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Original Article

Efficacy and safety of glucagon-like peptide-1 receptor agonist combined with sodium-glucose co-transporter-2 inhibitor in the treatment of type 2 diabetes mellitus patients with obesity: a retrospective analysis study

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Abstract: Background: Type 2 diabetes mellitus (T2DM) and obesity are metabolic diseases characterized by high economic and health burdens. A combination of sodium glucose cotransporter 2 (SGLT2) inhibitor dapagliflozin (DAPA) and glucagon-like peptide-1 receptor agonist (GLP1-RA) exenatide (ExQW) has not been explored as a treatment strategy for T2DM patients with obesity. Therefore, this retrospective analysis compared the efficacy and safety of dapagliflozin (DAPA) combined with GLP1-RAs Exenatide (ExQW) and dapagliflozin alone in the treatment of 125 T2DM patients with obesity. Methods: This study is a retrospective study. From May 2018 to December 2019, 62 T2DM patients with obesity were treated with DAPA + ExQW, labeled DAPA + ExQW group. From December 2019 to December 2020, 63 patients with T2DM and obesity were treated with DAPA + placebo, labeled the DAPA + placebo group. DAPA + ExQW group received DAPA at a dose of 10 mg/day plus ExQW at 2 mg/week and DAPA + placebo group was administered with DAPA at a dose of 10 mg/day plus a placebo. The primary outcome for the present study was change in HbA1c (%) at different treatment points relative to the baseline. The secondary outcomes included changes in fasting plasma glucose (FPG, mmol/L), systolic blood pressure (SBP, mm/Hg) and body weight (BW, kg). Study outcomes were evaluated at 0, 4, 8, 12, 24, and 52 weeks after initial treatment. All *P* values were two-sided, with a *P* value less than 0.05 indicating statistical significance. Results: A total of 125 patients completed the present study (62 in the DAPA + ExQW group and 63 in the DAPA group). Patients in the DAPA group showed a significant decrease in the level of HbA1c during the first 4 weeks, but the HbA1c level in this group remained stable for the remaining 48 weeks. Similar results were observed for other variables such as FPG, SBP, and BW. Patients who received a combination of DAPA and ExQW exhibited a continuous decline in the evaluated variables. The decrease in all the variables was greater in the DAPA + ExQW group than that in the DAPA group. Conclusions: A combination of DAPA and ExQW exerts a synergistic effect in the treatment of T2DM patients with obesity. However, the potential synergistic mechanism of this combination should be studied further.

Keywords: T2DM, SGLT2, GLP1-RA

Introduction

Previous findings indicate that more than 600 million adults present with diabetic mellitus worldwide and most of these subjects present with type 2 diabetic mellitus (T2DM) comorbidity [1]. Increase in the prevalence of obesity and T2DM comorbidity is associated with increase in mortality and disability rates. Findings from a previous multinational observational study showed that approximately 50% of T2DM patients present with microvascular complications (such as neuropathy, nephropathy, and retinopathy) and around 30% are diagnosed with macrovascular complications (such as peripheral vascular disease and coronary heart disease) [2]. Therefore, it is imperative to develop novel and effective treatment strategies for T2DM patients.

Obesity is a common complication of T2DM. Obesity has high prevalence worldwide and is associated with severe health consequences. The major complications of obesity include musculoskeletal disease, nonalcoholic fatty liver disease, cardiovascular disease, and even

some cancers, which increases the mortality rate of obese patients. Weight loss can reduce the risk of cardiometabolic disease associated with obesity. A recent randomized controlled study reported that significant and beneficial reductions in body weight can be achieved through intensive lifestyle interventions [3]. However, previous real-life primary care studies reported contrary results [4]. This implies that more targeted and effective intervention strategies should be explored for management of obesity patients. Effective weight loss is hindered by the complex physiological counter-regulatory mechanisms. For example, compensatory dietary intake and consumption hinders effective initial weight loss, which is the main reason for most weight loss failures. Therefore, a novel treatment strategy should be explored to effectively circumvent the limitations of conventional interventions and ensure long-term weight loss in obese subjects.

The main treatment strategies for T2DM patients complicated with obesity include agents with both glucose-lowering and weight loss effects, which include sodium glucose cotransporter 2 (SGLT2) inhibitors and glucagon-like peptide-1 receptor agonists (GLP-1RAs) [5, 6]. These two agents induce weight loss through different mechanisms. SGLT2 inhibitors inhibit reabsorption of glucose by the proximal renal tubules, resulting in an increase in the excretion of calories and glucose in urine. However, SGLT2 can induce a compensatory appetite increase [7, 8]. GLP-1RAs exert a weight loss effect by reducing appetite and delaying gastrointestinal emptying [9]. The two agents effectively reduce glucose level and body weight in T2DM patients, with a curative effect maintained for approximately 2-6 years [10-15].

The mechanisms of action of SGLT2 inhibitors and GLP1-RAs are different and potentially complementary, so clinicians hypothesize that a combination of these two agents can exert a synergistic effect in treating T2DM patients complicated with obesity. This retrospective analysis compared the efficacy and safety of dapagliflozin (DAPA) combined with GLP1-RAs Exenatide (ExQW) and dapagliflozin alone in the treatment of 125 T2DM patients with obesity.

Methods

Study design

This study is a retrospective study. From May 2018 to December 2019, 62 T2DM patients with obesity were treated with DAPA + ExQW, labeled DAPA + ExQW group. From December 2019 to December 2020, 63 patients with T2DM and obesity were treated with DAPA + placebo, labeled the DAPA + placebo group. We retrospectively compared the efficacy and safety of DAPA + ExQW versus DAPA + placebo in the treatment of T2DM with obesity. The DAPA + ExQW group received DAPA at a dose of 10 mg/day plus ExQW at 2 mg/week, and the DAPA + placebo group was administered with DAPA at a dose of 10 mg/day plus a placebo.

Procedures

Patients who met the following criteria were enrolled in the present study: a) patients diagnosed with T2DM according to the 2010 guideline [16]; b) obesity comorbidity, which was defined as more than 30 kg/m^2 body mass index (BMI); c) no major surgery conducted within the previous 3 years; and d) aged between 18-70 years. DAPA and ExQW are also beneficial for cardiovascular conditions, so patients complicated with cardiovascular disease were also enrolled to the study. The outcomes were evaluated at 0, 4, 8, 12, 24, and 52 weeks. Dapagliflozin was purchased from Shandong Lukang Pharmaceutical Co., Ltd. (lot number: H20213815). Exenatide was purchased from Qinghai Chenfei Pharmaceutical Co., Ltd. (lot number: H20223543).

Treatment

Eligible patients were subjected to a screening period for approximately 8 weeks. Subsequently, eligible patients were randomly assigned to two groups with one group receiving DAPA at a dose of 10 mg/day plus ExQW at a dose of 2 mg/week for 52 weeks, and the other group received DAPA plus placebo at the same dose for 52 weeks. All agents were administered using an open-label design. Oral and written guidelines were provided to patients to ensure that they followed the national guidelines for a balanced normal calorie diet and the subjects

were advised to exercise moderately (e.g., walk 30 minutes most of the time). The diet and exercise of the participants were not strictly monitored since the main purpose of this study was to evaluate the pharmacological effects of the drugs.

Outcomes

The primary outcome was the change in HbA1c (%) between the baseline and different stages of treatment. Latex agglutination reaction method was used to determine HbA1c levels. The percentage of HbA1c content in total hemoglobin Hb was directly determined by evaluating the interaction of HbA1c antigen and HbA1c antibody. Secondary outcomes included changes in fasting plasma glucose level (FPG, mmol/L), systolic blood pressure (SBP, mm/Hg), and body weight (BW, kg). Venous blood was collected after overnight fasting (no food for at least 8-10 hours, except drinking water) for FPG detection. SBP was measured using electronic sphygmomanometer after 10 minutes of sitting rest. BW was measured using a traditional weight scale. Exploratory efficacy outcomes included proportions of patients who lost ≥5% and ≥10% body weight. The changes in waist circumference and waist-to-hip ratio were evaluated, and heart rate and changes in fasting serum lipids were also monitored. Adverse events (AEs) were recorded and monitored according to the Medical Dictionary for Regulatory Activities (MedDRA) version 18.0. Additionally, AEs associated with DAPA and/or ExQW, including genital infections, urinary tract infections, changes in renal function, and events related to volume reduction, were recorded.

Statistical analysis

An intention to-treat (ITT) analysis was performed to compare the differences in the primary and secondary efficacy outcomes between the two groups. Adjusted mean changes in these outcomes from 0 to 24, from 24 to 52, and from 0 to 52 weeks between the two groups were compared, with a 95% confidence interval (CI). Continuous variables such as HbA1c, FPG, SBP and body weight, with normal distribution were compared using Student's t test to explore difference between the two groups. Mann-Whiney test was performed for continuous variables that did not exhibit normal distribution. Chi-square test was performed to compare the differences in categorical variables between the two groups. All statistical analyses and graphs were generated using R software (4.2.0). A p value less than 0.05 indicated statistical significance.

Results

Participants

A total of 179 patients were screened in our center from May 2018 to December 2020. A total of 138 patients met the inclusion criteria and were randomly assigned to two groups to receive Dapagliflozin QD 10 mg plus Exenatide QW 2 mg (DAPA + ExQW group, n = 67), or Dapagliflozin QD 10 mg + placebo injection QW (DAPA group, n = 71). A total of 5 patients (7.5%) in the DAPA + ExQW group and 8 patients (11.3%) in the DAPA group dropped out of the study during the 52 weeks of treatment. The detailed reasons for patient drop-out are presented in **Figure 1**. Therefore, a total of 125 patients completed the study (62 in the DAPA + ExQW group and 63 in the DAPA group). The baseline characteristics were not significantly different between the two groups (**Table 1**).

Efficacy outcomes

Glycemic variables: Patients in the DAPA group showed a significant decrease in the level of HbA1c at the first 4 weeks (**Figure 2**). However, the HbA1c level in the DAPA group was stable from week 4 to the end of the study. The results showed that a significant decrease in HbA1c occurred in the first half period of the study, and the efficacy of DAPA decreased in the later stages of the study (**Figure 2A**). Similar changes were observed for FPG. A significant decrease in FPG induced by DAPA was mainly observed in the first 4 weeks, whereas the FPG reduction effect of DAPA was not significant from week 4 to the end of the study (**Figure 2B**). In contrast, a combination of DAPA and ExQW induced a long-term effect in reducing HbA1c and reducing FPG level. The hypoglycemic effect of the combination of the two drugs was significantly better than that of DAPA alone throughout the study period. Other exploratory outcomes, such as oral glucose tolerance test (OGTT) showed similar trend as HbA1c and FPG (data not shown).

Cardiovascular variable: Changes in SBP were compared between the two groups at different treatment points to explore the potential car-

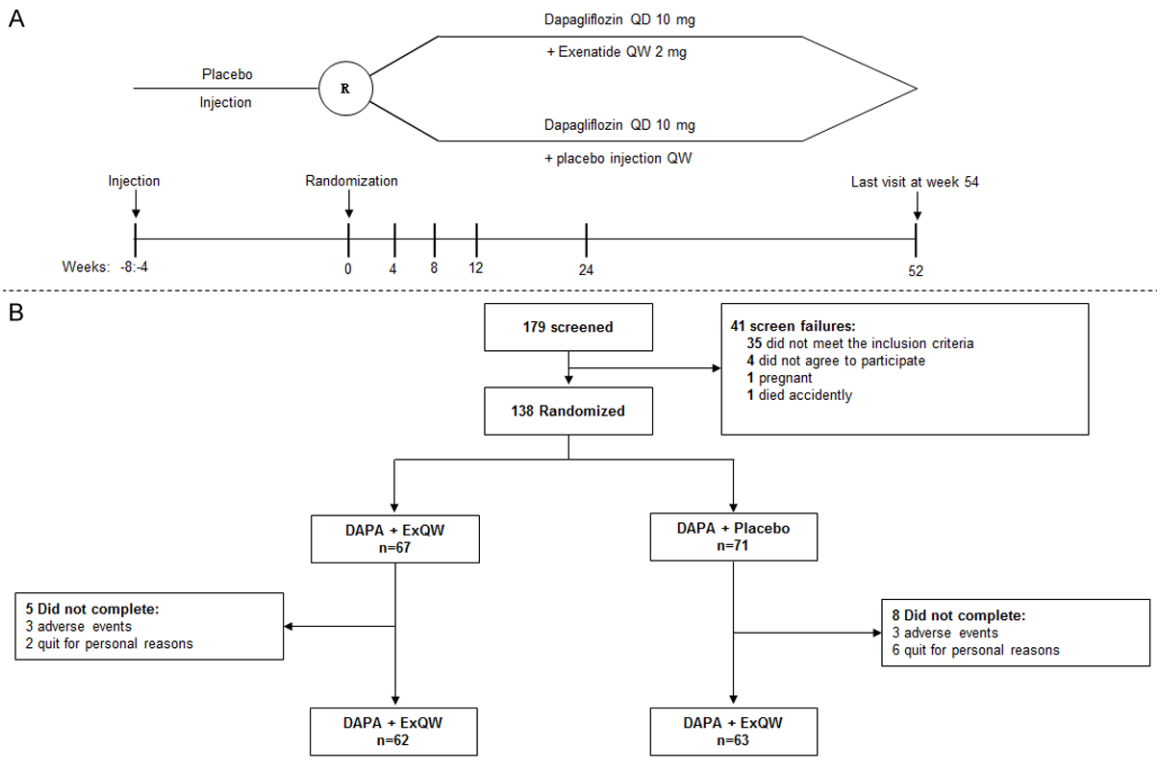

Figure 1. A flowchart of the study design.

Table 1. Baseline characteristics of subjects in the two groups

	DAPA + ExQW (n = 62)	DAPA + Placebo (n = 63)	*P* value
Sex:			0.128
Female	32 (51.6%)	23 (36.5%)	
Male	30 (48.4%)	40 (63.5%)	
Age	57.5 (9.90)	56.2 (10.2)	0.452
Course of T2DM (y)	8.16 (4.15)	8.57 (3.65)	0.560
Smoking history:			0.400
No	21 (33.9%)	16 (25.4%)	
Yes	41 (66.1%)	47 (74.6%)	
History of heart disease:			0.744
No	58 (93.5%)	57 (90.5%)	
Yes	4 (6.45%)	6 (9.52%)	
History of major surgery:			0.207
No	58 (93.5%)	62 (98.4%)	
Yes	4 (6.45%)	1 (1.59%)	
Baseline HbA1c (%)	8.33 (0.89)	8.62 (0.94)	0.072
Baseline FPG (mmol/L)	11.1 (1.37)	10.9 (1.42)	0.548
Baseline SBP (mmol/L)	134 (6.33)	135 (6.71)	0.863
Baseline Body weight (kg)	72.0 (4.84)	72.7 (4.65)	0.418

DAPA, dapagliflozin 10 mg/day; ExQW, exenatide 2 mg/week; T2DM, type 2 diabetic mellitus; HbA1c, glycated hemoglobin; FPG, fasting plasma glucose; SBP, systolic blood pressure.

diovascular benefit of the combination therapy. The combination of DAPA and ExQW and DAPA alone induced a similar decrease in SBP at the first 4 weeks (**Figure 2C**). However, SBP showed a slight increase after 4 weeks of treatment with DAPA alone (although the effect was not significant). In contrast, a combination of DAPA and ExQW induced a significant continuous decline in SBP in the last 48 weeks. The combination therapy induced a significant decrease in SBP compared with DAPA alone. The pharmacological effect of the combination therapy on other variables, such as heart rate and volume reduction, was also higher than DAPA alone (data not shown).

Body weight

BW is an important endpoint for T2DM patients with obesity. The

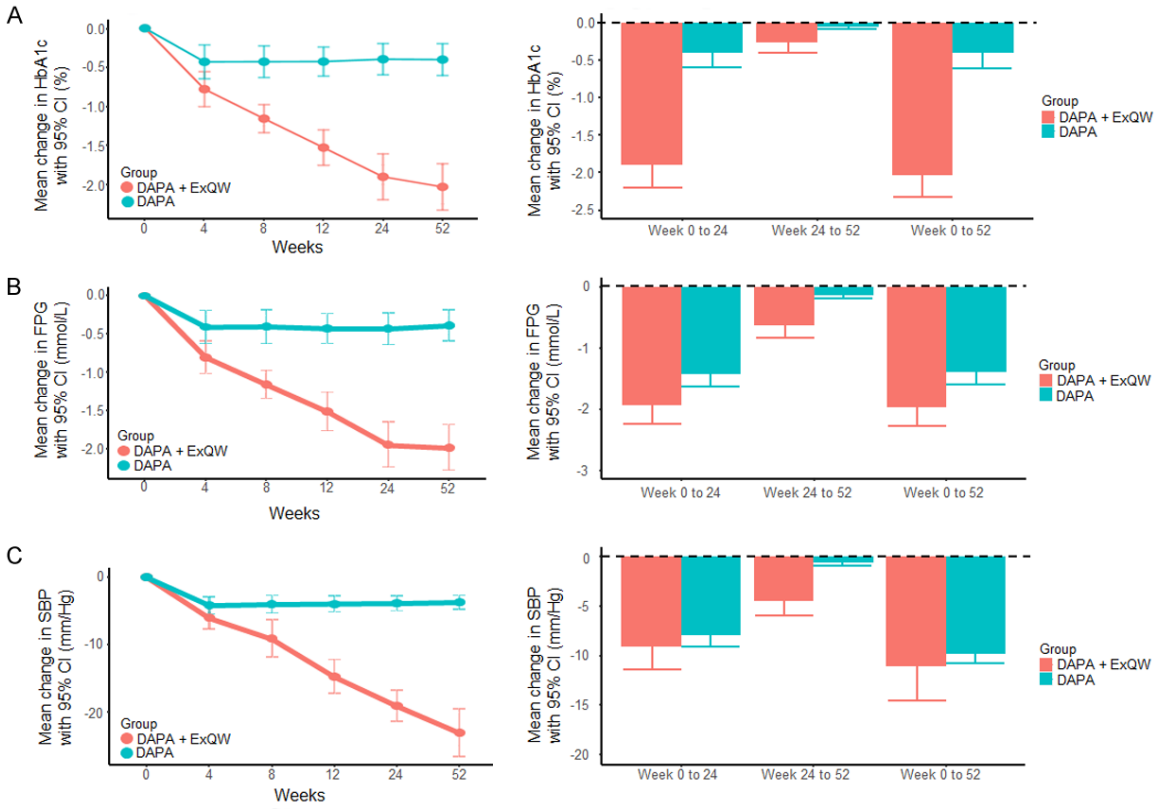

Figure 2. Differences in glycosylated hemoglobin Type A1C (HbA1c) (A), fasting plasma glucose (FPG, mmol/L) (B), and systolic blood pressure (SBP, mmHg) (C) at 4, 8, 12, 24, and 52 weeks compared with the baseline levels.

results showed that treatment with DAPA alone induced a significant reduction in BW in the first four weeks, whereas fluctuations in BW level were observed in the last 48 weeks, and stabilized at 52 weeks (**Figure 3**). The level of BW in the combination group showed a significant decline in the last 48 weeks, with a significantly higher decline than that of the DAPA group. The proportions of patients who lost ≥5% and ≥10% body weight were recorded to explore the specific efficacy of the two agents on single patient level. The patients who received DAPA combined with ExQW showed continuous weight loss, and the range of weight decrease was between 7-15% (**Figure 3C** and **3D**). However, patients who received DAPA alone only showed a significant weight loss in the first 4 weeks, with fluctuations observed in the last 48 weeks. The average decrease in weight loss was below 5%. Other BW-related variables, such as waist circumference and waist-to-hip ratio, did not show significant changes in patients who received DAPA alone, but a significant decrease was observed in student who received DAPA + ExQW (data not shown).

Safety outcomes

The results did not show no significant difference in the incidence of common AEs between the two groups (69.4% in the DAPA + ExQW group and 74.6% in DAPA group, P = 0.518; **Table 2**). Only one case of serious AEs was observed in each group.

Discussion

Obesity is a major cause of death and a key health burden, especially subjects presenting with T2DM. Long term weight loss is a challenge for obese patients. It is challenging to effectively reduce weight at the initial stage and maintaining the weight loss for a long time during follow-up, because the process is modulated by various physiological mechanisms, such as compensatory appetite increase. SGLT2 inhibitors and GLP1-RAs are highly effective in lowering glucose and have a complementary role in reducing appetite. Therefore, a combination of the two agents is a potential strategy to achieve a long-term weight loss and promote reduction of glucose level. In the pres-

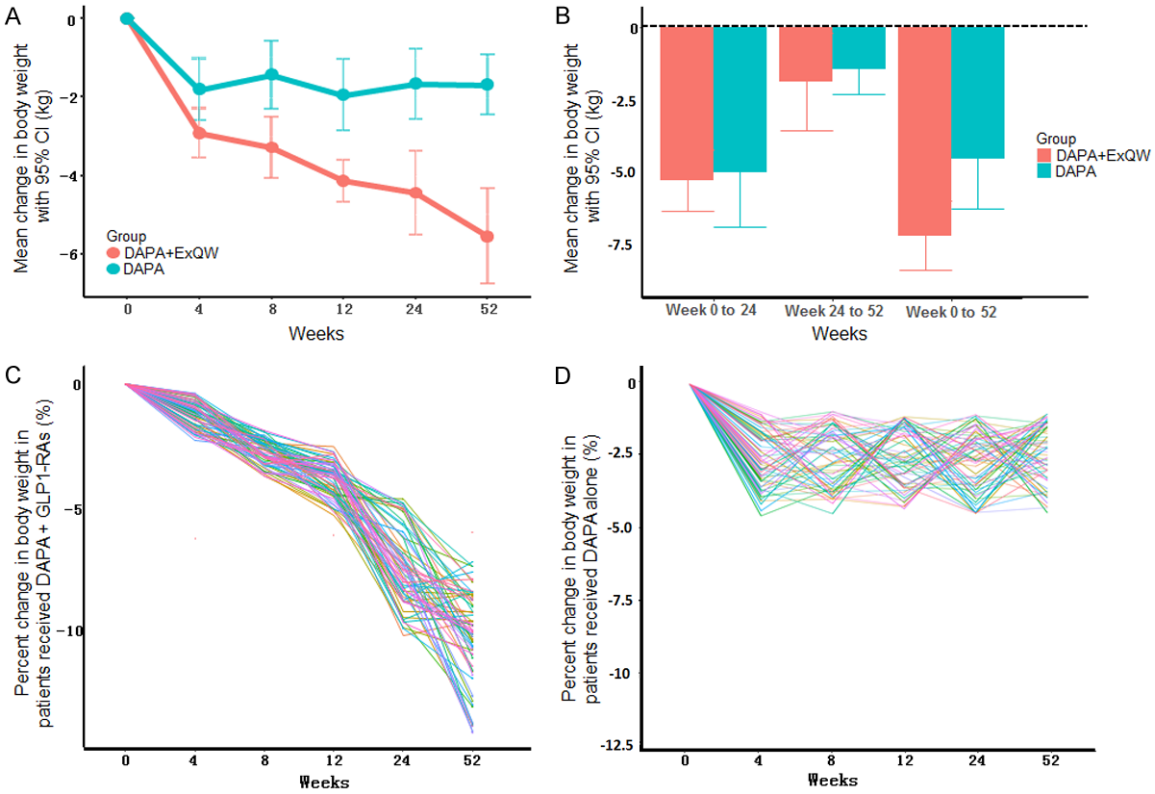

Figure 3. Change in body weight at 4, 8, 12, 24, and 52 weeks compared with the baseline body weight.

Table 2. Summary of adverse events (AEs) in the two groups

	DAPA + ExQW (n = 62)	DAPA + Placebo (n = 63)	*P* value
Any AEs	43 (69.4%)	47 (74.6%)	0.518
Treatment-related AEs	5 (8.1%)	8 (12.7%)	0.400
Serious AEs	1 (1.6%)	1 (1.6%)	0.991
Deaths	0 (0)	0 (0)	1.000
Common AEs occurred in > 5% patients in any group			
Decreased appetite	7 (11.3)	6 (9.5%)	0.749
Dizziness	5 (8.1%)	6 (9.5%)	0.775
Headache	7 (11.3)	7 (11.1%)	0.975
Nausea	4 (6.5%)	5 (7.9%)	0.750
Fatigue	6 (9.7%)	8 (12.7%)	0.595
AEs of special interest			
Urinary tract infection	9 (14.5%)	10 (15.9%)	0.834
Genital infection	7 (11.3)	5 (7.9%)	0.529
Volume reduction	1 (1.6%)	2 (3.2%)	0.571
Renal impairment	1 (1.6%)	0 (0)	0.321
Gastrointestinal symptoms	11 (17.7%)	10 (15.9%)	0.782

DAPA, dapagliflozin 10 mg/day; ExQW, exenatide 2 mg/week.

ent study, a randomized controlled trial was conducted to explore the efficacy and safety of DAPA combined with ExQW in the treatment of T2DM patients presenting with obesity.

The results showed that DAPA alone only induced a reduction in HbA1c and/or FPG level at the initial stages of the study, and its efficacy was not significant towards the end of the study period, which can be attributed to increased appetite. On the contrary, a combination of DAPA with ExQW induced a decrease in HbA1c throughout the study period, with a significantly higher decrease than use of DAPA alone. Similar results were observed for BW and cardiovascular variables. The synergetic effect of DAPA and ExQW can be attributed to several mechanisms. In addition to the decrease in appetite induced by SGLT2 inhibitors, GLP1-RAs can directly stimulate GLP1 receptor to promote insulin secretion, ultimately reducing the secretion of glucagon, thus antagonizing the increase in glucagon promoted by SGLT2 inhibitors [17]. This effect explains the observed synergistic hypoglycemic effect of a combination of the two agents. The present results were consistent with previous findings, whereby a combination of SGLT2 inhibitors and GLP1-RAs was exhibited a synergistic effect [18-20]. This implies that the two agents can be used clinically to treat T2DM patients with obesity.

This study had some limitations. Firstly, the present study was a single-center study and had a small sample size. Further studies with a large sample size should be carried out to validate the present results. Mechanistic experiments should be performed to explore the synergistic mechanism of the two drugs in detail, so as to provide a strategy to overcome AEs associated with drugs and identify potential novel targets for the drugs.

Disclosure of conflict of interest

None.

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