Glucocorticoid-Induced Insulin Resistance and Its Intervention in Children with Refractory Nephrotic Syndrome

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Abstract
The side effects of glucocorticoid-induced insulin resistance (IR) have drawn increasing attention, but the information is scarce regarding treatment of glucocorticoid-induced insulin resistance in children. The study was conducted in children who received prolonged high-dose glucocorticoid for refractory nephrotic syndrome. The Body Mass Index (BMI) was monitored and metabolic parameters were determined. Homeostatic model assessment for insulin resistance index (HOMA-IR) was used for assessing glucocorticoid-induced IR. There were 41 obese children with HOMA-IR>3.5. The HOMA-IR showed a positive correlation with prednisone dosage, LDL-C, age and BMI (P<0.01), respectively. Multiple linear regression analysis showed that prednisone dosage, LDL-C, age and BMI correlated independently with HOMA-IR (P<0.05). Twenty-one children received metformin therapy as treated group and 20 patients received placebo as control group. After 3 months of treatment, the BMI and IR were significantly improved and the BMI and HOMA-IR were also significantly reduced compared to the control group. No significant toxicity from metformin was seen. Metformin is safe and effective for treatment of glucocorticoid-induced obesity and IR.

Keywords: Metformin; Obesity; Insulin resistance; Glucocorticoids; Children

Introduction
Glucocorticoid-induced insulin resistance and its intervention in children with refractory nephrotic syndrome

Nephrotic Syndrome (NS) is a common type of kidney disease seen in children and glucocorticoids are commonly used in its treatment. However, prolonged high-dose glucocorticoid therapy has many common and potentially serious side effects. With the prevalence of insulin resistance in obese children, the side effects like glucocorticoid-induced insulin resistance (IR) have drawn increasing attention, but the information is scarce regarding treatment of glucocorticoid-induced insulin resistance in children with NS [1]. In this study, we monitored the side effects of glucocorticoid-induced obesity and IR and observed the efficacy of metformin to reduce Body Mass Index (BMI), hyperinsulinemia, hyperglycemia and Homeostatic model assessment for insulin resistance index (HOMA-IR) in children who received prolonged high-dose glucocorticoid therapy for refractory NS.

Materials and Methods
Subjects
We studied 41 children with refractory NS at our departments from January 2013 and December 2017. The study included 27 (66%) boys and 14 (34%) girls. The mean age was 10.2 ± 2.2 years (6-14 years) and the duration of illness was 5.4 ± 2.1 years. The inclusion criteria was the children with refractory NS who received prolonged high-dose glucocorticoid (prednisone cumulative amount within 3 months >100 mg/kg) and have glucocorticoid-induced obesity and insulin resistance (HOMA-IR score >3.5). We excluded those who received cyclosporine therapy for its effect on glucose homeostasis and insulin resistance, those who had NS secondary to other systemic diseases and those who were poor compliant to the study regimens [2]. Among 41 children with refractory NS, 36 children showed frequently relapsing or steroid-dependent NS and 5 children showed steroid-resistant idiopathic NS. Renal biopsy was performed in 14 children and showed minimal change disease (MCD) in 11 children, focal segmental glomerulosclerosis (FSGS) in 3 children. There were 38 patients that received immunosuppressive therapy (18 patients received cyclophosphamide, 20 patients received mycophenolate mofetil). All the patients recovered (urine albumin dipstick of 0 for at least two weeks and normalization of serum albumin to at least 3.5 g/dl). All the patients had a normal liver function, a normal blood count, a normal blood pressure and a normal endogenous creatinine clearance.

Methods
The initial treatment for new-onset NS included 60 mg/m2/day or 2 mg/kg/day (standard weight calculated by height) of prednisone for 4 to 6 weeks, followed by 60 mg/m2 or 2 mg/kg every other day for 4 to 8 weeks and then a gradual tapering of the dosage until it was discontinued [3]. The dose of glucocorticoid used in this study was constant and equal in all patients. If there were repeated relapses or steroid-dependence or steroid-resistance occurred, cyclophosphamide or mycophenolate mofetil was used. During the treatment period, the BMI and metabolic parameters were monitored monthly. The concentrations of fasting insulin (FINS) and C-peptide (CP) were determined by radioimmunoassay, the concentrations of serum Hemoglobin A1c (HbA1c) were determined by High Performance Liquid Chromatography and the levels of fasting glucose (FBG), cholesterol and triglyceride were measured with an automatic measuring analyzer. HOMA-IR was calculated from fasting insulin and glucose (insulin X glucose in mmol/l/22.5) for estimating insulin resistance [4-6]. Since glucocorticoid induced obesity and insulin resistance may be improved by the reduction of glucocorticoid dosage, we selected the patients who received prolonged high-dose glucocorticoid (prednisone
cumulative amount within 3 months >100 mg/kg) during which we reduced the glucocorticoid dosage for at least the last month. All the 41 patients were obese and had HOMA-IR score >3.5, 21 patients received metformin therapy as treated group and 20 patients received placebo as control group [7]. There was no difference in the two groups in age, sex, duration of the disease and glucocorticoid dosage used. The metformin hydrochloride dosage were as follows: 8-10 years old, 2-3 times per day; 0.25-0.5 g/dose; 11-14 years old, 0.5 g/dose 2-3 times per day (0.25 g initially and increase to 0.5 g after 1 week). The blood count, blood lactate concentration, FBG, liver function, renal function, height and body weight were measured every 4 weeks. The FINS, CP, HbA1c, cholesterol, triglyceride and HOMA-IR were recorded before and after 3 months of metformin therapy (Table 1).

**Statistical analysis**

All data were presented as the mean ± standard deviation. Statistical analysis was performed by the paired t test, t test, one-factor ANOVA and Fisher's exact test using the Statistical Package for Social Sciences software package for Windows (version 17.0, SPSS Inc.). Interrelationships between variables were analyzed by Pearson correlation analysis. Multiple linear regression analysis was used to determine independent predictors of HOMA-IR. For all statistical calculations p<0.05 was considered to be significant at a 95% confidence level. There was no missing data.

**Results**

**The effect of high-dose glucocorticoids on BMI and HOMA-IR**

Although the children with high-dose glucocorticoid were having reduced glucocorticoid dosage, their BMI was significantly increased (26.2 ± 4.7 kg/m² vs 22.1 ± 4.3 kg/m², P<0.01) and the HOMA-IR was also significantly increased (6.2 ± 2.3 vs 6.1 ± 1.4, P<0.01). By Pearson Correlation analysis, there was a significant positive relationship between HOMA-IR and BMI, ages, prednisone dosage, LDL-C and TG, respectively. Further multivariable linear regression analysis revealed that age, BMI, LDL-C and prednisone dosage were independently related with HOMA-IR (β=0.349, 0.250, 0.258, 0.329, respectively, P<0.05). The multiple regression equation was as follows: IR = -3.47 +0.322age +0.135BMI +0.637LDL-C +0.052Pre (F=25.865, P=0.000)

**The effect of metformin on BMI, cholesterol, triglyceride and insulin resistance**

After 3 months of metformin therapy in the 21 patients, their BMI and HOMA-IR were significantly decreased and the levels of TG, LDL-C, FBG, FINS, CP and HbA1c were also significantly reduced.
reduced the glucocorticoid dosage for at least the last month. Although the children were having reduced glucocorticoid dosage, their BMI was significantly increased, which further stresses the side effect of glucocorticoid-induced obesity.

The HOMA-IR index is a simplified computer-based method used to estimate insulin resistance and has been widely applied in clinic and research [10,11]. A study found that preterm infants born after glucocorticoid exposure (48 h before delivery) had elevated free fatty acids and HOMA-IR, suggesting that glucocorticoids can lead to the occurrence of insulin resistance [12]. Our study showed that long-term of high-dose glucocorticoids easily lead to HOMA-IR increased and insulin resistance. Moreover there was a significant positive relationship between HOMA-IR and ages, supporting insulin resistance as a predictor of age-related diseases [13].

Glucocorticoids are the most common cause of drug-induced diabetes, though the exact prevalence is not known, some observations suggest that glucocorticoid-induced diabetes or hyperglycemia is common [14,15]. Glucocorticoids decrease the liver's sensitivity to insulin and inhibit glucose uptake in muscle and fat, reducing insulin sensitivity. Glucocorticoids were also shown to cause various degrees of β-cell dysfunction, reducing insulin sensitivity and impairing β-cell function [16]. In addition, glucocorticoids exert their negative effects on insulin sensitivity by modifying lipid and protein metabolism [17,18]. In this study, the children with long-term use of high-dose glucocorticoids showed varying degrees of hyperlipidemia and the LDL-C levels were significantly associated with HOMA-IR.

Metformin has been proven to reduce hyperinsulinemia and hyperglycemia in adolescents with type 2 diabetes [19]. It is safe and effective for therapy-induced hyperglycemia in patients with acute lymphoblastic leukemia [20]. Metformin decreases hepatic glucose output and enhances primarily hepatic but also muscle insulin sensitivity. Metformin has the advantage of weight reduction, decrease in lipids without the risk of hypoglycemia [21]. In this study, the BMI and insulin resistance of the 21 children were significantly improved after 3 months metformin therapy. Our study supported that metformin may be efficacious in reducing BMI and insulin resistance among obese hyper insulinemic children and adolescents in the short term [22,23]. It is noteworthy that the patients experienced relapse in the glucocorticoid reduction, so that the amount of glucocorticoid increased in the process, which hasn't caused patients' weight gain and insulin resistance. It is suggested that early application of metformin treatment may be a key to prevent glucocorticoid-induced obesity and insulin resistance.

Metformin was well tolerated in the majority of patients. Among 21 children received metformin therapy, 5 cases (24%) had gastrointestinal symptoms including 3 cases of abdominal discomfort and 2 cases of diarrhea were noted. These side effects occurred during the initial phase of treatment and disappeared when the patients took metformin along with food.

Therefore, metformin is safe and effective for treatment of glucocorticoid-induced obesity and insulin resistance.

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Author Contributions

ZL, LN and SL performed the case and control sample collection and clinical management of patients. ZQ and YL were responsible for the data analyses. LJ designed the study and wrote the final version of the paper. LJ take the primary responsibility for the paper.

Ethical Statement

This study was approved by the appropriate ethics committee and funded by China Natural Scientific Foundation (No. 81273093). All procedures were performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments. All eligible children and respective parents signed the informed consent where the study objectives were explained, following the ethical aspects of confidentiality and voluntary participation.

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