REVIEW

Efficacy of GLP-1 RA Approved for Weight Management in Patients With or Without Diabetes: A Narrative Review

Mojca Jensterle · Manfredi Rizzo · Martin Haluzík · Andrej Janež

ABSTRACT

The approval of once daily liraglutide, 3.0 mg, and once weekly semaglutide, 2.4 mg, for chronic weight management provides a novel effective strategy against obesity. The reliable models that might predict weight reducing potential at the individual level have not been identified yet. However, the coexistence of diabetes has been consistently related with less effective response than in people without this comorbidity. We aimed to review the efficacy of GLP-1 RAs approved for weight management in individuals with and without diabetes and discuss some potential mechanisms for consistently observed differences in efficacy between these two populations. The mean weight loss difference between GLP-1 RAs and placebo as add-on to lifestyle intervention in patients with diabetes was 4% to 6.2% compared to 6.1 to 17.4% in people without diabetes. Semaglutide compared to liraglutide resulted in greater weight loss. Some hypothetical explanations for the weaker anti-obesity response for both GLP-1 RAs in people with diabetes include the background medications that promote weight gain, the fear of hypoglycaemia inherently related to the treatment of diabetes, a decrease in glycosuria and subsequently less weight loss in diabetics, an altered microbiota in patients with obesity and diabetes and a genetic background that predispose to weight gain in patients with diabetes. Moreover, people with diabetes may have had obesity for longer and may be less adherent to exercise, which seems to potentiate the effects of GLP-1 RA. Emerging multimodal approaches combining peptides targeting receptors at different levels might therefore be of additional benefit particularly in patients with diabetes.

Keywords: Liraglutide; Semaglutide; GLP-1 RAs; Obesity; Diabetes

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Key Summary Points

Liraglutide, 3.0 mg, and semaglutide, 2.4 mg, added to lifestyle intervention, provide a novel effective strategy against obesity in patients with and without diabetes.

Semaglutide compared to liraglutide resulted in greater weight loss.

The efficacy of antiobesity medication is consistently better in patients without diabetes than in those with diabetes.

We discuss some hypothetical explanations for weaker anti-obesity response of both GLP-1 RAs in people with diabetes.

INTRODUCTION

The pathophysiology of obesity is linked with dysregulation of appetite at the level of the brain's subcortical areas and counter-regulatory mechanisms that promote weight regain in response to calorie reduction [1]. Emerging antiobesity pharmacotherapy provides an option to correct maladaptive physiological and hormonal changes associated with obesity [2]. Drugs approved for weight management provide sufficient mean and categorical change in body weight [3]. Individuals with BMIs $\geq$ 30 kg/m^2 or $\geq$ 27 kg/m^2 in the presence of comorbidities including type 2 diabetes, hypertension, dyslipidaemia, sleep apnoea and/or cardiovascular disease were identified as appropriate candidates for such pharmacotherapy [3]. Efficacy and safety of these drugs have been proven for a representative sample of patients with different comorbidities, from the various demographic, ethnic and racial groups [2].

GLP-1 agonism with current GLP-1 RA and emerging novel combined anti-obesity compounds represents a benchmark for future pharmacological anti-obesity treatment. The first drug for weight management approved by the Food and Drug Administration (FDA) and European Medicine Agency (EMA) is GLP-1 RA liraglutide 3.0 mg with once daily administration [4]. The next generation GLP-1 RA semaglutide 2.4 mg is the latest anti-obesity medication, approved by the FDA in June 2021. Compared with liraglutide, semaglutide has been subjected to some minor structural changes that resulted in greater efficacy and gained pharmacokinetic properties that allow once weekly dosing of semaglutide vs. once daily administration of liraglutide [5].

For both drugs, there is substantially more interindividual variability regarding weight loss than there is for glycaemic control [6]. The interindividual variability in antiobesity efficacy is one of the most important challenges, because there are currently almost no reliable predictive models to assess the weight reducing potential at the individual level. The baseline BMI, BMI change at 1 month, incidence of nausea and vomiting, delayed gastric emptying shortly after intervention, baseline appetite and satiety measures and some polymorphisms in GLP-1 receptor were suggested as potential predictors by some smaller studies, but the results are inconclusive [7–9].

However, the coexistence of diabetes has been consistently related with less weight loss under medication than in patients without diabetes. Trials separately dedicated to patients with diabetes and without diabetes have been advised for the development of all products for weight management [3]. The purpose of this review is to provide an overview of the efficacy of GLP-1 RA approved for weight management in adults with and without diabetes and to discuss some potential mechanisms for consistently observed difference in efficacy between these two populations.

METHODS

ClinicalTrials.cov and PubMed (Inception January 15, 2022) were searched using the keywords liraglutide, semaglutide with obesity, anti-obesity, weight, high dose, "3 mg", "2.4 mg" and diabetes. Within Clinical
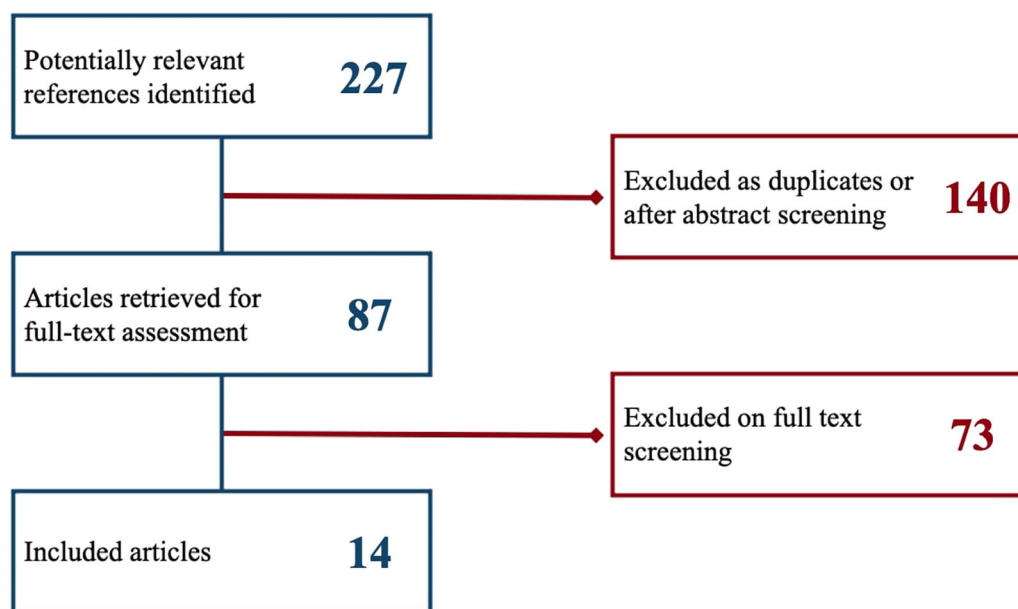
Fig. 1 Flowchart of study selection

Trils.gov, search results were narrowed to interventional clinical trial. We identified 28 studies with liraglutide and 20 studies with semaglutide. We included those completed and with results and published. In PubMed we identified 227 articles, 14 of them were selected for inclusion in the review. We excluded duplicates and some articles after the title and abstract screening and some after full text screeing. Figure 1 shows the flowchart of the study selection.

Altogether, we identified six RTC studies with liraglutide 3 mg [9–14], four RCT studies with semaglutide 2.4 mg/week [15–18] and one study that compared efficacy of semaglutide and liraglutide [19] in participants without diabetes. In participants with diabetes, we detected two RTCs studies with liraglutide 3.0 mg [20, 21] and one RTC that evaluated once-weekly subcutaneous semaglutide 2.4 mg [22]. All studies included lifestyle modifications as part of the protocol; one study with liraglutide and one study with semaglutide included additional dietary restrictions and intensive behavioural therapy [13, 16]. This 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

The differences in the efficacy of liraglutide 3.0 mg and semaglutide 2.4 mg in the weight management of patients with and without type 2 diabetes are presented in Tables 1 and 2. Figure 2 shows the changes of mean body weight from baseline for liragutide or semaglutide vs. placebo in the phase 3 trials designed to assess an antiobesity efficacy as a primary outcome. Figure 3 demonstrates the proportion of patients with ≥ 5% of weight loss from baseline for liragutide and/or semaglutide vs. placebo.

Trials on Liraglutide in Persons Without Diabetes

The efficacy of liraglutide 3.0 mg for weight management in participants without diabetes was assessed in three phase 3a SCALE trials [10–12] and one phase 3b SCALE trial [13] that altogether supported a market authorization approval of liraglutide for the treatment of obesity in one phase 2 trial [14] and in one

Table 1 Differences in the efficacy of liraglutide 3.0 mg and semaglutide 2.4 mg in the weight management of patients without type 2 diabetes

Reference	Population	Duration	Intervention	Mean body weight at baseline (kg)	Mean weight loss from baseline	Mean difference in GLP-1 RA vs. placebo-treated group	Weight loss of 5% (proportion)	Weight loss of 10% (proportion)
Pi-Sunyer SCALE Obesity and Prediabetes [10]	No type 2 diabetes, BMI ≥ 30 or ≥27 and treated or untreated dyslipidemia or hypertension	56 weeks	Liraglutide 3 mg (N = 2487)	106.2 ± 21.2	− 8.0%	− 5.3%	63.2%	33.1%
			Placebo (N = 1244)	106.2 ± 21.7	− 2.6%		27.1%	10.6%
Astrup A [14]	Obese individulas without diabetes	56 weeks	Liraglutide 3 mg (N = 93)	98.4 ± 13.0	− 9.2%	− 5.8%	73%	–
			Placebo (N = 98)	97.3 ± 12.3	− 3.1%		2.8%	
Halawi [9]	Healthy, local residents aged 18–65 with BMI ≥30	16 weeks	Liraglutide 3 mg (N = 19)	103.7 (90.0 to 112.2)	− 5.3 kg	–	–	–
			Placebo (N = 20)	99.1 (90.4 to 111.0)	− 2.5 kg			
Wadden SCALE Maintenance [11]	Obese individuals without diabetes (BMI≥ 30 or ≥27 with comorbidities) who lost 5% during run in period of a variable–length (4–12 weeks)	56 weeks	Liraglutide 3 mg (N = 212)	Start of run in: 106 ± 22.0 End of run in: 100.4 ± 20.8	− 6.2%	− 6.1%	50.5%	–
			Placebo (N = 210)	Start of run in: 105.0 ± 22.5 End of run in: 98.7 ± 21.2	− 0.2%		21.8%	

Table 1 continued

Reference	Population	Duration	Intervention	Mean body weight at baseline (kg)	Mean weight loss from baseline	Mean difference in GLP-1 RA vs. placebo-treated group	Weight loss of 5% (proportion)	Weight loss of 10% (proportion)
Blackman SCALE Sleep Apnea [12]	Non-diabetic participants with obesity who had moderate (AHI 15–29.9 events h (−1)) or severe (AHI≥30 events h (−1)) OSA and were unwilling/ unable to use continuous positive airway pressure	32 weeks	Liraglutide 3.0 mg (N = 180)	– (BMI 38.9 ± 6.4)	− 5.7%	− 4.2%	–	–
			Placebo (N = 179)	– (BMI 39.4 ± 7.4)	− 1.6%			
Wadden* SCALE IBT [13]	Obese individuals with and without diabetes trial in individuals with obesity	56 weeks	Liraglutide 3.0 mg (N = 142)	108.5 ± 22.1	− 7.5%	− 3.4%	61.5%	30.5%
			Placebo (N = 140)	106.7 ± 22.0	− 4.0%		38.8%	19.8%

Table 1 continued

Reference	Population	Duration	Intervention	Mean body weight at baseline (kg)	Mean weight loss from baseline	Mean difference in GLP-1 RA vs. placebo-treated group	Weight loss of 5% (proportion)	Weight loss of 10% (proportion)
Wilding STEP 1 [15]	Adults with a BMI of ≥ 30 or ≥ 27 in persons with ≥ 1 weight-related coexisting condition, who did not have diabetes	68 weeks	Semaglutide 2.4 mg (N = 1304)	105.4 ± 22.1	− 14.9%	− 12.4%	86.4%	69.1%
			Placebo (N = 655)	105.2 ± 21.5	− 2.4%		31.5%	12.1%
Wadden* STEP 3 [16]	Adults without diabetes and with either overweight (BMI ≥ 27) plus at least 1 comorbidity or obesity (BMI ≥ 30)	68 weeks	Semaglutide 2.4 mg (N = 407)	106.9 ± 22.8	− 16.0%	− 10.3%	86.6%	75.3%
			Placebo (N = 204)	103.7 ± 22.9	− 5.7%		47.6%	27.0%

Table 1 continued

Reference	Population	Duration	Intervention	Mean body weight at baseline (kg)	Mean weight loss from baseline	Mean difference in GLP-1 RA vs. placebo-treated group	Weight loss of 5% (proportion)	Weight loss of 10% (proportion)
Rubino STEP 4 [17]	Adults without diabetes and with BMI ≥ 27 plus 1 comorbidity or BMI ≥ 30 after a 20-week run-in with semaglutide titrated to 2.4 mg weekly	68 weeks: 20 weeks of open label run in period with semaglutide followed by 48 week-period continued by semaglutide or switched to placebo	Semaglutide 2.4 mg (N = 535) Switched to placebo (N = 268)	Week 0: 107.2 ± 22.7 Week 20 continued semaglutide: 96.5 ± 22.5 Week 20 Switched to placebo: 95.4 ± 22.7	− 17.4% vs. − 5% from week 0 to 68 − 7.9% vs. + 6.9% from week 20—68	− 12.4% from week 0 − 14.8% from week 20—68	88.7% from week 0 vs 47.6% from week 0	/
Friedrichsen [18]	Adults with obesity	20 weeks	Semaglutide 2.4 mg (N = 36) Placebo (N = 36)	106.2 ± 16.2 104.9 ± 14.0	− 9.9% − 0.4%	–	–	–

Table 1 continued

Reference	Population	Duration	Intervention	Mean body weight at baseline (kg)	Mean weight loss from baseline	Mean difference in GLP-1 RA vs. placebo-treated group	Weight loss of 5% (proportion)	Weight loss of 10% (proportion)
Rubino [19]	Adults with body mass index of 30 or greater or 27 or greater with 1 or more weight-related comorbidities, without diabetes	68 weeks	Semaglutide 2.4 mg (N = 126)	102.5 (25.3)	− 15.8%	− 13.9% Semaglutide vs. vs. placebo Liraglutide	87.2%	70.9%
			Liraglutide 3.0 mg (N = 127)	103.7 (22.5)	− 6.4%	− 4.5% − 9.4% vs. placebo	58.1%	25.6%
			Placebo (N = 85)	108.8 (23.1)	− 1.9%		29.5%	15.4%

BMI = body mass index, OSA = obstructive sleep apnoea, AHI = apnoea-hypopnea index

* All studies included lifestyle modifications as part of the methodology; SCALE IBT and STEP 3 included additional dietary restrictions and intensive behavioural therapy

Table 2 Differences in the efficacy of liraglutide 3.0 mg and semaglutide 2.4 mg in the weight management of patients with type 2 diabetes

References	Population	Duration	Intervention	Mean body weight at baseline (kg)	Mean weight loss from baseline	Mean difference in GLP-1 RA vs. placebo treated group	Weight loss of 5% (proportion)	Weight loss of 10% (proportion)
Davies SCALE Diabetes [19]	Adults with BMI of 27.0 or greater, age 18 years or older, taking 0 to 3 oral hypoglycemic agents (metformin, thiazolidinedione, sulfonylurea) with stable body weight, and glycated hemoglobin level 7.0% to 10.0%	56 weeks	Liraglutide 3 mg (N = 423)	105.7 ± 21.9	− 6%	− 4.0%	54.3%	25.2%
			Placebo (N = 212)	106.5 ± 21.3	− 2%		21.4%	6.7%
Garvey SCALE Insulin [20]	Individuals with overweight or obesity and type 2 diabetes treated with basal insulin and ≤ 2 oral antidiabetic drugs	56 weeks	Liraglutide 3 mg (N = 198)	100.6 ± 20.8	− 5.8 kg	− 4.3 kg	51.8%	–
			Placebo (N = 198)	98.9 ± 19.9	− 1.5 kg		24.0%	
Davies STEP 2 [21]	Adults with a BMI ≥ 27 kg/m² and glycated haemoglobin 7–10% (53–86 mmol/mol) who had been diagnosed with type 2 diabetes at least 180 days before screening with stable treatment of diet and exercise	68 weeks	Semaglutide 2.4 mg (N = 404)	99.9 ± 22.5	− 9.6%	− 6.2%	68.8%	–
			Placebo (N = 403)	100.5 ± 20.9	− 3.4%		28.5%	

BMI body mass index
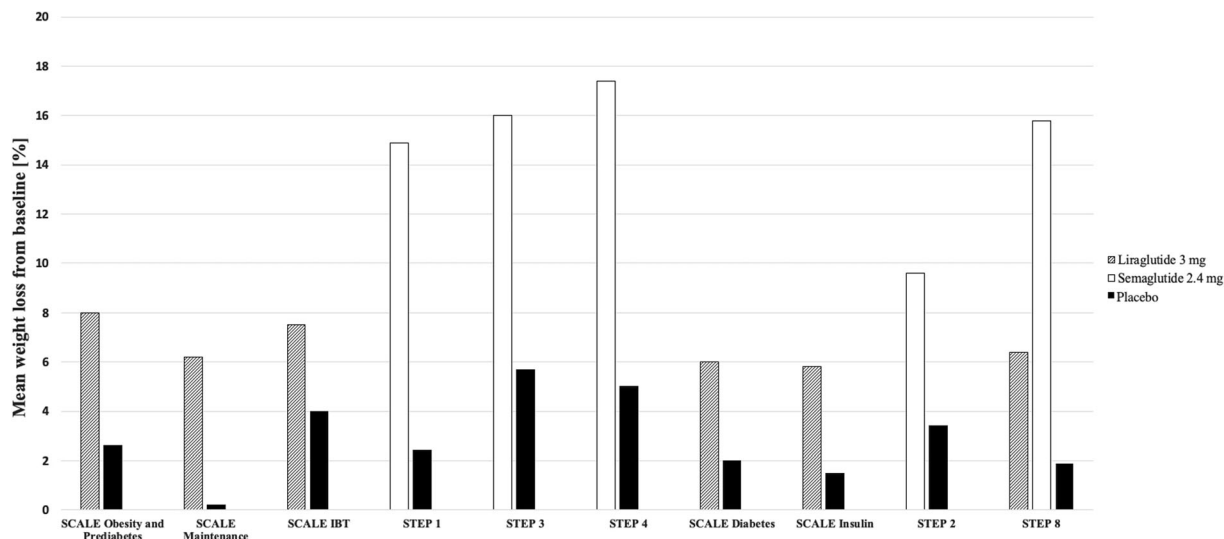
Fig. 2 Changes of mean body weight from baseline for liragutide and/or semaglutide vs. placebo
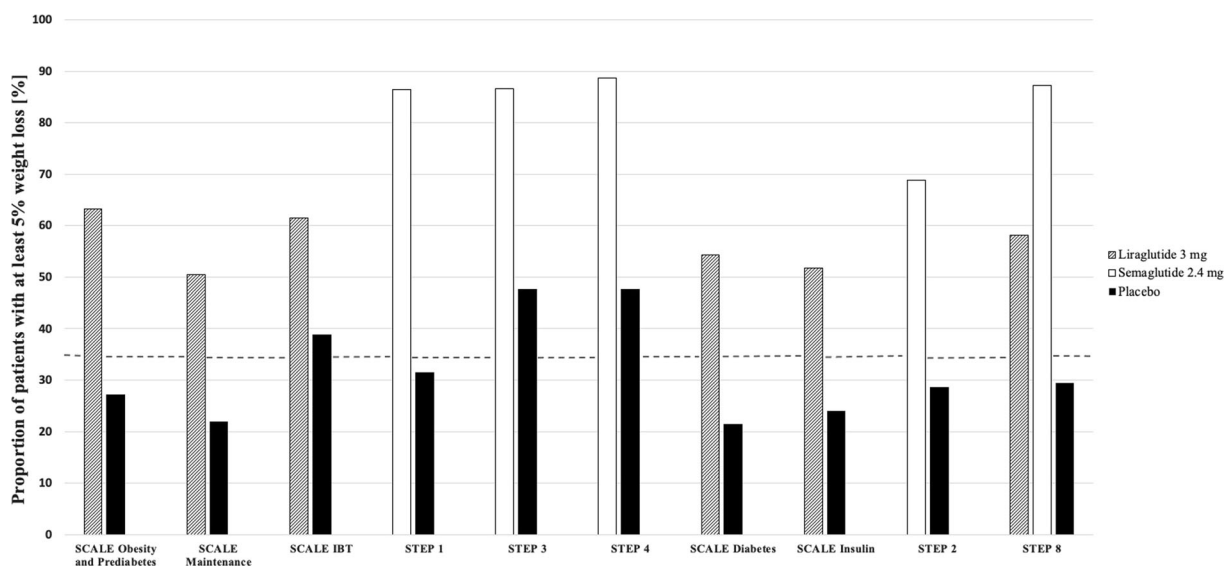
Fig. 3 Proportion of patients with $\geq$ 5% weight loss from baseline for liragutide and/or semaglutide vs. placebo. The horizontal broken line marks one of the benchmark criteria for weight management products where at least 35% of subjects lost $\geq$ 5% of baseline body weight.

Legend: The horizontal broken line marks one of the benchmark criteria for weight management products where at least 35% of subjects lost $\geq$ 5% baseline body weight

double-blind, placebo-controlled pilot trial at a single centre (Mayo Clinic, Rochester, MN, USA) [9]. Liraglutide resulted in 3.4 to 6.1% difference in mean weight loss compared to placebo [10–14, 19]. The proportion of subjects who lost $\geq$ 5% of baseline body weight was 50.5–73% [10–14, 19].

According to FDA Guidance for Industry Developing Products for Weight Manegment, efficacy benchmark criteria for weight management products are met if first, after 1 year of

treatment, the difference in mean weight loss between the active-product and placebo-treated groups is at least 5% or, second, if the proportion of subjects who lost ≥ 5% of baseline body weight in the active-product group is at least 35% and approximately double the proportion in the placebo-treated group [3]. Both critera were met in phase 2 study [14], SCALE Obesity and Predabetes [10] and SCALE Maintenance [11] trials.

Trials on Liraglutide in Persons with Diabetes

Patients with diabetes were enrolled in a phase 3a SCALE Diabetes trial [20] and phase 3b SCALE Insulin trial [21]. In both trials the difference in mean weight loss between the liraglutide and placebo-treated groups was < 5% after 1 year of treatment, but the proportion of subjects who lost ≥ 5% of baseline body weight in the liraglutide group was > 35%, from 51.8 to 54.3% [20, 21]. Notably, SCALE Insulin trial explored the antiobesity efficacy of liraglutide in diabetics treated with basal insulin that has well-established weight gain potential [21].

Trials on Semaglutide in Persons Without Diabetes

The efficacy of semaglutide 2.4. mg for obesity has been assessed in a STEP 1–4 clinical programme [15–17, 22] that was crucial for market authorization approval for semaglutide for the treatment of obesity and in one small short-term, single-centre, double-blind, parallel-group short RTC investigating the effects of once-weekly subcutaneous (s.c.) semaglutide 2.4 mg on gastric emptying, appetite and energy intake in adults with obesity [20]. Both efficacy benchmark criteria for weight management products were met in STEP 1, 3, 4 and 8 trials [15–17, 19]. Semaglutide resulted in 10.3–17.4% difference in mean weight compared to placebo [15–17, 19]. The proportion of subjects who lost ≥ 5% of baseline body weight was 86.4–88.7% [15–17, 19].

Trial on Semaglutide in Persons with Diabetes

There is only one double-blind, double-dummy, phase 3, superiority study STEP 2 that assessed the efficacy and safety of semaglutide 2.4 mg versus semaglutide 1.0 mg (the dose approved for diabetes treatment) and placebo for weight management in adults with overweight or obesity and type 2 diabetes [22]. Both efficacy benchmark criteria for weight management products were met in a STEP 2 trial [22]. Semaglutide resulted in 6.2% difference in mean weight loss vs. placebo [22]. The proportion of subjects who lost ≥ 5% of baseline body weight with semaglutide was 68.8% [22]. Importantly, insulin use was excluded in STEP 2 trial [22].

Trial on Semaglutide vs. Liraglutide in Persons Without Diabetes

The most recent randomized, open-label, phase 3 b trail, STEP 8, directly compared semaglutide, 2.4 mg, vs. liraglutide, 3.0 mg, for weight management in adults with overweight or obesity to rigorously assess differences in efficacy and adverse event profiles [19]. The STEP 8 trial found that weight loss with semaglutide was significantly greater than with liraglutide in adults with overweight or obesity without diabetes [19]. The placebo-adjusted weight loss and adverse effect profiles were similar to those in STEP 1 for semaglutide and to SCALE Obesity and Prediabetes for liraglutide [19].

Cohorts without diabetes were characterized by exclusion of the individuals with a history of type 1 diabetes mellitus or TD2 mellitus, HbA1c ≥ 6.5% or previous treatment with glucose-lowering agents or any antiobesity medication within the past 90 days before screening [23]. Protocols with cohorts with diabetes included an algorithm for the reduction or withdrawal of other antidiabetic drugs for patients who lose clinically significant amounts of weight.

In summary, participants without diabetes treated with high-dose liraglutide and

semaglutide reached both efficacy-benchmark criteria.

In patients with diabetes, both efficacy benchmarks were achieved by semaglutide [22], while the efficacy of liraglutide did not meet the criteria in mean difference between active product vs. placebo [20, 21]. While some patients with diabetes achieved ≥ 5 or 10% with placebo, higher levels of ≥ 15% in patients with diabetes were achieved almost exclusively with those who received liraglutide or semaglutide and not by those on placebo [20–22].

DISCUSSION

The principal goal in obesity management is clinically significant weight loss defined as a long-term reduction in fat mass with a goal to reduce morbidity and mortality through quantifiable improvements of biomarkers [3]. Lifestyle intervention alone is generally associated with moderate weight loss of around 5–7% that is gradually regained and yields a great proportion of poor responders [24]. Bariatric surgery is the most effective antiobesity management strategy characterized by average of 30–40% weight loss, but it comes at a cost of irreversibility, surgery-related complications and considerable percentage of late complications [2]. Until recently, the treatment gap existed in the therapeutic strategy to achieve ≥ 10 to ≥ 15% of weight loss, which leads to significant health benefits. GLP-1 RAs approved for weight management can fill this gap in a significant proportion of treated individuals.

It was previously noted in trials of other antiobesity medications that people with diabetes have more difficulty losing weight than individuals without diabetes, and differences between individuals with and without diabetes were consistently confirmed also for GLP-1RAs.

The underlying reasons for the weaker response for both GLP-1 RAs in people with diabetes compared to cohorts without diabetes are unclear, although there are some hypothetical explanations [1]. First, the concomitant medications that promote weight gain including sulfonyureas, insulin, beta-blockers and the fear of hypoglycaemia inherently related to the treatment of diabetes presumably reduce the efficacy of anti-obesity pharmacotherapy in diabetics. However, the background therapy and the fear of hypoglycaemia do not explain the differential effect of GLP-1 RA in patients treated with metformin or SGLP-2 inhibitors because these drugs do not promote hypoglycaemia or weight gain. Second, a decrease in glycusoria and subsequently less weight loss in patients with diabetes might also contribute the population-based difference in efficacy. Moreover, severely altered microbiome in patients with obesity and diabetes as well as a genetic background that predispose to weight gain in this population might also be considered as potential contributors [25]. Furthermore, people with type 2 diabetes may have had obesity for longer and be older than people with obesity in general and may be less adherent to exercise, which seems to potentiate the effects of GLP-1 RA. That may also explain some of the response differences [26]. Multimodal approaches combining peptides targeting receptors at different levels might therefore be of significant additional benefit in particular in patients with diabetes.

One limitation that could have impact on the inter-trial comparisons is that the studies with and without diabetes were not well balanced regarding sex and race [27]. While the STEP 2 trail included 51% female participants [22], the STEP 1, STEP 3 and STEP 4 trials included 73%, 81% and 79% female participants, respectively [15–17]. Thus, STEP 2 has a greater proportion of men (49.1%) than the other trials (19.0–25.9%). Given that it has been previously reported that females respond to GLP-1 RAs better than men, this limitation should be taken into consideration [28]. One reason for intersex difference is presumably related to exposure difference. Weight loss increased with greater exposure and appeared to level off at the highest exposures associated with GLP-1 RAs in most individuals, but did not fully plateau in men at the doses approved for weight management [29].

The variations in the race and ethnicity of participants across the trials could also have an impact on the differences in efficacy. STEP 1 and STEP 2 were designed to have Asians as at

least 10% of the population and have a greater proportion of Asians than the other trials [23]. The percentage of Caucasian participants in each study was 76%, 62%, 76% and 84% for the STEP 1–4 trials, respectively [15–17, 22]. Future additional studies should focus on different races and other minority populations.

The next important aspect to consider when interpreting the results of the SCALE and STEP trails is that all studies included lifestyle modifications as part of the protocol, and STEP 3 and SCALE IBT even included additional dietary restrictions and intensive behavioural therapy [13, 16]. Such engagement in lifestyle interventions may not always be representative of typical patient adherence in the general population and real-world data are needed.

Considering safety, additional adverse events of special interest were assessed in patients with diabetes. In the SCALE Insulin trial, fewer hypoglycaemic episodes were reported with liraglutide 3 mg than with placebo. Other adverse events of special interest were dehydration and renal impairment as consequences of nausea, vomiting or diarrhoea leading to volume depletion. The rates of these adverse events across SCALE and STEP trials were comparable between GLP-1 RAs and placebo. No new safety signals were identified comparing participants with diabetes to non-diabetic cohorts [29].

CONCLUSION

It is established that people with diabetes have more difficulty losing weight than individuals without diabetes and differences between individuals with and without diabetes were consistently confirmed also for GLP-1RAs. The mean weight loss difference between GLP-1 RAs and placebo in patients with diabetes was 4–6.2% compared to 6.1 up to 17.4% in individuals without diabetes. However, higher levels of weight loss of $\geq 15\%$ were achieved almost exclusively by participants with diabetes who received liraglutide or semaglutide, whereas this outcome has not been attainable by any other glucose-lowering intervention or with lifestyle intervention alone.

This observation is of clinical importance since loss of 15% or more of body weight can have a disease-modifying effect in people with diabetes. Some distinguished authors proposed that an existing and emerging anti-obesity pharmacotherapy should represent the new platform to implement a novel weight-centric primary treatment goal in people with diabetes, particularly at an early stage of the disease. A significant reduction in body weight should be seen as a target for treatment of type 2 diabetes [1]. A recently published study performed in the real-world setting complemented the data obtained from clinical trials and reinforced the benefits of liraglutide for obese patients with type 2 diabetes, showing beneficial actions on glycaemic parameters as well as cardiometabolic risk factors in both non-obese and obese patients with type 2 diabetes, with a greater efficacy in the latter [30]. The authors emphasized that this has a particular clinical relevance during the current pandemic, since patients with diabetes and obesity are exposed to the most severe forms of COVID-19, related complications and death; in addition, cardiometabolic complications have increased globally in the last 2 years because of the reduced access to healthcare facilities for patients with chronic diseases, such as those with diabetes and obesity [31]. Therefore, proper management of obese patients has to be prioritized.

In future, we encourage further research into individualisation of pharmacotherapy of obesity by exploring the differences in the weight loss by sex, race, concomitant therapies, effect of altered microbiota and genetic background. We also need to improve the ability to identify patients who respond better to weight loss and can lose at least 15% of their weight. The combined multimodal peptides that target GLP1-GIP receptors, will provide even more effective treatment than currently approved GLP-1 RA, in particular in patients with diabetes where the pathophysiology of obesity seems to be even more complex than in individuals without diabetes.

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