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Original article

Comparative effects of sitagliptin and metformin in patients with type 2 diabetes mellitus: a meta-analysis

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Abstract

Background:
Sitagliptin has been widely used in the treatment of type 2 diabetes mellitus (T2DM); however, the therapeutic efficacy of sitagliptin remains inconclusive in randomized controlled studies on T2DM in which metformin has served as a control.

Objectives:
The present meta-analysis aimed to compare the therapeutic efficacy of sitagliptin and metformin in the treatment of T2DM.

Methods:
We searched the following databases (Medline, Embase, Cochrane databases, Chinese Medical Journal Database, and the Chinese National Knowledge Infrastructure from inception until April 2013), and identified randomized controlled trials (RCTs) involving sitagliptin and metformin for T2DM. Two independent authors determined whether or not these trials met the inclusion criteria. Then, the variance of results from each study was calculated, and I^2 was employed for evaluation of heterogeneity.

Results:
One hundred and twenty-one studies were identified, of which seven were included for further analysis. For T2DM, the therapeutic efficacy of sitagliptin and metformin was comparable in reducing HbA1c ($P = 0.148$, standard mean difference [SMD] = 0.13, 95% confidence interval [CI] = −0.05, 0.30), decreasing BMI ($P = 0.063$, SMD = 0.26, 95% CI = −0.01, 0.54), and improving the homeostasis model assessment (HOMA)-β ($P = 0.285$, SMD = −0.05, 95% CI = −0.15, 0.04), but sitagliptin was inferior to metformin in improving HOMA-IR ($P = 0.003$, SMD = 0.16, 95% CI = 0.06, 0.27).

Conclusions:
Sitagliptin is similar to metformin in reducing HbA1c, decreasing body weight, and improving the function of beta cells, but is inferior to metformin in improving insulin sensitivity. More RCTs with large sample sizes are required to provide evidence for the rational application of sitagliptin.

Introduction

Type 2 diabetes mellitus (T2DM) is a common disease worldwide, the prevalence of which is on the rise[1,2]. The major manifestations of T2DM include insulin resistance, an increase in fasting or postprandial plasma glucose, and long-term hyperglycemia-induced complications, such as diabetic nephropathy, diabetic retinopathy[3], and diabetic peripheral neuropathy. Moreover, patients with T2DM are usually at increased risk for cardiovascular and

cerebrovascular diseases[4]. Thus, controlling blood glucose is crucial for preventing the occurrence and development of complications of DM[5].

Metformin, a classic drug for the treatment of T2DM, has been applied in clinical practice for >50 years, achieving acceptable therapeutic efficacy[6], and plays a role in insulin resistance (hyperinsulinemia) which is closely related to the pathogenesis and mechanisms of T2DM. To date, some new anti-DM drugs have been developed. DPP-4 inhibitors include sitagliptin, vildagliptin, saxagliptin, and linagliptin. Sitagliptin was approved in the treatment of T2DM by the US Food and Drug Administration (FDA) in 2006, and has been widely used in clinical practice. The glucose-lowering effect of sitagliptin has been confirmed in a number of studies[7–10]. In numerous clinical studies involving patients with T2DM, metformin is used as a control and the therapeutic efficacy of other drugs is compared to metformin, which may reduce the bias caused by subjective expectations of patients and researchers, and the conclusions may be more objective. Sitagliptin can improve insulin sensitivity[9–11], and the glucose-lowering effect is independent of glucose concentration, which makes sitagliptin have a low risk of hypoglycemia. These characteristics of sitagliptin are similar to metformin[12]. Both drugs are usually administered orally in the treatment of T2DM. Thus, RCTs comparing sitagliptin with metformin can indicate the comparative efficacy in the treatment of T2DM. Besides, as compared to studies using a placebo as a control, this design is beneficial for the treatment of patients. However, the findings and conclusions in RCTs such as the effects of lowering HbA1c (hemoglobin A1c) and plasma glucose levels, improving insulin sensitivity and obesity, which were conducted to compare metformin and sitagliptin, are conflicting, and the current RCTs and sample sizes are limited. Thus, it is necessary to integrate the available findings and conduct a meta-analysis of the current data to objectively evaluate the comparatively therapeutic efficacy of sitagliptin compared with metformin in the treatment of T2DM, which may provide better evidence for the clinical treatment of T2DM with sitagliptin.

Methods

Search strategy

We searched the following databases, and identified RCTs on the therapeutic efficacy of sitagliptin in comparison with metformin in patients with T2DM regardless of language and year of publication: Medline; Embase; Cochrane databases; Chinese Medical Journal Database; and the Chinese National Knowledge Infrastructure (from inception until April 2013).

The following terms were used in searching: patient selection ['diabetes mellitus' and 'type 2 diabetes']; exposure ('dipeptidyl peptidase-4 inhibitor', 'DPP-4 inhibitor', 'dipeptidyl peptidase-IV inhibitor', 'DPP-IV inhibitor', 'sitagliptin', 'incretin therapy', and 'metformin'); and study type ('randomized controlled trial').

Inclusion and exclusion criteria

Patients with T2DM, regardless of gender, age, course of disease, body shape, and race, were recruited. Patients were randomized to receive sitagliptin or metformin, but the dose of drugs and courses of treatment were not limited.

The exclusion criteria were as follows: data extraction and quality assessment; HbA1c; fasting blood glucose; postprandial blood glucose; body mass index (BMI); homeostasis model assessment-insulin resistance (HOMA-IR); and homeostasis model assessment-β (HOMA-β).

The methods used in the included studies were randomization, allocation concealment, blinding, and intention-to-treat (ITT) analysis. Identical results were obtained in quality evaluation.

Statistical analysis

Continuous data were expressed as the SMD (standard mean difference), and 95% confidence interval (CI) was calculated. The heterogeneity of the included studies was evaluated with a chi-square test. When no significant difference was noted in heterogeneity evaluation, meta-analysis was performed with a fixed effect model (fixed inverse variance method); when a significant difference was found in heterogeneity evaluation, a random effect model (random DerSimonian and Laird method) was used in the meta-analysis.

We calculated the I^2 statistic[13,14] to assess between-study heterogeneity, applying the following interpretation for I^2: 0–50 = low heterogeneity; 50–80 = moderate heterogeneity and worthy of investigation; 80–100 = severe heterogeneity and worthy of understanding; and 95–100 = aggregate heterogeneity with major caution.

Meta-analysis was performed with Stata software (version 11.0; Stata Corp, College Station, TX, USA), and a value of $P < 0.05$ was considered statistically significant.

Results

Search results

One hundred and twenty-one studies were identified, seven[15–21] of which met the inclusion criteria (Figure 1). A total of 1881 patients were included in the seven studies;

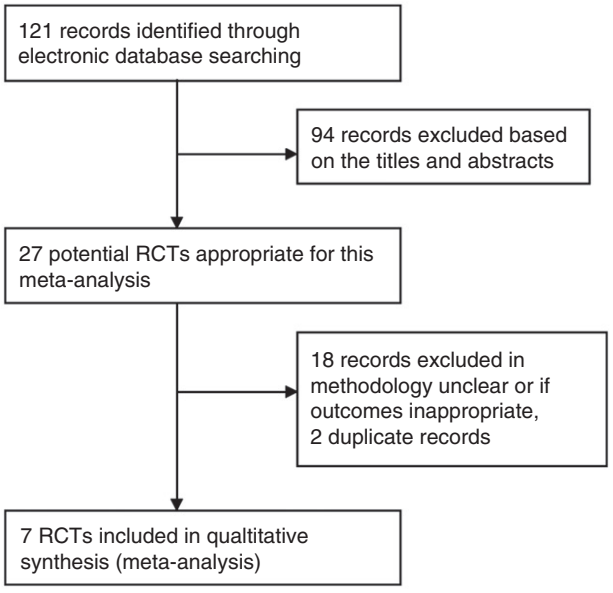

Figure 1. Results of the article search and the outlining of the entire flow chart of searching for articles for this meta-analysis.

908 were treated with sitagliptin and 973 were treated with metformin.

Methodologic quality of the included RCTs

The clinical characteristics were comparable between the sitagliptin and metformin groups at baseline and described in each study. The characteristics at baseline are shown in Table 1.

Meta-analysis

Effect on HbA1c in T2DM patients

In seven studies[15–21], the influence of both treatments on HbA1c was investigated, and a total of 1881 patients were recruited, of whom 908 were treated with sitagliptin and 973 were treated with metformin. Heterogeneity was noted among studies ($P = 0.029$, $I^2 = 57.3\%$). Thus, a random effect model was used for analysis. The meta-analysis showed that there was no significant difference in the influence of the two drugs on the HbA1c of the T2DM patients ($P = 0.148$, SMD = 0.13, 95% CI = −0.05, 0.30; Figure 2). Thus, we speculated that the two drugs had comparable ability in reducing HbA1c in T2DM patients.

Effect on fasting plasma glucose in T2DM patients

In these seven studies[15–21], the influence of both drugs on fasting plasma glucose was compared, and a total of 1881 patients were evaluated, of whom 908 were treated with sitagliptin and 973 were treated with metformin. Heterogeneity did not exist among the studies ($P = 0.131$, $I^2 = 39.1\%$). Thus, a fixed effect model was

Table 1. Characteristics of the included studies (sitagliptin and metformin) in adults with type 2 diabetes.

Study	Participants			Methodological quality					Intervention	
	N sitagliptin/metformin group	Age sitagliptin/metformin group	Withdrawal sitagliptin/metformin group	Course of treatment	Randomization	Blinding	Concealment	Baseline comparable	ITT	Sitagliptin	Metformin
Russell Jones *et al.*, 2012[15]	163/246	52 ± 11/54 ± 11	23/33	26 week	Yes	Yes	Yes	Yes	Yes	100 mg qd	2000 mg qd
Williams-Herman *et al.*, 2011[16]	55/59	51.8 ± 9.8/53.8 ± 9.6	22/13	24 week	Yes	Yes	NR	Yes	NR	100 mg qd	1000 mg bid
Aschner *et al.*, 2009[17]	528/522	NR	61/75	24 week	Yes	Yes	Yes	Yes	NR	100 mg qd	1000 mg bid
Derosa *et al.*, 2009[18]	75/76	57 ± 5/58 ± 6	6/8	12 month	Yes	Yes	Yes	Yes	NR	100 mg qd + pioglitazone 30 mg qd	850 mg bid + pioglitazone 30 mg qd
Goldstein *et al.*, 2007[19]	NR	NR	NR	24 week	Yes	Yes	NR	Yes	NR	100 mg qd	1000 mg bid
Dan *et al.*, 2012[20]	29/27	55 ± 12.5/54 ± 13.2	0/0	12 week	Yes	NR	NR	Yes	NR	100 mg qd	500 mg tid
Wan-jun *et al.*, 2012[21]	15/15	59 ± 10/57 ± 8	0/0	8 week	Yes	NR	NR	Yes	NR	100 mg qd	500 mg bid

N, number of participants; ITT, intent-to-treat population; qd, once daily; bid, twice daily; tid, three times daily; NR, not reported.

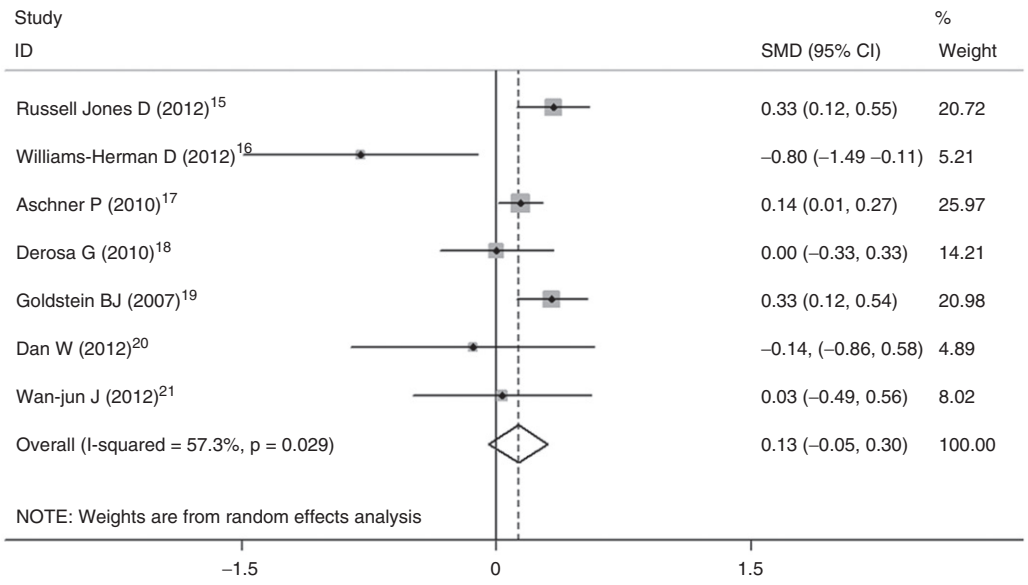

Figure 2. Effect of sitagliptin or metformin on HbA1c in T2DM patients.

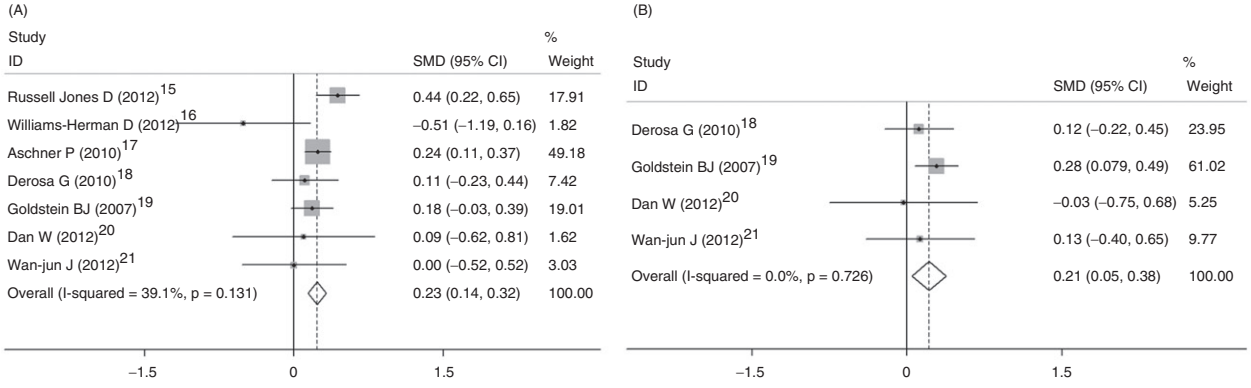

Figure 3. Effect of sitagliptin or metformin on (A) fasting plasma glucose and (B) postprandial plasma glucose in T2DM patients.

used for analysis. The meta-analysis showed that there was a significant difference in the influence on fasting plasma glucose level between metformin and sitagliptin ($P = 0.000$, SMD = 0.23, 95% CI = 0.14, 0.32; Figure 3A). Thus, sitagliptin is inferior to metformin in reducing fasting plasma glucose level.

Effect on postprandial plasma glucose level in T2DM patients

The influence on the postprandial blood glucose level was compared between metformin and sitagliptin in four studies[18–21], and a total of 575 patients were recruited, of whom 288 were treated with sitagliptin and 287 were treated with metformin. Heterogeneity did not exist among the studies ($P = 0.726$, $I^2 = 0.0\%$). Thus, a fixed effect model was used for analysis. The meta-analysis showed a significant difference in the influence on the postprandial blood glucose level between metformin and sitagliptin ($P = 0.011$, SMD = 0.21, 95% CI = 0.05, 0.38; Figure 3B). Thus, sitagliptin is inferior to metformin in reducing postprandial blood glucose level.

Effect on BMI in T2DM patients

The influence on BMI was compared in three studies[16,18,20], and a total of 243 patients were included, of whom 134 were treated with sitagliptin and 109 were treated with metformin. Heterogeneity was not observed among the studies ($P = 0.729$, $I^2 = 0.0\%$). Thus, a fixed effect model was used for analysis. The meta-analysis showed that no significant difference existed in the influence on BMI between metformin and sitagliptin ($P = 0.063$, SMD = 0.26, 95% CI = −0.01, 0.54; Figure 4). Thus, we conclude that sitagliptin and metformin have comparable ability in reducing body weight.

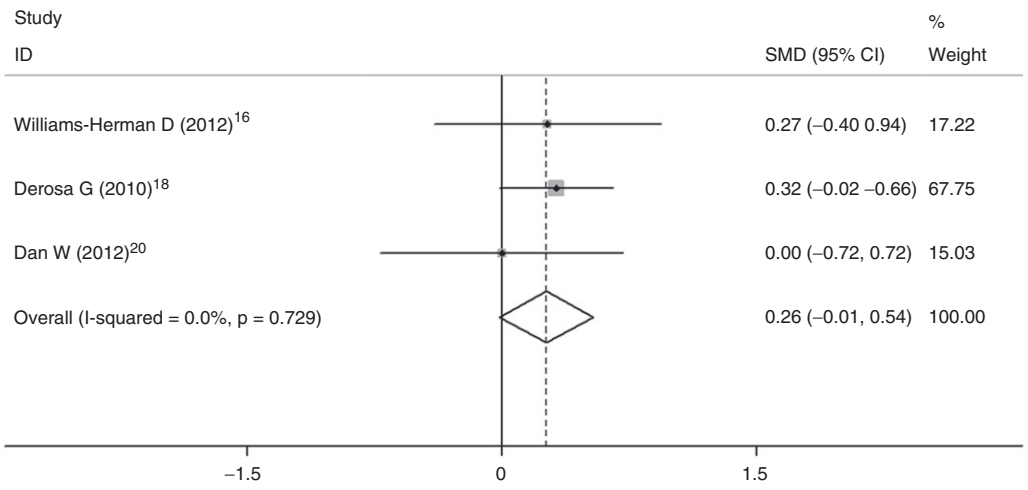

Figure 4. Effect of sitagliptin or metformin on BMI in T2DM patients.

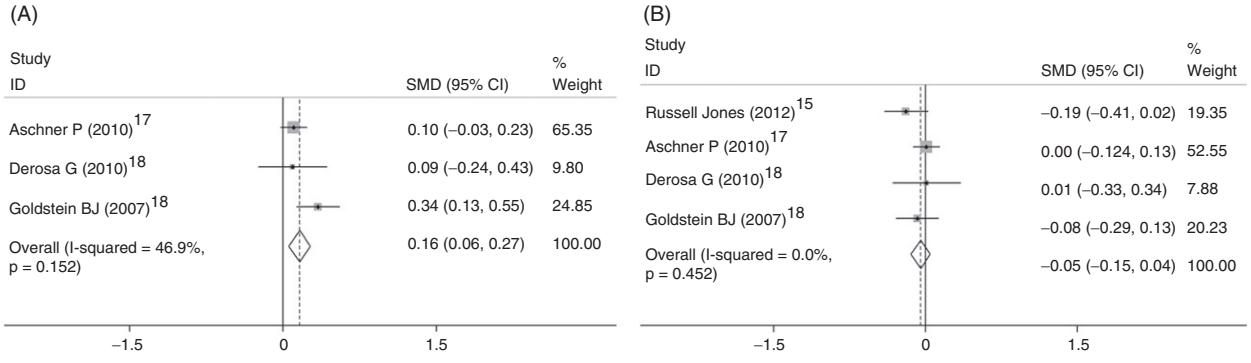

Figure 5. Effect of sitagliptin or metformin on (A) HOMA-IR and (B) HOMA-β in T2DM patients.

Effect on HOMA-IR in T2DM patients

HOMA-IR (HOMA-IR = fasting blood glucose [mmol/L] × fasting blood insulin [mIU/L]/22.5) is used to evaluate insulin sensitivity[22,23]. The influence of sitagliptin and metformin on HOMA-IR was evaluated in three studies[17–19]; a total of 1403 patients were recruited, of whom 711 were treated with sitagliptin and 692 were treated with metformin. Heterogeneity was not observed among the studies ($P = 0.152$, $I^2 = 46.9\%$). Thus, a fixed effect model was used for analysis. A significant difference was observed between sitagliptin and metformin in the influence on HOMA-IR ($P = 0.003$, SMD = 0.16, 95% CI = 0.06, 0.27; Figure 5A). Thus, sitagliptin is inferior to metformin in improving insulin sensitivity.

Effect on HOMA-β in T2DM patients

HOMA-β (HOMA-β = 20 × fasting blood insulin [mIU/L]/[fasting blood glucose {mmol/L} – 3.5] %) was used to evaluate the function of islet β cells[22,23]. The influence on HOMA-β was compared in four studies[16–19]; a total of 1442 patients were included, of whom 724 were treated with sitagliptin and 718 were treated with metformin. Heterogeneity was not observed among the studies ($P = 0.452$, $I^2 = 0.0\%$). Thus, a fixed effect model was used for analysis. No significant difference was observed between sitagliptin and metformin in the influence on HOMA-β ($P = 0.285$, SMD = –0.05, 95% CI = –0.15, 0.04; Figure 5B). Thus, sitagliptin was comparable to metformin in improving the function of islet β cells.

Discussion

This is the first meta-analysis in which the therapeutic efficacy of metformin and sitagliptin was compared in T2DM patients. Our findings revealed that both drugs had comparable ability in reducing HbA1c, decreasing body weight, and improving the function of islet β cells, but sitagliptin was inferior to metformin in improving insulin sensitivity.

Our results showed that although sitagliptin was inferior to metformin in reducing fasting blood glucose and 2 h postprandial blood glucose, both drugs were similar in reducing HbA1c, suggesting that sitagliptin is an effective

glucose-lowering drug. Measuring whether or not sitagliptin is effective in controlling blood glucose at other time points with Continuous Glucose Monitoring System (CGMS) is necessary in future investigations. Sitagliptin is a DPP-4 inhibitor and can prevent the degradation of intestinal insulinotropin by DPP-4, which then increases the plasma levels of glucagon-like peptide 1 (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP), and subsequently increases insulin release and reduces blood glucose[12,13]. In addition, sitagliptin can inhibit appetite, and may inhibit gastric emptying and delay the absorbance of carbohydrates in the intestine[24], which finally reduces postprandial blood glucose, that is similar to the characteristic of glucosidase inhibitors. In animal studies, sitagliptin was shown to be beneficial with respect to apoptosis of islet β cells[9,10]. Metformin may reduce the production of glycogen in the liver and increase the uptake and consumption of glucose in peripheral tissues to effectively reduce fasting and postprandial blood glucose. In addition, metformin has the ability to improve insulin sensitivity and reduce body weight[25,26]. In addition, there is a difference in the indications for metformin and sitagliptin in T2DM patients. Metformin is applicable in type 1 DM (T1DM) patients with insulin resistance[27], but sitagliptin has not been approved in the treatment of T1DM, although studies have been conducted to investigate the therapeutic efficacy of sitagliptin[28]. In addition, both drugs possess cardioprotection for diabetes patients[29–31], but this has not been investigated in the studies included the present meta-analysis. A previous meta-analysis was conducted to evaluate the effect of DPP-4 inhibitors on blood lipid levels[32], and the results revealed that DPP-4 inhibitors could slightly reduce cholesterol, but failed to control body weight, which are not consistent with our findings. Usually sitagliptin has a neutral influence on body weight[33]; however, the results of the meta-analysis revealed a similar effect of sitagliptin and metformin on weight loss in T2DM patients. There were studies[34–36] showing that GLP-1 receptor agonists had the effect of weight reduction by inhibiting appetite and taking in less food. Sitagliptin may reduce weight by sustaining and raising GLP-1 levels; however, more studies are needed to confirm the relationship between sitagliptin and body weight. The side effects were not systematically evaluated in three studies[16,18,21]. In four studies[15,17,19,20], the major side effects of both drugs were gastrointestinal discomfort, including diarrhea, nausea, dyspepsia, and constipation, but the incidence of side effects of sitagliptin was lower than that of metformin. There is evidence[37] showing that sitagliptin might cause pancreatitis, which was not observed in all the studies included in the present meta-analysis.

There were limitations in the present study. All studies were previously published, and the sample size varied among studies. In one study[17], a total of 1050 patients were randomized, but no more than 100 patients underwent randomization in some other studies[16,20,21]. In addition, there were differences in study design, methodology, and race, which may influence clinical heterogeneity and cause bias in results affecting the meta-analysis. The number of studies meeting the inclusion criteria was small, and thus analysis with a funnel plot was not performed. In one study[18], patients in both groups were also treated with pioglitazone, which may influence the results because sitagliptin and metformin have different influences on PPAR-γ. There were different emphases in distinct studies, which make the parameters small in number. For example, blood pressure and blood lipids were not investigated in these studies. Thus, the influence on blood pressure and blood lipid levels was not evaluated in our meta-analysis. In the evaluation of insulin resistance, only HOMA-IR was used in the included RCTs, but a glucose clamp was not used to further assess insulin resistance. In some studies[16,19–21], whether or not concealment and blinding were achieved was not described. There are studies showing that the absence of concealment and blinding may amplify the findings by >42%[38,39], and the exclusion rate ranges from 0%–30.7%. The reasons for withdrawing from studies and loss to follow-up included socioeconomic factors. Except for one study[15], ITT analysis was not performed, and thus bias from loss to follow-up due to withdrawal from studies could not be ruled out.

There were the following strengths in the present study. Systemic evaluation and meta-analysis were performed according to the description in the Cochrane Collaboration, and this report was prepared with adherence to the PRISMA declaration[40]. Search of the studies was conducted by a professional librarian, and language was not limited in the search. Finally, five articles in English[15–19] and two articles in Chinese[20,21] were included. There were strict inclusion and exclusion criteria in this meta-analysis. Two independent investigators (Q.D. and B.W.) evaluated the studies on the basis of the titles and abstract of these studies. The same studies were excluded[41,42]. Disagreements were resolved by consensus after consulting another reviewer (Y.-J.W.). The blood glucose level units in different studies were standardized as mmol/L. In the evaluation of influence of both drugs on HbA1c, heterogeneity was noted among studies, and thus the random DerSimonian and Laird method was used to reduce the influence of heterogeneity on results. In the evaluation of influence of both drugs on other parameters, heterogeneity was not observed, and thus a fixed inverse variance method was used for further analysis.

Conclusions

In conclusion, this is the first meta-analysis in which the therapeutic effect of sitagliptin and metformin was

compared in T2DM patients enrolled in RCTs. Our findings reveal that both drugs have comparable abilities in reducing HbA1c, decreasing body weight, and improving the function of β cells, but sitagliptin is inferior to metformin in improving insulin sensitivity. More multicenter RCTs with a large sample size and long-term follow-up are required, especially evaluating the influence of sitagliptin on dynamic blood glucose, body weight, and side effects (including pancreatitis). This may provide the needed evidence for the clinical application of sitagliptin.

Transparency

Declaration of funding

The authors received no payment in preparation of this manuscript.

Declaration of financial/other relationships

Q.D., B.W., Y.-J.W., S.Y., Y.-Y.Z., and Y.y.L. have disclosed that they have no significant relationships with or financial interests in any commercial companies related to this study or article.

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