

Clinical Efficacy Evaluation and Long-Term Prognosis of Glucagon-Like Peptide-1 Combined with Sodium Glucose Cotransporter-2 Inhibitor in Diabetes

YAN PI, TING TING DU AND PING ZHAO^{1*}

Department of Endocrinology, Chongqing Seventh People's Hospital, Banan, Chongqing 400054, ¹Dianjiang People's Hospital of Chongqing, Chongqing 4008300, China

Pi et al.: Evaluation of Glucagon-Like Peptide-1 Combined with Sodium Glucose Cotransporter-2 Inhibitor in Diabetes

To investigate the clinical worth of glucagon-like peptide-1 receptor agonist (liraglutide) combined with sodium glucose cotransporter-2 inhibitor (dapagliflozin) in the treatment of overweight or obesity patients with type 2 diabetes mellitus and to explore whether the beneficial effect of the combination can persist during a 1 y follow-up. Eighty overweight or obesity type 2 diabetes mellitus patients admitted to a hospital from January 2019 to January 2020 were randomly divided into a control group and an observation group, with 40 cases in each group. The control group was treated with liraglutide and the experimental group was treated with basic dapagliflozin in the control group. All patients were continuously treated for 12 w. The measurement results of parameters before and after treatment, the changes in glucose metabolism parameters, blood lipid metabolism parameters and the occurrence of adverse reactions during treatment were recorded. After that, 74 treated patients were followed up for 1 y (6 refused) and measurements of various parameters were recorded. The differences in body mass index, waist circumference, hemoglobin A1c, fasting plasma glucose, triglyceride, total cholesterol, high-density lipoprotein cholesterol, low-density lipoprotein cholesterol, homeostatic model assessment-insulin resistance, homeostatic model assessment-beta and insulin sensitivity index before and after treatment in the experimental group were higher than those in the control group ($p < 0.05$). Weight loss during treatment was sustained over 1 y in both groups, with more significant changes in the experimental group. The combination of glucagon-like peptide-1 agonist and sodium glucose cotransporter-2 inhibitor can improve diabetes in overweight or obesity patients with type 2 diabetes mellitus and effectively reduce blood glucose and body mass index, which is of great significance for reducing body weight and improving efficacy. Therefore, using glucagon-like peptide-1 agonists and sodium glucose cotransporter-2 inhibitors in overweight, diabetic patients is a promising option.

Key words: Diabetes mellitus, glucagon-like peptide-1 agonists, sodium glucose cotransporter-2 inhibitors, liraglutide, dapagliflozin

The term "obesity" has been cast-off to define the pathophysiological connection between Type 2 Diabetes Mellitus (T2DM) and obesity/overweight, most often since the middle of the 20th century^[1]. Type 2 diabetes prevalence has rapidly grown during the last several decades as obesity increases, with an estimated 422 million individuals afflicted globally lately^[2]. In many situations, bariatric surgery may considerably decrease weight and diabetes despite just recently being a viable choice for treating obesity^[3-5]. However, many patients are unwilling to undergo invasive procedures or pay relatively high prices. Additionally, there might be both short-term and long-term negative belongings from bariatric surgery. A metabolic disorder called T2DM

is characterized by ongoing hyperglycemia. Visceral adipose tissue, liver, skeletal muscle and excess cardiac tissue fat storage are characteristics of type 2 diabetes^[6]. Persistent hyperglycemia in the T2DM affected role leads to chronic damage to tissues and organs such as the retina, heart and kidney, as well as glucose metabolism abnormalities, which pose a major danger to the patient's life and health^[7]. Due to its anabolic effects, insulin

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*Address for correspondence
E-mail: ppl0629@163.com

treatment often causes weight gain, raising insulin resistance^[8,9].

Consequently, diabetologists treat overweight T2DM patients with very little time spent on these medications. Strengthening body weight management while reducing blood glucose should be a priority for treating overweight and obese T2DM patients^[10]. This calls for creating novel type 2 diabetes treatments that don't cause weight gain. Doctors often combine several additional antidiabetic medications to treat diabetes when metformin alone is unsuccessful. Because they are linked to weight reduction, Glucagon-Like Peptide-1 (GLP-1) agonists and Sodium Glucose Cotransporter-2 (SGLT-2) inhibitors are chosen medications. SGLT-2 and GLP-1 analog medically favorable preliminary findings have been seen in diabetic combination treatment with inhibitors^[11,12]. In these investigations, more individuals receiving combination treatment showed improvement in their modest weight loss and glycosylated hemoglobin levels (Hemoglobin A1c (HbA1c)). Liraglutide is a GLP-1 Receptor Agonist (GLP-1RA) that is often prescribed to persons through sort 2 diabetes for glycemic management. Liraglutide consumes several actions, enhancing repletion and stimulating glucose-dependent insulin release from beta-cells, lowering calorie intake and promoting weight reduction.

Liraglutide primarily targets subcutaneous fat; visceral fat is not affected^[13,14]. As an alternative, liraglutide causes a dose-dependent, fast weight loss lasting up to 2 y^[15,16]. While decreasing food consumption may account for some of the causes of weight reduction, yes GLP-1 analogues have been found to impact energy metabolism^[17]. In animal studies, GLP-1 analogues enhanced the heat production in Brown Adipose Tissue (BAT) and brown adipocyte degeneration, indicating that GLP-1 analogues may at least partially contribute to weight reduction *via* activating BAT^[18]. In contrast, some investigations^[19,20] have not been able to show an increase in energy expenditure after GLP-1 analogue therapy. Innovative therapy for diabetes with insulin resistance is dapagliflozin. It accomplishes the goal of reducing blood glucose and provides weight reduction and blood pressure regulation benefits by blocking SGLT2 in renal tubular epithelium. Here, we present the findings of a study on patients who were administered a GLP-1 agonist in conjunction with SGLT-2 inhibitors. 1 y of follow-up research, further exploration of the combination use of SGLT-2 inhibitors and GLP-1 agonists treatment of together temporary besides permanent consequences.

MATERIALS AND METHODS

General information:

Eighty overweight T2DM affected one, which was initially pickled within a hospital from January 2019 to January 2020 selected and altogether patients met the diagnostic criteria for T2DM. They remained haphazardly separated as control group and then the observation group, with 40 cases in each group. In the control group, there remained 21 men and 19 women; the mean age was (52.12±10.2) y, and the mean Body Mass Index (BMI) was (27.31±5.7) kg/m². In the observation group, there were 23 men and 17 women; the mean age was (51.23±10.4) y, and the mean BMI was (27.82±5.6) kg/m².

Exclusion criteria: Pregnant or lactating women; complicated with severe heart, lung, liver and kidney dysfunction and diagnosed with severe osteoporosis and provocative fracture. The education was accepted through the clinic morals board, and affected role besides their relatives and informed agreement form. The difference in overall statistics among the 2 groups obligated no statistical significance (p>0.05) with comparability.

Study methods:

Following admission, all patients received advice from a dietitian about their diabetic diets, medical professionals monitored their blood pressure and fingertip blood glucose levels and different parameter values were accurately measured and documented. Improve the detection of negative patient responses, therapy and workout advice. Liraglutide was injected subcutaneously into the abdomen of the control group once daily, just before breakfast. After a week of therapy, the dosage was proportionally raised to 1.8 mg/d from the original 0.6 mg/d. On the same schedule as the control group, dapagliflozin was given orally to the experimental group once a day, just before breakfast, at a dosage of 10 mg/time. All patients received continuous care in the hospital for 12 w, after which they had a year of follow-up.

Outcome measures:

All patients had their body weight and waist circumference measured before and after treatment, and their BMI was calculated. Additionally, their Triglyceride (TG), Total Cholesterol (TC), High-Density Lipoprotein Cholesterol (HDL-C), and Low-Density Lipoprotein Cholesterol (LDL-C) levels, Fasting Plasma Glucose

(FPG), Diastolic Blood Pressure (DBP) and Systolic Blood Pressure (SBP) levels were noted. Calculations were made for the Homeostatic Model Assessment-Beta (HOMA- β), the Insulin Sensitivity Index (ISI) and the HOMA-Insulin Resistance (HOMA-IR). Adverse responses that occurred during therapy were noted. The major outcomes of the follow-up survey were the changes in body weight, combined BMI and glycosylated hemoglobin. Among the secondary outcomes, there were alterations in insulin dosage, renal function and blood pressure.

Statistical methods:

Statistical software called Statistical Package for Social Sciences (SPSS) 23.0 stood cast-off aimed at statistics analysis. Enumeration statistics stood uttered as rate (%), associated with Chi-square (χ^2) test and $p > 0.05$, considered statistically significant. Dimension statistics were uttered by way of unkind typical eccentricity ($\bar{x} \pm s$), associated with t-test and follow-up results were analyzed by one-way analysis of variance to examine outcome of combined treatment. Any independent variables influencing the main or secondary positive

outcomes were investigated using linear regression.

RESULTS AND DISCUSSION

There was no noteworthy alteration in the baseline statistics before treatment between the two groups, with comparability as shown in Table 1.

The comparison of the anthropometric measurements (body weight, BMI, waist circumference, SBP), the glucose metabolism measurements HbA1c, FPG, HOMA-IR, HOMA, ISI), and the blood lipid measurements (total serum cholesterol, TG, HDL-C and LDL-C) between two groups revealed that all of the experimental groups measurements were higher than those of control group. ($p > 0.05$) the difference was statistically significant as shown in fig. 1-fig. 3 and Table 2.

The contrary replies occurred in two groups during the treatment recorded and it was observed that the frequency of gastrointestinal reactions in the experimental cluster stood slightly higher than that in the control group, and there was no noteworthy alteration in the incidence of other adverse reactions as shown in Table 3.

TABLE 1: COMPARISON OF BASELINE DATA BEFORE TREATMENT BETWEEN TWO GROUPS

| Item | Control group | Experimental group | T/ χ^2 | p value |
|--------------------------|------------------|--------------------|-------------|---------|
| Age (years) | 52.12 \pm 10.2 | 51.23 \pm 10.4 | 0.1 | 0.93 |
| Gender (M/F) | 21/19 | 23/17 | 0.2 | 0.91 |
| Disease duration (years) | 3.53 \pm 1.8 | 3.41 \pm 1.7 | 0.28 | 0.78 |
| Weight (kg) | 84.44 \pm 10.2 | 83.58 \pm 10.6 | 0.13 | 0.9 |
| BMI (kg/m ²) | 27.31 \pm 5.7 | 27.82 \pm 5.6 | 0.08 | 0.94 |
| HbA1c (%) | 7.41 \pm 0.8 | 7.32 \pm 0.9 | 0.01 | 0.98 |

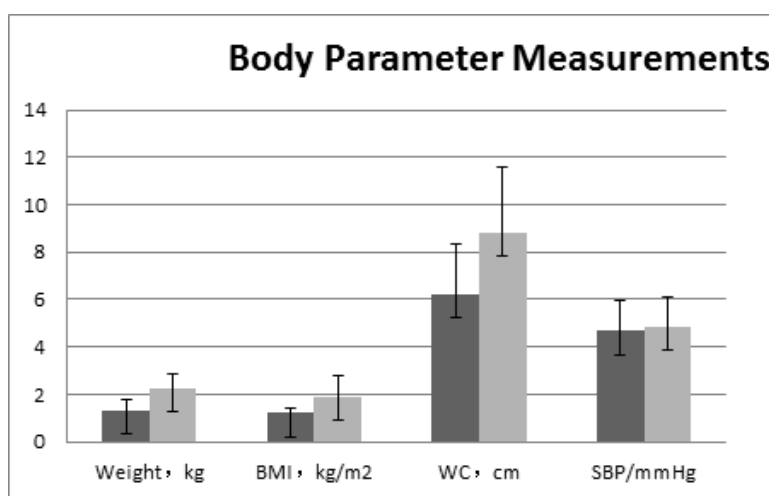


Fig. 1: Body parameter measurements

Note: (■): Control group and (□): Experimental group

Glucose Metabolism

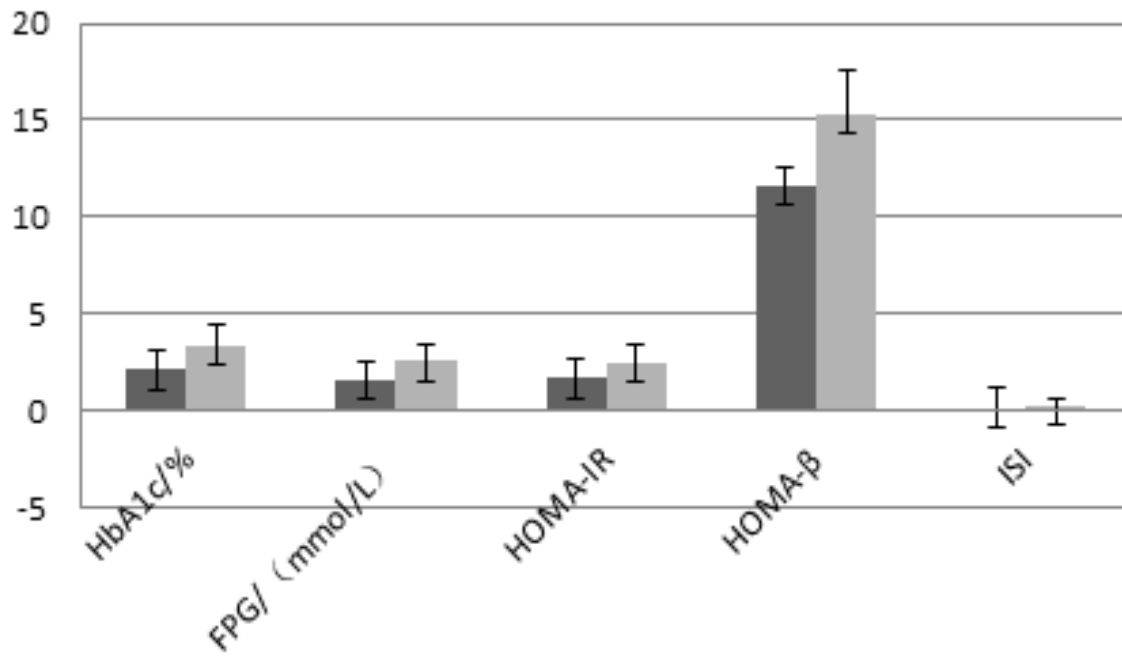


Fig. 2: Glucose metabolism parameters

Note: (■): Control group and (□): Experimental group

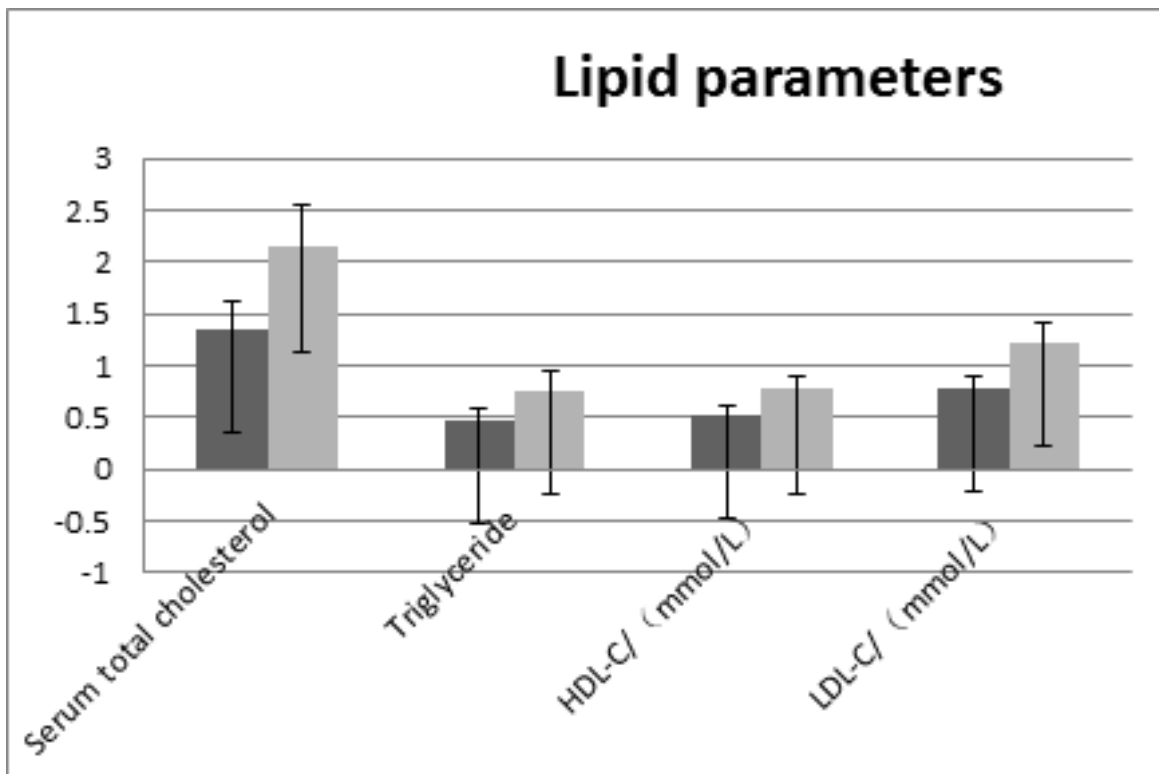


Fig. 3: Lipid parameters

Note: (■): Control group and (□): Experimental group

Out of the 80 patients, 74 were followed up for a year and 6 declined to take part; 4 in the control group and 2 in the experimental group. Survey findings revealed that the patient's metabolic parameters had greatly improved, with an average weight loss of 3.27 kg, a reduction in glycosylated hemoglobin of 2.88 % and a reduction in BMI of 2.33 kg/m². The mixture considerably decreased the need for insulin (mean 6.8 units). Although Estimated Glomerular Filtration Rate (EGFR) fell by 2.88 ml/min and mean creatinine rose by 1.67 mol/l, there was a general decline in renal function that was not statistically noteworthy. Baseline HbA1c was as an independent predictor of decreased glycosylated hemoglobin, according to multivariate analysis using linear regression as shown in Table 4.

The study's GLP-1 agonist SGLT-2 inhibitor combination treatment protocol was administered to overweight patients with T2DM. T2DM and obesity it is connected, causes insulin resistance and results in T2DM. Seizure risk factors^[21] being overweight and obesity when using insulin and some hypoglycemic medications, T2DM increased insulin resistance, weight gain and hypoglycemia are common in patients. A vicious loop between weight increase and dyslipidemia

will make the loss in pancreatic-cell function worse^[22]. Consequently, while treating T2DM caused by obesity and excess weight, when choosing a course of therapy for patients, numerous factors should be taken into account in addition to efficiently lowering blood sugar. In order to successfully decrease the pace of gastric emptying and raise the patient's satiety, liraglutide may increase the number of cells in the arcuate nucleus of the hypothalamus Cocaine and Amphetamine-Regulated Transcript (CART), messenger Ribonucleic Acid (mRNA) levels. This creates a positive feedback loop in the body that lowers the patient's BMI^[23]. Contrarily, dapagliflozin is a very selective SGLT2 inhibitor, and its hypoglycemic action is rarely reliant on the activity of islet cells, which may decrease SGLT2 expression in the tubular epithelium. This reduces the reabsorption of urine glucose^[24]. Dapagliflozin may efficiently remove glucose from patient's blood, lower patient's sugar consumption and restrict patient's calorie intake, all of which are helpful for weight reduction and treating obesity. Dapagliflozin T2DM combined with liraglutide efficient cardiovascular disease prevention and maintenance treatment of overweight and obesity individuals was made possible by effective glycemic control with considerable insulin dosage reduction BMI^[25].

TABLE 2: DIFFERENCES IN MONITORING INDICATORS BEFORE AND AFTER TREATMENT BETWEEN THE TWO GROUPS

| Variable | Control group | Experimental group | T value | p value |
|--------------------------------------|---------------|--------------------|---------|---------|
| Body parameter measurements | | | | |
| Weight (kg) | 1.32±0.45 | 2.25±0.64 | 6.147 | 0.01 |
| BMI (kg/m ²) | 1.21±0.23 | 1.91±0.87 | 7.732 | 0.01 |
| Waist circumference (cm) | 6.24±2.07 | 8.82±2.74 | 9.183 | 0.02 |
| SBP (mmHg) | 4.67±1.27 | 4.88±1.22 | -0.26 | 0.96 |
| Glucose metabolism parameters | | | | |
| HbA1c (%) | 2.11±0.72 | 3.38±1.05 | 9.188 | 0.01 |
| FPG (mol/l) | 1.60±0.37 | 2.55±0.89 | 7.703 | 0.01 |
| HOMA-IR | 1.67±0.62 | 2.48±0.95 | 4.601 | 0.01 |
| HOMA-B | 11.58±2.27 | 15.36±2.16 | 11.708 | 0.01 |
| ISI | 0.14±0.28 | 0.26±0.32 | 8.723 | 0.01 |
| Lipid parameters | | | | |
| Serum total cholesterol | 1.34±0.28 | 2.14±0.42 | 7.619 | 0.02 |
| Triglyceride | 0.46±0.13 | 0.76±0.18 | 8.793 | 0.01 |
| HDL-C (mol/l) | 0.52±0.08 | 0.77±0.12 | 8.243 | 0.01 |
| LDL-C (mol/l) | 0.78±0.11 | 1.21±0.19 | 3.089 | 0.03 |

TABLE 3: NUMBER OF CASES OF ADVERSE REACTIONS DURING TREATMENT IN THE TWO GROUPS

| Results | Control group | Experimental group |
|--|---------------|--------------------|
| Hypoglycemia | 6 | 8 |
| Dizziness | 2 | 1 |
| Infection | 2 | 3 |
| Gastrointestinal reactions (nausea and vomiting) | 4 | 7 |
| Diabetic ketoacidosis | 1 | 1 |

TABLE 4: STUDY OUTCOMES AT 6-12 MO FOR PATIENTS RECEIVING COMBINATION THERAPY

| Variable | Mean difference | 95 % confidence interval | p value |
|------------|-----------------|--------------------------|---------|
| Weight | 3.27 | 1.981-4.789 | 0 |
| HbA1c | 2.88 | 0.88-1.62 | 0 |
| BMI | 2.33 | 0.74-1.77 | 0 |
| SBP | 1.081 | 7.19-8.26 | 0.867 |
| Creatinine | -1.67 | 6.24-2.49 | 0.651 |
| EGFR | -2.884 | 2.34-6.89 | 0.384 |

In our study, combination treatment resulted in statistically noteworthy decreases in HbA1c, body mass and BMI. Affected role in the experimental group fared better than individuals in the control group; i.e., however, the combination had no statistically noteworthy impact on blood pressure management. Higher baseline HbA1c levels were exposed to stand a statistically noteworthy sovereign analyst of the grade of HbA1c decrease within additional treatments for T2DM in earlier studies^[26, 27]. Rosen stock and others had a new randomized, double-blind experiment, which shows that when the SGLT-2 inhibitor dapagliflozin was combined with other antidiuretic medications, higher baseline levels of HbA1c predicted bigger decreases in HbA1c levels^[28]. In our subsequent poll, the high difference in mean HbA1c levels at baseline may be the cause of the study's mean drop in HbA1c, which was 2.88 and 1.33. This finding is consistent with prior reports on the present difference effect of combination therapy. This research also showed that the experimental group's alterations in blood lipid metabolism levels were noticeably improved than persons in the control group. Liraglutide and dapagliflozin medication may alter blood lipid levels for several

reasons, but the most crucial is that the patient's blood glucose is under good control, followed by a decrease in the buildup of liver fat in the patient^[29]. Alternately, it has been discovered that SGLT receptor inhibition is linked to the synthesis of adiponectin and that dapagliflozin's hypoglycemia mechanism may impact processes related to fat metabolism^[30]. Patients with T2DM who are overweight or obesity have persistent hyperglycemia and hyperlipidemia, which may harm pancreatic beta-cells, raise insulin resistance and lower the effectiveness of conventional hypoglycemic medications.

Hyperlipidemic conditions put extra strain on the liver, which is harmful to controlling lipid and glucose metabolism^[31]. Therefore, patients must quickly restore islet function during the first stages of therapy and properly manage their blood sugar and cholesterol levels.

The findings of this research demonstrated that, before and after therapy, the islet function indicators of patients in the observation group were greater than those in the control group. The findings demonstrated that liraglutide combined with dapagliflozin effectively controlled blood sugar, decreased insulin resistance, improved insulin

sensitivity and partially reversed the vicious cycle of islet function impairment^[32,33]. This was beneficial for the management and prognosis of the patient's condition.

The incidence of adverse responses did not significantly vary between the two groups in this investigation. These findings support earlier studies^[34] and imply that the combination of liraglutide and dapagliflozin is safe and effective for treating T2DM. Then again, we have posed several research-related queries, particularly in light of recent clinical studies utilizing SGLT-2 inhibitors or GLP-1 agonists that have shown encouraging outcomes in cardiovascular and mortality in T2DM patients^[35, 36]. From a clinical and pharmacological perspective, GLP-1 analogues and SGLT-2 inhibitors should make an appropriate and sensible combination since they have little interaction potential^[37]. Besides antidiuretic benefits linked to various classes of these compounds, the potential for weight reduction is quite distinct and there could be a synergy in how they affect diabetes.

According to studies, the effectiveness of SGLT-2 inhibitors progressively diminishes over time^[35], probably because this class of medications causes a rise in pancreatic glucagon secretion, which is counteracted by GLP-1 agonists^[38]. Utilizing combination regimens in clinical practice should follow another logical reasoning line. In well-planned randomized controlled studies, the potential synergistic impact of this combination treatment in managing obesity has to be further investigated. A key clinical characteristic related to diabetes, abdominal obesity, has been linked to the use of GLP-1 agonists in the obesity affected role, according to a recent systematic appraisal besides meta-analysis^[39]. SGLT-2 inhibitors stand an unusual period of antidiuretic medications because of a wide range of non-glycemic positive effects they are linked to, including weight loss, blood pressure reduction, improved cardiovascular mortality and morbidity, renal protection and ease of administration as a verbal agent^[40].

The use of these two medication types in combination to treat obesity has not yet been thoroughly investigated. Because both of the patients in our study are Chinese men residing in Asia, it is also necessary to do more research into the causes of the considerable difference in diabetes results between our study and earlier studies. There have been reports of cultural disparities in the effectiveness of GLP-1 agonists^[41]. Various racial and ethnic groups may experience SGLT-2 inhibitor's (moreover unaided or in the mixture within extra drugs) effects differently. Treatment and hyperglycemia in patients with T2DM were the subjects of an update to the American Diabetes

Association/European Association for Study of Diabetes (ADA/EASD) policy report in 2015^[42].

The amended statement still lists metformin as the preferred medication for immunotherapy, but additional medications are mentioned as a viable option for second-line treatment due to the recent fast accumulation of information on SGLT-2 inhibitors. As long as adequate data from large randomized placebo-controlled clinical studies are available, techniques like the mixture of SGLT are evolving 0.2 inhibitors and GLP-1 agonists might be safe and successful and may be comprised of our medical arsenal aimed at the conduct of diabetes. In assumption, combination conduct for diabetes with SGLT-2 inhibitors and GLP-1 agonist's treatment was successful, resulting in moderate decreases in figure mass, BMI, HbA1c levels and insulin dosage, but the mixture had no observable impact on blood pressure.

Conflict of interests:

The authors declared no conflict of interests.

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