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Gut hormone co-agonists for the treatment of obesity: from bench to bedside

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The discovery and development of so-called gut hormone co-agonists as a new class of drugs for the treatment of diabetes and obesity is considered a transformative breakthrough in the field. Combining action profiles of multiple gastrointestinal hormones within a single molecule, these novel therapeutics achieve synergistic metabolic benefits. The first such compound, reported in 2009, was based on balanced co-agonism at glucagon and glucagon-like peptide-1 (GLP-1) receptors. Today, several classes of gut hormone co-agonists are in development and advancing through clinical trials, including dual GLP-1–glucose-dependent insulinotropic polypeptide (GIP) co-agonists (first described in 2013), and triple GIP–GLP-1–glucagon co-agonists (initially designed in 2015). The GLP-1–GIP co-agonist tirzepatide was approved in 2022 by the US Food and Drug Administration for the treatment of type 2 diabetes, providing superior HbA1c reductions compared to basal insulin or selective GLP-1 receptor agonists. Tirzepatide also achieved unprecedented weight loss of up to 22.5%—similar to results achieved with some types of bariatric surgery—in non-diabetic individuals with obesity. In this Perspective, we summarize the discovery, development, mechanisms of action and clinical efficacy of the different types of gut hormone co-agonists, and discuss potential challenges, limitations and future developments.

Obesity has already reached pandemic dimensions worldwide, yet the percentage of people with obesity is increasing[1–5]. According to the World Health Organization, worldwide obesity has nearly tripled since 1975; in 2016, more than 1.9 billion adults were overweight, and more than 650 million were obese. In keeping with these numbers, 39% of all adults were overweight, and 13% were obese, worldwide[6], and according to the World Obesity Federation, the number of people with obesity (body mass index (BMI) ≥ 30 kg/m^2) has increased to 764 million in 2020 (ref. 7).

The gastrointestinal tract is a source of endocrine signals that are, among other functions, involved in the regulation of energy balance. Bariatric surgery is the most effective intervention for inducing weight loss among individuals with obesity and becoming increasingly common as it is considered relatively safe and substantial weight loss is typically sustained for many years[8]. In addition to reversing obesity, this procedure also mitigates type 2 diabetes (T2D) and reduces other cardiometabolic risk factors.

There are different types of bariatric surgery, each one with different efficacy, and weight loss is due to changes in the physiology of body weight regulation[9]. The mechanisms of bariatric surgery are complex and multifactorial, yet not understood fully[10], but reduction of energy intake, changes in food selection and modifications in the levels of different hormones and bile acids are certainly involved. However, there is considerable heterogeneity in the outcomes and the benefits across time in some patients[11] and thus the development of pharmacological approaches is of relevance. In particular, long-acting derivatives of

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GLP-1 are now used for the pharmacotherapy of T2D and obesity[12] and, more recently, emerging data support the combination of agonism at receptors for two or more peptides, unimolecular multi-agonists, which are the focus of this Perspective.

The proglucagon gene is expressed by pancreatic islet alpha cells, in specific enteroendocrine cells (L cells) of the intestinal mucosa, and by a discrete set of neurons within the nucleus of the solitary tract[13]. The proglucagon gene encodes structurally related proglucagon-derived peptides, including glucagon, GLP-1, glucagon-like peptide-2 (GLP-2), glicentin and oxyntomodulin. The relative amounts and forms of these peptides in different cell types depend on tissue-specific posttranslational modifications by prohormone convertases (for a detailed review on this topic, see ref. 13).

Overview of relevant gastrointestinal hormones

Glucagon

Glucagon is a peptide hormone secreted by alpha cells in pancreatic islets in response to fasting or hypoglycaemia[14]. Its primary physiological role is preventing blood glucose from dropping too low by different mechanisms including the conversion of glycogen into glucose (glycogenolysis) or stimulating hepatic glucose production. With a substantial presence of glucagon receptors on hepatocytes, glucagon also regulates hepatic fatty acid metabolism, as it stimulates fatty acid oxidation while inhibiting lipogenesis thereby reducing hepatic lipid accumulation and secretion. Glucagon secretion is reciprocally inhibited by insulin action and, consequently, hyperglucagonaemia is observed in most forms of diabetes, in humans and in animal models[15].

Indeed, pharmacological suppression of glucagon actions on its receptor efficiently lowers blood glucose levels in rodents[15,16] and individuals with T2D[17]. In addition to effects on glucose homeostasis, glucagon stimulates energy expenditure, as its infusion increases oxygen consumption in humans[18], an effect that seems to be independent of brown fat activation[19]. Moreover, glucagon also triggers lipolysis in several species including humans[20] and, more recently, it has been demonstrated that glucagon can activate the glucagon-like peptide-1 receptor (GLP-1R) on beta cells (with a lower potency compared with its interaction with the glucagon receptor), which may play an important role in the paracrine stimulation of insulin secretion[21] (Fig. 1).

Glucose-dependent insulinotropic polypeptide

GIP is a 42-amino-acid peptide produced in, and secreted from, intestinal K cells in the proximal small intestine (duodenum and jejunum) in response to eating[22]. The glucose-dependent insulinotropic polypeptide receptor (GIP-R) is abundantly expressed in pancreatic beta cells, and, similar to GLP-1, GIP stimulates insulin secretion in a glucose-dependent manner[23]. While the secretion of GIP in individuals with T2D is not generally different[24], the insulinotropic action of GIP in these individuals is reduced[25]. In rodents, GIP-R-expressing neurons in the arcuate, dorsomedial and paraventricular nuclei of the hypothalamus are involved in the reduction of food intake[26], and exogenous GIP reduces food intake in male mice[27].

Despite all this preclinical evidence, in humans, an acute infusion of GIP does not cause any significant effect on appetite, energy intake or energy expenditure[28,29]. Intriguingly, preclinical data concerning the potential therapeutical value of GIP-R agonism show that both antagonism[30,31] and agonism[32] decrease adiposity. For instance, GIP-R antagonizing antibodies improve body weight and glucose control in mice and non-human primates[33].

In contrast to these data, overexpression of GIP improves body weight and glycaemia in diet-induced obese mice[34]. Furthermore, deletion of mouse GIP-R and also humanized GIP-R in the central nervous system decreases body weight and improved glucose metabolism after high-fat-diet feeding in male mice[27]. The lower body weight of these mice is accompanied by decreased food intake without changes in energy expenditure[27]. The same study reported that central and peripheral administration of fatty acyl-GIP acutely and chronically decreased body weight, food intake and blood glucose in wild-type diet-induced obese mice, but these actions were absent in mice with depletion of GIP-R in the brain[27]. These discrepancies suggest that the precise mechanism of action of GIP is yet to be understood, and certainly its role in humans remains to be clarified (Fig. 1).

Glucagon-like peptide-1

GLP-1 is a peptide hormone produced and secreted by intestinal enteroendocrine L cells[35], specific neurons in the brainstem (nucleus of the solitary tract)[36] and a subpopulation of alpha cells within human islets[37]. GLP-1 regulates blood glucose levels through its combined stimulation of insulin and suppression of glucagon secretion (both highly glucose dependent), and the deceleration of gastric emptying, and reduction in food intake[38]. The major stimulus for GLP-1 secretion is the ingestion of nutrients, including glucose and fatty acids. GLP-1 also inhibits food intake and promotes satiety in healthy individuals and people with obesity and diabetes[39] (for a detailed review on this topic, see ref. 40; Fig. 1). These results highlighting the importance of GLP-1R signalling to attenuate hunger and reduce body weight in humans prompted the development of GLP-1 agonists, as summarized below.

GLP-1 agonists: current pharmacotherapy for type 2 diabetes and obesity

The first GLP-1R agonist approved by the US Food and Drug Administration (FDA) for the treatment of T2D was exenatide in 2005, followed by others like liraglutide (2010), dulaglutide (2014), lixisenatide (2016) and semaglutide (2017 for subcutaneous application, 2019 for oral administration). Liraglutide was the first GLP-1R agonist that was also approved for the treatment of obesity in 2014; in clinical trials, 3 mg liraglutide once daily achieved a weight loss of 8.4 kg after 56 weeks in people who were overweight and had a BMI > 27 kg/m^2 together with at least one comorbid condition or obesity (BMI > 30 kg/m^2)[41]. In another trial, liraglutide achieved 6% weight loss over 52 weeks in people with T2D treated with 3 mg liraglutide once daily[42].

More recently, once-weekly subcutaneous semaglutide was approved by FDA for the treatment of overweight and obesity. In a trial enrolling 1,961 adults with obesity or a BMI > 27 kg/m^2 with at least one weight-related pre-existing condition, semaglutide was administered for 69 weeks at a final dose of 2.4 mg. The mean weight loss in semaglutide-treated individuals was 16.9% versus 2.4% with placebo[43] and a different study with 711 patients with T2D showed that oral semaglutide decreased HbA1c similarly to liraglutide but was superior in decreasing body weight compared with both liraglutide and placebo at 26 weeks[44].

Another trial enrolled 1,210 adults, who were overweight or had obesity and T2D, and semaglutide 2.4 mg weekly was subcutaneously administered for 68 weeks, resulting in a mean body weight reduction of −9.6% with semaglutide versus −3.4% with placebo[45]. A further study in adults with overweight or obesity without diabetes found that weekly subcutaneous semaglutide, together with counselling for diet and physical activity, had greater efficacy than once-daily subcutaneous liraglutide to reduce body weight at 68 weeks[46]. In a phase 3 study enrolling 1,201 patients with T2D, semaglutide was also superior to dulaglutide in improving glycaemic control and reducing body weight[47]. Such results have established GLP-1R agonists as an important class for the effective injectable treatment of T2D and obesity (for comprehensive reviews on GLP-1 agonists, see refs. 12,48).

Glucagon–GLP-1 co-agonists

Although the idea to dispense glucagon to patients with obesity and/or T2D appears counterintuitive at first sight, given its hyperglycaemic effects, the principle for including glucagon into a combinatorial drug candidate is based on its widely overlooked thermogenic,

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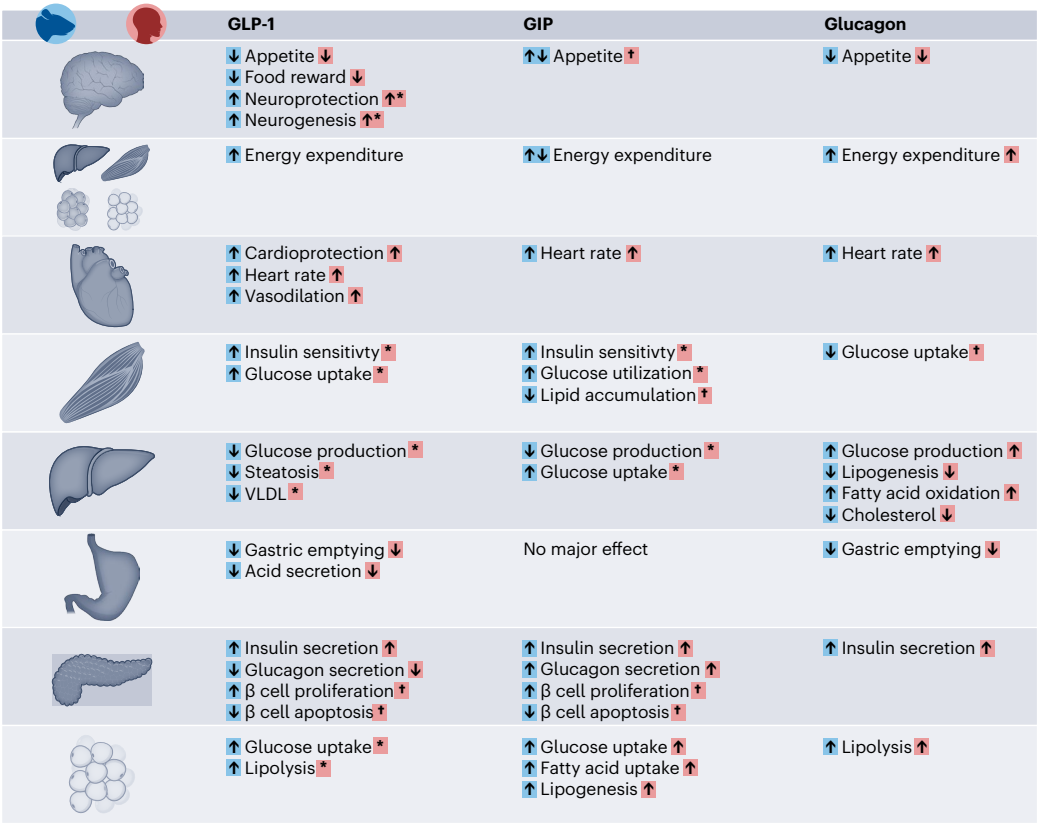

Fig. 1 | Summary of the main actions and target tissues of glucagon-like peptide-1, glucose-dependent insulinotropic polypeptide and glucagon. Black arrows indicate data in rodents. Red arrows indicate data in humans. Asterisks indicate likely indirect effects (for example, mediated by changes in insulin or glucagon secretion) in humans. Daggers indicate absence of evidence in humans.

satiety-inducing and lipolytic actions, which offer potential synergy with metabolic benefits of GLP-1R agonism. In parallel, a molecule by the name of oxyntomodulin, which is structurally largely identical to glucagon, was the subject of several studies, which demonstrated that this hormone inhibited food intake and increased energy expenditure in both preclinical models and humans[49–51]. However, this effect was preserved in glucagon receptor knockout mice[49] indicating lack of glucagon-like activity in vivo.

In 2009, the discovery of the first fully active synthetic gut hormone polyagonist, a unimolecular glucagon–GLP-1 co-agonist, was reported[52]. Different balances for the interaction with GLP-1Rs and glucagon receptors have been tested. The more balanced compounds massively decreased food intake and increased energy expenditure and thereby normalized adiposity and glucose tolerance in diet-induced obese male mice in an unprecedented manner[52]. Another study validated this discovery by showing again that simultaneous activation of both the GLP-1R and the glucagon receptor would cause impressive weight loss, lipid-lowering activity and antihyperglycaemic efficacy[53]. Although the reasons for the discontinuation of these first dual agonists have not been disclosed, other glucagon–GLP-1 co-agonists (namely NN1177, NN1151 and NN1359), which have different GLP-1-to-glucagon receptor ratios, were tested not only in diet-induced obese mice but also in rats. The results indicated that the effects of these compounds are different depending on the species, the doses used and study length[54]. In addition, phase 1 trials investigating the safety, tolerability, pharmacokinetics and pharmacodynamics of NN1177 administered subcutaneously once weekly to individuals with overweight or obesity showed that even though treatment with NN1177 was associated with dose-dependent weight loss, there were unacceptable safety concerns[55].

Thereafter, different variants of glucagon–GLP-1 co-agonists have been developed and were tested in preclinical and clinical trials primarily for their body weight lowering and antihyperglycemic effects. Among the different trials (see reviews in refs. 56,57), clinical phase 2 trial data from two glucagon–GLP-1 co-agonists (SAR425899 and MEDI0382, or cotadutide) have been published. The results confirm safety as well as significant weight loss and glucose-lowering efficacy.

In a phase 2a randomized, placebo-controlled, double-blind, multiple-ascending doses (max 200 µg for 41 d) trial enrolling 51 adults with controlled T2D and a BMI between 27 and 40 kg/m^2, cotadutide was subcutaneously administered once daily[58]. Cotadutide significantly reduced blood glucose and body weight, but also caused marked improvements of blood lipids. Side effects, specifically nausea and vomiting, occurred no more frequently with cotadutide than with selective GLP-1R agonists, and the majority of these adverse events were mild or moderate in severity[58]. Similarly, a phase 1 study carried out in Asian participants showed that cotadutide reduced glucose concentrations, and most of the events were mild 'gastrointestinal' symptoms[59].

Another independent phase 2a study confirmed the glucose-lowering effects of cotadutide after 49 d in overweight individuals or patients with obesity and T2D (on metformin monotherapy) and suggested that this was mediated by enhanced insulin secretion and delayed gastric emptying[60]. These initial studies did not compare the efficacy of cotadutide with other antiobesity drugs. However, a further 54-week randomized phase 2b study performed in 834 adults with BMI ≥ 25 kg/m^2 and T2D inadequately controlled with metformin were randomized to double-blind cotadutide at 100 µg, 200 µg or 300 µg, placebo or liraglutide at 1.8 mg. Cotadutide reduced HbA1c and body weight versus placebo. Furthermore, cotadutide (300 µg), but not

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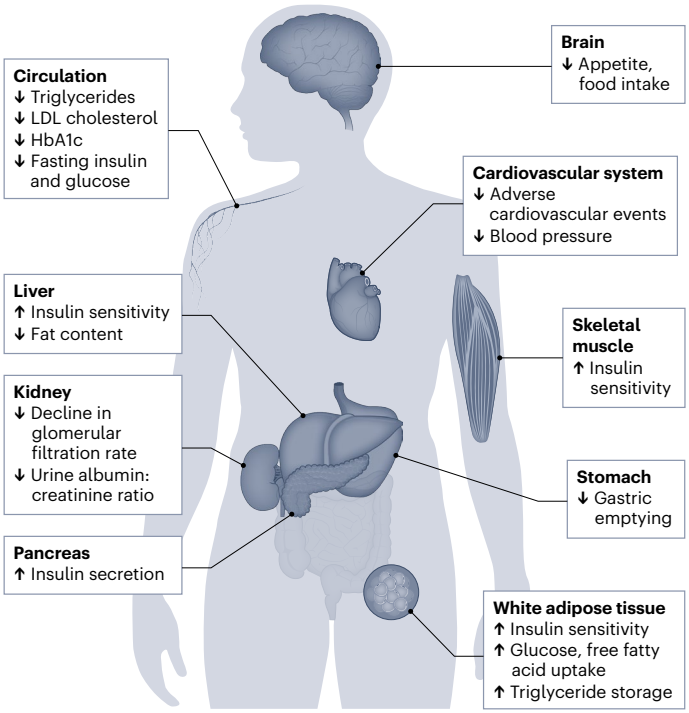

Fig. 2 | Main actions and target tissues for gut hormone co-agonists. Results obtained from phase 1, 2 and 3 trials with dual agonists and triagonists.

liraglutide, improved hepatic parameters and non-alcoholic fatty liver disease-related fibrosis, assessed by reduced levels of circulating transaminases, FIB-4 index and non-alcoholic fatty liver disease fibrosis score. Weight loss with 200 µg cotadutide was similar to that with 1.8 mg liraglutide and greater with 300 µg cotadutide versus 1.8 mg liraglutide[61]. Cotadutide is under clinical development by AstraZeneca and currently in the phase II and phase III clinical pathways to evaluate its safety and efficacy in participants with non-cirrhotic, non-alcoholic steatohepatitis with fibrosis (NCT05364931).

In another trial, human participants received a single dose of 0.05, 0.075 or 0.1 mg SAR425899 daily for 21 d to assess the adverse event profile at higher doses. The most frequently reported adverse event with the highest dose was vomiting[62]. In a second trial, overweight men and women or men and women with obesity and T2D received either an escalated dose of SAR425899 (0.03, 0.06 and 0.09 mg, or 0.06, 0.12 and 0.18 mg) or placebo daily over a period of 21 d. Again, the most frequent side effects with the high doses were 'gastrointestinal' symptoms and decreased appetite, which were less pronounced in patients with T2D compared to healthy volunteers[62]. SAR425899 significantly reduced levels of fasting plasma glucose and glycated haemoglobin in patients with T2D. Furthermore, SAR425899 reduced average body weight by up to 5.3 kg in non-diabetic volunteers and by 5.5 kg in patients with T2D[62]. A subsequent study in 36 participants with overweight or obesity with T2D who received different doses of SAR425899 or placebo daily for 28 d found that this drug improved postprandial glucose control by significantly enhancing beta cell function and slowing glucose absorption rates[63].

A phase 2b study in 75 participants with overweight or obesity with T2D compared the effects of once-daily SAR425899 (0.12, 0.16 and 0.20 mg daily), liraglutide (1.8 mg) or placebo for 26 weeks. The results indicated that the dual agonists improved postprandial glycaemia more than liraglutide did, which might be explained by an enhanced beta cell responsiveness induced by this new type of co-agonist when compared to mono-agonists[64] (Fig. 2 and Table 1). However, results from phase 2 trials were subsequently halted by Sanofi due to high rates of treatment-emergent adverse events, mainly gastrointestinal disorders, leading to several treatment discontinuations and participant withdrawals.

GIP–GLP-1 co-agonists

Based on the hypothesis that GIP-R agonism would offer an additional action profile with benefits that include decreased appetite and food intake, weight loss and improved glucose as well as lipid metabolism, GIP–GLP-1 co-agonists were developed as a novel class in 2013. The promising translational value of these molecules was already shown in the first publication, which reported data from studies in mice, rats, monkeys and humans using the first ever GIP–GLP-1 co-agonist (RG7697 and, later, NNC0090-2746) with balanced co-agonism at both receptors. This molecule decreased body weight in a dose-dependent manner and improved glucose and lipid metabolism, more effectively than mono-agonists[65].

Phase 1 trials enrolling 51 healthy volunteers in a double-blind, placebo-controlled study used once-daily doses of up to 3.6 mg of this drug, which were well tolerated overall, with similar 'gastrointestinal' adverse effects to those observed with selective GLP-1 agonists[66]. In a subsequent 12-week, randomized, placebo-controlled, double-blind phase 2a trial, patients with T2D that was inadequately controlled with metformin received 1.8 mg of NNC0090-2746 or placebo subcutaneously once daily, and 1.8 mg of liraglutide was also administered as an open-label reference arm[67]. NNC0090-2746 reduced blood glucose, body weight and total cholesterol significantly versus placebo; however, no convincing differences in efficacy versus liraglutide were evident from this study[67]. The fact that NNC0090-2746 did not outperform liraglutide may be the reason for the discontinuation of this drug in 2019.

Another GIP–GLP-1 co-agonist, tirzepatide (formerly LY3298176) was developed and first results were published in 2018 (ref. 68). Tirzepatide has now become the first unimolecular dual agonist approved for the treatment of T2D (Mounjaro). Tirzepatide is a 39-amino-acid peptide, which is quite similar in size to both GLP-1 and GIP, but with an exenatide-derived C-terminal tail. Like liraglutide and semaglutide, a free fatty (di-)acid side chain promotes binding to albumin and prolongs the elimination half-life. Tirzepatide preferentially activates human GIP-R over GLP-1R (5:1 ratio)[68].

Tirzepatide enhanced insulin secretion and improved glucose tolerance in mice, and its chronic administration significantly diminished body weight and fat mass of diet-induced obese mice, more potently than semaglutide, an effect that could be explained by reduced food intake and a slight but significant increase in energy expenditure[68]. Furthermore, in healthy participants, similarly to dulaglutide, tirzepatide reduced both fasting and postprandial glycaemia and increased the insulin response during an oral glucose tolerance test[68]. However, the highest doses of tirzepatide achieved weight loss greater than with dulaglutide after 29 d, while in patients with T2D, the decrease in body weight with tirzepatide was found to be smaller than that in healthy participants[68]. In a double-blind, randomized, phase 2 study in patients with T2D receiving once-weekly subcutaneous LY3298176 (1 mg, 5 mg, 10 mg or 15 mg), dulaglutide (1.5 mg) or placebo for 26 weeks[69], tirzepatide showed greater efficacy on body weight loss and glucose control compared to dulaglutide, with an overall acceptable safety and tolerability profile[69].

The clinical trial programme directed to address the effectiveness, safety and tolerability of tirzepatide for the treatment of T2D (SURPASS) has partially been reported, but is still ongoing (for a review, see ref. 70). These phase 3 clinical trials used identical doses of tirzepatide (5, 10 and 15 mg per week) starting the dose at 2.5 mg per week and escalating in steps of 2.5 mg per week every 4 weeks. In SURPASS, tirzepatide was compared with placebo and other glucose-lowering medications including the selective GLP-1 agonist semaglutide or basal insulin preparations[71–76].

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Table 1 | Main primary and adverse effects reported in clinical trials investigating selective GLP-1R agonists (semaglutide), dual agonists and triagonists in glycaemic control

Compound/ phase	Indication studied/ comparator	Number of patients	Dosage/initial up-titration? (yes/no)	Interval between doses	Duration	HbA1c (change versus baseline)	Body weight (change versus baseline)	Adverse effects (% reporting nausea)	Discontinuation rate (%)	Ref. and comment
GLP-1 agonist										
Semaglutide (s.c.) Phase 2	T2D/liraglutide	705	0.05, 0.1, 0.2 or 0.3 mg No	Daily (s.c.)	26 weeks	−1.9%	−8.2 kg	25.4%	4.7%	100 Semaglutide at doses up to 0.3 mg per day resulted in greater reductions in HbA1c and body weight compared with liraglutide
Semaglutide (oral) Phase 3	T2D/liraglutide	711	14 mg Yes	Daily (oral)	52 weeks	−1.2%	−5 kg	20%	11%	44 Oral semaglutide was similar to subcutaneous liraglutide in decreasing HbA1c and superior in decreasing body weight
Glucagon–GLP-1 co-agonists										
Cotadutide Phase 2	T2D	61	100, 200, 300 µg No	Daily	48 d	−1.24%	−3.34%	47%	0%	59 Significant improvement in glycaemic control and weight loss
Cotadutide Phase 2	T2D	51	300 µg 200 µg No	Daily	22 d 41 d	−0.9%	−3.84 kg	52%	12%	58 Significant improvement in glycaemic control and weight loss
Cotadutide Phase 2	T2D	65	50–300 µg Yes	Weekly or biweekly	49 d	−0.67%	−3.41%	19%	0%	60 Significant improvement in glycaemic control and weight loss
Cotadutide Phase 2	T2D/liraglutide	834	100 µg, 200 µg, 300 µg No	Daily	54 weeks	−1.19%	−5.02 kg	41%	21.5%	61 Weight loss with cotadutide 200 µg similar to that with liraglutide 1.8 mg and greater with cotadutide 300 µg versus liraglutide 1.8 mg No differences in HbA1c between cotadutide and liraglutide
SAR425899 Phase 1	T2D	36	Escalated dose of 0.03, 0.06 and 0.09 mg, dose regimen 0.06, 0.12 and 0.18 mg Yes	Daily	28 d	−0.59%	−5.46 kg	83.3%	5%	62 Significant improvement in glycaemic control and weight loss
SAR425899 Phase 1	T2D	36	0.03, 0.06 and 0.09 mg or 0.06, 0.12 and 0.18 mg Yes	Daily	28 d	−8.3 mmol min l^{-1}	−5.05 kg	No data	No data	63 Significant improvement in postprandial glucose control and weight loss
SAR425899 Phase 1	T2D/liraglutide	75	0.12, 0.16 and 0.20 mg No	Daily	26 weeks	−1.9%	−3.2 kg	No data	No data	64 SAR425899 and liraglutide had similar effects in postprandial glucose control. Higher enhancement in beta cell function was shown by SAR425899 than liraglutide

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Table 1 (continued) | Main primary and adverse effects reported in clinical trials investigating selective GLP-1R agonists (semaglutide), dual agonists and triagonists in glycaemic control

Compound/ phase	Indication studied/ comparator	Number of patients	Dosage/initial up-titration? (yes/no)	Interval between doses	Duration	HbA1c (change versus baseline)	Body weight (change versus baseline)	Adverse effects (% reporting nausea)	Discontinuation rate (%)	Ref. and comment
GIP–GLP-1 co-agonists										
RG7697/ NNC0090-2746 Phase 1	Pharmacodynamics, pharmacokinetics, safety and tolerability	51	From 0.03 to 5 mg No	Daily	3 d	No effect on glucose AUC	No data	100%	No data	66 Single s.c. injections up to 3.6 mg were generally well tolerated
RG7697/ NNC0090-2746 Phase 2	T2D/liraglutide	108	1.8 mg No	Daily	12 weeks	−1.36%	−3.43%	35.1%	10.8%	67 Similar effects between RG7697 and liraglutide on glucose and body weight
LY3298176/ tirzepatide Phase 1	T2D	56	Single-ascending dose: 0.25–8 mg Yes	Weekly	4 weeks	−0.46%	−1.75 kg	0%	0%	68 Significant improvement in glycaemic control and weight loss
LY3298176/ tirzepatide Phase 1	T2D/dulaglutide	33	Multiple-ascending doses: 0.5–10 mg Yes	Weekly	4 weeks	−1%	−5.09 kg	57.1%	0%	68 Tirzepatide achieved weight loss greater than with dulaglutide
LY3298176/ tirzepatide Phase 2	T2D/dulaglutide	318	1 mg, 5 mg, 10 mg, or 15 mg No	Weekly	26 weeks	−1.94%	−11.3 kg	39.6%	24.5%	69 Tirzepatide showed greater efficacy on body weight loss and glucose control compared to dulaglutide
LY3298176/ tirzepatide phase 3	T2D/semaglutide	478. SURPASS-1	5, 10 or 15 mg Yes	Weekly	40 weeks	−2.07% versus 0.04%	−9.5 kg	18%	7%	71 Significant improvement in glycaemic control and weight loss
LY3298176/ tirzepatide phase 3	T2D/semaglutide	1878. SURPASS-2	5 mg, 10 mg or 15 mg Yes	Weekly	40 weeks	2.3%	−11.2 kg	22%	8.5%	72 Reductions in body weight and glucose were greater with tirzepatide than with semaglutide
LY3298176/ tirzepatide Phase 3	T2D/insulin degludec	2874. SURPASS-3	5 mg, 10 mg or 15 mg Yes	Weekly	52 weeks	−2.37%	−12.9 kg	24%	11%	73 Tirzepatide induced more nausea than insulin degludec
LY3298176/ tirzepatide Phase 3	T2D/insulin glargine	1995. SURPASS-4	5 mg, 10 mg or 15 mg Yes	Weekly	52–104 weeks	−2.58%	−11.7 kg	23%	11%	74 Tirzepatide had superior effect reducing HbA1c than glargine, and the percentage of nausea was also higher than glargine
LY3298176/ tirzepatide Phhase 3	T2D	475. SURPASS-5	5 mg, 10 mg or 15 mg Yes	Weekly	40 weeks	−2.59%	−8.8 kg	18%	10.8%	75 Significant improvement in glycaemic control and weight loss
GLP-1R–GIP-R–glucagon triagonists										
SAR441255 Phase 1	Pharmacodynamics, pharmacokinetics, safety and tolerability	48	3, 9, 20, 40, 80 or 150 µg No	Single dose	12 h	3.75 mmol l^{-1} glucose versus approxi-mately 4 mmol l^{-1}	No data	50%	0%	87 Adverse effects, similar to those reported for GLP-1R and dual agonists
LY3437943 Phase 1	T2D/dulaglutide	47	0.1, 0.3, 1, 3, 4.5 or 6 mg Yes	Single dose	43 d	Not significant	−3.52 kg	40%	0%	90 Superior effect than dulaglutide in reducing HbA1c and body weight

Only representative trials using semaglutide are indicated to summarize its efficacy (higher than other GLP-1 agonists). AUC, area under the curve. HbA1c: maximum change from baseline to the end of the study at all the doses used. Body weight: maximum change from baseline to the end of the study at all the doses used. Adverse effects: maximum percentage of nausea (as the main treatment-emergent adverse event) to the end of the study at all the doses used.

Overall, these studies have shown that tirzepatide reduced HbA1c and fasting glucose levels more efficiently than titrated insulin degludec[73] and insulin glargine[75,76] or semaglutide (1 mg per week, the standard dose used in most T2D trials)[72]. The reduction in HbA1c was independent of age, duration of diabetes or baseline levels of HbA1c (reviewed in ref. 70). Regardless of the high efficacy of tirzepatide in controlling glycaemia, it must be noted that approximately 11% of the patients did not respond to the highest dose.

In addition, tirzepatide has been also shown to reduce liver fat content as well as visceral and subcutaneous adipose tissue in a trial involving 296 patients with T2D[77] and improved kidney outcomes in patients with T2D (2,002 individuals from SURPASS-4) by slowing the estimated glomerular filtration rate and lowering the urine albumin:creatinine ratio[76]. Similarly to selective GLP-1 agonists, the main adverse effects found in these trials with tirzepatide were nausea, vomiting, diarrhoea and constipation, perhaps slightly less than with dulaglutide (phase 2)[78] or semaglutide (phase 3)[72] at doses resulting in equivalent glycaemic or body weight control[70].

Two recent multicentre, randomized, phase 3 trials were carried out in Japanese populations (SURPASS J programme). One of those studies (SURPASS J-mono) compared the efficacy and safety of tirzepatide with dulaglutide and showed a superior effect of tirzepatide for glycaemic control and reduction in body weight with a similar safety profile[79]. In another study (SURPASS J-combo), patients with inadequately controlled T2D who were receiving oral antihyperglycaemic monotherapy received 5, 10 or 15 mg per week of tirzepatide (same escalation schedule as described above) for 52 weeks[80]. Tirzepatide showed improvement in glycaemic control and body weight, independent of the type of oral antihyperglycaemic medication and was also well tolerated[80]. Some other additional effects of tirzepatide were to lower the concentrations of very-low-density lipoproteins and triglycerides, reducing blood pressure and increasing high-density lipoprotein concentrations. Interestingly, the SURPASS trials have detected a positive correlation between weight loss and the decrease in HbA1c in participants receiving tirzepatide[70], indicating that the degree of weight reduction obtained impacts on metabolic health.

Given the efficacy of the compound in reducing body weight in patients with T2D, the effect of tirzepatide as an antiobesity drug has also been investigated in the SURMOUNT-1 trial (part of the SURMOUNT programme). This phase 3 double-blind, randomized, controlled trial enrolled 2,539 adults with a BMI of 30 or more, or 27 or more and at least one weight-related complication, excluding diabetes, who received once-weekly subcutaneous tirzepatide (5, 10 or 15 mg) or placebo for 72 weeks[81]. The reduction in body weight in response to therapy with tirzepatide shows high inter-individual heterogeneity. The range of changes versus baseline in body weight with the highest dose, 15 mg per week, ranged from −38.4 kg to + 9.0 kg in patients with T2D (1) and from −38.4 kg to +9.0 kg in individuals with obesity but without diabetes mellitus (2). In the one T2D study reporting such details (online supplementary material in ref. 73), weight reduction with 5, 10 and 15 mg per week tirzepatide was −7.5 ± 0.4 kg, −10.7 ± 0.4 kg and −12.9 ± 0.4 kg, respectively (mean ± s.e.m.), and 1.5%, 1.0% and 0.5% of these populations either had no weight loss, or even a weight gain versus baseline, respectively, and could be addressed as non-responders. In the treatment of obesity without T2D, these figures were −15.4 ± 0.5 kg, −20.7 ± 0.5 kg and −22.1 ± 0.5 kg, respectively, and 3.5%, 2.5% and 2.0% without weight loss or even with weight gain (online Supplementary material in ref. 81).

For comparison, in patients with T2D, the selective GLP-1R agonist semaglutide led to an average weight reduction of 3.7 ± 0.4 kg and 4.5 ± 0.4 kg with doses of 0.5 mg and 1.0 mg per week in T2D patients, respectively, with 16% and 15% of the patients displaying no weight loss or even weight gain[82]. In a study comparing higher doses of semaglutide (2.4 mg per week) and liraglutide (3 mg per day) than those used for the treatment of T2D, for the treatment of obese individuals without T2D, body weight reductions were 15.3 ± 1.0 kg and 6.8 ± 1.0 kg, respectively, and 6.5% and 17.5%, respectively, failed to achieve any weight loss or displayed weight gain[46]. The main adverse effects were similar to the ones reported in SURPASS trials with patients with T2D.

Obviously, the proportion of body weight reduction non-responders when using GLP-1R agonists or the dual agonist tirzepatide tends to be smaller with more effective therapy, for example, with higher doses of tirzepatide, or with more effective agents (tirzepatide versus selective GLP-1R agonists). With respect to the probability of a non-response regarding body weight reduction, there is no obvious difference in comparing the treatment of individuals with T2D versus individuals without diabetes (except the greater overall efficacy in individuals without diabetes[73,81]). It should be noted that the inter-individual variability in therapeutic responses generally is lower for effects on glycaemic control. The high inter-individual variability in body weight responses may be related to individual dispositions for hypothalamic responses to food images after the administration of GLP-1R agonists[83].

These findings indicate that tirzepatide may be a potential therapeutic option for individuals living with obesity. Actually, on 6 October 2022, the FDA granted fast-track designation for the investigation of tirzepatide for the treatment of adults with obesity, or overweight adults with weight-related comorbidities (Fig. 2 and Tables 1 and 2).

GLP-1R–GIP-R–glucagon triagonists in clinical trials

In 2015, after the development of the first dual agonists, a unimolecular triple agonist combining the activity at GLP-1R–GIP-R–glucagon receptors was reported. The metabolic benefits of this triagonist were superior to those of a GLP-1–GIP co-agonist in obese male mice, displaying a higher reduction in body weight as well as a more significant decrease in circulating concentrations of insulin and cholesterol[84]. A subsequent study showed that the effect of the triagonist on body weight was equally efficient in male and female mice, but in females the reversion of diet-induced steatohepatitis was clearer[85]. Similar results were obtained by the same team using a GLP-1R–GIP-R–glucagon receptor triagonists with optimized receptor potency ratio, which reduced body weight in diet-induced obese mice more efficiently than GLP-1R mono-agonists and GLP-1R/GIPR co-agonists[86].

Early in 2022, the first report addressing the effects of a GLP-1R–GIP-R–glucagon receptor triagonist, namely SAR441255, in obese diabetic monkeys and lean-to-overweight healthy humans was published[87]. SAR441255 decreased body weight in obese monkeys by 12% after 7 weeks. Moreover, a phase 1 study enrolling 48 participants tested single ascending subcutaneous doses of SAR441255 (3, 9, 20, 40, 80 and 150 µg) or placebo, and found that the two highest doses reduced fasting blood glucose levels and postprandial circulating glucose[87]. Single doses of SAR441255 were well tolerated and 'gastrointestinal' symptoms were the most frequent adverse effects, similar to what has been reported for GLP-1R and dual agonists[87]. However, the development programme for SAR441255 was discontinued.

More recently, a novel GLP-1R–glucagon receptor–gastrin triagonist was tested in different models of the metabolic syndrome, namely db/db and diet-induced obese mice, showing that the anti-diabetic effect of this triagonist was superior to cotadutide and liraglutide, while its antiobesity effect was comparable to cotadutide but was significantly better than liraglutide[88]. Finally, another GLP-1–glucagon–GIP triagonist (LY3437943), also reduced weight gain, fat mass, blood glucose and insulin levels in diet-induced obese mice[89]. These effects were, at least partially, mediated by an increased energy expenditure and lipid oxidation. The same study also reported a phase 1 study enrolling 47 healthy participants receiving a single ascending dose of LY3437943 (0.1, 0.3, 1, 3, 4.5 or 6 mg) or placebo[89]. Fasting glucose levels did not change from baseline to day 43 (as these participants had no diabetes), but fasting triglycerides were reduced at day 8 for 3 mg and 6 mg doses,

Table 2 | Main primary and adverse effects reported in clinical trials investigating selective GLP-1R agonists (semaglutide), dual agonists and triagonists in body weight control in patients without T2D

Compound/ phase	Indication studied/ comparator	Number of patients	Dosage/ initial up-titration? (yes/no)	Interval between doses	Duration	Body weight (change versus baseline)	Adverse effects (percentage reporting nausea)	Discontinuation rate (%)	Ref. and comment
GLP-1 agonist									
Semaglutide/ placebo/ phase 2	Obesity/placebo	1961	2.4 mg Yes	Weekly	69 weeks	−15.3 kg	62.6%	4.5%	43 Substantial and sustained weight loss
Semaglutide/ liraglutide/ phase 3	Obesity/ liraglutide	338	2.4 mg Yes	Weekly	68 weeks	−15.3 kg	61.1%	3.2%	46 Greater weight loss than daily liraglutide (added to counselling for diet and physical activity)
GIP–GLP-1 co-agonists									
LY3298176/ tirzepatide /phase 3	Obesity/placebo	2,539	5 mg, 10 mg or 15 mg Yes	Weekly	72 weeks	−20.9%	33.3%	7.1%	81 Substantial and sustained weight loss

Body weight: maximum change from baseline to the end of the study at all the doses used. **Adverse effects:** maximum percentage of nausea (as the main treatment-emergent adverse event) to the end of the study at all the doses used.

and body weight was also decreased in a dose-dependent manner, with differences that were significant when compared to placebo at days 8 through 43 (ref. 89). According to appetite visual analogue scores, LY3437943 doses of 0.3 mg and higher showed a reduction in appetite, which was highest at day 2 and day 3 after dose[89]. The proportion of participants with treatment-emergent adverse events increased from 16.7% to 100% with increased doses of LY3437943 compared to 30% in the placebo arm, and the most frequent events were 'gastrointestinal' disorders such as vomiting, abdominal distention and nausea[89].

A further phase 1b trial investigated adults with T2D who received once-weekly subcutaneous injections of LY3437943 at 0.5 mg ($n = 9$), 1.5 mg ($n = 9$), 3 mg ($n = 11$), 3/6 mg ($n = 11$) and 3/6/9/12 mg ($n = 12$); placebo ($n = 15$); or dulaglutide 1.5 mg ($n = 5$) over a 12-week period[90]. LY3437943 showed a half-life of approximately 6 d and treatment-emergent adverse events were reported by 63%, 60% and 54% of participants who received LY3437943, dulaglutide and placebo, respectively, with gastrointestinal disorders being the most frequent ones. At week 12, plasma glucose and HbA1c significantly decreased from baseline at the three highest-dose LY3437943 groups. The reduction in body weight with LY3437943 was dose dependent (up to −9.0 kg in the 3-, 6-, 9- and 12-mg groups; ref. 90, Fig. 2 and Table 1).

Another triagonist, named HM15211 has been presented by Hanmi Pharmaceuticals in preclinical models of T2D, non-alcoholic steatohepatitis and Parkinson disease[91,92]. In mice, HM15211 injected every other day reduced body weight, reduced hyperglycaemia and increased energy expenditure at a higher extent than twice-daily liraglutide[92]. HM15211 significantly lowered blood cholesterol and hepatic steatosis in high-sucrose-fed rats and methionine choline–deficient mice, two models of non-alcoholic steatohepatitis[92]. A phase 1 study was designed to assess safety, pharmacokinetics and pharmacodynamics of a single subcutaneous dose of HM15211 in people with obesity but otherwise healthy adults (41 adults with mean BMI 33.6 kg/m^2). HM15211 was safe and well tolerated, and there were no serious adverse events and no discontinuations[93]. There are other GLP-1R–GIP-R–glucagon receptor triagonists in phase 1 and phase 2 (NCT03661879), but results have not been disclosed yet.

Concluding remarks and future perspectives

Pharmacotherapy for obesity and its consequences has, in principle, been available. But certainly, limited effectiveness and side effects have prohibited widespread use and have led to withdrawal of such treatments from the market. Meanwhile, bariatric surgery, the most effective procedure to reduce body weight, has significantly improved in terms of safety and has been more widely used recently. However, the efficacy of novel drugs like semaglutide and, most recently, tirzepatide to decrease body weight and the management of glycaemia may have opened a new era in the treatment of obesity and T2D.

Currently, dual agonists or triagonists are being developed and studied in preclinical models. Typically, dual agonists have been found to be more efficacious than mono-agonists, and triagonists were even more effective, and are now entering clinical development. Despite the remarkable additions to our therapeutic armamentarium, some issues still deserve our attention: (a) Despite the high efficacy of tirzepatide in controlling glycaemia, approximately 11% of the patients did not even reach an HbA1c < 7.0%. This indicates heterogeneity among T2D patients and differential responses even to such effective treatments. (b) The mechanism of action for especially GIP–GLP-1 co-agonists is still far from clear, in particular concerning the role of GIP-R agonism in improving glycaemic control and body weight regulation. Regardless of our incomplete understanding of how multi-agonists trigger their biological actions, the initial results in patients with obesity and T2D are highly promising, and may help in defining a new role for antiobesity treatment as part of diabetes management, or to reduce other adverse consequences of obesity[94,95], and lead to a more widespread use to effectively counter the present obesity/diabetes mellitus pandemic.

Given the increasing prevalence of obesity in adolescents, it will also be interesting whether these new multi-agonists are efficient in this population. In this sense, GLP-1R agonists have been tested: liraglutide (3.0 mg) plus lifestyle therapy reduced BMI standard-deviation score more significantly than placebo plus lifestyle therapy[96] and once-weekly treatment with a 2.4-mg dose of semaglutide plus lifestyle intervention resulted in a greater reduction in BMI than lifestyle intervention alone[97]. In terms of T2D, mono-agonists also showed some positive results: in children and adolescents with T2D, liraglutide (1.8 mg) per day added to metformin not only improved glycaemic control over 52 weeks but also caused increased frequency of gastrointestinal adverse events[98]. Treatment with dulaglutide (once weekly, 0.75 mg or 1.5 mg) also improved glycaemic control over 26 weeks among youths with T2D[99]. However, these effects of GLP-1R agonists on glycaemic control in adolescents were limited, so multi-agonists might have a greater potential in this population. Given some similarity and overlap regarding the mechanisms of action of Roux-en-Y gastric bypass or

sleeve gastrectomy[9], unimolecular peptide multi-agonists activating two or more relevant gastroenteropancreatic hormone receptors may eventually replace bariatric procedures by offering highly effective pharmacotherapy with similar metabolic outcomes.

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Author contributions

Conceptualization, writing, editing and revising were a joint effort by R.N., M.A.N. and M.H.T.

Competing interests

R.N. declares no competing interests. M.A.N. has been a member on advisory boards or has consulted with Boehringer Ingelheim, Eli Lilly & Co., Medtronic, Merck, Sharp & Dohme, NovoNordisk, Pfizer, Regor, Sun Pharma and Structure Therapeutics (ShouTi, Gasherbrum). M.A.N. has received grant support from Merck, Sharp & Dohme. M.A.N. has also served on the speakers' bureau of Eli Lilly & Co., Menarini/Berlin Chemie, Merck, Sharp & Dohme, Medscape, Medical Learning Institute and NovoNordisk. M.H.T. is a member of the scientific advisory board of ERX Pharmaceuticals. M.H.T. was a member of the Research Cluster Advisory Panel (ReCAP) of the Novo Nordisk Foundation between 2017 and 2019. M.H.T. attended a scientific advisory board meeting of the Novo Nordisk Foundation Center for Basic Metabolic Research, University of Copenhagen, in 2016. M.H.T. received funding for his research projects from Novo Nordisk (2016–2020) and Sanofi-Aventis (2012–2019). M.H.T. was a consultant for Bionorica SE (2013–2017), Menarini Ricerche S. p.A. (2016) and Bayer Pharma AG Berlin (2016). As former Director of the Helmholtz Diabetes Center and the Institute for Diabetes and Obesity at Helmholtz Zentrum München (2011–2018), and since 2018, as CEO of Helmholtz Zentrum München, M.H.T. has been responsible for collaborations with a multitude of companies and institutions worldwide. In this capacity, M.H.T. discussed potential projects with and has signed/signs contracts for his institute(s) and for the staff for research funding and/or collaborations with industries and academia worldwide, including, but not limited to, pharmaceutical corporations like Boehringer Ingelheim, Eli Lilly, Novo Nordisk, Medigene, Arbormed, BioSyngen and others. In this role, M.H.T. was/is further responsible for commercial technology transfer activities of his institute(s), including diabetes-related patent portfolios of Helmholtz Zentrum München as, for example, WO/2016/188,932 A2 or WO/2017/194,499 A1.

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