, abnormal metabolism and cardiovascular risk. If not treated in time, it will lead to the development of early atherosclerosis and type 2 diabetes[1]. Although many obese children with hyperinsulinemia have normal blood sugar range, they need to produce high levels of insulin to maintain the blood sugar in normal levels. Insulin resistance will be accompanied by hyperinsulinemia, which can deposit fat in adipose tissue leading to the aggravation of obesity symptoms[2]. Therefore, the important link to treat obese children with hyperinsulinemia is to treat hyperinsulinemia and reduce insulin resistance. Metformin has been approved by the United States (US) Food and Drug Administration and it is a therapeutic drug for patients with type 2 diabetes who are ≤10 y old. At this stage, it is commonly used in the treatment of childhood obesity[3]. Metformin is a non-pancreatic hypoglycemic drug, which has a good effect on patients with hyperglycemia. However, despite the research development in the therapeutic drug effects, a complete picture of the pharmacological actions of metformin, the most widely used hypoglycemic agent, has yet to be realized[4]. Metformin might exert its primary antidiabetic effect by inhibiting gluconeogenesis in the liver[5]. According to the consensus statement of insulin resistance of Children Endocrine Association, the primary plan for obese children with hyperinsulinemia is lifestyle intervention, which guides the application of metformin in selected patients[6]. At present, there is no report on the changes of fasting blood glucose and insulin levels in obese children with hyperinsulinemia at different time points after taking metformin. Therefore, this study selected obese children with hyperinsulinemia

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as the observation objects and analyzed the effects of metformin treatment on metabolic indices and serum adiponectin, resistin and leptin levels.

MATERIALS AND METHODS

General information:

90 obese children with hyperinsulinemia admitted to Shenzhen Maternity and Child Healthcare Hospital from March 2021 to March 2023 were selected for research and divided into two groups with 45 children in each group. There were 23 males and 22 females in the control group, aged 10-14 y, with an average of (12.73±1.67) y. There were 24 males and 21 females in the study group, aged 10-15 y with an average of (13.12±1.35) y. There was no statistical difference in general data between the two groups ($p>0.05$).

Inclusion criteria:

All the children were in accordance with the diagnostic criteria formulated by the Working Group on Obesity in China, 2016[7]; fasting insulin ≥15 mIU/l, Fasting Plasma Glucose (FPG) <7.0 mmol/l and Body Mass Index (BMI) ≥25 kg/m^2.

Exclusion criteria:

Patients with polycystic ovary syndrome; those with congenital diseases; patients with liver, kidney, lung and other organ dysfunction; patients with endocrine diseases such as adrenal cortical hyperplasia[8] and patients who withdrawn from this research for various reasons were excluded from the study.

Research method:

Exercise and diet control were adopted in the control group and obese children with hyperinsulinemia were advised to pay attention to diet and calorie intake. Suitable food such as oat flour and corn flour containing various trace elements, vitamins and dietary fiber are helpful to control blood sugar. Further bean products which are rich in protein, polyunsaturated fatty acids, inorganic salts and vitamins can reduce blood fat. Spinach, celery, bitter gourd, etc., are all vegetables rich in water-soluble vitamins. Similarly cellulose can promote the decrease of blood sugar after meals. Patients are advised to pay attention to reduce the consumption of foods that will increase blood sugar levels, including all kinds of sugar, chocolate, cakes, juice, jam, desserts and ice creams, etc. Common foods that promote blood lipid increase include animal viscera, fat, fried food and food containing cream, etc. It should be pointed out that high-fat foods and high-sugar drinks should be restricted, the intake of beans and fiber foods should be increased, and sufficient nutrients should be supplied to meet the growth and development needs of children (1000-1200 kcal per day for children aged 10-14 y). Exercise instruction which includes instruct children to change their current static lifestyle and ensure that the aerobic endurance exercise time range is 0.5-1 h every day, and that the aerobic exercise time is moderate and they can carry out swimming, cycling, ball games, running, striding and skipping rope, etc. After each exercise, the heart rate should exceed 120 beats/min and continue step by step.

The study group adopted metformin (Manufacturer: Shanxi Good Doctor Pharmaceutical Co., Ltd.; Production batch number: National Medicine Zhunzi H14021914). Metformin is taken with meals, 1 tablet once, 2-3 times/day. For children with gastrointestinal symptoms such as diarrhea, the dosage is appropriately reduced and after 7 d of continuous treatment, the dosage is increased to the standard dosage, and continuous treatment is carried out for 3 mo.

Observation indicators:

Evaluation of treatment effect: According to the symptoms of obese children with hyperinsulinemia, the treatment effect of the two groups was judged. Remarkable effect means the children basically disappeared clinical symptoms and returned to normal body indicators. Effective means the child obviously relieves clinical symptoms and improves various body indexes. Ineffective means the clinical symptoms of the child have not improved and may be aggravated.

Effective rate of treatment=(Remarkable effect+effective)/Number of cases×100 %.

Metabolic index evaluation: It is evaluated by measuring and calculating the BMI of the two groups of children before and after treatment. All the children were kept in a fasting state for 8-10 h and venous blood samples were taken through elbow vein in the morning. The fasting blood glucose and fasting insulin of the two groups of children were detected by automatic biochemical analyzer before and after treatment, and the insulin resistance index

was Homeostatic Model Assessment for Insulin Resistance (HOMA-IR)[9] was calculated by steady-state simulation evaluation method before and after treatment.

HOMA-IR=Fasting insulin×fasting blood glucose/22.5

Evaluation of serum lipid-derived sex hormones: All children were kept on an empty stomach for 8-10 h and venous blood samples were taken through elbow vein in the morning. Before and after treatment, resistin and adiponectin were detected by Enzyme-Linked Immunosorbent Assay (ELISA). Before and after treatment, leptin in two groups was detected by radioimmunoassay[10].

Evaluation of adverse reactions: The number of patients with adverse reactions in two groups of children was recorded in detail and the evaluation indicators included abdominal discomfort, diarrhea and subcutaneous lipodystrophy. The lower the incidence of adverse reactions, then the better the clinical effect of metformin.

Statistical analysis:

Statistical Package for the Social Sciences (SPSS) 19.0 version was used to analyze the data. The measured data was represented by mean±Standard Deviation (SD), the count data was represented by n (%) and the Chi square (χ^2) test was performed, and $p<0.05$ indicated that the difference was statistically significant.

RESULTS AND DISCUSSION

According to the therapeutic effects of the two groups, the effective rate of the study group (95.56 %) was significantly higher than that of the control group (80.00 %), with statistical significance between the two groups ($p<0.05$), as shown in Table 1.

There was no significant difference in metabolic indices between the two groups before treatment ($p>0.05$). After treatment, fasting blood glucose, fasting insulin, HOMA-IR and BMI in the study group were significantly lower than those in the control group, with statistical significance ($p<0.05$), as shown in Table 2.

Before treatment, there was no significant difference in serum lipid-derived sex hormones between the two groups ($p>0.05$). After treatment, resistin and leptin in the study group decreased significantly compared with the control group, and adiponectin increased significantly with statistical significance ($p<0.05$), as shown in Table 3.

The incidence of adverse reactions in the study group (4.44 %) was significantly lower than that in the control group (17.78 %), which was statistically significant ($p<0.05$), as shown in Table 4.

TABLE 1: COMPARISON OF THERAPEUTIC EFFECTS BETWEEN TWO GROUPS OF OBESE CHILDREN WITH HYPERINSULINEMIA, n (%)

Group	n	Remarkable effect	Effective	Ineffective	Effective rate of treatment (%)
Research	45	26 (57.78)	17 (37.78)	2 (4.44)	43 (95.56)
Control	45	17 (37.78)	19 (42.22)	9 (20.00)	36 (80.00)
χ^2					5.075
p					24

TABLE 2: COMPARISON OF METABOLIC INDICES BETWEEN TWO GROUPS OF OBESE CHILDREN WITH HYPERINSULINEMIA (MEAN±SD)

Metabolic indices	Treatment	Groups (n=45)		t	p
		Research	Control		
Fasting blood glucose (mmol/l)	Before	5.38±1.26	5.79±1.52	1.393	161
	After	4.23±1.35	5.03±1.67	2.499	0.014
Fasting insulin (mU/l)	Before	35.62±3.57	35.18±3.42	0.597	0.552
	After	14.63±2.79	21.06±2.48	11.555	0
HOMA-IR	Before	5.30±1.34	5.69±1.22	1.444	0.152
	After	3.41±0.75	4.67±0.86	7.407	0
BMI	Before	30.14±2.39	30.73±2.45	1.156	0.251
	After	23.12±2.42	28.40±2.38	10.435	0

TABLE 3: COMPARISON OF SERUM LIPID-DERIVED SEX HORMONES BETWEEN TWO GROUPS OF OBESE CHILDREN WITH HYPERINSULINEMIA (MEAN±SD)

Group (n=45)	Resistin (μg/l)		Adiponectin (mg/l)		Leptin (μg/l)	
	Before treatment	After treatment	Before treatment	After treatment	Before treatment	After treatment
Research	21.42±2.63	16.50±2.35	7.32±1.35	8.93±1.73	26.43±2.30	19.31±2.61
Control	21.68±2.54	19.42±2.49	7.21±1.43	7.65±1.68	26.57±2.41	22.17±2.53
t	0.477	5.721	0.375	3.561	0.282	5.278
p	0.635	0	0.708	0.001	0.779	0

TABLE 4: COMPARISON OF ADVERSE REACTIONS BETWEEN THE TWO GROUPS OF OBESE CHILDREN WITH HYPERINSULINEMIA, n (%)

Group (n=45)	Abdominal discomfort	Diarrhea	Subcutaneous lipodystrophy	Incidence rate of adverse reactions (%)
Research	1 (2.22)	1 (2.22)	0 (0.00)	2 (4.44)
Control	3 (6.67)	3 (6.67)	2 (4.44)	8 (17.78)
χ^2				4.05
p				0.044

Obesity is a manifestation of abnormal glucose and lipid metabolism, in which insulin, leptin, resistin and lipid-derived sex hormones all play a key role, and will also participate in the occurrence of diseases such as hypertension and type 2 diabetes[11]. Hyperinsulinemia is a common phenomenon in children's obesity. Under normal circumstances, hyperinsulinemia can maintain a stable blood sugar level in an fasting state, but after intake of food, a large amount of insulin is needed to maintain a stable blood sugar level, thereby increasing the insulin level of children[12]. Hyperinsulinemia is a transitional stage of type 2 diabetes[13]. Generally speaking, the increase of insulin secretion is caused by insulin resistance, but some scholars also believe that the increase of insulin occurs far before occurrence of insulin resistance and plays a key role in the early onset of obesity[14]. Therefore, for children, controlling hyperinsulinemia is the key link to treat obese children and prevent diabetes. Clinically, it is generally treated by diet and exercise. Although this method has a certain clinical effect, the effect is not obvious and it lasts for a long time, and the children's cooperation is poor[15].

Metformin is a hypoglycemic drug that does not affect the function of pancreas and it belongs to insulin sensitizer that does not play a role in pancreas. Metformin acts in children's liver, which can increase the sensitivity of children's peripheral tissues to insulin, reduce the absorption of blood sugar in children and inhibit gluconeogenesis in children[16]. In addition, metformin can well inhibit the oxidation of fatty acids and reduce the blood sugar concentration of children[17,18]. Because metformin will dissolve quickly in children's stomachs reaches high concentration in a short time, which will stimulate children's gastric mucosa and cause gastrointestinal side effects[19,20]. Therefore, in the course of treatment, the following measures can be taken to reduce the side effects of the drug on children by gradually increasing the dosage from less to more; try not to take it on an empty stomach; according to the children's condition, adjust the type of drug regimen timely; when taking diuretics, anti-inflammatory agents and steroids, metformin should be avoided as much as possible[21,22].

The results of this study show that metformin treatment can improve the treatment efficiency compared with exercise and diet control ($p<0.05$). It can be seen that metformin can exert good efficacy and further improve the therapeutic effect. The results of this study showed that after treatment, the fasting blood glucose, fasting insulin, HOMA-IR, BMI, resistin, leptin and adiponectin levels in the study group were significantly lower than those in the control group ($p<0.05$). It can be seen that the physiological dose of adiponectin can promote the consumption of energy and the oxidation of fatty acids in muscle cells, regulate tyrosine phosphorylation, reduce the level of intracellular triglycerides and improve insulin sensitivity. Leptin can promote the consumption of body energy and suppress appetite in children. After metformin treatment, it effectively reduces insulin resistance, maintain stable blood sugar level and serum lipid-derived sex hormone levels. Because metformin can improve the hepatic

resistance of insulin to inhibit gluconeogenesis, so that endogenous hepatic glucose production can be reduced, inhibit lipolysis, reduce blood free fatty acids and triglyceride concentrations. At the same time, it improves the sensitivity of peripheral tissues (skeletal muscle, adipose tissue weaving) to insulin which significantly increases glucose uptake and utilization of glucose. The results of this study also showed that the incidence of adverse reactions in the study group was significantly lower than that in the control group ($p<0.05$). It can be seen that although long-term use of metformin may lead to adverse drug use, combined exercise and diet control with good measures can reduce the possibility of adverse reactions and ensure safe treatment. Of course, the sample size of this study is relatively small, the observation time is only 3 mo, and a multicenter large-sample long-term follow-up is needed to further demonstrate the efficacy and safety of metformin for the treatment of hyperinsulinemia in obese children.

In summary, metformin treatment for obese children with hyperinsulinemia can stabilize their metabolic function, improve serum lipid-derived sex hormones, improve the treatment efficiency and reduce the incidence of adverse reactions, which has high practical value.

Ethical approval:

This study was verified by the Ethics Committee of Shenzhen Maternity and Child Healthcare Hospital and all the participants agreed to conduct this study.

Conflict of interests:

The authors declared no conflict of interests.

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