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Efficacy and safety of dapagliflozin combined with insulin in overweight or obese individuals with type 2 diabetes

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Abstract: To investigate the efficacy and safety of dapagliflozin plus insulin in overweight or obese individuals with type 2 diabetes, from January to June 2019, 85 patients with type 2 diabetes were treated at Harrison International Peace Hospital and were randomized to either a combination group (43 cases) or a control group (42 cases). The control group received insulin, whereas the combination group additionally received dapagliflozin. On the first, second, fifth and tenth days, insulin doses and the time taken for standardized blood glucose were documented and their effectiveness and safety were compared. The time taken for standard insulin in the combination group was shorter vs. control group [(4.32±0.41) d vs. (6.93±0.57) d] and the difference in the dosage of insulin statistically significant (all $P<0.05$); there were significant differences in fasting blood glucose (FPG), 2h postprandial blood glucose (2hPBG) and hemoglobin a1c (HbA1c), fasting serum insulin (FINS) and homeostatic model assessment of beta (HOMA-β) between the two groups and within the two groups (all $P<0.05$); the incidence of adverse reactions was lower in the combination grou [4.65% (2/43) vs. 11.90% (6/42)] ($P<0.05$). Dapagliflozin plus insulin improves blood glucose and islet β cell activity with a good safety profile in overweight or obese individuals with type 2 diabetes.

Keywords: Type 2 diabetes, dapagliflozin, insulin, overweight, obese, efficacy, safety.

INTRODUCTION

Diabetes mellitus is a common endocrine disease caused mainly by pancreatic β-cell dysfunction and insulin resistance (Ma *et al*., 2022). With the advent of a fast-paced society and the prevalence of a low energy consumption and high calorie intake lifestyle, the incidence of diabetes mellitus and hypertension has shown an overall increasing trend worldwide. The number of people with type 2 diabetes will probably surge from 415 million to 642 million by 2040, while hypertension is even more common, with systematic population-based analyses from 90 countries showing that approximately 1.39 billion people worldwide have hypertension. Recent global risk assessment surveys show that about 1.4 million people died from diabetes in 2017, while about 7.8 million people died from hypertension (systolic blood pressure ≥140 mmHg) in 2015. As a country with a large population, China faces an even more serious challenge (Siasos *et al*., 2020).

Clinically, the treatment of diabetes focuses on its pathogenesis and symptoms, regulating lipids, anti-inflammation, controlling blood glucose, improving pancreatic β-cell function and regulating the patient's endocrine status (Kurian *et al*., 2022). Insulin is a powerful hypoglycaemic agent that inhibits lipolysis, suppresses inflammation and relieves the symptoms of diabetes mellitus. However, the long-term use of large amounts of insulin injections can increase the incidence of obesity, hypoglycaemia and exogenous hyperinsulinemia in patients (Tinajero *et al*., 2021). In contrast, oral administration combined with insulin can reduce insulin dosage while controlling blood glucose and avoid the adverse effects associated with high doses of insulin.

In recent years, the discovery of sodium-glucose cotransporter 2 (SGLT-2) inhibitors as a new class of hypoglycaemic agents has revolutionised the treatment of patients with type 2 diabetes. Among the sodium-glucose cotransporter family with more than 200 members, SGLT-2 was found to be highly expressed in the human kidney and responsible for approximately 90% of glucose reabsorption in the proximal tubule of the kidney (Dugani *et al*., 2021).

SGLT-2 inhibitors improve blood glucose mainly by reducing the absorption of glucose by the kidneys and promoting the excretion of glucose in the urine. As the first SGLT-2 inhibitor to be marketed in China, dapagliflozin has received a lot of attention from researchers. Dapagliflozin reduces the renal tubular reabsorption capacity of glucose by inhibiting the function of SGLT2 in the renal tubules, thereby increasing urinary glucose excretion, lowering blood glucose and directly reducing the pathologically elevated renal glucose threshold. Thus, its glucose-lowering mechanism is not dependent on pancreatic β-cell function (Chertow *et al*., 2021).

Nonetheless, western medicine drugs are associated with adverse reactions. At present, Chinese medicine treatment is widely used and respected for its symptomatic differentiation, ideal efficacy and high drug safety. On the one hand, Chinese medicine can improve the clinical

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symptoms associated with the disease. On the other hand, it can also regulate the functions of the body to achieve a balance between yin and yang, which in turn improves the functions of the body and ensures that the disease is well controlled. It can further ensure stable control of blood sugar and avoid complications that endanger the health and safety of patients.

To this end, the present study explored the efficacy of Dapagliflozin combined with insulin in type 2 diabetes to provide a feasible strategy for its treatment.

MATERIALS AND METHODS

Subjects

85 patients who were treated in Harrison International Peace Hospital with newly diagnosed diabetes from January 2019 to June 2019 were enrolled. The initial sample size calculation estimated that 40 patients per group would be required to determine between-group differences in a two-sided significance test with a power of 0.8 and an alpha error level of 0.05. Finally 85 cases were enrolled. The baseline characteristics were similar in the two groups (P>0.05).

Randomisation was conducted via an online web-based randomisation tool (http://www.randomizer.org/). In order to conceal allocation, the randomisation procedure and allocation were managed by an independent research assistant who was blinded to the screening and assessment of participants.

The trial was conducted as per the guidelines of Declaration of Helsinki. The protocol obtained approval from institutional review boards or ethics committees (KI-LI20190102). All patients provided written informed consent prior to the commencement.

Inclusion criteria: (1) Patients who were diagnosed as type 2 diabetes; (2) initial-onset diabetes; (3) fasting blood glucose ≥ 9.0 mmol /L; (4) BMI ≥ 24kg/m^2 ; (5) no previous diabetes-related drug treatment.

Exclusion criteria: (1) Patients with secondary diabetes; (2) patients diagnosed as type 1 diabetes; (3) patients with complications of diabetes; (4) pregnant or lactating patients; (5) patients with co-infection; (6) patients with severe diseases of the heart, brain, liver, kidney and other important organs; (7) patients with diabetic lactic acidosis and diabetic ketoacidosis; (8) allergies to dapagliflozin, insulin or contraindications.

Methods

Patients in both groups were given health education, including controlling diet, taking rest and maintaining moderate exercise. The control group was given aspartic insulin injection 30 [SDFA approval No. S20133006, Novo Nordisk (China) Pharmaceutical Co., Ltd.]; the initial dose was 10-12 U/d and the dose could be adjusted every 2-3 d thereafter according to the patient's blood glucose level until the standard was reached (fasting blood glucose ≤7.0mmol/L, 2h postprandial blood glucose ≤11.1mmol/ L is achieved). Patients in the combination group additionally received dapagliflozin (SDFA approval No.J20170040, AstraZeneca Pharmaceuticals Ltd.) at a dose of 5-10mg orally once daily before breakfast. Patients in both groups were intervened to improve circulation, lower blood pressure and lower blood lipids.

On the basis of treatment in the two groups, they were treated with Liangxue Sanyu Decoction. The formula is composed of American ginseng 25g, Astragalus 25g, Poria 20g, *Paeonia suffruticosa* 15g, Anemarrhena 6g, *Rehmannia glutinosa* 10g, Trichosanthes 15g, Scrophulariaceae 10g, Gardenia 6g, *Lycopus lucidus* 10g, *Serissa japonica* 15g, Ghost Arrow Feather 15g, jujube kernels 20g, *Albizia julibrissin* 15g, *Salvia miltiorrhiza* 15g, *Coptis chinensis* 6g, licorice 6g.

The medicine was added and subtracted according to the symptoms are as follows: For those with fatigue and weakness, add 10g of fried Atractylodes; for those with stagnation of heat, add 20g of turmeric; for those with insomnia, add 10g of vine multiflower knotweed and 15g of mother of pearl; for those with constipation, add 10g of *Citrus aurantium* and 6g of rhubarb; for those with dry eyes, add 15g of Dendrobium; add *Ophiopogon japonicus* 15g for those who are thirsty. 400mL liquid medicine was obtained after being decocted and administered orally in the morning and evening, 1 dose per day. The treatment spanned for 1 consecutive month.

Outcome measures

(1) Insulin dosage of patients on the 0d, 2d, 5d and 10d was recorded, as well as the time taken for blood glucose reaching the standard in both groups; (2) Fasting blood glucose (FPG), 2h postprandial blood glucose (2hPBG) and hemoglobin a1c (HbA1c) were detected by automatic biochemical analyzer before treatment and one month after treatment; (3) Homeostatic model assessment of beta (HOMA-β) function was measured before treatment and one month after treatment; (4) The adverse reaction of patients in the two groups was observed and compared; (5) After discharge, the patients were followed up either by outpatient channel or telephone once a month for half a year, and the prognosis of the two groups was compared.

STATISTICAL ANALYSIS

The normality of data distribution was determined with the Shapiro-Wilk test. SPSS 22.0 software was used to analyze the data. The normal-distributed measurement data were examined by t-test or Student’s t test (t test), analysis of variance (ANOVA) and the count data

were analyzed using χ^2 test. $P<0.05$ was the threshold for statistical difference.

RESULTS

Dosage of insulin and the time taken for reaching the standard

The time taken for insulin to reach the standard in the combination group was (4.32±0.41) d, which was lower than the (6.93±0.57) d in the control group (t=24.280, $P<0.001$); the dosage of insulin in the two groups was statistically different (***$P<0.001$) (table 1-2 and fig. 1).

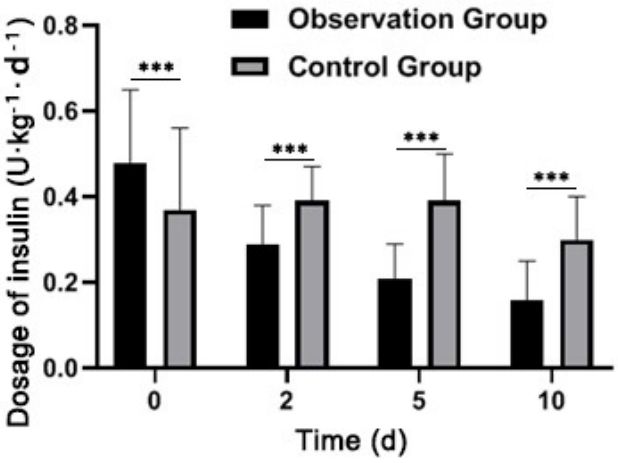

Fig. 1: Comparison of insulin dosages at different times in both groups

Blood-glucose-related indexes

FPG, 2h PBG and HbA1c values were homogenuous in the two groups before treatment; there were significant differences in the levels of FPG, 2h PBG and HbA1c between the two groups after treatment and significant improvements in FPG, 2h PBG and HbA1c were observed in the combination group ($P<0.05$) (table 3).

Function of pancreatic β cell

The two groups showed insignificant differences in FINS and HOMA-β before treatment ($P>0.05$). The FINS and HOMA-β of the two groups were comparable after treatment, with better outcomes in the combination group ($P<0.05$) (table 4).

Adverse reactions

The incidence of adverse reactions was lower in the combination group vs. control group [4.65% (2/43) vs. 11.90% (6/42)] ($P<0.05$) (table 5).

Follow-up and prognosis

Both groups were followed up for half a year. During the follow-up, 90.70% (39/42) of the patients in the combination group achieved the target blood glucose values with no intervention of hypoglycemic drugs, which was significantly higher than 73.81% (31/42) of the control group ($\chi^2=4.170$, $P=0.041$).

DISCUSSION

Type 2 diabetes is characterised by insulin resistance and/or inadequate secretion of pancreatic islet β-cells (Leccisotti *et al*., 2022). In the clinical management of type 2 diabetes, oral hypoglycaemic drugs are usually given first to stimulate insulin secretion in order to achieve glucose reduction. However, some patients still require insulin therapy though it has been recognised that long-term, high-dose insulin use is associated with adverse responses. And in outpatient clinics for the treatment of type 2 diabetes, oral hypoglycaemic agents are mostly used in combination with insulin therapy to reduce the adverse effects of high-dose insulin (Zelniker *et al*., 2019). However, there are many different types of oral hypoglycaemic drugs and numerous different processes. Therefore, the choice of oral hypoglycaemic agents to be used in conjunction with insulin for treatment is a clinical focus and a test.

SGLT2 is expressed in the anterior segment of the renal proximal tubule and D-glucose is transported at a sodium-glucose ratio of 1:1, of which 90% can be reabsorbed [9]. Dapagliflozin is a highly selective agent that inhibits SGLT2, thereby inhibiting renal reabsorption of glucose and promoting urinary glucose excretion. Its glucose-lowering process is an insulin-dependent glucose-lowering mode (Cocchi *et al*., 2021). Therefore, dapagliflozin has been of great clinical interest to doctors and patients since its development and launch.

In this study, the control group received conventional treatment combined with insulin, on top of which the combination group received dapagliflozin. In contrast, the insulin dosage and the time taken for blood glucose to reach standard levels were significantly lower in the combination group than in the control group. The possible explanation is that dapagliflozin improves blood glucose in patients with T2DM better than conventional hypoglycaemic drugs. Unlike previous drugs that rely on pancreatic B-cell function or tissue sensitivity to insulin, dapagliflozin mainly acts on the sodium-glucose co-transporter in the renal tubules, significantly reducing renal tubular glucose reabsorption and achieving hypoglycaemia (Guo *et al*., 2021). In addition, dapagliflozin can significantly reduce patients' weight and blood lipids while lowering blood glucose and reduce the accumulation of fat in the liver. This may be because dapagliflozin promotes the elimination of excess glucose from the body, creating a state of negative energy balance and increasing the oxidation of fatty acids, thereby reducing lipid levels such as TG, which greatly reduces the time required for hypoglycaemia (Wiviott *et al*., 2019).

Table 1: Baseline clinical information of the two groups

Clinical information	Combination group (n = 43)	Control group (n=42)	χ^2/t	*P*
Gender				
Male	25	22	0.285	0.593
Female	18	20		
Age (years)	45.27±5.33	44.96±5.69	0.259	0.804
Disease course (months)	9.26±2.17	9.77±2.39	1.030	0.306
BMI(kg·m^{-2})	27.95±3.07	28.65±3.95	0.914	0.364
HbA1c (%)	8.96±1.88	9.77±1.51	2.187	0.223
Systolic pressure	131.25±8.13	133.66±8.01	1.376	0.172
Diastolic pressure	80.33±7.62	81.47±7.06	0.715	0.477
2h C-Peptide / C-Peptide (times)	2.48±0.52	2.39±0.73	0.656	0.514
Family history of diabetes mellitus				
Yes	24	21	0.420	0.517
No	19	22		

Table 2: Dosage of insulin in the two groups

Group	Dosage of insulin (U·kg^{-1}· d^{-1})			
	0th d	2nd d	5th d	10th d
Combination group (n = 43)	0.48±0.17	0.29±0.09	0.21±0.08	0.16±0.09
Control group (n = 42)	0.37±0.19	0.39±0.08	0.39±0.11	0.30±0.10
F	24.47			
P	<0.001			

Table 3: Comparison of blood-glucose-related indexes before and after treatment between the two groups

Group	FPG		2h PBG		HbA1c	
	Before treatment	After treatment	Before treatment	After treatment	Before treatment	After treatment
Combination group (n = 43)	11.52±1.93	5.13±1.77*	18.96±3.39	7.69±1.33*	8.96±1.88	5.02±1.19*
Control group (n=42)	12.07±1.88	7.94±1.95*	18.62±3.17	10.87±1.97*	9.77±1.51	8.22±0.97*
t	1.089	6.960	0.477	8.741	0.567	13.570
P	0.280	<0.001	0.634	<0.001	0.572	<0.001

Note: * refers to the comparison with the data before treatment, *P*<0.05

Table 4: Comparison of the function of pancreatic β cell

Group	FINS (mU /L)		HOMA-β	
	Before treatment	After treatment	Before treatment	After treatment
Combination group (n=43)	8.21±2.69	12.07±1.22*	4.08±0.83	5.77±1.19*
Control group (n=42)	8.15±2.57	9.05±1.25*	4.15±0.76	4.85±1.09*
t	0.105	11.270	0.405	3.714
P	0.916	<0.001	0.686	<0.001

Note: * refers to the comparison with the data before treatment, *P*<0.05

Table 5: Adverse reactions in the two groups

Group	Diarrhea	Urinary tract infection	Debilitation	Hypoglycemia	Incidence of adverse reactions (%)
Combination group	0	0	2	0	4.65(2/43)
Control group	2	1	3	2	11.90(6/42)
χ^2					4.242
P					0.039

After 1 month of treatment, the blood glucose indexes such as FPG, 2hPBG and HbA1c in the combination group were better than those in the control group, suggesting that dapagliflozin combined with insulin could significantly improve the blood glucose situation. The function of pancreatic β-cells (FINS, HOMA-β levels) in the combined group was better than that in the control group, suggesting that dapagliflozin can significantly improve the function of pancreatic β-cells. The reason for this may be that the patients' blood glucose can be rapidly reduced to standard levels and the pancreatic β-cells are rested (Jongs *et al*., 2021). In addition, abnormal islet cell function is central to the development and progression of T2DM and protection of islet cell function is important in controlling the progression of the disease. Dapagliflozin has also been shown to have a protective effect on islet β-cells. As the hypoglycaemic mechanism of dapagliflozin is not linked to the insulin sensitivity of tissue cells or the function of pancreatic β-cells, it can rapidly reduce blood glucose levels and keep blood glucose within a safe range. Animal experiments have also shown that SGLT2 inhibitors can significantly increase the total number of islet β cells and the hypolipidemic, anti-inflammatory and GLP-1 promoting effects of dapagliflozin can also indirectly protect islet β cells (Tamborlane *et al*., 2022).

The control group was more prone to hypoglycaemia and urinary tract infections, which may be related to the lower insulin dosage in the combination group. All of these results suggest that dapagliflozin combined with insulin has significant efficacy and a high safety profile. The reasons for this may be as follows: The inhibitory effect of dapagliflozin on renal glucose reabsorption directly lowers the renal glucose threshold and lowers blood glucose concentrations after promoting renal glucose excretion; this in turn reduces the hypoglycaemic load on islet cells, thereby correcting the problem of inadequate insulin secretion (Rizzo *et al*., 2022). Dapagliflozin does not increase insulin secretion and is also indicated in patients with severely impaired islet cell function and higher insulin doses.

In addition, we also gave them traditional Chinese medicine. Traditional Chinese medicine believes that type 2 diabetes belongs to the category of "xiaoke" and is mostly caused by improper diet, which leads to the accumulation of phlegm and dampness. After a long time, both qi and yin are deficient, the veins are blocked, the operation is not smooth and the blood is viscous. Therefore, the disease should be treated by clearing away heat, nourishing qi and nourishing yin (Karagiannis *et al*., 2021).

In Liangxue Sanyu Decoction, American ginseng has the effect of clearing heat and promoting body fluid, nourishing qi and nourishing yin; Astragalus has the effect of promoting qi; Poria has the effect of diuretic and swelling; Gardenia and Cortex Moutan have the effect of clearing heat and cooling blood; Trichosanthes, Rehmannia glutinosa and Scrophularia have the effect of clearing heat; Coptis has the effect of clearing away heat and dampness; Anemarrhena has the effect of nourishing yin and clearing away heat; Salvia miltiorrhiza has the effect of regulating qi, promoting blood circulation and removing blood stasis; Serissa japonica has the effect of clearing away heat and dampness; all the medicines have the effect of nourishing qi, promoting qi, removing blood stasis and clearing away heat. The results of modern pharmacological studies show that astragaloside IV has the functions of lowering blood sugar and improving insulin resistance, thus playing a role in the treatment of type 2 diabetes. Moreover, in animal experiments, American ginseng stem and leaf saponins can reduce blood sugar in hyperglycemic mice and increase their serum insulin levels. Salvia miltiorrhiza salvianolic acid B has a good function of regulating glucose and lipid metabolism. Poria cocos contains Poria polysaccharides, triterpenoids and ergosterol, which have certain promoting effects on regulating body metabolism and lowering blood sugar (Zhao *et al*, 2022; Bao *et al*, 2021; Zhang *et al*, 2022; Dou *et al*., 2021).

Our study also has some shortcomings. Firstly, this study is a single-centre study with a small sample size included, and is only representative of the efficacy of dapagliflozin in overweight or obese patients with T2DM in a local area. Future multi-centre studies with large samples could be conducted nationwide. Secondly, the follow-up period of this study was relatively short and did not provide a good indication of the overall efficacy of dapagliflozin in patients with type 2 diabetes. A database could be established for long-term follow-up in the future. Finally, the patients in this study were receiving different types of basic glucose-lowering medication. Although there were no significant differences in medication between the two groups, the potential impact of different medications on the study cannot be ruled out. Future studies are needed to increase the reliability of the results.

CONCLUSION

To sum up, dapagliflozin combined with insulin reduces the dose of insulin in overweight or obese patients with T_2DM and significantly improves blood glucose and pancreatic beta-cell function with a good safety profile. This protocol deserves promotion in clinic.

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