Effects of basal insulin combined with Sitagliptin Phosphate Tablets on blood glucose control, oxidative stress and inflammatory response

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ABSTRACT

Objective: To study the effects of basal insulin combined with Sitagliptin Phosphate Tablets on blood glucose control, oxidative stress and inflammatory response. Methods: Type 2 diabetic patients with poor blood glucose control after metformin monotherapy in our hospital between March 2015 and July 2017 were selected as the research subjects and divided into two groups by random number table method. The experimental group received metformin + basal insulin + sitagliptin treatment, while control group were treated with metformin + glimepiride. The levels of glycosylated hemoglobin as well as the contents of oxidative stress indexes and inflammatory response indexes were measured before treatment and 3 months after treatment. Results: Compared with those before treatment, glycosylated hemoglobin levels, serum AGEs, MDA, CRP, TNF-α, IL-6, IL-8 and VCAM-1 contents as well as peripheral blood Nrf2, HO-1, NOX2 and NOX4 expression intensity of both groups were significantly decreased while serum SOD and CAT contents were significantly increased 3 months after treatment, and glycosylated hemoglobin level, serum AGEs, MDA, CRP, TNF-α, IL-6, IL-8 and VCAM-1 contents as well as peripheral blood Nrf2, HO-1, NOX2 and NOX4 expression intensity of experimental group 3 months after treatment were significantly lower than those of control group whereas serum SOD and CAT contents were significantly higher than those of control group (P<0.05). Conclusion: Basal insulin combined with Sitagliptin Phosphate Tablets can improve the blood glucose control condition and reduce the oxidative stress and inflammatory response in type 2 diabetic patients with poor blood glucose control after metformin monotherapy.

1. Introduction

Type 2 diabetes mellitus is the most common endocrine system disease in China, its incidence rate is increasing year by year and it also increases the risk of cerebral infarction, myocardial infarction and other cardiovascular and cerebrovascular diseases. Metformin is a first-line drug for the treatment of type 2 diabetes mellitus. When metformin monotherapy cannot effectively control the blood glucose, it is necessary to use glucose-lowering drugs with different mechanisms to control the blood glucose. Sulfonylureas glimepiride may act on the ATP-sensitive potassium channels on the islet β cells to promote the secretion of insulin, and its combination with metformin can effectively control blood glucose, but strong effect that promotes insulin secretion will increase the risk of hypoglycemia and enlarge the range of the blood glucose fluctuations[1,2]. Basal insulin can continuously and stably release insulin, avoid insulin peak and control basal blood glucose, and sitagliptin may inhibit the degradation of incretin to enhance the activity of incretin and control postprandial blood glucose; metformin combined with basal insulin and sitagliptin can more stably control blood glucose and decrease blood glucose fluctuations[3,4]. In recent years, the studies on blood glucose
fluctuations in the course of type 2 diabetes mellitus have shown that the greater the blood glucose fluctuation, the more significant the activation of oxidative stress and inflammation in the body, which will further increase the occurrence risk of a variety of diabetic macrovascular and microvascular complications. In the following studies, we specifically analyzed the effects of basal insulin combined with Sitagliptin Phosphate Tablets on blood glucose control, oxidative stress and inflammatory response.

2. Case information and research methods

2.1 Case inclusion and information

Patients with type 2 diabetes mellitus who were treated in our hospital between March 2015 and July 2017 were selected as the research subjects, and all patients were diagnosed with type 2 diabetes mellitus by oral glucose tolerance test, received metformin monotherapy for more than 3 months, had poor blood glucose control, and were with glycosylated hemoglobin of 7%-9% and fasting glucose of 8-11 mmol/L; patients with contraindications of insulin detemir, sitagliptin phosphate and glimepiride were excluded. A total of 124 cases were enrolled and divided into two groups by random number table method, each with 62 cases. There were 33 males and 29 females in the experimental group, they were 39-57 years old, and the course of diabetes was 4-8 months; there were 34 males and 28 females in the control group, they were 37-58 years old, and the course of diabetes was 4-9 months. There was no significant difference in the general data between the two groups (P>0.05).

2.2 Research methods

2.2.1 Therapy

On the basis of oral metformin hydrochloride treatment, experimental group were treated with basal insulin and sitagliptin, and the method was as follows: oral administration of Metformin Hydrochloride Tablets 1 000-2 000 mg/d, oral administration of Sitagliptin Phosphate Tablets 0.1 g/d as well as subcutaneous injection of insulin detemir with starting dose of 0.2 U/kg, which was adjusted according to blood glucose levels. On the basis of oral metformin hydrochloride treatment, control group were treated with glimepiride, and the method was as follows: oral administration of Metformin Hydrochloride Tablets 1 000-2 000 mg/d and oral administration of Glimepiride Tablets 2-4 mg/d.

2.2.2. Laboratory detection

Before treatment and 3 months after treatment, fasting cubital venous blood was collected respectively, automatic glycosylated hemoglobin meter was used to measure the glycosylated hemoglobin levels, the manual process of radioimmunoprecipitation kit was referred to determine the contents of SOD, CAT, AGEs and MDA, the manual process of Elisa kit was followed to detect the CRP, TNF-α, IL-6, IL-8 and VCAM-1 levels, and the microplate reader and accessory kit were used to detect the expression intensity of Nrf2, HO-1, NOX2 and NOX4.

2.3 Statistical methods

Software SPSS 21.0 was used to input the data, the difference in measurement data between two groups was analyzed by t test and P<0.05 showed statistical significance in the differences.

3. Results

3.1 Blood glucose control indexes

Before treatment, the glycosylated hemoglobin levels of experimental group and control group were (8.51±0.93)% and (8.44±0.86)%, respectively; 3 months after treatment, the glycosylated hemoglobin levels of experimental group and control group were (6.46±0.89)% and (7.15±0.78)%, respectively. After t test, glycosylated hemoglobin levels of both groups were statistically different between before and after treatment (P<0.05), glycosylated hemoglobin levels were not significantly different between groups before treatment (P>0.05) whereas glycosylated hemoglobin levels were statistically different after treatment (P<0.05), and glycosylated hemoglobin level of experimental group was lower than that of control group.

3.2 Oxidative stress indexes

Before treatment and 3 months after treatment, analysis of serum oxidative stress indexes SOD (U/L), CAT (U/L), AGEs (μg/mL) and MDA (μmol/L) as well as peripheral blood oxidative stress indexes Nrf2, HO-1, NOX2 and NOX4 in the two groups of patients was as follows: serum SOD, CAT, AGEs and MDA contents as well as peripheral blood oxidative stress indexes Nrf2, HO-1, NOX2 and NOX4 expression intensity were statistically different between before and after treatment within group (P<0.05); serum SOD, CAT, AGEs and MDA contents as well as peripheral blood Nrf2, HO-1, NOX2 and NOX4 expression intensity were not significantly different between the two groups.
of patients before treatment (P>0.05) while they were significantly different after treatment (P<0.05), and serum SOD and CAT contents of experimental group were higher than those of control group whereas serum AGEs and MDA contents as well as peripheral blood Nrf2, HO-1, NOX2 and NOX4 expression intensity were lower than those of control group.

### 3.3 Inflammatory response indexes

Before treatment and 3 months after treatment, analysis of serum inflammatory response indexes CRP (mg/L), TNF-α (ng/L), IL-6 (ng/L), IL-8 (ng/L) and VCAM-1 (μg/L) in the two groups of patients was as follows: serum CRP, TNF-α, IL-6, IL-8 and VCAM-1 contents were statistically different between before and after treatment within group (P<0.05); serum CRP, TNF-α, IL-6, IL-8 and VCAM-1 contents of experimental group were lower than those of control group.

### 4. Discussion

Metformin is a first-line drug in clinical treatment of type 2 diabetes mellitus, and different mechanisms of hypoglycemic drugs are also needed for patients with poor efficacy of metformin monotherapy. Glimepiride is insulin secretagogue and promotes the secretion of insulin to exert hypoglycemic effect, and although it is complementary to metformin in mechanism and has exact hypoglycemic effect, the risk of hypoglycemia is relatively large and the blood glucose fluctuation is also big during treatment. Basal insulin and sitagliptin have been the drugs for diabetes developed in recent years; the former is insulin analogue synthesized by gene recombination technology, and after subcutaneous injection, it can continuously and stably release insulin to blood circulation and avoid insulin peak to facilitate the smooth control of blood glucose[5]; the latter is dipeptidyl peptidase-4 inhibitor, and it inhibits the degradation of dipeptidyl peptidase-4 on incretin to further enhance the activity of incretin, and play the role of incretin to lower postprandial blood glucose[6,7]. In the study, in order to define the value of basal insulin combined with sitagliptin for type 2 diabetic patients with poor blood glucose control after metformin monotherapy, the changes in glycosylated hemoglobin levels were used to reflect the situation of blood glucose control, and comparison of glycosylated hemoglobin between the two groups showed that compared with those of same group before treatment, glycosylated hemoglobin levels of both groups of patients were significantly decreased after treatment, and glycosylated hemoglobin level of experimental group was lower than that of control group. This indicates that the basal insulin combined with sitagliptin is better than glimepiride to control the blood glucose of type 2 diabetic patients with poor blood glucose control after metformin monotherapy, and the overall blood glucose level is lower.

As the insulin secretagogue, glimepiride strongly promotes insulin secretion. The risk of hypoglycemia is relatively high and the
fluctuation range of blood glucose is also large when it is used for diabetes treatment; the basal insulin is the stable release of insulin, and sitagliptin mainly reduces postprandial blood glucose, so the risk of hypoglycemia is relatively low and the fluctuation range of blood glucose is small. In recent years, research on blood glucose fluctuations has shown that excessive blood glucose fluctuation will increase the generation of AGEs and enhance the oxidative stress responses in the body to increase the risk of microvascular and macrovascular complications. In the process of blood glucose fluctuations, the mass generation of AGEs can stimulate the generation of oxygen free radicals, then activate oxidative stress reaction and have oxidizing reaction with the lipid in the cell membrane to produce MDA[8,9]. At the same time, the mass generation of oxygen free radicals will also lead to the constant consumption of various antioxidant enzymes in the body, SOD can reduce the oxygen free radicals to hydrogen peroxide, and the CAT can further reduce the peroxide hydrogen into water molecules and discharge them[10]. Analysis of the effect of basal insulin combined with sitagliptin on the oxidative stress response in type 2 diabetic patients with poor blood glucose control after metformin monotherapy showed that compared with those of same group before the treatment, serum SOD and CAT contents of both groups were increased whereas AGEs and MDA contents were decreased after treatment, and serum SOD and CAT contents of experimental group were higher than those of control group whereas AGEs and MDA contents were lower than those of control group. This indicates that the basal insulin combined with sitagliptin is better than glimepiride to relieve the oxidative stress response in type 2 diabetic patients with poor blood glucose control after metformin monotherapy.

The activation of oxidative stress response and the mass production of oxygen free radicals in diabetic patients depend on the abnormal expression of various signaling molecules. Nrf2 pathway is an important antioxidant pathway in cells, which is combined with Keap1 under physiological conditions and is in a suppressed state; under the stimulation of oxygen free radicals, Nrf2 is dissociated with Keap1 and activated, and then it starts the expression of antioxidant enzyme HO-1 via downstream ARE and exert antioxidant effect[11,12]. Therefore, the compensatory activation degree of Nrf2 has a good consistency with the degree of oxidative stress response. NOX2 and NOX4 are the NOXs family members that are closely related to the generation of oxygen free radicals in patients with diabetes, and can transfer electrons from NADPH to oxygen molecules and generate oxygen free radicals[13,14]. Analysis of the effect of basal insulin combined with sitagliptin on oxidative stress-related signal molecule expression in type 2 diabetic patients with poor blood glucose control after metformin monotherapy showed that compared with those of same group before the treatment, peripheral blood Nrf2, HO-1, NOX2 and NOX4 expression intensity of both groups were decreased after treatment, and peripheral blood Nrf2, HO-1, NOX2 and NOX4 expression intensity of experimental group were lower than those of control group. It means that the basal insulin combined with sitagliptin is superior to glimepiride to inhibit the oxidative stress-related signal molecules in type 2 diabetic patients with poor blood glucose control after metformin monotherapy.

There is also continuous micro inflammation in the course of type 2 diabetes mellitus, and the mass generation of AGEs and the excessive activation of oxidative stress response caused by blood glucose fluctuations will further amplify inflammatory reaction and increase the secretion of various inflammatory cytokines[15]. CRP is an acute phase protein synthesized by liver cells under the action of various pro-inflammatory cytokines, and its secretion is consistent with the process of inflammatory response[16]. TNF-α is the first cytokine secreted in the process of inflammatory reaction, and has strong pro-inflammatory activity[17]; IL-6 and IL-8 are the interleukin family members with multiple biological functions, which mainly play the roles of chemokines in the process of inflammatory response and can promote the chemotactic movement of a variety of inflammatory cells and amplify inflammatory reaction[18]; VCAM-1 is a cytokine mediating the adhesion between inflammatory cells and endothelial cells, and inflammatory cells can adhere to vascular endothelial cells to cross through the blood vessels through deformation, which is conducive to the mass infiltration of inflammatory cells within the local tissue[19]. Analysis of the effect of basal insulin combined with sitagliptin on inflammatory cytokine levels in type 2 diabetic patients with poor blood glucose control after metformin monotherapy showed that compared with those of same group before the treatment, serum CRP, TNF-α, IL-6, IL-8 and VCAM-1 contents of both groups were decreased after treatment, and serum CRP, TNF-α, IL-6, IL-8 and VCAM-1 contents of experimental group were lower than those of control group. It shows that the basal insulin combined with sitagliptin is superior to glimepiride to inhibit the inflammatory response in type 2 diabetic patients with poor blood glucose control after metformin monotherapy.

The above research data of this study show that the basal insulin combined with sitagliptin is better than glimepiride as a whole for type 2 diabetic patients with poor blood glucose control after metformin monotherapy, and can more significantly improve the blood glucose control and relieve the oxidative stress and inflammatory response in the course of the disease.

References


