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REVIEW

Weight loss with subcutaneous semaglutide versus other glucagon-like peptide 1 receptor agonists in type 2 diabetes: a systematic review

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Abstract

Glucagon-like peptide 1 receptor agonists (GLP-1 RAs) reduce elevated blood glucose levels and induce weight loss. Multiple GLP-1 RAs and one combined GLP-1/glucose-dependent insulinotropic polypeptide agonist are currently available. This review was conducted with the aim of summarising direct comparisons between subcutaneous semaglutide and other GLP-1 RAs in individuals with type 2 diabetes (T2D), particularly with respect to efficacy for inducing weight loss and improving other markers of metabolic health. This systematic review of PubMed and Embase from inception to early 2022 was registered on PROSPERO and was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses and Meta-Analysis of Observational Studies in Epidemiology guidelines. Of the 740 records identified in the search, five studies fulfilled the inclusion criteria. Comparators included liraglutide, exenatide, dulaglutide and tirzepatide. In the identified studies, multiple dosing regimens were utilised for semaglutide. Randomised trials support the superior efficacy of semaglutide over other GLP-1 RAs with respect to weight loss in T2D, but tirzepatide is more effective than semaglutide.

Introduction

Type 2 diabetes (T2D) is a major cause of morbidity and mortality worldwide. T2D is triggered by genetic and environmental factors and is characterised by insulin resistance, β–cell dysfunction and resultant overt hyperglycaemia.[1] Obesity, which affects the majority of individuals with T2D, usually underpins the development of insulin resistance and is associated with poorer blood glucose control and long-term clinical outcomes.[2,3]

Dietary modification and exercise are the first-line approaches for weight loss and improved blood glucose control in patients with T2D. However, these interventions are usually unsuccessful in the long term.[4] It is now appreciated that the frequent failure to achieve sustained weight loss and the tendency to rebound weight gain reflect potent social factors and physiological counterregulatory mechanisms, supporting the rationale for sustained pharmacological management.[5,6] In relation to the latter, therapies based on the incretin hormones glucagon-like peptide1 (GLP-1), and more recently glucose-dependent insulinotropic polypeptide (GIP), have become available. The incretins are secreted by enteroendocrine cells located in the intestinal mucosa, primarily in response to ingested nutrients, and stimulate insulin secretion in a glucose-dependent

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manner, which confers minimal risk of hypoglycaemia.[7] GLP–1 receptor agonists (GLP-1 RAs), such as semaglutide, are now used widely to reduce elevated blood glucose levels in T2D. Contrary to several other antihyperglycaemic agents, including sulphonylureas and insulin, which promote weight gain, the GLP-1 RAs lead to significant weight loss.[8] The mechanisms by which GLP–1 RAs induce weight loss are poorly defined but are likely to include centrally mediated mechanisms with reduced appetite and increased satiety.[9,10]

Several GLP-1 RAs are now available for the treatment of T2D, with the majority administered by subcutaneous injection. In addition, the combined GLP-1/GIP agonist tirzepatide was recently approved by the Food and Drug Administration. Accordingly, this systematic review was undertaken to evaluate the effects of subcutaneous semaglutide compared with other GLP-1 RAs on body weight in T2D, the associations between weight loss and other markers of metabolic health and adverse effects.

Methods

An agreed protocol was established that was prospectively registered with PROSPERO (number CRD42022303859) and followed PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) 2020 and MOOSE (Meta-Analysis of Observational Studies in Epidemiology) reporting guidelines.[11,12]

Search strategy and selection criteria

The population, intervention, comparator group and outcome framework was used to formulate the research question and inclusion criteria. The population included individuals with a diagnosis of T2D. The intervention was subcutaneous semaglutide. The comparator group included individuals with T2D treated with non-semaglutide GLP-1 RAs or the dual GLP-1/GIP RA tirzepatide. The primary outcome of interest was weight loss. Secondary outcomes were measures of metabolic health, including body mass index (BMI), waist circumference, systolic blood pressure (BP), glycated haemoglobin (HbA_{1c}) and fasting plasma glucose (FPG). Only studies that reported extractable data regarding these outcomes in patients prescribed semaglutide or a comparator GLP-1 RA were included, and those not reporting primary research data were excluded. Editorials, perspectives, letters and conference abstracts were also excluded. PubMed (incorporating MEDLINE) and Embase were searched from database inception on 15 January 2022. Searches were not limited by language; no publication restrictions were implemented. The search methodology is reported in Appendices 1 and 2.

Data extraction and analysis

Two reviewers (BN and TM) independently screened titles and abstracts, reviewed full texts and extracted data using a standardised form. Screening of titles and abstracts was performed through a web application (Rayyan, Qatar Computing Research Institute, Ar-Rayyan, Qatar).[13] In the case of an inability to reach consensus, a third reviewer (BS) acted as an arbiter. Extracted data included study design and setting, population characteristics, intervention characteristics, comparator characteristics, quantitative outcomes, methodological quality information and other information relevant to the review questions. Data relevant to study outcomes were summarised to determine effect sizes across the included studies. Methodological quality was independently assessed by two reviewers using the Cochrane Collaboration's Tool.[14] No statistical tests or software were used in the analyses. Unless otherwise stated, the central tendency of results is reported as mean values.

Ethics/data

Ethical approval was not required or sourced for the conduct of this systematic review. The current article is based on previously conducted studies and does not contain any new studies with human participants or animals performed by any of the authors.

Results

Our search identified a total of 740 records (407 unique reports), from which 62 full-text articles were retrieved. Five studies were included in the systematic review (Fig. 1). During the search process, five full texts could not be obtained. Characteristics of the included studies are shown in Table 1. The oldest study was published in 2016 and the most recent in 2021. All included publications were randomised controlled trials and were multisite, international collaborations. Outcomes of included studies are detailed in Tables 2–5.

There was significant heterogeneity with respect to doses, concurrent medications and duration of intervention. Within the five studies, there were 11 semaglutide groups (with seven different dosing regimens). In all cases, semaglutide was administered by once–weekly subcutaneous injection, with the most commonly used dose of 1.0 mg being used in three studies[15–18] and the lowest being 0.1 mg.[19] Metformin was used

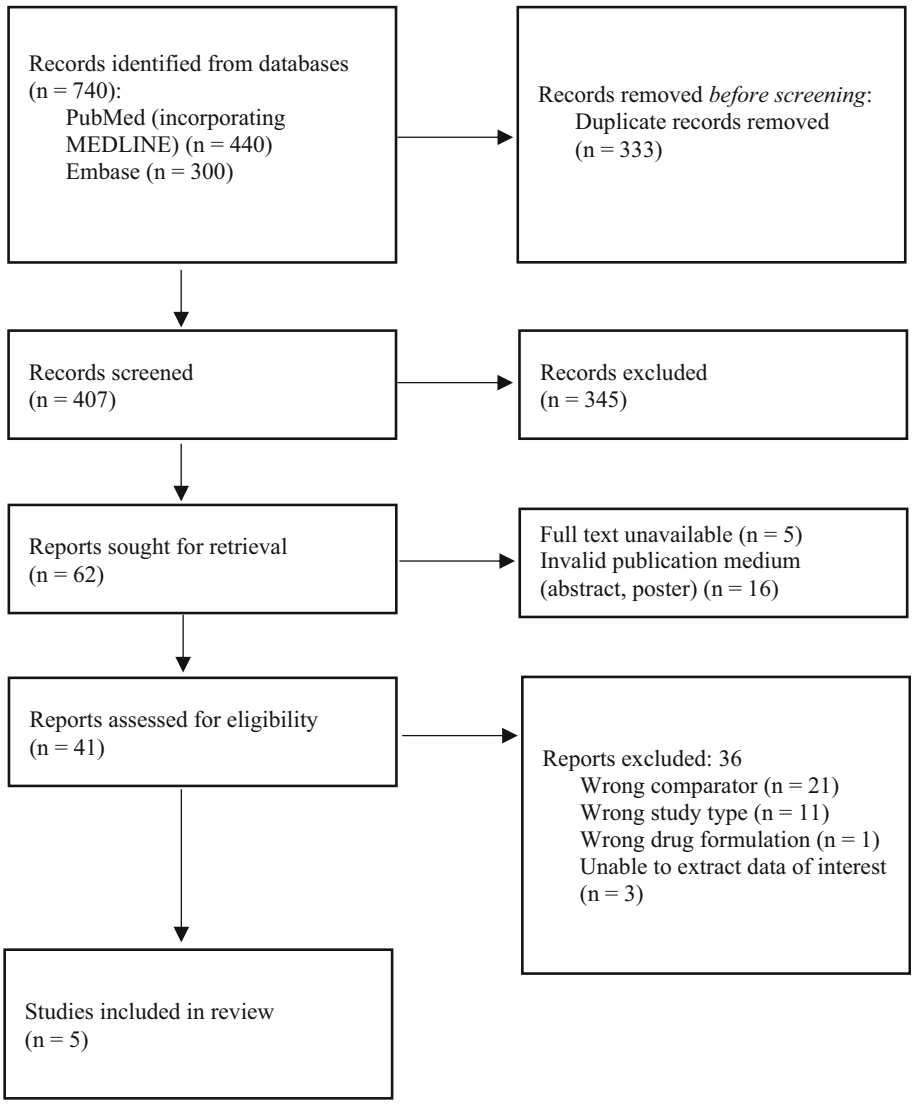

Figure 1 Study selection.

Table 1 Study characteristics

First author	Year	Design	Country	Total cohort size	Men/women (%)	Duration of intervention	Comparator	Risk of bias
Ahmann[15]	2018	RCT	International	813	55.3/44.7	56 weeks	Exenatide	Low
Capehorn[16]	2020	RCT	International	577	56.7/43.3	30 weeks	Liraglutide	Low
Frias[17]	2021	RCT	International	1879	47/53	40 weeks	Tirzepatide	Low
Nauck[19]	2016	RCT	International	415	65/35	12 weeks	Liraglutide	Low
Pratley[18]	2018	RCT	International	1201	55/45	40 weeks	Dulaglutide	Low

RCT, randomized controlled trial.

concurrently with semaglutide in all groups, whereas sodium–glucose cotransporter 2 (SGLT2) inhibitors were used concurrently with semaglutide in one group. There was no concurrent insulin use in any of the semaglutide groups. There were two 'fast–escalation' groups in which dose escalation was more rapid than the standard protocol.[19]

There were nine comparator groups across the five studies: two groups received dulaglutide (0.75 mg and 1.5 mg subcutaneous once weekly),[18] one group received long-acting exenatide (2.0 mg subcutaneous once weekly),[15] three groups received liraglutide (two using 1.2 mg once daily and the third using 1.8 mg once daily)[16,19] and three received tirzepatide (5 mg, 10 mg

Table 2 Changes in weight and other markers of metabolic health with semaglutide

			Weight (kg)				BMI (kg/m^2)			Waist circumference (cm)			Fasting plasma glucose (mmol/L)			Systolic blood pressure (mmHg)			HbA_{1c}		
Dose	Frequency	Follow-up (weeks)	Pre	Post	Delta (kg)	Delta (%)	Pre	Post	Delta	Pre	Post	Delta	Pre	Post	Delta	Pre	Post	Delta	Pre	Post	Delta
1.6 mg	Fast escalation	12	84.5	83.3	1.2	1.4	30.9			103			9	6.4	2.6				8	6.3	1.7
1.0 mg	Once weekly	40	95.5	89	6.5	6.8	33.6	31.3	2.3	111	105.8	5.2	9.8	7	2.8	133	128.1	4.9	8.2	6.4	1.8
1.0 mg	Once weekly	40	93.7	87.5	6.2	6.6	34.2	32	2.2	109.04	103.7	5.34	9.5	6.8	2.7	129.96	126.36	3.6	8.3	6.4	1.9
1.0 mg	Once weekly	30	96.6	90.8	5.8	6.0	33.7	31.7	2	111.4	106.2	5.2	9.8	8.6	1.2	136.4	131.9	4.5	8.2	6.5	1.7
1.0 mg	Once weekly	56	96.2	90.6	5.6	5.8	34	32	2		106.1			7.7			128.9		8.4	6.9	1.5
0.8 mg	Once weekly	12	85.9	82.8	3.1	3.6	30.7			101			9.5	7.1	2.4				8.2	6.7	1.5
0.8 mg	Fast escalation	12	85.7	81.4	4.3	5.0	31.2			104			9.6	7.2	2.4				8	6.8	1.2
0.5 mg	Once weekly	40	96.4	91.8	4.6	4.7	33.7	32.1	1.6	111	106.7	4.3	9.8	7.6	2.2	134	131.6	2.4	8.3	6.8	1.5
0.4 mg	Once weekly	12	87	85	2	2.3	29.7			105			9.3	7.7	1.6				8.1	7	1.1
0.2 mg	Once weekly	12	86.3	85.3	1	1.2	30.4			104			9.5	8.4	1.1				8.2	7.3	0.9
0.1 mg	Once weekly	12	89.5	88.7	0.8	0.9	31.5			106			9.8	9.3	0.5				8.2	7.6	0.6

BMI, body mass index; HbA_{1c}, glycated haemoglobin.

Table 3 Changes in weight and other markers of metabolic health with comparator GLP–1 RAs and tirzepatide

				Weight (kg)				BMI (kg/m^2)			Waist circumference (cm)			Fasting plasma glucose (mmol/L)			Systolic blood pressure (mmHg)			Hba1c		
Drug	Dose	Follow-up (weeks)	Frequency	Pre	Post	Delta (kg)	Delta (%)	Pre	Post	Delta	Pre	Post	Delta	Pre	Post	Delta	Pre	Post	Delta	Pre	Post	Delta
Dulaglutide	0.75 mg	40	Once weekly	95.6	93.3	2.3	2.4	33.6	32.8	0.8	111	108.6	2.4	9.7	7.8	1.9	133	130.8	2.2	8.2	7.1	1.1
Dulaglutide	1.5 mg	40	Once weekly	93.4	90.4	3	3.2	33.1	32	1.1	109	106.1	2.9	9.6	7.4	2.2	132	129.1	2.9	8.2	6.8	1.4
Exenatide	2.0 mg	56	Once weekly	95.4	94.5	0.9	0.9	33.6	33	3.6		108.9			8.5			131.3		8.3	7.4	0.9
Liraglutide	1.2 mg	30	Once daily	97.2	95.3	1.9	2.0	33.7	33	0.7	111.4	108.9	2.5	9.9			136.4	132.9	3.5	8.3	7.3	1
Liraglutide	1.2 mg	12	Once daily	90.5	88.6	1.9	2.1	31			106			9	7.3	1.7				8	6.8	1.2
Liraglutide	1.8 mg	12	Once daily	87.2	82.3	4.9	5.6	30.9			102			9.3	6.8	2.5				8.1	6.8	1.3
Tirzepatide	5 mg	40	Once weekly	92.5	84.7	7.8	8.4	33.8	31.3	2.5	108.1	102.4	5.7	9.7	6.5	3.2	130.5	125.7	4.8	8.3	6.2	2.1
Tirzepatide	10 mg	40	Once weekly	94.8	84.5	10.3	10.9	34.3	30.5	3.8	110.6	99.8	10.8	9.7	6.2	3.5	131.5	126.2	5.3	8.3	5.9	2.4
Tirzepatide	15 mg	40	Once weekly	93.8	81.4	12.4	13.2	34.5	29.7	4.8	109.6	99.4	10.2	9.6	6.1	3.5	130.5	124	6.5	8.3	5.8	2.4

BMI, body mass index; GLP-1 RA, glucagon-like peptide 1 receptor agonist; HbA_{1c}, glycated haemoglobin.

Table 4 Adverse events with semaglutide

Dose	Frequency	Nausea (%)	Diarrhoea (%)	Constipation (%)	Vomiting (%)	Decreased appetite (%)	Hypoglycaemia (%)	Gall bladder disorders (%)	Pancreatitis (%)	TAE (%)	Adverse events causing discontinuation (%)
1.0 mg	Once weekly	17.9	11.5	5.8	8.3	5.3	0.4	0.4	0.6	64.2	4.1
1.0 mg	Once weekly	21	14	5	10	9	2	1	0	69	10
1.0 mg	Once weekly	21.8	15.6	5.9	10.4					70.6	11.40
1.0 mg	Once weekly	22.3	11.4	6.4	7.2	7.9				75	9.4
0.8 mg	Once weekly	59.5	19	2.4	40.5	0				85.7	
0.8 mg	Fast escalation	39.5	16.3	7	30.2	4.7				72.1	
0.5 mg	Once weekly	23	14	5	10	8	1	1	0	68	8
0.4 mg	Once weekly	27.1	14.6	4.2	14.6	2.1				72.9	
0.2 mg	Once weekly	11.6	4.70	4.7	7	0				55.8	
0.1 mg	Once weekly	8.5	10.6	0	0	0				59.6	

TAE, number of individuals with one or more adverse event (percentage of cohort).

Table 5 Adverse events with comparators

Comparator	Dose	Frequency	Nausea (%)	Diarrhoea (%)	Constipation (%)	Vomiting (%)	Decreased appetite (%)	Hypoglycaemia (%)	Gall bladder disorders (%)	Pancreatitis (%)	TAE (%)	Adverse events leading to discontinuation (%)
Dulaglutide	0.75 mg	Once weekly	13	8	3	4	3	1	1	0	62	5
Dulaglutide	1.5 mg	Once weekly	20	18	5	10	10	2	3	0	74	7
Exenatide	2.0 mg	Once weekly	11.9	8.4	5.2	6.2	5.2				76.3	7.2
Liraglutide	1.2 mg	Once daily	15.7	12.2	3.5	8					66.2	6.6
Liraglutide	1.2 mg	Once daily	24.4	4.4	6.7	8.9	2.2				55.6	
Liraglutide	1.8 mg	Once daily	8	14	2	12	2				62	
Tirzepatide	5 mg	Once weekly	17.4	13.2	6.8	5.7	7.4	0.6	0.9		63.6	6
Tirzepatide	10 mg	Once weekly	19.2	16.4	4.5	8.5	7.2	0.2	0.9		69.7	8.5
Tirzepatide	15 mg	Once weekly	22.1	13.8	4.5	9.8	8.9	1.7	0.9		68.9	8.5

TAE, number of individuals with one or more adverse event (percentage of cohort).

and 15 mg subcutaneous once weekly).[17] Metformin was used concurrently with a comparator in all nine groups, SGLT2 inhibitors were used concurrently in one group[16] and one group reported 0.2% of participants received concurrent insulin.[15]

Meta-analysis was precluded because of heterogeneity in reported data across the included studies. There was a low risk of bias for the included studies (Table 1).

Weight loss

All participants had a baseline body weight > 84 kg. Participants prescribed semaglutide had a minimum baseline body weight of 84.5 kg[19] and a maximum of 96.6 kg.[16] The minimum baseline mean body weight in participants prescribed a comparator was 87.2 kg[19] and the maximum was 97.2 kg.[16] The maximum mean group difference between preintervention and postintervention mean body weights described in a single group was a 12.4–kg reduction over 40 weeks in the 15–mg tirzepatide group (93.8–81.4 kg).[17] This group also had the greatest weight loss when evaluated as a percentage of the preintervention weight (reduction in weight of 13.2% from preintervention baseline).

The maximum weight difference achieved in a semaglutide cohort was 6.5 kg (6.8% of preintervention weight, 95.5–89 kg) with 40 weeks in the 1.0–mg once–weekly group.[18] The least difference between the pre and post semaglutide intervention mean group was 0.8 kg (0.9% of preintervention weight, 89.5–88.7) with 12 weeks of 0.1–mg semaglutide once weekly.[19]

The minimum difference between preintervention and postintervention mean weights in a comparator was 0.9 kg (0.94% of preintervention weight, 95.4–94.5) with 56 weeks of 2–mg once–weekly exenatide.[15]

In direct comparisons, 1.0–mg semaglutide resulted in significantly greater weight loss than 2.0–mg exenatide (−3.78 kg [95% confidence interval (CI), –4.58 to −2.98], $P < 0.0001$),[15] 1.2–mg liraglutide (−3.83 kg [95% CI, −4.57 to −3.09], $P < 0.0001$)[16] and 1.5–mg dulaglutide (−3.55 kg [95% CI, −4.32 to −2.78], $P < 0.0001$). Conversely, all doses of tirzepatide were associated with greater reductions in weight than 1.0–mg semaglutide (5 mg: −1.9 kg [95% CI: −2.8 to −1.0], $P < 0.001$), (10 mg: −3.6 kg [95% CI, −4.5 to −2.7], $P < 0.001$) and (15 mg: −5.5 kg [95% CI, −6.4 to −4.6], $P < 0.001$).[17]

Body mass index

In patients receiving semaglutide, the greatest difference between mean preintervention and postintervention BMI was 2.3 kg/m^2 (from a baseline BMI of 33.6 kg/m^2) with 0.1 mg over 40 weeks.[18] The least difference in a semaglutide group was a 1.6–kg/m^2 reduction, from 33.7 kg/m^2, with 40 weeks of 0.5 mg.[18] The greatest difference in a comparator GLP-1 RA was a reduction of 4.8 kg/m^2 (from a baseline BMI of 34.5–29.7 kg/m^2) in a cohort prescribed 15 mg of subcutaneous tirzepatide over 40 weeks.[17]

When direct comparisons were undertaken, 1.0 mg of semaglutide resulted in a greater reduction in BMI than 1.5 mg of dulaglutide (−1.25 [95% CI, –1.52 to −0.98], $P < 0.0001$),[18] 1.2 mg of liraglutide (−1.35 [95% CI, –1.61 to −1.09], $P < 0.0001$)[16] and exenatide (−1.36 [95% CI, –1.64 to −1.07], $P < 0.0001$).[15]

Waist circumference

In patients receiving semaglutide, the greatest difference in preintervention and postintervention mean waist circumference was −5.3 cm (109–103.7 cm) with 1.0 mg over 40 weeks.[17] The least difference in a semaglutide group was −4.3 cm (11–106.7 cm) with 0.5 mg over 40 weeks.[18] The greatest difference between preintervention and postintervention mean waist circumference for comparators was −10.75 cm (110.55–99.8 cm) with 40 weeks of 10–mg tirzepatide.[17]

In direct comparisons, semaglutide 1.0 mg resulted in a greater reduction in mean waist circumference than 2.0–mg exenatide (−2.76 [95% CI, –3.63 to −1.89], $P < 0.0001$),[15] 1.2–mg liraglutide (−2.73 [95% CI, –3.62 to −1.84], $P < 0.0001$)[16] and 1.5–mg dulaglutide (−2.27 [95% CI, –3.21 to −1.33], $P < 0.0001$).[18]

Systolic BP

There was variable reporting of systolic BP. The timing of BP recordings (both time of day and preprandial vs postprandial) was not detailed and therefore likely heterogeneous across studies. Only four groups, from three studies, reported both preintervention and postintervention systolic BP.[16–18] The greatest difference in mean systolic BP among the semaglutide groups was −4.9 mm Hg (133–128.1 mm Hg) with 0.1 mg over 40 weeks.[18] Of the comparator groups, the greatest difference among these was a reduction of −6.5 mm Hg (130.45–123.95 mm Hg) with 40 weeks of 15–mg tirzepatide.[17]

In direct comparisons, 1.0–mg semaglutide resulted in a greater reduction in systolic BP than 2.0–mg exenatide (−2.37 [95% CI, –4.29 to −0.45], $P = 0.0158$) but was not superior to 1.5–mg dulaglutide (−2.02 [95% CI, –4.14 to 0.09], $P = 0.0607$).[18] No doses of semaglutide were superior to 1.2– or 1.8–mg liraglutide[16,19] for systolic BP reduction.

Fasting glucose

The greatest change between preintervention and postintervention FPG for semaglutide was a reduction of 2.8 mmol/L with 40 weeks of 0.1 mg subcutaneous once weekly.[18] For comparators, the greatest reduction was 3.5 mmol/L with 40 weeks of tirzepatide, 10 mg subcutaneous once weekly.[17]

In direct comparisons, 1.0–mg semaglutide demonstrates greater reductions in FPG than 1.2–mg daily subcutaneous liraglutide (−1.24 mmol/L [95% CI, −1.54 to −0.93], $P < 0.0001$)[16] and 1.5–mg dulaglutide (−0.58 mmol/L [95% CI, –0.91 to −0.26], $P = 0.0005$).[18] Tirzepatide, however, at doses of 5, 10 and 15 mg appeared superior in FPG reduction than 1.0–mg semaglutide; no P values were reported.[17]

Glycated haemoglobin

The greatest difference between preintervention and postintervention mean HbA_{1c} for semaglutide was with 40 weeks of 1.0 mg subcutaneous once weekly (8.25–6.42, a difference of 1.83).[17] The least observed difference was 0.6 (8.2–7.6), seen with 12 weeks of 0.1–mg semaglutide. In comparator groups, the largest difference in HbA_{1c} was 2.44 (8.26–5.82) with 40 weeks of 15–mg tirzepatide[17] and the smallest change was 0.9, seen with 56 weeks of 2.0–mg exenatide once weekly (8.3–7.4).

Direct comparisons indicate that semaglutide 1.0 mg was associated with greater reductions in HbA_{1c} when compared with exenatide 2.0 mg (−0.62 [95% CI, –0.80 to −0.44], $P < 0.0001$),[15] liraglutide 1.2 mg (0.69 [95% CI, 0.82–0.56], $P < 0.0001$)[16] and 1.5–mg dulaglutide (−0.41 [95% CI, –0.57 to −0.25], $P < 0.0001$).[18] However, semaglutide was inferior to tirzepatide across all doses (−0.15 [95% CI, −0.28 to −0.03], $P = 0.02$) with tirzepatide 5 mg (−0.39 [95% CI, −0.51 to −0.26], $P < 0.001$) with tirzepatide 10 mg and (−0.45 [95% CI, −0.57 to−0.32], $P < 0.001$) with tirzepatide 15 mg.[17]

Safety/adverse events

Adverse effects of semaglutide and comparators that may contribute to weight loss are detailed in Tables 4 and 5. The method of evaluation of adverse side effects was not routinely reported, but assessment methodologies disclosed include the Diabetes Treatment Satisfaction Questionnaire status and 36-item Short-Form Health Survey-V2 scores.[15,16,18] Gastrointestinal (GI) symptoms were assessed using self-reported measures. The lowest reported incidence of participants experiencing one or more adverse event was with semaglutide (64.2% in the 1.0–mg subcutaneous once–weekly group),[17] whereas the highest was 93.6% in participants prescribed 1.6 mg of semaglutide using a fast escalation protocol.[19] Nausea was the most commonly reported adverse effect, with rates ranging from 8.5% in the 0.1–mg subcutaneous once–weekly group[19] to 59.5% in the 0.8–mg subcutaneous once–weekly group.[19] Adverse events attributable to semaglutide were severe enough to cause discontinuation in several groups; interestingly, the highest and lowest reported discontinuation rates occurred in two groups prescribed the same dose of semaglutide. The highest reported discontinuation rate was 4.1% in the 1.0–mg group[17] and the lowest was 1.4% in another 1.0–mg group.[16] The comparators generally demonstrated fewer adverse events than semaglutide, with the lowest reported incidence of participants experiencing one or more adverse event with 1.2–mg subcutaneous liraglutide once daily (55.6%)[19] and the highest was 76.3% in the 2.0–mg once–weekly exenatide group.[15] It is not explicitly stated in any included studies whether participants were encouraged to stay in the study or continue the medication if symptoms were tolerable. The association between weight loss and GI adverse effects was not evaluated.

Discussion

The outcome of this review suggests that the GLP–1 RA agent, dose and participants' baseline characteristics are all relevant to the effects of GLP–1 RAs on body weight. Semaglutide has been compared in randomised clinical trials with several alternative GLP-1 RAs, including liraglutide, exenatide, dulaglutide and, most recently, the dual GLP-1/GIP RA tirzepatide. The findings establish that semaglutide results in weight loss in patients with T2D of approximately 1–2% every 10 weeks and is generally greater than other GLP-1 RAs except for tirzepatide. Weight loss is generally more significant with higher doses of semaglutide (1.0 mg subcutaneous is seemingly the most effective regimen, with no significant increases in observed adverse effects). Weight loss facilitated by semaglutide is also, generally, associated with positive changes in markers of metabolic health and we found evidence that semaglutide has superior effects on glycaemic control, central adiposity/waist circumference and BP when compared with other GLP-1 RAs. It is noteworthy that the improvements seen in systolic BP, HbA_{1c} and FPG with semaglutide were similar to those expected with equivalent degrees of nonpharmacotherapy-assisted weight loss.[20,21] Conversely, improvements in these markers with tirzepatide exceeded those that would be anticipated from weight loss alone.

It is important to appreciate that tirzepatide, unlike the other GLP-1 RAs, is also a GIP analogue. This may

potentially account for the superior efficacy of tirzepatide observed in relation to weight loss and markers of metabolic health.[22]

GI symptoms such as nausea, vomiting and bowel habit changes are not uncommon with GLP-1 RA use and could feasibly contribute to reduced oral intake. Therefore, a key issue is whether improvements in weight and other metabolic health markers are associated with GI adverse effects. All of the studies suffer from the limitation that GI adverse effects were evaluated by self-report, which is unreliable and may be influenced by precebo and nocebo effects and participant interpretation of terminology.[23] This limitation could be averted by the use of validated questionnaires; these are used widely in clinical trials relating to functional GI disorders but are nonetheless still prone to recall bias. This, in combination with blinded studies, would vastly improve our understanding of these drugs and how they work. No statistical analysis of adverse effects was performed in the included studies, but previous (retrospective, *post hoc*) mediation analyses of the direct and indirect effects of semaglutide have suggested that only a very small proportion of weight loss was attributable to nausea and vomiting (0.05–0.5 kg).[24,25] Moreover, nausea and vomiting generally diminish with sustained use of GLP-1 RAs, so they do not appear to adequately explain the sustained weight loss. Rather, it seems likely that weight loss occurs through central effects on appetite and satiety that are not adverse effect driven. There is also evidence – contrary to previous supposition – that long-acting GLP–1 RAs maintain some effect to slow gastric emptying with sustained use, albeit less than for short-acting GLP–1 RAs.[8] However, slowing of emptying and associated changes in intragastric meal distribution are unlikely to be a major driver of weight loss.[26]

This study has several limitations. First, because there is substantial heterogeneity in dosing for individual GLP-1 RAs, this review, which included only five studies, does not provide a definitive answer to the relative benefits of semaglutide over other agents in the class. The heterogeneity of the data also precluded a meta-analysis. This review methodology was chosen to minimise the risk of selection bias by considering only direct evidence relevant to the clinical question and so precluded a network meta-analysis; however, our results are in keeping with a prior network meta-analysis on the topic, but with an updated synthesis of the new publications, analysis of a wider dose range and the inclusion of a tirzepatide comparator.[27] Weight loss (and HbA_{1c} reduction) tends to be more rapid initially and then plateau, and long-term studies are required to determine the durability of the weight loss. Because of this, the results of the shorter interventions cannot be extrapolated (i.e. the weight loss from a 12-week intervention cannot simply be multiplied to determine weight loss over 52 weeks). The original search terms did not include the code names for semaglutide ('NN-9535' OR 'NN9535' OR 'NNC 0113-0217' OR 'NNC-0113-0217'). A *post hoc* grey literature search for these terms did not result in any new inclusions. It is also unclear whether the GLP-1 RA was provided in conjunction with a complementary exercise and diet programme, so the nonpharmacological contribution to the outcomes remains uncertain, which may be abrogated in future research that utilises a factorial design study. The studies that reported BP did not state whether measurements were made under fasting or postprandial conditions, which is relevant because of the well-documented phenomenon of postprandial hypotension, to which people with T2D are prone, particularly when complicated by autonomic dysfunction.[28] Presumably, the methodology was consistent within studies, but variations in methodology between studies potentially diminishes the reliability of interstudy comparisons. Finally, exenatide has been included in this review as an alternative GLP-1 RA to semaglutide; however, both the short-acting (twice–daily administration) and long-acting (once–weekly administration) forms have been discontinued and are no longer available on the Australian pharmaceutical benefits scheme.

The most commonly identified methodological issue was the use of open-label interventions, such that both the patients and personnel assessing the outcomes were often aware of the intervention they received. This was largely necessitated by different devices and dosage regimens for different groups, which would make a blinded design very difficult to achieve. This is a major methodological problem; however, as weight is an objective assessment, it does help to reduce bias. Further, more complex drug administration devices may have affected or contributed to lower group performance; however, this is at least emblematic and reflects a real-life setting. Nevertheless, the persistent attendant doubts around adverse events contributing to weight loss necessitate the need for independent investigator-led randomised, blinded controlled trials with rigorous, systematised preplanned adverse event data collection.

Despite all of the included studies, including multiple centres and countries, the majority of participants (between 75.7%[8] and 92.2%[16]) were of White race. Although it is unlikely that the benefits of semaglutide would be negated based on the ethnicity of the patient, it is certainly plausible that GLP-1 RAs may be more or less effective depending on ethnicity, as has been documented for ACE inhibitors in Black populations.[29] A thorough examination of GLP-1 RAs in a broad range of ethnicities is therefore imperative, particularly in light of

how the pathogenesis of T2D may differ in different ethnic groups.[30]

This review only addressed the effects of subcutaneous semaglutide on individuals with T2D. Semaglutide is, however, available in some countries as an oral formulation. Oral semaglutide, given once a day, can similarly facilitate weight loss and improve glycaemic control, possibly more effectively than either subcutaneous dulaglutide or liraglutide.[31,32] Oral semaglutide is available in 3–, 7– and 14–mg formulations with greater efficacy observed in higher–dose regimens, suggesting that the effect of semaglutide relates to serum levels rather than the route of administration.[31,32]

Subcutaneous semaglutide is approved at doses up to 1.0 mg weekly for T2D; however, the doses used to achieve weight loss in nondiabetic obese cohorts are substantially higher (0.4 mg/d[33] or 2.4 mg/wk[34]). Semaglutide has recently been approved at a higher dose (2 mg) for patients with T2D, and at an even higher dose (2.4 mg) for the management of obesity (with or without T2D). Furthermore, dulaglutide is also now available at 3–mg and 4.5–mg doses (with greater weight loss than 1.5 mg), but these higher doses have not been compared with semaglutide or other GLP–1 RAs. It is noteworthy that tirzepatide (5–10 mg/wk) has recently demonstrated impressive weight loss in such populations.[35] Another limitation is the inclusion of early trials such as that by Nauck *et al.*[18] which was designed as a dose-ranging trial with small numbers per group and used very low doses of semaglutide that have not been approved for clinical use and of duration too short to be a useful comparator.

Conclusion

This systematic review synthesised the existing evidence base to examine the effects of semaglutide on body weight in patients with T2D compared with other GLP-1 RAs. There is evidence to support the superiority of semaglutide over comparator GLP–1 RAs, with respect to weight loss and glycaemic control but not to tirzepatide, a dual mechanism of GLP-1/GIP RA. This review provides a comprehensive assessment of currently available GLP-1 RAs, demonstrating their therapeutic benefit and potential for large contributions to the reduction in morbidity and mortality related to T2D worldwide. The results suggest that when unable to prescribe tirzepatide, 1.0 mg of semaglutide per week confers a good balance between significant results and tolerance of adverse effects. Further direct comparisons between tirzepatide and a higher range of semaglutide doses should now be considered. It will also be important to achieve greater mechanistic understanding of why tirzepatide appears more effective than all existing GLP-1RA comparators, including the contribution of GIP receptor agonism.

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