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Novel pharmacotherapies for weight loss: Understanding the role of incretins to enable weight loss and improved health outcomes

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Abstract

Obesity and type 2 diabetes mellitus (T2D) are widespread diseases that significantly impact cardiovascular and renal morbidity and mortality. In the recent years, intensive research has been performed to assess the role of adipose tissue and body fat distribution in the development of metabolic and non-metabolic complications in individuals with obesity. In addition to lifestyle modifications, glucagon-like peptide-1 receptor agonists (GLP-1-RA) have become a meaningful treatment expansion for the management of both disorders. In addition to improving metabolic control and reducing body weight, treatment with GLP-1-RAs reduces cardiovascular and renal events in individuals with obesity with and without diabetes. These important benefits of GLP-1-RAs have triggered new interest in other enteroendocrine and enteropancreatic peptides for treating obesity and its metabolic and non-metabolic consequences. The first peptide dual-agonist targeting glucose-dependent insulinotropic polypeptide (GIP) and GLP-1 receptors has been approved for the treatment of T2D and obesity. GIP/GLP-1 dual-agonism appear to provide better metabolic control and greater weight reduction compared with GLP-1-R mono-agonism. Other peptide and non-peptide co-agonists are in clinical development for obesity, T2D, metabolic dysfunction-associated steatotic liver disease (MASLD) and other metabolic disorders. This narrative review aims to summarize the available data on approved and emerging enteroendocrine and enteropancreatic based treatment approaches for obesity and metabolic disorders. In addition to available clinical efficacy measures, side effects, limitations and open challenges will also be addressed.

KEYWORDS
adipocytes, co-agonists, incretins, obesity

Plain Language Summary

All over the world, obesity developed to a fast-growing healthcare challenge, driving numerous serious complications like type 2 diabetes mellitus, fatty liver disease, cardiovascular disease, heart

failure, obstructive sleep apnoea, several malignancies and others. Recent intensive research provided a much better understanding about the function and physiology of adipose tissue and the molecular pathways linking increased body weight with the obesity related complications. Although lifestyle modifications with dietary modifications and an increase in physical activity represent the backbone in the treatment of obesity, they most often fail to preserve significant body weight reduction over longer time periods. Numerous enteroendocrine peptides released from different gut cells have been identified to play an important role in postprandial metabolism and energy balance. Some of these peptides are now under preclinical or clinical investigation for the treatment of obesity and related metabolic disorders. Activation of the classical incretin receptors glucagon like peptide 1 receptor (GLP-1-R) and the glucose dependent insulinotropic peptide receptor (GIP-R) was shown to exert beneficial effects on glucose control, lipid profile, body weight and to modify adipocyte function. Several GLP-1 receptor agonists and a first dual incretin receptor agonist (GIP and GLP-1) have been approved for the treatment of type 2 diabetes mellitus and obesity. In a huge number of clinical studies, these incretin receptor agonists were shown to improve glucose metabolism and decrease body weight in obese subjects with and without type 2 diabetes mellitus. In addition, an improvement in the overall cardiovascular risk profile and a decrease in cardiovascular morbidity and mortality could be demonstrated in these patient populations. Other studies were able to prove beneficial effects on liver fat content and fibrosis, renal function, heart muscle contractility, or in patients with obstructive sleep apnoea. Beside these classical incretins other enteroendocrine peptides like glucagon, amylin, peptide YY, ghrelin, and others have achieved increasing scientific attention as potential candidates for the treatment of obesity and its metabolic and non-metabolic complications. Numerous pre-clinical and clinical studies are under way to investigate the effects of these peptides or the combinations of them for the treatment of obesity and its complications. In addition to the peptide-based receptor agonists, small molecules to interfere with peripheral and central incretin receptor signalling are under development. With all these beneficial and promising clinical effects in mind, there are several side effects and limitations which need to be addressed. Gastrointestinal side effects are more or less common with all incretin based treatment approaches. Careful and slow dose titration can help to minimize these gastrointestinal adverse side effects and to improve the adherence of the patients. Another important limitation is loss of muscle mass in association with overall weight loss. Intensification of physical activity and enriching the daily dietary protein uptake can help to counteract the loss of muscle tissue. New enteroendocrine based treatment approaches with less negative effects on muscle mass are under clinical investigation. Even all available data on the incretin-based treatments indicate a good safety profile, further long-term safety vigilance data are required, especially for the newer drug entities. [Plain language summary added 28 February 2025, after original online publication].

1 | BACKGROUND/INTRODUCTION

Overnutrition, leading to obesity and its medical consequences, has created significant global healthcare challenges. Obesity and changes in fat tissue distribution and function worsen metabolic control, leading to insulin resistance, poor glucose control, dyslipidaemia, hypertension and metabolic dysfunction-associated steatotic liver disease (MASLD)[1–4] Altogether increasing the risk of cardiac and renal complications in this population. Additionally, obesity appears to be associated with an augmented incidence in certain types of cancers.[5–7]

Sustained overnutrition with weight gain increases overall fat mass and alters fat distribution and function. White adipose tissue (WAT) in the subcutaneous space is a crucial space for energy storage, acting as a buffer for circulating lipids. It plays a role in maintaining energy balance and systemic insulin sensitivity.[8] In the postprandial state, adipocytes in WAT absorb non-esterified fatty acids (NEFAs) from circulation and store them as triglycerides after re-esterification.[9,10] The enzyme lipoprotein lipase (LPL), located in the vascular wall of WAT capillaries drives NEFAs uptake in adipocytes by hydrolysing triglycerides in chylomicrons and other lipoproteins. The activity of LPL and uptake of NEFAs from the circulation into adipocytes is regulated by insulin, which at the same time inhibits lipolysis and NEFAs release from the adipocytes into the circulation. During starvation, NEFAs are released from WAT adipocytes by hormone-sensitive lipases (HSL) and adipose tissue triglyceride lipases (ATGL). The ability of adipocytes in WAT to reverse from lipid storage in case of feed to lipid delivery in case of starvation demonstrates its important role in lipid buffering and energy homeostasis.[11] In response to ongoing overnutrition and

positive energy balance, WAT has an immense potential to increase lipid storage through adipocyte hyperplasia and hypertrophy. Adipocyte hypertrophy is thought to represent the primary mechanisms for increasing lipid storage capacity, which is associated with adipocyte apoptosis and proinflammatory responses.[12,13] In the context of long-lasting overnutrition, the lipid storage capacity of WAT is exceeded, and a spillover of NEFA's results in triglyceride storage in the visceral compartments and in the form of intracellular ectopic fat in the liver, myocardium, pancreas, skeletal muscle and other tissues.[14–18]

2 | GLP-1 AND GIP

Over the last two decades, the interest in the roles of enteroendocrine and enteropancreatic peptides in postprandial metabolic control and energy homeostasis has tremendously increased. An overview of key enteroendocrine and enteropancreatic peptides and potential modes of action is summarized in Table 1. Pharmacological interest in these peptides raised with the discovery of incretins, which are defined as peptides released from the gut to amplify insulin release from the beta cell in response to a meal.[16,19] The most intensively studied incretins are glucose-dependent insulinotropic polypeptide (GIP) and glucagon-like peptide (GLP-1). Both peptides are insulinotropic, activating their respective receptors on beta-cell surfaces and increase the release of insulin in a strictly glucose-dependent matter. GIP and GLP-1 together account for more than 60% of insulin released from the beta cells in response to food ingestion.[20] In healthy individuals, GIP has a stronger insulinotropic effect than GLP-1.[21] In people with T2D, the effect of GIP is blunted but can be partially restored by normalizing glucose levels or administering supra-physiological levels of GLP-1.[22,23] In addition to the insulinotropic effects, GLP-1 exerts glucagonostatic effects during rising glucose levels, while GIP augments the glucagon release from the alpha cells during low glucose concentrations.[24,25]

Along with their effects on alpha and beta cells in the pancreas, incretins modulate the neuroendocrine gut-brain axis with an increase in satiety and a reduction in food intake. While GLP1 evolves anorexic effect by stimulation of subcortical receptors in the brainstem, the effect of GIP appears to be more complex. Thus, short-term GIP infusion has only minor effects on food intake, whereas long-term GIP activation reduces food intake and body weight.[26–30] Animal studies have shown that long-acting GIPR agonists equally decrease food intake in wildtype and GLP-1R KO mice, but the ability of GIP to suppress food intake vanishes in mice with loss of GIPR in either the CNS or more specifically in GABAergic neurons.[31,32] GLP-1 and GIP both exhibit anorexic effects in the area postrema, nucleus tractus solitarius, hypothalamus, amygdala and mesolimbic reward system.[31,33]

The effect of GLP-1 in adipose tissue physiology remains elusive. While some studies indicated GLP-1 induced adipocyte differentiation and lipogenesis,[34–36] other studies could not show effects of GLP-1 on adipocyte function in the WAT.[37–39] Unlike GLP-1, GIP plays an important role in postprandial triglyceride clearance and storage in the subcutaneous WAT. It increases adipose tissue blood flow via vasodilation and capillary recruitment.[40] In the presence of insulin, GIP activates LPL in the vascular wall and enhances the uptake and storage of NEFAs in adipocytes.[41–43] GIP increases the energy storage capacity by de novo adipogenesis, expands WAT's ability to store excess energy and reduces the spillover of triglycerides to ectopic fat depositions.[13,14] Peroxisome proliferator-activated receptor γ (PPARγ) is a master regulator of WAT triglyceride storage, and the GIPR is known as a downstream target of PPARγ.[44,45] By increasing insulin sensitivity in the WAT, GIP improves postprandial glucose and triglyceride uptake in adipocytes.[46,47]

In addition to these classical incretin hormones, several other enteroendocrine and enteropancreatic peptides have gained attention as potential candidates to address obesity and metabolic disorders (Table 1).

TABLE 1 Sources of enteroendocrine and enteropancreatic peptides and their main metabolic effects.

	GLP-1	GIP	PYY_{3-36}	Glucagon	Amylin
Source	L-cells	K-cells	L-cells	Alpha cells	Beta cells
Receptor	GLP-1-R	GIP-R	Y2R	Peptide YY	CTR, AMYR
Effect on glucose levels	Decrease	Decrease	No proven effect	Increase	Decrease
Glucagon release from alpha cells	Suppression during high glucose levels	Augmented during low glucose level	No proven direct effect	No proven direct effect	Suppression during high glucose levels
Insulin release from beta cells	Augmented during high glucose levels	Augmented during high glucose levels	No proven direct effect	Augmented during high glucose levels	No proven direct effect
Anorexigenic effects	Central neuronal pathways	Central neuronal pathways	Central neuronal pathways	Liver vagus cns signalling	Central neuronal pathways
Energy expenditure	No proven direct effect	No proven direct effect	No proven direct effect	Increases energy expenditure	No proven direct effect
Stomach motility	Decrease	No Proven Direct Effect	Decrease	Decrease	Decrease

3 | GLUCAGON

Glucagon is a 29-amino acid peptide released from the alpha cells within the islets of Langerhans. Although glucagon receptors are predominately found on liver cells, they are also expressed in beta cells, where they increase insulin secretion at high glucose concentrations.[48–51] After being released into the portal vein, glucagon reaches its main target, the liver and increases hepatic glucose output by enhancing glycogenolysis and gluconeogenesis.[50,52] Glucagon increases satiety and reduces food intake by activating the liver-vagus-hypothalamic axes.[53] Unlike GLP-1 or GIP, glucagon increases resting energy expenditure and stimulates beta-oxidation of fatty acids in the liver.[54–58] Glucagon increases LDL receptor expression and enhance hepatic cholesterol uptake and degradation.[59–61]

4 | AMYLIN

Amylin is a 37-amino acid peptide co-secreted with insulin from beta cells. Amylin exerts its clinical effects by stimulating the calcitonin receptor and three different amylin receptors that are most abundant in the area postrema and the arcuate nucleus of the hypothalamus.[62–65] In addition to increasing satiety and reducing food intake, amylin inhibits glucagon release and reduces gastric motility.[62,64,66]

5 | PEPTIDE YY (PYY)

Neuropeptide Y (NPY) and peptide YY (PYY) both 36-amino acids are members of the NPY family that bind to G protein-coupled Y receptors in the central nervous system and modulate eating behaviour.[67–69] PYY is released from L-cells in the intestinal mucosa of the ileum and large intestine.[70] The full-length $PYY_{1\text{-}36}$ is processed by dipeptidyl peptidase IV (DPPIV) to form $PYY_{3\text{-}36}$, which binds to the neuropeptide Y2 receptor (Y2R) within the hypothalamic arcuate nucleus.[71–73] Stimulation of Y2R produces anorexic effects by increasing satiety through pro-opiomelanocortin neurons in the hypothalamus. PYY inhibits gastric emptying as well as jejunal and colonic motility.[70,72]

6 | GHRELIN

Ghrelin is an enteroendocrine 28 – amino acid peptide produced in the oxyntic glands of the gastric fundus.[74,75] Ghrelin is known as the hunger hormone, as its blood concentration increases with starvation.[76,77] Ghrelin modulates metabolism via obesogenic signalling in the hypothalamic arcuate nucleus and specific growth hormone-releasing neurons.[78,79] Ghrelin stimulates gastric motility, acid secretion[80] and taste sensation[81,82]; suppresses brown fat thermogenesis[83,84]; and inhibits muscle atrophy.[85,86] Ghrelin exists in the human body in two forms, unacylated ghrelin and acylated ghrelin, the latter being the biologically active form. Activation of unacylated ghrelin to acylated ghrelin by the enzyme ghrelin-O-acyltransferase (GOAT) is essential for the biological effects of ghrelin.[87,88]

7 | APPROVED INCRETIN-BASED TREATMENTS FOR OBESITY

7.1 | GLP-1 receptor agonists

GLP1-RAs have been initially introduced as agents for the treatment of patients with T2D, in whom they have been shown to improve glucose control, reduce body weight and lower the risk of cardiovascular and renal complications.[89] In the meantime, liraglutide and semaglutide have also been approved for the treatment of obesity.[90]

7.2 | Liraglutide

The impact of liraglutide on weight loss and metabolic control in individuals with obesity has been investigated in clinical trials in the SCALE (Satiety and Clinical Adiposity – Liraglutide Evidence in individuals with and without diabetes) study programme (Table 2).[91] In adults with obesity, treatment with liraglutide 3.0 mg significantly decreased body weight after 56 weeks by −8.4 kg compared with placebo with −2.8 kg.[92] In the liraglutide treatment group, 63.5% compared with 27.1% in the placebo group lost more than 5% body weight, and 33.1% in the liraglutide group compared with 10.6% in the placebo group lost more than 10% of their body weight. In overweight or obese subjects with prediabetes, treatment with liraglutide 3.0 mg over 160 weeks reduced body weight by −6.1 kg compared with −1.9 kg in the placebo group.[93] In the liraglutide group, 49.6% compared with 23.7% in the placebo group lost more than 5% body weight and 24.8% in the liraglutide group compared with 9.9% in the placebo group lost more than 10% of their body weight. Patients on liraglutide treatment achieved significant improvements in glycaemic control, systolic blood pressure,[93,94] triglycerides[94] and high-sensitivity C-reactive protein.[93] Over a 3-year treatment period, liraglutide (3.0 mg) delayed the onset of diabetes by 79%.[93] Fifty-two weeks of liraglutide 1.8-mg treatment was associated with improvements in glucose tolerance, fasting plasma glucose (FPG), glycated haemoglobin (HbA1c) and body weight in women with previous gestational diabetes.[95] Liraglutide was superior to placebo in reducing weight in a population of adolescents with obesity, with or without T2DM.[96]

7.3 | Semaglutide

The effects of semaglutide on body weight and clinical outcomes were investigated in the STEP (Semaglutide Treatment Effect in People with Obesity) study programme (Table 3). In the STEP 1 study, in individuals with obesity without T2DM, treatment with semaglutide 2.4 mg combined with lifestyle interventions over 68 weeks

TABLE 2 Weight-related outcomes from the clinical trials of liraglutide.

Study (study length)	Study design	Population	Treatment (*n*)	Weight-related endpoints
Without T2D				
SCALE Obesity and Prediabetes (56 weeks)[92]	Phase 3, randomized, double-blind, placebo-controlled, international	Patients with a BMI of ≥30 kg/m^2 or ≥27 kg/m^2 with dyslipidaemia or hypertension	LIRA 3.0 mg (2487) PL (1244)	LIRA versus PL Change in BW: −8.4 versus −2.8 kg (p < 0.001) ≥5% loss of BW: 63.2% versus 27.1% (p < 0.001) ≥10% loss of BW: 33.1% versus 10.6% (p < 0.001)
SCALE Obesity and Prediabetes (160 weeks)[93]	Phase 3, randomized, double-blind, placebo-controlled, international extension	Patients with a BMI of ≥30 kg/m^2 or ≥27 kg/m^2 with dyslipidaemia or hypertension with prediabetes at screening (HbA1c 5·7–6·4% and/or FPG 5·6–6·9 mmol/L and/or 2-hr post-challenge plasma glucose 7·8–11·0 mmol/L)	LIRA 3.0 (1505) PL (749)	LIRA versus PL Change in BW: −6.1 versus −1.9 kg (p < 0.0001) ≥5% loss of BW: 49.6% versus 23.7% (p < 0.0001) ≥10% loss of BW: 24.8% versus 9.9% (p < 0.0001)
Kim et al. 2013 (14 weeks)[94]	Phase 3, randomized, double-blind, placebo-controlled, US only	Patients with a BMI of 27–40 kg/m^2 with prediabetes (FPG 5.6–6.9 mmol/L or 2-hr glucose 7.8–11.0 mmol/L after a 75 g oral glucose challenge)	LIRA 1.8 mg (24) PL (27)	LIRA versus PL Change in BW: −6.8 versus −3.3 kg (p < 0.001) ≥5% loss of BW: 88% versus 22% (p < 0.001) ≥10% loss of BW: 17% versus 0% (p < 0.04)
With T2D				
SCALE Diabetes (56 weeks)[199]	Phase 3, randomized, double-blind, placebo-controlled, international	Patients with a BMI of ≥27 kg/m^2 with T2D (HbA1c 7–10%) treated with diet ±1–3 and oral glucose-lowering agents	LIRA 3.0 mg (423) LIRA 1.8 mg (211) PL (212)	LIRA 3.0 and 1.8 versus PL Change in BW: −6.0% and −4.7% versus −2.0% (p < 0.001, all LIRA vs. PL) ≥5% loss of BW: 54.3% and 40.4% versus 21.4% (p < 0.001, all LIRA vs. PL) >10% loss of BW: 25.2% and 15.9% versus 6.7% (p < 0.01, all LIRA vs. PL)
SCALE Insulin (56 weeks)[200]	Phase 3, randomized, double-blind, placebo-controlled, international	Patients with a BMI of ≥27 kg/m^2 with T2D (HbA1c 6–10%) treated with basal insulin and ≤ 2 oral glucose-lowering agents	LIRA 3.0-mg plus intensive behavioural therapy (198) PL plus intensive behavioural therapy (198)	LIRA versus PL Change in BW: −5.8% versus −1.5% (p < 0.0001) ≥5% loss of BW: 51.8% versus 24.0% (p < 0.0001) >10% loss of BW: 22.8% versus 6.6% (p < 0.0001)
With or without T2D				
Kelly et al. 2020 (56 weeks)[96]	Phase 3, randomized, double-blind, placebo-controlled, international	Adolescents aged 12 to <18 years with a BMI ≥30 kg/m^2 or within the 95th or higher percentile for age and sex and a poor response to lifestyle therapy alone	LIRA 3.0 mg (125) PL (126)	LIRA versus PL Change in BW: −2.3 versus 2.3 kg ≥5% reduction in BMI: 43.3% versus 18.7% ≥10% reduction in BMI: 26.1% versus 8.1%

Abbreviations: BMI, body mass index; BW, body weight; FPG, fasting plasma glucose; HbA1c, glycated haemoglobin; LIRA, liraglutide; PL, placebo; SCALE, satiety and clinical adiposity-liraglutide evidence in nondiabetic and diabetic individuals; T2D, type 2 diabetes; US, United States.

decreased body weight by −14.9% compared with −2.4% with placebo.[97] In the liraglutide treatment group, 86.4% compared with 31.5% in the placebo group lost more than 5% body weight, and 69.1% liraglutide treated subjects versus 12.0% placebo treated subjects reduced more than 10% of their body weight. In the STEP 3 study, with an identical study design as STEP 1, but only performed in the United States, treatment with semaglutide 2.4 mg over 68 weeks reduced body weight by −16.0% compared with −5.7% in the placebo group.[98] In the semaglutide group, 86.6% compared with 47.6% in the placebo group lost more than 5% body weight, and

TABLE 3 Weight-related outcomes from the clinical trials of semaglutide.

Study (study length)	Study design	Population	Treatment (*n*)	Weight-related endpoints
Without T2D				
STEP 1 (68 weeks)[97]	Phase 3, randomized, double-blind, placebo-controlled, international	Patients with ≥1 self-reported unsuccessful diet attempt and a BMI of ≥30 kg/m^2 or ≥ 27 kg/m^2 with ≥1 weight-related comorbidity	SEMA 2.4 mg (1306) PL (655)	SEMA versus PL Change in BW: −14.9% versus −2.4% (p < 0.001) ≥5% loss of BW: 86.4% versus 31.5% (p < 0.001) ≥10% loss of BW: 69.1% versus 12.0% (p < 0.001)
STEP 3 (68 weeks)[98]	Phase 3a, randomized, double-blind, placebo-controlled, US only	Patients with ≥1 self-reported unsuccessful diet and a BMI of ≥30 kg/m^2 or ≥27 kg/m^2 with ≥1 weight-related comorbidity	SEMA 2.4 mg (407) PL (204)	SEMA versus PL Change in BW: −16.0% versus −5.7% (p < 0.001) ≥5% loss of BW: 86.6% versus 47.6% (p < 0.001) ≥10% loss of BW: 75.3% versus 27.0% (p < 0.001)
STEP 4 (48 weeks after a 20-week SEMA lead-in period)[201]	Phase 3, randomized, double-blind, placebo-controlled, international	Patients with ≥1 self-reported unsuccessful diet attempt and a BMI of ≥30 kg/m^2 or ≥ 27 kg/m^2 with ≥1 weight-related comorbidity	SEMA 2.4 mg (535) PL (268)	68 weeks of SEMA versus 20 weeks of SEMA and 48 weeks of PL (weeks 0–68) Change in BW: −17.4% versus −5.0% (weeks 20–68: −7.9% vs. 6.9%; p < 0.001) ≥5% loss of BW: 88.7% versus 47.6% ≥10% loss of BW: 79.0% versus 20.4%
STEP 5 (104 weeks)[202]	Phase 3, randomized, double-blind, placebo-controlled, international	Patients with ≥1 self-reported unsuccessful diet attempt and a BMI of ≥30 kg/m^2 or ≥27 kg/m^2 with ≥1 weight-related comorbidity	SEMA 2.4 mg (152) PL (152)	SEMA versus PL Change in BW: −15.2% versus −2.6% (p < 0.0001) ≥5% loss of BW: 77.1% versus 34.4% (p < 0.0001) ≥10% loss of BW: 61.8% versus 13.3% (p < 0.0001)
STEP 8 (68 weeks)[203]	Phase 3, randomized, open-label, active- and placebo-controlled, US only	Patients with ≥1 self-reported unsuccessful diet attempt and a BMI of ≥30 kg/m^2 or ≥27 kg/m^2 with ≥1 weight-related comorbidity	SEMA 2.4 mg (126) LIRA 3.0 mg (127) PL (85)	SEMA versus LIRA Change in BW: −15.8% versus −6.4% (p < 0.001) ≥5% loss of BW: 87.2% versus 58.1% ≥10% loss of BW: 70.9% versus 25.6% (p < 0.001)
With T2D				
STEP 2 (68 weeks)[99]	Phase 3, randomized, double-blind, double-dummy placebo-controlled, international	Patients with a BMI of ≥27 kg/m^2 with T2D (HbA1c 7–10%)	SEMA 2.4 mg (404) SEMA 1.0 mg (403) PL (403)	SEMA 2.4 and 1.0 versus PL Change in BW: −9.6% and −7.0% versus −3.4% (p < 0.0001 SEMA 2.4 vs. SEMA 1.0 and PL) ≥5% loss of BW: 68.8% and 57.1% versus 28.5% (p < 0.0001, SEMA 2.4 vs. PL) ≥10% loss of BW: 45.6% and 28.7% versus 8.2% (p < 0.0001, SEMA 2.4 vs. PL)
With or without T2D				
STEP 6 (68 weeks)[100]	Phase 3a, randomized, double-blind, double-dummy, placebo-controlled, Japan and South Korea only	Patients with a BMI of ≥27 kg/m^2 with ≥2 weight-related comorbidities or ≥35 kg/m^2 with ≥1 weight-related comorbidities (at least one being	SEMA 2.4 mg (199) SEMA 1.7 mg (101)	SEMA 2.4 and 1.7 versus PL Change in BW: −13.2% and 9.6% versus −2.1% (p < 0.0001, all SEMA vs. PL)

(Continues)

TABLE 3 (Continued)

Study (study length)	Study design	Population	Treatment (*n*)	Weight-related endpoints
		hypertension, dyslipidaemia or T2D [Japan only]) and ≥1 self-reported unsuccessful diet attempt	PL (101)	≥5% loss of BW: 83% and 72% versus 21% ($p < 0.0001$, all SEMA vs. PL) ≥10% loss of BW: 61% and 42% versus 5% ($p < 0.0001$, all SEMA vs. PL)
STEP TEENS (68 weeks)[204]	Phase 3a, randomized, double-blind, placebo-controlled, international	Adolescents aged 12 to <18 years with a BMI within the 95th or higher percentile for age and sex or in the 85th percentile or higher with ≥1 weight-related comorbidity, ≥1 self-reported unsuccessful diet attempt	SEMA 2.4 mg (134) PL (67)	SEMA versus PL Change in BW: −15.3 versus 2.4 kg ≥5% loss of BW: 73% versus 18% ≥10% loss of BW: 62% versus 8%

Abbreviations: ABMI, body mass index; BW, body weight; HbA1c, glycated haemoglobin; LIRA, liraglutide; PL, placebo; SEMA, semaglutide; STEP, Semaglutide Treatment Effect in People with obesity; T2D, type 2 diabetes; US, United States.

75.3% in the semaglutide group compared with 27.0% in the placebo group lost more than 10% of their body weight. In patients with obesity and T2DM, the STEP 2 trial demonstrated a weight reduction of −9.6% (2.4 mg) and − 7.0% (1 mg) with semaglutide treatment over 68 weeks compared with −3.4% with placebo.[99] More than 5% weight reduction was achieved in 68.8% with 2.4 mg and in 57.1% with 1-mg semaglutide compared with 28.5% with placebo. More than 10% weight reduction was achieved in 45.6% with 2.4 mg and in 28.7% with 1-mg Semaglutide compared with 8.2% with placebo. In an Asian population with obesity and without diabetes mellitus, semaglutide 2.4-mg treatment over 68 weeks achieved greater weight loss than placebo in the STEP 6 trial.[100] In this study, body weight loss was associated with a significant reduction in abdominal visceral fat mass.

Data on semaglutide for the treatment of MASH provide conflicting results with some studies showing MASH resolution without change in fibrosis,[101] and other studies showing no significant improvement in MASH measures.[102] The effect of semaglutide 2.4 mg compared with placebo was investigated in obese subjects with biopsy proven Metabolic Dysfunction Associated Steatohepatitis (MASH) and fibrosis stage 2 or 3 in the ESSENCE (Effect of Semaglutide in Subjects with Non-cirrhotic Non-alcoholic Steatohepatitis) trial.[103] In a first press release from Novo Nordisk, it was announced that in people treated with 2.4-mg semaglutide over 72 weeks 62.9% achieved resolution of steatohepatitis with no worsening of fibrosis compared with 34.1% on placebo. In 37.0% of people treated with semaglutide, improvement in liver fibrosis with no worsening of steatohepatitis compared with 22.5% in people on placebo was observed.[104]

A sub-analysis of the STEP trials revealed significantly greater improvements in blood pressure, lipids and FPG with semaglutide 2.4 mg/week compared with placebo.[105] Data from patients with prediabetes in another sub-analysis of the STEP trials showed that semaglutide 2.4-mg QW treatment significantly improved glucose control compared with placebo treatment in patients with obesity.[106]

The SELECT (Semaglutide Effects on Cardiovascular Outcomes in People with Overweight or Obesity) trial investigated the effect of 2.4-mg semaglutide once weekly (QW) on a composite cardiovascular endpoint in 17 604 overweight or obese nondiabetic patients with established cardiovascular disease.[107] Over a mean follow-up of 39.8 months, a 20% relative risk reduction in the primary composite cardiovascular endpoint (cardiovascular death, non-fatal myocardial infarction or non-fatal stroke) was found in the semaglutide group compared with the placebo group.[70]

7.4 | Oral peptide GLP-1 receptor agonist

Oral semaglutide is a formulation of semaglutide containing the absorption enhancer sodium N-(8–[2-hydroxybenzoyl] amino)caprylate (SNAC).[108] SNAC prevents semaglutide degradation in the stomach and improves transcellular absorption through the gastrointestinal mucosa.[109] Oral semaglutide (up to 14 mg once daily) was investigated in patients with T2D in the PIONEER 1 study. Compared with placebo, oral semaglutide recipients showed significantly greater HbA1c and body weight improvements in this trial.[108] In the active-controlled PIONEER study programme, weight loss with oral semaglutide was greater than that with empagliflozin,[110] dulaglutide[111] and liraglutide.[112,113] In the OASIS 1 study, oral treatment with semaglutide 50 mg once daily in adults with overweight or obesity for 68 weeks reduced body weight by −15.1% versus −2.4% for placebo.[114] Significantly more participants in the semaglutide group lost more than 5% of baseline body weight (85%) compared with the placebo group (26%).

7.5 | GIP/GLP-1 receptor agonists

Tirzepatide is a 39-amino-acid, unimolecular peptide based on the sequence of GIP and is modified to activate the GIP and GLP-1

receptors in a ratio of roughly 5:1.[115] Tirzepatide activates the GLP-1 receptor with a bias toward cAMP signalling compared with ß-arrestin signalling, causing decelerated GLP-1-R internalization and enhanced insulinotropic effects.[116,117] As demonstrated in Table 1, combining GIP and GLP-1 receptor agonism promises several complementary effects on postprandial metabolic control and body weight regulation. In addition to its effects on postprandial glucose and lipid metabolism, activation of GLP-1 and GIP receptors in the central nervous system promise additive anorexic effects.[118] In addition to improving glucose control, postprandial activation of GIP receptors in WAT will improve lipid control and reduce ectopic fat accumulation.[11,39–41]

The efficacy and safety of tirzepatide in persons with overweight or obesity who did not have diabetes were assessed in the SURMOUNT study programme (Table 4). In the SURMOUNT-1 trial, the effect of tirzepatide (5, 10 and 15 mg QW) was investigated in overweight or obese persons without T2D over a study period of 72 weeks.[119] Those treated with tirzepatide achieved significantly greater weight reduction with −20.9% (15 mg), −19.5% (10 mg) and − 15.0% (5 mg) compared with placebo with −3.1%. More than 5% body weight reduction was observed in 90.9% with 15 mg, 88.9% with 10 mg and 85.1% with 5 mg of tirzepatide compared with 34.5% with placebo. More than 10% weight reduction was found in 83.5%

TABLE 4 Weight-related outcomes from the clinical trials of tirzepatide in patients with overweight/obesity.

Study (study length)	Study design	Population	Treatment (*n*)	Weight-related endpoints
Without T2D				
SURMOUNT-1 (72 weeks)[119]	Phase 3, randomized, double-blind, placebo-controlled, international	Patients with ≥1 self-reported unsuccessful diet attempt and a BMI of ≥30 kg/m^2 or ≥27 kg/m^2 with ≥1 weight-related comorbidity	TIRZ 15 mg (630) TIRZ 10 mg (636) TIRZ 5 mg (630) PL (643)	TIRZ 15, 10, 5 versus PL Change in BW: −20.9%, −19.5%, −15.0% versus −3.1% (p < 0.001) ≥5% loss of BW: 90.9%, 88.9%, 85.1% versus 34.5% (p < 0.001) ≥10% loss of BW: 83.5%, 78.1%, 68.5% versus 18.8% (p < 0.001)
SURMOUNT-3 (72 weeks after a 12-week intensive lifestyle lead-in period)[124]	Phase 3, randomized, double-blind, placebo-controlled, international	Patients with obesity and a BMI ≥30 kg/m^2 or overweight patients with a BMI ≥27 kg/m^2 and with weight-related comorbidities	TIRZ 10 or 15 mg (287) PL (292)	Change in BW TIRZ: Additional −21.1% loss from randomization (p < 0.001 vs. PL) PL: A regain of 3.3% ≥5% loss of BW: TIRZ: 94.4% PL: 10.7% (p < 0.001) ≥10% loss of BW: TIRZ: 88.0% PL: 4.8% (p < 0.001)
SURMOUNT-4 (52 weeks following a 36-week TIRZ lead-in period)[125]	Phase 3, randomized, double-blind, placebo-controlled, international	Patients with obesity and a BMI ≥30 kg/m^2 or overweight patients with a BMI ≥27 kg/m^2 and with weight-related comorbidities	TIRZ 10 or 15 mg (335) PL (335)	Change in BW TIRZ: Additional −6.7% loss from randomization PL: A regain of 14.8% (p < 0.001) ≥5% loss of BW: TIRZ: 98.5% PL: 69.0% (p < 0.001) ≥10% loss of BW: TIRZ: 94.0% PL: 44.4% (p < 0.001)
With T2D				
SURMOUNT-2 (72 weeks)[123]	Phase 3, randomized, double-blind, placebo-controlled, international	Patients with T2D with HbA1c 7–10% and BMI ≥27 kg/m^2, on diet and exercise alone or oral glucose-lowering therapy	TIRZ 15 mg (311) TIRZ 10 mg (312) PL (315)	TIRZ 15 and 10 versus PL Change in BW: −14.7% and −12.8% versus −3.2% (p < 0.0001) ≥5% loss of BW: 83% and 79% versus 32% (p < 0.0001) ≥10% loss of BW: 65% and 61% versus 9% (p < 0.0001)

Abbreviations: BMI, body mass index; BW, body weight; HbA1c, glycated haemoglobin; PL, placebo; T2D, type 2 diabetes; TIRZ, tirzepatide.

with 15 mg, 78.1% with 10 mg and 68.5% with 5 mg of tirzepatide compared with 18.8% in the placebo group. In a post hoc analysis of SURMOUNT-1, a 69% reduction in the 10-year predicted risk for developing T2D and a 23.5% reduction in the predicted risk of atherosclerotic cardiovascular disease (ASCVD) compared with placebo was observed in patients treated with tirzepatide.[120,121] In an extension of the SURMOUNT 1 study up to 3 years, in those patients with prediabetes at baseline, the hazard ratio for progression to T2DM was reduced by 93% in those persons on tirzepatide compared with placebo.[122]

In the SURMOUNT-2 trial, the effect of 72 weeks treatment with tirzepatide (10 or 15 mg QW) on body weight was investigated in patients with obesity and T2D.[123] Those patients treated with tirzepatide achieved significantly greater weight reduction with −14.7% (15 mg), −12.8% (10 mg) compared with placebo with −3.2%. More than 5% body weight reduction was achieved in 83% of persons in the 15-mg group, 79% in the 10 mg group compared with 32% in the placebo group. More than 10% body weight reduction was achieved in 65% of persons in the 15-mg group, 61% in the 10 mg group compared with 9% in the placebo group. HbA1c levels were significantly better controlled with tirzepatide than with a placebo in patients with obesity and T2D.

In the SURMOUNT-3 study, tirzepatide 10 and 15 mg QW were compared with placebo in obese or overweight subjects.[124] After a 12-week run-in period with intensive lifestyle modifications, including a diet of 1200 kcal/day for women and 1500 kcal/day for men and increased physical activity, those patients who achieved a weight reduction of ≥5.0% were randomized to tirzepatide 10 or 15 mg or placebo. Patients randomized to tirzepatide achieved further weight reduction, reaching a mean of 25% body weight loss after 72 weeks. Patients randomized to placebo slightly started to regain weight after the end of the lifestyle intervention period.

In the SURMOUNT-4 study, subjects with obesity or overweight received an up-titration with tirzepatide to 15-mg QW over 36 weeks and were than randomized to continue with tirzepatide or placebo.[125] Patients on ongoing tirzepatide experienced further weight loss with a median reduction of 25% weight loss after 88 weeks, while those on placebo started to regain weight.[125] Post hoc analysis of the study data revealed reductions in triglycerides, non-HDL cholesterol and an increase in HDL levels with tirzepatide treatment.[123] Tirzepatide treatment was also associated with a reduction in blood pressure (BP), waist circumference and liver fat content.[119,123,124,126]

The SYNERGY-NASH trial is a phase 2 study investigating the effect of tirzepatide over 52 weeks on MASH progression in 157 patients with biopsy-confirmed MASH and stage F2 or F3 fibrosis.[127] Treatment with 5-, 10- or 15-mg tirzepatide led to MASH resolution without increasing fibrosis in 55% of patients on 5 mg, 56% on 10 mg and 62% on 15 mg compared with 10% with placebo. An improvement in fibrosis of at least at one stage was found 55% in the 5-mg, 51% in the 10-mg and 51% in the 15-mg tirzepatide group, compared with 30% in the placebo group. The effect of tirzepatide on liver fibrosis appears to be independent of dose in the range between 5 and 15 mg.

In the SURMOUNT-OSA study, tirzepatide treatment was investigated in patients with obesity with moderate-to-severe obstructive sleep apnoea syndrome (OSA).[128] The apnoea-hypopnea-index (AHI), the primary endpoint of this study, significantly improved by 55% with 10- or 15-mg tirzepatide compared with placebo. Body weight, hypoxic burden, hs-CRP levels and systolic blood pressure improved with tirzepatide treatment in patients with obesity and OSA.

In the SUMMIT trial the effect of tirzepatide was investigated in obese subjects with heart failure and an ejection fraction of at least 50% (HFpEF).[129,130] Treatment with tirzepatide up to 15 mg for 1 year reduced the risk for a composite of death from cardiovascular causes or worsening of heart failure compared with placebo. A significant improvement in health status as evaluated with the Kansas City Cardiomyopathy Questionnaire clinical summary score (KCCQ-CSS) could be achieved with tirzepatide treatment.

Recently, in a press release from Lilly, first outcome data from the SURMOUNT 5 study comparing tirzepatide in maximum tolerated dose (10 or 15 mg) compared with semaglutide in maximum tolerated dose (1.7 mg or 2.4 mg) in overweight or obese persons were reported. In that study, treatment with tirzepatide over a period of 72 weeks lead to an average weight reduction of 20.2% compared with 13.7% with semaglutide.[131]

The SURMOUNT-MMO study (NCT05556512), which investigates the impact of tirzepatide on morbidity and mortality in adults with obesity and an increased risk of cardiovascular disease, is still ongoing.

8 | DRUGS IN CLINICAL DEVELOPMENT

8.1 | Non-peptide oral GLP-1 receptor agonists

Orforglipron is an oral, non-peptide GLP-1-RA administered once daily. Orforglipron induces a biased activation at the GLP-1 receptor, with stronger activation of the cAMP signalling pathway compared with the ß-arrestin signalling pathway, probably amplifying metabolic signalling and clinical efficacy.[115,132]

In patients with obesity or overweight without diabetes, 26 weeks of orforglipron treatment at doses of 12, 24, 36 or 45 mg resulted in mean body weight reduction between 9.4% and 14.7% with orforglipron versus 2.3% with placebo.[133] Body weight reduction of ≥10% was achieved in 46–75% of patients with orforglipron, and plateau was not reached by study end at 26 weeks. In patients with T2DM, orforglipron at doses of 3, 12, 24, 36 or 45 mg resulted in mean weight loss of up to −10.1 kg versus −2.2 kg in the placebo group and −3.9 kg in the dulaglutide group.[134] Up to 81% of participants achieved a body weight reduction of ≥5% with orforglipron, compared with 22% with placebo and 35% with dulaglutide.

With these promising results obtained for the orforglipron, more non-peptide GLP-1 RAs are in early clinical development.[135,136]

8.2 | GLP-1/Glucagon receptor agonists

Glucagon exerts anorexic effects via a mode of action partly different from that of GLP-1 or GIP. Glucagon increases satiety and reduces food intake by activating the liver-vagus-hypothalamic axis and not by direct stimulation of receptors in the CNS.[53,137] In contrast to GLP-1 or GIP, glucagon increases energy expenditure and activates liver glycolysis and lipolysis.[54,55,59,138] Therefore, combining glucagon with incretins appears to be a promising approach for the treatment of obesity and obesity-related complications such as MASLD.[139]

Several dual GLP-1/glucagon peptide agonists are in clinical development and are investigated for different indications in ongoing studies.

Mazdutide is a long-acting analogue of oxyntomodulin currently in phase 2 development in China.[140–142] In overweight or obese individuals, mazdutide was associated with greater weight loss and reduction in BMI (body mass index) than placebo. In addition, improvements in HbA1c, FPG, postprandial glucose and insulin resistance were observed during treatment with mazdutide.[141,142]

Cotadutide and survodutide are unimolecular GLP-1/glucagon peptide co-agonist evolving approximately five times stronger activation at the GLP-1 receptor compared with the glucagon receptor.[137] In individuals with overweight or obesity, survodutide significantly decreased placebo corrected body weight by up to 14% after 16 weeks.[143,144] Recently, data on the effect of survodutide on MASH progression in 293 patients with biopsy-confirmed MASH and fibrosis stages F1–F3 have been published.[145] Treatment with survodutide resulted in a significant improvement in a composite histological score with a ≥2-point decrease in the non-alcoholic fatty liver disease (NAFLD) activity score and a ≥1-point decrease in either lobular inflammation or hepatocellular ballooning, with no worsening of fibrosis. Survodutide significantly improved liver fibrosis as a secondary endpoint. The clinical effects of survodutide are currently under investigation in the SYNCHRONIZE phase III study programme.

8.3 | Glucagon/GIP/GLP-1 receptor agonists

Retatrutide is a 39 amino acid, fatty acid-acylated peptide that activates GIP, GLP-1 and glucagon receptors in a ratio of approximately 5:1:1.[145,146] Like tirzepatide and orforglipron, it exerts biased stimulation of GLP-1-R with reduced β-arrestin 2 activation.[147] In a 48-week phase 2 trial, in persons with obesity without diabetes, retatrutide dose-dependently reduced body weight by −8.7% up to −24.2% for 1–12-mg doses versus −2.1% for placebo. In this study, 100% of participants achieved ≥5% weight loss and over 90% achieved ≥10% weight loss in participants receiving at least 8 mg of retatrutide.[148] In a sub analysis of that trial, significant liver fat reduction occurred with retatrutide, with higher doses (8 and 12 mg) achieving reductions of over 80% in liver fat after 24 weeks.[149] In persons with obesity with T2D, 36 weeks of treatment with retatrutide reduced body weight by 3.2% up to −16.9% for 0.5–12-mg doses versus 2.0% for dulaglutide.[148,150]

8.4 | Other enteroendocrine and enteropancreatic co-agonists

Multiple other enteroendocrine and enteropancreatic multi-agonists are in clinical development.

In several clinical studies, long-acting amylin agonists have been shown to suppress food intake and reduce body weight.[151,152] Cagrilintide, an acylated long-acting amylin agonist, suppresses food intake and reduces body weight in overweight and obese subjects.[153,154] CagriSema is a peptide mixture with a fixed combination of 2.4 mg of cagrilintide and 2.4 mg of semaglutide, administered once weekly.[153] Treatment with CagriSema in patients with obesity and T2D over 32 weeks resulted in a mean reduction in HbA1c of up to 2.2% and a reduction in body weight of up to 15.6% and did not reach plateau yet by the end of the study.[155]

In a recent press release from NOVO Nordisk, first outcomes of the REDEFINE 1 trial, comparing CagriSema with the individual components cagrilintide 2.4 mg and semaglutide 2.4 mg in overweight or obese persons were announced.[156] In this study, CagriSema resulted in average weight reduction of 22.7% compared with 16.1% with semaglutide and 11.8% with cagrilintide alone. Other studies from the REDEFINE clinical trial programme investigating the effects of CagriSema in overweight or obese individuals with and without diabetes are ongoing.

As already addressed, ghrelin is an orexigenic peptide that induces hunger by inhibiting hypothalamic pro-priomelanocortin receptors and stimulating neuropeptide Y neurons.[157,158] Clinical studies on the effects of ghrelin antagonists in humans have yielded conflicting results. Treatment with the deacylated ghrelin agonist AZP-531 has been shown to reduce body weight in overweight and patients with obesity and T2D.[159] Despite reducing the ratio of acylated to unacylated ghrelin by more than 80% with the GOAT inhibitor BI 1356225, no effects on body weight, appetite, food carvings, ad libitum food intake or obesity-related biomarkers were observed in overweight or patients with obesity.[160]

The activation of central neuropeptide Y receptors has shown promising anorexic effects in lean and obese subjects.[161] Preclinical data have demonstrated a reduction in body weight and modulation of food intake during treatment with NPY2R agonists.[162] In a recent study, the treatment effects of a potent specific NPY2R agonist, BI 1820237, alone and in combination with liraglutide, were investigated in overweight and patients with obesity. In this study, promising reductions in ad libitum food intake from a standardized meal buffet with a reduction of −622.0 kcal (−350.0 to 875.0) after a single dose of 1.2 mg of BI 18200237 and by −1069 kcal (−806 to 1218) after a single dose of 1.8 mg of BI 18200237 was observed.[163]

Fibroblast growth factor 21 (FGF21) is a peptide expressed in liver, white and brown adipose tissue.[164,165] FGF21 exerts several clinical effects like induction of heat production, increasing insulin sensitivity and regulation of lipid metabolism.[166] FGF21 agonists and the combination of FGF21 agonists with incretins are under clinical investigation for the treatment of obesity, T2DM and MASLD.[167–169]

8.5 | Limitations and tolerability of incretin-based treatments for obesity

Overall, treatments with incretin co-agonists appear to be safe and well tolerated, but some specific side effects need to be addressed.

The most common side effects of incretins are gastrointestinal adverse events, such as nausea, vomiting, diarrhoea and constipation.[170–172] In most cases, they are temporary, primarily occurring at the start of treatment and can be mitigated by careful and slow-dose up-titration.[33] Evidence has shown an increased risk of gallbladder or biliary diseases during weight reduction with incretins.[173,174] In a recent meta-analysis of nine RCTs, no statistically significant association was found between tirzepatide use and the incidence of cholelithiasis, cholecystitis, biliary diseases or a composite of the gallbladder or biliary diseases compared with all control groups (including placebo, basal insulin and GLP1-RA).[175]

Like with other weight-reducing interventions, a loss of lean body mass was found during weight loss with incretin-based pharmacological treatments.[176–178] There has been some discussion about the use of muscle hypertrophy-stimulating drugs to counteract lean body mass during weight loss.[179] Bimagrumab is a high-affinity monoclonal antibody that inhibits the activin type-2 receptor, leading to increased muscle mass and decreased fat mass.[180,181] Combination of enteroendocrine or enteropancreatic peptides with bimagrumab is considered to be a promising approach to achieve significant weight reduction without loss of lean body mass.

Some early reports have raised the issue of a possible association between incretin treatment and pancreatitis or pancreatic cancer. This association was not confirmed in cardiovascular outcome trials of incretin-based treatments for patients with T2DM.[182,183] In a recently published retrospective propensity-matched cohort study with a sample size of 258 238 people with T2D or obesity and a history of acute pancreatitis, the reappearance rate of an acute pancreatitis was significantly lower in people treated with semaglutide or tirzepatide.[184] A relationship between the risk of thyroid cancer and the use of incretins has been suggested based on the findings of C-cell hyperplasia and C-cell adenomas in rodents.[185,186] In humans, the risk of thyroid disease during incretin treatment remains controversial.[187,188] The European Medical Agency Pharmacovigilance Assessment Committee concluded that the available evidence did not support a causal association between thyroid cancer and the use of the GLP-1 RAs, exenatide, liraglutide, dulaglutide, semaglutide or lixisenatide in humans.[189]

Due to pharmacovigilance data, the risk of depression and increased suicidality during weight loss with incretins has been discussed. An increased risk of depression or suicidality has not been observed in clinical studies or recent reviews.[190–192] A recent meta-analysis, including five randomized controlled trials and one prospective cohort study, with an observational period between 24 and 60 weeks, indicated an improvement in depression rating scale scores comparing GLP-1-RA with control groups.[193] Even up to now, there is no substantial evidence for increased depression rates or suicidal behaviour, the long-term effects of weight loss with these kind of drugs on emotional health warrants further observation.

The LEADER and SUSTAIN 6 studies suggested an increased risk of diabetic retinopathy with the GLP-1 receptor agonists, liraglutide and semaglutide.[194,195] In a systematic search and meta-analysis, no significant differences in complications due to diabetic retinopathy were observed between GLP-1 RAs and insulin treatment.[196] Recently, a retrospective matched-cohort study indicated a very small but significantly increased risk of non-arteritic anterior ischaemic optic neuropathy (NAION) in patients treated with semaglutide.[197] Whether there is a causal relationship between the use of liraglutide or semaglutide and these ophthalmological complications remains unclear. If this potential retinal risk can also be conferred to obese subjects without diabetes needs further evaluation.

Although a slight increase in heart rate has been consistently reported with GLP-1 RAs, the long-term cardiac safety of these drugs has been proven in numerous clinical trials.[89] In a clinical trial of retatrutide, cases of cardiac arrhythmia were reported.[148]

It should me mentioned that after terminating treatment with GLP1 receptor agonists as well as with tirzepatide weight gain reappears.[125,198]

Long-term safety data and real-world data from broader populations for newer incretin-based therapies are lacking and are the topic of ongoing studies.

9 | SUMMARY

Obesity and associated complications pose a global challenge in medical care. Increasing knowledge about the distinct roles of fat tissue and adipocyte function in different body compartments provides a better understanding of the complex interactions between obesity, increased fat mass and the associated metabolic and non-metabolic outcomes.

While lifestyle modifications remain the backbone of obesity treatment, pharmacotherapy and metabolic surgery achieved significant roles in the treatment of obesity. A more detailed understanding of the role of incretins in the crosstalk between intestinal enteroendocrine cells, adipocytes and central brain areas involved in the regulation of energy homeostasis has allowed the development of new pharmacological approaches for the treatment of obesity and metabolic diseases. The regulatory approval of the GLP-1 RAs liraglutide and semaglutide for treating obesity has opened new avenues for the pharmacological treatment of obesity and its complications. Tirzepatide is the first approved monopeptide with dual agonism on GIP and GLP-1 receptors. This dual incretin agonism has been shown to suppress body weight and enhance the metabolic effects achieved with GLP-1 mono receptor agonists. Numerous other dual and triple co-agonists are in clinical development and may further broaden our opportunities for treating obesity and related metabolic and non-metabolic diseases.

In addition to the weight-lowering effects of these new drugs, their benefits with regard to cardiovascular risk, MASLD, MASH and renal function underline their potency in the treatment of obesity and metabolic disorders. Research is also broadening to use these

new treatment approaches in other patient populations, including adolescents, those experiencing weight regain following metabolic surgery, and the prevention of diabetes in high-risk groups.

Widening the armamentarium for the pharmacological treatment of obesity will come along with the challenge to clinically characterize and define those patients that can achieve best medical benefits from these new drugs for obesity and its metabolic and non-metabolic complications.

AUTHOR CONTRIBUTIONS

TF, CDB, SDP, SA, JF, AL, BL, MM, CM, TDM and OS were involved in writing the manuscript.

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DATA AVAILABILITY STATEMENT

Data sharing is not applicable to this study because no datasets were generated or analysed.

ETHICS STATEMENT

Not applicable.

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