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Efficacy and safety of dapagliflozin plus saxagliptin vs monotherapy as added to metformin in patients with type 2 diabetes

A meta-analysis

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Abstract

Background: This study aim at evaluating the efficacy and safety of dapagliflozin plus saxagliptin vs monotherapy as added to metformin in patients with type 2 diabetes mellitus (T2DM).

Method: PubMed, Cochrane library, Embase, CNKI and Wanfang databases were searched up to 31 December 2019. Randomized controlled trials (RCTs) applicable in dapagliflozin plus saxagliptin vs monotherapy as added to metformin in the treatment of T2DM were included. The outcomes included changes in HbA1c, FPG, body weight, SBP, DBP and adverse reactions. Fixed or random effects model were used to assess these outcomes.

Results: In this study, 8 RCTs involved 7346 patients were included. Compared with dapagliflozin plus metformin(DM) group, patients treated with dapagliflozin plus saxagliptin add on to metformin(DSM) could significantly increase the adjusted mean change levels of HbA1c, FPG, SBP and DBP($P < .00001$, SMD = −4.88, 95%CI = −6.93~−2.83; $P < .00001$, SMD = −6.50, 95%CI = −8.55~−4.45; $P < .00001$, SMD = −0.97, 95%CI = −1.15~−0.78; $P < .00001$, SMD = −2.00, 95%CI = −2.20~−1.80), but no major difference in body weight loss showed($P = .12$, SMD = 0.92, 95%CI = −0.22~2.06). Furthermore, DSM therapy displayed better effects than saxagliptin plus metformin(SM) in the adjusted mean change levels of HbA1c, FPG, body weight and SBP($P < .00001$, SMD = −7.75, 95%CI = −8.84~−6.66; $P < .00001$, SMD = −7.75, 95%CI = −8.84~−6.66; $P = .04$, SMD = −3.40, 95%CI = −6.64~−0.17; $P = .04$, SMD = −7.75, 95%CI = −8.84~−6.66), whereas no obvious difference in lowering DBP($P = .18$, SMD = −16.35, 95%CI = −40.12~7.41). Additionally, compared with DM and SM groups, there were no remarkable difference in the incidence of nausea, influenza, headache, diarrhea, urinary tract infection and renal failure for patients taking DSM, but the incidence of genital infection and hypoglycemia were higher in DSM group.

Conclusions: Patients taking the DSM therapy had better effects in reducing the level of HbA1c, FPG, body weight, SBP and DBP than the DM and SM therapy. However, patients treated with DSM therapy are more likely to have hypoglycemia and genital infection. Dapagliflozin plus saxagliptin may be a suitable therapy strategy for patients with T2DM inadequately controlled with metformin, and this will provide a clinical reference for the treatment of T2DM.

Abbreviations: DBP = diastolic blood pressure, DM = diabetes mellitus, DPP-4 = dipeptidyl peptidase-4, FPG = fasting plasma glucose, GLP-1 = glucagon like polypeptide-1, HbA1c = glycosylated hemoglobin, RCTs = randomized controlled trials, SBP = systolic blood pressure.

Keywords: type 2 diabetes mellitus, dapagliflozin, saxagliptin, randomized controlled trials, meta-analysis

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All data generated or analyzed during this study are included in this published article [and its supplementary information files].

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The datasets generated during and/or analyzed during the current study are publicly available.

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1. Introduction

Diabetes mellitus (DM) is a metabolic disease characterized by hyperglycemia, and resulting from defects in insulin secretion and insulin action or both.[1] Globally, the number of people with DM reached 415 million in 2015, and the population will be raised to 642 million in 2040.[2] At present, DM has become the third serious disease threatening public health, and type 2 diabetes mellitus (T2DM) accounts for 90% of all DM patients.[3] The main pathological mechanism of T2DM is the dysfunction of β-cells and insulin resistance, and environmental change also play an important role in the development of T2DM.[4] The therapeutic strategy for the treatment of T2DM included oral agents, insulin injectable and weight control. However, traditional drugs for the treatment of T2DM failed to effectively control HbA1c and also led to some diabetes complications. Recent study found that new therapeutic drugs containing sodium glucose co-transporter 2(SGLT2) inhibitors, dipeptidyl peptidase-4 inhibitors and glucagon-like polypeptide-1(GLP-1) analogue had better glycemic control when monotherapy or combination with other drugs are taken for T2DM.[5]

Good management of blood glucose plays a key role in improving metabolic dysfunction and lowering the risk of diabetic complications as cardiovascular diseases and nervous system diseases.[6] Metformin is a synthetic biguanide drug which has been used as a first-line hypoglycemic drug in patients with T2DM that lifestyle modification alone has proved to be insufficient. Reportedly, metformin monotherapy was effective in cutting blood glucose and reducing weight for T2DM patients, but patients frequently showed hypoglycemia and glucose tolerance, and then combination therapy emerged.[7] SGLT2 inhibitors are considered as the second or third-line drugs can be used in monotherapy or combination with other antidiabetic drugs for T2DM patients.[8] Dapagliflozin is a selective oral SGLT2 inhibitor which can decrease renal glucose reabsorption and increase urinary glucose excretion, exhibiting better hypoglycemic effects.[9] A meta-analysis of six RCTs indicated that dapagliflozin monotherapy was effective in decreasing the levels of HbA1c, fasting plasma glucose (FPG) and body weight for patients with T2DM, and without raising hypoglycemia.[10] RCTs found that dapagliflozin could significantly lower the levels of HbA1c and FPG, and reduce overall glucose variability for T2DM patients that were inadequately controlled with insulin or metformin.[11] The latest study found that dapagliflozin could significantly lower the rate of cardiovascular death and the hospitalization for heart failure, but showed minimal effects in alleviating cardiovascular adverse events.[12]

Saxagliptin is a selective orally dipeptidyl peptidase 4(DPP-4) inhibitor. The mechanism of the inhibitors focused on increasing the concentrations of glucose dependent insulinotropic peptide (GIP) and GLP-1, and then promoting the secretion of insulin and inhibited glucagon secretion, which showed major effects on lowering the blood glucose and body weight.[13] A systematic review and meta-analysis showed that saxagliptin monotherapy has better effects in lowering the level of HbA1c and decreasing the events of adverse reactions (ARs), and better control on glycemia than liraglutide and dapagliflozin.[14] A phase 3 RCT showed that dapagliflozin plus metformin therapy beat the saxagliptin plus metformin combination in cutting HbA1c, FPG, systolic blood pressure (SBP) and body weight, but urinary tract infection was more likely to emerge in patients taking daglitazone plus metformin.[15] Although the therapy of dapagliflozin and saxagliptin adding on to metformin could evidently improve glycemic control, better therapy regimen was still needed to be explored as high level of HbA1c and ARs events pose major concerns.

Furthermore, a phase 3 RCT found that dapagliflozin plus saxagliptin was similar effects with insulin glargine in lowering blood glucose and decreasing ARs, but the body weight control of the combination was superior to insulin glargine in T2DM patients who had inadequate glycemic control with metformin.[16] In addition, a 52-week RCT indicated saxagliptin combination with dapagliflozin and metformin contributed to greater improvements in glycemic control and reduction of body weight, and without increasing the risk of hypoglycemia.[17] Currently, studies have been conducted to delve into the effects of dapagliflozin plus saxagliptin for the treatment of T2DM, but definite conclusions were not reached. Therefore, we carried out this study to comprehensively evaluate the efficacy and safety of dapagliflozin plus saxagliptin vs monotherapy as added to metformin in T2DM patients.

2. Method

2.1. Search strategy

Several electronic databases including PubMed, Cochrane library, Embase, CNKI and Wanfang were systematically searched without langue restriction and with publication deadline set on 31 December 2019. We used the following search terms: "sodium–glucose co-transporter 2 inhibitor or dapagliflozin" and "dipeptidyl peptidase 4 inhibitor or saxagliptin" and "metformin" and "diabetes mellitus or type 2 diabetes mellitus," and the article types were restricted to RCTs.

2.2. Study selection

The inclusion criteria are as follows. First, RCTs included in this study were conducted to assess the efficacy and safety of dapagliflozin plus saxagliptin vs monotherapy as added to metformin in patients with T2DM. Second, all participants were aged ≥18 years, and diagnosed with T2DM according to the standards criteria of American Diabetes Association. Third, the patients had body mass index ≤45 kg/m^2, HbA1c 7.5% to 10.0%, FPG ≤15 mmol/L and received metformin dosage of 1500 mg/day for more than 8 weeks. Fourth, the trials last for at least 16 weeks and the outcomes contained the change of HbA1c, FPG, body weight, SBP, DBP and adverse reactions. Lastly, the types of studies were protocol, non-randomized controlled trial and observational research should be excluded. Articles with such obvious shortcomings as insufficient data and outcomes were eliminated.

2.3. Data extraction

All data were independently extracted by two researchers (YZ and MFY). According to the inclusion and exclusion criteria, the researchers deliberately scanned the baseline characteristics of participants to extract the data of interest. During data extraction, any result discrepancies were discussed and achieve the same results.

2.4. Quality assessment

The Cochrane risk of bias tool was used to evaluate the methodological quality of all included studies. Factors that assess

the risk of bias include selection bias, performance bias, detection bias, attrition bias, reporting bias and other bias. The quality scores of each study were graded by Jadad score scale, and the scores ranged from 0 to 7. For this study, ethical approval and informed consent were not required.

2.5. Statistical analysis

We conducted the meta-analysis to assess the outcomes by RevMan software 5.3. For continuous outcomes, we calculated the weighted mean differences (WMD) and 95% confidence interval (95% CI). For dichotomous outcomes, we calculated the odds ratios (OR) and 95% CI. I^2 statistic was used to evaluate the heterogeneity and $P < .05$ indicated significant difference for heterogeneity. The values of I^2 in the range of 0 to 25%, 25% to 50% or above 50% indicated low, moderate and high heterogeneity, respectively. Fixed effect models were used to analyze the outcomes when I^2 less than 50% and $P > .05$, and random effect model was used when I^2 values $> 50\%$. Subgroup analysis was applied to decrease heterogeneity. The funnel plot was performed to assess the publication bias, and sensitive analysis was conducted to exclude the potential bias. $P < .05$ was considered as significant difference.

3. Results

3.1. Description of the studies

A total of 439 studies were sifted out according to the search strategies, and no records identified through other sources (Fig. 1). After removing the duplicated studies, a total of 414 studies were remained, then 402 articles was excluded after screening the type of article contains review, observational trials, meta-analysis, and clinical guidelines. Finally, 8 studies[18–25] were included in this systematic review and meta-analysis. The baseline characteristics of all included studies were summarized in Table 1. Among of the studies, the range of mean age of all patients were from 53 to 57.2 years, and 2195 patients received DSM, 1452 patients received DM and 1128 with SM. The dosage of dapagliflozin was 10 mg, and saxagliptin was 5 mg, whereas metformin dosage ranged from 500 to 1500 mg per day. All studies had a Jadad score, the values of 6 studies were 4 or higher and other two studies were less than 4. In addition, the funnel plot indicated that all included studies had potential publication bias (Fig. 2).

3.2. HbA1c

A total of 6 studies involving 2316 patients assessed the effects of DSM vs DM on the change level of HbA1c, five studies with 1776 patients evaluated the effects of DSM vs SM on the change of HbA1c, and the results were showed in Figure 3. Due to high heterogeneity ($P < .00001$, $I^2 = 99\%$ and 98%), random effect models and subgroup analysis were used to analyzed this outcome. DSM therapy displayed better effects increasing the adjusted mean change level of HbA1c than the therapies of DM and SM ($P < .00001$, SMD = −4.88, 95%CI = −6.93∼−2.83; $P < .00001$, SMD = −6.72, 95%CI = −8.48∼−4.96). In addition, according to the different dosage of dapagliflozin and metformin, subgroup analysis was used to assess the change of HAb1c, and the results were shown in Supplementary Digital Content, Figure 1 (http://links.lww.com/MD/E599). DSM therapy could significant lower the level of HbA1c ($P < .00001$, SMD = −5.64,

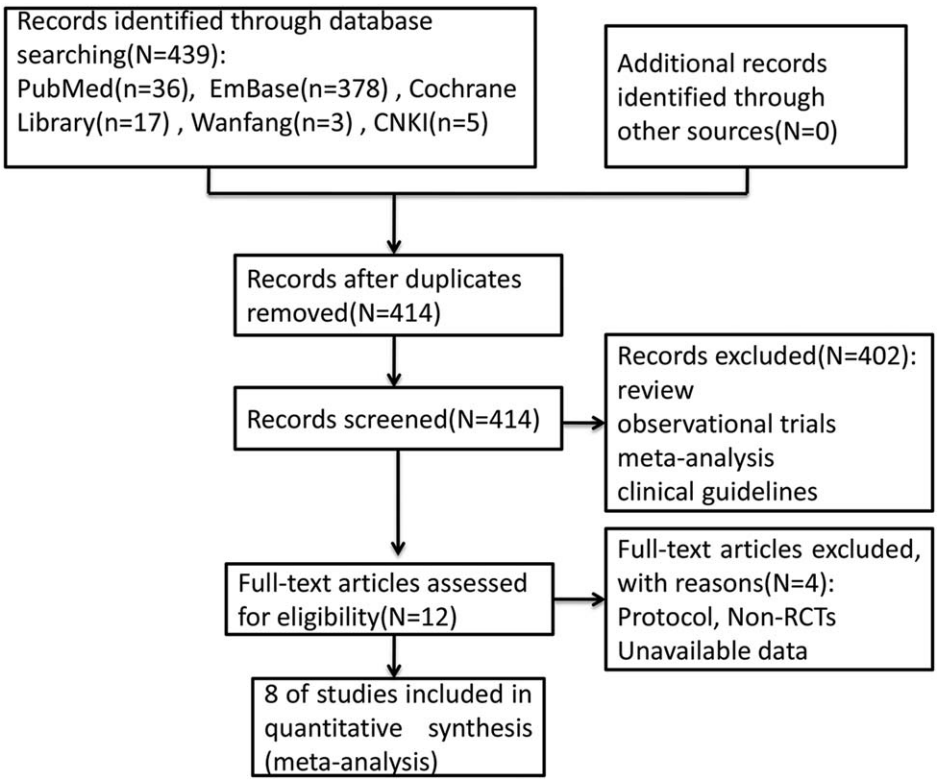

Figure 1. Flow diagram of studies identification and selection.

Table 1

Baseline characteristics of all included studies in this meta-analysis.

References	Study design	Sample size	Age(mean ± SD)			Duration (weeks)	Regimen per day, mg			Outcomes	Jadad scores
			DSM	DM	SM		D	S	M		
Mathaei et al[18]	RCTs	857	54.7 ± 9.8	54.5 ± 9.3	-	24	10	5	500	HbA1C, FPG, Hypoglycemia UTI, GI	5
Mathaei et al[19]	RCTs	484	54.7 ± 9.8	54.5 ± 9.3	-	52	10	5	1000	HbA1C, FPG, Hypoglycemia UTI, GI,RF	5
Mathieu et al[20]	RCTs	818	55.2 ± 8.6	-	55.0 ± 9.6	24	10	5	500	HbA1C, FPG,BW,SBP,DBP Hypoglycemia, UTI, GI	3
Mathieu et al[21]	RCTs	320	55.2 ± 8.6	-	55.0 ± 9.6	52	10	5	500	HbA1C, FPG,BW, UTI, GI Hypoglycemia, RF, diarrhea	3
Prato et al[22]	RCTs	1169	54 ± 9	54 ± 10	55 ± 10	24	10	5	1500	HbA1C, Hypoglycemia, UTI GI,RF, nause, diarrhea	4
Rosenstock et al[23]	RCTs	1282	53 ± 10	54 ± 10	53 ± 10	24	10	5	1500	HbA1C, FPG,BW, UTI, GI Hypoglycemia	5
Rosenstock et al[24]	RCTs	1058	57.2 ± 10.7	55.9 ± 10.9	57.0 ± 9.9	24	5	5	500	HbA1C, FPG,BW,SBP,DBP Hypoglycemia, RF, nause	5
Wieland et al[25]	RCTs	1358	59.2 ± 7.9	57.4 ± 9.4	-	52	10	5	1500	HbA1C, FPG,BW,SBP Hypoglycemia, UTI, GI	7

BW = body weight, DBP = diastolic blood pressure(mm Hg), DM = dapagliflozin + saxagliptin + metformin, DSM = dapagliflozin + saxagliptin + metformin, FPG = fasting plasma glucose, GI = genital infection, HbA1c = glycosylated hemoglobin, RCTs = randomized controlled trials, RF = renal failure, UTI = urinary tract infection, SBP = systolic blood pressure(mm Hg), SM = saxagliptin + metformin.

95%CI = −7.48∼−3.80), and the results were consistent with previous results.

3.3. FPG

Seven studies involving a total of 6606 participants evaluated the FPG changes in this research. Among these studies, 5 studies compared DSM with DM on the effects of FPG, and 4 studies compared the FPG changes of DSM and DM therapies. Random effect models were used because heterogeneity between the groups was significant ($P < .00001$, $I^2 = 99\%$ and 93%). Moreover, subgroup analysis was performed to compare DSM with DM, SM in terms of the level of FPG. The results indicated that DSM could significantly decrease the level of FPG when compared with DM and SM ($P < .00001$, SMD = −6.50, 95% CI = −8.55∼−4.45; $P < .00001$, SMD = −7.75, 95%CI = −8.84∼−6.66) (Fig. 4).

3.4. Body weight (BW)

In this study, 2 studies was included to compare DSM with DM on the effects of weight loss, and 4 articles were included to compare DSM with SM in terms of weight change. As shown in Figure 5, subgroup analysis was used to compare the difference between DSM, DM and SM groups. Random effect models were used as significant heterogeneity was observed ($P < .00001$, $I^2 = 98\%$ and

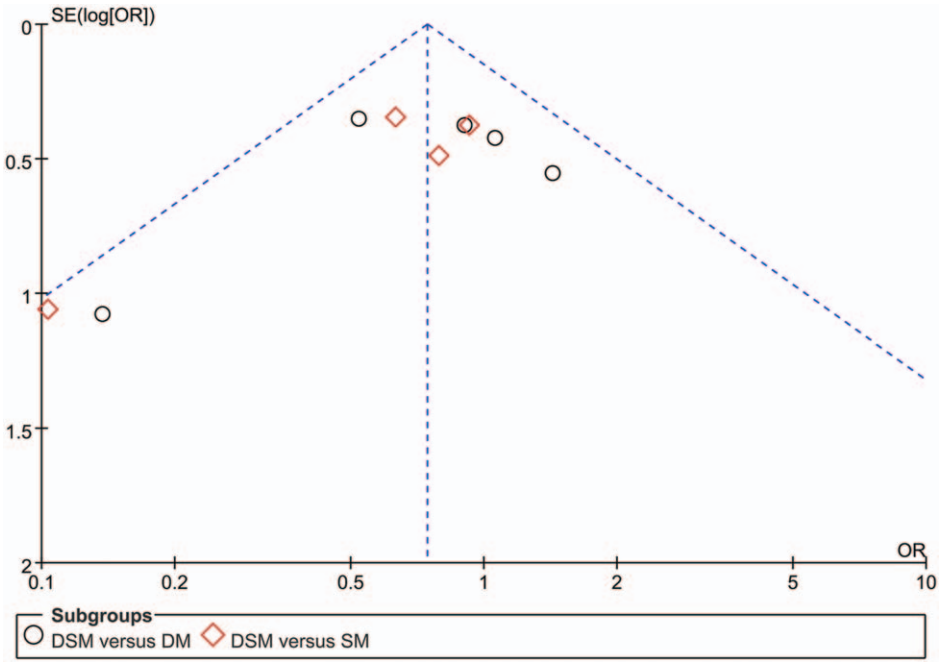

Figure 2. Funnel plot for evaluating the risk of bias in the meta-analysis. DSM = dapagliflozin plus saxagliptin and metformin, DM = dapagliflozin plus metformin, SM = saxagliptin plus metformin, SE = standard error.

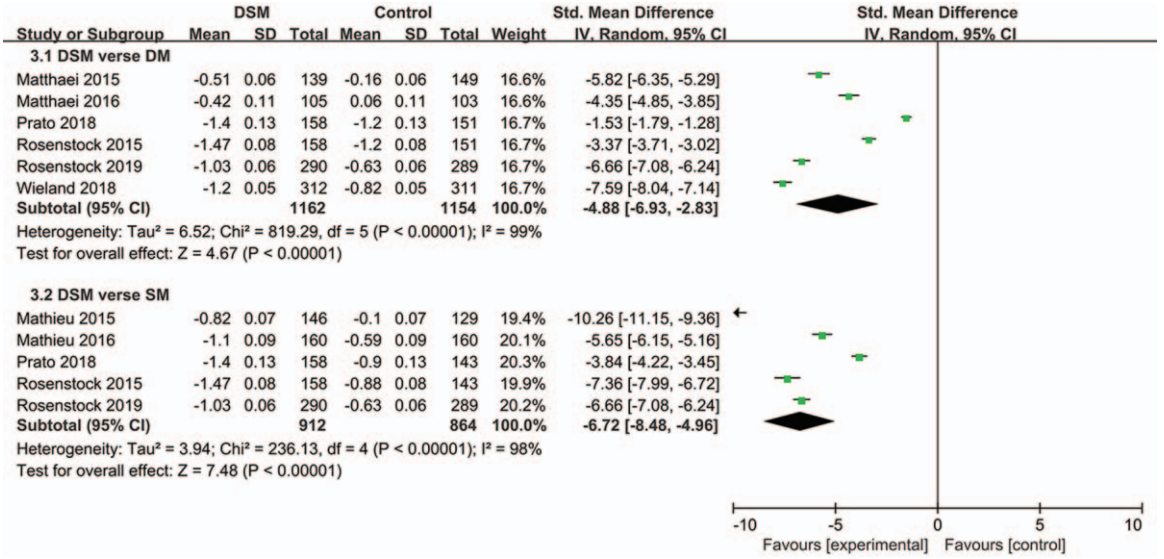

Figure 3. Comparison of the effect of DSM, DM and SM on the adjusted mean change level of HbA1c. DSM = dapagliflozin plus saxagliptin and metformin, DM = dapagliflozin plus metformin, SM = saxagliptin plus metformin, IV = inverse variance method.

100%). There showed no major difference in decreasing body weight between DSM and DM for the treatment of T2DM ($P = .12$, SMD = 0.92, 95%CI = −0.22~2.06). However, DSM proved to be more effective in weight cut than SM for T2DM patients ($P = .04$, SMD = −3.40, 95%CI = −6.64~−0.17).

3.5. SBP and DBP

Two studies with 1200 participants assessed the effects of DSM and DM on the change of SBP, and other two studies compared DSM with SM for SBP variations. Random effect models were used because there were significant heterogeneity between the three groups ($P = .12$, $I^2 = 58\%$; $P < .00001$, $I^2 = 100\%$). Patients taking DSM showed significantly lower level of SBP compared with patients taking DM or SM ($P < .00001$, SMD = −0.97, 95% CI = −1.15~−0.78; $P = .04$, SMD = −7.75, 95%CI = −8.84~−6.66) (Fig. 6A). For DBP, only one study compared the effect of DSM and DM on DBP, and two studies compared DSM with SM when used for the treatment of T2DM patients. Random effect model was used because high heterogeneity ($P < .00001$, $I^2 = 100\%$). DSM could obviously reduce DBP level when compared with DM therapy ($P < .00001$, SMD = −2.00, 95%CI = −2.20~−1.80). However, no significant difference was observed between patients taking DSM and SM ($P = .18$, SMD = −16.35, 95%CI = −40.12~7.41) (Fig. 6B).

3.6. Safety

During medication, a series of side effects including hypoglycemia, nausea, influenza, headache, diarrhea, urinary tract

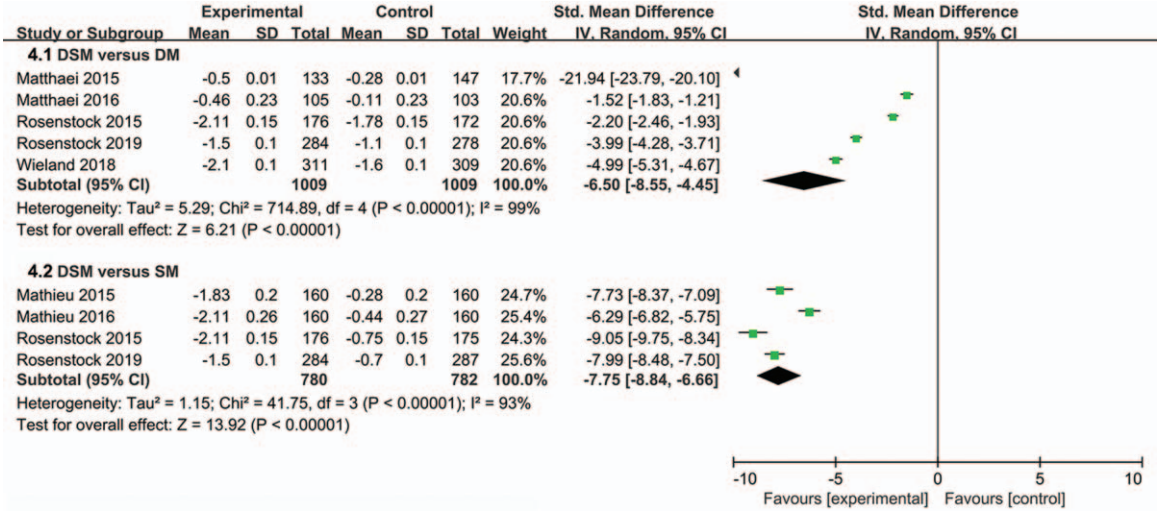

Figure 4. Effects of DSM, DM and SM on the FPG changes. DSM = dapagliflozin plus saxagliptin and metformin, DM = dapagliflozin plus metformin, SM = saxagliptin plus metformin, IV = Inverse variance method.

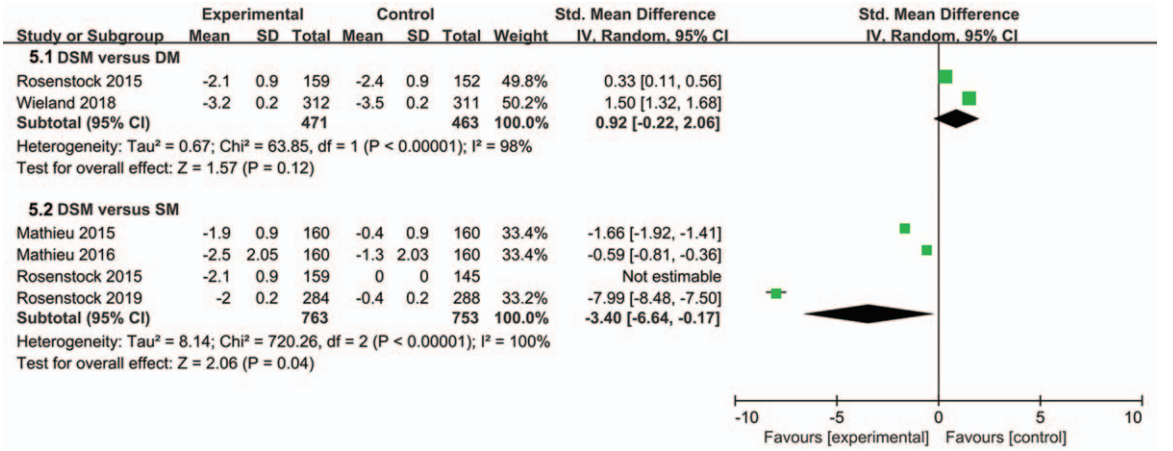

Figure 5. Comparison of the effect of DSM, DM and SM on the change of body weight. DSM = dapagliflozin plus saxagliptin and metformin, DM = dapagliflozin plus metformin, SM = saxagliptin plus metformin, IV = inverse variance method.

infection, genital infection and renal failure, could emerge. In contrast to patients taking DM, there were no significant different in increasing the adverse events such as hypoglycemia, nausea, influenza, urinary tract infection and renal failure in patients with DSM (P=.19, OR=1.36, 95%CI=0.86 ~2.16; P=.73, OR=1.15, 95%CI=0.51~2.62; P=.26, OR=0.67, 95%CI=0.34~1.33; P=.22, OR=0.78, 95%CI=0.53~1.16; P=.26, OR=1.46, 95%CI=0.76~2.79)(Table 2). However, patients taking DSM had lower occurrence rate of genital infection (P=.0009, OR=0.46, 95%CI=0.29~0.72).

Compared with patients taking SM, patients used DSM dramatically increased the incidence of hypoglycemia and genital infection (P=.03, OR=2.21, 95%CI=1.09 ~4.47; P=.002, OR=4.53, 95%CI=1.72~11.93). However, the 2 treating

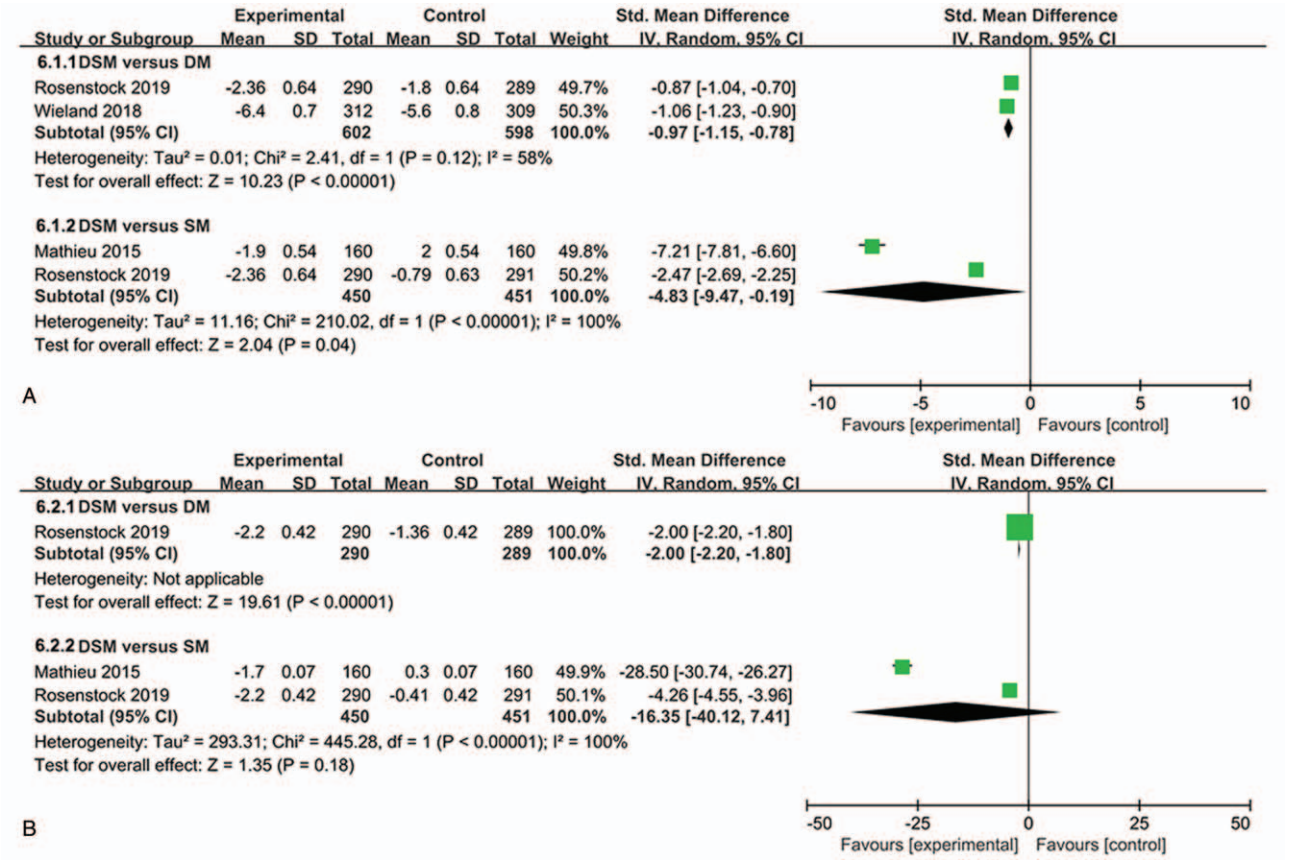

Figure 6. Comparison of the effect of DSM, DM and SM on the change of SBP and DBP. (A) For SBP (B) For DBP. DSM = dapagliflozin plus saxagliptin and metformin, DM = dapagliflozin plus metformin, SM = saxagliptin plus metformin, IV = inverse variance method.

Table 2

Summary of adverse events in all included studies.

Types	Heterogeneity (I^2, P)	OR(95%CI) DSM vs DM	P values	Heterogeneity (I^2, P)	OR(95%CI) DSM vs SM	P values
Hypoglycemia	(15%, .32)	1.36(0.86, 2.16)	.19	(0%, .67)	2.21(1.09, 4.47)	.03
Nausea	(0%, .92)	1.15(0.51, 2.62)	.73	(50%, .16)	0.89(0.40, 1.97)	.77
Influenza	(37%, .21)	0.67 (0.34, 1.33)	.26	(0%, .82)	0.83 (0.52, 1.33)	.44
Headache	–	–	–	(0%, .92)	0.85 (0.52, 1.41)	.54
Diarrhea	–	–	–	(0%, .66)	0.63 (0.35, 1.13)	.12
UTI	(31%, .22)	0.78 (0.53, 1.16)	.22	(24%, .27)	0.70 (0.45, 1.08)	.10
Genital infection	(3%, .39)	0.46 (0.29, 0.72)	.0009	(0%, .68)	4.53 (1.72, 11.93)	.002
Renal failure	(0%, .76)	1.46 (0.76, 2.79)	.26	(30%, .24)	1.64 (0.86, 3.12)	.13

DSM = dapagliflozin + saxagliptin + metformin, DM = dapagliflozin + saxagliptin + metformin, SM = saxagliptin + metformin, UTI = urinary tract infection.

approaches showed no significant difference in the incidence of nausea, influenza, headache, diarrhea, urinary tract infection and renal failure were observed ($P = .77$, OR = 0.89, 95%CI = 0.40~1.97; $P = .44$, OR = 0.83, 95%CI = 0.52~1.33; $P = .54$, OR = 0.85, 95%CI = 0.52~1.41; $P = .12$, OR = 0.63, 95%CI = 0.35~1.13; $P = .1$, OR = 0.70, 95%CI = 0.45~1.08; $P = .13$, OR = 1.64, 95%CI = 0.86~3.12).

3.7. Sensitive analysis

During the analysis process of outcomes, sensitive analysis was conducted to assess the accuracy of the results. The values of SMD and OR were close under fixed effect model or random effect model. In addition, sensitive analysis was conducted by excluding the studies with potential publication bias, but the results were still of no significant difference.

4. Discussion

An ideal therapy strategy for T2DM should be effective in controlling HbA1c and body weight without causing hypoglycemia. According to the statements from American Association of Clinical Endocrinologists and American College of Endocrinology, glycemic control, weight reduction and lower blood pressure are accurate indicators to evaluate T2DM, and the triple oral medication achieved unanimous improvement among new diagnosed T2DM patients with HbA1c level of 9%.[26] At present, metformin combining with other hypoglycemic agents such as sulfonylurea, GLP-1 analogue, DPP-4 inhibitors or SGLT2 inhibitors become main clinical triple oral hypoglycemic regimens for the treatment of T2DM, but the related clinical evidence of triple oral medication on safety and effectiveness are still insufficient.

Some clinical trials had explored the effectiveness and safety of dapagliflozin plus saxagliptin for the treatment of T2DM patients who had inadequate glycemic control with metformin alone, and significant reduction of HbA1c was observed after medication. Moreover, the sustained-release dapagliflozin/saxagliptin tablet of fixed-dosage combination could better improve the level of HbA1c, and this is consistent bioequivalence with taking dapagliflozin and saxagliptin.[27] Additionally, dapagliflozin/saxagliptin have complementary mechanism in improving alpha and beta cells integrity, increasing the concentrations of C-peptide and insulin, and boosting beta cells function.[28]

In our study, we systematically evaluated the effectiveness and safety of dapagliflozin plus saxagliptin vs monotherapy as added to metformin in patients with T2DM, the results indicated that dapagliflozin plus saxagliptin and metformin could significantly increase adjusted mean change levels of HbA1c and FPG, which beat dapagliflozin plus metformin or saxagliptin plus metformin therapies. These results were consistent with previous studies.[25] Among all included studies, the maximum of adjusted mean reduction of HbA1c were 1.47%, 1.2% and 0.9% in recipients of dapagliflozin plus saxagliptin plus metformin, dapagliflozin plus metformin, and saxagliptin plus metformin, respectively. Recently study found that the durability of glycemia control with dapagliflozin was greater than saxagliptin in patients with T2DM, which lasted more than 24 weeks.[29] Other study indicated that dapagliflozin plus saxagliptin as add-on to metformin also exhibit better tolerance in glycemia control.[30]

As for body weight effects, our results indicated that no obvious difference was observed among patients taking DSM and DM ($P > .05$), but DSM therapy proved to be more effective in body weight loss than SM ($P < .05$). Previous researches confirmed that SGLT2 inhibitors could lower blood glucose and control weight at the same time, and the mechanism of weight loss resided in higher glucose excretion through the kidneys, promoting the breakdown of glycogen, thus maintaining a negative energy balance of the whole body and resulting in weight control.[31] A post hoc analysis suggested that the reduction of weight loss was 2.29 kg in patients treated with dapagliflozin for 24 weeks, and the reduction would increase to 4.5 kg when the medication span extended to over 2 years.[32] Meanwhile, DPP-4 inhibitors exhibited neutral effects for weight loss. A Bayesian network meta-analysis indicated that only linagliptin could significantly lower body mass index compared with other DPP-4 inhibitors or placebo, and no statistical significance on body weight control observed when DPP-4 inhibitors were compared with placebo.[33]

With respect to blood pressure, there was a significant gap of the adjusted mean changes from baseline in SBP between patients with DSM and DM. One study assessed the effects of DSM and DM on the changes of DBP, and two studies evaluated the effects of DSM and SM on the changes of DBP. The results showed that DSM remarkably increased the adjusted mean change of DBP from baseline, which beat the DM therapy, and no statistical significance was observed when compared with SM. However, this was not consistent with the results of a previous study. In a 24-week RCT, the study indicated that DSM worked obviously better on lowering the DBP than SM, while there was no difference between DSM and DM.[24] Therefore, the accuracy of these results still needs further verifications.

With regard to the side effects, the common adverse reactions of SGLT-2 inhibitors include hypoglycemia, urinary tract

infection, genital infection and renal impairment or failure. Previous study found that dapagliflozin was associated with high incidence risk of urinary tract infection and genital infection, and had a dose-dependent relationship.[34] In addition, a meta-analysis evaluated the relationship between SGLT-2 inhibitors and the risk of infections, the results showed that SGLT-2 inhibitors were correlated with higher risk of genital infection, and no such correlation with urinary tract infection detected, but high-dosage of dapagliflozin was associated with an increased risk of urinary tract infections.[35] For DPP-4 inhibitors, the common adverse reactions included hypoglycemia, gastrointestinal problems, pancreatitis, upper respiratory tract infection and urinary tract infection, while the symptoms of the side effects were mild.[36] In our study, it is indicated that there were no significant difference in the incidence of hypoglycemia, nausea, influenza, urinary tract infection and renal failure between DSM and DM, but DSM had obviously lower risk of genital infection than DM. Furthermore, there was also no significant difference in the incidence of nausea, influenza, headache, diarrhea, urinary tract infection and renal failure between DSM and SM, but a dramatically higher risk of hypoglycemia and genital infection were observed when DSM compared with SM.

However, there are some potential limitations in our research. First, 7 studies were included in this meta-analysis, but three of them were continuous studies, and this might cause over-estimated results. Second, high heterogeneity and potential publication bias were existed during the process of data analysis, which would undermine the accuracy of results. Lastly, small sample size and insufficient data in the selected studies may weaken the credibility of results. Therefore, further research efforts are still needed to further confirm the efficacy and safety of the combination therapy of dapagliflozin-saxagliptin-metformin for the treatment of T2DM.

To sum up, it was indicated that dapagliflozin plus saxagliptin had better effects in reducing the level of HbA1c, FPG, body weight, SBP and DBP than the monotherapy for the treatment of T2DM when inadequately controlled with metformin alone. Additionally, no more serious side effects were observed when taking with DSM and DM or SM therapy, and DSM could lower the risk of genital infection. Clinically, genital infection should be cautiously monitored when treated with DSM or DM. Therefore, triple therapy with dapagliflozin plus saxagliptin and metformin may be a suitable therapy regimen for patients with T2DM inadequately controlled with metformin, and future clinical application of the therapy will still uncover more pros and cons of the combined treating approach and in turn serve as guides for marginal improvement.

Author contributions

This article was put forward by Y Zhuang and MX Li. J Song and MF Ying designed this review and collected the data. Y Zhuang performed the initial analysis and wrote the manuscript. All authors reviewed the analysis and critically reviewed the manuscript.

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