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The role of weight control in the management of type 2 diabetes mellitus: Perspectives on semaglutide

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ABSTRACT

Glucagon-like peptide-1 receptor agonists (GLP-1 RAs) are widely used to address multiple aspects of type 2 diabetes mellitus (T2DM) management, including glycaemic control, weight loss, and cardiovascular risk reduction. Semaglutide, a well-established GLP-1 RA approved for T2DM treatment and weight management, demonstrates marked efficacy in achieving these clinically important goals. The American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD) consensus report emphasizes the importance of a holistic approach to T2DM treatment, with weight control as a key component for improving patient outcomes. Notably, semaglutide is mentioned in the consensus report as having 'very high' efficacy for both glucose lowering and weight loss in T2DM treatment. Nevertheless, as has been observed with other weight-lowering drugs, weight loss observed with semaglutide appears less profound in individuals with T2DM than in those with obesity without T2DM, a phenomenon requiring further investigation. The semaglutide safety and tolerability profiles are well established, and it is approved in some countries to reduce cardiovascular risk in certain populations with T2DM. Thus, semaglutide offers a well-established therapeutic option that aligns well with guideline recommendations for T2DM management, emphasizing the high importance of weight control and amelioration of other cardiometabolic risk factors.

1. Introduction

Body weight is intricately linked with insulin resistance and glycaemic control in type 2 diabetes mellitus (T2DM)[1–5], and people with T2DM and overweight or obesity face increased risk of complications[6,7], including cardiovascular disease and liver disease[8] and microvascular disease such as kidney disease. Obesity, prediabetes, and T2DM constitute a disease continuum[5,9,10], and in people with obesity and prediabetes, weight loss reduces the risk of developing T2DM[11]. Weight loss has been shown to lead to remission of diabetes [12,13] and amelioration of a range of diabetes-related risk factors[14], illustrating how weight control constitutes a central part of T2DM care, aimed at reducing these risks and enhancing overall quality of life[15]. Importantly, as shown in the seminal Look AHEAD study, the greater the weight loss, the greater the health benefits, including on glycaemic control in diabetes[16].

In clinical practice, weight management in people with T2DM should adhere to official recommendations such those from the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD)[15]. The ADA/EASD consensus report outlines key strategies for weight control in T2DM, including lifestyle interventions, pharmacotherapy, and, in certain cases, bariatric surgery. Traditionally, the primary focus of the consensus report has been on comprehensive lifestyle management, which encompasses dietary modification, physical activity, and behaviour change. Arguably, with the most recent version of the report, a more holistic approach to diabetes care is recommended with equal emphasis on lifestyle management and on weight control to obtain better glycaemic control, as well as on management of cardiometabolic risk factors and cardiorenal protection.

Weight management in T2DM remains a multifaceted endeavour, which is usually personalized, reflecting the needs, preferences, and circumstances of each individual[15]. Bariatric surgery is recommended for patients with a body mass index (BMI) of 35 kg/m^2 or higher, who have not achieved significant weight loss through lifestyle interventions and pharmacotherapy, and who have serious weight-related comorbidities[15]. Bariatric surgery has been shown to achieve substantial and sustained weight loss[17], leading to improvements in glycaemic control, cardiovascular risk factors, and quality of life[18,19].

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Pharmacotherapy for weight management in T2DM can be considered when lifestyle interventions do not yield sufficient weight loss or when the individual has a high risk of comorbid conditions[15]. Medications are selected based on their ability to achieve weight loss and improve glycaemic control while minimizing side effects. The choice of medication is individualized, considering factors such as efficacy, safety, cost, side effects, and personal preferences.

The glucagon-like peptide-1 (GLP-1) receptor agonists (RAs) semaglutide and liraglutide are the only drugs currently approved for both glycaemic control management in people with T2DM[20–22] and for weight management in those with obesity or overweight[23,24]. However, their approvals for T2DM (liraglutide, s.c. semaglutide and oral semaglutide) do not include weight management in obesity/overweight (liraglutide and s.c. semaglutide), and vice versa.

Semaglutide is the only GLP-1 RA mentioned in the ADA/EASD consensus report as having 'very high' efficacy with regards to both weight loss and lowering of blood glucose in the treatment of people with T2DM[15]. Here, we provide a focused review of the effects of semaglutide in people with T2DM with emphasis on weight loss, selected cardiometabolic benefits, and safety and tolerability.

2. The biology and pharmacology of GLP-1

The exploration of gastrointestinal incretin hormones began with the discovery of secretin in 1902 by Starling and Bayliss[25], highlighting the hormonal regulation of duodenal secretion. This was followed by the identification of glucose-dependent insulinotropic polypeptide (GIP) in 1971[26,27], and GLP-1 (1–37) a decade later[28]. Jens Juul Holst and Joel Habener independently identified active insulinotropic forms of GLP-1, GLP-1 (7–37), and GLP-1 (7–36) amide in 1987[29,30] In addition to the effect on glucose-dependent insulin secretion, in 1996, GLP-1 was realised to impact appetite as well[31].

GLP-1 (7–37), a 31-amino-acid peptide secreted in response to meals and by certain central nervous system neurons, prompted substantial interest in drug discovery due to its pharmacological potential[32]. In its native form, GLP-1 has a short plasma half-life limiting its clinical applicability. This led to the development of GLP-1 analogues, including liraglutide, the first successful once-daily analogue, which demonstrated prolonged duration of action due to a C16 fatty-acid side chain attachment, promoting slow absorption and a plasma half-life of about 12 h [33,34].

Later efforts led to the creation of semaglutide, a once-weekly GLP-1 analogue with a longer fatty acid side chain and a spacer enhancing albumin binding[33,34]. An amino acid substitution in semaglutide protects it from dipeptidyl peptidase-IV (DPP-IV) mediated inactivation. Consequently, semaglutide exhibits high GLP-1 receptor potency, a plasma half-life of approximately one week, potential for oral availability, and a differential distribution in rodents compared to liraglutide in brain areas relevant for appetite regulation[35].

Early research emphasized the incretin effect of GLP-1 and GIP, underscoring their role in enhanced insulinotropic response to orally administered glucose. The incretin system is defective in T2DM[36], contributing to its characteristic aberrant glucose metabolism. However, the endocrine pancreas remains responsive to GLP-1 in T2DM, explaining how pharmacological stimulation of the GLP-1 receptor (GLP-1R) augments insulin secretion[37].

The presence of GLP-1R's across multiple tissues explains the pleiotropic impacts of GLP-1 beyond glucose metabolism. Monoclonal antibodies have been employed to more accurately establish GLP-1R's presence[38], confirming its location in the pancreas, heart, duodenum, arterial walls in the kidney and lung, and the brain. The presence of GLP-1R in areas of the brain associated with appetite regulation underscores the role of GLP-1R agonism in weight management[39,40].

Rodent studies have shown that semaglutide, like liraglutide, has limited access to the brain when administered peripherally and does not in general pass the blood–brain barrier[35,41]. However, semaglutide appears to act directly on distinct and accessible neurons in the hypothalamus and hindbrain involved in food intake and control, potentially regulating body weight by influencing appetite-modulating relay stations[35].

The major biological and pharmacological effects of GLP-1 and GLP-1 RAs with focus on glucose metabolism and weight management are summarised in Fig. 1. For further in-depth descriptions of the biology of GLP-1, readers are referred to a recent comprehensive review by Müller and colleagues[32].

3. SUSTAIN and PIONEER: Semaglutide in type 2 diabetes

Semaglutide was first developed as a once-weekly subcutaneous (s.c.) injection in the SUSTAIN programme[42–56] and later as a once-daily oral option in the PIONEER programme[57–66].

In the initial phase 3a SUSTAIN programme, dose levels 0.5 mg and 1.0 mg were tested in the multiple randomised clinical trials, which included the SUSTAIN 6 cardiovascular outcomes trial (CVOT) to document the cardiovascular safety of the compound[42]. The SUSTAIN FORTE[47] trial later tested the efficacy and safety of a higher dose level (2.0 mg once weekly) and other trials have evaluated the clinical effects of the drug across in various relevant populations and ethnicities [48,49,54]. In the PIONEER phase 3a programme comprising ten phase 3a trials, semaglutide at dose levels 3, 7 and 14 mg were given as once-daily doses as orally administered tablets. Recently, higher doses of oral semaglutide (25 and 50 mg) have been tested for the treatment of T2DM in the PIONEER PLUS trial[67] and for weight management in obesity in the OASIS trials, e.g., OASIS 1[68] as discussed below.

While not the primary objective of the SUSTAIN and PIONEER trials, these trials consistently demonstrated that semaglutide provides clinically meaningful weight loss in people with T2DM. However, although GLP-1 RAs are highlighted in the ADA/EASD consensus report with respect to both glycaemic control and lowering of body weight[15], once-weekly s.c. semaglutide for T2DM (Ozempic®) and once-daily oral semaglutide for T2DM (Rybelsus®) is currently not indicated to lower body weight in people with T2DM. A large randomised controlled trial (STEP 2) has been conducted to primarily study the weight-lowering effect of semaglutide in people with both T2DM and obesity or overweight as discussed below[69].

Selected key efficacy-related results from the SUSTAIN and PIONEER programmes are summarised in the next sections and in Table 1.

3.1. Weight loss

The change in body weight during the SUSTAIN trials was evaluated as secondary confirmatory outcomes[42–56]. Weight loss with the 1.0 mg dose of semaglutide was greater than with comparators and was up to 6.5 kg[52] after 40 weeks with up to around 63% of the trial participants achieving a clinically meaningful weight reduction of at least 5%[52]. The weight-reducing effect was greatest in people with higher BMI at trial entry but did not appear to depend on the age of the trial participants, time since diabetes diagnosis, or pre-existing treatments [70,71]. In the SUSTAIN FORTE trial testing a higher dose level of 2.0 mg for the T2DM indication, weight losses of 6.9 kg vs. 6.0 kg were observed with 2.0 mg and 1.0 mg once-weekly semaglutide s.c., respectively[47] In the PIONEER programme[57–66], oral semaglutide at up to 14 mg also produced clinically relevant weight loss (Table 1). The 68-week PIONEER PLUS trial with once-daily oral semaglutide 25 and 50 mg in people with T2DM found weight losses at week 52 of up to 7.0 kg and 9.2 kg, respectively, from a baseline body weight of 96.4 kg, which was superior to the weight loss observed for oral semaglutide 14 mg (4.5 kg)[67].

Real-world studies and pragmatic clinical trials from multiple regions and areas have corroborated the weight loss potential of semaglutide s.c. in people with T2DM beyond the setting of randomised controlled trials. The SURE programme comprised a range of

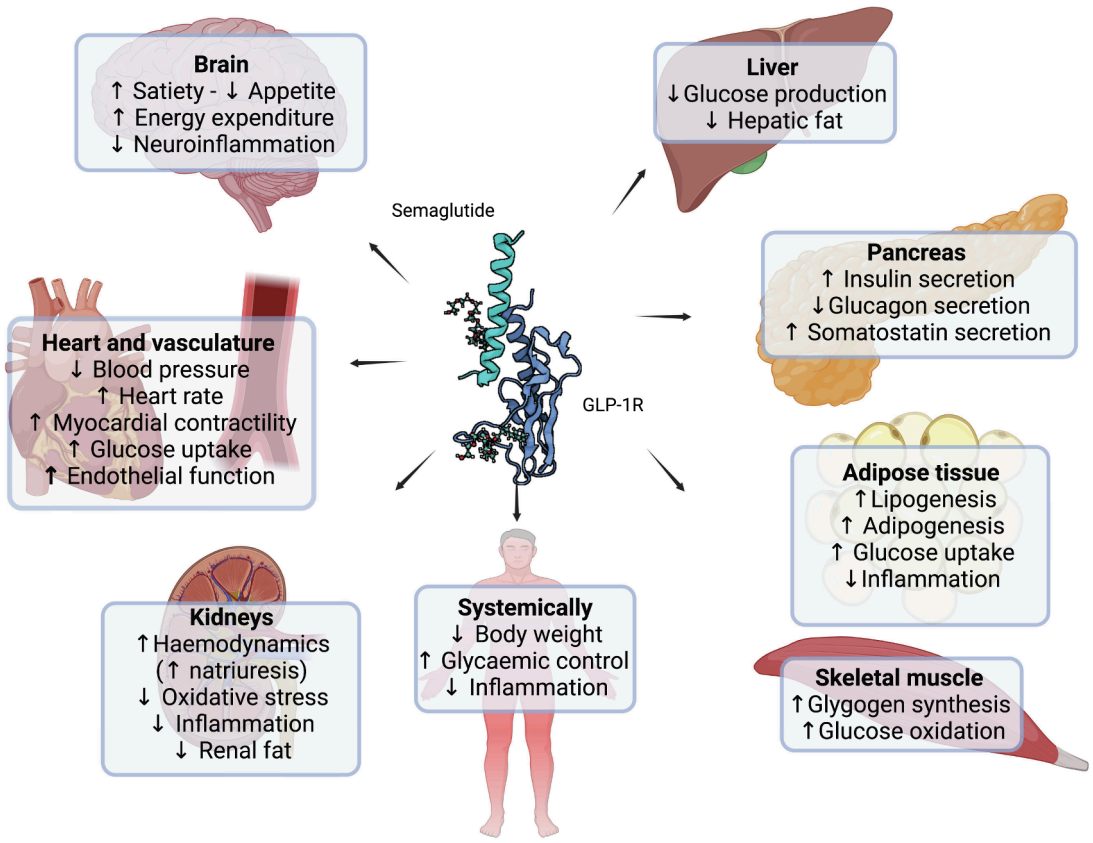

Fig. 1. The diabetes- and obesity-related effects of GLP-1. Native glucagon-like peptide 1 (GLP-1) and pharmacological analogues of the incretin hormone such as semaglutide have multiple biological effects across the human body[32]. The figure shows a selection of both well-established and potential effects with focus on those relevant in diabetes and obesity. Semaglutide is depicted bound to the extracellular domain of the GLP-1 receptor (GLP-1R) based on the crystal structure published as 4zgm. Created with BioRender.com.

observational studies to test the dose levels of once-weekly semaglutide s.c. indicated for use in T2DM[72–78]. For example, during the 30-week observation periods in the SURE UK[73] and SURE Germany studies [74], treatment of adults with T2DM led to statistically significant weight losses of 5.8 kg and 4.2 kg, respectively. Across the SURE studies, up to around 50% of the people observed achieved a clinically meaningful weight loss of at least 5%[72–78]. Year-1 results from the open-label, randomized, pragmatic SEPRA study[79] conducted in the United States in health-insured adults with T2DM showed a weight loss of 4.03 kg with once-weekly semaglutide s.c. compared with 2.36 kg with standard-of-care, which was mostly other GLP-1 RAs (71.3%) or SGLT-2 inhibitors (15.5%)[80].

3.2. Glycaemic control

The SUSTAIN programme showed significant improvements in glycaemic control in people with T2DM using the 1.0 mg dose of semaglutide, reducing HbA_{1c} by up to −1.8% (-19.4 mmol/mol), showing superiority vs comparators, and helping up to 80% of participants reach the recommended HbA_{1c} < 7.0% (<53 mmol/mol) goal[42–56]. Of note, these improvements were achieved without weight gain or severe hypoglycaemia. However, a need for further treatment intensification in people with advanced T2DM was later identified, leading to the conduct of the SUSTAIN FORTE phase 3b trial[47] This 40-week trial showed greater HbA_{1c} reduction with the 2.0 mg dose level than with 1.0 mg (-2.2 %-points vs. –1.9 %–points [–23.7 mmol/mol vs. −21.2 mmol/mol]), with the effect being consistent across baseline characteristics. Glycaemia-related results for oral semaglutide in the PIONEER trials were similar to the results in SUSTAIN][57–66].

4. STEP: Semaglutide in weight management

The phase 3a STEP development program supported the regulatory approval of semaglutide 2.4 mg for once-weekly s.c. injection for weight management in people with overweight and relevant comorbidities (BMI > 27 kg/m^2) or obesity (BMI > 30 kg/m^2)[81–88]. The programme included multiple phase 3a trials designed to evaluate the efficacy and safety of semaglutide 2.4 mg vs. placebo and other comparators across various populations and treatment regimens relevant to weight management. Semaglutide treatment was used in addition to supervised lifestyle changes.

Except for the STEP 2 trial[82], the STEP trials enrolled adult participants without T2DM but with overweight plus at least one weight-associated complication or with obesity. In STEP 2, participants had both T2DM and overweight or obesity, and this trial evaluated semaglutide at dose levels 1.0 and 2.4 mg in comparison with placebo.

In STEP 2, participants achieved an average weight loss of up to 10.6 kg at the end of the 68-week treatment period with semaglutide 2.4 mg [82]. In comparison, weight loss in those treated with semaglutide 1.0 mg or placebo was 7.5 and 3.1 kg, respectively. Thus, semaglutide 2.4 mg provided superior weight loss vs. both comparators in this population ($p < 0.0001$) and was also statistically significantly more likely than placebo in enabling participants achieving a ≥ 5 or ≥ 10% weight loss.

In the other STEP trials involving people without T2DM, the weight-loss potential of semaglutide was confirmed.

The results from STEP 1, particularly its extension part, highlight that obesity is a chronic disease and suggest that weight management is not a curative intervention but should be seen as a long-term endeavour. Lifestyle interventions, while important and required, can contribute only to a certain extent. This aspect is reflected in the ADA/EASD

Table 1
Selected key results from clinical trials with semaglutide in people with type 2 diabetes.

	SUSTAIN 1[45] **Monotherapy 30 weeks**	**SUSTAIN 7**[52] **H2H dulaglutide40 weeks**	**SUSTAIN FORTE**[47] **Higher dose s.c.40 weeks**	**PIONEER 1**[57] **Monotherapy26 weeks**	**PIONEER PLUS**[67] **Higher dose oral68 weeks**[a]	**STEP 2**[82] **Obesity and T2DM68 weeks**
Population	388 adults with T2DM	1201 adults with T2DM	961 adults with T2DM on metformin	703 adults with T2DM	1,606 adults with T2DM	1210 adults with overweight or obesity and T2DM
Semaglutide	0.5 and 1.0 mg OW s.c.	0.5 and 1.0 mg OW s.c.	2.0 mg OW s.c.	3, 7 and 14 mg OD oral	25 and 50 mg OD oral	2.4 OW s.c.
Comparator	Placebo	Dulaglutide0.75 and 1.5 mg	Semaglutide 1.0 OW s.c.	Placebo	Semaglutide 14 mg OD oral	Semaglutide 1.0 OW s.c. Placebo
BASELINE CHARACTERISTICS (total means [b])						
Age, years (SD)	53.7 (11.3)	56 (10.6)	58.0 (10.0)	55.0 (11.0)	58.2 (10.8)	55.0 (11.0)
Body weight, kg (SD)	91.9 (23.8)	95.2 (22.6)	99.3 (23.5)	88.1 (22.1)	96.4 (21.6)	88.1 (22.1)
Duration of diabetes, years (SD)	4.2 (5.5)	7.4 (5.7)	9.5 (6.2)	3.5 (4.9)	9.3 (6.2)	8.0 (6.1)
HbA_{1c}, % (SD)	8.1 (0.85)	8.2 (0.92)	8.9 (0.6)	8.0 (0.7)	9.0 (0.8)	8.1 (0.8)
HbA_{1c}, mmol/mol (SD)	64.5 (9.31)	66.4 (10.0)	73.3 (6.9)	63.0 (8.0)	74.4 (8.3)	65.3 (8.7)
Systolic blood pressure, mmHg (SD)	128–130 (13–14)	132–134 (14–15)	134 (14)	129–132 (14–16)	132–133 (14)	130 (14)
RESULTS AT STUDY END (estimated means)						
Body weight Change from baseline, kg	Sema 0.5 mg: −3.7* Sema 1.0 mg: −4.5*Placebo: −1.0	Sema 0.5 mg: −4.6* Sema 1.0 mg: −6.5*Dula 0.75 mg: −2.3 Dula 1.5 mg: −3.0	Sema 2.0 mg: −6.9* Sema 1.0 mg: −6.0	Sema 14 mg: −4.1* Sema 7 mg: −2.5* Sema 3 mg: −1.7Placebo: −1.5	Sema 50 mg: −9.2* Sema 25 mg: −7.0* Sema 14 mg: −4.5	Sema 2.4 mg: −10.6*[c] Sema 1.0 mg: −7.5 Placebo: −3.1
≥ 5% weight loss% of participants	Sema 0.5 mg: 37[#] Sema 1.0 mg: 45[#]Placebo: 7	Sema 0.5 mg: 44[#] Sema 1.0 mg: 63[#]Dula 0.75 mg: 23 Dula 1.5 mg: 30	Sema 2.0 mg: 59.2[#] Sema 1.0 mg: 51.3	Sema 14 mg: 44[#] Sema 7 mg: 29[#] Sema 3 mg: 21Placebo: 16	Sema 50 mg: 76[#] Sema 25 mg: 63[#] Sema 14 mg: 44	Sema 2.4 mg: 73.2[#c] Sema 1.0 mg: 59.2 Placebo: 27.6
≥ 10% weight loss % of participants	Sema 0.5 mg: 8[#] Sema 1.0 mg: 13[#]Placebo: 2	Sema 0.5 mg: 14[#] Sema 1.0 mg: 27[#]Dula 0.75 mg: 3 Dula 1.5 mg: 8	Sema 2.0 mg: 28.4[#] Sema 1.0 mg: 22.6	Sema 14 mg: 15.4[#] Sema 7 mg: 8.7[#] Sema 3 mg: 2.7 Placebo: 1.5	Sema 50 mg: 44[#] Sema 25 mg: 32[#] Sema 14 mg: 16	Sema 2.4 mg: 49.9[#c] Sema 1.0 mg: 29.7 Placebo: 7.1
HbA_{1c} Change from baseline, %-points	Sema 0.5 mg: −1.5* Sema 1.0 mg: −1.6*Placebo: −0.02	Sema 0.5 mg: −1.5* Sema 1.0 mg: −1.8*Dula 0.75 mg: −1.1 Dula 1.5 mg: −1.4	Sema 2.0 mg: −2.2* Sema 1.0 mg: −1.9	Sema 14 mg: −1.5* Sema 7 mg: −1.3* Sema 3 mg: −0.8* Placebo: −0.1	Sema 50 mg: −2.2* Sema 25 mg: −1.9* Sema 14 mg: −1.5	Sema 2.4 mg: −1.9* Sema 1.0 mg: −1.7 Placebo: −0.3
HbA_{1c} Change from baseline, mmol/mol	Sema 0.5 mg: −15.9* Sema 1.0 mg: −17.0* Placebo: −0.27	Sema 0.5 mg: −16.5* Sema 1.0 mg: −19.4* Dula 0.75 mg: −12.1 Dula 1.5 mg: −14.9	Sema 2.0 mg: –23.7* Sema 1.0 mg: −21.2	Sema 14 mg: −16.0* Sema 7 mg: −14.0* Sema 3 mg: −8.0* Placebo: −1.0	Sema 50 mg: –24.4* Sema 25 mg: −20.4* Sema 14 mg: −15.9	Sema 2.4 mg: −20.3* Sema 1.0 mg: −18.3 Placebo: −3.5
Systolic blood pressure Change from baseline, mmHg	Sema 0.5 mg: −2.6 Sema 1.0 mg: −2.7Placebo: −1.7	Sema 0.5 mg: −2.4 Sema 1.0 mg: −4.9Dula 0.75 mg: 2.2 Dula 1.5 mg: −2.9	Sema 2.0 mg: −5.3 Sema 1.0 mg: −4.5	Sema 14 mg: −5* Sema 7 mg: −4 Sema 3 mg: −4 Placebo: −2	Sema 50 mg: −6.3* Sema 25 mg: −5.6 Sema 14 mg: −4.3	Sema 2.4 mg: −4.5* Sema 1.0 mg: −3.3 Placebo: 0.3

* estimated change from baseline statistically significantly different ($p < 0.05$) from change with comparator(s). # estimated odds of achieving ≥ 5%/10% weight loss at end-of-treatment was statistically significantly higher than with comparator(s). a. The total duration of PIONEER PLUS was 68 weeks; results are the presented for week 52, which was the time point of the primary evaluation. b. for SUSTAIN 1, SUSTAIN 7, PIONEER 1 and PIONEER PLUS, baseline means for systolic blood pressure is mean range across treatment groups. c. versus both semaglutide 1.0 mg and placebo. Results at study end are estimates based on the trial product estimand (estimates based on data collected while on treatment with study medication and before any initiation of rescue medication). Dula, dulaglutide; H2H, head-to-head; OD, once-daily; OW, once-weekly; s.c., subcutaneous; SD, standard deviation; sema, semaglutide; T2DM, type 2 diabetes mellitus.

consensus report[15], which emphasizes that withdrawing treatment with semaglutide leads to increases in body weight, underlining the chronic nature of weight management in people with T2DM with and without obesity or overweight.

A higher semaglutide s.c. dose level of 7.2 mg once weekly is currently being tested in the ongoing STEP UP (ClinicalTrials.gov ID NCT05646706) and STEP UP T2DM (ClinicalTrials.gov ID NCT05649137) studies in people with obesity and without and with T2DM, respectively. In addition, data from the OASIS clinical development program indicate that once-daily oral semaglutide 50 mg can provide weight loss of magnitudes comparable to those seen with once-weekly semaglutide 2.4 mg in the STEP program[68], although this was not tested in people with T2DM in addition to obesity/overweight.

5. Management of cardiometabolic disease and risk factors

As mentioned in the beginning of this review, cardiovascular disease, including kidney disease, is a prevalent sequela of obesity and diabetes. Consequently, the mitigation of cardiovascular morbidity and mortality in individuals with obesity and diabetes hinges on effective weight reduction, enhanced glycaemic control, and comprehensive management of cardiometabolic risk factors such as increased waist circumference, inflammation, and blood pressure[14].

5.1. Cardiovascular safety and risk reduction

The cardiovascular safety of GLP-1 RAs, such as semaglutide, has been proven in large cardiovascular outcomes trials (CVOTs) in people

with T2DM[42,62,89–94]. The CVOTs also indicated that the GLP-1 RA drug class can reduce the risk of cardiovascular outcomes[95]. In certain countries, including the United States[96–98], once-weekly semaglutide and liraglutide are indicated to reduce the risk of major adverse cardiovascular events (MACE) in adults with T2DM and established cardiovascular disease, and once-weekly dulaglutide is indicated to reduce the risk of MACE in adults with T2DM and established cardiovascular disease or multiple cardiovascular risk factors. A *meta*-analysis by Sattar and colleagues reported that the GLP-1 RA drug class across eight completed CVOTs was associated with a relative reduction in the risk of MACE of 14% (hazard ratio [HR] 0.86; 95%CI: 0.80–0.93; $p < 0.0001$ vs placebo)[95]. The completed CVOTs for semaglutide in T2DM (SUSTAIN 6 for s.c. semaglutide 1.0 mg[42] and PIONEER 6 for oral semaglutide 14 mg[62]) were among the eight CVOTs analysed. In these two CVOTs, semaglutide (vs. placebo) reduced the risk of MACE by 21% to 26% (HR of 0.74 [95%CI: 0.58 to 0.95] and 0.79 [95%CI: 0.57 to 1.11] in SUSTAIN 6 and PIONEER 6, respectively).

In SUSTAIN 6, superiority vs. placebo was documented for s.c. semaglutide 1.0 mg ($p = 0.016$)[42]. Conversely, superiority vs. placebo was not shown for oral semaglutide 14 mg in PIONEER 6 ($p = 0.17$), which, like SUSTAIN 6, was designed as a pre-approval cardiovascular safety study and not powered to confirm a cardiovascular benefit of oral semaglutide[62] Analysing data from SUSTAIN 6 and PIONEER 6 together, semaglutide (s.c. or oral) was associated with a relative reduction in the risk of MACE of 24% (HR: 0.76; 95%CI: 0.62 to 0.92) [99].

In addition, additional CVOTs are ongoing to investigate potential cardiovascular benefits of semaglutide in people with T2DM and relevant comorbidities (SOUL[100], ClinicalTrials.gov ID NCT03914326) as well as in individuals with overweight or obesity and established cardiovascular disease but without T2DM (SELECT[101,102], ClinicalTrials.gov ID NCT03574597).

5.2. Cardiometabolic risk factors

Waist circumference, a key marker of visceral adiposity associated with poor T2DM and obesity outcomes[103–105], has been found to reduce with semaglutide treatment in some SUSTAIN trials and across the STEP trials. The reduction was statistically significantly greater with semaglutide than with placebo but lowest in STEP 2, i.e., in people with obesity/overweight and T2DM.

For hypertension, a cardiometabolic risk factor associated with T2DM, trials with semaglutide, including the SUSTAIN trials, have consistently shown reductions in systolic and diastolic blood pressure (SBP and DBP). A post-hoc analysis of data from SUSTAIN 1–5 showed that although greater weight reduction was associated with greater SBP reduction, the SBP reduction was driven by mechanisms not directly dependent on weight loss[106]. Blood pressure reductions have also been documented for semaglutide in the PIONEER and STEP programmes[107].

Inflammation is central to the pathophysiology of diabetes and obesity, and systemic inflammation is a risk factor associated with cardiometabolic diseases[108], including T2DM and cardiovascular disease [109]. Semaglutide has been found to reduce blood levels of C-reactive protein (CRP), a surrogate for systemic inflammation. Post-hoc analysis of select SUSTAIN and PIONEER trials suggested that the effect of semaglutide on CRP levels appears to be driven by reductions in HbA_{1c} and body weight, but also potentially by a direct effect of semaglutide [110]. An evaluation of the STEP 1, 2, and 3 trials demonstrated that semaglutide reduced CRP levels irrespective of baseline HbA_{1c} levels or BMI in participants with obesity or weight and T2DM[111]. However, in the STEP 2 trial, the placebo-adjusted reduction in CRP levels was not statistically significant[111].

Poor kidney function is closely associated with obesity and T2DM, and diabetes is a key underlying cause of chronic kidney disease[112]. Clinical trials with GLP-1 RAs, including semaglutide, have shown that the drug class can reduce the risk of kidney outcomes[95,112]. Notably, the glycaemic efficacy of semaglutide is retained in people with very low kidney function, and evidence suggests a potential benefit of semaglutide on kidney function, which will be studied in the FLOW kidney outcomes study (Clinicaltrials.gov ID NCT03819153) and in the mechanisms-of-action trial REMODEL (Clinicaltrials.gov ID NCT04865770), both in people with T2DM and CKD. The positive effects of GLP-1 RAs on kidney function are believed to be driven by improvements in glycaemic control, reductions in systemic inflammation, and other indirect weight loss-related benefits such as reduced intrarenal pressure and general blood pressure reductions[112]. Improved kidney function has been shown across the development programs for semaglutide in T2DM and weight management[113–116]. Whereas GLP-1 RAs are mentioned in recent treatment guidelines as a therapeutic option in people with T2DM and reduced kidney function[117,118], it is not currently indicated to improve kidney function.

6. Safety and tolerability

The SUSTAIN and PIONEER development programmes established the safety and tolerability profiles of s.c. semaglutide at doses of 0.5, 1.0, and 2.0 mg, and oral semaglutide at doses of 3, 7, 14, 25, and 50 mg, respectively, in people with T2DM[42–67]. The profiles for semaglutide s.c. 2.4 mg once weekly in weight management were established in the STEP programme[81–88]. The safety and tolerability profiles of semaglutide across all indications have since been corroborated through real-world clinical data, encompassing>9.5 million person-years of exposure (Novo Nordisk, *data on file*). These and all additional evidence collected in the future will contribute to further increasing the understanding of the long-term benefits and risks of semaglutide.

Regulatory labels describe the current evidence supporting the well-established safety and tolerability profiles of semaglutide[20,22,24]. Notably, the safety and tolerability of semaglutide 2.4 mg in weight management as observed in the STEP studies[24] are similar to those established in the SUSTAIN and PIONEER programmes[20,22]. In specific populations, such as the elderly or those with kidney disease, the safety and tolerability of semaglutide may vary and can require careful consideration[20,22,24].

The clinical use of s.c. or oral semaglutide, regardless of the dose, is predominantly associated with gastrointestinal side effects, particularly nausea and vomiting[42-66,81-88]. These side effects are usually transient, easy to manage, and can be mitigated through dose-escalation regimens, which improve the gastrointestinal tolerability of all marketed GLP-1 RAs[20,22,24]. Of note, weight loss with semaglutide is considered a direct effect and was not associated with nausea or vomiting in the SUSTAIN programme[119]. Semaglutide is associated with a risk of hypoglycaemia; however, due to the glucose-dependent mode-of-action of semaglutide, the risk is relatively small compared to other diabetes treatments such as insulin and can be lowered by reducing the dose of insulins and insulin secretagogues such as sulfonylureas when initiating semaglutide. Other warnings and precautions related to the treatment with semaglutide across indications are mentioned in the respective labels[20,22,24]. Lastly, as discussed earlier, the cardiovascular safety of semaglutide has been thoroughly documented and established [95,120,121].

7. Considerations and future perspectives

GLP-1 receptor agonists generally, and semaglutide in particular as the arguably most effective compound of the drug class, provide an opportunity to lower body weight while at the same time correcting elevated blood glucose level in people with T2DM[69,81]. Moreover, the effects of semaglutide on blood glucose and body weight are associated with reduction of cardiovascular risk as confirmed in SUSTAIN 6 [42], indicated in PIONEER 6[62] and further explored in ongoing investigations such the SOUL[100] and SELECT[101,102] CVOTs.

Semaglutide, as well as other GLP-1 RAs such as dulaglutide and liraglutide, are indicated to improve glycaemic control in people with T2DM[32]. Although semaglutide in addition is indicated for weight management in individuals with obesity or overweight, this explicit indication does not extend to weight management in those with T2DM. Nevertheless, the potential of GLP-1 RAs, including semaglutide, for facilitating weight control in people with T2DM is highlighted in the recent ADA/EASD consensus report[15], reflecting an increasing acknowledgment of the pleiotropic metabolic benefits of the drug class.

It remains to be fully understood why body weight loss realized following treatment with semaglutide in people with T2DM and obesity or overweight tend to be lower than in those without T2DM as discussed earlier[82]. The biological basis for this difference is incompletely understood, but it is generally believed that the blood-glucose-lowering effect of GLP-1 RAs, leading to less glucose loss via the urine, may result in a relative energy retention, which can attenuate weight loss [122]. Furthermore, the presence of insulin resistance could potentially enhance fat storage in the body. Concurrent use of other medications for T2DM, such as insulin or sulfonylureas, known to promote weight gain, may also impede the weight loss effect. The dysfunction of pancreatic β cells central to T2DM might also impact the response to GLP-1 RAs. Additionally, alterations in metabolic rate and energy expenditure, commonly seen in T2DM, could affect the effectiveness of weight loss interventions. Despite individual differences, these factors collectively could explain why weight loss with semaglutide tends to be lower in those with T2DM compared to those without[82].

With the aim of finding new and more effective therapies that target excess both blood glucose and body weight, it would be helpful to fully comprehend the underlying parameters that limit the weight loss in the diabetic population. However, while understanding mechanisms may be one approach towards better therapies, another avenue would be to move from monotherapy to combination therapy, taking advantage of complementary pharmacological actions of semaglutide and other molecular principles either as hybrid molecules or as combinations made possible by pharmaceutical formulation. An example of a hybrid molecule is tirzepatide, which has very recently entered the market[123] Tirzepatide has been designed to combine the effects of GLP-1 and GIP receptor agonism to maximize the efficacy of the two incretins [123,124]. Tirzepatide has shown convincing effects in T2DM in the SURPASS phase 3 programme[125,126] and is being developed for weight management[127] (SURMOUNT programme) and other indications such as cardiovascular risk (ClinicalTrials.gov ID NCT04255433). Another approach has been to combine GLP-1 receptor agonism (semaglutide) with amylin receptor agonism (cagrilintide, a long-acting amylin analogue). In a 32-week phase 2 study, this 'Cagri-Sema' combination option provided an additive weight-lowering effect in people with T2DM and overweight/obesity (weight loss of up to 15.6%)[128], and is currently progressing through clinical trials (e.g., REDEFINE 1 in weight management, Clinicaltrials.gov ID NCT05567796).

Whereas semaglutide is the most effective GLP-1 receptor agonist at this time, future research may further improve weight loss and glucose lowering mediated via the GLP-1 receptor. One approach to potentially facilitate greater efficacy could be design of receptor agonists resulting in biased signalling downstream of the GLP-1 receptor[129,130]. While such research is ongoing, a variety of GLP-1 derived combination options for the treatment of diabetes are likely to appear to provide people with T2DM with the greatest possible weight loss while bringing blood glucose concentrations to near normal levels.

Author contributions

All authors contributed equally to the preparation of this article. All authors approved the final article.

Declaration of Competing Interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: Peter Kurtzhals reports a relationship with Novo Nordisk AS that includes: employment and equity or stocks. Frederik Flindt Kreiner reports a relationship with Novo Nordisk AS that includes: employment and equity or stocks. Rubdeep Singh Bindra reports a relationship with Novo Nordisk AS that includes: employment and equity or stocks.

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