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Original Research

Investigating the changes in the levels of HbA1c, blood fat and insulin sensitivity in elder patients with type II diabetes mellitus due to combined medication of pioglitazone and melbine and single-use of pioglitazone

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Abstract: This study was founded for the purpose investigate the differences in effects of combined medication of pioglitazone and melbine and single-use of pioglitazone on the levels of hba1c, blood fat and insulin sensitivity of elder patients with type II diabetes mellitus (T2DM), to provide clinical reference and guidance for the treatment of T2DM in elder patients. For this purpose, we selected a total of 120 elder patients with T2DM who visited the clinic or were admitted to this hospital between July 2016 and July 2017 and divided them into the observation group and the control group (n=60 for each group). For the control group, they only took pioglitazone for treatment, while those in the observation additionally took melbine for treatment. Then, we observed the levels of FPG, 2hPG, HbA1c, blood fat, FINS, 2hINS and HOMA-IR. Results showed that after treatment, significant decreases were seen in levels of FPG, 2hPG and HbA1c in patients of two groups compared to the levels before treatment, and the levels in the observation group decreased more evidently than those in the control group ($p<0.05$); besides, the levels of total glyceride, total cholesterol and LDL-C were all significantly lower than those before treatment, with an elevated HDL-C, and those levels of TG, TC and LDL-C in the observation group were significantly lower than those in the control group; the level of HDL-C was higher than the control group ($p<0.05$). Similar decreases were identified in the levels of FINS, 2hFINS and HOMA-IR after treatment ($p<0.05$), and the levels in the observation group were also significantly lower than those in the control group ($p<0.05$). In the observation group, the incidence rate of adverse reactions was 10% (6/60), while in the control group was 8.33% (5/60), but the difference between the two groups showed no statistical significance ($p>0.05$). It is concluded that combined medication of pioglitazone and melbine can effectively reduce the levels of plasma glucose, blood fat and the HOMA-IR, with an elevated sensitivity to insulin, but no severe adverse reactions, manifesting a promising safety in long-term administration. It is worthy of being promoted in clinical practice.

Key words: Pioglitazone; Melbine; T2DM; HbA1c; Blood fat; Insulin.

Introduction

Diabetes mellitus (DM), the third chronic non-infectious disease only secondary to the malignancies and cardiovascular diseases, has become an emergent public health issue facing the world (1). With the rapid development in life quality and the changes in life style, a rapid increase has been witnessed in the population of DM: Currently, there have been 250 million DM patients in the world, and according to the estimate of International Diabetes Federation, this digit will finally surpass 330 million by the year of 2025. In China, people are also suffering from DM: In 2016, the population of DM patients has increased to more than 30 million, and simultaneously, China is facing the tremendous burden posed by the treatment of DM, as well as its complications (2). Based on the current understandings, DM is defined as a kind of chronic metabolic disease with a deficiency in insulin secretion of pancreatic β cell and declines in the sensitivity of surrounding tissues to the insulin, with elevated plasma glucose as the major feature, and is regarded as a kind of clinical condition with extreme heterogeneity in pathogenesis. Type 2 DM (T2DM) has affected about 90% to 95% of the DM patients and has been considered as a chronic disease requiring the life-long treatment. Poor management of plasma glucose, or let alone the development of the disease, will result in acute metabolic disorder, or even death (3). The acute increase in the elder population also contributes to the rapid growth of T2DM patients, which has been regarded as a rigorous social problem. Research has shown effective management of plasma glucose, so as to maintain the plasma glucose at an ideal level, has become the major method in the prophylaxis of the T2DM and reducing its complications in elder patients (4).

A major role of insulin has been confirmed in the development of T2DM. Insulin is secreted and synthesized by pancreatic cells, and delivered to the target cells to bind to the specific receptor, so as to induce the intracellular metabolic process of substance; disorders in any link will cause metabolic disorder, and DM arises (5). Insulin resistance, a status that the biological response of the body to the insulin has been reduced below the normal status, is characterized mainly by the decrease in sensitivity of target organs or tissues to the insulin.

It has been proved that lipid tissue and damaged sugar tolerance are closely correlated with insulin resistance, which gives rise to the significance of research on the blood fat levels in T2DM patients (6). Besides, plasma glucose is a major indicator reflecting the efficacy of treatment on T2DM, and the long-term control of plasma glucose has shown a critical effect on reducing the complications of T2DM. According to the existing studies, every drop of 1% in HbA1c will contribute to a reduction of 15% or so of the endpoint or death events, and a decrease of more than 10% in the all-cause mortality (7).

Research has confirmed that despite the rigorous situation in combating the DM, massive evidence-based medical evidence has proved that DM and its complications can be delayed or even interfered: Rational diet, exercise, good mentality, smoking and alcohol cessation and strict control of blood pressure and fat are also critical to the prophylaxis and delay of DM and its complications (8). At present, treatment against the T2DM is mainly carried out through the medication, including α-glucosidase inhibitor, melbine, nateglinide and thiazolidone, etc., which can ameliorate the metabolic disorder through varying mechanisms, thus controlling the plasma glucose.

So far, melbine and pioglitazone are used as common drugs in the treatment of T2DM. Pioglitazone, as the thiazolidone antidiabetics, is a major regulator in mediating the differentiation of adipocytes, stability of lipid and effect of insulin, and increases insulin sensitivity, manifesting a critical effect in increasing the sensitivity of tissues to the insulin and alleviating the insulin resistance. By acting upon the peroxisome proliferator-activated receptor Y, it can decrease the insulin resistance, so as to ameliorate the pancreatic cells. Animal experiments and clinical experiments have shown that pioglitazone can reduce the increased plasma glucose caused by insulin resistance, and ameliorate the sensitivity of patients with insulin-resistance to the insulin, thus improving the responses of insulin to cells, and maintaining the balance of glucose for a long period (9). Melbine can enhance the binding of insulin with its receptor to increase the sensitivity against the insulin and inhibit the hepatic gluconeogenesis and glucose output, thus increasing the anaerobic glycolysis to a certain degree (10). Studies have indicated that melbine has been used as the first-line drug in the treatment of T2DM in patients who have no response to the simple control of diet and sports therapy, especially that obesity-type T2DM and the combined medication with other drugs show promising synergistic effect (11).

It has been confirmed in clinical studies that single-use, or combined medication of these two drugs, can decrease the plasma glucose with an improving effect on the sensitivity to insulin; nevertheless, the varying action mechanisms and sites of these two drugs require in-depth studies, especially for those elder T2DM patients. In this study, we selected a total of 156 elder patients with T2DM who visited the clinic or were admitted to this hospital between July 2016 and July 2017 to investigate the differences in effects of combined medication of pioglitazone and melbine and single-use of pioglitazone on the levels of HbA1c, blood fat and insulin sensitivity of elder patients with type II diabetes mellitus (T2DM), so as to provide clinical reference and guidance for the treatment of T2DM in elder patients.

Materials and Methods

Subjects

We selected a total of 156 elder patients with T2DM who visited the clinic or were admitted to this hospital between July 2016 and July 2017.

Enrollment criteria

a) Diagnoses of all patients conforming to the criteria of T2DM stipulated by World Health Organization (WHO) in 1999: for patients with typical manifestations, fasting plasma glucose (FPG) ≥7.0mmol/L or postprandial plasma glucose (PPG) ≥11.1mmol/L; for patients with no typical manifestations, FPG ≥ 7.0 mmol/L or PPG ≥ 11.1 mmol/L, twice or more; for patients with no typical manifestations, 2 h postprandial plasma glucose (2hPPG) ≥ 11.1 mmol/L in intraperitoneal glucose tolerance test; patients that satisfied any condition above were diagnosed as DM; b) patients aged above 60 years old; c) patients who were newly diagnosed as T2DM and responded poorly to the diet control or sports therapy, without any medication history; d) patients with a body mass index (BMI) between 19 kg/m^2 and 35 kg/m^2; e) patients who were informed of the protocol of this study and volunteered to participate in this study, and signed the written informed consents; f) this study had been approved by the Ethic Committee of this hospital.

Exclusive criteria

a) Patients with Type I DM, or complicated with acute complications of DM, including hyperosmolar non-ketotic coma or diabetic ketoacidosis; b) patients who had participated in any other studies within 3 months; c) patients who were sensitive to the drugs used in this study, or were hypersensitive; d) patients with severe dysfunctions in heart, liver or kidney, or with disorders in the endocrine system, malignancies or severe organic lesions; e) patients with a severe mental disorder, or drug abuse; f) patients with diseases that might interfere the studies based on the evaluation of researchers.

Methods

Treatment methods

After screening in accordance with the enrollment and exclusive criteria, we finally excluded 29 patients from 156 patients, including 2 patients with malignancies, 1 with suspicious malignancy,1 with thyroid dysfunction and 4 with coronary heart disease that had not received any standard treatment; 7 patients quitted the study for difficulties in a follow-up. From the remaining 120 patients who were eligible for this study, we demanded the disease history of patients and recorded their general data, including the age, gender, height, weight, diastolic blood pressure (DBP) and systolic blood pressure (SBP). These patients were divided into two groups randomly, i.e. the observation group (n=60) and the control group (n=60). Regular health education and follow-up were carried out weekly for patients, and the-

ir diet and exercise were strictly controlled. Meanwhile, treatment for both groups was carried out as follows: For the control group, patients only took pioglitazone 30 mg per day (Beijing Sunpharm Co., Ltd., 30 mg, SFDA approval No.: H20063525); for observation group, patients received the combined medication of 30 mg pioglitazone and 1.5 g melbine per day (Beijing Shenyong Pharmaceutical Co., Ltd., 0.5 g, SFDA approval No.: H20058567). Medication for patients in two groups lasted for 12 weeks, and any discomfort, e.g. dizziness or fatigue, was treated appropriately in time.

Follow-up

Follow-up was conducted once every six weeks, twice, including physical examination, blood pressure measurement, echocardiography, FPG, 2hPPG and glycosylated hemoglobin (HbA1c) determination. For patients with poor control of plasma glucose, drug dose was expanded according to the instruction, and for those with extremely low plasma glucose, the dose was reduced, or one of the drugs was suspended; meanwhile, these patients would receive additional follow-up to monitor the progression of disease closely. Adverse events were also recorded.

Exit criteria

a) Patients who failed to accomplish the study for poor compliance; b) patients who required to exit the study; c) patients who withdrew from follow-up; d) patients responded poorly to the increased dose of drugs; e) patients who could not tolerate the adverse reactions.

Observation index

Plasma glucose

FPG and 2hPG levels were determined regularly using the biochemical analyzer and HbA1c using the automatic HbA1c analyzer and high-performance liquid chromatography.

Blood fat

An automatic biochemical analyzer was utilized to measure the level of blood fat, oxidase endpoint method to measure the levels of total cholesterol (TC) and triglyceride (TG), and immunoturbidimetry to measure the levels of high-density lipoprotein cholesterol (HDL-C) and low-density-lipoprotein cholesterol (LDL-C).

Insulin

Fasting venous blood (3 mL) was drawn from patients in the morning following 12 h of fasting and coagulated using the serum separator for 30 min. After centrifugation at 1000 r/min for 15 min, serum was kept at -70°C. A kit for measurement of insulin was used to determine the levels of fasting insulin (FINS) and insulin at 2 h after a meal (2hINS) through immunoturbidity, while the insulin resistance (IR) was evaluated through homeostasis model assessment (HOMA). HOMA-IR was calculated according to the following formula: HOMA-IR = FINS × FPG/22.5.

Adverse reactions

During treatment, we recorded the adverse reactions caused by the administration of these drugs, including hypoglycemia, blurred vision, dizziness, gastrointestinal responses, or edema, in which hypoglycemia was further divided into the asymptomatic hypoglycemia, symptomatic hypoglycemia and severe hypoglycemia.

Statistics

Data were processed using SPSS 14.5 software. Enumeration data and measurement data were presented as the rate (%) and mean ± standard deviation ($\bar{x} \pm s$). Chi-square test and *t*-test were applied for intergroup comparisons with an inspection level of α=0.05. $p<0.05$ suggested that the difference had statistical significance.

Results

Comparison of the general data between two groups

In these two groups, we finally enrolled 120 patients without any exits. In the observation group, there were 33 males and 27 females with a gender ratio of 1.2:1; patients' ages ranged from 62 to 85 years old with an average of (72.30±5.75) years old, their BMI from 19 to 30 kg/m^2 with an average of (23.55±3.00) kg/m^2, disease course from 1 to 6 years with an average of (2.72±1.32) years, SBP from 104 to 159 mmHg with an average of (131.46±10.35) mmHg, DPB from 60 to 99 mmHg with an average of (84.81±9.14) mmHg. In the control group, there were 39 males and 21 females with a gender ratio of 1.8:1; patients' ages ranged from 62 to 88 years old with an average of (73.20±5.34) years old, their BMI from 19 to 32 kg/m^2 with an average of (23.49±2.95) kg/m^2, disease course from 1 to 6 years with an average of (2.68±1.32) years, SBP from 111 to 153 mmHg with an average of (129.36±8.55) mmHg, DPB from 61 to 98 mmHg with an average of (84.39±8.89) mmHg. Comparisons on the baseline data showed no statistically significant differences, suggesting that data of the two groups were comparable ($p>0.05$; Table 1).

Comparison of the plasma glucose in two groups before and after treatment

For comparisons of the levels of FPG, 2hPG and HbA1c, differences showed no statistical significance ($p>0.05$); after treatment, the levels of these indices were significantly decreased in comparison with the

Table 1. Comparison of the general data between two groups.

Item	Observation group (n=60)	Control group (n=60)	χ^2 or *t*	*p*-value
Male/female	33/27	39/21	1.249	0.265
Age	72.30±5.75	73.20±5.34	-0.886	0.378
BMI (kg/m^2)	23.55±3.00	23.49±2.95	0.109	0.914
Disease course (years)	2.72±1.32	2.68±1.32	0.157	0.876
SBP (mmHg)	131.46±10.35	129.36±8.55	1.209	0.33
DBP (mmHg)	84.81±9.14	84.39±8.89	0.252	0.802

Table 2. Comparisons of the plasma glucose levels of patients in two groups before and after treatment ($\bar{x} \pm s$)

Group	Time	FPG (mmol/L)	2hPG (mmol/L)	HbA1c (%)
Observation group (n=60)	Before treatment	7.96±0.81	12.41±1.42	7.71±2.50
	After treatment	5.16±0.97[ab]	7.54±1.80[ab]	5.47±1.21[ab]
Control group (n=60)	Before treatment	8.00±0.86	12.80±1.87	8.05±2.35
	After treatment	6.88±1.24[a]	9.94±3.16[a]	6.87±1.68[a]

Note: [a]$p<0.05$ *vs.* levels before treatment; [b]$p<0.05$ *vs.* levels after treatment.

Table 3. Comparison of the blood fat levels before and after treatment between two groups ($\bar{x} \pm s$, mmol/L)

Group	Time	TG	TC	LDL-C	HDL-C
Observation group (n=60)	Before treatment	1.80±0.32	5.92±0.94	3.37±0.78	1.28±0.18
	After treatment	1.43±0.20[ab]	4.41±0.41[ab]	1.86±0.16[ab]	1.85±0.18[ab]
Control group (n=60)	Before treatment	1.85±0.31	5.98±1.01	3.37±0.68	1.29±0.20
	After treatment	1.68±0.22[a]	5.04±0.56[a]	2.45±0.29[a]	1.46±0.23[a]

Note: [a]$p<0.05$ *vs.* the levels before treatment; [b]$p<0.05$ *vs.* the control group.

Table 4. Comparisons of the BMI, FINS and HOMA-IR before and after treatment between two groups ($\bar{x} \pm s$).

Group	Time	BMI (kg/m^2)	FINS (mU/L)	HOMA-IR
Observation group (n=60)	Before treatment	23.55±3.00	10.14±2.28	3.88±1.07
	After treatment	23.60±2.99[a]	7.02±1.89[c]	2.24±0.78[c]
Control group (n=60)	Before treatment	23.49±2.95	10.26±2.16	3.81±1.06
	After treatment	23.74±3.26[ab]	8.86±2.17[cd]	2.78±1.07[cd]

Note: [a]$p<0.05$, [c]$p<0.05$ *vs.* the levels before treatment; [b]$p<0.05$, [d]$p<0.05$ *vs.* control group.

Table 5. Comparisons of the adverse reactions between two groups during treatment.

Group	Case (n)	Hypoglycemia	Visual dimness	Dizziness	Gastrointestinal reactions	Edema	Total
Observation group	60	2(3.33)	1(1.67)	2(3.33)	1(1.68)	0	6(10.00)
Control group	60	2(3.33)	2(3.33)	1(1.67)	0(0.00)	0	5(8.33)
χ^2				0.100			
p				0.752			

levels before treatment, and the differences had statistical significance ($p<0.05$); decreases in the observation group were more significant than the control group, and the difference had statistical significance ($p<0.05$; Table 2).

Comparison of the blood fat levels of patients in two groups before and after treatment

In comparisons of the levels of TG, TC and LDL-C before treatment, no statistically significant difference was identified ($p>0.05$), and after treatment, those levels were significantly decreased when compared with those before treatment ($p<0.05$), with more significant decreases in the observation group ($p<0.05$). As for HDL-C, intergroup comparison before treatment showed no statistically significant differences ($p>0.05$); after treatment, the level of HDL-C was augmented obviously in two groups ($p<0.05$), and the augmentation in the observation group was much more obvious than the control group with statistically significant difference ($p<0.05$; Table 3).

Comparisons of the BMI, FINS and HOMA-IR before and after treatment between two groups

Before treatment, no statistical significance was identified in differences of the BMI, FINS or HOMA-IR in patients of two groups ($p>0.05$). After treatment, BMI showed no obvious changes in two groups ($p>0.05$); FINS level in two groups were significantly decreased ($p<0.05$); in the observation group, HOMA-IR was decreased in comparison with the level before treatment, while no significant change was identified in the control group ($p>0.05$); intergroup comparisons showed that the levels of FINS and HOMA-IR in the observation group were significantly lower than those in the control group ($p<0.05$; Table 4).

Comparisons of the adverse reactions between two groups during treatment

In the observation group, the incidence rate of complications in patients was 10.00%, higher than 8.33% in the control group, but the difference had no statistical significance ($p>0.05$; Table 5).

Discussion

Diabetes mellitus (DM), a most common form of endocrine disease, severely threatens the health of human beings. Generally, DM refers to a group of diseases caused by disorders in the metabolism of carbon hydrate, fat and proteins, mainly manifested by the chronic increase in plasma glucose, and has been regarded as a

kind of chronic disease requiring lifelong treatment [12]. A study has indicated that DM is also one of high-risk factor contributing to the cardio- or cerebrovascular diseases, and poor control of plasma glucose, without any intervention, results in complications in vessels, eyes, feet or nerve system, or even severe condition threatening the physical health and life quality of patients (13). In addition, it is reported that deficiency in insulin secretion and resistance to insulin (IR) constitute the major pathogenesis of T2DM, in which IR can dramatically decrease the intake, use and preserve abilities of peripheral tissues against the glucose, while curbing the output of plasma glucose, thereby leading to an increase in plasma glucose (14). IR can induce the excessive secretion of insulin by pancreatic B cells, and activate some vascular factors with a negative effect to increase the risk of lesions in vessels (15). Persistent IR and increase in plasma glucose give rise to the damage to pancreatic B cells, decrease the intake of glucose by adipose tissues or skeletal muscle while increasing the release of hepatic glucose and free fatty acid, so as to induce the hyperglycemia or disorders in lipid metabolism (16). T2DM is mainly seen in the elder population, which has prioritized the clinical research on the strategy for effective control of plasma glucose and improve insulin sensitivity in elder patients. Research has shown that treatment for T2DM should be designed for delaying the decline in function of pancreatic β cells and improving insulin sensitivity in addition to the control of plasma glucose. Thus, oral administration has been regarded as a major treatment strategy (17).

T2DM, a kind of chronic long-term progressive disease, is caused by the deficiency in compensation of pancreatic β cells and insulin resistance, and with the aggravation in dysregulation of glucose metabolism and continuous increase in output of hepatic glucose, pancreatic β cells experience progressive failure; in addition, due to development of insulin resistance occurring before the DM, there remains no effective hypoglycemic agent that could successfully control the progression of DM for a long term. Therefore, the combined administration of drugs that are complementary to each other has been considered as the major method in the treatment of DM so far. There are a variety of drugs that are developed for clinical treatment of DM, including thiazolidinedione, biguanide, sulfonylomocznik or nateglinide. Sulfonylurea has been widely applied as a kind of oral hypoglycemic drug; despite the similarity between sulfonylurea and nateglinide, they bind to different sites in cells, and sulfonylurea, instead of nateglinide, can act on the pancreatic β cells. Thiazolidinedione is a drug that can directly increase insulin sensitivity, while biguanide is preferred in the treatment of DM in an early stage. All these agents function through different action mechanisms to effectively control the plasma glucose, and in clinical practice, combined medication can be considered against the condition of patients.

A study (18) has pointed out that the derivative of thiazolidinedione can enhance the effect of insulin on peripheral tissues through binding to the peroxisome proliferators-activated receptor to activate the receptor. Peroxisome proliferators-activated receptor, a member of Nuclear Receptor Superfamily, shows significant effect on the fat storage and metabolism, in which the peroxisome proliferators-activated γ receptor, mainly distributed in the target cells of insulin, can affect the expression of genes in relation with the metabolism of glucose and lipid metabolism in pre-adipocytes (19). Pioglitazone, a kind of derivative of thiazolidinedione, can bind to the peroxisome proliferators-activated γ receptor, so as to modulate the expression of INS protein, control the synthesis, transportation and utilization of plasma glucose and improve the metabolism of plasma glucose (20). Clinical trials have indicated that after the administration of pioglitazone, T2DM patients have a significant decrease in the plasma glucose with obvious amelioration in blood fat, a decrease in HbA1c, increase in insulin sensitivity, but no enforced secretion of insulin (21). The results of this study showed that after 12 weeks of a single administration of pioglitazone, patients in the control group had lower levels of FPG, 2hPG, HbA1c, FIN and HOMA-IR in comparison with the levels before treatment, while the levels of TG, TC and LDL-C were significantly decreased with an increase in HDL-C; in addition, there was no obvious change in BMI. Thus, we infer that single administration of pioglitazone can decrease the level of insulin and increase the insulin sensitivity, finally attaining to efficient control of plasma glucose and amelioration in insulin resistance; moreover, in addition to the effective control of plasma glucose, it can also decrease the blood fat, showing a magnificent prophylactic effect on complications of DM.

Melbine, a kind of biguanide, can directly act on the body to promote the utilization of glucose in adipose tissues or muscle, decrease the output of hepatic glucose, enhance the intake, transportation and utilization of glucose in peripheral tissues, inhibit the degradation of fat, increase the oxidization of glucose, absorption of glucose in the gastrointestinal tract and block the entrance of glucose into the peripheral blood, thereby decreasing the level of plasma glucose (22, 23). Research has shown that after administration of melbine, T2DM patients had a lowered level of plasma glucose, and 12 weeks later, FPG was decreased to 3.0 to 5.0 mmol/L, PPG to 7.1 to 8.0 mmol/L and HbA1c to 1.5% to 2.0% (24, 25). It has been reported that the application of melbine for T2DM patients can effectively prevent the occurrence of complications in micro- or macro-vessels, thus protecting the cardiovascular system and decreasing the incidence of cardiovascular diseases (26). Scholars have noted that melbine can improve the blood fat profile, alleviate the vascular inflammation, improve the disorders in endothelial functions and prevent or even reduce the vascular lesions (27). A number of guidelines for diagnosis and treatment of DM have mentioned melbine as the preferred agent in controlling the plasma glucose. At an early stage, a single administration of melbine can manage the plasma glucose due to the massive residual functions of pancreatic β cells, but as it progresses and residual function of pancreatic β cells remains 5% or below with continuous deterioration in pancreatic function, melbine along can hardly handle the plasma glucose, which requires combined medication with other hypoglycemic agents, so as to ameliorate the dysfunction in insulin secretion, protect the function of pancreatic β cells, and minimize the risk of a hypoglycemic event (28, 29).

T2DM is mainly caused by the dysfunction in compensation of pancreatic β cells and IR which exist extensively among these patients. With the dysregulation in plasma glucose, hepatic glucose is continuously output, and pancreatic β cells manifest progressive failure. It has been indicated that diet control and rational exercise can lower the weight to increase the sensitivity to insulin with a decrease in blood fat and amelioration in IR, which can gain the control of the plasma glucose and defer the progression of DM (30, 31). During treatment of T2DM patients, oral medication is considered, but no available drugs can be applied in the control of plasma glucose for the long term with the progression of DM. Thus, combined medication is necessary. Previous studies have shown that single administration failed in controlling the progression of DM; patients with single administration can hardly attain the goal of plasma glucose control, and their levels of HbA1c remain above 7.0%; although control of plasma glucose could be achieved in some patients, fewer than half of them can sustain after 2 two years of treatment (32). In light of this, a great number of studies on combined medication have been performed by scholars, aiming to control the plasma glucose for a longer period through the combined medication of drugs that are complementary to each other in action mechanisms. In addition, multiple hypoglycemic agents can be used to attain the synergistic effect according to the varying pathological characteristics. Combined medication can not only reduce the dose of drugs but also decrease the side effect of drugs, with a significant improvement in plasma glucose control. Aiming to sustain the physical health of patients and prophylaxis of complications, combined medication can effectively control the blood fat and decrease the incidence of vascular lesions. In this study, pioglitazone in combination with melbine can manage the risk factors affecting plasma glucose and cardiovascular diseases. It has been reported that pioglitazone is different from melbine in terms of the action mechanism: The former can control the plasma glucose through increase the output of glucose-mediated by muscular insulin, while the latter can promote the intake of glucose in adipose tissues and decrease the absorption in the intestinal tract, so as to decrease the plasma glucose. The combined medication shows the promising synergistic effect (33, 34).

T2DM is mainly featured by an increase in plasma glucose, and FPG, 2hPG and HbAlc are the major indicators in monitoring the changes in plasma glucose. In this study, after 12 weeks of a single administration of pioglitazone or combined administration of pioglitazone and melbine, FPG, 2hPG and HbAlc were significantly reduced, showing significant differences in comparison with the levels before treatment ($p<0.05$); patients receiving the combined medication had much lower levels of FPG, 2hPG and HbAlc than their counterparts in the control group ($p<0.05$). This suggested that in comparison with the single administration of pioglitazone, pioglitazone in combination with melbine can decrease the plasma glucose of T2DM patients more efficiently. Disorders in lipid metabolism exist extensively among T2DM patients, in which lipid levels can reflect the status of lipid metabolism. Results of this study showed that after 12 weeks of a single administration of pioglitazone or combined administration of pioglitazone and melbine, TG, TC and LDL-C levels were significantly decreased, manifesting a significant difference in comparison with the levels before treatment ($p<0.05$), with a significant increase in the level of HDL-C ($p<0.05$); moreover, combined medication was more efficient in these changes than the control group. Thus, it is inferred that combined medication can evidently control the blood fat of patients, further decreasing the risk of vascular lesion, in which the underlying mechanism might be that combined medication can promote the differentiation of adipocytes and increase in small cells, which redistributing the fat. IR is the major mechanism of T2DM, in which FIN, 2hINS and HOMA-IR are the important indicators of IR and insulin sensitivity. In this study, after 12 weeks of treatment, both combined and single medication could decrease the levels of FINS, 2hINS and HOMA-IR, manifesting significant differences in comparison with the levels before treatment ($p<0.05$), and differences after the combined medication were more significant ($p<0.05$), prompting that in comparison of the single medication of pioglitazone, pioglitazone in a combination of melbine was much more efficient in decreasing the insulin levels of patients, and can decrease the plasma glucose through alleviating the IR and improving the insulin sensitivity without any increase of the insulin secretion. For elder T2DM patients, physicians should focus on not only the improvement in efficacy but also the risk of complications. In this study, the incidence rate of complications in patients undergoing single administration of pioglitazone was 8.33%, slightly lower than 10.00% in those undergoing combined medication, but the difference showed no statistical significance ($p>0.05$). Thus, combined medication can gain better efficacy without any significant increases in adverse reactions.

More research is needed on the management, control and treatment of diabetes. Also, the use of medicinal plants (35-38) and the application of new biotechnological methods such as genome editing (39) should be considered.

In conclusion, combined medication of pioglitazone and melbine can effectively reduce the levels of plasma glucose, blood fat and the HOMA-IR, with an elevated sensitivity to insulin. Besides, in T2DM elder patients, combined medication shows no severe adverse reactions, manifesting a promising safety in long-term administration, and it is worthy of being promoted in clinical practice.

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