# The efficacy and safety of dapagliflozin combined with oral hypoglycemic agents in patients with type 2 diabetes: a systematic review and meta-analysis

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**Background:** There were reports that many patients with type 2 diabetes mellitus (T2DM) could not maintain the normal level of glycemic, who were treated with the antidiabetic agents. The sodium-glucose co-transporter-2 (SGLT2) inhibitors could improve patients' blood glucose level by inducing glycosuria, improving insulin sensitivity and the function of β-cell and decreasing glucose toxicity. Which was unlike with other agents, indicating that the SGLT2 inhibitors might be effective alone or in combination with any other drugs. As a SGLT2 inhibitor, Dapagliflozin could be used in patients with T2DM.

**Methods:** Studies' identification were conducted with the literature search, and we searched studies published between 1950 and 2021 in PubMed, the Cochrane Library and Embase. A meta-analysis was performed using RevMan 5.3 software. Continuous data are presented as the means and standard deviations of differences in performance before and after active or control interventions. Adverse events were also assessed.

**Results:** Fifteen studies that provided individual data were included. Treatment with dapagliflozin was compared with treatment with placebo and resulted in a significantly greater change in HbA1c levels, fasting plasma glucose (FPG) and weight. In terms of the incidence of adverse drug reactions, the incidence of hypoglycemic events was not significantly different between the experimental and control groups. However, the incidences of genital infection and urinary tract infection were higher in the experimental group than in the control group.

**Discussion:** According to the available data, dapagliflozin combined with oral hypoglycemic agents can effectively reduce the level of HbA1c and body weight; however, it does not increase the incidence of hypoglycemia but can cause urinary tract infection and genital infection. Due to the limited literature included, the above conclusions need to be verified through more high-quality studies.

**Keywords:** Dapagliflozin; diabetes; oral hypoglycemic agents; meta-analysis; randomized controlled trial (RCT)

## Introduction

As we all know that the chronic and macrovascular were normal symptoms found in the patients with diabetes, who's life was seriously influenced (1). At the same time, the life expectancies of patients with diabetes were less than normal people. These patients were more likely to suffer from such diseases including cardiovascular disease and cognitive impairment (2). With the development and improvement of medical level, the great progress had been made in the treatment of patients with type 2 diabetes (3). From the perspective of pharmacological methods, the means of treating diabetes have been continuously developed. As an effective drug for treating diabetes, the glucagon-like peptide 1 (GLP-1) receptor agonists (4) and the sodium-glucose co-transporter-2 (SGLT2) inhibitors (5-7) had been gradually studied and developed by scholars. The drugs of dapagliflozin (8), canagliflozin (9), empagliflozin (10) and ipragliflozin (11) were used or studied as SGLT2 inhibitors.

The patients treated with SGLT2 inhibitors were found with the reduction of renal glucose excretion and the levels of plasma glucose, followed with an increasing levels of urinary glucose excretion. It was reported that the β-cell insulin secretion and sensitivity could be raised by the glycosuria caused by controlling SGLT2.

Dapagliflozin (8,12,13), a representative SGLT2 inhibitor, inhibits kidney glucose re-absorption and promotes urine glucose excretion. However, there are few large studies of dapagliflozin in combination with other hypoglycemic agents to treat patients with type 2 diabetes.

We present the following article in accordance with the PRISMA reporting checklist (14) (available at https://apm.amegroups.com/article/view/10.21037/apm-22-121/rc).

## Methods

### Search strategy

All studies were retrieved using a literature search of PubMed, the Cochrane Library and Embase from 1990 to 2021. Dapagliflozin, diabetes, oral hypoglycemic agents, meta-analysis, and randomized controlled trial (RCT) were used as keywords to perform the search strategy. The other electronic database search strategies were established on this basis of the PubMed search strategy. The selected studies were limited to RCTs that were published in English.

### Study selection

The inclusion criteria of each study were conducted on the basis of PICOS (population, interventions, comparator, outcomes, and study design) categories. The study could be enrolled in this meta-analysis which covered the terms of PICOS: the type of study was a RCT; the subjects were adults with type 2 diabetes; the intervention in the experimental group was dapagliflozin combined with other oral hypoglycemic agents, whereas the intervention in the control group was placebo combined with other oral hypoglycemic agent or placebo alone; changes in hemoglobin A1c (HbA1c), body weight, and fasting plasma glucose (FPG) were used to evaluate the efficacy of dapagliflozin in combination with hypoglycemic agents; and the incidences of hypoglycemia, urinary tract infection and genital infection were investigated on patients who were treated with dapagliflozin combined with other oral hypoglycemic agents.

The criteria for exclusion were as follows: patients in the study were given dapagliflozin alone; duplicate studies; and studies where important data were not available.

### Data extraction

Two researchers independently screened the literature, extracted data and made cross-comparisons. If there was a disagreement, the two researchers discussed it, and the results were confirmed through consultation with a third investigator. The first step in literature screening was to read the topic and eliminate obvious irrelevance. Meanwhile, the acceptance of the study was determined by further reading the abstract and full text. The data extracted by researchers from each study were as follows: publication data (source of publication, study title, first author, and year), baseline characteristics of each study (sample size, age, weight, HbA1c, FPG), patient interventions (oral hypoglycemic agents, treatment duration), main evaluation indicators (change in weight, HbA1c, FPG in patients before and after treatment), and adverse events (hypoglycemia, urinary tract infection and genital infection). We tried to select studies using the same dose of dapagliflozin combined with oral hypoglycemic agent treatment for statistical analysis.

### Statistical analysis

All statistical analyses were performed with the Review Manager statistical software package (Version 5.3). Continuous variables were presented as the mean difference (mean difference, MD), and categorical variables were presented as the hazard ratio (risk ratio, RR), and each
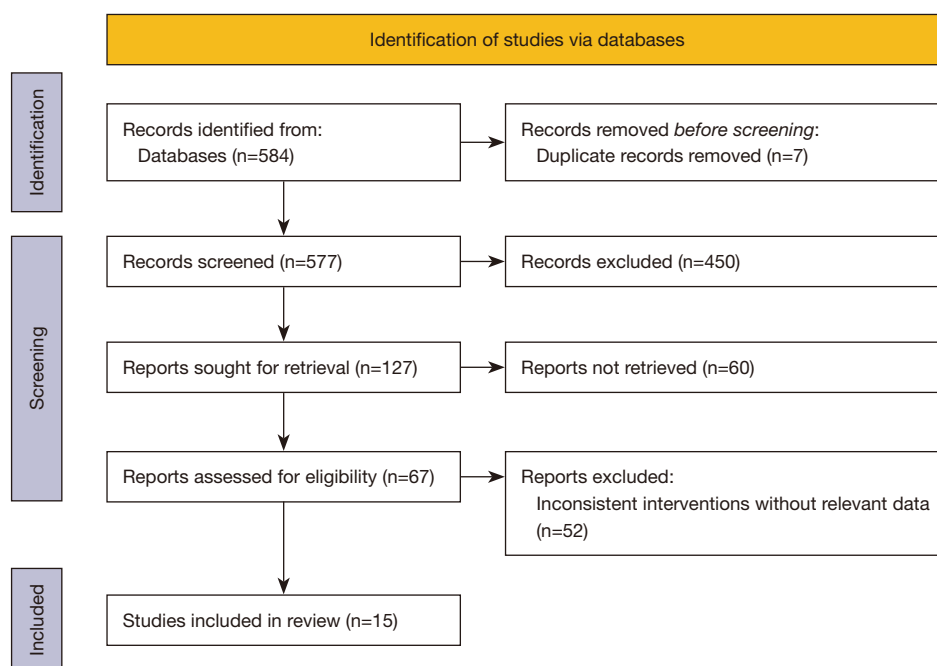
**Figure 1** The flowchart of included studies.

effect size was estimated using a 95% CI. The heterogeneity between the included study results was analyzed by the $\chi^2$ test (the test level was $\alpha=0.1$), and the heterogeneity size was measured quantitatively as the $I^2$. When the statistical heterogeneity was not found between the study results, we would use the fixed effect models to conduct the meta-analysis. When the statistical heterogeneity was found among the findings, we would perform the further analysis to look for the reasons of heterogeneity, and the random effects model was used to show the results after removing the effects of apparent clinical heterogeneity. Significant clinical heterogeneity was treated using descriptive analysis only. The risk of bias assessment was performed using the RCT risk of bias assessment tool as recommended by the Cochrane manual 5.1.0 (15).

## Results

### study characteristics

A total of 584 relevant documents were obtained from the preliminary examination. According to our inclusion criteria, after layer-by-layer screening, 15 RCTs (16-30) were considered to be appropriate for inclusion in the meta-analysis: 7 RCTs (16-20,22,28) that studied the influence of dapagliflozin combined with metformin; 4 RCTs (25-28)

that studied the influence of dapagliflozin combined with insulin; 3 RCTs (20,21,23) that studied the influence of dapagliflozin combined with exenatide; and 1 RCT (30) that studied the influence of dapagliflozin combined with metformin or insulin. The searching process of studies and results were shown in *Figure 1*. The studies' basic characteristics were described in *Table 1*.

### Methodological quality

Studies selected in this meta-analysis were all placebo-controlled, double-blind trials, all of which reported the inclusion criteria.

### HbA1c changes

A total of 15 RCTs with 3,943 patients were included to compare the difference in HbA1c between the dapagliflozin and placebo groups. The meta-analysis results of the random effects model showed that the changes in HbA1c in the dapagliflozin group were greater than those in the placebo group, indicating that dapagliflozin can reduce the HbA1c level of patients more effectively (MD =−0.46, 95% CI: −0.58 to −0.34, P<0.00001). Meanwhile, subgroup analysis was performed by the type of combination hypoglycemic

**Table 1** Baseline characteristics and interventions of patients in the included RCTs

| Studies included | Age (y) (ave) | | Interventions | | Intervention time (weeks) |
|---|---|---|---|---|---|
| | Experimental | Control | Experimental | Control | |
| O. Ljunggren 2012 | 60.6±8.2 | 60.8±6.9 | Dapagliflozin + Metformin | Placebo + Metformin | 50 |
| R. R. Henry 2012 | 51.0±10.1 | 52.7±10.4 | Dapagliflozin + Metformin | Placebo + Metformin | 24 |
| Robert R. Henry 2018 | 56.0±6.9 | 53.2±10.7 | Dapagliflozin + Metformin | Placebo + Metformin | 4 |
| Robert R. Henry 2018 | 57.7±7.3 | 60.4±7.1 | Dapagliflozin + Insulin | Placebo + Insulin | 4 |
| Serge A. Jabbour 2018 | 54.2 | 54.2 | Dapagliflozin + Exenatide | Placebo + Exenatide | 52 |
| Wenying Yang 2016 | 54.6±9.5 | 53.5±9.2 | Dapagliflozin + Metformin | Placebo + Metformin | 24 |
| Wenying Yang 2018 | 56.5±8.14 | 58.6±8.9 | Dapagliflozin + Insulin | Placebo + Insulin | 24 |
| Clifford J. Bailey 2010 | 52.7±9.9 | 53.7±10.3 | Dapagliflozin+ Metformin | Placebo | 24 |
| Clifford J. Bailey 2013 | 52.7±9.9 | 53.7±10.3 | Dapagliflozin + Metformin | Placebo + Metformin | 102 |
| J. Bolinder 2014 | 60.6±8.2 | 60.8±6.9 | Dapagliflozin + Metformin | Placebo + Metformin | 102 |
| Jan Bolinder 2012 | 60.6±8.2 | 60.8±6.9 | Dapagliflozin + Metformin | Placebo + Metformin | 24 |
| John P. H. Wilding 2009 | 55.7±9.2 | 58.4±6.5 | Dapagliflozin + Insulin | Placebo + Insulin | 12 |
| John P. H. Wilding 2012 | 59.3±8.8 | 58.8±8.6 | Dapagliflozin + Insulin | Placebo + Insulin | 48 |
| John P. H. Wilding 2014 | 59.3±8.8 | 58.8±8.6 | Dapagliflozin + Insulin | Placebo + Insulin | 104 |
| Juan P. Frías 2018 | ≥65 | ≥65 | Dapagliflozin + Exenatide | Placebo + Exenatide | 28 |
| Juan P. Frías 2016 | ≥65 | ≥65 | Dapagliflozin + Exenatide | Placebo + Exenatide | 28 |

Data are n (%) or means ± SD, unless otherwise indicated. RCTs, randomized controlled trials.

agent. The results showed that compared with placebo, dapagliflozin combined with metformin (MD =−0.45, 95% CI: −0.61 to −0.29, P<0.00001), insulin (MD =−0.59, 95% CI: −0.83 to −0.36, P<0.00001), or exenatide (MD =−0.26, 95% CI: −0.53 to 0.01, P<0.00001) showed a significant reduction in the level of HbA1c (*Figure 2*).

### FPG changes

A total of 8 RCTs (16,17,19,20,22,25,26,28) with 2,217 patients were included to compare the difference in FPG between the dapagliflozin and placebo groups. The meta-analysis of the random effects model showed that the changes in FPG in the dapagliflozin group were greater than those in the placebo group, indicating that dapagliflozin can reduce the FPG levels in patients more effectively (MD =−0.77, 95% CI: −1.19 to −0.36, P<0.00001). Moreover, a subgroup analysis was performed according to the type of combined hypoglycemic agents. The results showed that compared with placebo, dapagliflozin combined with metformin (MD =−0.94, 95% CI: −0.99 to −0.90,

P<0.00001), insulin (MD =−0.66, 95% CI: −1.38 to 0.06, P<0.00001), or exenatide (MD =−0.08, 95% CI: −0.14 to −0.02) showed a significant reduction in the level of FPG (*Figure 3*).

### Weight changes

A total of 13 RCTs (16-20,22-29) with 3,722 patients were included to compare the weight differences between the dapagliflozin and placebo groups. The meta-analysis of the random effects model showed that the changes in weight in the dapagliflozin group were greater than those in the placebo group, indicating that dapagliflozin can reduce the weight levels of patients more effectively (MD =−1.95, 95% CI: −2.13 to −1.77, P<0.00001). Moreover, a subgroup analysis was performed according to the type of combined hypoglycemic agents. The results showed that compared with placebo, dapagliflozin combined with metformin (MD =−2.06, 95% CI: −2.34 to −1.77, P<0.00001), insulin (MD =−1.99, 95% CI: −2.50 to −1.48, P<0.00001), or exenatide (MD =−1.87, 95% CI: −2.21 to −1.53, P<0.00001) showed a
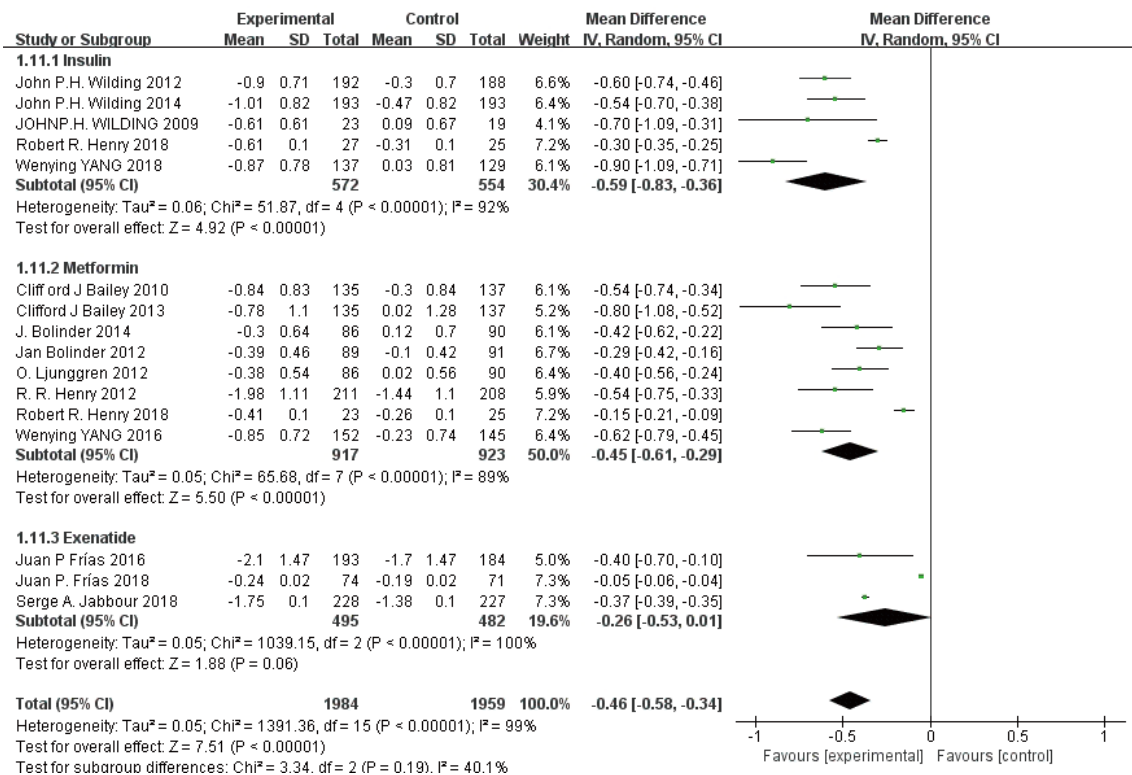
**Figure 2** Meta-analysis of HbA1c changes between the dapagliflozin group and placebo group. HbA1c, hemoglobin A1c; SD, standard deviation; 95% CI, 95% confidence interval; P value, probability value; MD, mean difference; IV, inverse variance methods.
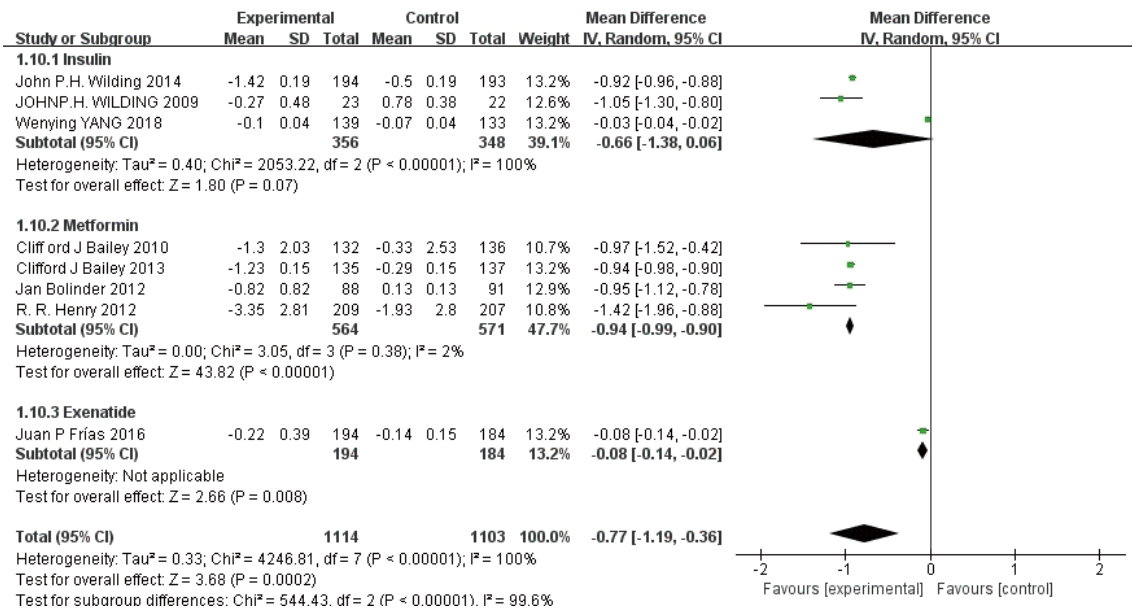


**Figure 3** Meta-analysis of FPG changes in the dapagliflozin group and placebo group. FPG, fasting plasma glucose; SD, standard deviation; 95% CI, 95% confidence interval; P value, probability value; MD, mean difference; IV, inverse variance methods.
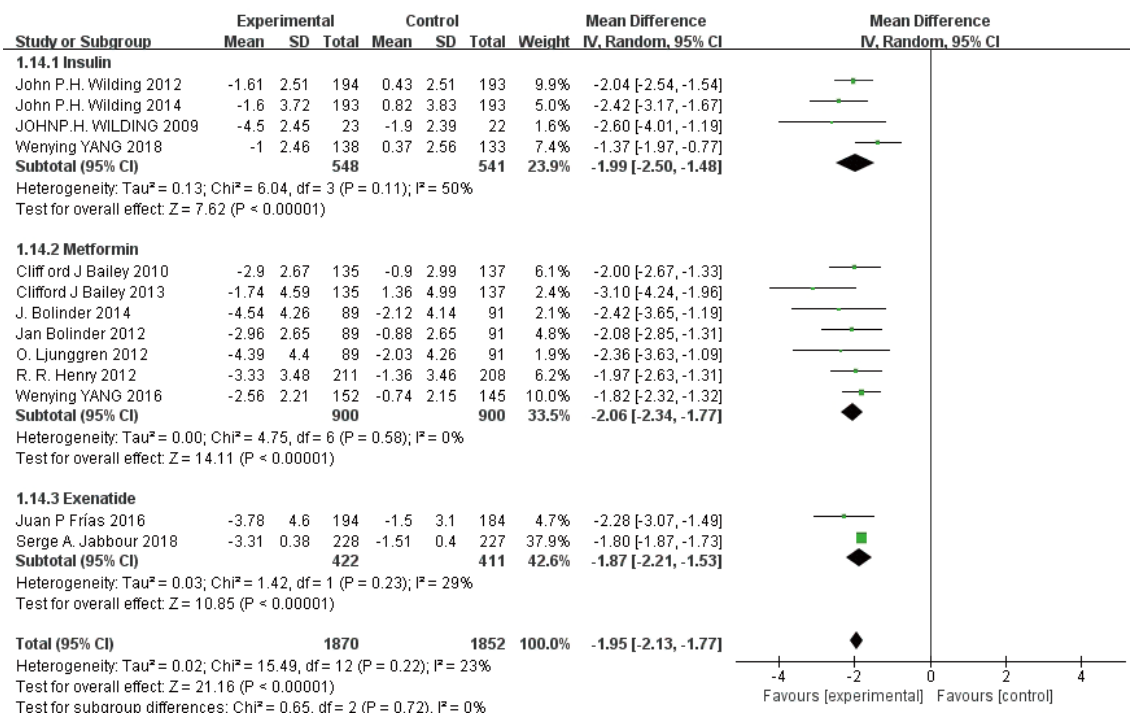
       

**Figure 4** Meta-analysis of weight changes in the dapagliflozin group and placebo group. SD, standard deviation; 95% CI, 95% confidence interval; P value, probability value; MD, mean difference; IV, inverse variance methods.

**Table 2** Incidence of adverse reactions in the dapagliflozin group and placebo group

| Test index | Number of studies included | Heterogeneity test | | Effect of the model | Results of the meta-analysis | |
|---|---|---|---|---|---|---|
| | | P value | I² value | | RR (95% CI) | P value |
| Genital infection | 7 | 0.93 | 0% | Fixed | 3.74 (2.35, 5.96) | <0.00001 |
| Urinary tract infection | 10 | 0.55 | 0% | Fixed | 1.44 (1.06, 1.95) | 0.02 |
| Hypoglycemia | 12 | 0.86 | 0% | Fixed | 1.04 (0.93, 1.17) | 0.49 |

RR, risk ratio; 95% CI, 95% confidence interval; P value, probability value.

significant reduction in the change of weight (*Figure 4*).

### Incidence of adverse events

A total of 12 RCTs (16-20,22,23,25,26,28-30) with 3,651 patients reported the occurrence of hypoglycemic events during treatment. The meta-analysis of the fixed effects model showed that there was no significant difference in the incidence of hypoglycemic events between the dapagliflozin and placebo groups (RR =1.04, 95% CI: 0.93 to 1.17, P=0.49) (*Table 2*).

A total of 10 RCTs (16-20,25,26,28-30) with 2,797 patients reported the occurrence of urinary tract infection during treatment. The meta-analysis of the fixed effects model showed that the incidence of urinary tract infection in the dapagliflozin group was significantly higher than that in the placebo group (RR =1.44, 95% CI: 1.06 to 1.95, P=0.02) (*Table 2*).

A total of 7 RCTs (18-20,23,25-27) with 2,109 patients reported the occurrence of genital infection during treatment. The meta-analysis of the fixed effects model showed that the incidence of genital infection in the dapagliflozin group was significantly higher than that in the placebo group (RR =3.74, 95% CI: 2.35 to 5.96,
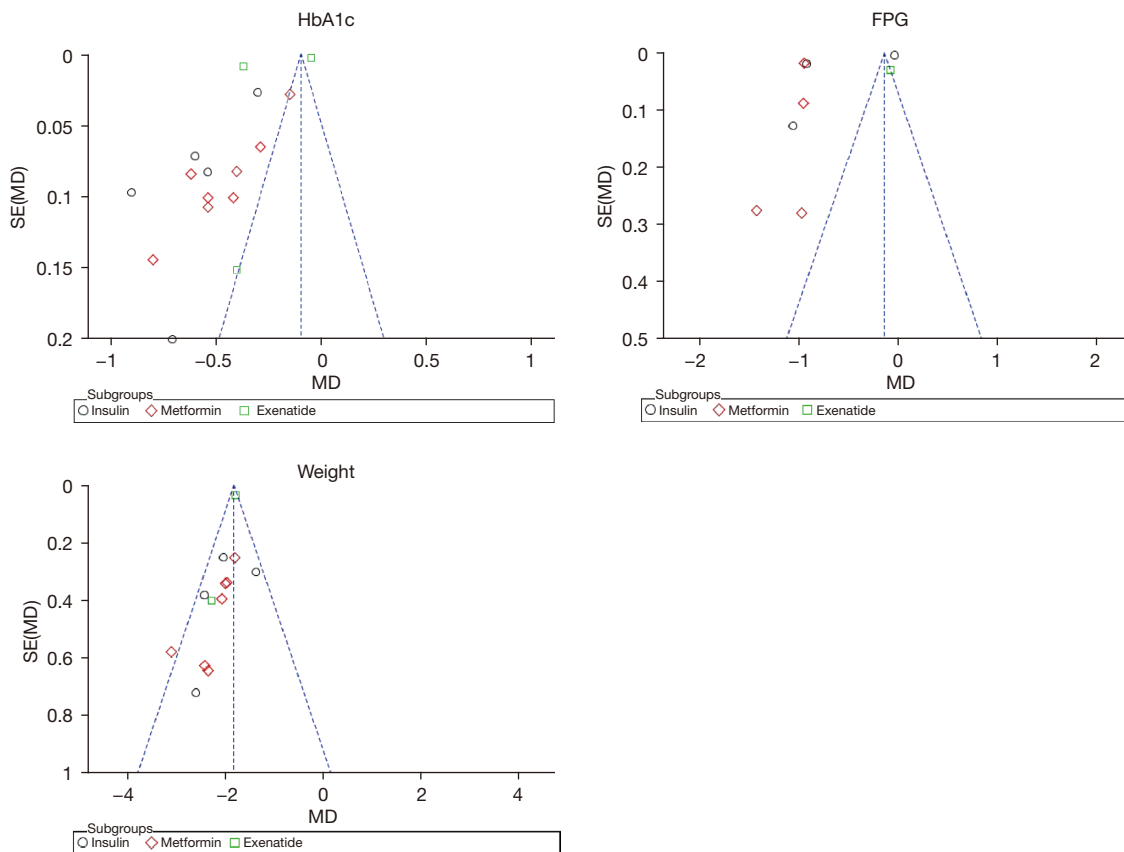
*Ann Palliat Med* 2022;11(3):1028-1037 | https://dx.doi.org/10.21037/apm-22-121

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**Figure 5** Funnel plots of HbA1c, FPG, and weight. HbA1c, hemoglobin A1c; FPG, fasting plasma glucose; MD, mean difference; SE, standard error.

P<0.00001) (*Table 2*).

### *Publication bias*

The publication bias test was performed by using the outcomes HbA1c, FPG and weight to draw a funnel plot. There was left and right asymmetry between each study point, which indicated that there may be publication bias in these studies (*Figure 5*).

### Discussion

HbA1c is an indicator used to evaluate long-term glycemic control and is an important basis for guiding the clinical adjustment of treatment programs (31). HbA1c reflects the average levels of blood glucose over the past 2–3 months. HbA1c has been recommended as a biomarker for the detection and monitoring of diabetes mellitus, especially type 2 diabetes mellitus (31,32). The results of this meta-

analysis showed that dapagliflozin can reduce HbA1c levels more effectively than placebo. We performed a subgroup analysis according to the combined type of hypoglycemic agents, and the results suggested that dapagliflozin in combination with metformin, insulin, or exenatide outperformed all three monotherapies in reducing HbA1c levels. This result may be due to a synergistic effect that was caused by the combination of dapagliflozin and other oral hypoglycemic agents acting on different targets. The hypoglycemic mechanism of dapagliflozin is independent of insulin secretion, which can prevent drug resistance and islet function decline caused by the overstimulated secretion of pancreatic β cells (8) and may potentially protect the function of β cells. Thus, dapagliflozin could be a new option for people with type 2 diabetes.

FPG is defined as the blood glucose level after fasting (no food, except water, for at least 8–10 hours). FPG is the most commonly used indicator of diabetes and islet β cell function, generally representing the secretory function of

basal insulin. Research has demonstrated that controlling FPG as soon as possible can promote HbA1c to reach the standard levels (33,34) and can facilitate whole-day blood glucose management and bring multiple benefits to patients. Considering the association between FPG and efficacy in HbA1c changes, the results of this meta-analysis show that dapagliflozin could reduce FPG levels more effectively than placebo, which confirms the effect of HbA1c by dapagliflozin.

The results of this study also showed that dapagliflozin could reduce the body quality level compared with placebo based on the change in body weight. Yang *et al.* (28) found that dapagliflozin reduced total body fat mass by using a double-energy X-line absorption assay and reduced subcutaneous and visceral adipose tissue by using magnetic resonance imaging. Therefore, the weight loss in dapagliflozin group may be caused by the decreasing of visceral and subcutaneous adipose tissue. In the early stage, weight loss was due to mild osmotic diuresis caused by dapagliflozin, followed by a loss of excess energy through the excretion of glucose in the urine, thus gradually reducing weight and waist circumference, which was associated with a reduction in fat mass.

Hypoglycemia is an unavoidable adverse reaction in diabetic patients in the process of hypoglycemic treatment and a restriction factor on the long-term maintenance of normal blood glucose levels (2). Severe episodes of hypoglycemia can cause great harm to patients. Therefore, we need to pay attention to the risk of hypoglycemia when choosing hypoglycemic drugs. The risk of hypoglycemia was evaluated in patients treated with dapagliflozin combined with oral hypoglycemic agents because of the significant reduction in blood pressure by SGLT-2 inhibitors. The results of the meta-analysis showed that there was no significant difference in the incidence of hypoglycemia and hypotension in the dapagliflozin group compared with the placebo group, indicating that diabetic patients could be treated effectively by dapagliflozin without increasing the incidence of hypoglycemia and hypotension.

The most common adverse effects of dapagliflozin are urinary tract and genital infections, which may be related to reducing glucose re-absorption in near-curvature tubules and increasing the hypoglycemic mechanism of urinary glucose excretion. A study of risk factors for urinary tract infection in women with diabetes found that urinary glucose levels did not affect the risk of urinary tract infection (35). However, the results of this meta-analysis showed that the incidence of urinary tract infection and genital infection was higher in the dapagliflozin group than in the placebo group. Although this study suggests that the combination of dapagliflozin would increase the risks of genital infection and urinary tract infection, these infections are mild and moderate and resolve without intervention or routine clinical management. No subjects quit the trial; however, urinary tract and genital infections were common in patients with diabetes. Therefore, we could use these results to identify people at high risk of urinary tract and genital infections so that patients could receive better treatment.

However, as a meta-analysis, this study has several limitations. Although the evaluation was conducted in strict accordance with the retrieval strategy used to collect published studies, a small number of published studies were still missing due to various constraints.

## Conclusions

In summary, the RCTs included in this study were double-blind RCTs, the results of which were of high quality and credibility. However, due to the different inclusion criteria and medication regimens, there may be some clinical heterogeneity in the results.

Dapagliflozin combined with oral hypoglycemic agents could effectively reduce HbA1c and body quality without increasing the incidence of hypoglycemia, but there is a high risk of urinary tract and genital infections.

## Footnote

*Reporting Checklist:* The authors have completed the PRISMA reporting checklist. Available at https://apm.amegroups.com/article/view/10.21037/apm-22-121/rc

*Conflicts of Interest:* All authors have completed the ICMJE uniform disclosure form (available at https://apm.amegroups.com/article/view/10.21037/apm-22-121/coif). The authors have no conflicts of interest to declare.

*Ethical Statement:* The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are

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appropriately investigated and resolved.

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