Systematic Review and Meta-Analysis

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Efficacy and hypoglycemic risk of sitagliptin in obese/overweight patients with type 2 diabetes compared with GLP-1 receptor agonists

A meta-analysis

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Abstract

Objective: The purpose of this study was to assess the efficacy and hypoglycemic risk of sitagliptin versus that of GLP-1 receptor agonists in the management of obese/overweight patients with T2DM.

Methods: EMBASE, PubMed, Cochrane Library, and ClinicalTrials.gov were searched; randomized controlled trials comparing the efficacy of sitagliptin versus that of GLP-1 receptor agonists in obese/overweight patients with T2DM were included. The mean BMI of participants for each study was ≥30 kg/m^2. We conducted a meta-analysis according to the methods specified in the Cochrane Handbook for Systematic Reviews of Interventions. RevMan 5.1 software was used to perform the meta-analysis. The Cochrane *Q* test and I^2 statistics were used to estimate the heterogeneity among studies. The results are expressed as the mean difference (MD) or risk ratio (RR) with 95% confidence intervals.

Results: A total of 8 eligible studies were included in our meta-analysis. Compared with GLP-1 receptor agonists, sitagliptin was less effective at reducing HbA1c (0.42 [0.27, 0.56]), FPG (0.78 [0.36, 1.19]), PPG (2.61 [1.35, 3.87]), and body weight (1.42 [0.71, 2.14]). Conversely, there were no significant differences in SBP reduction (0.38 [−1.14, 1.89]), DBP reduction (−0.30 [−1.00, 0.39]), and hypoglycemic risk (1.09 [0.50, 2.35]).

Conclusion: For obese/overweight patients, sitagliptin may exert a less potent effect on HbA_{1C}, FPG, PPG, and weight reduction than GLP-1 receptor agonists, but these drugs had a similar efficacy in reducing blood pressure; furthermore, there was no significant difference in hypoglycemic risk.

Abbreviations: BMI = body mass index, DBP = diastolic blood pressure, DPP-4 = dipeptidyl peptidase-, FPG = fasting plasma glucose, GLP-1 = glucagon-like peptide-1, HbA_{1C} = hemoglobin A_{1C}, MD = mean difference, NCT = National Clinical Trial, PPG = postprandial plasma glucose, RCT = randomized controlled trial, RR = risk ratio, SBP = systolic blood pressure, T2DM = type 2 diabetes.

Keywords: efficacy, GLP-1 receptor agonists, hypoglycemic risk, meta-analysis, obese, overweight, sitagliptin, T2DM

1. Introduction

Type 2 diabetes (T2DM) is a chronic and progressive disease characterized by fasting and postprandial hyperglycemia and impaired carbohydrate, lipid, and protein metabolism.[1,2] Over the past 3 decades, the prevalence of diabetes has more than doubled globally[3] and is expected to increase to greater than 7.5% of the world's total population.[4] T2DM results from heritable genetic, lifestyle, gut metagenome, and other factors. Among these factors, a variety of lifestyle factors are important to T2DM, especially obesity.[2] Being overweight or obese can disrupt multiple active factors secreted by adipose tissue, which induces insulin resistance and has various adverse effects on glucose metabolism.[5] Insulin resistance has been demonstrated to be related to lipid metabolic disorders, such as hypertriglyceridemia and high levels of free fatty acid, which in turn promote further insulin resistance.[4,5] As a result, the probability of developing T2DM is increased by obesity. In recent years, increasing numbers of obese or overweight patients have been diagnosed with T2DM, and nearly 90% of patients with diabetes develop T2DM mostly because of excessive body weight according to the World Health Organization (2011).[2] Therefore, researchers should focus on T2DM, especially that in obese or overweight patients.

Advances in the management of T2DM include glucagon-like peptide-1 (GLP-1) receptor agonists and dipeptidyl peptidase-4 (DPP-4) inhibitors, which are relatively recent additions to the available antihyperglycemic drugs.[6,7] GLP-1 receptor agonists can stimulate glucose-dependent insulin secretion, delay gastric

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emptying, and increase satiety.[8] Sitagliptin, the first registered representative of the DPP-4 inhibitors, works by inhibiting the DPP-4 enzyme and reduces the degradation of endogenous GLP-1, resulting in physiological levels of GLP-1.[7,9] These pharmacological effects contribute to the improvement of glycemic control without risking weight gain, unlike other antihyperglycemic drugs, such as sulfonylurea, glinides, glitazones, and insulin, which increase body weight within a few years by up to 8 kg, with potential negative effects on cardiovascular organs.[10] According to the UK National Institute for Health and Clinical Excellence (NICE) guidelines, DPP-4 inhibitors were suggested in dual or triple therapy, while GLP-1 receptor agonists are an alternative for patients with obesity who fail in triple therapy.[11] A previous review performed by Scheen suggested that GLP-1 receptor agonists were more potent with regard to the glucose-lowering effect, weight loss and systolic blood pressure reduction than DPP-4 inhibitors; in contrast, DPP-4 inhibitors were easier to administer, less expensive and had better gastrointestinal tolerance.[12] Nevertheless, both NICE and the review did not completely focus on obese patients. Meanwhile, Li and colleagues observed the effect of sitagliptin on patients with insulin treatment-induced obesity and found that sitagliptin could reduce body mass index (BMI) and the occurrence of hypoglycemia in obese patients.[13] Similarly, a cohort study performed by Kodera et al indicated that sitagliptin was effective in controlling glucose metabolic disorders in obese Japanese patients with T2DM.[14] These results raise the question of how effective sitagliptin is in the management of obese/overweight patients with T2DM. Consequently, we performed a meta-analysis to evaluate the efficacy and hypoglycemic risk of sitagliptin in obese/overweight patients with T2DM.

2. Methods

We conducted a meta-analysis according to the methods specified in the Cochrane Handbook for Systematic Reviews of Interventions.[15] No ethical approval is needed because all analyses in our study were performed based on data extracted from studies which were published previously.

The clinical efficacy outcomes were decreases in hemoglobin A1c (HbA_{1C}) levels, the percentage of patients achieving an HbA_{1C} goal of <7%, weight loss, decreases in fasting plasma glucose (FPG) and postprandial plasma glucose (PPG), and decreases in systolic blood pressure (SBP) and diastolic blood pressure (DBP). Hypoglycemic risk was measured by the incidence of hypoglycemia.

2.1. Data sources

Eligible trials were identified through electronic searches [conducted by 2 independent reviewers, (D. D. and Y. M.)]. Searches were performed in EMBASE, PubMed, Cochrane Library, and ClinicalTrials.gov from their inception until March 2018. The search was limited to English language articles. The search strategy is shown in Table S1, http://links.lww.com/MD/D217. In addition, the reference lists of eligible studies were scanned to identify additional relevant studies.

2.2. Study selection

The electronic search results were imported into management software, and duplicate results were deleted. Two reviewers (D. D. and Y. M.) independently screened all titles and abstracts for eligible studies. Studies were included if they met the following criteria:

1. T2DM was diagnosed unequivocally;
2. the mean BMI of enrolled participants was $\geq 30\,kg/m^2$;
3. the study design was a randomized controlled trial (RCT);
4. the study included sitagliptin and GLP-1 receptor agonists;
5. the study included one of the predefined outcome measures; and
6. the study was published in English.

2.3. Data extraction

Two authors extracted data independently (D. D. and Y. M.). Any dispute was settled by discussion or by a third investigator (H. J.). Study characteristics were extracted from each study, including author identification, year of publication, National Clinical Trial (NCT) number, sample size, study location, study design, duration of intervention, and participant baseline characteristics (age, sex, HbA_{1C}, BMI).

2.4. Quality assessment

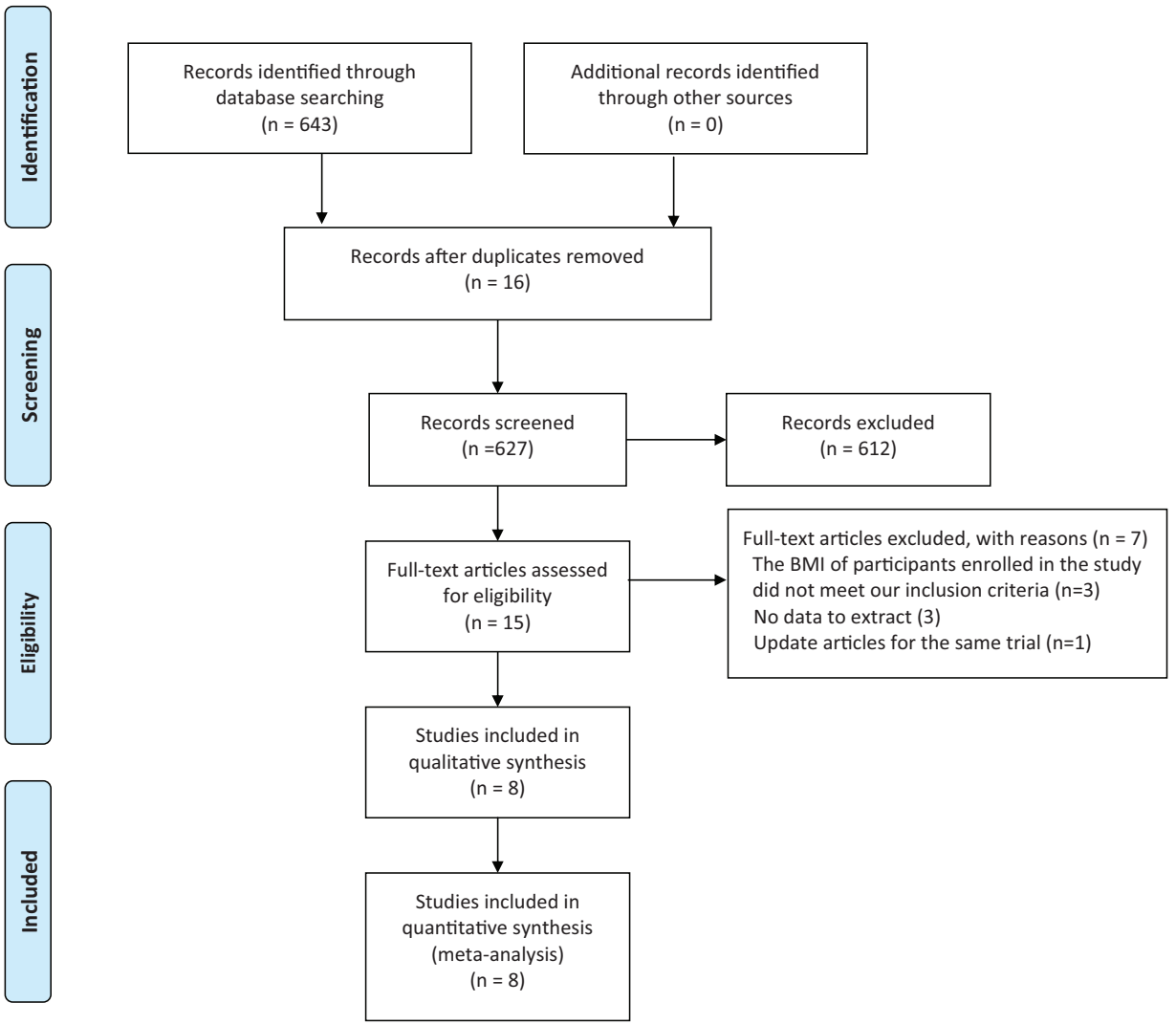
Cochrane Collaboration's risk of bias tool was adopted to evaluate the risk of bias of the included studies. This tool included selection bias (random sequence generation and allocation concealment), performance bias (blinding of participants, personnel and outcome assessment), completeness of outcome data, reporting bias, and other sources of bias.[16] All these domains were summarized to produce an overall risk of bias, and the judgments were categorized as "low risk" of bias, "high risk" of bias, or "unclear risk" of bias (either insufficient information or uncertainty to identify the potential risk of bias). Two authors (D. D. and Y. M.) independently evaluated the risk of bias and resolved disagreements by discussion or by a third investigator if necessary.

2.5. Data analysis

The meta-analysis was accomplished by RevMan 5.1 (Cochrane IMS). The Cochrane Q test and I^2 statistics were used to estimate the heterogeneity among studies. I^2 values of over 25%, 50%, and 75% represent low, moderate, and considerable heterogeneity, respectively.[17,18] In the presence of heterogeneity, a random effects model was selected because it involves an assumption that accounts for variations across studies as well as sampling variability.[15] The Mantel–Haenszel method was used to calculate the results and 95% confidence intervals for each study. The results are expressed as the mean difference (MD) for continuous outcomes and risk ratio (RR) for dichotomous outcomes. Any data that were not provided in the published paper could be obtained from www.ClinicalTrials.gov. If a standard deviation was not available in a study, we would calculate it from the sample size and the standard error.

To explore the heterogeneity among different studies, we performed subgroup analysis when more than 2 studies were included in the analysis and studies were stratified by

1. type of GLP-1 receptor agonists (exenatide, liraglutide);
2. formulation of GLP-1 receptor agonists (long-acting GLP-1 receptor agonists, short-acting GLP-1 receptor agonists);



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For more information, visit www.prisma-statement.org.

Figure 1. Flow chart of study selection.

3. studies excluding the potential confounding factor (studies might enroll participants with BMI $<25\,kg/m^2$) compared with studies including the potential confounding factor.

To test the robustness of the main results, we performed sensitivity analyses by re-analyzing the data:

1. using a fixed effects model and
2. omitting 1 study at a time.

The results for the sensitivity analysis were only reported if the conclusions differed.

3. Results

3.1. Literature search

The study selection process for inclusion is shown in Figure 1. The electronic searches identified 643 potentially relevant articles. After duplicates were excluded and the initial screening, 15 relevant articles were selected, and 7 articles were excluded for the reasons shown in Table S2, http://links.lww.com/MD/D217. A total of 8 studies comparing sitagliptin with GLP-1 receptor agonists were included in the meta-analysis.[6,7,19,20,24–27] We did not obtain any additional studies by scanning the reference lists of eligible studies.

3.2. Study characteristics

The characteristics of the included studies are summarized in Table 1. Seven RCTs were parallel studies, and 1[6] was a crossover study. Patients had been treated with a stable metformin regimen in 7 trials and metformin or thiazolidinedione in 1 trial.[6] The mean BMI at baseline ranged from $31\,kg/m^2$ to $36.8\,kg/m^2$ in the sitagliptin group and $31\,kg/m^2$ to $36.8\,kg/m^2$ in the GLP-1 receptor agonist group. The mean values of HbA_{1C} at

Table 1

Characteristics of the included studies.

Author, year (NCT number)	Study type	Background therapy	Treatment	Age (years)	Background HbA_{1c} (%) Mean (SD)	Duration (weeks)	BMI (kg/m^2) Mean (SD)	Population no.	Female (%)	Race (%)				Population that withdrew from the study
										White	Black	Asian	*Other	
Gaal, 2014 NCT00976937	Double-blind, double-dummy, randomized, active-controlled, parallel-group	metformin	C: lixisenatide 100 mcg QD	C: 42.7 (5.2)	C: 8.16 (0.89)	24	C: 36.8 (7.3)	C: 158	C: 65.2	C: 83.5	C: 5.1	C: 0.6	C: 10.8	C:16
			I: sitagliptin 100 mg QD	I: 43.4 (4.7)	I: 8.10 (1.00)		I: 36.8 (6.3)	I: 161	I: 54.7	I: 78.9	I: 6.8	I: 0.6	I: 13.7	I: 11
†Berg, 2011 NCT00729326	2-peiod, crossover, double-blind, double-dummy, randomized, active comparator trial	metformin or thiazolidinedione	C: exenatide 10 μg BID	54 (10)	8.3 (1.0)	4	34.9 (5.5)	83	57.8	93	6	0	1	C: 10
			I: sitagliptin 100 mg QD											I: 9
Pratley, 2010 NCT00700817	Randomized, parallel, open label	metformin	C: lilaglutide 1.2 mg QD	C:55.9 (9.6)	C: 8.4 (0.8)	26	C: 32.6 (5.2)	C: 221	C: 48.4	C: 87.3	C: 7.2	C: 1.8	C: 3.7	C: 56
			I: sitagliptin 100 mg QD	I: 55.0 (9.0)	I: 8.5 (0.7)		I: 32.6 (5.4)	I: 219	I: 45.2	I: 90.9	I: 4.6	I: 0.5	I: 4	I: 25
Charbonnel, 2013 NCT01296412	multinational, randomized, open-label, active-controlled, parallel-arm study	metformin	C: liraglutide 1.2 mg QD	C: 57.6 (10.8)	C: 8.1 (0.9)	26	C: 32.7 (6.1)	C: 327	C: 45	C: 84	C: 6	NR	C: 10	C: 70
			I: sitagliptin 100 mg QD	I: 56.9 (10.0)	I: 8.2 (1.1)		I: 32.6 (5.9)	I: 326	I: 45	I: 86	I: 3	NR	I: 11	I: 51
Russell-Jones, 2012 NCT00676338	Randomized, parallel assignment, double-blind	metformin	C: exenatide 2 mg QW	C: 54 (11)	C: 8.5 (1.2)	26	C: 31.4 (5.3)	C: 248	C: 44	C: 68.1	C: 2.8	C: 22.2	C: 6.9	C: 38
			I: sitagliptin 100 mg QD	I: 52 (11)	I: 8.5 (1.3)		I: 31.8 (5.4)	I: 163	I: 42.3	I: 69.3	I: 1.8	I: 20.2	I: 8.6	I: 23
Skrivanek, 2014 NCT00734474	Multi-center, randomized, double-blind placebo-controlled	metformin	C: Dulaglutide 1.5 mg QW	C: 54.35 (9.81)	C: 8.19 (1.11)	26	C: 31.15 (4.44)	C: 302	C: 55.6	NR	NR	NR	NR	C: 34
			I: sitagliptin 100 mg QD	I: 53.75 (12.27)	I: 8.09 (1.09)		I: 31.02 (4.20)	I: 315	I: 52.1	NR	NR	NR	NR	I: 45
Gadde, 2017 NCT01652729	randomized, open-label, multi-center, active- and placebo-controlled study	metformin	C: exenatide 2 mg QW	C: 53.4 (9.8)	C: 8.4 (1.0)	28	C: 32.1 (5.4)	C: 181	C: 50.8	C: 81.8	C: 13.3	C: 5	C: 0	C: 26
			I: sitagliptin 100 mg QD	I: 54.3 (9.0)	I: 8.5 (1.0)		I: 31.6 (5.8)	I: 122	I: 45.9	I: 80.3	I: 14.8	I: 1.6	I: 3.3	I: 13
Bergenstal, 2010 NCT00637273	Randomized, double-blind, double-dummy, controlled	metformin	C: exenatide 2 mg QW	C: 52 (10)	C: 8.6 (1.2)	26	C: 32(5)	C:160	C: 44.4	C: 33	C: 12	C: 23	C: 32	C:33
			I: sitagliptin 100 mg QD	I: 52(11)	I: 8.5(1.2)		I: 32(5)	I: 166	I: 48.2	I: 30	I: 12	I: 25	I: 33	I: 22

* Other means other races except White, Black, and Asian.

† Berg, 2011: This was a crossover trial.

BMI = body mass index, C = control group, HbA1c = Hemoglobin A1c, HbA_{1C} = hemoglobin A_{1C}, I = interventional group, NCT = National Clinical Trial, NR = not reported, QD = every day, QW = every week.

Table 2

Summary of meta-analyses for outcome measures from included studies.

Outcome	No. of studies contributing data	Risk Ratio (95% CI), sitagliptin vs GLP-1 receptor agonists	Mean Difference (95% CI), sitagliptin vs GLP-1 receptor agonists	No. of participants of experimental group	No. of participants of control group	I^2 heterogeneity, %	*P*
Decrease in HbA_{1C}	7		0.42 [0.27, 0.56]	1376	1473	68	<.00001
participants achieving HbA_{1C} goal of <7.0%	7	0.70 [0.58, 0.83]		1391	1493	80	<.0001
Decrease in FPG	8		0.78 [0.36, 1.19]	1418	1514	86	.0003
Decrease in PPG	3		2.61 [1.35, 3.87]	238	242	75	<.00001
Decrease in body weigh	6		1.42 [0.71, 2.14]	1115	1226	85	<.00001
Decrease in SBP	5		0.38 [−1.14, 1.89]	954	1073	50	.63
Decrease in DBP	5		−0.30 [−1.00, 0.39]	954	1073	5	.4
Participants experiencing hypoglycemia	8	1.09 [0.50, 2.35]		1543	1666	77	.84

DBP = diastolic blood pressure, FPG = fasting plasma glucose, HbA_{1C} = hemoglobin A_{1C}, PPG = postprandial plasma glucose, SBP = systolic blood pressure.

baseline ranged from 8.1% to 8.5% in the sitagliptin group and 8.1% to 8.6% in the GLP-1 receptor agonist group. After the study by Skrivanek et al was excluded, as it did not report these parameters, 1240 patients were included in the sitagliptin group, and 75.8% were White, 7.2% were Black, 7.7% were Asian (a study by Charbonnel et al did not report this value) and 9.3% were other races; 1378 patients were included in the GLP-1 receptor agonist group, and 76.2% were White, 6.1% were Black, 6.4% were Asian (a study by Charbonnel et al did not report this value), and 11.3% were other races.

Oral sitagliptin was given at a dose of 100 mg once daily in the interventional group, long-acting GLP-1 receptor agonists were given once weekly, and short-acting ones were given once or twice daily in the control group (Table S5, http://links.lww.com/MD/D217).

3.3. Clinical efficacy

A summary of the meta-analysis is shown in Table 2, forest plots are shown in Figure 2, and all subgroup analyses are shown in Table 3. The outcomes of efficacy and hypoglycemia are shown in Tables S3 and S4, http://links.lww.com/MD/D217.

3.3.1. HbA_{1C}. Seven studies reported a decrease in HbA_{1C}. There were 1376 patients in the sitagliptin group and 1473 patients in the GLP-1 receptor agonist group. GLP-1 receptor agonists led to a greater reduction in HbA_{1C}, and the mean difference was 0.42% (95% CI 0.27–0.56, $P < .00001$) for sitagliptin vs GLP-1 receptor agonists. There was, however, considerable heterogeneity observed across studies ($I^2 = 68\%$) (Table 2, Fig. 2a). The percentage of patients achieving an HbA_{1C} goal of <7.0% was lower in the sitagliptin group than the GLP-1 receptor agonist group, and the RR was 0.70 (95% CI 0.58 to 0.83, $I^2 = 80\%$, $P < .00001$) (Table 2, Fig. 2b).

In subgroup analyses for HbA_{1C} reduction, a significant difference was observed in all subgroups. In subgroup analyses for the percentage of patients achieving an HbA_{1C} goal of <7%, a significant difference was observed in studies using exenatide, studies using long-acting GLP-1 receptor agonists, studies excluding the potential confounding factor and studies including the potential confounding factor. However, no significant difference was observed among subgroups using liraglutide and short-acting GLP-1 receptor agonists. The results are shown in Table 3.

3.3.2. FPG. All 8 studies reported a reduction in FPG. This result is shown in Table 2 and Fig. 2c. We conducted a meta-analysis with 1418 participants in the sitagliptin group and 1514 participants in the GLP-1 receptor agonist group. The reduction in FPG was greater for patients in the GLP-1 receptor agonist group than for those in the sitagliptin group (MD = 0.78, 95% CI 0.36 to 1.19, $I^2 = 86\%$, $P = .0003$).

In subgroup analyses for FPG reduction, all subgroups showed a major difference except subgroups that used short-acting GLP-1 receptor agonists and excluded the potential confounding factor. The results are shown in Table 3.

3.3.3. PPG. Three trials reported a decrease in PPG. There were 238 patients in the sitagliptin group and 242 patients in the GLP-1 receptor agonist group. Both sitagliptin and GLP-1 receptor agonists significantly reduced PPG from baseline, but GLP-1 receptor agonists resulted in a greater reduction. The mean difference was 2.61 mmol/L (95% CI 1.35–3.87, $I^2 = 75\%$, $P < .00001$) for sitagliptin versus that of GLP-1 receptor agonists (Table 2, Fig. 2d).

3.3.4. Weight loss. Six studies reported weight loss. There were 1115 participants in the sitagliptin group and 1226 participants in the GLP-1 receptor agonist group in our meta-analysis. GLP-1 receptor agonists were associated with a greater reduction in body weight than sitagliptin. The mean difference was 1.42 kg (95% CI 0.71–2.14, $I^2 = 85\%$, $P < .00001$) (Table 2, Fig. 2e) for the sitagliptin group versus the GLP-1 receptor agonist group.

The results of subgroup analyses for weight loss are shown in Table 3. A significant difference was observed in all subgroups except the subgroup including the potential confounding factor.

3.3.5. Blood pressure. Five studies reported changes in blood pressure from baseline to the end of the study period. There were 954 participants in the sitagliptin group and 1073 participants in the GLP-1 receptor agonist group. Our results did not show a significant difference in lower blood pressure between sitagliptin and GLP-1 receptor agonists; the mean difference for SBP and DBP was 0.38 mm Hg (95% CI-1.14–1.89, $I^2 = 50\%$, $P = .63$) (Table 2, Fig. 2f) and −0.30 mm Hg (95% CI -1.00–0.39, $I^2 = 5\%$, $P = .4$) (Table 2, Fig. 2g).

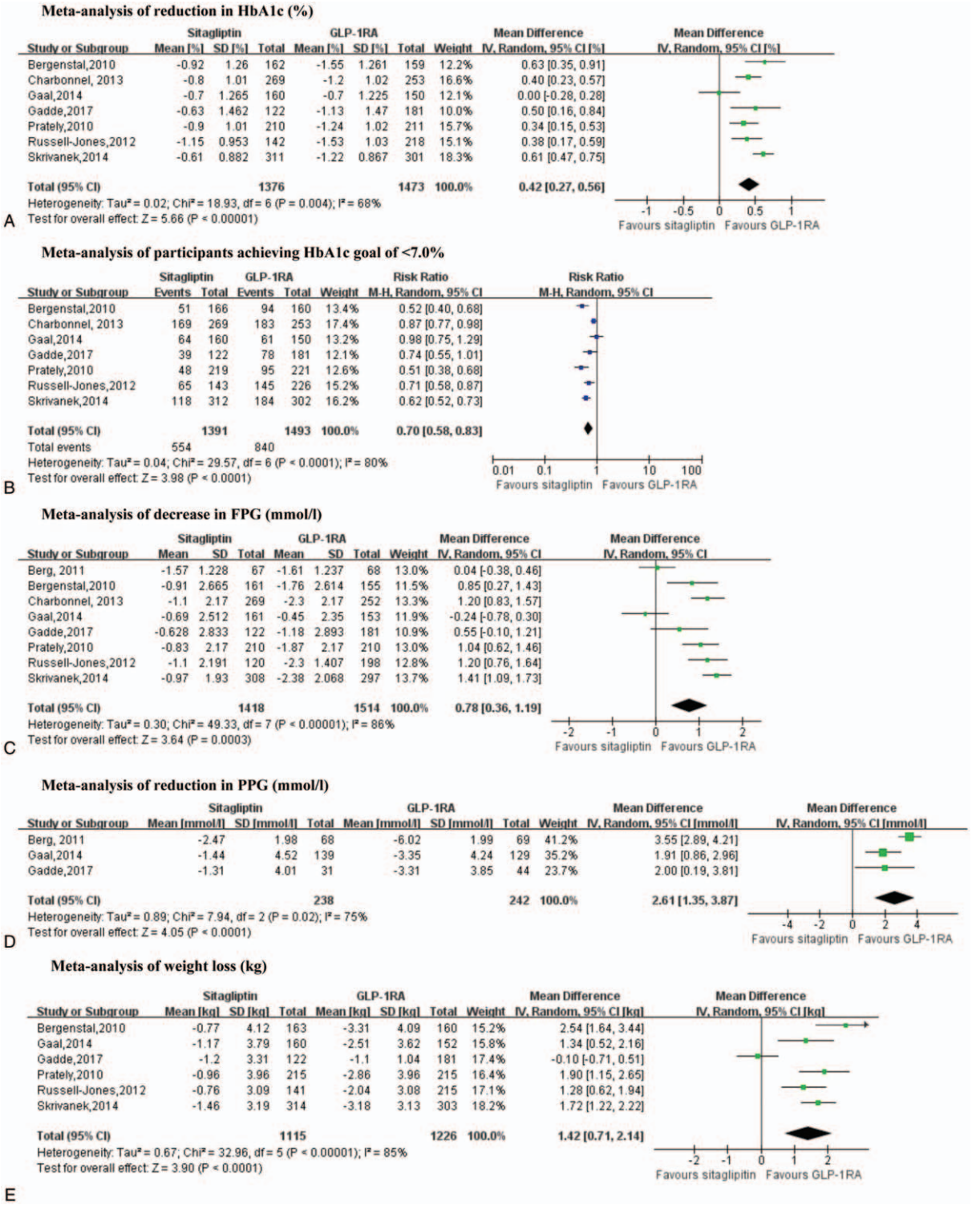

Figure 2. Forest plots.

3.4. Hypoglycemic risk

All 8 studies reported the proportion of patients experiencing hypoglycemia, and the definition of hypoglycemia of the included studies is shown in Table S6, http://links.lww.com/MD/D217. There were 1543 participants in the sitagliptin group and 1666 participants in the GLP-1 receptor agonist group. There was no difference in hypoglycemic risk between the GLP-1 receptor agonist group and the sitagliptin group, and the RR was 1.09 (95% CI 0.50 to 2.35, I^2=77%, P=.84) (Table 2, Fig. 2h).

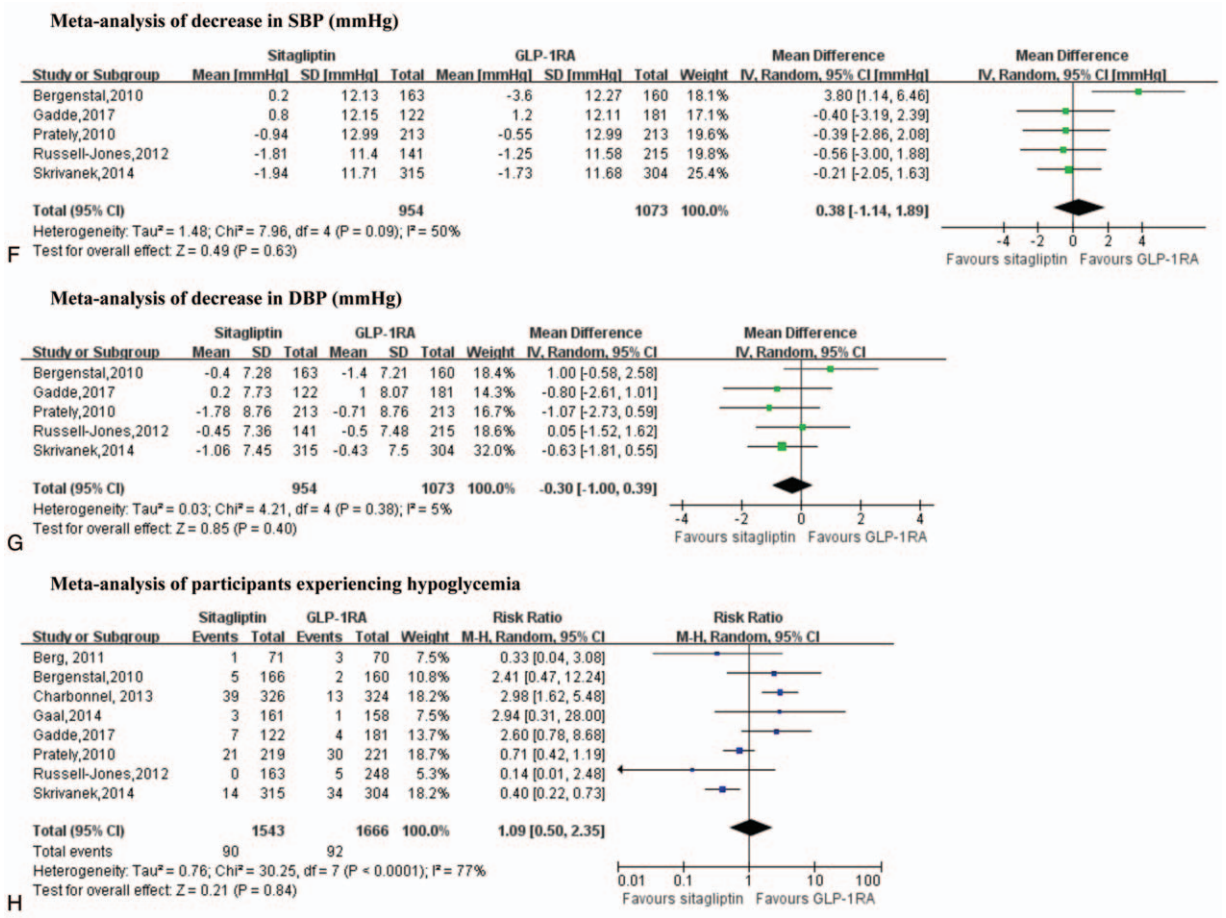

Figure 2. Continued.

The results of subgroup analyses for hypoglycemic risk are shown in Table 3. No significant difference was observed in any of the subgroups.

3.5. The quality assessment of the included studies

The participants of all 8 trials were randomly allocated, 5 studies adequately described the methods of randomization and others did not mention it.[6,7,20] There were no differences in the baseline characteristics between the sitagliptin group and the GLP-1 receptor agonist group. Studies by Charbonel et al and Gadde et al were not blinded to the participants.[24,25] All 8 studies clearly reported participants withdrawing from the trial and accounted for it. A summary for the risk of bias for the included studies is shown in Figure 3.

4. Discussion

As mentioned above, obesity or being overweight contributes to insulin resistance, which makes it more difficult to control blood glucose and promotes complications of diabetes.[21] Furthermore, some T2DM treatments can induce weight gain, which has a negative effect on the management of diabetes and worsens the weight issue already present.[21] Moreover, the prevalence of abdominal overweight and obesity is directly related to increasing incidence of hypertension and dyslipidemia.[4] As a result, weight control is a very important factor in diabetes treatment, and even modest weight loss has a favorable effect on preventing the progression of diabetes.[4] A study evaluating the relationship between weight change and glycemic control indicated that weight loss of ≥3% was associated with improved glycemic control in patients newly treated for T2DM.[22] As a result, a study on obese/overweight patients with T2DM is of great clinical value. Sitagliptin and GLP-1 receptor agonists can reduce glucose without risking hypoglycemia and weight gain compared with other antihyperglycemic agents.[23] Our study found that for obese/overweight patients, sitagliptin exerts a less potent effect on the decrease in HbA_{1C}, FPG, PPG, and body weight than GLP-1 receptor agonists, but there was no significant difference in terms of hypoglycemic risk. Our results were similar to the meta-analysis performed by Wang et al,[9] in which the researchers found that DPP-4 inhibitors were less efficacious at reducing HbA_{1C}, FPG, PPG, and body weight than GLP-1 receptor agonists. Therefore, according to these 2 studies (Wang and ours), whether patients are of normal weight or elevated weight, GLP-1 receptor agonists were more effective than DPP-4 inhibitors. In order to provide a more accurate analysis of these 2 classes of incretin therapy in obese/overweight, we are planning to conduct an RCT or a prospective study to compare other drugs of DPP-4 inhibitors with GLP-1 receptor agonists in the management of T2DM with obesity/overweight.

In subgroup analyses, we found that compared with long-acting GLP-1 receptor agonists, sitagliptin was less effective

Table 3

Subgroup analyses.

Factor	Studies, n	Mean Difference (95% CI), sitagliptin vs GLP-1 receptor agonists	Risk Ratio (95% CI), sitagliptin vs GLP-1 receptor agonists	I^2 (%)	*P*
Subgroup analyses for decrease in HbA1c (%)					
Type of GLP-1 receptor agonists					
Exenatide	3	0.48 [0.33, 0.63]		2	< .00001
liraglutide	2	0.37 [0.24, 0.50]		0	< .00001
Formulation of GLP-1 receptor agonists					
Long-acting GLP-1 receptor agonists	4	0.54 [0.42, 0.66]		19	< .00001
Short-acting GLP-1 receptor agonists	3	0.27 [0.06, 0.48]		66	.01
the potential confounding factor (studies might enroll participants with BMI <25 kg/m^2)					
Studies excluding the potential confounding factor	3	0.42 [0.06, 0.79]		87	.02
Studies including the potential confounding factor	4	0.39 [0.28, 0.49]		0	< .00001
Subgroup analyses for the percentage of patients achieving HbA1c goal of <7.0%					
Type of GLP-1 receptor agonists					
Exenatide	3			50	<.00001
liraglutide	2		0.68[0.39, 1.18]	92	.17
Formulation of GLP-1 receptor agonists					
Long-acting GLP-1 receptor agonists	4		0.64 [0.56, 0.73]	29	<.00001
Short-acting GLP-1 receptor agonists	3		0.77 [0.55, 1.07]	85	.12
the potential confounding factor (studies might enroll participants with BMI <25 kg/m^2)					
Studies excluding the potential confounding factor	3		0.68[0.49, 0.94]	83	.02
Studies including the potential confounding factor	4		0.71[0.56, 0.89]	78	.003
Subgroup analyses for decrease in FPG (mmol/l)					
Type of GLP-1 receptor agonists					
Exenatide	4	0.66 [0.09, 1.22]		80	.02
liraglutide	2	1.13 [0.85, 1.41]		0	<.00001
Formulation of long-acting GLP-1 receptor agonists					
Long-acting GLP-1 receptor agonists	4	1.08 [0.72, 1.44]		56	<.00001
Short-acting GLP-1 receptor agonists	4	0.52 [−0.16, 1.21]		90	.13
the potential confounding factor (studies might enroll participants with BMI <25 kg/m^2)					
Studies excluding the potential confounding factor	4	0.52 [−0.30, 1.35]		93	.21
Studies including the potential confounding factor	4	1.08 [0.85, 1.31]		7	<.00001
Subgroup analyses for weight loss (kg)					
Formulation of GLP-1 receptor agonists					
Long-acting GLP-1 receptor agonists	4	1.33 [0.31, 2.36]		90	.01
Short-acting GLP-1 receptor agonists	2	1.65 [1.09, 2.20]		0	<.00001
the potential confounding factor (studies might enroll participants with BMI <25 kg/m^2)					
Studies excluding the potential confounding factor	3	1.82 [1.24, 2.41]		49	<.00001
Studies including the potential confounding factor	3	1.01 [−0.16, 2.19]		89	.09
Subgroup analyses for participants experiencing hypoglycemia					
Type of GLP-1 receptor agonists					
Exenatide	4			48	.89
liraglutide	2		1.44[0.35, 5.94]	92	.61
Formulation of GLP-1 receptor agonists					
Long-acting GLP-1 receptor agonists	4		0.90 [0.25, 3.29]	73	.88
Short-acting GLP-1 receptor agonists	4		1.28 [0.43, 3.84]	79	.66
the potential confounding factor (studies might enroll participants with BMI <25 kg/m^2)					
Studies excluding the potential confounding factor	4		0.83[0.27, 2.62]	55	.76
Studies including the potential confounding factor	4		1.32[0.46, 3.80]	81	.60

BMI = body mass index, FPG = fasting plasma glucose, GLP-1 = glucagon-like peptide-1, HbA_{1C} = hemoglobin A_{1C}.

in FPG reduction and resulted in a lower proportion of participants achieving the HbA_{1C} target (<7.0%), while compared with short-acting GLP-1 receptor agonists, there were no significant differences. A previous review examined the efficacy and safety of long-acting GLP-1 receptor agonists, and their results were similar to our findings. These researchers found that long-acting GLP-1 receptor agonists had a more sustained effect on FPG and greater HbA_{1C} reduction but fewer gastrointestinal side effects than short-acting GLP-1 receptor agonists.[12] At present, to the best of our knowledge, no studies have examined this phenomenon and compared sitagliptin and long- and short-acting GLP-1 receptor agonists. Nevertheless, long-acting GLP-1 receptor agonists might be more beneficial in the management of obese/overweight patients who fail with oral or insulin agents. Therefore, further research is needed to demonstrate the definitive superiority of long-acting GLP-1 receptor agonists over the other 2 classes.

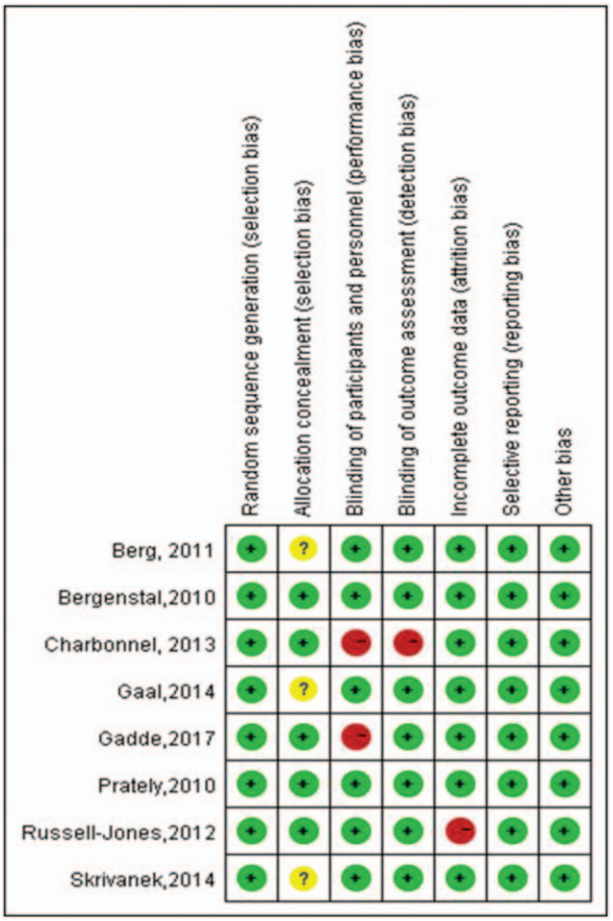

Figure 3. Risk of bias for the included studies.

Considerable heterogeneity was observed in our meta-analysis, and many factors, such as different control groups, different exposure durations, and the potential confounding factor, might lead to this heterogeneity. For example, in subgroup analyses by different control groups (exenatide, liraglutide), the values of I^2 decreased in outcome of HbA_{1C} reduction, while for FPG reduction, the values of I^2 decreased to 0 when we conducted subgroup analysis based on studies using liraglutide. Notably, the exposure duration of these 2 studies was 26 weeks.[25,27] Accordingly, we believe that the exposure duration might also be an important factor for heterogeneity among studies. However, due to the limited data, subgroup analyses by exposure duration could not be conducted. Further analysis comparing different durations is needed.

There were several strengths of our meta-analysis. First, the quality of studies included in our meta-analysis was high. Second, a variety of outcomes were evaluated. Third, sensitivity analyses conducted by reanalyzing the data using a fixed effects model and omitting 1 study at a time demonstrated that our conclusion was robust (Table S7 and S8, http://links.lww.com/MD/D217). Furthermore, our subgroup analyses were sufficient.

Nevertheless, our study has several limitations. First, although we searched widely, there were only 8 studies included. Therefore, the sample size was small. As a result, we were unable to perform subgroup analysis for all outcome measures, and future study with large sample size was needed to confirm our conclusions. Second, different control groups, different exposure durations and the confounding factor of the included studies led to considerable heterogeneity in our meta-analysis. Moreover, because there was a shortage of individual data, obese and overweight patients could not be assessed separately. This was also one of reasons for considerable heterogeneity. Third, the standard deviation in our study was calculated from the sample size and the standard error, and therefore, the calculation error might not be avoided. Finally, the exposure durations of the included studies were 4–28 weeks, which was too short to evaluate endpoint events such as cardiovascular events, all-cause mortality and so on. One study had an exposure duration of only 4 weeks; therefore, our results concerning HbA_{1C} might be somewhat biased.

In conclusion, for obese/overweight patients, sitagliptin might exert a less potent effect regarding HbA_{1C}, FPG, PPG, and weight reduction than GLP-1 receptor agonists; however, there was no difference in hypoglycemic risk. Meanwhile, long-acting GLP-1 receptor agonists seemed more effective in reducing FPG. However, further research with more participants and longer treatment durations is needed to demonstrate the real superiority of GLP-1 receptor agonists, especially long-acting GLP-1 receptor agonists, over sitagliptin in terms of efficacy and safety, which could then help clinicians provide a more favorable therapeutic regimen for obese patients with T2DM in clinical practice.

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Author contributions

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