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INVITED REVIEW

The future of incretins in the treatment of obesity and non-alcoholic fatty liver disease

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Abstract

In the last few decades, glucagon-like peptide-1 receptor (GLP-1R) agonists have changed current guidelines and improved outcomes for individuals with type 2 diabetes. However, the dual glucose-dependent insulinotropic polypeptide receptor (GIPR)/GLP-1R agonist, tirzepatide, has demonstrated superior efficacy regarding improvements in HbA_{1c} and body weight in people with type 2 diabetes. This has led to increasing scientific interest in incretin hormones and incretin interactions, and several compounds based on dual- and multi-agonists are now being investigated for the treatment of metabolic diseases. Herein, we highlight the key scientific advances in utilising incretins for the treatment of obesity and, potentially, non-alcoholic fatty liver disease (NAFLD). The development of multi-agonists with multi-organ targets may alter the natural history of these diseases.

Keywords Glucagon-like peptide-1 · Glucose-dependent insulinotropic polypeptide · Incretins · Non-alcoholic fatty liver disease · Obesity · Review

Abbreviations

GCGR	Glucagon receptor
GIP	Glucose-dependent insulinotropic polypeptide
GIPR	Glucose-dependent insulinotropic polypeptide receptor
GLP-1	Glucagon-like peptide-1
GLP-1R	Glucagon-like peptide-1 receptor
NAFLD	Non-alcoholic fatty liver disease
NASH	Non-alcoholic steatohepatitis
STEP	Semaglutide Treatment Effect in People with Obesity

Introduction

Obesity is one of the biggest health challenges, affecting millions of individuals worldwide. It is associated with decreased quality of life and disabling complications, shortening lives, and costing billions in healthcare costs and loss of workability [1, 2]. Since 2006, glucagon-like peptide-1 receptor (GLP-1R) agonists have caused a dramatic change in the treatment of type 2 diabetes, with clinically relevant and sustained effects on glycaemic control and body weight combined with cardioprotective mechanisms [3, 4]. The body-weight lowering effect of GLP-1R agonists has subsequently been utilised for the treatment of obesity. Until recently, no therapeutic potential was associated with the other incretin hormone, glucose-dependent insulinotropic polypeptide (GIP), as preclinical studies have suggested potential obesogenic effects. However, the dual GIP receptor (GIPR)/GLP-1R agonist, tirzepatide, has demonstrated superior efficacy in reducing HbA_{1c} and body weight in people with type 2 diabetes [5]. The emergence of GIPR/GLP-1R co-agonists has fostered a growing interest in the actions of GIP and glucagon-like peptide-1 (GLP-1) in metabolically relevant tissues, including liver, muscle and adipose tissue, regarding the control of glucose and lipid homeostasis. Interestingly, the discovery of poly-agonist drugs that activate multiple gut–brain pathways promises

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to further transform the management of metabolic diseases besides type 2 diabetes, including obesity and non-alcoholic fatty liver disease (NAFLD) [6–8]. With NAFLD affecting 25–30% of the global population, up to 60–70% of people with type 2 diabetes and almost all individuals with severe obesity [9, 10], an available pharmacotherapy for NAFLD is highly warranted.

This review highlights established and emerging concepts regarding the use of incretins for controlling body weight and treating obesity and, potentially, NAFLD.

Incretin hormones in the regulation of body weight

The knowledge of the complex mechanisms controlling body weight is evolving rapidly. However, the understanding of hunger, satiety and weight control is still mainly based on findings from preclinical studies with rather limited translational value in humans. In addition, limited data are available on the pathophysiological neuroendocrine regulation of satiety in the development of human obesity.

GIP was the first incretin hormone to be discovered; however, the understanding of GIP's biology was overshadowed by research focusing on GLP-1 and its impact in diabetes and obesity treatment [4, 11–14]. Today it is recognised that the hypothalamus is a key region of the brain that is implicated in homeostatic regulation and is suggested to be an integral centre for the control of feeding behaviour [15, 16]. It has also been shown that neuronal tissue has a dense expression of both the GIPR and the GLP-1R [17]. Interestingly, exogenously administered GIP and GLP-1 seem to access the brain predominately via leaks in the blood–brain barrier, where the underlying neuronal tissue has dense expression of their receptors [11–13, 17] (Fig. 1). However, early work indicated that GIP was obesogenic (Fig. 1), limiting interest in developing GIPR agonists to treat type 2 diabetes [18]. However, recent GIP research has reinvigorated interest in this peptide, and paradoxical observations with different approaches have been discussed for treating obesity, one promoting GIPR agonism and the other GIPR antagonism [19]. Different hypotheses are considered, including a compensatory relationship between incretin receptors by which GIPR enhances GLP-1R activity and/or that chronic GIPR agonism produces desensitisation and loss of GIPR activity, thus, mimicking antagonism. However, a more profound understanding of GIP biology in relation to satiety and body weight remains to be fully elucidated [19].

In contrast to GIP, a substantial number of preclinical and clinical studies link GLP-1 as a central peptide that, through hormonal and neural pathways, not only regulates pancreas function but also hunger and satiety (Fig. 1). The importance of brain-derived GLP-1, the direct vs indirect actions of GLP-1 and GLP-1-induced control of neural activity is extensively discussed since many organs and cellular targets of GLP-1 action do not exhibit detectable levels of GLP-1R [20–23]. Studies using exogenous GLP-1 infusion in humans demonstrated reduced energy intake, reduced appetite and decreased brain responses to food anticipation and consumption without direct changes in energy expenditure, and data strongly suggest that body-weight loss ensuing from GLP-1R agonist administration in humans largely reflects reductions in food intake [24, 25]. Whereas the relative contribution of brain-derived GLP-1, which is synthesised in the nucleus of the solitary tract, on the reduction in food intake or body weight remains to be elucidated [16].

GLP-1R agonists were initially developed for the treatment of type 2 diabetes. However, due to their efficacy in inducing body-weight loss, extensive evidence with high doses of GLP-1R agonists have demonstrated clinically relevant and sustained effects on body weight in obesity [26]. Recently, through the engagement of their respective receptors, studies have shown that GIP and GLP-1 have a synergistic effect on appetite and body weight when the peptides are combined in pharmacology [6, 8], but the exact mechanisms underlying the enhanced weight loss exhibited by GIPR/GLP-1R co-agonism are still to be elucidated.

Incretin-based therapies for treatment of obesity

The concept of incretin-based treatment of overweight and obesity was driven by the effect of native GLP-1 and GLP-1R agonists on appetite and satiety in combination with an observed loss in body weight in trials investigating liraglutide for the treatment of type 2 diabetes [27]. The first incretin-based treatment regimen to be approved for the management of overweight and obesity was liraglutide 3.0 mg once-daily, which was followed by semaglutide 2.4 mg once weekly [16]. Recently, the dual GIPR/GLP-1R co-agonist, tirzepatide, has demonstrated a marked effect on body weight in individuals with overweight and obesity, and Phase III trials of this drug are expected to be completed in 2023 [28].

Body-weight reductions The efficacy and safety of liraglutide for the treatment of overweight and obesity was investigated in the Satiety and Clinical Adiposity – Liraglutide Evidence (SCALE) programme [29–33]. The trials included individuals with overweight (BMI ≥27 kg/m^2) and ≥1 weight-related complication, including dyslipidaemia, hypertension, sleep apnoea, impaired glucose tolerance and/or impaired fasting glucose and type 2 diabetes, or individuals with obesity (BMI ≥30 kg/m^2) with or without complications. When combined with lifestyle changes and not

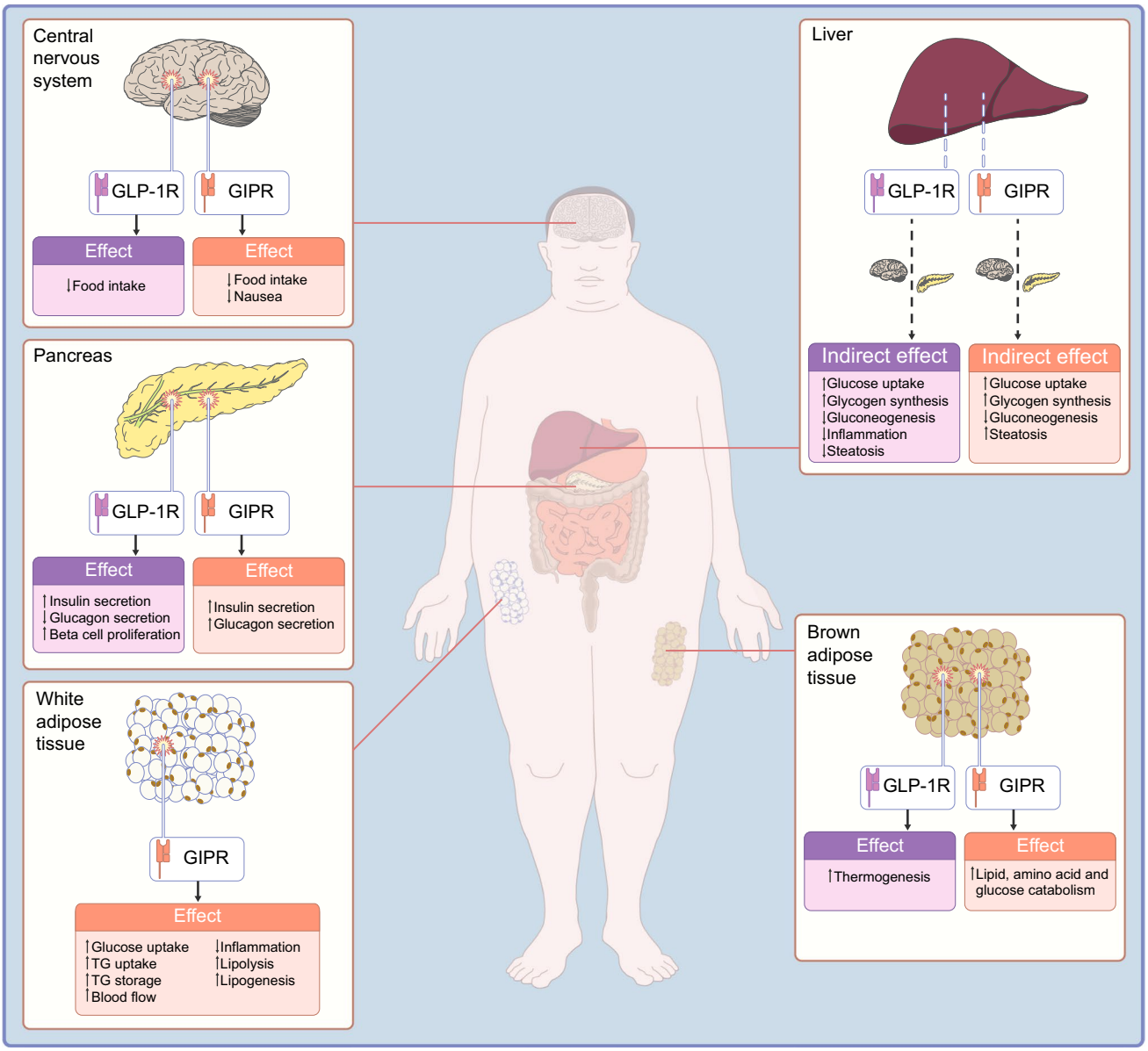

Fig. 1 Simplified summary of the biological actions of GIP and GLP-1 as pharmacological targets in obesity and NAFLD. In the liver, GIP and GLP-1 have indirect effects that may be generated by changes in plasma insulin and glucagon concentrations (depicted by the image of the pancreas) and neural regulation signals (depicted by the image of the brain). Solid lines, direct effects; dashed lines, indirect effects. TG, triglycerides. This figure is available as part of a downloadable slideset

preceded by body-weight loss due to low-energy diet, daily administration of 3.0 mg of liraglutide provided an additional body-weight loss of 4.0–5.4% compared with placebo [30–32] (Fig. 2), which was sustained after 3 years of treatment [33]. Although providing clinically meaningful body-weight loss, the efficacy of once-daily liraglutide has been markedly exceeded by 2.4 mg of semaglutide once weekly [34]. The efficacy and safety of weekly semaglutide (2.4 mg) for the treatment of overweight and obesity was investigated in the Semaglutide Treatment Effect in People with Obesity (STEP) programme, which included individuals with overweight (BMI ≥27 kg/m^2) and complications, including dyslipidaemia, hypertension, sleep apnoea, cardiovascular disease and type 2 diabetes, or individuals with obesity (BMI ≥30 kg/m^2) with or without complications [26, 34–39]. Compared with placebo, the smallest percentage body-weight loss was observed in individuals with type 2 diabetes, with an estimated treatment difference of 6.2% after 68 weeks of treatment [35], whereas an additional body-weight loss of 10.3–12.5% after 68 weeks of treatment (without prior run-in with semaglutide) was observed in individuals without diabetes in trials aiming to directly

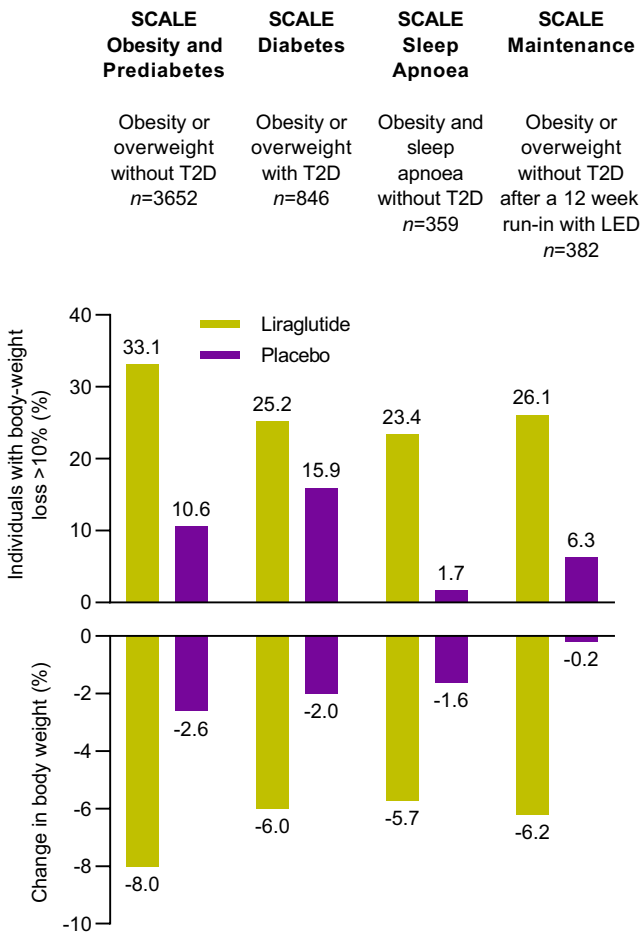

Fig. 2 Overview of body-weight loss in the Satiety and Clinical Adiposity – Liraglutide Evidence (SCALE) trials. In all trials, participants were administered 3.0 mg of liraglutide daily or placebo. The SCALE trials included individuals with overweight (BMI ≥27 kg/m^2) and ≥1 weight-related complication, including dyslipidaemia, hypertension, sleep apnoea, impaired glucose tolerance, impaired fasting glucose and type 2 diabetes, or individuals with obesity (BMI ≥30 kg/m^2) with or without complications. The SCALE Obesity and Prediabetes trial included individuals with obesity/overweight without type 2 diabetes (*n*=3652), SCALE Diabetes participants had obesity/overweight with type 2 diabetes (*n*=846), SCALE Sleep Apnoea participants had obesity and sleep apnoea without type 2 diabetes (*n*=359), and SCALE Maintenance involved individuals who had obesity/overweight without type 2 diabetes and were randomised after achieving a ≥5% body-weight loss after following a low-energy diet for 12 weeks (*n*=382). Data are reported as observed means for change in body weight and proportions for individuals with body-weight loss >10%, using the last observation carried forward, except for SCALE Diabetes for which data are estimated means using multiple imputations. LED, low-energy diet; T2D, type 2 diabetes. This figure is available as part of a downloadable slideset

compare semaglutide with placebo [26, 36, 38, 39] (Fig. 3). In a head-to-head trial, mean body-weight loss was 15.8% with semaglutide compared with 6.4% in the liraglutide group [34] (Fig. 3). A continuous decline in body weight for the first 60 weeks of treatment with semaglutide has been demonstrated, followed by a stable body weight for up to 104 weeks with continued treatment [38]. Importantly, discontinuation of semaglutide after 20 weeks of treatment led to regain of body weight, whereas maintaining treatment led to continued body-weight loss over an additional 48 weeks of treatment, underlining that life-long treatment is necessary to maintain treatment effect [37]. Recently, semaglutide (2.4 mg once weekly) has also been investigated for the treatment of childhood obesity in children aged 12 years to <18 years with overweight (BMI ≥85th percentile) and ≥1 weight-related complication, or with obesity (BMI ≥95th percentile) [40]. In children receiving lifestyle intervention, semaglutide resulted in an additional 16.7% body-weight loss compared with placebo.

Safety GLP1-R agonists have been utilised in clinical practice for decades and long-term safety is well described. Though adverse effects of the emerging co-agonists have been extensively studied in developmental programmes, potential long-term adverse effects cannot be excluded for obvious reasons. Adverse events in relation to GLP-1R agonists for the treatment of obesity are mainly gastrointestinal side effects, including nausea, diarrhoea, vomiting and constipation, which is consistent with observations in type 2 diabetes, and rates of discontinuation due to adverse events are generally higher with GLP-1R agonists treatment compared with placebo [26, 30–39]. Furthermore, there is an increased risk of gallbladder-related disorders, which is consistent with the known association between rapid weight loss and gallbladder-related disorders [41, 42]. The STEP 8 trial demonstrated similar rates of adverse events for semaglutide and liraglutide, but with less discontinuation due to adverse events with semaglutide [33]; however, it should be noted that this study had a relatively small number of participants (*n*=338) [34].

Future incretin-based therapies Future research in incretin-based treatment of overweight and obesity aims to investigate the potential of combining GLP-1-R agonism with the targeting of other peptide hormones to achieve synergistic effects, with the most prominent targets of interest being the GIPR, the glucagon receptor (GCGR) and the amylin receptor [16]. GIPR/GLP-1R co-agonism has already proved efficient in clinical trials in obesity. Results from the first Phase III trial in obesity and overweight investigating the GIPR/GLP-1R co-agonist tirzepatide, which is currently approved for the treatment of type 2 diabetes and has resulted in marked body-weight reductions in type 2 diabetes [5, 43–46], were published in 2022 [28]. In this trial, three doses of tirzepatide (5 mg, 10 mg and 15 mg once weekly) were compared with placebo in individuals with overweight (BMI ≥27 kg/m^2) and complications, or with obesity (BMI ≥30 kg/m^2). Individuals with diabetes

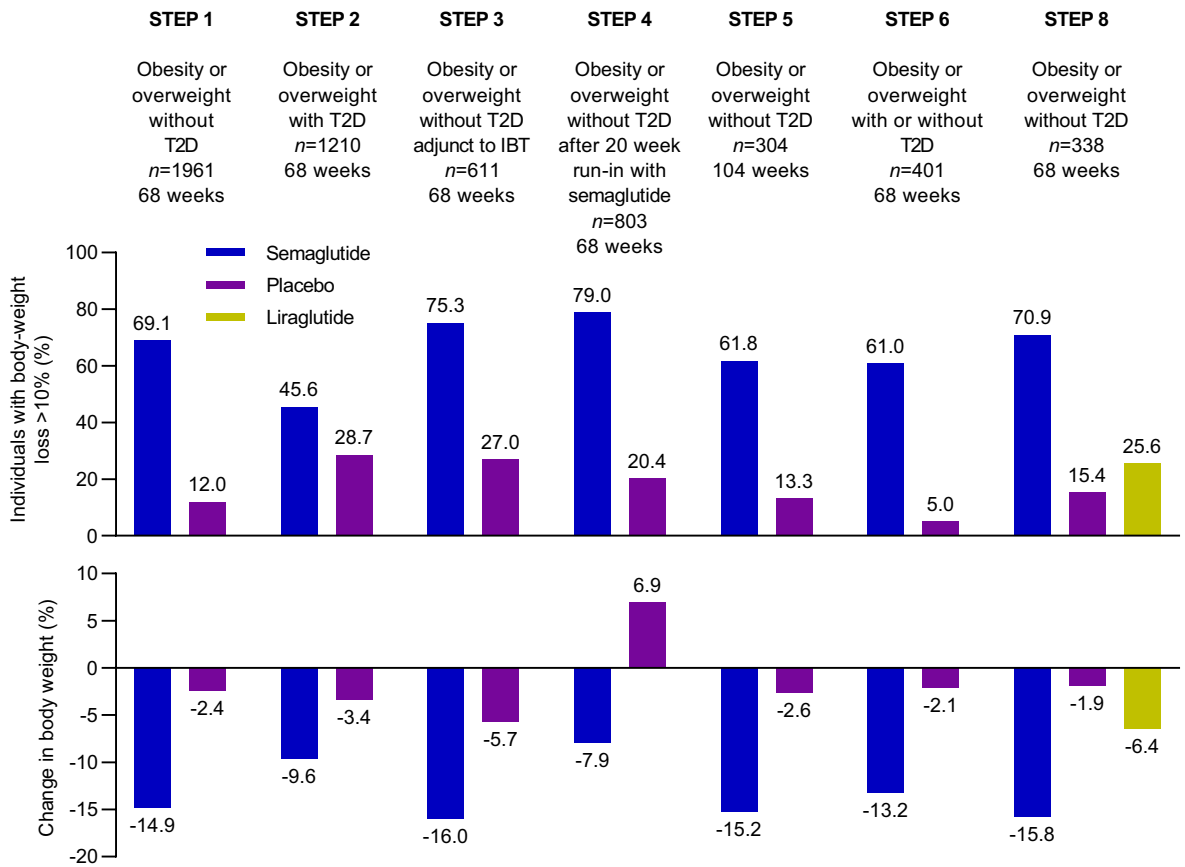

Fig. 3 Overview of body-weight loss in the STEP trials. The STEP programme included individuals with overweight (BMI ≥27 kg/m^2) and complications, including dyslipidaemia, hypertension, sleep apnoea, cardiovascular disease and type 2 diabetes, or individuals with obesity (BMI ≥30 kg/m^2) with or without complications. Participants were administered 2.4 mg of semaglutide once weekly or placebo and were observed for 68 weeks in all trials apart from the STEP 5 trial, in which they were observed for 104 weeks. The STEP 1 trial included individuals with obesity/overweight without type 2 diabetes (*n*=1961), STEP 2 participants had obesity/overweight with type 2 diabetes (*n*=1210), STEP 3 participants had obesity/overweight without type 2 diabetes and received semaglutide/placebo as an adjunct to intensive behavioural therapy (*n*=611), STEP 4 participants had obesity/overweight without type 2 diabetes and were observed after taking semaglutide for 20 weeks (*n*=803), STEP 5 participants had obesity/overweight without type 2 diabetes (*n*=304), STEP 6 participants had obesity/overweight with or without type 2 diabetes (*n*=401), and the STEP 8 trial included individuals who had obesity/overweight without type 2 diabetes who were either allocated (3:1:3:1) to receive semaglutide or matching placebo, or 3.0 mg of liraglutide daily or matching placebo (*n*=338). Data are reported as observed means for change in body weight and proportions for individuals with body-weight loss >10%, and represent the treatment policy estimands (intention-to-treat analysis). IBT, intensive behavioural therapy; T2D, type 2 diabetes. This figure is available as part of a downloadable slideset

were excluded. Compared with placebo, tirzepatide provided an additive body-weight loss of 11.9%, 16.4% and 17.8% with an increasing dose of 5 mg, 10 mg and 15 mg, respectively, and 83.5% of participants in the 15 mg group had ≥10% body-weight loss [28]. Recently, after 72 weeks of treatment, adults with obesity or overweight and type 2 diabetes had a mean weight loss of 12.8% and 14.7% with 10 mg and 15 mg tirzepatide, respectively, vs 3.2% with placebo [47]. In the group treated with 15 mg of tirzepatide, 48% had ≥15% body-weight loss. Tirzepatide has not been directly compared with semaglutide 2.4 mg in individuals with overweight or obesity; however, when compared with semaglutide 1.0 mg in type 2 diabetes, in doses of 5 mg, 10 mg and 15 mg, tirzepatide resulted in significantly greater body-weight reductions [5]. As alluded to above, the rationale for combining GLP-1R agonism with either GIPR agonism or antagonism is, however, still debated, and how the GIPR agonistic properties of tirzepatide contribute to body-weight loss remains unclear [19]. It is noteworthy that the combined GIPR antagonist and GLP-1R agonist AMG 133 demonstrated a body-weight loss of 14.5% at the highest dose (420 mg every 4 weeks) after 12 weeks in a Phase I trial, and this compound will now enter Phase II trials [48]. Hence, research is needed to elucidate the underlying mechanisms of GIPR as a therapeutic target in obesity.

Currently, several co- and tri-agonists targeting the GLP-1R and the GIPR in combination with the GCGR are under investigation for metabolic conditions including

obesity. Previous studies have demonstrated a synergistic effect of co-infusion of GLP-1 and glucagon on food intake, and GCGR agonism may provide an additive effect due to increased energy expenditure [49, 50]. However, balancing the body-weight lowering effect of GCGR agonism with its hyperglycaemic effect is a challenge. Hence, combining GCGR agonism with the glucose-lowering effect of GLP-1R and GIPR agonism is a necessity. The GIPR/GLP-1R/GCGR tri-agonist LY3437943 has been compared with dulaglutide 1.5 mg and placebo in a Phase I study in individuals with type 2 diabetes [51]. In this study, dose-escalation of LY3437943 to 12 mg once weekly over a period of 12 weeks resulted in an additional body-weight loss of 9 kg compared with both the placebo and dulaglutide, while demonstrating an acceptable safety profile.

Another approach has been to combine the long-acting acylated amylin analogue cagrilintide with semaglutide. Cagrilintide as a monotherapy has demonstrated an ability to induce significant body-weight reductions compared with placebo, with synergistic effects when added to semaglutide [52, 53]. In a study comparing different once-weekly doses of cagrilintide in combination with 2.4 mg of semaglutide with semaglutide (2.4 mg) monotherapy in individuals with overweight or obesity, the combination of cagrilintide 2.4 mg and semaglutide 2.4 mg resulted in a 17.1% body-weight loss compared with a 9.8% body-weight loss with semaglutide as a monotherapy [53].

Incretins: a potential therapy in NAFLD

Based on the impressive effect of GLP-1R agonists on body weight and also the ability of these drugs to improve liver enzymes [54], incretin-based therapy for the treatment of NAFLD is currently being explored. NAFLD is a group of metabolism-related liver conditions that are characterised by ectopic hepatic lipid accumulation not attributed to excessive alcohol consumption [55]. Increased fat accumulation can lead to inflammation (non-alcoholic steatohepatitis [NASH]) and liver fibrosis, and can further advance to NASH-related cirrhosis, which is the fastest-growing indication for liver transplantation in western countries [10]. The incidence of NAFLD is rapidly increasing worldwide, concurrently with the epidemics of obesity and type 2 diabetes [56]. The exact cause of NAFLD is unknown. The complex pathophysiology involves multiple features, such as metabolic disturbances, lipotoxicity, insulin resistance, chronic inflammation, fibrosis, intestinal function and the gut microbiome [57], and is closely associated with obesity, type 2 diabetes and the metabolic syndrome [58]. NASH has a strong genetic component, which may be amplified by co-existing obesity [59, 60]. Currently, no pharmacotherapies are available for the treatment of NAFLD/NASH and the disease is managed by targeting lifestyle changes and treating cardiometabolic risk factors [61]. Thus, novel treatment options for NAFLD/NASH are highly warranted. Incretin-based therapy may target the underlying metabolic and hormonal pathways that are thought to be involved in developing NAFLD. Incretin-based therapy may also have a role in the treatment of NASH, especially in those carrying a high polygenic risk for this condition.

The independent and combined hepatic effects of GIP and GLP-1 have been explored in preclinical studies and potential beneficial effects on NAFLD/NASH have been demonstrated [6, 62–66]. GIP and GLP-1 have indirect hepatic effects that are thought to be generated by changes in portal and peripheral plasma insulin and glucagon concentrations and may partly be related to neural regulation signals (Fig. 1). In preclinical studies, GLP-1R agonists have been demonstrated to improve hepatocyte mitochondrial function and hepatic insulin sensitivity [67], and reduce adipose tissue lipotoxicity both due to body-weight loss and mechanisms independent of body-weight reductions [68]. An overview of the randomised controlled trials conducted in humans to evaluate the potential of GLP-1R agonists for treating NAFLD/NASH is shown in Table 1. The largest and longest trial to date includes 320 individuals with biopsy-confirmed NASH and fibrosis randomised to treatment with once-daily semaglutide (0.1 mg, 0.2 mg or 0.4 mg) vs placebo [69]. Semaglutide dose-dependently reduced liver enzymes, and resulted in greater NASH resolution (reduced ballooning and lobular inflammation) without worsening of fibrosis, as compared with placebo after 72 weeks of treatment. Semaglutide 0.4 mg once-daily significantly improved NASH compared with placebo (NASH improved in 59% vs 17% of participants). In contrast, the difference in liver fibrosis resolution stage did not reach statistical significance (liver fibrosis staging improved in 43% of participants in the semaglutide arm vs 33% in the placebo arm), potentially owing to a lack of power within the study or the relatively short follow-up time of 72 weeks. Notably, there was a relatively high proportion of individuals with fibrosis resolution in the placebo arm (observed in 33% of participants). Liver fibrosis staging (NASH clinical research network [CRN] score) depends on a complex classification that is based on several subjective histological evaluations that have low sensitivity [70, 71]. It has therefore been considered suboptimal when evaluating treatment effects in clinical trials [71, 72]. Currently, the effects of 2.4 mg semaglutide once weekly are being explored in 1200 participants with biopsy-confirmed NASH in a Phase III clinical trial with a combined primary endpoint of resolution of NASH without worsening fibrosis, improvement in liver fibrosis without worsening of steatohepatitis, and time

Table 1 An up-to-date overview of randomised controlled trials with GLP-1R agonists for the treatment of NAFLD/NASH

GLP-1R agonists	Comparator	Participants	Duration	Outcome
Liraglutide 1.8 mg/day [90]	Placebo	NASH (biopsy-confirmed) (*n*=52)	48 weeks	Compared with placebo, greater resolution of NASH, no change in NAS or fibrosis stage, and no fibrosis improvements. Increase in fibrosis worsening in the placebo group compared with baseline
Exenatide 5–10 μg twice daily [91]	Placebo	T2D and 95% with NAFLD (MRI-assessed) (*n*=44)	26 weeks	Compared with placebo, reduction in liver fat content
Liraglutide 1.8 mg/day [92]	Insulin glargine or sitagliptin	T2D and NAFLD (MRI-assessed) (*n*=75)	26 weeks	Compared with baseline, decrease in liver fat content in liraglutide and sitagliptin group
Liraglutide 3.0 mg/day [93]	Lifestyle interventions	Obesity and NAFLD (MRI-assessed) (*n*=30)	26 weeks	Compared with baseline, decrease in liver fat content in both groups. No difference in liver fat content between groups
Exenatide 1.8 mg/day [94]	Insulin or placebo	T2D and NAFLD (MRI-assessed) (*n*=96)	24 weeks	Compared with placebo, decrease in liver fat content in exenatide and insulin group. No difference in liver fat content between exenatide and insulin groups
Liraglutide 1.8 mg/day [95]	Placebo	T2D and NAFLD (MRI-assessed) (*n*=49)	26 weeks	Compared with placebo, no change in liver fat content
Dulaglutide 1.5 mg/week [96]	Placebo	T2D and NAFLD (MRI-assessed) (*n*=48)	24 weeks	Compared with placebo, decrease in liver fat content (absolute and relative change), but no change in liver stiffness assessed via FibroScan (ultrasound-based technology)
Liraglutide 1.8 mg/day [97]	Insulin glargine or placebo	T2D and NAFLD (MRI-assessed) (*n*=96)	26 weeks	Compared with placebo, decrease in liver fat content (absolute and relative change). No difference in liver fat content between insulin and liraglutide groups
Liraglutide 1.8 mg/day [98]	Pioglitazone	T2D and NAFLD (biopsy-confirmed) (*n*=60)	24 weeks	Compared with pioglitazone, decrease in liver fat content (absolute and relative change)
Semaglutide 2.4 mg/week + cilofexor 30 mg/day, semaglutide 2.4 mg/week + cilofexor 100 mg/day, semaglutide 2.4 mg/week + firsocostat 20 mg/day, or semaglutide 2.4 mg/week + cilofexor 30 mg/day + firsocostat 20 mg/day [80]	Semaglutide 2.4 mg/week	NASH (MRI-assessed or biopsy-confirmed) (*n*=108)	24 weeks	Compared with semaglutide alone, additional improvements in liver steatosis and biochemistry measures
Semaglutide 2.4 mg/week [99]	Placebo	NASH (biopsy-confirmed) and compensated cirrhosis (*n*=71)	48 weeks	Compared with placebo, no improvement in hepatic fibrosis or resolution of NASH
Semaglutide 0.1 mg/day, 0.2 mg/day or 0.4 mg/day [69]	Placebo	NASH and fibrosis (biopsy-confirmed) (*n*=320)	72 weeks	Compared with placebo, dose-dependent improvements in NASH resolution, but no improvements in or worsening of fibrosis stage

NAS, NAFLD activity score; T2D, type 2 diabetes.

Table 2 An overview of ongoing clinical trials with GLP-1R agonist and incretin combination therapies for the treatment of NAFLD/NASH

Compound	Comparator	Participants	Duration	Outcome	Trial no.
GLP-1R agonist: semaglutide 2.4 mg/week	Placebo	NASH (biopsy-confirmed) (*n*=1200)	72 weeks	(1) Resolution of NASH without worsening fibrosis; (2) improvement in liver fibrosis without worsening of steatohepatitis; and (3) time to first liver-related clinical event	NCT04822181[a]
GLP-1R agonist +SGLT-2i: semaglutide 0.5 mg/week + luseogliflozin 2.5 mg/day	Semaglutide 0.5 mg/week	T2D and NASH (biopsy-confirmed) (*n*=60)	52 weeks	(1) Resolution of NASH without worsening of liver fibrosis; (2) improvement in NAS by at least one point and no worsening of NASH without worsening of liver fibrosis[c]; and (3) improvement of at least one fibrosis stage on the Kleiner fibrosis classification scale and no worsening of NASH[d]	jRCTs061210009[b]
GIP/GLP-1R agonist: tirzepatide 5 mg/week, 10 mg/week or 15 mg/week	Placebo	Overweight or obesity with NASH (biopsy-confirmed) (*n*=196)	52 weeks	Percentage of participants with absence of NASH with no worsening of fibrosis as assessed by liver histology	NCT04166773[a]
GCGR/GLP-1R agonist: pemvidutide (ALT-801) dose level 1, dose level 2 or dose level 3	Placebo	Overweight and obesity and NAFLD (MRI-confirmed) (*n*=72)	12 weeks	(1) Number of participants with one or more TEAEs; and (2) change from baseline in liver fat fraction	NCT05006885[a]
GCGR/GLP-1R agonist: efinopegdutide 10.0 mg/monthly	Semaglutide 1 mg/week	Overweight and NAFLD (MRI-confirmed) (*n*=145)	24 weeks	Relative reduction from baseline in liver fat content	NCT04944992[a]

[a]ClinicalTrials.gov registration no.

[b]Japan Registry of Clinical Trials (JRCT) registration no

[c]Worsening of liver fibrosis defined as an increase by one stage or more on the Kleiner fibrosis classification scale [100]

[d]According to the NASH Clinical Research Network (CRN) criteria, worsening of NASH is defined as an increase of 1 point or more in either the lobular inflammation score or the hepatocyte ballooning score [101]

NAS, NAFLD activity score; SGLT-2i, sodium-glucose cotransporter 2 inhibitors; T2D, type 2 diabetes; TEAE, treatment-emergent adverse event

to first liver-related clinical event (NCT04822181) (see Table 2). A recent meta-analysis based on available data from placebo-controlled randomised trials confirms that GLP-1R agonists are associated with reduced liver fat content, improved liver enzyme levels, and greater histological resolution of NASH without worsening of liver fibrosis [73].

While GIP is less-well studied, it is suggested to have an essential role in lipid metabolism, to enhance lipid deposition in the liver and to induce inflammatory changes within the liver [74, 75]. GIP appears to have both beneficial and potentially deleterious effects. The effects of GIP appear to be beneficial when combined with GLP-1 or when GIP is administrated in pharmacological doses [76]. Fifty-two weeks of treatment with the once-weekly dual GIPR/GLP-1R agonist tirzepatide has been demonstrated to reduce liver fat content and improve liver enzyme levels compared with insulin degludec; however, histological changes and liver fibrosis stage were not assessed in this study [77]. Once-weekly tirzepatide (5 mg, 10 mg and 15 mg) is currently being explored in 196 participants with overweight or obesity and biopsy-confirmed NASH in a Phase II clinical trial (NCT04166773; see Table 2).

GLP-1R agonists may be ideally suited for combination therapy in NAFLD/NASH, as most of their mechanisms do not directly target the liver. Thus, poly-agonist drugs may complement classical incretin actions on NASH pathophysiology, providing a promising therapeutic approach. Dual (GCGR/GLP-1R and GIPR/GLP-1R) and triple (GCGR/GIPR/GLP-1R) agonists have led to improvements in lipid metabolism and hepatic steatosis [6, 64–66]. Moreover, studies suggest that dual and triple receptor agonists may have additional effects on histological NASH features vs high-dose GLP-1R agonists alone, and that these may be independent of changes in body weight [78]. In addition, combining GLP-1R agonists with other peptide agonists or small-molecule therapeutics, including fibroblast growth factor 21 (FGF21), the farnesoid X receptor (FXR) agonist cilofexor with/without the acetyl coenzyme A carboxylase inhibitor firsocostat, a long-acting amylin agonist, cannabinoid receptor antagonists and sodium-glucose cotransporter 2 inhibitors (SGLT-2i), is currently being explored and may lead to additional improvements in NASH features vs GLP-1R agonists therapy alone [79–83]. An overview of ongoing clinical trials with GLP-1R agonist and incretin combination therapy is provided in Table 2. It is unclear how much of the hepatic improvements observed with use of GLP-1R agonists and GIPR/GLP-1R agonists are driven by a reduction in body weight. Larger Phase III trials with liver-associated histological endpoints are needed to establish the therapeutic role of incretins for NAFLD/NASH.

Conclusions and perspectives

Body-weight homeostasis relies on complex mechanisms and the development of obesity occurs on a background of genetic susceptibility and an environment promoting reduced physical activity and increased energy intake. The pathophysiology of common obesity links neuroendocrine and metabolic disturbances with behavioural changes, genetics, epigenetics and cultural habits. Diet and lifestyle modification are necessary but not sufficient for sustained body-weight loss in the majority of individuals with obesity [84]. As of today, no pharmacotherapies are available for the treatment of NASH and the disease is managed by lifestyle changes targeting weight loss [85]; however, most people with NASH cannot lose weight through lifestyle interventions or sustain the weight loss achieved [86]. The therapeutic potential of GLP-1R agonists alone or in combination with other peptide agonists or other small-molecule therapeutics for the treatment of overweight/obesity and NASH is under evaluation, with a specific focus on efficacy and safety. Ongoing trials in people with obesity will further clarify the safety of mono, dual and triple receptor agonists, and pivotal studies are underway in individuals with fatty liver disease [87] and cardiovascular disease [88] that will define whether these peptides represent effective and safe therapies for people suffering from diseases beyond diabetes. So far, the therapeutic potential of combination therapies seems to be huge with predictable side effects and no major safety concerns. Moreover, based on the reduction in major cardiovascular events observed with use of GLP-1R agonists in cardiovascular outcome trials in people with type 2 diabetes [89], large-scale outcome trials in overweight and obesity have been initiated (ClinicalTrials.gov registration no. NCT03574597 and NCT05556512). These trials will investigate the ability of semaglutide and tirzepatide to reduce cardiovascular disease and mortality, potentially expanding evidence of clinical benefit of these therapies and establishing a benchmark for future pharmacotherapies in overweight and obesity. As the development of additional gut-hormone poly-agonists progresses, pharmacotherapies used for the treatment of obesity may become as efficient as bariatric surgery for reducing weight. These developments have the potential to reshape the treatment landscape for individuals with metabolic disorders, offering new hope for effective management and improved quality of life.

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References

1. Bray GA, Kim KK, Wilding JPH (2017) Obesity: a chronic relapsing progressive disease process. A position statement of the World Obesity Federation. Obes Rev 18(7):715–723. https://doi.org/10.1111/OBR.1255110.1111/obr.12551
2. Ng M, Fleming T, Robinson M et al (2014) Global, regional, and national prevalence of overweight and obesity in children and adults during 1980–2013: a systematic analysis for the Global Burden of Disease Study 2013. Lancet 384(9945):766–781. https://doi.org/10.1016/S0140-6736(14)60460-8
3. Pottegård A, Andersen JH, Søndergaard J, Thomsen RW, Vilsbøll T (2022) Changes in the use of glucose-lowering drugs: a Danish nationwide study. Diabetes Obes Metab. https://doi.org/10.1111/DOM.14947
4. Andreasen CR, Andersen A, Knop FK, Vilsbøll T (2021) Understanding the place for GLP-1RA therapy: translating guidelines for treatment of type 2 diabetes into everyday clinical practice and patient selection. Diabetes Obes Metab 23(S3):40–52. https://doi.org/10.1111/DOM.14500
5. Frías JP, Davies MJ, Rosenstock J et al (2021) Tirzepatide versus semaglutide once weekly in patients with type 2 diabetes. N Engl J Med 385(6):503–515. https://doi.org/10.1056/nejmoa2107519
6. Finan B, Ma T, Ottaway N et al (2013) Unimolecular dual incretins maximize metabolic benefits in rodents, monkeys, and humans. Sci Transl Med 5(209):209ra151. https://doi.org/10.1126/SCITRANSLMED.3007218
7. Tschöp MH, Finan B, Clemmensen C et al (2016) Unimolecular polypharmacy for treatment of diabetes and obesity. Cell Metab 24(1):51–62. https://doi.org/10.1016/J.CMET.2016.06.021
8. Bass J, Tschöp MH, Beutler LR (2023) Dual gut hormone receptor agonists for diabetes and obesity. J Clin Invest 133(3):e167952. https://doi.org/10.1172/JCI167952
9. Younossi ZM, Golabi P, de Avila L et al (2019) The global epidemiology of NAFLD and NASH in patients with type 2 diabetes: a systematic review and meta-analysis. J Hepatol 71(4):793–801. https://doi.org/10.1016/j.jhep.2019.06.021
10. Le MH, Yeo YH, Li X et al (2022) 2019 global NAFLD prevalence: a systematic review and meta-analysis. Clin Gastroenterol Hepatol 20(12):2809-2817.e28. https://doi.org/10.1016/j.cgh.2021.12.002
11. Holst JJ (2021) Treatment of type 2 diabetes and obesity on the basis of the incretin system: the 2021 Banting Medal for Scientific Achievement award lecture. Diabetes 70(11):2468–2475. https://doi.org/10.2337/DBI21-0026
12. Drucker DJ (2018) Mechanisms of action and therapeutic application of glucagon-like peptide-1. Cell Metab 27(4):740–756. https://doi.org/10.1016/J.CMET.2018.03.001
13. Campbell JE, Drucker DJ (2013) Pharmacology, physiology, and mechanisms of incretin hormone action. Cell Metab 17(6):819–837. https://doi.org/10.1016/J.CMET.2013.04.008
14. Andreasen CR, Andersen A, Knop FK, Vilsbøll T (2021) How glucagon-like peptide 1 receptor agonists work. Endocr Connect 10(7):R200–R212. https://doi.org/10.1530/ec-21-0130
15. Turton MD, O'Shea D, Gunn I et al (1996) A role for glucagon-like peptide-1 in the central regulation of feeding. Nature 379(6560):69–72. https://doi.org/10.1038/379069a0
16. Drucker DJ (2022) GLP-1 physiology informs the pharmacotherapy of obesity. Mol Metab 57:101351. https://doi.org/10.1016/J.MOLMET.2021.101351
17. Smith C, Patterson-Cross R, Woodward O et al (2022) A comparative transcriptomic analysis of glucagon-like peptide-1 receptor- and glucose-dependent insulinotropic polypeptide-expressing cells in the hypothalamus. Appetite 174:106022. https://doi.org/10.1016/J.APPET.2022.106022
18. Miyawaki K, Yamada Y, Ban N et al (2002) Inhibition of gastric inhibitory polypeptide signaling prevents obesity. Nat Med 8(7):738–742. https://doi.org/10.1038/NM727
19. Campbell JE (2021) Targeting the GIPR for obesity: to agonize or antagonize? Potential mechanisms. Mol Metab 46:101139. https://doi.org/10.1016/J.MOLMET.2020.101139
20. McLean BA, Wong CK, Campbell JE, Hodson DJ, Trapp S, Drucker DJ (2021) Revisiting the complexity of GLP-1 action from sites of synthesis to receptor activation. Endocr Rev 42:101–132. https://doi.org/10.1210/endrev/bnaa032
21. Varin EM, Mulvihill EE, Baggio LL et al (2019) Distinct neural sites of GLP-1R expression mediate physiological versus pharmacological control of incretin action. Cell Rep 27(11):3371-3384.e3. https://doi.org/10.1016/J.CELREP.2019.05.055
22. Gabery S, Salinas CG, Paulsen SJ et al (2020) Semaglutide lowers body weight in rodents via distributed neural pathways. JCI Insight 5(6):e133429. https://doi.org/10.1172/jci.insight.133429
23. Sisley S, Gutierrez-Aguilar R, Scott M, D'Alessio DA, Sandoval DA, Seeley RJ (2014) Neuronal GLP1R mediates liraglutide's anorectic but not glucose-lowering effect. J Clin Invest 124(6):2456–2463. https://doi.org/10.1172/JCI72434
24. Friedrichsen M, Breitschaft A, Tadayon S, Wizert A, Skovgaard D (2021) The effect of semaglutide 2.4 mg once weekly on energy intake, appetite, control of eating, and gastric emptying in adults with obesity. Diabetes Obes Metab 23(3):754–762. https://doi.org/10.1111/DOM.14280
25. van Bloemendaal L, Veltman DJ, Ten Kulve JS et al (2015) Brain reward-system activation in response to anticipation and consumption of palatable food is altered by glucagon-like peptide-1 receptor activation in humans. Diabetes Obes Metab 17(9):878–886. https://doi.org/10.1111/DOM.12506
26. Wilding JPH, Batterham RL, Calanna S et al (2021) Once-weekly semaglutide in adults with overweight or obesity. N Engl J Med 384(11):989–1002. https://doi.org/10.1056/NEJMOA2032183
27. Andersen A, Lund A, Knop FK, Vilsbøll T (2018) Glucagon-like peptide 1 in health and disease. Nat Rev Endocrinol 14(7):390–403. https://doi.org/10.1038/s41574-018-0016-2
28. Jastreboff AM, Aronne LJ, Ahmad NN et al (2022) Tirzepatide once weekly for the treatment of obesity. N Engl J Med 387:205–216. https://doi.org/10.1056/NEJMoa2206038
29. Wadden TA, Hollander P, Klein S et al (2013) Weight maintenance and additional weight loss with liraglutide after low-calorie-diet-induced weight loss: the SCALE Maintenance randomized study. Int J Obes 37(11):1443–1451. https://doi.org/10.1038/IJO.2013.120
30. Pi-Sunyer X, Astrup A, Fujioka K et al (2015) A randomized, controlled trial of 30 mg of liraglutide in weight management. N Engl J Med 373(1):11–22. https://doi.org/10.1056/NEJMoa1411892
31. Davies MJ, Bergenstal R, Bode B et al (2015) Efficacy of liraglutide for weight loss among patients with type 2 diabetes: the SCALE diabetes randomized clinical trial. JAMA 314(7):687–699. https://doi.org/10.1001/jama.2015.9676
32. Blackman A, Foster GD, Zammit G et al (2016) Effect of liraglutide 3.0 mg in individuals with obesity and moderate or severe obstructive sleep apnea: the SCALE Sleep Apnea randomized clinical trial. Int J Obes 40(8):1310. https://doi.org/10.1038/IJO.2016.52
33. Le Roux CW, Astrup AV, Fujioka K et al (2017) 3 years of liraglutide versus placebo for type 2 diabetes risk reduction and weight management in individuals with prediabetes: a

randomised, double-blind trial. Lancet 389(10077):1399–1409. https://doi.org/10.1016/S0140-6736(17)30069-7
34. Rubino DM, Greenway FL, Khalid U et al (2022) Effect of weekly subcutaneous semaglutide vs daily liraglutide on body weight in adults with overweight or obesity without diabetes: the STEP 8 randomized clinical trial. JAMA 327(2):138–150. https://doi.org/10.1001/JAMA.2021.23619
35. Davies M, Færch L, Jeppesen OK et al (2021) Semaglutide 2.4 mg once a week in adults with overweight or obesity, and type 2 diabetes (STEP 2): a randomised, double-blind, double-dummy, placebo-controlled, phase 3 trial. Lancet 397(10278):971–984. https://doi.org/10.1016/S0140-6736(21)00213-0
36. Wadden TA, Bailey TS, Billings LK et al (2021) Effect of subcutaneous semaglutide vs placebo as an adjunct to intensive behavioral therapy on body weight in adults with overweight or obesity: the STEP 3 randomized clinical trial. JAMA 325(14):1403–1413. https://doi.org/10.1001/JAMA.2021.1831
37. Rubino D, Abrahamsson N, Davies M et al (2021) Effect of continued weekly subcutaneous semaglutide vs placebo on weight loss maintenance in adults with overweight or obesity: the STEP 4 randomized clinical trial. JAMA 325(14):1414–1425. https://doi.org/10.1001/JAMA.2021.3224
38. Garvey WT, Batterham RL, Bhatta M et al (2022) Two-year effects of semaglutide in adults with overweight or obesity: the STEP 5 trial. Nat Med 28(10):2083–2091. https://doi.org/10.1038/S41591-022-02026-4
39. Kadowaki T, Isendahl J, Khalid U et al (2022) Semaglutide once a week in adults with overweight or obesity, with or without type 2 diabetes in an east Asian population (STEP 6): a randomised, double-blind, double-dummy, placebo-controlled, phase 3a trial. Lancet Diabetes Endocrinol 10(3):193–206. https://doi.org/10.1016/S2213-8587(22)00008-0
40. Weghuber D, Barrett T, Barrientos-Pérez M et al (2022) Once-weekly semaglutide in adolescents with obesity. N Engl J Med 387(24):2245–2257. https://doi.org/10.1056/NEJMOA2208601
41. Bergmann NC, Davies MJ, Lingvay I, Knop FK (2023) Semaglutide for the treatment of overweight and obesity: a review. Diabetes Obes Metab 25(1):18–35. https://doi.org/10.1111/DOM.14863
42. Lin Q, Xue Y, Zou H, Ruan Z, Ung COL, Hu H (2022) Efficacy and safety of liraglutide for obesity and people who are overweight: a systematic review and meta-analysis of randomized controlled trials. Expert Rev Clin Pharmacol 15(12):1461–1469. https://doi.org/10.1080/17512433.2022.2130760
43. Rosenstock J, Wysham C, Frías JP et al (2021) Efficacy and safety of a novel dual GIP and GLP-1 receptor agonist tirzepatide in patients with type 2 diabetes (SURPASS-1): a double-blind, randomised, phase 3 trial. Lancet 398(10295):143–155. https://doi.org/10.1016/S0140-6736(21)01324-6
44. Ludvik B, Giorgino F, Jódar E et al (2021) Once-weekly tirzepatide versus once-daily insulin degludec as add-on to metformin with or without SGLT2 inhibitors in patients with type 2 diabetes (SURPASS-3): a randomised, open-label, parallel-group, phase 3 trial. Lancet 398(10300):583–598. https://doi.org/10.1016/S0140-6736(21)01443-4
45. Del Prato S, Kahn SE, Pavo I et al (2021) Tirzepatide versus insulin glargine in type 2 diabetes and increased cardiovascular risk (SURPASS-4): a randomised, open-label, parallel-group, multicentre, phase 3 trial. Lancet 398(10313):1811–1824. https://doi.org/10.1016/S0140-6736(21)02188-7
46. Dahl D, Onishi Y, Norwood P et al (2022) Effect of subcutaneous tirzepatide vs placebo added to titrated insulin glargine on glycemic control in patients with type 2 diabetes: the SURPASS-5 randomized clinical trial. JAMA 327(6):534–545. https://doi.org/10.1001/jama.2022.0078
47. Lilly (2023) Lilly's tirzepatide achieved up to 15.7% weight loss in adults with obesity or overweight and type 2 diabetes in SURMOUNT-2. Available from: https://investor.lilly.com/node/48776/pdf. Accessed: 4 May 2023
48. Amgen (2022) Amgen presents new AMG 133 Phase 1 clinical data at WCIRDC 2022. Available from: www.amgen.com/newsroom/press-releases/2022/12/amgen-presents-new-amg-133-phase-1-clinical-data-at-wcirdc-2022. Accessed: 2 March 2023
49. Cegla J, Troke RC, Jones B et al (2014) Coinfusion of low-dose GLP-1 and glucagon in man results in a reduction in food intake. Diabetes 63(11):3711–3720. https://doi.org/10.2337/DB14-0242
50. Müller TD, Finan B, Bloom SR et al (2019) Glucagon-like peptide 1 (GLP-1). Mol Metab 30:72–130. https://doi.org/10.1016/J.MOLMET.2019.09.010
51. Urva S, Coskun T, Loh MT et al (2022) LY3437943, a novel triple GIP, GLP-1, and glucagon receptor agonist in people with type 2 diabetes: a phase 1b, multicentre, double-blind, placebo-controlled, randomised, multiple-ascending dose trial. Lancet 400(10366):1869–1881. https://doi.org/10.1016/S0140-6736(22)02033-5
52. Lau DCW, Erichsen L, Francisco AM et al (2021) Once-weekly cagrilintide for weight management in people with overweight and obesity: a multicentre, randomised, double-blind, placebo-controlled and active-controlled, dose-finding phase 2 trial. Lancet 398(10317):2160–2172. https://doi.org/10.1016/S0140-6736(21)01751-7
53. Enebo LB, Berthelsen KK, Kankam M et al (2021) Safety, tolerability, pharmacokinetics, and pharmacodynamics of concomitant administration of multiple doses of cagrilintide with semaglutide 2.4 mg for weight management: a randomised, controlled, phase 1b trial. Lancet 397(10286):1736–1748. https://doi.org/10.1016/S0140-6736(21)00845-X
54. Buse JB, Klonoff DC, Nielsen LL et al (2007) Metabolic effects of two years of exenatide treatment on diabetes, obesity, and hepatic biomarkers in patients with type 2 diabetes: an interim analysis of data from the open-label, uncontrolled extension of three double-blind, placebo-controlled trials. Clin Ther 29(1):139–153. https://doi.org/10.1016/j.clinthera.2007.01.015
55. Eslam M, Sanyal AJ, George J et al (2020) MAFLD: a consensus-driven proposed nomenclature for metabolic associated fatty liver disease. Gastroenterology 158(7):1999-2014.e1. https://doi.org/10.1053/J.GASTRO.2019.11.312
56. Paik JM, Golabi P, Younossi Y, Mishra A, Younossi ZM (2020) Changes in the global burden of chronic liver diseases from 2012 to 2017: the growing impact of NAFLD. Hepatology 72(5):1605–1616. https://doi.org/10.1002/HEP.31173
57. Sheka AC, Adeyi O, Thompson J, Hameed B, Crawford PA, Ikramuddin S (2020) Nonalcoholic steatohepatitis: a review. JAMA 323(12):1175–1183. https://doi.org/10.1001/JAMA.2020.2298
58. Byrne CD, Targher G (2015) NAFLD: a multisystem disease. J Hepatol 62(1):S47–S64. https://doi.org/10.1016/J.JHEP.2014.12.012
59. Romeo S, Sanyal A, Valenti L (2020) Leveraging human genetics to identify potential new treatments for fatty liver disease. Cell Metab 31(1):35–45. https://doi.org/10.1016/J.CMET.2019.12.002
60. Romeo S, Sentinelli F, Dash S et al (2010) Morbid obesity exposes the association between PNPLA3 I148M (rs738409) and indices of hepatic injury in individuals of European descent. Int J Obes 34(1):190–194. https://doi.org/10.1038/IJO.2009.216
61. Targher G, Tilg H, Byrne CD (2021) Non-alcoholic fatty liver disease: a multisystem disease requiring a multidisciplinary and holistic approach. Lancet Gastroenterol Hepatol 6(7):578–588. https://doi.org/10.1016/S2468-1253(21)00020-0
62. Mantovani A, Byrne CD, Targher G (2022) Efficacy of peroxisome proliferator-activated receptor agonists, glucagon-like peptide-1 receptor agonists, or sodium-glucose cotransporter-2

inhibitors for treatment of non-alcoholic fatty liver disease: a systematic review. Lancet Gastroenterol Hepatol 7(4):367–378. https://doi.org/10.1016/S2468-1253(21)00261-2
63. Finan B, Yang B, Ottaway N et al (2014) A rationally designed monomeric peptide triagonist corrects obesity and diabetes in rodents. Nat Med 21(1):27–36. https://doi.org/10.1038/nm.3761
64. Jall S, Sachs S, Clemmensen C et al (2017) Monomeric GLP-1/GIP/glucagon triagonism corrects obesity, hepatosteatosis, and dyslipidemia in female mice. Mol Metab 6(5):440–446. https://doi.org/10.1016/j.molmet.2017.02.002
65. Day JW, Ottaway N, Patterson JT et al (2009) A new glucagon and GLP-1 co-agonist eliminates obesity in rodents. Nat Chem Biol 5(10):749–757. https://doi.org/10.1038/NCHEMBIO.209
66. Henderson SJ, Konkar A, Hornigold DC et al (2016) Robust anti-obesity and metabolic effects of a dual GLP-1/glucagon receptor peptide agonist in rodents and non-human primates. Diabetes Obes Metab 18(12):1176–1190. https://doi.org/10.1111/dom.12735
67. Kalavalapalli S, Bril F, Guingab J et al (2019) Impact of exenatide on mitochondrial lipid metabolism in mice with nonalcoholic steatohepatitis. J Endocrinol 241(3):293–305. https://doi.org/10.1530/JOE-19-0007
68. Gastaldelli A, Cusi K (2019) From NASH to diabetes and from diabetes to NASH: mechanisms and treatment options. JHEP Rep 1(4):312–328. https://doi.org/10.1016/J.JHEPR.2019.07.002
69. Newsome PN, Buchholtz K, Cusi K et al (2021) A placebo-controlled trial of subcutaneous semaglutide in nonalcoholic steatohepatitis. N Engl J Med 384:1113–1124. https://doi.org/10.1056/nejmoa2028395
70. Pai RK, Kleiner DE, Hart J et al (2019) Standardizing the interpretation of liver biopsies in non-alcoholic fatty liver disease clinical trials. Aliment Pharmacol Ther 50(10):1100. https://doi.org/10.1111/APT.15503
71. Brunt EM, Clouston AD, Goodman Z et al (2022) Complexity of ballooned hepatocyte feature recognition: defining a training atlas for artificial intelligence-based imaging in NAFLD. J Hepatol 76(5):1030–1041. https://doi.org/10.1016/J.JHEP.2022.01.011
72. Davison BA, Harrison SA, Cotter G et al (2020) Suboptimal reliability of liver biopsy evaluation has implications for randomized clinical trials. J Hepatol 73(6):1322–1332. https://doi.org/10.1016/J.JHEP.2020.06.025
73. Mantovani A, Petracca G, Beatrice G, Csermely A, Lonardo A, Targher G (2021) Glucagon-like peptide-1 receptor agonists for treatment of nonalcoholic fatty liver disease and nonalcoholic steatohepatitis: an updated meta-analysis of randomized controlled trials. Metabolites 11:1–13
74. McClean PL, Irwin N, Cassidy RS, Holst JJ, Gault VA, Flatt PR (2007) GIP receptor antagonism reverses obesity, insulin resistance, and associated metabolic disturbances induced in mice by prolonged consumption of high-fat diet. Am J Physiol Endocrinol Metab 293(6):E1746–E1755. https://doi.org/10.1152/ajpendo.00460.2007
75. Joo E, Harada N, Yamane S et al (2017) Inhibition of gastric inhibitory polypeptide receptor signaling in adipose tissue reduces insulin resistance and hepatic steatosis in high-fat diet–fed mice. Diabetes 66(4):868–879. https://doi.org/10.2337/DB16-0758
76. Thondam SK, Cuthbertson DJ, Wilding JPH (2020) The influence of glucose-dependent insulinotropic polypeptide (GIP) on human adipose tissue and fat metabolism: implications for obesity, type 2 diabetes and non-alcoholic fatty liver disease (NAFLD). Peptides 125:170208. https://doi.org/10.1016/J.PEPTIDES.2019.170208
77. Gastaldelli A, Cusi K, Fernández Landó L, Bray R, Brouwers B, Rodríguez Á (2022) Effect of tirzepatide versus insulin degludec on liver fat content and abdominal adipose tissue in people with type 2 diabetes (SURPASS-3 MRI): a substudy of the randomised, open-label, parallel-group, phase 3 SURPASS-3 trial. Lancet Diabetes Endocrinol 10(6):393–406. https://doi.org/10.1016/S2213-8587(22)00070-5
78. Kannt A, Madsen AN, Kammermeier C et al (2020) Incretin combination therapy for the treatment of non-alcoholic steatohepatitis. Diabetes Obes Metab 22(8):1328–1338. https://doi.org/10.1111/dom.14035
79. Gilroy CA, Capozzi ME, Varanko AK et al (2020) Sustained release of a GLP-1 and FGF21 dual agonist from an injectable depot protects mice from obesity and hyperglycemia. Sci Adv 6(35):1–13. https://doi.org/10.1126/sciadv.aaz9890
80. Alkhouri N, Herring R, Kabler H et al (2022) Safety and efficacy of combination therapy with semaglutide, cilofexor and firsocostat in patients with non-alcoholic steatohepatitis: A randomised, open-label phase II trial. J Hepatol 77(3):607–618. https://doi.org/10.1016/J.JHEP.2022.04.003
81. Baggio LL, Drucker DJ (2020) Glucagon-like peptide-1 receptor co-agonists for treating metabolic disease. Mol Metab 46:101090
82. Miyake T, Yoshida O, Matsuura B et al (2022) additional effect of luseogliflozin on semaglutide in nonalcoholic steatohepatitis complicated by type 2 diabetes mellitus: an open-label, randomized, parallel-group study. Diabetes Ther 13(5):1083–1096. https://doi.org/10.1007/S13300-022-01239-7
83. Zizzari P, He R, Falk S et al (2021) CB1 and GLP-1 receptors cross talk provides new therapies for obesity. Diabetes 70(2):415–422. https://doi.org/10.2337/DB20-0162
84. The Look AHEAD Research Group (2006) The Look AHEAD study: a description of the lifestyle intervention and the evidence supporting it. Obesity 14(5):737–752. https://doi.org/10.1038/OBY.2006.84
85. Brunner KT, Henneberg CJ, Wilechansky RM, Long MT (2019) Nonalcoholic fatty liver disease and obesity treatment. Curr Obes Rep 8(3):220–228. https://doi.org/10.1007/S13679-019-00345-1
86. Malespin MH, Barritt AS, Watkins SE et al (2022) Weight loss and weight regain in usual clinical practice: results from the TARGET-NASH observational cohort. Clin Gastroenterol Hepatol 20(10):2393-2395.e4. https://doi.org/10.1016/J.CGH.2021.01.023
87. Harrison SA, Calanna S, Cusi K et al (2020) Semaglutide for the treatment of non-alcoholic steatohepatitis: trial design and comparison of non-invasive biomarkers. Contemp Clin Trials 97:106174. https://doi.org/10.1016/J.CCT.2020.106174
88. Lingvay I, Brown-Frandsen K, Colhoun HM et al (2023) Semaglutide for cardiovascular event reduction in people with overweight or obesity: SELECT study baseline characteristics. Obesity 31(1):111–122. https://doi.org/10.1002/OBY.23621
89. Sattar N, Lee MMY, Kristensen SL et al (2021) Cardiovascular, mortality, and kidney outcomes with GLP-1 receptor agonists in patients with type 2 diabetes: a systematic review and meta-analysis of randomised trials. Lancet Diabetes Endocrinol 9(10):653–662. https://doi.org/10.1016/S2213-8587(21)00203-5
90. Armstrong MJ, Gaunt P, Aithal GP et al (2016) Liraglutide safety and efficacy in patients with non-alcoholic steatohepatitis (LEAN): a multicentre, double-blind, randomised, placebo-controlled phase 2 study. Lancet 387(10019):679–690. https://doi.org/10.1016/S0140-6736(15)00803-X
91. Dutour A, Abdesselam I, Ancel P et al (2016) Exenatide decreases liver fat content and epicardial adipose tissue in patients with obesity and type 2 diabetes: a prospective randomized clinical trial using magnetic resonance imaging and spectroscopy. Diabetes Obes Metab 18(9):882–891. https://doi.org/10.1111/DOM.12680

92. Yan J, Yao B, Kuang H et al (2019) Liraglutide, sitagliptin, and insulin glargine added to metformin: the effect on body weight and intrahepatic lipid in patients with type 2 diabetes mellitus and nonalcoholic fatty liver disease. Hepatology 69(6):2414–2426. https://doi.org/10.1002/HEP.30320
93. Khoo J, Hsiang JC, Taneja R et al (2019) Randomized trial comparing effects of weight loss by liraglutide with lifestyle modification in non-alcoholic fatty liver disease. Liver Int 39(5):941–949. https://doi.org/10.1111/LIV.14065
94. Liu L, Yan H, Xia MF et al (2020) Efficacy of exenatide and insulin glargine on nonalcoholic fatty liver disease in patients with type 2 diabetes. Diabetes Metab Res Rev 36(5):e3292. https://doi.org/10.1002/DMRR.3292
95. Bizino MB, Jazet IM, de Heer P et al (2020) Placebo-controlled randomised trial with liraglutide on magnetic resonance endpoints in individuals with type 2 diabetes: a pre-specified secondary study on ectopic fat accumulation. Diabetologia 63(1):65–74. https://doi.org/10.1007/S00125-019-05021-6
96. Kuchay MS, Krishan S, Mishra SK et al (2020) Effect of dulaglutide on liver fat in patients with type 2 diabetes and NAFLD: randomised controlled trial (D-LIFT trial). Diabetologia 63(11):2434–2445. https://doi.org/10.1007/S00125-020-05265-7
97. Guo W, Tian W, Lin L, Xu X (2020) Liraglutide or insulin glargine treatments improves hepatic fat in obese patients with type 2 diabetes and nonalcoholic fatty liver disease in twenty-six weeks: a randomized placebo-controlled trial. Diabetes Res Clin Pract 170:108487. https://doi.org/10.1016/j.diabres.2020.108487
98. Zhang LY, Qu XN, Sun ZY, Zhang Y (2020) Effect of liraglutide therapy on serum fetuin A in patients with type 2 diabetes and non-alcoholic fatty liver disease. Clin Res Hepatol Gastroenterol 44(5):674–680. https://doi.org/10.1016/J.CLINRE.2020.01.007
99. Loomba R, Abdelmalek MF, Armstrong MJ et al (2023) Semaglutide 2.4 mg once weekly in patients with non-alcoholic steatohepatitis-related cirrhosis: a randomised, placebo-controlled phase 2 trial. Lancet Gastroenterol Hepatol 8(6):511–522. https://doi.org/10.1016/S2468-1253(23)00068-7
100. Kleiner DE, Brunt EM, Van Natta M et al (2005) Design and validation of a histological scoring system for nonalcoholic fatty liver disease. Hepatology 41(6):1313–1321. https://doi.org/10.1002/HEP.20701
101. Juluri R, Vuppalanchi R, Olson J et al (2011) Generalizability of the NASH CRN histological scoring system for nonalcoholic fatty liver disease. J Clin Gastroenterol 45(1):55–58. https://doi.org/10.1097/MCG.0B013E3181DD1348