META-ANALYSIS

Clinical Efficacy of Different Doses of Canagliflozin Combined with Metformin in the Treatment of Type 2 Diabetes: Meta-Analysis

GuangZhi Li, MD; Dongmei Zhang, MD; Jie Ni, MD; Shizhen Wang, MD

ABSTRACT

Background • With social development, an aging population, and the increasing trend of obesity, type 2 diabetes (T2DM) has become one of the major problems affecting human health across the globe.

Methods • Information on controlled trials was retrieved from four databases to obtain the effects of different doses of canagliflozin combined with metformin for treating T2DM. After a rigorous evaluation of the quality of the literature, data analysis was performed using RevMan 5.3 software.

Results • We included 8 studies in this meta-analysis. The least square (LS) means of HbA_{1c} and FPG in the test group were statistically lower than the control group. Our analysis revealed that the adverse reactions were not significantly different between the experimental and control groups (OR: 1.03; 95% Cl: 0.94, 1.12; $P = .555$). Also, we found that the urinary tract infection of the experimental group was not statistically different from the control group (OR: 0.94; 95% Cl: 0.71, 1.24; $P = .648$). Moreover, we identified that the blood pressure and blood lipids of the experimental group did not statistically differ from the control group.

Conclusion • The meta-analysis demonstrates that high doses of canagliflozin combined with metformin may be potentially effective in patients with T2DM, as evidenced by LS means of HbA_{1c} and FPG, and the above conclusions need to be verified by more high-quality studies. (*Altern Ther Health Med.* 2023;29(7):328-334).

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INTRODUCTION

With social development, an aging population, and the increasing trend of obesity, type 2 diabetes (T2DM) has become one of the major problems affecting the global human health.[1] According to statistics, the number of diabetic patients worldwide exceeds 300 million, and is expected to increase to 592 million by 2035.[2] There are about 114 million diabetic patients in China, accounting for 27% of the world's total, and China is the country with the largest number of diabetic patients in the world. Among them, the prevalence of adult diabetes has increased significantly, reaching up to 10.4%.[3] The complications associated with diabetes not only seriously affect patients' quality of life but also increase the economic burden on their families and society.[4] According to predictions by researchers from many countries, the global economic burden of diabetes will increase from US$1.3 trillion in 2015 to US$2.2 trillion in 2030, and the proportion of global GDP will increase from 1.8% in 2015 to 2.2% in 2030.[5]

Patients with T2DM are still mainly controlled by lifestyle changes[6] and drug treatment,[7,8] etc. Traditional hypoglycemic drugs for T2DM, such as sulfonylurea, can cause metabolic and nutritional disorders in patients, induce hypoglycemia, and even lead to hypoglycemia coma, and the long-term use can accelerate the failure of pancreatic β-cells and promote weight gain in patients.[9] Non-sulfonylurea hypoglycemic drugs such as nateglinide and repaglinide can cause gastrointestinal reactions such as abdominal pain and diarrhea, and nervous system reactions such as headache and dizziness;[10] α-glucosidase inhibitors such as acarbose can induce liver toxicity, arrhythmia, or severe rash;[11] biguanides can cause gastrointestinal symptoms such as nausea and abdominal distension; and, thiazolidinediones can increase the workload of the heart and present the risk of lower extremity edema and osteoporosis.[12,13] Metformin is crucially used for treating T2DM. It can effectively increase insulin sensitivity, improve islet β-cell function, inhibit hepatic glycogen output, and improve the uptake and utilization rate

of peripheral tissues, so as to play a hypoglycemic role.[14] However, as the disease develops, single agents struggle to meet the treatment needs. Therefore, clinical attempts are made to improve the efficacy of the treatment by combining drugs.[15] Guidelines recommend the combined use of sodium-glucose cotransporter 2 inhibitors, dipeptidyl peptidase-4 inhibitors, etc.[16] Among them, sodium-glucose cotransporter inhibitors have good efficacy and safety, whether used as single agents or in combination with other hypoglycemic drugs, and their clinical applications are increasing.[17-19] Dapagliflozin is a sodium-glucose co-transporter inhibitor, which does not rely on the action of insulin, and can selectively block sodium-glucose co-transporters by itself, thereby reducing the reabsorption of glucose by the proximal convoluted blood vessels and facilitating the decrease in the patient's blood sugar levels.[20-22] Mou Lunpan et al.[23] reported that dapagliflozin and linagliptin have definite hypoglycemic efficacy and comparable safety in overweight and obese patients with T2DM who are otherwise poorly controlled by oral hypoglycemic drugs, and dapagliflozin has advantages in controlling blood sugar, weight, and blood pressure effectively.

It was demonstrated that the treatment regimen of dapagliflozin combined with metformin also has certain advantages in terms of economics.[24] However, the effect of distinct doses of canagliflozin on T2DM has not been studied. Therefore, we have conducted a meta-analysis for exploring the efficacy of different doses of canagliflozin combined with metformin in the treatment of T2DM.

MATERIALS AND METHODS

Selection of Studies

Study design type includes published controlled trials on the effects of different doses of canagliflozin combined with metformin for T2DM treatment. However, the animal trials were excluded.

Selection of Participants

The study includes T2DM patients who are treated with distinct doses of canagliflozin in combination with metformin.

Types of Interventions

The intervention group includes patients with T2DM receiving canagliflozin 300 mg per day in combination with metformin and the control group includes patients with T2DM receiving canagliflozin 100 mg per day in combination with metformin.

Types of Outcome Measures

The outcome indicators are patients with T2DM. According to research, the assessment tools for canagliflozin and metformin on the efficacy of patients with T2DM are: (1) HbA_{1c}, (2) fasting Plasma Glucose (FPG), (3) adverse reactions, (4) urinary tract infection, (5) blood pressure, and (6) blood lipids. The literature included in this study evaluated outcome measures using at least one of the above scales.

Search Strategy

The computer retrieved the following databases: Cochrane Library, PubMed, Embase, and Web of Science. The search terms used are "metformin", "diabetes", and "canagliflozin". The search time was from the establishment of the library until May 2022. The specific steps of literature search are: (1) search for relevant documents in English databases, read the title, abstract, and keywords to further identify the search terms for this study; (2) the English database search used "MeSH Terms" to identify the subject terms and searched using a combination of subject words and keywords.

Data Extraction and Quality Assessment

After the initial screening of the abstract, the screened literature was selected after reading the full text, and the process was completed independently by 2 researchers. Exchanging screening results, discussing dissenting literature, or consulting a third researcher were done until the results were agreed upon. The information extracted from the data included the following criteria: basic information about the literature, type of study, study object, sample size, intervention content, outcome measures, etc.

Statistical Analysis

This meta-analysis was conducted using Review Manager (RevMan). (1) Effects were combined: The outcome measures in this study were all measured data and the tools used to evaluate were different, so there were differences between scores. Therefore, we used the standardized mean difference (SMD) and 95% Letters to the zone (confidence interval, CI) as an indicator of effect. (2) Heterogeneity test: We utilized the Chi-square test to determine whether there was heterogeneity between studies. If $P > .1$, $I^2 < 50\%$, the included studies were assumed to be more homogeneous, and proceeded with a fixed-effects model of meta-analyses; while, if $P < .1$, $I^2 \geq 50\%$, heterogeneity was indicated in the included studies and analyzed heterogeneous sources; while, if there was no clinical heterogeneity, a random-effects model was used in the meta-analyses. Furthermore, possible differences in qualitative factors in subgroups were analyzed.

RESULTS

Searching and selection of studies

We identified the 1303 literature articles based on our search strategies. Then, we selected the 682 studies based on matching abstracts and titles after removing the duplication of studies. We considered the 12 studies after evaluating the full text. Then we excluded the 4 articles for the following causes: mismatch of provided data in the studies (n = 2) and missing data (n = 2). Finally, we selected 8 studies[25-32] for this meta-analysis (Table 1). Figure 1 showed the flow chart of the PRISMA statement for this meta-analysis.

HbA_{1c} and FPG: 6 studies reported the LS means of HbA_{1c} in the test group and the control group

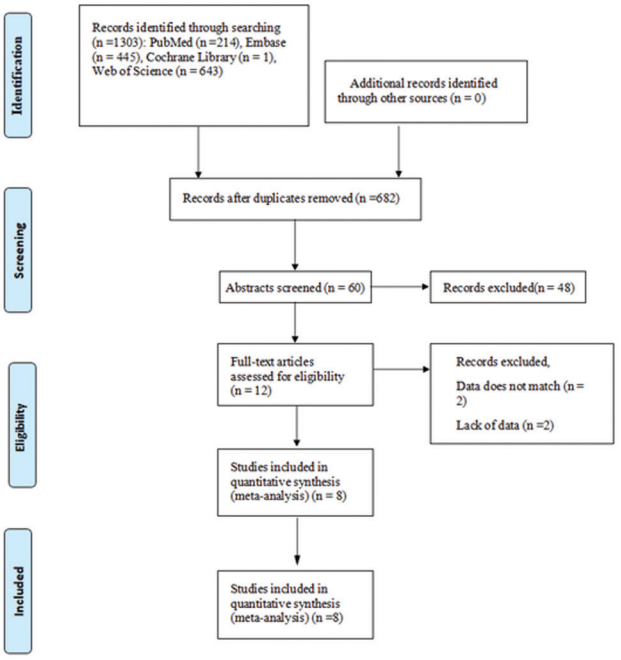
The mean of the least square (LS) means of HbA_{1c} in the test group was statistically lower than that of the control

Table 1. The Basic Characteristics of the Included Studies

Study（Ref.）	Sample Size(T/C)	Man/Woman	Age (years)(T/C)	T	C	Main Outcomes
Ji, 2015[25]	227/223	237/213	56.4 ± 9.2/56.5 ± 8.3	CANA300＋MET	CANA100＋MET	①②③④⑤⑥
Rosenstock, 2012[26]	64/64	72/56	52.3 ± 6.9/51.7 ± 8.0	CANA300＋MET	CANA100＋MET	①③④
Wilding, 2013[27]	156/157	163/150	56.1 ± 8.9/57.4 ± 10.5	CANA300＋MET	CANA100＋MET	①②③④⑤⑥
Forst, 2014[28]	114/113	140/87	56.7 ± 10.4/56.7 ± 10.4	CANA300＋MET	CANA100＋MET	①②③④⑤⑥
Lavalle-González, 2013[29]	367/368	339/396	55.3 ± 9.2/55.5 ± 9.4	CANA300＋MET	CANA100＋MET	①②③④⑤⑥
Cefalu, 2013[30]	485/483	493/475	55.8 ± 9.2/56.4 ± 9.5	CANA300＋MET	CANA100＋MET	③④⑤⑥
Qiu, 2014[31]	93/93	84/102	56.7 ± 10.3/58.6 ± 8.9	CANA300＋MET	CANA100＋MET	①②③④⑤⑥
Rosenstock, 2016[32]	237/237	223/251	55.4 ± 9.8/54.2 ± 9.6	CANA300＋MET	CANA100＋MET	①②③④⑤⑥

Abbreviations: T, Trial Group; C, Control; ① HbA_{1c}; ② Fasting plasma glucose (FPG); ③ Adverse reactions; ④ Urinary tract infection; ⑤ Blood pressure; ⑥ Blood lipids.

Figure 1. Flow Chart of the Meta-Analysis



group. What's more, every LS mean of HbA_{1c} in the test group was lower than that of the control group. 5 studies reported the LS mean of FPG in the test group and the control group. LS mean of FPG in the test group was statistically lower than that of the control group. What's more, 4 studies reported that LS means of FPG in the test group was lower relative to the control group.

Analysis of adverse reactions

We found the comparative data of adverse reactions between the 2 groups in the 8 studies selected. We revealed that the adverse reactions of the experimental group were not statistically differentiated from the control group (OR: 1.03; 95% Cl: 0.94, 1.12; $P = .555$, Figure 2). Although we found an asymmetrically distributed total effective rate in the funnel plot (Figure 3), Egger's test showed no potential publish bias ($P = .477$). Since the trials showed moderate heterogeneity, we conducted the sensitivity analysis (Figure 4).

Figure 2. Forest Illustration of the Adverse Reactions

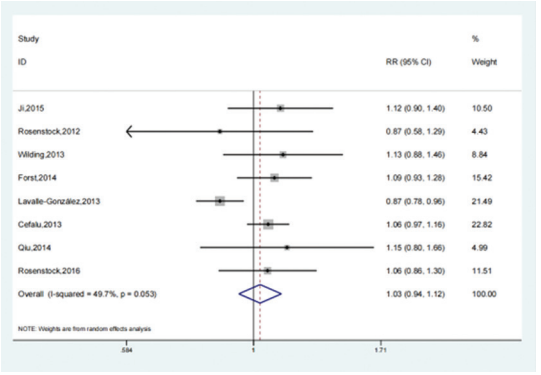


Figure 3. Funnel Plot of the Adverse Reactions

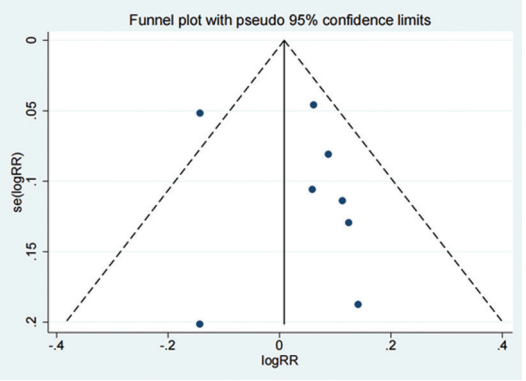


Figure 4. Sensitivity Analysis of the Adverse Reactions

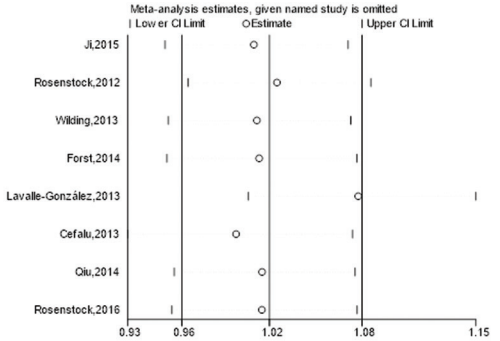


Figure 5. Forest Illustration of the Urinary Tract Infection

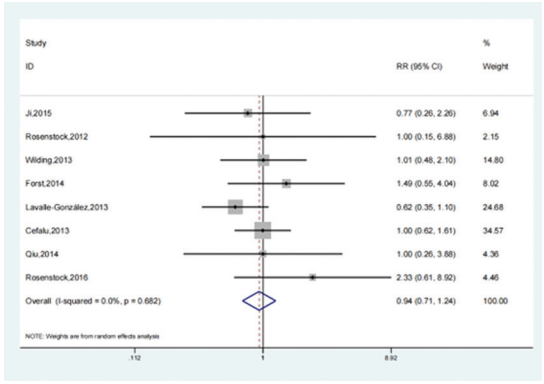


Figure 6. Funnel Plot of the Urinary Tract Infection

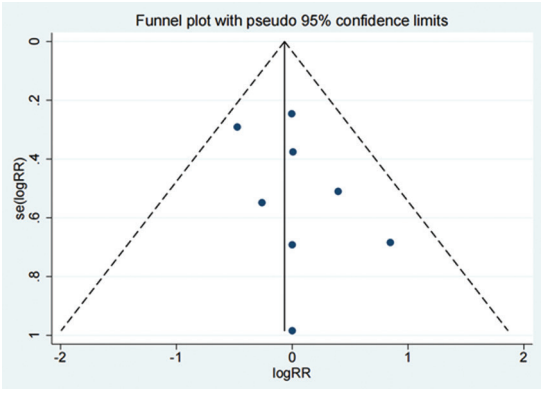


Figure 7. Sensitivity Analysis of the Urinary Tract Infection

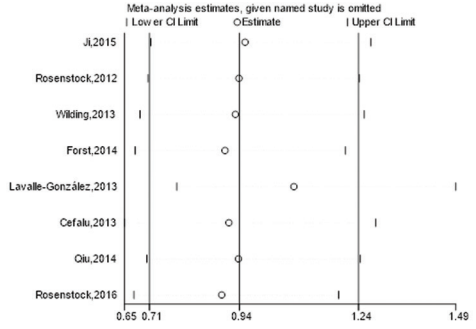


Figure 8. Forest Illustration of the Systolic Blood Pressure

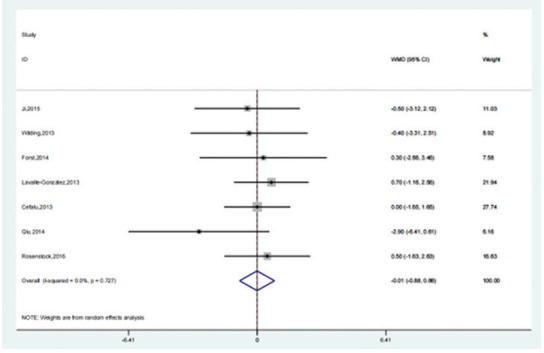


Figure 9. Forest Illustration of the Diastolic Blood Pressure

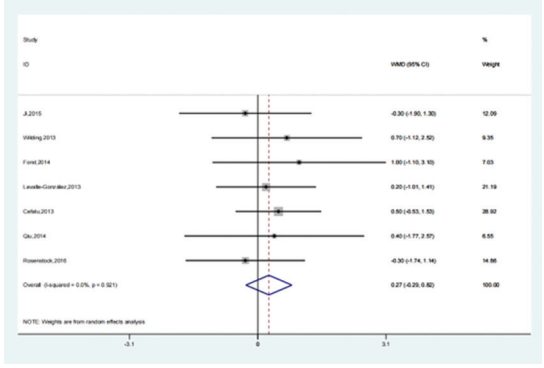
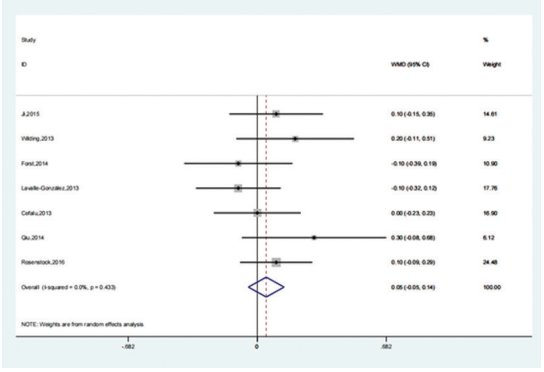


Figure 10. Forest Illustration of the Triacylglycerol



Urinary tract infection

8 studies reported the urinary tract infection in the test group and the control group. Meta-analysis showed that the adverse reactions of the experimental group were not statistically different from the control group (OR: 0.94; 95% Cl: 0.71,1.24; *P* = .648, Figure 5). Although we found an asymmetrically distributed total effective rate in the funnel plot (Figure 6), the Egger's test showed no potential publish bias (*P* = .286). The results of all these trials showed moderate heterogeneity, thus a sensitivity analysis was conducted (Figure 7).

Blood pressure

We found the data on the blood pressure from 7 studies to compare the test group with the control group. The analysis revealed that the systolic blood pressure was not statistically different between the experimental and control groups (SMD: -0.01; 95% Cl: -0.88, 0.86; *P* = .982, Figure 8). Moreover, the diastolic blood pressure of the experimental group showed a similar trend to the systolic blood pressure (SMD: 0.27; 95% Cl: -0.29,0.82; *P* = .334, Figure 9).

Analysis of blood lipids

We collected the data on blood lipids from the 8 studies for comparing the test and control groups. When comparing the test group with the control group, we found that the triacylglycerol content was not statistically differentiated between these groups (SMD: 0.05; 95% Cl: -0.05,0.14; *P* = .327, Figure 10). Meta-analysis showed that the low-density lipoprotein cholesterol of the experimental group was not statistically different from that of the control group

Figure 11. Forest Illustration of the Low-Density Lipoprotein Cholesterol

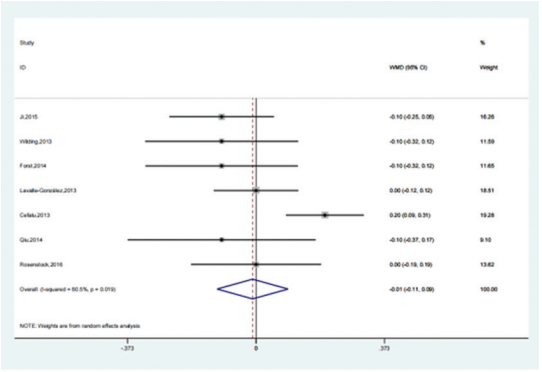
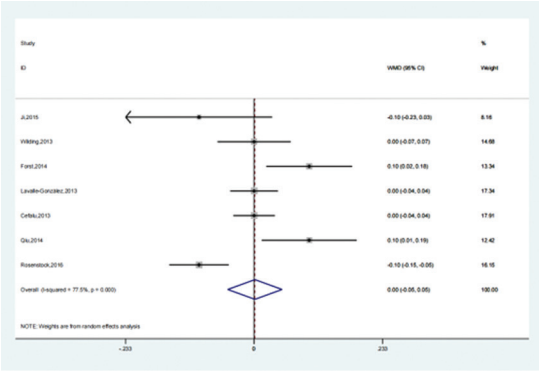


Figure 12. Forest Illustration of the High-Density Lipoprotein Cholesterol



(SMD: -0.01; 95% Cl: -0.11,0.09; P = .849, Figure 11). Furthermore, the analysis showed that the high-density lipoprotein cholesterol of the experimental group was also not statistically different from that of the control group (SMD: 0.00; 95% Cl: -0.05,0.05; P = .954, Figure 12).

DISCUSSION

According to a recent study,[33] there will be approximately 537 million people with diabetes worldwide in 2021, and it is estimated that the figure will rise to 783 million by 2045, at an alarming rate. Diabetes mainly includes type 1, type 2, and other special types. Among them, T2DM has the fastest growth rate and is a leading health concern among the rapidly growing global diabetes population. The increase in the global diabetic population has led to a surge in the expenditure on diabetes treatment. It is estimated that the estimated expenses on diabetes treatment in China was 165.3 billion in 2021, which represents a huge burden for the families of patients with T2DM and the medical and health system. Among the direct medical expenses of T2DM,[34] T2DM-related complications are the main factor of related expenses. The maintenance of the healthy physiological state of the human body requires the simultaneous functioning of many systems and pathways that contribute to the steady state and homeostasis of the organism. Abnormal homeostasis can lead to the damage of various organs and the development of pathological states.[35] T2DM is an usual metabolic disease, mainly caused by insulin resistance (IR) and impaired pancreatic cell function.[36] The progression of the disease impairs the underlying systems and pathways needed to maintain blood glucose homeostasis, resulting in abnormal glucose metabolism.[37]

Glucose transport *in vivo* is mainly related to sodium-glucose co-transporter (SGLT) and glucose transporter (GLUT). Canagliflozin is a sodium-glucose cotransporter inhibitor (SGLTi). Among them, there are two types of SGLT- SGLT1 and SGLT2. SGLT1 is mainly distributed in the brush border of the small intestinal mucosa and the S3 segment of the proximal convoluted tubule of the kidney, and is expressed in a small amount in the heart and trachea. It is a transporter with high affinity and low transport capacity. SGLT2 is mainly distributed in the S1-S2 segments of the proximal convoluted tubules of the kidney, and is a transporter with low affinity and high transport capacity. After the oral administration of the drug into the intestine, it can inhibit intestinal SGLT1 and reduce glucose absorption.[38] 10% of the glucose in the glomerular filtrate is reabsorbed through SGLT1, and 90% is reabsorbed through SGLT2.[39] Canagliflozin inhibits SGLT1 and SGLT2 in the proximal convoluted tubule, thereby inhibiting 30% to 50% of renal glucose reabsorption. Reabsorption increases the role of urinary glucose excretion. In terms of reducing intake and promoting excretion, double hypoglycemia achieves non-insulin-dependent hypoglycemia. A study found that the maximum SGLT2 inhibition rate of canagliflozin on renal tubular S1 and S2 segments was close to 100%, and it could continue to inhibit SGLT2 within 24 hours. After 24 hours, the inhibition rate of canagliflozin decreased linearly to 70% (100mg) or 90% (300mg).[40] The reabsorption of glucose in patients with T2DM is significantly higher than that of normal people, which is mainly due to the increase in renal glucose threshold (220 mg/dL) and the overexpression of SGLT2.[41] The normal population renal threshold for glucose (RTG) is 180 mg/dL and canagliflozin can reduce the pathologically elevated RTG (70-90 mg/dL), increase urinary glucose excretion, and thus lower the blood sugar level. When the blood glucose level is lower than 4.44 mmol/L, which is below the renal glucose threshold of SGLT2i, studies discovered that urine glucose is hardly excreted, avoiding further reduction of blood glucose and increasing the risk of hypoglycemia.[42] A meta-analysis showed that SGLT2i reduced glycated hemoglobin (HbA_{1c}) by 0.59% to 0.82% compared to the placebo.[43]

Modern people take in more energy than they consume, and the excess energy can lead to increased postprandial and free fatty acid levels, leading to insulin resistance, hyperinsulinemia, and insufficient β-cell compensation, ultimately causing T2DM.[44] In terms of energy utilization, patients with T2DM also show altered barrier substrates, low energy efficiency, and increased load. On the one hand, SGLT2i reduces renal tubular reabsorption of glucose, reduces RTG, and increases urinary glucose excretion. For example, by taking 100 mg of canagliflozin daily, the 24-hour

urine glucose excretion (UGE) can reach about 100 g, which is equivalent to losing about 400 kcal of heat. On the other hand, SGLT2i can reduce insulin secretion, increase glucagon release (lower insulin/glucagon ratio), promote lipolysis, fat oxidation, and ketone body generation, and convert cardiorenal metabolic substrates from carbohydrates to lipids.[45] With the action of SGLT2i, the ratio of insulin/glucagon decreases, the oxidation of free fatty acids increases, and the uptake and utilization of ketone bodies (β-hydroxybutyric acid) are accelerated by tissues and are oxidized in preference to fatty acids. In addition, the application of SGLT2i can reduce the extracellular volume by 5% to 10%,[46] and the hematocrit increases, which releases more O_2 in the tissue, both of which together accelerate the decomposition of β-hydroxybutyric acid to protect the cardiovascular function.

In addition to hypoglycemia, SGLT2i can also reduce a variety of other cardiovascular risk factors such as blood lipids, body weight, blood uric acid, blood pressure, etc. A study at the Scientific Annual Meeting of the American Diabetes Association pointed out that free fatty acid (FFA) and triglyceride (TG) levels can be reduced after the application of SGLT2i, and high-density lipoprotein cholesterol (HDL-C) Levels can be elevated. After 52 weeks of dapagliflozin treatment, low-density lipoprotein cholesterol (LDL-C) decreased by 5.8% and HDL-C increased by 6.9%.[47] During an animal experiment, researchers demonstrated that SGLT2i could interfere with the energy metabolism pathway in mice, limiting the rate of fatty acid synthesis and promoting lipid oxidative decomposition to regulate excess energy metabolism.[48] SGLT2i can effectively reduce body weight while efficiently reducing blood sugar, whose mechanism may be related to the energy loss caused by urinary glucose excretion, the increased fluid loss due to osmotic diuresis, and by promoting the conversion of the body's material metabolism from glucose metabolism to lipid metabolism.[49] Initial weight loss may result from diuretic fluid loss, while the continued caloric loss may result in subcutaneous and visceral fat loss.[50] A randomized, double-blind, active-controlled registry study of 1450 patients with T2DM on metformin background therapy randomized (1:1:1) to receive canagliflozin 100 mg or 300 mg or glimepiride treatment. After 104 weeks, the results showed that the weight loss after combined use of canagliflozin 100 mg/d and 300 mg/d was 4.1% and 4.2%, whereas with the use of glimepiride the body weight increased by 0.9 percent in the control group.[51]

SGLT2i is also beneficial for blood pressure control, which can steadily reduce systolic blood pressure (3-5 mmHg) and diastolic blood pressure (2-3 mm Hg) in the absence of compensated tachycardia.[52] SGLT is a sodium-glucose co-transporter. SGLT2i suppresses the reabsorption of sodium ions and increases the excretion of sodium ions while inhibiting the reabsorption of glucose, thereby reducing the retention of water and sodium in the body. This continuously helps to reduce the plasma volume and the blood pressure. In addition, the increased concentration of sodium ions in the renal tubules can reduce the release of renin after flowing through the dense plaque, thus blocking the renin-angiotensin-aldosterone system (RAAS), relieving glomerulosclerosis and degree of arteriosclerosis, and lowering the blood pressure.[53] SGLT2i can also reduce LDL-C, TG, body weight, and uric acid, all of which are beneficial to the reduction of blood pressure, thereby reducing cardiac afterload.

We included 8 studies in this meta-analysis. The mean of LS means of HbA_{1c} and FPG of the experimental group were statistically lower than that of the control group. Besides, we found that the adverse reactions (OR: 1.03; 95% Cl: 0.94, 1.12; $P = .555$) and the urinary tract infection (OR: 0.94; 95% Cl: 0.71, 1.24; $P = .648$) of the experimental group was not statistically different from that of the control group. Meta-analysis showed that the blood pressure and blood lipids of the experimental group also did not statistically differ from the control group.

Limitations

The limitations of this systematic review are: searching only the English literature, there may be incomplete research inclusion, and selection bias. Hence, some of the results of this meta-analysis should be viewed objectively.

CONCLUSION

This meta-analysis demonstrates that high doses of canagliflozin combined with metformin may be effective in patients with T2DM, as evidenced by LS means of HbA_{1c} and FPG, and the above conclusions need to be verified by more high-quality clinical studies.

DATA AVAILABILITY

The data used to support this study is available from the corresponding author upon request.

FUNDING

No funding was received for this study.

AUTHOR DISCLOSURE STATEMENT

The authors declare that they have no conflicts of interest.

ACKNOWLEDGEMENT

GuangZhi Li and Dongmei Zhang have contributed equally to this study.

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