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META-ANALYSIS

The safety and efficacy of once-weekly glucagon-like peptide-1 receptor agonist semaglutide in patients with type 2 diabetes mellitus: a systemic review and meta-analysis

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Abstract

Objectives To investigate the safety and efficacy of once-weekly glucagon-like peptide-1 (GLP-1) receptor agonist semaglutide as monotherapy or add-on to other antihyperglycaemic agents (AHAs) in patients with type 2 diabetes mellitus (T2DM).

Methods PubMed, Embase, Cochrane library and ClinicalTrials.gov were searched from the inception to January 18, 2018. Randomised controlled trials (RCTs) comparing semaglutide with placebo or other AHAs in T2DM patients were included in our meta-analysis. Risk ratio (RR) and mean difference (MD) with 95% confidence intervals (CI) were used to evaluate the outcomes.

Results A total of 11 studies with 9519 patients were included in our meta-analysis. The results revealed that compared with placebo or other AHAs, semaglutide had further reduced the level of haemoglobin A1c (HbA1c) [MD 1.03%, 95% CI (0.85%, 1.22%), $p < 0.00001$], self-measured plasma glucose (SMPG) [MD 1.19 mmol/L, 95% CI (0.84 mmol/L, 1.53 mmol/L), $p < 0.00001$], fasting plasma glucose (FPG) [MD 1.33 mmol/L, 95% CI (0.97 mmol/L, 1.69 mmol/L), $p < 0.00001$] and weight [MD 3.61 kg, 95% CI (3.05 kg, 4.17 kg), $p < 0.00001$] and significantly increased participants who achieved HbA1c < 7.0% [RR 2.26, 95% CI (1.89, 2.70), $p < 0.00001$] in T2DM patients. Semaglutide had a significant increase in the incidence of adverse events (AEs) [RR 1.06, 95% CI (1.02, 1.11), $p < 0.0001$] and an analogous incidence in serious adverse events (SAEs) [RR 0.94, 95% CI (0.86, 1.02), $p = 0.11$] and hypoglycaemic events (severe or blood glucose (BG)-confirmed symptomatic) [RR 0.93, 95% CI (0.74, 1.16), $p = 0.50$] compared with the control group.

Conclusions This article revealed that semaglutide had a favourable efficacy and safety in treating T2DM patients. It maybe a superior choice for T2DM patients who have obesity or a poor adherence to daily AHAs.

Keywords Safety · Efficacy · Semaglutide · Type 2 diabetes mellitus · Meta-analysis

Introduction

The prevalence of T2DM is rising in many countries, affecting an estimated 114.4 million (10.9%) adults in China and 425 million (8.8%) adults worldwide [1, 2]. Although several T2DM treatments are available [3], many patients with type 2 diabetes do not achieve recommended blood glucose concentrations [4], therefore, at risk of developing several chronic complications of diabetes, including cardiovascular disease [5, 6]. Additionally, avoidance of both hypoglycaemia and weight gain is recommended as important therapeutic considerations when selecting treatments and individualising treatment goals [7, 8].

GLP-1 receptor agonists are a novel series of AHAs. GLP-1 receptor agonists decrease blood glucose of T2DM

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patients by stimulating insulin secretion and inhibiting the release of glucagon in a glucose-dependent manner, targeting the pathophysiological factors underlying the islet cell dysfunction associated with type 2 diabetes [9]. Importantly, GLP-1 receptor agonists have been shown to a low risk of hypoglycaemia and reduce body weight as a consequence of reduced appetite and energy intake [10–12].

Short-acting GLP-1 receptor agonists that require administration once or twice per day were the first generation in this class. However, a substantial proportion of people with T2DM do not take their medication as prescribed [13, 14]. Recent efforts have been made to develop GLP-1 receptor agonists that require less frequent dosing, which could improve patient adherence and reduce treatment burden. Several GLP-1 receptor agonists were approved that are dosed once a week, and the results of meta- analysis showed that these agonists varied in safety and efficacy [15].

Semaglutide is a once-weekly GLP-1 analogue which was approved by the US Food and Drug Administration for the treatment of type 2 diabetes. It has 94% structural homology to natural GLP-1, and is similar to liraglutide [16]. The GLP-1 moiety of semaglutide is modified by the addition of a fatty diacid chain and two amino acid substitutions, and important structural modifications make semaglutide less susceptible to degradation by the enzyme DPP-4, and thus more enzymatically stable [16, 17]. Recently, many studies [17–19] which had tested the efficacy and safety of semaglutide as monotherapy or add-on to other AHAs in the treatment of T2DM were published. Nevertheless, there still lacks a comprehensive evaluation of the available evidence to support the use of semaglutide in clinical practice.

We conducted a systematic review and meta-analysis to test the efficacy and safety of semaglutide in patients with T2DM.

Methods

We followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement for conducting a high-quality meta-analysis [20, 21] and the Cochrane handbook guidelines [22]. This meta-analysis was registered in PTOSPERO (CRD42018090285).

Data source and searching

We systemically searched Pubmed, Embase and Cochrane library for eligible studies from the inception to January 18, 2018. We used the combination of the following medical subject heading (MeSH) and free-text terms: diabetes, diabetes mellitus, type 2 diabetes mellitus, DM, T2DM, semaglutide, ozempic, NN9936, NN9935 and NN9934. To find out newly developed clinical trials, we searched the ClinicalTrials.gov. Finally, we carried out an additionally manual search of the references of included trials, former meta-analyses and diabetes-related journals to identify other newly published and unpublished studies. The detailed search strategy was clearly described in Supplemental Table 1.

Study selection

Two researchers independently selected eligible studies which were included in the meta-analysis. If there existed a disagreement, they would solve by consulting another researcher. Inclusion criteria were listed as the followings: (1) RCTs; (2) semaglutide versus placebo or any other AHAs; (3) treatment duration ≥12 weeks; (4) T2DM patients; (5) at least one of the following outcomes was reported in a trial: reduction in HbA1c, reduction in SMPG, reduction in FPG, number of participants achieving HbA1c <7.0%, weight loss, AEs, SAEs and hypoglycaemic events (severe or BG-confirmed symptomatic) and (6) patients were ≥18 years. Studies were excluded if they are (1) non-RCTs; (2) published in the form of abstracts, short communications, or brief reports; (3) trials tested in animals or healthy human subjects; (4) not report information of interest and (5) trials whose treatment duration was shorter than 12 weeks. If several papers had been published about one trial, the paper which contains more adequate information was included in our meta-analysis.

Data extraction

We extracted the information of included studies in three aspects: the baseline characteristics of included trials and participants, the basic outcomes and the quality of included studies. Two independent researchers extracted the required information, if there existed a disagreement, they would reach a consensus by discussing with a third researcher. We collected the following information in each trial: first author, publication year, National Clinical Trial (NCT) number, medications in treatment and control group, sample size, average age, gender ratio, baseline HbA1c, diabetes duration, body weight, treatment duration and safety and efficacy outcomes (reduction in HbA1c, reduction in SMPG, reduction in FPG, number of participants achieving HbA1c <7.0%, weight loss, AEs, SAEs and hypoglycaemic events (severe or BG-confirmed (<3.1 mmol/L) symptomatic)). The authors of these included studies were not contacted for additional information.

Quality assessment

We assessed the risk of bias in the included studies with the Cochrane Collaboration's tool [20]. The risk of bias

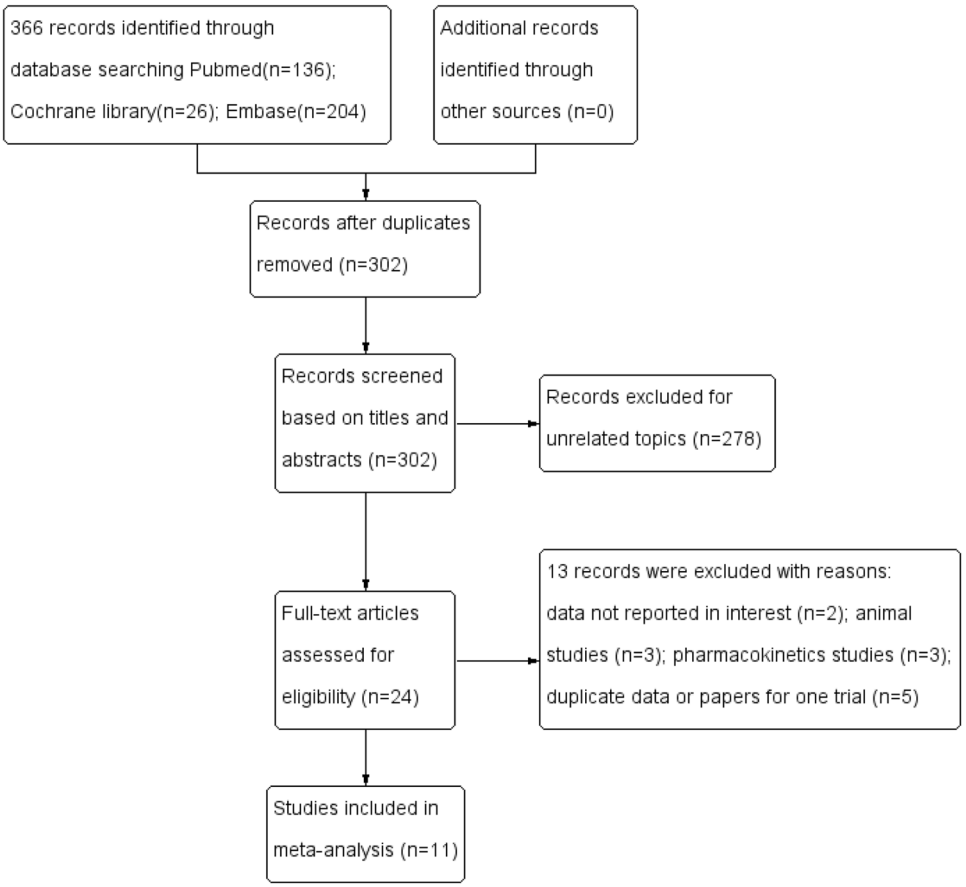

Fig. 1 Flow diagram of trial identification and selection

was described and assessed in seven specific domains: random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective reporting and other bias. The results of these domains were graded as a 'low' risk of bias, a 'high' risk of bias or an 'unclear' risk of bias.

Statistical analysis

RR and 95% CI were applied to dichotomous outcomes, whereas MD and 95% CI were applied to continuous outcomes. Two-tailed, $p < 0.05$ was considered statistically significant. Statistical heterogeneity was assessed by χ^2 test, $p < 0.10$ and $I^2 > 50\%$ was considered to be significant heterogeneity. Pooled analyses were performed using a random-effect model. Subgroup analysis was performed according to different dosages of semaglutide and different treatment methods in the control group. Sensitivity analysis was made to test the robustness of a primary outcome. All analyses were conducted with Revman5.3 (Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, Denmark) and Stata11.0 (Stata Corp, College Station, TX, USA).

Results

Search results

The study identification and selection process were summarised in Fig. 1. Of 366 records identified by initial electronic search, 11 studies [17–19, 23–30] involving 9519 T2DM patients met our inclusion criteria for narrative synthesis. No additional study was identified by manual search. The characteristics of the included trials and patients were described in Table 1. All trials have a NCT number and therefore were registered in ClinicalTrials.gov. All studies were published between 2016 and 2018. The sample size ranged from 75 to 3297. Among 11 trials, 5 trials [17, 23, 25, 28, 29] compared the efficacy and safety of semaglutide with placebo and 6 trials [18, 19, 24, 26, 27, 30] compared the efficacy and safety of semaglutide with other AHAs. In the included studies, the diabetes duration ranged from 3.62 to 14.3 years and the treatment duration ranged from 12 to 104 weeks.

Risk of bias in included studies, and quality of evidence

The bias assessment of all 11 trials was detailed in Fig. 2. A total of 10 studies [17–19, 23–27, 29, 30] explicitly

Table 1 The basic characteristics of included studies and patients

Trial name	NCT	Study arms	Patients	Age (years)	Male, *n* (%)	Baseline HbA1c (%)	Diabetes duration (years)	Body weight (kg)	Treatment duration (weeks)
Christoph Kapitza2017	NCT02212067	Semaglutide 1.0 mg	37	56	27 (73.0)	7.3	8.3	93.2	12
		Placebo	38	57	24 (63.2)	7.3	8.7	90	
Kohei Kaku2018	NCT02207374	Semaglutide 0.5 mg	239	58.0 ± 10.6	166 (69.5)	8.0 ± 0.9	8.1 ± 6.0	71.0 ± 15.4	56
		Semaglutide 1.0 mg	241	58.7 ± 10.2	174 (72.2)	8.1 ± 1.0	9.4 ± 6.5	71.7 ± 15.9	
		One additional OAD	121	59.2 ± 10.1	90 (74.2)	8.1 ± 0.9	9.3 ± 7.0	72.2 ± 14.9	
Melanie Davies2017	NCT01923181	Semaglutide 1.0 mg	69	56.8 ± 11.8	48 (69.6)	7.8 ± 0.7	5.6 ± 5.0	88.8 ± 15.4	26
		Placebo	71	58.9 ± 10.3	40 (56.3)	8.0 ± 0.8	6.7 ± 5.1	93.8 ± 18.1	
SUSTAIN12017	NCT02054897	Semaglutide 0.5 mg	128	54.6 ± 11.1	60 (47)	8.09 ± 0.89	4.81 ± 6.10	89.81 ± 22.96	30
		Semaglutide 1.0 mg	130	52.7 ± 11.9	80 (62)	8.12 ± 0.81	3.62 ± 4.88	96.87 ± 25.59	
		Placebo	129	53.9 ± 11.0	70 (54)	7.95 ± 0.85	4.06 ± 5.48	89.05 ± 22.16	
SUSTAIN22017	NCT01930188	Semaglutide 0.5 mg	409	54.8 ± 10.2	207 (51)	8.0 ± 0.9	6.4 ± 4.7	89.9 ± 20.4	56
		Semaglutide 1.0 mg	409	56.0 ± 9.4	205 (50)	8.0 ± 0.9	6.7 ± 5.6	89.2 ± 20.7	
		Sitagliptin 100 mg	407	54.6 ± 10.4	208 (51)	8.2 ± 0.9	6.6 ± 5.1	89.3 ± 19.7	
SUSTAIN32018	NCT01885208	Semaglutide 1.0 mg	404	56.4	219 (54.2)	8.4	9	96.2	56
		Exenatide ER 2.0 mg	405	56.7	228 (56.3)	8.3	9.4	95.4	
SUSTAIN42017	NCT02128932	Semaglutide 0.5 mg	362	56.5 ± 10.3	197 (54)	8.1 ± 0.8	7.8 ± 5.1	93.7 ± 21.4	30
		Semaglutide 1.0 mg	360	56.7 ± 10.4	182 (51)	8.3 ± 0.9	9.3 ± 7.2	94.0 ± 22.5	
		Insulin glargine	360	56.2 ± 10.6	195 (54)	8.1 ± 0.9	8.6 ± 6.3	92.6 ± 21.5	
SUSTAIN52016	NCT02305381	Semaglutide 0.5 mg	132	59.1 ± 10.3	74 (56.1)	8.36 ± 0.83	NA	92.74 ± 19.57	30
		Semaglutide 1.0 mg	131	58.5 ± 9.0	77 (58.8)	8.31 ± 0.82	NA	92.49 ± 22.23	
		Placebo	133	58.8 ± 10.9	71 (53.4)	8.42 ± 0.88	NA	89.88 ± 21.06	
SUSTAIN62016	NCT01720446	Semaglutide 0.5 mg	826	64.6 ± 7.3	495 (59.9)	8.7 ± 1.4	14.3 ± 8.2	91.8 ± 20.3	104
		Semaglutide 1.0 mg	822	64.7 ± 7.1	518 (63.0)	8.7 ± 1.5	14.1 ± 8.2	92.9 ± 21.1	
		Placebo 0.5 mg	824	64.8 ± 7.6	482 (58.5)	8.7 ± 1.5	14.0 ± 8.5	91.8 ± 20.3	
		Placebo 1.0 mg	825	64.4 ± 7.5	507 (61.5)	8.7 ± 1.5	13.2 ± 7.4	91.9 ± 20.8	
SUSTAIN72018	NCT02648204	Semaglutide 0.5 mg	301	56 ± 10.9	169 (56)	8.3 ± 0.9	7.7 ± 5.9	96.4 ± 24.4	40
		Semaglutide 1.0 mg	300	55 ± 10.6	162 (54)	8.2 ± 0.9	7.3 ± 5.7	95.5 ± 20.9	
		Dulaglutide 0.75 mg	299	55 ± 10.4	160 (54)	8.2 ± 0.9	7.0 ± 5.5	95.6 ± 23.0	
		Dulaglutide 1.5 mg	299	56 ± 10.6	171 (57)	8.2 ± 0.9	7.6 ± 5.6	93.4 ± 21.8	
Yutaka Seino2017	NCT02254291	Semaglutide 0.5 mg	103	58.8 ± 10.4	79 (77)	8.2 ± 1.0	8.0 ± 5.2	67.8 ± 11.7	30
		Semaglutide 1.0 mg	102	58.1 ± 11.6	75 (74)	8.0 ± 0.9	7.8 ± 6.9	70.8 ± 16.4	
		Sitagliptin 100 mg	103	57.9 ± 10.1	81 (79)	8.2 ± 0.9	8.1 ± 6.7	69.4 ± 12.9	

NCT National Clinical Trial number, *OAD* oral antidiabetic drug, *ER* extended release, *n* number of participants, *HbA1c* haemoglobin A1c, *NA* not available

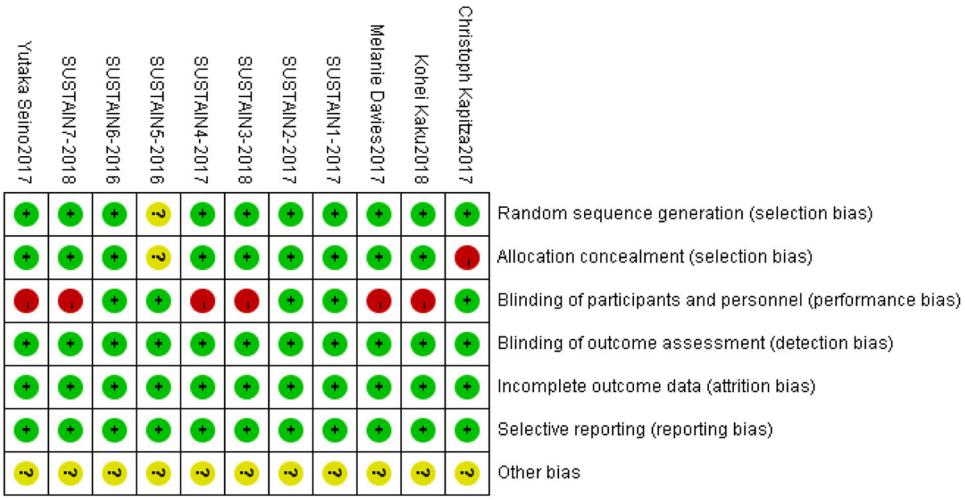

Fig. 2 Risk of bias graph and summary for included studies

described the random sequence generation, mainly by interactive voice response system or web response system. In total, nine studies [17–19, 24–27, 29, 30] used unpredicted methods to generate a random sequence which stated a low risk of allocation concealment process, whereas one study [28] lacked random sequence generation method and one study [23] that performed allocation in an unblinded method was regarded as having an unclear risk and a high risk in allocation concealment, respectively. In total, five trials [17, 18, 23, 28, 29] indicated that they adopted a double-blind design, while six trials [19, 24–27, 30] employed an open design. All 11 trials [17–19, 23–30] had a blinded design in outcome assessment. There was no trial that described neither the number of withdrawal or loss to follow-up and the reason for these aspects, therefore all trials were regarded as having a low risk in this domain. All included studies were considered to have a low risk of bias in selective reporting, according to the review of their protocols in ClinicalTrials.gov. All trials were considered to have an unclear risk of bias in the domain of other bias.

Efficacy outcomes

All outcomes were reported in total and subgroup analysis. We made subgroup analysis of both efficacy and safety outcomes according to predefined groups.

Reduction in HbA1c is the primary outcome in this meta-analysis. In total, ten trials [17–19, 24–30] reported data on reduction in HbA1c (Fig. 3). The pooled evidence showed that compared with placebo or other AHAs, semaglutide had further reduced the level of HbA1c in T2DM patients [MD 1.03%, 95% CI (0.85%, 1.22%), $p < 0.00001$].

Compared with the control group, semaglutide was associated with a significantly stronger reduction in SMPG [MD 1.19 mmol/L, 95% CI (0.84 mmol/L, 1.53 mmol/L), $p < 0.00001$], FPG [MD 1.33 mmol/L, 95% CI (0.97 mmol/L, 1.69 mmol/L), $p < 0.00001$] and weight [MD 3.61 kg, 95% CI (3.05 kg, 4.17 kg), $p < 0.00001$] (Supplemental Figures 1–3). As shown in Supplemental Figure 4, there were significantly more participants who achieved HbA1c < 7.0% in the semaglutide group than in the control group [RR 2.26, 95% CI (1.89, 2.70), $p < 0.00001$].

Safety outcomes

The safety endpoints were AEs, SAEs and hypoglycaemic events (severe or BG-confirmed symptomatic). As shown in Supplemental Figure 5, semaglutide had slightly increased the incidence of AEs compared with the control group [RR 1.06, 95% CI (1.02, 1.11), $p < 0.0001$]. The pooled evidence indicated that compared with the control group, semaglutide had an analogous safety background in terms of SAEs [RR 0.94, 95% CI (0.86, 1.02), $p = 0.11$] and hypoglycaemic events (severe or BG-confirmed symptomatic) [RR 0.93, 95% CI (0.74, 1.16), $p = 0.50$] (Supplemental Figure 6–7).

Subgroup analysis and sensitivity analysis

By dividing the treatment group into 0.5-mg semaglutide group and 1.0-mg semaglutide group, we made subgroup analysis of all eight outcomes. The results of subgroup analysis were described in Table 2.

Meta-analysis revealed that HbA1c significantly decreased by 0.89% [95% CI (0.64%, 1.15%), $p < 0.00001$] with 0.5-mg semaglutide and 1.03% [95% CI (0.89%, 1.40%), $p < 0.00001$] with 1.0-mg semaglutide. SMPG significantly decreased by 1.04 mmol/L [95% CI (0.49 mmol/L, 1.59 mmol/L), $p < 0.00001$] with 0.5-mg semaglutide and 1.31 mmol/L [95% CI (0.86 mmol/L, 1.76 mmol/L), $p < 0.00001$] with 1.0-mg semaglutide. FPG significantly decreased by 1.05 mmol/L [95% CI

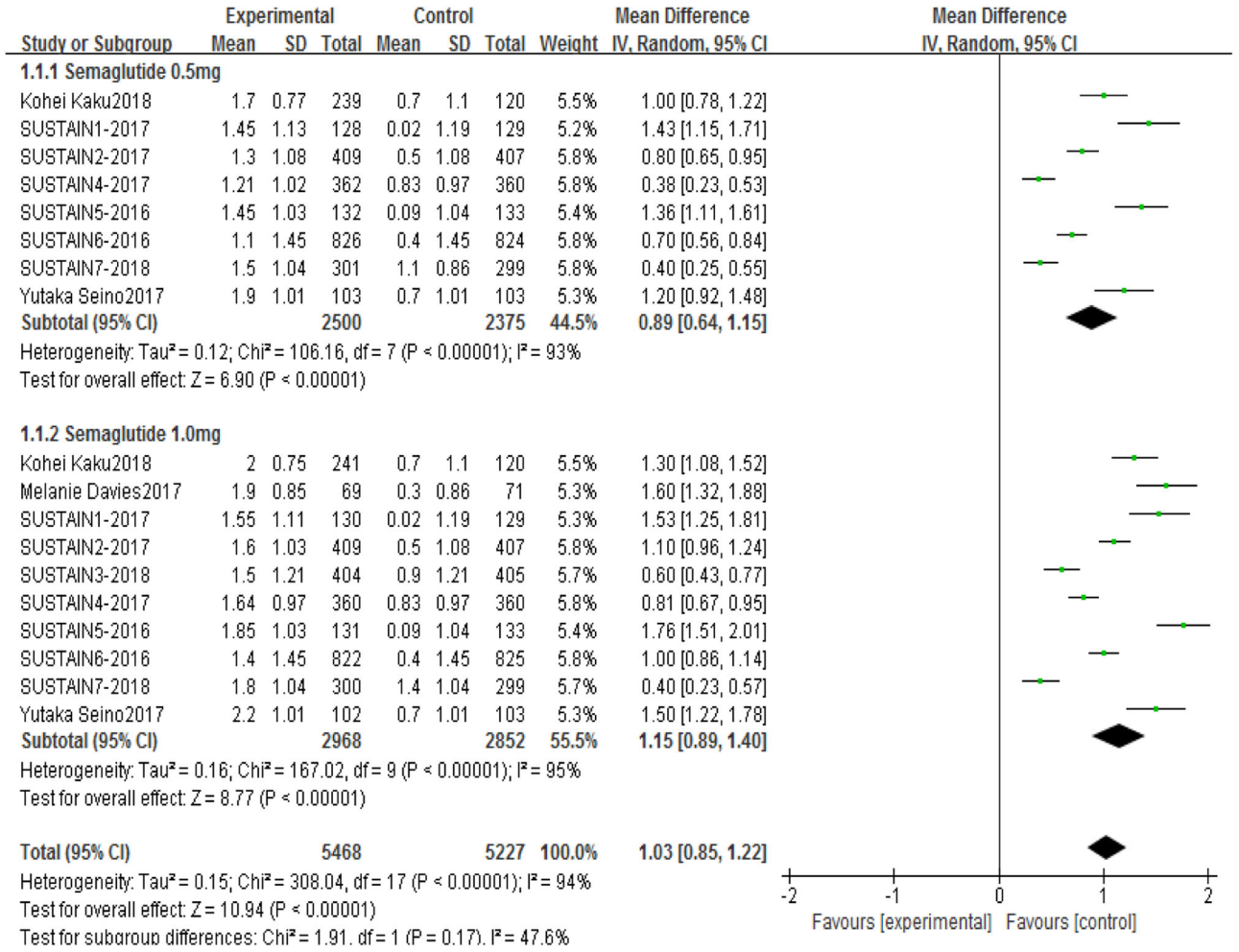

Fig. 3 Individual and summary mean difference (MD) with 95% CI of reduction in HbA1c

(0.51 mmol/L, 1.59 mmol/L), $p < 0.00001$] with 0.5-mg semaglutide and 1.55 mmol/L [95% CI (1.08 mmol/L, 2.01 mmol/L), $p < 0.00001$] with 1.0-mg semaglutide. The number of participants achieving HbA1c < 7.0% significantly increased with 0.5-mg semaglutide [RR 2.14, 95% CI (1.66, 2.75), $p < 0.00001$] and 1.0-mg semaglutide [RR 2.37, 95% CI (1.81, 3.11), $p < 0.00001$]. Body weight significantly decreased by 2.67 kg [95% CI (2.00 kg, 3.35 kg), $p < 0.00001$] with 0.5-mg semaglutide and 4.31 kg [95% CI (3.74 kg, 4.88 kg), $p < 0.00001$] with 1.0-mg semaglutide. AEs were slightly increased with 0.5-mg semaglutide [RR 1.09, 95% CI (1.02, 1.17), $p = 0.0008$] and 1.0-mg semaglutide [RR 1.05, 95% CI (1.00, 1.11), $p = 0.004$]. Both doses of semaglutide have a similar incidence rate to the control group in SAEs and hypoglycaemia (severe or BG-confirmed symptomatic).

As shown in Table 2, we also carried out subgroup analysis by dividing the control group into placebo-controlled group and active-controlled group. Compared with placebo, semaglutide significantly increased the reduction in HbA1c [MD 1.33%, 95% CI (1.02%, 1.64%), $p < 0.00001$], SMPG [MD 1.88 mmol/L, 95% CI (1.62 mmol/L, 2.14 mmol/L), $p < 0.00001$], FPG [MD 1.95 mmol/L, 95% CI (1.41 mmol/L, 2.48 mmol/L), $p < 0.00001$] and weight [MD 3.74 kg, 95% CI (3.03 kg, 4.46 kg), $p < 0.00001$]. There were significantly more patients achieving HbA1c < 7% in semaglutide arm than in placebo arm [RR 4.01, 95% CI (2.84, 5.66), $p < 0.00001$]. Compared with placebo, semaglutide was associated with a significant increase in AEs [RR 1.05, 95% CI (0.99, 1.12), $p = 0.01$] and a significant decrease in SAEs [RR 0.91, 95% CI (0.83, 0.99), $p = 0.03$]. No significant difference was found in hypoglycaemia (severe or BG-confirmed symptomatic) [RR 1.07, 95% CI (0.93, 1.25), $p = 0.30$] between semaglutide and placebo. The main AHAs used in the active-controlled group were sitagliptin, exenatide ER, insulin glargine and dulaglutide. Compared with these AHAs, semaglutide had significantly reduced the level of HbA1c [MD 0.85%, 95% CI (0.64%, 1.06%), $p < 0.00001$], SMPG [MD 0.90 mmol/L, 95% CI (0.55 mmol/L,

Table 2 Summary of subgroup analyses for type 2 diabetes mellitus patients

Outcomes	Subgroup	Included trials	Included patients	RR/MD (95% CI)
Reduction in HbA1c	0.5-mg semaglutide	8	4875	0.84 [0.60, 1.07]
	1.0-mg semaglutide	10	5820	1.10 [0.84, 1.36]
	Placebo controlled	4	4482	1.33 [1.02, 1.64]
	Active controlled	6	6213	0.85 [0.64, 1.06]
Reduction in SMPG	0.5-mg semaglutide	6	3019	1.04 [0.49, 1.59]
	1.0-mg semaglutide	7	3828	1.31 [0.86, 1.76]
	Placebo controlled	2	1045	1.88 [1.62, 2.14]
	Active controlled	5	5802	0.90 [0.55, 1.25]
Reduction in FPG	0.5-mg semaglutide	7	3225	1.05 [0.51, 1.59]
	1.0-mg semaglutide	9	4173	1.55 [1.08, 2.01]
	Placebo controlled	3	1185	1.95 [1.41, 2.48]
	Active controlled	6	6213	1.08 [0.67, 1.49]
Number of participants achieving HbA1c <7.0%	0.5-mg semaglutide	8	4875	2.14 [1.66, 2.75]
	1.0-mg semaglutide	11	5895	2.37 [1.81, 3.11]
	Placebo controlled	3	1185	4.01 [2.84, 5.66]
	Active controlled	6	6213	1.83 [1.56, 2.15]
Weight loss	0.5-mg semaglutide	8	4875	2.67 [2.00, 3.35]
	1.0-mg semaglutide	11	5895	4.31 [3.74, 4.88]
	Placebo controlled	5	4557	3.74 [3.03, 4.46]
	Active controlled	6	6213	3.51 [2.69, 4.33]
Adverse events	0.5-mg semaglutide	8	4875	1.09 [1.02, 1.17]
	1.0-mg semaglutide	11	5895	1.05 [1.00, 1.11]
	Placebo controlled	5	4557	1.05 [0.99, 1.12]
	Active controlled	6	6213	1.07 [1.01, 1.12]
Serious adverse events	0.5-mg semaglutide	8	4875	0.90 [0.81, 1.01]
	1.0-mg semaglutide	11	5820	0.97 [0.87, 1.09]
	Placebo controlled	4	4482	0.91 [0.83, 0.99]
	Active controlled	6	6213	1.08 [0.89, 1.31]
Hypoglycaemia (severe or BG-confirmed symptomatic)	0.5-mg semaglutide	7	4059	0.79 [0.45, 1.38]
	1.0-mg semaglutide	9	5004	0.98 [0.74, 1.30]
	Placebo controlled	4	4482	1.08 [0.93, 1.25]
	Active controlled	5	4581	0.69 [0.49, 0.97]

1.25 mmol/L), $p < 0.00001$], FPG [MD 1.08 mmol/L, 95% CI (0.67 mmol/L, 1.49 mmol/L), $p < 0.00001$] and weight [MD 3.51 kg, 95% CI (2.69 kg, 4.33 kg), $p < 0.00001$]. More patients achieved HbA1c < 7% in semaglutide arm than in other AHA arms [RR 1.83, 95% CI (1.56, 2.15), $p <$ 0.00001]. Semaglutide significantly increased the risk of AEs [RR 1.07, 95% CI (1.01, 1.12), $p = 0.01$] and decreased the risk of hypoglycaemia (severe or BG-confirmed symptomatic) [RR 0.69, 95% CI (0.49, 0.97), $p = 0.03$] compared with these AHAs. No significant difference was found in SAEs [RR 1.08, 95% CI (0.89, 1.31), $p = 0.44$] between semaglutide and other AHAs.

Sensitive analysis was conducted with Stata software. As shown in Supplemental Figure 8, we found similar overall results for the primary outcome after excluding each individual study.

Discussion

The results of this meta-analysis showed that 0.5-mg and 1.0-mg semaglutide given once per week were superior to placebo or other AHAs in improving glycaemic control and weight loss in patients with T2DM. In the subgroup analysis of placebo-controlled group and active-controlled group, semaglutide had significantly improved the glycaemic control and weight loss compared with either placebo or other AHAs. Semaglutide had a similar safety background

to placebo and other AHAs in terms of AEs, SAEs and hypoglycaemia (severe or BG-confirmed symptomatic). A sensitivity analysis on primary outcome generated similar results, which indicated that the results of the present meta-analysis were generalisable.

ADA recommends that the optimal HbA1c target is 7% for most nonpregnant adults with T2DM and HbA1c should be maintained at 7% at every stage of their disease [31, 32]. Our meta-analysis showed that 74% patients in the semaglutide group had achieved HbA1c < 7%, the proportion is more than two times of T2DM patients in the control group. The results achieved with semaglutide are of clinical relevance because improvements in HbA1c have been shown to reduce the risk of both diabetes-related complications and mortality [33]. With a glucose-dependent mechanism of action, GLP-1 receptor agonists have numerically fewer episodes of hypoglycaemia that occurred [34, 35]. Semaglutide has similar and significantly lower risk of hypoglycaemia (severe or BG-confirmed symptomatic) compared with placebo and other AHAs, respectively, which is complied with other GLP-1 receptor agonists. The low risk of hypoglycaemia and less medication frequency of semaglutide may contribute to improve adherence for T2DM patients.

Cardiovascular disease is the leading cause of death and complications in patients with T2DM [36]. To date, empagliflozin and liraglutide have already been shown to improve cardiovascular outcomes in patients with type 2 diabetes who were at high risk for cardiovascular events [37, 38]. SUSTAIN6 [29] was designed to assess cardiovascular safety of semaglutide in patients with T2DM. Despite an increase in pulse rate, 0.5- and 1.0-mg semaglutide led to a significant reduction in cardiovascular risk with fewer occurrences of cardiovascular death, non-fatal myocardial infarction, or non-fatal stroke compared with placebo. Nonetheless, long-term and large-scale RCTs are needed to test whether the findings of SUSTAIN6 are applicable to T2DM patients with no or fewer cardiovascular risk.

In this meta-analysis, both doses of semaglutide led to significant weight loss, compared with either placebo or other AHAs. Semaglutide is also associated with significant weight loss in subjects with obesity [39, 40]. Obesity is associated with an increase in the risk of cardiovascular complications and other comorbidities, as well as a reduction in quality of life [41–43]. The results from studies also suggest that weight gain can lead to frustration, reduced motivation, and decreased adherence to treatment [44, 45]. In addition, sustained weight loss in patients with T2DM contributed to improve glycaemic control and reduce the need for glucose-lowering medications [46].

Although acute pancreatitis has been reported after treatment with GLP-1 receptor agonists, a causal link has not been shown [47, 48], and the occurrence of pancreatitis in the studies included in this meta- analysis was low. Only 18 patients in the semaglutide group and 15 patients in the control group were reported to have pancreatitis throughout the course of clinical trials. There was an unexpected higher rate of retinopathy complications in the semaglutide group. There are studies which have reported that rapid glucose lowering is associated with worsening of retinopathy in patients with type 1 diabetes [49, 50]. Therefore, this finding might be related to the fast reduction in glucose concentrations, rather than a direct effect of semaglutide treatment.

To our knowledge, there are five [51–55] recently published meta-analyses that mentioned the efficacy and safety of semaglutide in T2DM patients. They also recommended semaglutide for T2DM patients which is consistent with our results. In the meta-analyses conducted by Witkowski et al. [51, 52] and Sharma et al. [53], they only made an indirect comparison by network meta-analysis and compared semaglutide with a class of antidiabetic agents such as GLP-1 receptor agonists and sodium–glucose cotransporter 2 inhibitors. Compared with the other two meta-analyses made by Shi et al. [54] and Andreadis et al. [55], we think we have several advantages: First, we focused on the safety and efficacy of semaglutide injection which was approved by US Food and Drug Administration. Second, we have assessed the quality of included trials in seven specific domains which was recommended by Cochrane Collaboration. Third, we have made subgroup analysis according to different dosages of semaglutide in the experimental group and different treatment therapies in the control group. Finally, sensitivity analysis was made to test the robustness of obtained outcomes.

We noted several limitations in this study. First, the power of our analysis may be restricted because of the limited study numbers and population sizes. Second, there was significant heterogeneity in some outcomes. Our research is a study-level meta-analysis, studies varied in relation to the study population, combined treatment method and treatment duration. All of these confounding factors may contribute to heterogeneity in some outcomes. Finally, only published data were included, which may lead to a reporting bias by overestimating the effect of semaglutide. All these aspects reinforce the need to perform more large, well-designed trials involving the safety and efficacy of semaglutide in patients with T2DM.

Conclusions

In conclusion, semaglutide had a favourable efficacy and safety as monotherapy or add-on to other AHAs in the treatment of T2DM patients. It maybe a superior choice for

T2DM patients with obesity or T2DM patients who have a poor adherence to daily AHAs. Semaglutide is generally well tolerated and has obviously better efficacy than either placebo or other AHAs in treating T2DM.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval This article does not contain any studies with human participants or animals performed by any of the authors.

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