EFFECTS OF VITAGLIPTIN COMBINED WITH METFORMIN ON GLUCOSE METABOLISM, INSULIN RESISTANCE, AND HEMORHEOLOGY IN PATIENTS WITH TYPE 2 DIABETES

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ABSTRACT

Objective*: To study the effects of vitagliptin combined with metformin on glucose metabolism, insulin resistance, and hemorheology in patients with type 2 diabetes.*

Methods*: We randomly selected 104 patients diagnosed with type 2 diabetes in our hospital and divided them into a control group (52 cases) and an experimental group (52 cases) with different treatment schemes. Patients in the control group were treated orally with metformin hydrochloride tablets, with doses of 0.5 g administered three times per day. Patients in the experimental group were treated with vitagliptin on the basis of the control group with twice-daily doses of 50 mg. The T2DM patients in both groups were treated continuously for three months. The effects and adverse reactions after treatment in the two groups of patients were observed and analyzed, and we compared the glucose metabolism indicators [fasting blood glucose (FBG), postprandial 2 h blood glucose (2hPG), and glycated hemoglobin (HbA1c)], islet β-cell function indicators [fasting C-peptide, postprandial 2hC-peptide content and steady-state model insulin secretion index (HOMA-β), and insulin resistance index (HOMA-IR)] and hemorheology indicators [whole blood viscosity (high-cut), whole blood viscosity (medium-cut), whole blood viscosity (low-cut), plasma viscosity, and hematocrit] before and after treatment in the two groups.*

Results*: The total effective rate of the experimental group was 94.23%, which was significantly higher than that of the control group (80.77%) (P<0.05). After treatment, the levels of FBG, 2hPG, and HbA1c in the two groups were significantly lower than before treatment; in the experimental group, the levels of FBG, 2hPG, and HbA1c were significantly lower than those in the control group (P<0.05). The fasting C-peptide and postprandial 2hC-peptide content were not significantly different from those before treatment (P>0.05). In both groups, HOMA-β was significantly higher after treatment, while HOMA-IR was significantly lower after treatment (P<0.05); HOMA-β was significantly higher in the experimental group than in the control group (P<0.05). There was no significant difference in HOMA-IR between the two groups (P>0.05). The whole blood viscosity (high-cut), whole blood viscosity (medium-cut), whole blood viscosity (low-cut), and plasma viscosity and hematocrit of the two groups of patients after treatment were significantly lower than before treatment, and those in the experimental group were significantly lower than the control group. No significant adverse reactions occurred in T2DM patients in both groups.*

Conclusion*: Vitagliptin combined with metformin is effective in treating patients with T2DM with no significant adverse reactions, and can control blood glucose levels effectively, promote islet β-cell function recovery, and improve blood viscosity and blood flow velocity in patients with T2DM.*

Keywords: *vitagliptin, metformin, type 2 diabetes, glucose metabolism, insulin resistance, hemorheology.*

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Introduction

Type 2 diabetes (T2DM) is the most common type of diabetes, which refers to endocrine and metabolic diseases that are characterized by chronic hyperglycemia due to abnormal insulin secretion or dysfunction[(1)]. The current number of T2DM cases increases rapidly with the development of human quality of life, population aging, living habits, and diagnostic technologies. This trend is especially strong in developing countries, where cases are expected to increase to 170% by 2025, becoming the third-most serious non-communicable disease that threatens people's life and health[(2-3)]. The early stages of the onset are mainly characterized by insulin resistance and hyperinsulinemia but no hy-

perglycemia. As the disease progresses, the patient's compensation mechanism becomes abnormal, which leads to T2DM, eventually leading to many complications and severely injuring the patient's life and health[3-4]. Patients with T2DM should be given diet control supplemented by proper exercise to reduce blood glucose concentration. If the therapeutic effect does not reach the expected target, oral hypoglycemic drugs or insulin can be used[5]. However, these drugs are not ideal for the reduction of islet β-cells and islet dysfunction in T2DM patients and are likely to cause many adverse reactions such as low blood-sugar levels and gastrointestinal reactions. Therefore, exploring drugs that can effectively control blood glucose levels and alleviate the patient's condition is one of the primary directions that clinical staff are currently exploring[6-7].

Metformin is the first drug to treat patients with T2DM. Vitagliptin is a dipeptidyl peptidase-4 inhibitor that plays a powerful role in lowering blood sugar because of its unique mechanism of action. The drug has no side effects such as severe hypoglycemia and weight gain and has thus become a new option for treating T2DM[8-9]. In this study, we treated patients with T2DM with vitagliptin combined with metformin to study the effects on glucose metabolism, insulin resistance, and hemorheology.

Materials and methods

General data

We randomly selected 104 patients diagnosed with T2DM in our hospital from December 2016 to March 2018. The inclusion criteria were as follows:

• patients who met the diagnostic criteria for T2DM in the "Guidelines for the Diagnosis and Treatment of Type 2 Diabetes in China" formulated in 2013;

• patients aged 18 to 75 years;

• patients whose blood pressure maintained a normal level for the past three months;

• patients who were diagnosed as T2DM for the first time;

• patients who signed informed consent;

• this study was approved by the hospital ethics committee.

Exclusion criteria:

• those who dropped out of treatment due to intolerance;

• patients with type 1 diabetes;

• patients with a diabetic foot. The 104 patients with T2DM selected by these criteria were divided into a control group (52 cases) and an experimental group (52 cases) with different treatment schemes.

There were 32 males and 20 females in the control group, with an average age of 56.43 ± 6.89 years, and 28 males and 24 females in the experimental group with an average age of 57.23 ± 5.99 years. There was no significant difference in general data between the two groups of T2DM patients (P>0.05).

Methods

T2DM patients in both groups controlled their diets and exercised appropriately. Patients in the control group were treated with metformin hydrochloride tablets (specification: 0.5 g/tablet, Sinopharm: H20181986, produced by Beijing Wanhui Shuanghe Pharmaceutical Co., Ltd.) orally, 0.5g each time, three times a day. Patients in the experimental group were treated with vitagliptin (specification: 50 mg/tablet, Sinopharm: H20180023, produced by NovartisPharmaSteinAG) based on the control group, 50mg each time, twice daily. The T2DM patients in both groups were treated continuously for three months.

Fasting venous blood and 2 h postprandial venous blood were collected from the two groups of T2DM patients one day before treatment and three months after treatment. After centrifugation, the blood samples were stored in a low-temperature refrigerator for testing.

Observation indicators

• Compare the total effective rate of T2DM patients in the two groups. Significant effect: normal blood glucose level or body mass index (BMI) at 20~25 kg·m-2; effective: control blood glucose level within the normal range or BMI at 25~28 kg·m-2 for more than 3/4 time; invalid: increased blood glucose level or BMI>28 $kg \cdot m^{-2}$. Total effective rate = (significant effect + effective) / total number of observations × 100%.

• Fasting blood glucose (FBG) and 2 h postprandial blood glucose (2hPG) were measured by the hexokinase method in two groups of T2DM patients; the immunosuppressive turbidimetric method was used to determine glycation in the two groups of T2DM patients' hemoglobin (HbA1c) levels.

• The chemiluminescence method was used to determine the fasting C-peptide and 2hC-peptide content of T2DM patients in the two groups.

• We calculated the insulin secretion index β (HOMA-β) = 20 × Fasting insulin (FINS) / (FBG-

3.5) and the insulin resistance index (HOMA-IR) = FBG × FINS / 22.5.

• Whole blood viscosity (high-cut), whole blood viscosity (medium-cut), whole blood viscosity (low-cut), plasma viscosity, and hematocrit of the two groups of T2DM patients were tested by a hemorheology tester.

• We closely observed the patients' health during the treatment and recorded adverse reactions during this period.

Statistical methods

The data of the experimental group and the control group were analyzed using the SPSS 22.0 software package. The treatment effects and adverse reactions of the two groups were tested by χ^2 and expressed as [n (%)]. The glucose metabolism indicators and islet β-cell function indicators of the two groups were tested with a t-test ($\bar{x}\pm s$). P<0.05 was considered a significant difference.

Results

Comparison of the efficacy of T2DM patients in the two groups

The total effective rate of the experimental group was 94.23%, which was significantly higher than that of the control group (80.77%) (P <0.05). See Table 1.

Groups	n	Significant effect	Effective	Invalid	Total effective rate
Control group	52	24(46.15)	18(34.62)	10(19.23)	42(80.77)
Experimental group	52	30(7.69)	19(36.54)	3(5.77)	49(94.23)
χ^2					4.308
P					0.038

Table 1: Comparison of efficacy between two groups of T2DM patients [n (%)].

Comparison of glucose metabolism indicators in T2DM patients between the two groups

After treatment, the levels of FBG, 2hPG and HbA1c in the two groups were significantly lower than before treatment; in the experimental group, the levels of FBG, 2hPG, and HbA1c were significantly lower than those in the control group (P <0.05). See Table 2.

Comparison of islet β-cell function indicators between the two groups

After treatment, the contents of fasting C-peptide and postprandial 2hC-peptide were not significantly different from those before treatment (P>0.05). In both groups, HOMA-β was significantly higher than before treatment, and HOMA-IR was significantly lower than before treatment (P <0.05); HOMA-β in the experimental group was significantly higher than in the control group (P<0.05). There was no significant difference in HOMA-IR between the experimental group and the control group (P>0.05). See Table 3.

Groups	n	Time	FBG (mmol/L)	2hPG (mmol/L)	HbA1c (%)
Control group	52	Before treatment	9.49±1.76	13.87±2.56	8.34±1.67
		After treatment	7.08±1.89*	9.09±2.45*	7.21±1.19*
Experimental group	52	Before treatment	9.46±1.80	13.96±2.76	8.31±1.56
		After treatment	5.89±1.51*#	7.39±1.33*#	6.23±1.23*#

Table 2: Comparison of glucose metabolism indexes between two groups of T2DM patients ($\bar{x}\pm s$).
*Note: * means P <0.05 compared to the pre-treatment value; # means P <0.05 compared with the control group.*

Groups	n	Time	Fasting C-peptide (ng/mL)	Postprandial 2hC-peptide (ng/mL)	HOMA-β	HOMA-IR
Control group	52	Before treatment	1.88±0.98	4.67±1.31	31.05±6.09	3.89±1.17
		After treatment	1.91±1.02	4.71±1.28	50.56±7.98*	3.32±0.98*
Experimental group	52	Before treatment	1.84±1.00	4.65±1.41	30.23±6.13	3.86±1.28
		After treatment	2.02±0.99	5.12±1.56	60.23±10.24*#	3.21±1.04*

Table 3: Comparison of islet β-cell function indicators between two groups of T2DM patients ($\bar{x}\pm s$).
*Note: * means P <0.05 compared with the pre-treatment value; # means P <0.05 compared with the control group.*

Comparison of hemorheology indicators of T2DM patients between two groups

After treatment, the blood viscosity (high-cut), blood viscosity (medium-cut), blood viscosity (low-cut), and plasma viscosity and hematocrit of the two groups were significantly lower than before treatment; those in the experimental group were significantly lower than those in the control group. See Table 4.

Indicators	Control group		Experimental group	
	Before treatment	After treatment	Before treatment	After treatment
Blood viscosity (high-cut)	5.90±1.30	5.43±1.23*	5.93±1.32	4.97±1.14*#
Blood viscosity (medium-cut)	9.19±2.89	8.80±2.27*	9.23±2.86	8.24±2.16*#
Blood viscosity (low-cut)	12.86±3.37	11.57±2.48*	12.94±3.42	10.34±2.39*#
Plasma viscosity	1.80±0.48	1.65±0.43*	1.84±0.47	1.49±0.38*#
Hematocrit (%)	45.72±5.60	38.02±4.92*	45.89±5.78	27.80±4.44*#

Table 4: Comparison of hemorheological indicators between two groups of T2DM patients ($\bar{x}\pm s$).
*Note: * means P <0.05 compared to the pre-treatment value; # means P <0.05 compared with control group.*

Comparison of adverse reactions in T2DM patients between the two groups

No significant adverse reactions occurred in T2DM patients in either group.

Discussion

Islet β-cell dysfunction and insulin resistance play an important role in the rapid progress of T2DM. Therefore, the timely restoration of islet β-cell function is the key to maintaining normal blood glucose levels. Although biguanide and sulfonylurea drugs can reduce blood glucose to a cer-

tain extent, they cannot prevent islet β-cell function from declining fundamentally. This decline causes unstable blood glucose levels and eventually leads to complications such as diabetic nephropathy and diabetic foot[10-11].

Metformin is a first-line drug for the treatment of T2DM that can be applied to patients with early diabetes and lower blood glucose levels in a short time but cannot inhibit the decline of islet β-cell function. If used in large doses, the drug can cause a variety of adverse reactions[12]. Vitagliptin can bind to the dipeptidyl peptidase-4 enzyme to inhibit the activity of the enzyme and block the degradation of glucagon-like peptide-1, leading to an increase in endogenous glucagon-like peptide levels and biological activity. The drug thus promotes the recovery of islet β-cell function and ultimately plays a role in controlling blood glucose[13]. Some studies have shown that the levels of FBG, 2hPG, and HbA1c in T2DM patients are significantly reduced after treatment with vitagliptin[14].

Clinical studies have confirmed that vitagliptin can cooperate with metformin to promote insulin secretion, thereby improving insulin resistance and promoting islet β function recovery. Previous studies have indicated that T2DM patients tolerate vitagliptin combined with metformin, which may be related to the inhibition of dipeptidyl peptidase-4 by vitagliptin[15].

The total effective rate of the experimental group was 94.23%, which was significantly higher than that of the control group (80.77%). No significant adverse reactions occurred in T2DM patients in both groups. This showed that the combined use of the two drugs was better than a single drug, which significantly improved the clinical efficacy and the clinical symptoms, and the patients did not have obvious adverse reactions and had higher safety. After treatment, the levels of FBG, 2hPG, and HbA1c in the two groups were significantly lower than before treatment; those in the experimental group were significantly lower than in the control group ($P<0.05$).

This suggested that vitagliptin combined with metformin can effectively control blood glucose levels in patients with T2DM, in addition to reducing the incidence of blood glucose. The contents of fasting C-peptide and postprandial 2hC-peptide were not significantly different from those before treatment ($P>0.05$). In both groups, HOMA-β was significantly higher than before treatment, and HOMA-IR was significantly lower than before treatment ($P<0.05$); HOMA-β in the experimental group was significantly higher than that in the control group ($P<0.05$). There was no significant difference in HOMA-IR between the experimental group and the control group ($P>0.05$). This showed that vitagliptin combined with metformin could promote islet β function recovery and improve insulin resistance in a short time.

However, the fasting C-peptide and 2hC-peptide levels of the two groups of patients did not improve significantly, which may be related to the study's relatively small sample size and short monitoring time. After treatment, the blood viscosity (high-cut), blood viscosity (medium-cut), blood viscosity (low-cut), plasma viscosity, and hematocrit of the two groups of patients were significantly lower than before treatment; those in the experimental group were significantly lower than those in the control group. This indicated that vitagliptin combined with metformin can significantly improve the blood viscosity and increase the hemorheology of patients.

All in all, vitagliptin combined with metformin is ideal in treating T2DM patients with no significant adverse reactions, and can effectively control blood glucose levels, promote the recovery of islet β-cell function, and improve blood viscosity and blood flow velocity in T2DM patients.

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