Peptides 187 (2025) 171380

Contents lists available at ScienceDirect

Peptides

journal homepage: www.elsevier.com/locate/peptides

# Multifunctional incretin peptides in therapies for type 2 diabetes, obesity and associated co-morbidities

Clifford J. Bailey [a], Peter R. Flatt [b], J. Michael Conlon [b,*]

[a] Life and Health Sciences, Aston University, Birmingham B4 7ET, UK
[b] Diabetes Research Centre, School of Biomedical Sciences, Ulster University, Coleraine, Northern Ireland BT52 1SA, UK

ARTICLE INFO

*Keywords:*
Incretin
Multiagonist
Type 2 diabetes
Obesity
Cardiovascular
Renal

ABSTRACT

Recent studies with peptide-based incretin therapies have focussed mainly on the glucagon-like peptide-1 (GLP-1) receptor agonist semaglutide and the dual agonist tirzepatide that engages receptors for GLP-1 and glucose-dependent insulinotropic polypeptide (GIP). Randomised clinical trials and 'real-world' studies have confirmed the marked glucose-lowering and weight-lowering efficacy of these agents across diverse populations. These include different ethnic groups, young and elderly individuals with and without diabetes and/or overweight or obesity. Recent studies have also confirmed protections against the development and progression of cardiovascular and renal diseases that are additive to the benefits conferred by improved control of blood glucose and body weight. Emerging evidence suggests that incretin therapies could additionally ameliorate fatty liver disease, chronic inflammation, sleep apnea and possibly degenerative bone disorders and cognitive decline. New incretin-based peptide therapies in development include a long-acting glucagon receptor agonist (LY3324954), dual GLP-1/glucagon receptor agonists (survodutide, pemvidutide, mazdutide, G49), triple GLP-1/GIP/glucagon receptor agonists (retatrutide, efocipegtrutide), a combination of semaglutide with the amylin analogue cagrilintide (CagriSema), a unimolecular GLP-1/amylin receptor dual agonist (amycretin), and a GIP receptor antibody with GLP-1 receptor agonism (MariTide). The creation of multi-targeting incretin-based synthetic peptides provides opportunities for improved management of type 2 diabetes and obesity as well as new therapeutic approaches to an expanding list of associated co-morbidities. The aim of the review is to acquaint the reader with developments in the field from 2023 to the present (February 2025).

## 1. Introduction

The incretin peptides glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP) are key regulators of nutrient metabolism that have been adapted as pharmacotherapies. GLP-1 receptor agonists (GLP-1RAs) are used to lower blood glucose in type 2 diabetes mellitus (T2DM) and reduce body weight in the management of obesity [1,2]. To enhance efficacy, mixtures of peptides as well as long-acting single-molecule mono-, dual- and multi-agonists have been developed to interact with receptors for GLP-1, GIP, glucagon (GCG), amylin and other peptides [1]. As shown in Table 1, several injectable and one oral GLP-1RA and one injectable GLP-1R/GIPR co-agonist are available in Europe and North America, with more available in other regions (reviewed in [3,4]). The years from 2023 to the present have seen an explosion of interest in incretin peptides, primarily the GLP-1RA semaglutide and the GIPR/GLP-1R co-agonist tirzepatide, among physicians, biomedical researchers, patients and healthy individuals concerned with body image. These years have led to realization that beyond their metabolic and weight-lowering effects, these agents have been shown to reduce the risk or severity of cardiovascular (CV) and renal diseases and to benefit other co-morbidities independently of glucose and weight control [5–7]. Previous reviews in the journal have focused upon the results of clinical trials of semaglutide, and tirzepatide involving primarily patients with T2DM and/or obesity up until 2022 [3,4]. This article emphasizes the properties of recently introduced incretin peptides and provides evidence for their increased therapeutic relevance.

## 2. Metabolic efficacy

The glucose-lowering and weight-lowering effects of GLP-1RAs in individuals with T2DM across the age spectrum, with and without CV

* Corresponding author.
*E-mail address:* jmconlon1@gmail.com (J.M. Conlon).

https://doi.org/10.1016/j.peptides.2025.171380
Received 27 January 2025; Received in revised form 3 March 2025; Accepted 5 March 2025
Available online 11 March 2025

**Table 1**
Efficacy of currently available incretin-based peptide agents in phase 3 trials that assessed lowering of A1C and body weight.

| Agent *(Brand)* | Trial name *n number Duration (wks)* | Route, timing Dose(s) | Efficacy in phase 3 randomised control trial* | |
|---|---|---|---|---|
| **Type 2 diabetes** | | | | |
| | | | **Baseline** A1C %; BMI kg/m$^2$ | **Efficacy*** ↓A1c%; ↓BW kg |
| Exenatide[a] *(Byetta)* | Amigo−1 *n 272, 30 wks* | SC, BD 5, 10 ug | A1C 8.2 BMI 34.2 | ↓ A1c 0.8 ↓ BW 2.8 |
| Exenatide *(Bydureon)* | Duration−1 *n 295, 30 wks* | SC, QW 2 mg | A1C 8.3 BMI 35 | ↓ A1c 1.9 ↓ BW 3.9 |
| Lixisenatide[b] *(Lyxumia)* | GetGoal−1 *n 484, 24 wks* | SC, OD 20 ug | A1C 8.1 BMI 32.1 | ↓ A1c 0.4 ↓ BW 1.1 |
| Liraglutide[c] *(Victoza)* | Lead−2 *n 1091, 26 wks* | SC, OD 0.6, 1.2, 1.8 mg | A1C 8.4 BMI 30.9 | ↓ A1c 1.1 ↓ BW 3.8 |
| Dulaglutide *(Trulicity)* | Award−1 *n 976, 26 wks* | SC, QW 0.75, 1.5 mg | A1C 8.1 BMI 33 | ↓ A1c 1.0 ↓ BW 2.5 |
| Semaglutide ** *(Ozempic)* | Sustain−1 *n 388, 30 wks* | SC, QW 0.25, 0.5, 1, 2 mg | A1C 8.0 BMI 32.9 | ↓ A1c 1.5 ↓ BW 3.5 |
| Semaglutide *(Rybelsus)* | Pioneer−1 *n 703, 26 wks* | Oral, OD 3, 7, 14 mg | A1C 8.0 BMI 31.8 | ↓ A1c 1.1 ↓ BW 2.3 |
| Tirzepatide *** *(Mounjaro)* | Surpass−1 *n 478, 40 wks* | SC, QW 0.25, 0.5, 0.75, 10, 12.5. 15 mg | A1C 7.9 BMI 31.9 | ↓ A1c 2.3 ↓ BW 8.8 |
| **Obesity** | | | | |
| | | | **Baseline** BW kg BMI kg/m$^2$ | **Efficacy** ↓ BW kg (%) |
| Liragluride *(Saxenda)* | Scale−1 *n 3731, 56 wks* | SC, OD 3 mg | BW 106.2 BMI 38.3 | ↓ BW 5.6 (5.2 %) |
| Semaglutide *(Wegovy)* | Step−1 *N 1961, 68 wks* | SC, QW 2.4 mg | BW 105.4 BMI 37.8 | ↓ BW 12.7 (12.4 %) |
| Semaglutide *(Rybelsus)* | Oasis−1 *n 667, 68 wks* | Oral, OD 50 mg | BW 105.4 BMI 37.5 | ↓ BW 13.0 (12.7 %) |
| Tirzepatide *(Zepbound)* | Surmount−1 *n 2539, 72 wks* | SC, QW 5, 10, 15 mg | BW 105.6 BMI 38.1 | ↓ BW 21.2 (17.8 %) |

A1c, HbA1c (glycated haemoglobin); BD, twice daily; BMI, body mass index (kg/m$^2$); BW, body weight; OD, once daily; QW, once weekly; SC, subcutaneous injection; wks, weeks; ↓, decrease

* Efficacy was calculated as placebo-subtracted change in A1C or body weight using data from a phase 3 randomised controlled trial. In trials involving individuals **with** type 2 diabetes, test agent or placebo was administered as add-on to lifestyle (diet ± exercise) or lifestyle plus metformin. In trials involving individuals **without** diabetes, test agent or placebo was administered as add-on to lifestyle.

** Data for semaglutide in individuals **with** type 2 diabetes are based on 1 mg dose. In a subsequent 40 week trial (n = 961, baseline A1C 8.9 % and BMI 34.6), a 2 mg dose of semaglutide once weekly lowered A1c by 0.3 % more and body weight by 0.9 kg more than with a 1 mg dose.

*** Data for tirzepatide in individuals **with** type 2 diabetes are based on the 15 mg dose which was taken for 20 weeks after a 20-week dose titration period.

[a] Byetta was discontinued in 2024: biosimilar products may be available in some regions.

[b] Lyxumia was discontinued in 2023: biosimilar products may be available in some regions.

[c] Victoza: biosimilar products may be available in some regions.

disease, chronic kidney disease (CKD) and fatty liver disease are now well established [3,4,8]. GLP-1RAs administered by once weekly (QW) subcutaneous (SC) injection have generally produced greater metabolic effects in T2DM patients than other therapeutic drugs, provided that dose escalation is undertaken slowly to minimise initial (usually temporary) gastrointestinal side effects [9]. Amongst agents injected QW, semaglutide (*Ozempic*, 2 mg) and tirzepatide (*Mounjaro,* up to 15 mg) reduced HbA1c by 2.2 % and 2.4 % respectively and reduced body weight by 6.9 kg and 11.3 kg respectively during 40 week randomised controlled trials in overweight/obese individuals with T2DM [10,11]. The weight-reducing efficacy of incretins is typically greater in individuals without T2DM (Table 1). Thus, in obese adults without diabetes, injection of semaglutide (*Wegovy,* 2.4 mg QW) reduced weight by 15.7 kg (14.9 %) over 68 weeks (STEP-1 trial) [12], and tirzepatide (*Zepbound*, 15 mg QW) reduced weight by 21.9 kg (20.9 %) in a similar trial in obese non-diabetic adults for 72 weeks (SURMOUNT-1 trial) [13]. Comparable results were obtained in SURMOUNT 4 [14] and STEP 4 [15] trials. A high dose (50 mg daily) of an oral formulation of semaglutide reduced weight by 15.1 % over 68 weeks (OASIS-1 trial) in obese adults without diabetes [16]. In consequence, both semaglutide and tirzepatide have been widely adopted for weight loss management with efficacy across ethnic groups and the age spectrum [3,4,17,18]. Both semaglutide and tirzepatide can also reduce progression of prediabetes to diabetes in obese individuals [13,19].

Given the substantial cost of incretin-based medicines, their long-term use to treat obesity has been questioned and several trials have included 'off-treatment' extension periods. These have invariably shown 'off-treatment' weight regain, but without rebound to above pretreatment weight over periods up to 1 year [20–22]. Debate continues over how long and at what dose treatment should be continued when adequate weight reduction has been achieved, and which lifestyle strategies or alternative therapies can best mitigate weight regain [22,23].

## 3. Mechanisms of metabolic effects

The main mechanisms responsible for the anti-hyperglycaemic and anti-obesity effects of GLP-1RAs are well recognised, notably potentiation of nutrient-stimulated insulin secretion ('incretin effect'), suppression of prandial glucagon secretion, a centrally-mediated satiety effect and delayed gastric emptying [8,24]. Because GLP-1RAs do not initiate insulin secretion or impede 'counter-regulatory' glucagon secretion at low glucose concentrations, these agents do not cause overt hypoglycaemia, which enables their continuous use at high therapeutic concentrations.

GIP also potentiates nutrient-stimulated insulin secretion but this effect becomes much reduced during protracted exposure to hyperglycaemia in T2DM [8,25]. This may be due to chronic stimulation of pancreatic β-cells by persistent hyperglycaemia causing a switching of the sub-types of the GIP G-protein coupled receptors from Gs to Gq because GIP activates Gs but not Gq. In contrast, GLP-1 maintains its insulinotropic effect because GLP-1 can activate both Gs and Gq [25]. In addition, GIP can increase glucagon secretion and adipose tissue deposition which seems inconsistent with the glucose-lowering and weight-lowering efficacy conferred by GIP receptor agonism either alone or together with GLP-1 receptor agonism in the GIPR/GLP-1R co-agonist tirzepatide [26]. This calls into question the role of GIPR agonism by tirzepatide. It has been suggested that the agent exerts a sufficiently potent and effective GLP-1R agonism to overcome the effects of GIPR agonism on glucagon and adipose deposition. In addition, the peptide may interact with the GIPR to create a biased agonism in which long-term metabolic signalling of the GIPR is reduced while that of the GLP-1R is increased [27]. The biased agonism could occur if the structure of tirzepatide alters the conformation of the GIPR so as to favour activation of arrestins that mediate increased endocytosis and degradation of the receptor. In contrast, biased agonism might reduce endocytosis of the GLP-1R and so increase the effects of a GLP-1RA [27–29]. Such a mechanism has been implicated in the ability of GIP and GLP-1 to exert additive effects on pancreatic β-cells [30–33]. This type of biased agonism is also consistent with the ability of GIPR antagonists to improve glucose and weight control in obese hyperglycaemic states [34].

A further uncertainty relating to GIP concerns its effect on food

intake. Previous studies in rodents, non-human primates and human subjects involving either GIPR activation or inhibition have provided inconsistent results (reviewed in [25,28]). GIP does not acutely affect appetite or food intake in humans but recent studies in mice have found that chronic exposure to long-acting GIPRAs reduces food intake through direct effects within the central nervous system involving regions of the hypothalamus and hind brain [35,36]. This is consistent with the strong long-term weight loss effect of tirzepatide but does not account for the effectiveness of GIPR antagonism [11,13,14,34]. The multifunctional activities of GLP-1 and GIP are compared and contrasted in Fig. 1.

## 4. Cardiovascular effects

CV outcome trials (CVOTs) conducted with newly introduced glucose-lowering agents have noted fewer major adverse cardiac events (MACE) including non-fatal myocardial infarction, stroke or severe heart failure among individuals treated with a GLP-1RA compared with placebo. For individual agents these may be numerical differences (not statistically significant) but meta-analyses have shown significant reductions in MACE across the GLP-1RA class. For example, recent meta-analyses of GLP-1RA use in randomised clinical trials have reported reductions of MACE by13–14 %, all-cause mortality by ~12 % and heart failure by ~11 % [37]. A pooled analysis of trials with injected semaglutide has noted reduced progression of heart failure irrespective of baseline ejection fraction [38] and a CVOT (SOUL trial) with the oral formulation of semaglutide (*Rybelsus*) found a 14 % reduction in MACE [39].

Considering the heavy burden of CV disease for people with diabetes, appreciation of the CV benefits of GLP-1RAs has resulted in the inclusion of these agents as first line pharmacological therapies alongside metformin and sodium-glucose co-transporter-2 (SGLT2) inhibitors in some of the latest guidelines for treatment of T2DM [40,41]. In particular, GLP-1RAs are considered appropriate for individuals who already have established atherosclerotic CV disease or who are considered to be at especially high CV risk. Recent randomised placebo-controlled trials have also noted modest reductions in the onset or progression of heart failure (with reduced or preserved ejection fraction) during treatment with semaglutide or tirzepatide in overweight/obese people with or without diabetes. For example, in overweight/obese patients with CV disease and without diabetes, semaglutide (2.4 mg QW for 39 months) afforded numerical reductions in CV death by 15 % and heart failure by 18 % [42]. In obese patients with preserved ejection fraction heart failure and without diabetes tirzepatide (up to 15 mg QW for 52 weeks) reduced CV death or worsening heart failure by 38 % [43]. In these and other trials, patients have reported that the incretin treatment improved their health status as assessed using the Kansas City Cardiomyopathy Questionnaire [44].

Because the cardiovascular effects of GLP-1RAs show little correlation with the extent of glucose-lowering or weight-lowering in T2DM or overweight/obese people without diabetes, the possibility of direct actions on the CV system has generated much interest [45]. GLP-1 receptors are expressed by cardiac and vascular tissues, and GLP-1RAs improve the blood lipid profile and reduce blood pressure. The former effect is mostly attributed to reduced nutrient intake and the latter to increased endothelial production of nitric oxide and reduced production of angiotensin II [46,47]. GLP-1RAs also reduce chronic inflammation (see Section 6.1) and appear to impede various steps in the atherogenic process while acting directly on myocardial cells to enhance nutrient metabolism and reduce oxidative stress [48,49]. Accordingly, semaglutide has recently been approved to reduce the complication of overweight/obesity in people with severe CV conditions, and there is debate regarding the potential use of GLP-1RAs to reduce CV risk independently of diabetes or obesity [50,51].

Preliminary evidence from the SURPASS trials suggests that tirzepatide also offers CV benefits similar to those seen with GLP-1RAs [52,53]. GIP receptors are expressed in cardiac and vascular tissues, and GIP is known to reduce blood pressure, improve the lipid profile and reduce atherosclerosis in rodent models of CV disease [6,54]. Endothelial effects of GIP that are similar to GLP-1 have been reported, such as increased vasodilation via increased nitric oxide production and reduced inflammation [55,56].

## 5. Renal effects

Treatment of patients with T2DM with a GLP-1RA has typically reduced the onset and progression of albuminuria independently of the extent of reductions in blood glucose, body weight or blood pressure, and generally with little effect on the rate of decline in estimated glomerular filtration rate (eGFR) [57,58]. Recently, reductions of

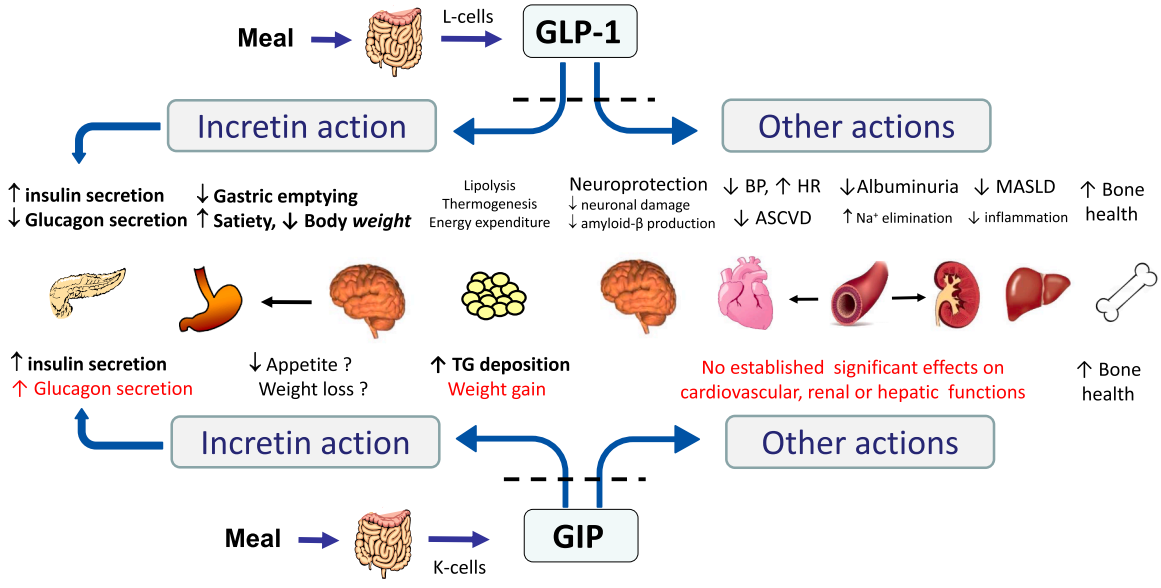


**Fig. 1. An illustration of the diverse actions of glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP) with therapeutic significance.** ASCVD, atherosclerotic cardiovascular disease; BP, blood pressure; heart rate; MASLD, metabolic dysfunction-associated steatotic liver disease; TG, triglyceride. ↑, increase; ↓, decrease. The dashed line indicates that GLP-1 and GIP are susceptible to rapid degradation by the enzyme dipeptidyl peptidase-4.

albuminuria have been noted in overweight/obese individuals without diabetes. For example, in the STEP trials semaglutide (2.4 mg QW for 68 weeks) reduced the urinary albumin-creatinine ratio (UACR) by 32 % without a significant effect on eGFR in overweight/obese non-diabetic adults [59]. Similarly, in the SELECT trial, semaglutide (2.4 mg QW for 3 years) reduced the UACR by 31 % in overweight/obese non-diabetic individuals with macroalbuminuria and CV disease [60].

Most patients in these trials had a normal eGFR at baseline which was little affected by the GLP-1RA therapy but individuals with CKD often showed a reduced rate of decline in eGFR during therapy. In the FLOW trial which enrolled T2DM patients with CKD and albuminuria (eGFR 25–75 ml /min/ 1.73 $m^2$ and UACR 100–5000 mg/g), semaglutide (1 mg QW for 3.4 years) reduced UACR by 38 % and slowed the rate of decline in eGFR by 1.16 ml/min/ 1.73 $m^2$ [61]. Other studies with semaglutide and with tirzepatide have also noted reductions in albuminuria in people with or without CKD and with or without T2DM [37, 62,63]. Indeed, semaglutide and other GLP-1RAs have been used to improve glycaemic control and achieve weight loss in people with end stage renal disease and on dialysis [64,65] Studies evaluating how GLP-1RAs can affect kidney function independently of glycaemia, weight and blood pressure have favoured reduced inflammation as a likely mechanism. GLP-1RAs may also help to protect glomerular integrity by suppressing the receptor for advanced glycation end products (RAGE) and reducing oxidative damage via reduced NAD(P)H oxidase activity [66,67].

## 6. Other possible benefits

In the 10 years since the first long-acting GLP-1RA (exenatide) became available, circumstantial evidence has suggested that these agents offer additional therapeutic opportunities beyond their metabolic and cardiorenal benefits.

### 6.1. Inflammation

A number of clinical studies have observed a decrease in pro-inflammatory markers during use of a GLP-1RA, and an anti-inflammatory effect has been considered to contribute to the pleiotropic properties of these agents across metabolic, cardiorenal, neurodegenerative, osteoarthritic and other diseases [47,68,69]. Although it is difficult to identify mechanisms in most of the clinical studies, *in vitro* experiments indicate a direct effect of GLP-1RAs on immune cells and other cell types to suppress the activation of nuclear factor-kappa B (NF-κB), thereby reducing production of a range of pro-inflammatory cytokines including C-reactive protein, interferon-γ, IL-1β. IL-2, IL-6, IL-17, and tumor-necrosis factor-α, and

GLP-1RAs can also stimulate production of anti-inflammatory Il-10 [(reviewed in [70]). Indeed, use of a GLP-1RA may reduce the excessive inflammatory response and improve survival during Covid-19 infection and reduce airway inflammation in asthma and other respiratory conditions [71–73].

### 6.2. Fatty liver

The expansion and re-designation of non-alcoholic fatty liver disease into metabolic dysfunction-associated steatotic liver disease (MASLD) or metabolic dysfunction-associated steatohepatitis (MASH) has been accompanied by the inclusion of GLP-1RAs into guidelines as potentially useful for prevention and treatment [74–77]. For example, several retrospective studies have noted that use of a GLP-1RA or tirzepatide has reduced progression of steatotic liver disease and the development of cirrhosis, while prospective studies have observed reductions in liver fat content, transaminases, lipid stiffness and fibrosis [78–84]. The mechanism likely involves reduced visceral adiposity, although direct effects on hepatic lipid metabolism are possible. Molecules that combine GCGR agonism together with a GLP-1RA are gaining traction as a potential new approach to the treatment of steatotic liver disease, eg pemvidutide, mazdutide, efinopeglutide, AZD9550 and the triple agonist retatrutide [85].

### 6.3. Neurocognitive disorders

A neuroprotective effect of GLP-1RAs is well recognised in preclinical experimentation and this is variously attributed to reductions in inflammation, apoptosis and oxidative stress, as well as increased autophagy and activation of various intracellular signalling proteins in nerve cells [86–88]. However, clinical studies of motor function in Parkinson's disease and cognitive function in dementia/Alzheimer's disease have given mixed results [89]. An analysis of prospective data gathered during the CVOTs in T2DM found that the risk of new-onset dementia with liraglutide or semaglutide was more than halved over 4 years, and lixisenatide has been reported to slow motor deterioration in Parkinson's disease [90]. Other studies have been less positive and several meta-analyses of studies involving Parkinson's and Alzheimer's patients have been inconclusive, noting that there are considerable variations in the design of these studies, and many have probably been too short to allow measurable changes [91–93]. Accordingly, investigations are continuing to explore the potential for GLP-RAs to contribute to the treatment of neural disorders.

### 6.4. Type 1 diabetes

Intensive insulin therapy in adults with type 1 diabetes mellitus (T1DM) may result in overweight or obesity. In a small-scale study involving 50 patients with T1DM treated with either semaglutide or tirzepatide and 50 appropriately matched T1DM control subjects not receiving these agents, off-label use over 1 year produced weight loss of 9.1 % in the semaglutide group and 21.4 % in the tirzepatide group. Improved glucose control was observed in both groups [94].

Separate injections as well as fixed-ratio mixtures of a GLP-1RA with a basal insulin have improved glycaemic control with reductions of insulin requirement and weight gain in both T2DM and type 1 diabetes ) [95]. However, uptake has been limited, particularly for T1DM, and recent studies assessing efficacy using continuous glucose monitoring (CGM) have noted the difficulty in determining how to reduce the insulin dose to avoid 'time below range' when a GLP-1RA is introduced [96]. Pharmacokinetic studies with an up-coming QW fixed-ratio combination of the basal insulin icodec with semaglutide (*IcoSema*) may help to alleviate this concern and simplify use [97].

### 6.5. Osteoarthritis and bone health

Although preclinical studies have consistently shown that both GIP and GLP-1 promote bone formation involving increased activity of osteoblasts and decreased activity of osteoclasts, clinical evidence remains inconclusive. Some recent clinical studies with GLP-1RAs have reported decreased risk of fractures and positive changes in markers of bone metabolism, but others have been unable to confirm beneficial effects on bone health and long-term studies are ongoing [98,99].

The indirect effects of GLP-1RAs on weight loss and glucose-lowering in conjunction with possible direct effects on inflammatory pathways and cartilage preservation has suggested a role for these agents in management of osteoarthritis [100,101]. In a 68-week, double-blind, randomized, placebo-controlled trial involving 407 participants with obesity and knee osteoarthritis with moderate-to-severe pain, once-weekly injection of semaglutide (2.4 mg) resulted in significantly greater reductions in body weight and pain related to knee osteoarthritis than placebo. Adverse events (primarily gastrointestinal disorders) leading to discontinuation of the trial regimen occurred in 6.7 % of the participants in the treatment group and in 3.0 % in the placebo group [102]

### 6.6. Additional potential uses of incretin therapies

Accumulating evidence indicates that GLP-1RAs and the GIPR/GLP-1R co-agonist tirzepatide are beneficial in the management of obstructive sleep apnoea in people with obesity, and tirzepatide has recently gained approval by the FDA for this indication [103–105]. Studies have now linked the use of GLP-1RAs to reductions in craving behaviours for specific foods as well as alcohol and opiate abuse that are mediated centrally through dopaminergic pathways [106,107]. Possible links between the use of GLP-1RAs and the prevalence of anxious or depressive behaviours, and suicidal ideation have been claimed but remain to be substantiated [108–111].

## 7. Cautions and limitations of incretin therapies

The therapeutic use of GLP-1RAs and tirzepatide has been limited by possible loss of muscle mass and gastrointestinal (GI) tolerability and as well as with high cost and limited availability. Controversy regarding the effect of GLP-1RA therapies on loss of lean body mass is no closer to resolution following two recent meta-analyses. An analysis of dual-energy X-ray absorptiometry (DEXA) data found that loss of fat-free mass accounted for 20–40 % of overall weight loss [112]. However, another analysis that included data from DEXA, bioimpedance, magnetic resonance imaging and computed tomography suggested a smaller loss of lean body mass (average about 1 kg) which was comparable with the loss of lean body mass by individuals achieving similar overall weight loss without using a GLP-1RA [113]. Caution continues to be needed regarding the use of a GLP-1RA in sarcopenia especially in the case of frail individuals, noting also that such patients may be more susceptible to hypoglycaemia with GLP-1RA therapy [114].

Initial GI disturbances are common and in clinical trials 10–30 % of patients have reported at least one bout of nausea or vomiting. These are generally temporary, mostly occurring during the first 1–2 months of therapy. They are reduced by delaying dose titration and account for discontinuation in $< 5$ % of patients in most of the recent clinical trials [115]. A recent comprehensive study analysing health outcomes in 2 million people using a range of antihyperglycemic agents concluded that GLP-1RAs reduce risks of neurocognitive, cardiovascular and respiratory disorders and substance abuse but increase risks of gastrointestinal issues, hypotension and pancreatitis [116]. A more recent analysis of the safety profile of once-weekly subcutaneous semaglutide (2.4 mg) involving patients enrolled in the SELECT study identified a small but significant increased frequency of gallbladder-related disorders in the semaglutide group versus placebo (2.8 % vs. 2.3 %; $p = 0.04$), mainly driven by cholelithiasis [117]. The risk of developing neutralizing antibodies remains a consideration. However, anti-drug antibodies have been identified in very few recipients of incretin-based peptides, and therapeutic efficacy has not been significantly affected [3].

Risk of increased progression ('early worsening') of retinopathy has been noted in some studies in which semaglutide has been prescribed for T2DM individuals with already-established retinopathy [118]. Early worsening has been attributed in part to a large, rapid and sustained reduction in glycaemia but this is not a consistent finding and remains under investigation [119]. A link between long-term administrations of GLP-1RAs and nonarteritic anterior ischemic optic neuropathy (NAION) has been suggested but remains to be firmly established [120]. A study involving a cohort of 424,152 Danish patients with T2D concluded that during five years of observation the use of once-weekly semaglutide more than doubled the risk of NAION [121]. However, a retrospective multinational population-based study involving a global electronic medical records database suggested that semaglutide may not be associated with an increased risk of NAION in the general population, It was concluded that avoidance of semaglutide based solely on concerns regarding the risk of NAION may not be warranted because its potential benefits for blood glucose control and cardiovascular health likely outweigh its potential risks [122].

The cost of GLP-1RAs and allied injectable incretin medicines continues to restrict individual usage and has demoted the positioning of these medicines in some treatment algorithms. Increased demand for incretin therapies associated with their uptake for the management of obesity has given rise to shortages. There is evidence that the availability of *Wegovy* and *Zepbound* has led to an increase in "fat shaming" and paediatricians are concerned by the increasing numbers of healthy schoolchildren and adolescents who are requesting these medications as a result of peer-pressure (C.A. MacGeorge, unpublished observations).

The short-acting GLP-1RAs, namely exenatide (*Byetta*) and lixisenatide (*Lyxumia*) have been discontinued in some countries in 2024. This has provided market access for compounded versions and appearance of fake products that have been linked to altered efficacy or adverse reactions. This has deterred some prospective users [123–125]. Accounts in the popular press suggest that fake products are usually acquired on-line and used independently of a healthcare professional. Some have contained insulin or amphetamines which cause hypoglycaemia or a racing pulse. Others have contained the highest dose of the peptide which has been injected without the required gradual dose titration. However, it is anticipated that improved methodologies for solid-phase peptide synthesis will facilitate the commercial production of *bona fide* incretin peptides and help to contain costs [126].

## 8. Incretins in development

The markedly increased efficacy of semaglutide and tirzepatide compared with earlier incretin-based therapies has ignited a surge in medical and non-medical demand for ever more potent weight-loss agents, preferably with fewer side effects, longer durations of action and/or oral delivery. The oral formulation of semaglutide is now approved and widely adopted, and the introduction of further orally-active incretin peptide formulations is anticipated. The development of effective and orally-active non-peptide agents would undoubted have a marked effect on the market as such compounds would be easiest to synthesize than the currently available injectable GLP-1RAs and so presumably at less cost to the patient. Although several small molecule GLP-1RAs (gliprons) have received preclinical and early clinical assessment, few have proceeded into a phase 3 clinical program and some have been discontinued due to raised liver transaminases and/or insufficient efficacy [127,128]. However, daily oral administration of the small molecule, orforglipron showed promise in phase 2 clinical trials producing significant weight reduction and improvement in lipid profile while mild to moderate adverse events were similar to those with injectable GLP-1 receptor agonists [129,130]. Phase 3 clinical trials conducted by Eli Lilly are expected to be completed by 2026. This apart, peptide molecules constitute the most advanced prospects for new incretin-based therapies in the near future. Newly introduced long-acting GLP-1RAs include ecnoglutide, a modified GLP-1 (7–37) peptide containing the substitution $Ala^8 \rightarrow Val$ and a C-18 fatty acid at $Lys^{30}$ [131] and XT002 [132]. However, most novel agents under investigation are unimolecular dual or triple agonists that interact with the GLP-1R and/or GIPR and/or GCGR (Table 2). The primary structures, where available, of the agents presented in this review are shown in Fig. 2.

Several GLP-1R/GCGR dual agonists have shown significant weight-lowering efficacy (eg survodutide [133], pemvidutide [134] and mazdutide [135]). Although GCGRA activity may seem counterintuitive (discussed earlier, Section 3), it is relevant to note here that GCGRAs reduce appetite and increase energy consumption, thereby giving additive weight-lowering efficacy [1–4]. Indeed, treatment of diet-induced obese mice with the long-acting GCGRA, LY3324954 stimulated energy expenditure, weight loss, reduction of adiposity and benefited whole-body lipid homeostasis [136]. However, it is worthwhile to point out that in the past a number of potential anti-obesity drugs that function by increasing energy expenditure have been withdrawn because of adverse cardiac complications [137]. A combination of a GCGRA with a

**Table 2**
Incretin-based peptide agents in clinical development: evidence from randomised clinical trials.

| Agent<br>*Sponsor* | Receptor targets | Route<br>Timing<br>Phase | Patients, trial duration<br>Primary trial results | Ref |
|---|---|---|---|---|
| MariTide (AMG133)<br>*Amgen* | GLP−1RA/GIPRi | SC, QM<br>Phase 2 | OW/O T2DM, 52 wks, ↓A1C ~2.2 %, ↓BW ~17 %<br>OW/O, 52 wks, ↓BW ~20 % | [144] |
| Amycretin<br>*Novo* | GLP−1RA/ amylinRA | Or, OD<br>Phase 1 | OW/O, 12 wks, ↓BW 13.1 % | [148] |
| CagriSema<br>*Novo* | GLP−1RA + amylinRA mix | SC, QW<br>Phase 2<br>SC, QW<br>Phase 3 | OW/O T2DM, 32 wks, ↓A1C ~2.2 %, ↓BW 15.6 %<br>OW/O, 68 wks, ↓BW 20.4 % | [146] [147] |
| CT−388<br>*Carmot* | GLP−1RA/GIPRA | SC, QW<br>Phase 1 | OW/O, 24 wks, ↓BW 18.8 % | [141] |
| Ecnoglutide<br>*Sciwind* | GLP−1RA | SC, QW<br>Phase 2 | NW/OW T2DM, 20 wks,<br>↓A1C 2.39 %, ↓BW 2.26 kg | [131] |
| Mazdutide<br>*Lilly* | GLP−1RA/GCGRA | SC, QW<br>Phase 3 | OW/O, 48 wks, ↓BW 13.3 % | [135] |
| Pemvidutide<br>*Altimmune* | GLP−1RA/GCGRA | SC, QW<br>Phase 2 | OW/O MASLD ± T2DM, 12 wks, ↓BW 3.5 %, rrLFC 57.1 % | [134] |
| Retatrutide<br>*Lilly* | GLP−1RA/GIPRA/ GCGRA | SC, QW<br>Phase 2 | OW/O T2DM, 24 wks, ↓A1C 2.02 %; 36 wks ↓BW 16.9 %<br>OW/O, 48 wks, ↓BW 24.2 %<br>OW/O MASLD, 24 wks, ↓BW 17.6 %, rrLFC 82.4 % | [138] [139] |
| Survodutide<br>*BI* | GLP−1RA/GCGRA | SC, QW<br>Phase 2 | OW/O, 46 wks, ↓BW 14.9 % | [133] |
| VK−2735<br>*Viking* | GLP−1RA/GIPRA | SC, QW<br>Phase 2<br>PO, OD<br>Phase 1 | OW/O, 13 wks, ↓BW 14.7 %<br>OW/O, 4 wks, ↓BW 8.29 % | [142] |
| ZT−002<br>Beijing QL | GLP−1RA | SC, QM<br>Phase 1 | OW/O, 14 wks, ↓BW 13.1 % | [132] |

Trial results refer to top dose tested. BI, Boehringer Ingelheim; MASLD, metabolic dysfunction-associated steatotic liver disease; Mix, mixture within same injection, NW, normal body weight; OD, once daily; OW, overweight; PO, per oral; QM, once monthly; QW, once weekly; RA, receptor agonist; Ri, receptor inhibitor; rrLFC, relative reduction in liver fat content.

GLP-1RA enables the GLP-1RA to counter the rise in blood glucose by inhibiting endogenous glucagon secretion and increasing insulin secretion. GLP-1R/GCGR dual agonists have shown encouraging effects to reduce liver fat content in individuals with metabolic dysfunction-associated steatotic liver disease (MASLD) and may be particularly suited for this purpose [81,84]. The once weekly GIPR/GLP-1R/GCGR triple agonist retatrutide has shown marked glucose-lowering and weight-lowering potency in phase 2 trials to treat T2DM and obesity and is effective in MASLD [85,138,139]. Efocipegtrutide (HM12511), a GLP-1R/GCGR/GIPR triple agonist chemically conjugated with the constant region of human immunoglobulin via a non-peptidyl flexible linker, has also shown promise in the treatment of non-alcoholic steatohepatitis [140].

Following the introduction of tirzepatide, several GLP-1RA/GIPRA peptides are proceeding in development such as CT-388 [141], VK-2735 [142] and G49 [143]. Although the chronic action of the GIPRA component is unclear (see Section 3), evidence that GIPR antagonism (as well as GIPR agonism) can reduce blood glucose and body weight, has encouraged the development of MariTide (maridebart cafraglutide, formerly AMG133) comprising a bispecific monoclonal anti-human GIPR antagonist antibody covalently linked to two GLP-1RAs. This agent is given by once monthly subcutaneous injection. In a phase 1 trial involving overweight/obese participants without diabetes, MariTide (420 mg QM) reduced body weight by 14 % after 3 months and most of this effect was maintained for a further 2–3 months without further treatment [34]. In a 52-week phase 2 trial, overweight/obese participants without diabetes who received MariTide (280 or 420 mg QM) lost 17–20 % body weight, while overweight/obese participants with diabetes who received the same doses lost 14–17 % body weight with reductions of HbA1c by 2.0–2.2 % [144].

Renewed interest in the weight-lowering properties of amylin analogues has emerged, noting that a soluble (non-aggregating) short-acting analogue of amylin (pramlintide) has been available in some regions since 2005. Pramlintide is used as an adjunct to insulin therapy to improve glycaemic control by suppression of post-prandial glucagon release and reduce weight gain by suppressing appetite via slowing of gastric emptying [145]. The reduction in body weight has been accentuated with a longer-acting amylin analogue, cagrilintide, which has an N-terminal C-20 fatty acid chain to enable binding to albumin (Fig. 2). When cagrilintide was administered together with semaglutide (both at a dose of 2.4 mg by QW injection) HbA1c was reduced by 2.2 % and body weight by 15.6 % in a 32-week phase 2 trial in overweight/obese T2DM adults [146]. A phase 3 trial (REDEFINE-1) of 3417 overweight/obese participants without diabetes noted that 68 weeks of treatment with CagriSema (a fixed dose combination of cagrilintide 2.4 mg and semaglutide 2.4 mg by QW injection once per week) was associated with a 22.7 % weight loss compared with 2.3 % with placebo [147]. The weight loss in each of the two trials above was greater than either cagrilintide or semaglutide alone at the same dose. Amycretin, a single peptide amylin receptor/GLP-1RA co-agonist molecule containing salcaprozate sodium (sodium *N*-[8-(2-hydroxybenzoyl) amino] caprylate; SNAC) as a permeation enhancer, has been developed and formulated into a once-daily 50 mg tablet for oral delivery. In a phase 1 study administration of the tablet achieved a 13 % weight loss in 12 weeks in obese individuals [148]. The functionality of the amylin receptor system (AMY1, AMY2 and AMY3), which comprise heterodimers of the calcitonin receptor, is especially complicated. Interplay with calcitonin has prompted preclinical studies showing that dual amylin/calcitonin receptor agonists (DACRAs) can achieve greater weight loss than amylin analogues alone [149,150]. At a preclinical stage there are even more complex multi-agonists in development that exert amylin receptor agonism. For example, PTT-A is a long-acting tetra-agonist acting at the GLP-1, GIP, amylin and calcitonin receptors that decreased food intake and body weight in diet-induced obese rats [151].

Appetite suppression is an important attribute of GLP-1RAs, and the appetite-suppressing properties of other gut peptides such as peptide tyrosine tyrosine (PYY), pancreatic polypeptide, GLP-2 and secretin as well as the inhibition of appetite stimulants such as neuropeptide Y are being considered in preclinical studies as templates for potential anti-obesity drugs [152,153]. Further potential partners for anti-obesity incretin therapies are neurokinin-2 activators which increase energy expenditure [154].

Because incretin peptides and the various appetite-suppressing energy-expending peptides considered above generally do not cause overt

**GLP-1R monoagonist**

Semaglutide HXEGTFTSDVSSYLEGQAAKEFIAWLVRGRG
Econoglutide HVEGTFTSDVSSYLEEQAAREFIKWLVRGRG

**GLP-1R monoagonist**

Semaglutide HXEGTFTSDVSSYLEGQAAKEFIAWLVRGRG
Econoglutide HVEGTFTSDVSSYLEEQAAREFIKWLVRGRG
XT002

**GCGR monoagonist**

LY3324954 YXQGTFTSDYSKYLDXKKAKEFVEWLLETGPSSGAPPPS.$NH_2$

**GLP-1R/GCGR dual agonists**

Pemvidutide HXQGTFTSDYSKYLDEKAAKEFIQWLLQT.NH2 (Lactam:E-16,K-20)
survodutide HΔQGTFTSDYSKYLDERAAKDFIKESA.$NH_2$
Mazdutide HXQGTFTSDYSKYLDEKKAKEFVEWLLEGGPSSG.$NH_2$
G49 HSQGTFTSDYSKYLEEEAVRLFICWLMNT.$NH_2$

**GIPR/GLP-1R dual agonists**

Tirzepatide YXEGTFTSDYSIXLDKIAQKAFVQWLIAGGPSSGAPPPS
CT-388

**GIPR agonist/GIPR antagonist**

MariTide [HXEGTFTSDYSSYLEEQAAKEFIAWLVKGGGK.$NH_2$]$_2$.Ab

**GIPR/GLP-1R/GCGR triple agonists**

Retatrutide YXQGTFTSDYSI▼LDKKAQXAFIEYLLEGGPSSGAPPPS.$NH_2$
Efocipegtrutide

**Amylin analogue and dual amylin/calcitonin receptor agonist (DACRA)**

Cagrilintide KCNTATCATQRLAEFLRHSSNNFGPILPPTNVGSNTP.$NH_2$
KBP-066A Ac.CSNLSTCXLGRLSQDLHRLQTYPKTDVGANAP.$NH_2$

**GLP-1R/amylin receptor dual agonist**

Amycretin

**GLP-1R/GIPR/amylin receptor/calcitonin receptor tetraagonist**

PTT-A

**X** = α-aminoisobutyric acid, **Δ** = 1-amino-1-cyclobutanecarboxylic acid, **▼** = α-methyl-L-leucine, **K** denotes the site of attachment of a fatty acid or fatty di-acid. **K** denotes the site of attachment of two GLP-1R agonists to a human monoclonal GIPR antibody. **C** denotes the site of attachment of a 40 kDa polyethylene glycol (PEG) moiety.

**Fig. 2. Some recently introduced incretin peptides with therapeutic potential.** **X** = α-aminoisobutyric acid, **Δ** = 1-amino-1-cyclobutanecarboxylic acid, **▼** = α-methyl-L-leucine, **K** denotes the site of attachment of a fatty acid or fatty di-acid. **K** denotes the site of attachment of two GLP-1R agonists to a human monoclonal GIPR antibody (Ab). C denotes the site of attachment of a 40 kDa polyethylene glycol (PEG) moiety.

hypoglycaemia when administered at pharmacological doses, they can be utilised in long-acting and continuous delivery systems, such as monthly injections, hydrogel-based subcutaneous depots, nano-capsules and skin patches. Technologies for oral administration of peptides including absorption enhancers for gastrointestinal uptake continue to advance, and although bioavailability presents an on-going challenge it has been possible to deliver a high dose (50 mg) of semaglutide in tablet form for obesity treatment [15,155].

## 9. Conclusions

The manipulation of incretin molecules has created glucose-lowering and weight-lowering agents with sufficient potency to challenge the position of bariatric surgery in the management of T2DM and obesity

[156]. Several recent studies have reported weight-lowering by > 15 % in overweight/obese individuals without T2DM and reductions in HbA1c by about 2 % in individuals with T2DM. Incretin-based agents, alone or in combination with other therapies, can offer cardioprotective and nephroprotective effects that favour use in patients with atherosclerotic disease and albuminuric chronic kidney disease. This is now recognised in the positioning of various incretin therapies earlier in the treatment algorithms for T2DM patients with these co-morbidities. Emerging evidence also suggests potential benefits against inflammatory disorders, fatty liver, and sleep apnea and possibly for neurological conditions and bone health - all potential future therapeutic applications for incretin-based agents. Thus, with due attention to tolerability, cost and availability, multi-agonist incretin-based peptides offer the opportunity to customize treatments that address a variety of targets against T2DM, obesity and associated co-morbidities.

It is fitting that this article should be included in the special issue **A centennial tribute to Viktor Mutt** as the first dual agonist incretin peptide, the CGGRA/GLP-1RA oxyntomodulin, was purified and characterized by Bataille and co-workers in Prof. Mutt's laboratory in 1981 [157]. Infusions of oxyntomodulin reduce food intake and increases energy expenditure in humans as well as improving glucose tolerance in T2DM patients which led to the prediction in 2013, now fully realized, that "dual agonists of the GCGR and GLP-1R represent new promising treatments for diabetes and obesity with the potential for weight loss and glucose lowering superior to that of GLP-1R agonists" [158]. Thus, we see yet another example of fundamental work carried out under the direction of Prof. Mutt that has led to major advances in the treatment of human diseases.

## Author contributions

All authors contributed to the writing of this review.

## CRediT authorship contribution statement

**Conlon J. Michael:** Writing – review & editing, Writing – original draft. **Flatt Peter R.:** Writing – review & editing, Writing – original draft. **Bailey Clifford J.:** Writing – review & editing, Writing – original draft.

## Conflict of Interest

CJB has served on steering committees for clinical trials and advisory boards for several pharmaceutical companies. PRF and JMC are named on patents held by Ulster University for peptide therapeutics and have served as advisor to several pharmaceutical companies.

## Data availability

No data was used for the research described in the article.

## References


[1] M. Tschöp, R. Nogueiras, B. Ahrén, Gut hormone-based pharmacology: novel formulations and future possibilities for metabolic disease therapy, Diabetologia 66 (2023) 1796–1808, https://doi.org/10.1007/s00125-023-05929-0.

[2] A.K. Chetty, E. Rafi, N.J. Bellini, Buchholz, D. Isaacs, A review of incretin therapies approved and in late-stage development for overweight and obesity management, Endoc. Pract. 30 (2024) 292–303, https://doi.org/10.1016/j.eprac.2023.12.010.

[3] C.J. Bailey, P.R. Flatt, J.M. Conlon, An update on peptide-based therapies for type 2 diabetes and obesity, Peptides 161 (2023) 170939, https://doi.org/10.1016/j.peptides.2023.170939.

[4] C.J. Bailey, P.R. Flatt, J.M. Conlon, Recent advances in peptide-based therapies for obesity and type 2 diabetes, Peptides 173 (2024) 71149, https://doi.org/10.1016/j.peptides.2024.171149.

[5] A. Solini, D. Tricò, S. Del Prato, Incretins and cardiovascular disease: to the heart of type 2 diabetes? Diabetologia 66 (2023) 820–1831, https://doi.org/10.1007/s00125-023-05973-w.

[6] J. Goldney, J.A. Sargeant, M.J. Davies, Incretins and microvascular complications of diabetes: neuropathy, nephropathy, retinopathy and microangiopathy, Diabetologia 66 (2023) 1832–1845, https://doi.org/10.1007/s00125-023-05988-3.

[7] F.B. Rivera, L.L. Cruz, J.V. Magalong, J.M.M.J. Muyeras, J.P. Aparece, N.R. B. Bantayan, et al., Cardiovascular and renal outcomes of glucagon-like peptide 1 receptor agonists among patients with and without type 2 diabetes mellitus: a meta-analysis of randomized placebo-controlled trials, Am. J. Prev. Cardiol. 18 (2024) 100679, https://doi.org/10.1016/j.ajpc.2024.100679.

[8] M.A. Nauck, T.D. Müller, Incretin hormones and type 2 diabetes, Diabetologia 66 (2023) 1780–1795, https://doi.org/10.1007/s00125-023-05956-x.

[9] H. Yao, A. Zhang, D. Li, Y. Wu, C.-Z. Wang, J.-Y. Wan, et al., Comparative effectiveness of GLP-1 receptor agonists on glycaemic control, body weight, and lipid profile for type 2 diabetes: systematic review and network meta-analysis, BMJ 384 (2024) e076410, https://doi.org/10.1136/bmj-2023-076410.

[10] J.P. Frías, P. Auerbach, H.S. Bajaj, Y. Fukushima, I. Lingvay, S. Macura, et al., Efficacy and safety of once-weekly semaglutide 2·0 mg versus 1·0 mg in patients with type 2 diabetes (SUSTAIN FORTE): a double-blind, randomised, phase 3B trial, Lancet Diabetes Endocrinol. 9 (2021) 563–574, https://doi.org/10.1016/S2213-8587(21)00174-1.

[11] J.P. Frías, M.J. Davies, J. Rosenstock, F.C. Pérez Manghi, L.F. Landó, Brandon K, Tirzepatide versus semaglutide once weekly in patients with Type 2 diabetes, N. Engl. J. Med. 385 (2021) 503–515, https://doi.org/10.1056/NEJMoa2107519.

[12] J.P.H. Wilding, R.L. Batterham, S. Calanna, M. Davies, L.F. Van Gaal, I. Lingvay, et al., Once- weekly semaglutide in adults with overweight or obesity, N. Engl. J. Med. 384 (2021) 989–1002, https://doi.org/10.1056/NEJMoa2032183.

[13] J.M. Jastreboff, C.W. le Roux, A. Stefanski, L.J. Aronne, B. Halpern, S. Wharton S, et al., Tirzepatide for obesity treatment and diabetes prevention, Nov 13, N. Engl. J. Med. (2024), https://doi.org/10.1056/NEJMoa2410819.

[14] L.J. Aronne, N. Sattar, D.B. Horn, H.E. Bays, S. Wharton, W.-Y, et al., Continued treatment With tirzepatide for maintenance of weight reduction in adults with obesity: The SURMOUNT-4 randomized clinical trial, JAMA 331 (2024) 38–48, https://doi.org/10.1001/jama.2023.24945.

[15] D. Rubino, N. Abrahamsson, M. Davies, D. Hesse, F.L. Greenway, C. Jensen, et al., 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 (2021) 1414–1425, https://doi.org/10.1001/jama.2021.3224.

[16] F.K. Knop, V.R. Aroda, R.D. do Vale, T. Holst-Hansen, P.N. Laursen, J. Rosenstock J, et al., Oral semaglutide 50 mg taken once per day in adults with overweight or obesity (OASIS 1): a randomised, double-blind, placebo-controlled, phase 3 trial, Lancet 402 (10403) (2023) 705–719, https://doi.org/10.1016/S0140-6736(23)01185-6.

[17] D. Weghuber, T. Barrett, M. Barrientos-Pérez, I. Gies, D. Hesse, K. Jeppesen, et al., Once-weekly semaglutide in adolescents with obesity, 15, N. Engl. J. Med. 387 (2022) 2245–2257, https://doi.org/10.1056/NEJMoa2208601.

[18] D. Rubino, H. Angelene, A. Fabricatore, J. Ard, Efficacy and safety of semaglutide 2.4mg by race and ethnicity: A post hoc analysis of three randomized controlled trials, Obes. (Silver Spring) 32 (2024) 1268–1280, https://doi.org/10.1002/oby.24042.

[19] S.E. Kahn, J.E. Deanfield, O.K. Jeppesen, S.S. Emerson, T.W. Boesgaard, H. M. Colhoun, et al., Effect of semaglutide on regression and progression of glycemia in people with overweight or obesity but without diabetes in the SELECT trial, Diabetes Care 47 (2024) 1350–1359, https://doi.org/10.2337/dc24-0491.

[20] J.P.H. Wilding, R.L. Batterham, M. Davies, L.F. Van Gaal, K. Kandler, K. Konakli, et al., Weight regain and cardiometabolic effects after withdrawal of semaglutide: The STEP 1 trial extension, Diabetes Obes. Metab. 24 (2022) 1553–1564, https://doi.org/10.1111/dom.14725.

[21] L.J. Aronne, N. Sattar, D.B. Horn, H.E. Bays, S. Wharton, W.-Y. Lin, et al., Continued treatment with tirzepatide for maintenance of weight reduction in adults with obesity: the SURMOUNT-4 randomized clinical trial, JAMA 331 (2024) 38–48, https://doi.org/10.1001/jama.2023.24945.

[22] S.B.K. Jensen, M.B. Blond, R.M. Sandsdal, L.M. Olsen, C.R. Juhl, J.R. Lundgren, et al., Healthy weight loss maintenance with exercise, GLP-1 receptor agonist, or both combined followed by one year without treatment: a post-treatment analysis of a randomised placebo-controlled trial, EClinicalMedicine 69 (2024) 102475, https://doi.org/10.1016/j.eclinm.2024.102475.

[23] N.U. Paddu, B. Lawrence, S. Wong, S.J. Poon, G. Srivastava, Weight maintenance on cost-effective antiobesity medications after 1 year of GLP-1 receptor agonist therapy: a real-world study, Obesity 32 (2024) 2255–2263, https://doi.org/10.1002/oby.24177.

[24] Z. Zheng, Y. Zong, Y. Ma, Y. Tian, Y. Pang, C. Zhang, J. Gao, Glucagon-like peptide-1 receptor: mechanisms and advances in therapy, Signal Transduct. Target Ther. 9 (2024) 234, https://doi.org/10.1038/s41392-024-01931-z.

[25] T.D. Müller, A. Adriaenssens, B. Ahrén, M. Blüher, A. Birkenfeld, J.E. Campbell, et al., Glucose-dependent insulinotropic polypeptide (GIP), Mol. Metab. (2025) 102118, https://doi.org/10.1016/j.molmet.2025.102118 (Online ahead of print).

26] C. De Block, C. Bailey, C. Wysham, A. Hemmingway, S.E. Allen, J. Peleshok, J. Tirzepatide for the treatment of adults with type 2 diabetes: An endocrine perspective, Diabetes Obes. Metab. 25 (2023) 3–17, https://doi.org/10.1111/dom.14831.

[27] L.S. Gasbjerg, M.M. Rosenkilde, J.J. Meier, J.J. Holst, F.K. Knop, The importance of glucose-dependent insulinotropic polypeptide receptor activation for the

effects of tirzepatide, Diabetes Obes. Metab. 25 (2024) 3079–3092, https://doi.org/10.1111/dom.15216.
[28] C.J. Bailey, P.R. Flatt, Duodenal enteroendocrine cells and GIP as treatment targets for obesity and type 2 diabetes, Peptides 174 (2024) 171168, https://doi.org/10.1016/j.peptides.2024.171168.
[29] J.D. Douros, J. Mokrosinski, B. Finan, The GLP-1R as a model for understanding and exploiting biased agonism in next-generation medicines, J. Endocrinol. 261 (2024) e230226, https://doi.org/10.1530/JOE-23-0226.
[30] H.S. Kizilkaya, K.V. Sørensen, J.S. Madsen, P. L.inquist, J.D. Douros, J. Bork-Jensen, et al., Characterization of genetic variants of GIPR reveals a contribution of β-arrestin to metabolic phenotypes, Nat. Metab. 6 (2024) 1268–1281, https://doi.org/10.1038/s42255-024-01061-4.
[31] A.H. Shilleh, K. Viloria, J. Broichhagen, J.E. Campbell, D.J. Hodson, GLP1R and GIPR expression and signaling in pancreatic alpha cells, beta cells and delta cells, Peptides 175 (2024) 171179, https://doi.org/10.1016/j.peptides.
[32] J.E. Campbell, T.D. Müller, B. Finan, R.D. DiMarchi, M.H. Tschöp, D.A. D'Alessio, GIPR/GLP-1R dual agonist therapies for diabetes and weight loss-chemistry, physiology, and clinical applications, Cell. Metab. 35 (2023) 519–1529, https://doi.org/10.1016/j.cmet.2023.07.010.
[33] N. Zaïmia, J. Obeid, A. Varrault, J. Sabatier, C. Broca, P. Gilon, et al., GLP-1 and GIP receptors signal through distinct β-arrestin 2-dependent pathways to regulate pancreatic β cell function, Cell Rep. 42 (2023) 113326, https://doi.org/10.1016/j.celrep.2023.113326.
[34] M.M. Véniant, S.-C. Lu, L. Atangan, R. Komorowski, S. Stanislaus, Y. Cheng, et al., GIPR antagonist conjugated to GLP-1 analogues promotes weight loss with improved metabolic parameters in preclinical and phase 1 settings, Nat. Metab. 6 (2024) 90–303, https://doi.org/10.1038/s42255-023-00966-w.
[35] A. Liskiewicz, A. Khalil, D. Liskiewicz, A. Novikoff, G. Grandl, G. Maity-Kumar, et al., Glucose-dependent insulinotropic polypeptide regulates body weight and food intake via GABAergic neurons in mice, Nat. Metab. 5 (2023) 2075–2085, https://doi.org/10.1038/s42255-023-00931-7.
[36] J.E. Lewis, D. Nuzzaci, P.P. James-Okoro, M. Montaner, E. O'Flaherty, T. Darwish T, et al., Stimulating intestinal GIP release reduces food intake and body weight in mice, Mol. Metab. 84 (2024) 101945, https://doi.org/10.1016/j.molmet.2024.101945.
[37] S.V. Badve, A. Bilal, M.M.Y. Lee, N. Sattar, H.C. Gerstein, C.T. Ruff, Effects of GLP-1 receptor agonists on kidney and cardiovascular disease outcomes: a meta-analysis of randomised controlled trials, Lancet Diabetes Endocrinol. 13 (2025) 15–28, https://doi.org/10.1016/S2213-8587(24)00271-7.
[38] M.N. Kosiborod, J. Deanfield, R. Pratley, B.A. Borlaug, J. Butler, M.J. Davies, et al., Semaglutide versus placebo in patients with heart failure and mildly reduced or preserved ejection fraction: a pooled analysis of the SELECT, FLOW, STEP-HFpEF, and STEP-HFpEF DM randomised trials, Lancet 404 (10456) (2024) 949–961, https://doi.org/10.1016/S0140-6736(24)01643-X.
[39] Reuter report: Rybelsus cardiovascular outcome trial. October 2024. ⟨https://www.reuters.com/business/healthcare-pharmaceuticals/novo-nordisks-oral-diabetes-drug-cuts-heart-related-risks-by-14-study-2024-10-21/easd/ada⟩ guideline.
[40] S.L. Samson, P. Vellanki, L. Blonde, E.A. Christofides, R.J. Galindo, I.B. Hirsch, et al., American Association of Clinical Endocrinology consensus statement: Comprehensive Type 2 diabetes management algorithm - 2023 Update, Endocr., Pract. 29 (2023) 305–340, https://doi.org/10.1016/j.eprac.2023.02.001. Erratum in: Endocr. Pract. 29 (2023)746. doi:10.1016/j.eprac.2023.06.009. Erratum in: Endocr. Pract. 29 (2023) 1025. doi:10.1016/j.eprac.2023.09.008.
[41] O. Schnell, K. Barnard-Kelly, T. Battelino, A. Ceriello, H.E. Larsson, B. Fernández-Fernández, et al., VOT summit report 2023: new cardiovascular, kidney, and metabolic outcomes, Cardiovasc. Diabetol. 23 (2024) 104, https://doi.org/10.1186/s12933-024-02180-8.
[42] A.M. Lincoff, K. Brown-Frandsen, H.M. Colhoun, J. Deanfield, S.S. Emerson, S. Esbjerg, et al., Semaglutide and cardiovascular outcomes in obesity without diabetes, N. Engl. J. Med. 389 (2023) 2221–2232, https://doi.org/10.1056/NEJMoa2307563.
[43] M. Packer, M.R. Zile, C.M. Kramer, S.J. Baum, S.E. Litwin, V. Menon, et al., Tirzepatide for heart Failure with preserved ejection fraction and obesity, N. Engl. J. Med. (2024), https://doi.org/10.1056/NEJMoa2410027.
[44] M.N. Kosiborod, S.Z. Abildstrøm, B.A. Borlaug, J. Butler, S. Rasmussen, M. Davies, et al., Semaglutide in patients with heart failure with preserved ejection fraction and obesity, N. Engl. J. Med. 389 (2023) 1069–1084, https://doi.org/10.1056/NEJMoa2313917.
[45] F.B. Rivera, L.L.A. Cruz, J.V. Magalong, J.M.M.J. Ruyeras, J.P. Aparece, N.R. B. Bantayan, et al., Cardiovascular and renal outcomes of glucagon-like peptide 1 receptor agonists among patients with and without type 2 diabetes mellitus: A meta-analysis of randomized placebo-controlled trials, Am. J. Prev. Cardiol. 18 (2024) 100679, https://doi.org/10.1016/j.ajpc.2024.100679.
[46] S. Pandey, S. Mangmool, W. Parichatikanond, Multifaceted roles of GLP-1 and its analogs: a review on molecular mechanisms with a cardiotherapeutic perspective, Pharmaceuticals 16 (2023) 836, https://doi.org/10.3390/ph16060836.
[47] J.R. Ussher, D.J. Drucker, Glucagon-like peptide 1 receptor agonists: cardiovascular benefits and mechanisms of action, Nat. Rev. Cardiol. 20 (2023) 463–474, https://doi.org/10.1038/s41569-023-00849-3.
[48] S.F. Mehdi, S. Pusapati, M.S. Anwar, D. Lohana, P. Kumar, S.A. Nandula, et al., Glucagon-like peptide-1: a multi-faceted anti-inflammatory agent, Front. Immunol. 14 (2023) 1148209, https://doi.org/10.3389/fimmu.2023.114820.
[49] X. Wang, X. Yang, X. Qi, G. Fan, L. Zhou, Z. Peng Z, et al., Anti-atherosclerotic effect of incretin receptor agonists, Front. Endocrinol. (Lausanne) 15 (2024) 1463547, https://doi.org/10.3389/fendo.2024.1463547.
[50] D.J. Drucker, The benefits of GLP-1 drugs beyond obesity, Science 385 (2024) 258–260, https://doi.org/10.1126/science.adn4128.
[51] Medicines and Healthcare Products Regulatory Agency. Press release. MHRA approves GLP –1 receptor agonist semaglutide to reduce risk of serious heart problems in obese or overweight adults, 23 July 2024. ⟨https://www.gov.uk/government/news/mhra-approves-glp-1-receptor-agonist-semaglutide-to-reduce-risk-of-serious-heart-problems-in-obese-or-overweight-adults⟩.
[52] F. Taktaz, R.A. Fontanella, L. Scisciola, A. Pesapane, M.G. Basilicata, P. Ghosh, et al., Bridging the gap between GLP1-receptor agonists and cardiovascular outcomes: evidence for the role of tirzepatide, Cardiovasc. Diabetol. 23 (2024) 242, https://doi.org/10.1186/s12933-024-02319-7.
[53] M.I. Stefanou, A. Theodorou, K. Malhotra, D. Aguiar de Sousa, M. Katan, L. Palaiodimou, et al., Risk of major adverse cardiovascular events and stroke associated with treatment with GLP-1 or the dual GIP/GLP-1 receptor agonist tirzepatide for type 2 diabetes: A systematic review and meta-analysis, Eur. Stroke J. 9 (2024) 530–539, https://doi.org/10.1177/23969873241234238.
[54] R. Hammoud, D.J. Drucker, Beyond the pancreas: contrasting cardiometabolic actions of GIP and GLP1, Nat. Rev. Endocrinol. 19 (2023) 201–216, https://doi.org/10.1038/s41574-022-00783-3.
[55] S. Sachs, A. Götz, B. Finan, A. Feuchtinger, R.D. DiMarchi, Y. Döring, et al., GIP receptor agonism improves dyslipidemia and atherosclerosis independently of body weight loss in preclinical mouse model for cardio-metabolic disease, Cardiovasc. Diabetol. 22 (2023) 217, https://doi.org/10.1186/s12933-023-01940-2.
[56] M. Terasaki, H. Yashima, Y. Mori, T. Saito, N. Inoue, T. Matsui, et al., Glucose-dependent insulinotropic polypeptide inhibits AGE-induced NADPH oxidase-derived oxidative stress generation and foam cell formation in macrophages partly via AMPK activation, Int. J. Mol. Sci. 25 (2024) 9724, https://doi.org/10.3390/ijms25179724.
[57] H. Yao, A. Zhang, D. Li, Y. Wu, C.-Z. Wang, J.-Y. Wan, et al., Comparative effectiveness of GLP-1 receptor agonists on glycaemic control, body weight, and lipid profile for type 2 diabetes: systematic review and network meta-analysis, BMJ 384 (2024) e076410, https://doi.org/10.1136/bmj-2023-076410.
[58] D. Yuan, H. Sharma, A. Krishnan, V.N. Vangaveti, U.H. Malabu, Effect of glucagon-like peptide 1 receptor agonists on albuminuria in adult patients with type 2 diabetes mellitus: A systematic review and meta-analysis, Diabetes Obes. Metab. 24 (2022) 1869–1881, https://doi.org/10.1111/dom.14776.
[59] H.J.L. Heerspink, E. Apperloo, M. Davies, D. Dicker, K. Kandler, J. Rosenstock, et al., Effects of semaglutide on albuminuria and kidney function in people with overweight or obesity with or without Type 2 diabetes: Exploratory analysis from the STEP 1, 2, and 3 trials, Diabetes Care 46 (2023) 801–810, https://doi.org/10.2337/dc22-1889.
[60] H.M. Colhoun, I. Lingvay, P.M. Brown, J. Deanfield, K. Brown-Frandsen, S. E. Kahn SE, et al., Long-term kidney outcomes of semaglutide in obesity and cardiovascular disease in the SELECT trial, Nat. Med. 30 (2024) 2058–2066, https://doi.org/10.1038/s41591-024-03015-5.
[61] V. Perkovic, K.R. Tuttle, P. Rossing, K.W. Mahaffey, J.F.E. Mann, G. Bakris, et al., Effects of semaglutide on chronic kidney disease in patients with Type 2 diabetes, N. Engl. J. Med. 391 (2024) 109–121, https://doi.org/10.1056/NEJMoa2403347.
[62] E.M. Apperloo, J.L. Gorriz, M.J. Soler, S.C. Guldris, J.M. Cruzado, M.J. Puchades, et al., Semaglutide in patients with overweight or obesity and chronic kidney disease without diabetes: a randomized double-blind placebo-controlled clinical trial, Nat. Med. (2024), https://doi.org/10.1038/s41591-024-03327-6.
[63] P. Karakasis, D. Patoulias, N. Fragakis, A. Klisic, M. Rizzo, Effect of tirzepatide on albuminuria levels and renal function in patients with type 2 diabetes mellitus: A systematic review and multilevel meta-analysis, Diabetes Obes. Metab. 26 (2024) 1090–1104, https://doi.org/10.1111/dom.15410.
[64] L. Vanek, A. Kurnikowski, S. Krenn, S. Mussnig, M. Hecking, Semaglutide in patients with kidney failure and obesity undergoing dialysis and wishing to be transplanted: A prospective, observational, open-label study, Diabetes Obes. Metab. 26 (2024) 5931–5941, https://doi.org/10.1111/dom.15967.
[65] J.J. Long, S.S. Sahi, A.I. Lemke, J. Na, O.A. Garcia Valencia, P. Budhiraja, et al., The Use of semaglutide in patients with renal failure - a retrospective cohort study, Endoc. Pract. 30 (2024) 963–969, https://doi.org/10.1016/j.eprac.2024.07.008.
[66] K.C. Sourris, Y. Ding, S.S. Maxwell, A. Al-Sharea, P. Kantharidis, M. Mohan, et al., Glucagon-like peptide-1 receptor signaling modifies the extent of diabetic kidney disease through dampening the receptor for advanced glycation end products–induced inflammation, Kidney Int 105 (2024) 132–149, https://doi.org/10.1016/j.kint.2023.09.029.
[67] M.C. Thomas, M.E. Cooper, The GLP-1 receptor agonist revolution comes to nephrology, Nat. Rev. Nephrol. 20 (2024) 637–638, https://doi.org/10.1038/s41581-024-00876-4.
[68] W. Masson, M. Lobo, J.P. Nogueira, A.M. Rodriguez-Granillo, L.E. Barbagelata, D. Siniawski, Anti-inflammatory effect of semaglutide: updated systematic review and meta-analysis, Front. Cardiovasc. Med. 11 (2024) 1379189, https://doi.org/10.3389/fcvm.2024.1379189.
[69] H. Bliddal, H. Bays, S. Czernichow, J.U. Hemmingsson, J. Hjelmesæth, T. H. Morville, et al., Once-weekly semaglutide in persons with obesity and knee osteoarthritis, N. Engl. J. Med. 391 (2024) 1573–1583, https://doi.org/10.1056/NEJMoa2403664.
[70] S.H. Alharbi, Anti-inflammatory role of glucagon-like peptide 1 receptor agonists and its clinical implications, Ther. Adv. Endocrinol. Metab. 15 (2024) 20420188231222367, https://doi.org/10.1177/20420188231222367.

[71] M. Yu, R. Wang, L. Pei, X. Zhang, J. Wei, Y. Wen, et al., The relationship between the use of GLP-1 receptor agonists and the incidence of respiratory illness: a meta-analysis of randomized controlled trials, Diabetol. Metab. Syndr. 15 (2023) 164, https://doi.org/10.1186/s13098-023-01118-6.

[72] G.E. Batiha, H.M. Al-Kuraishy, A.I. Al-Gareeb, N.A. Ashour, W.A. Negm, Potential role of tirzepatide towards Covid-19 infection in diabetic patients: a perspective approach, Inflammopharmacol 31 (2023) 1683–1693, https://doi.org/10.1007/s10787-023-01239-4.

[73] B.M. Scirica, A.M. Lincoff, I. Lingvay, P. Bogdanski, S. Buscemi, H. Colhoun, et al., The Effect of semaglutide on mortality and COVID-19–related deaths: an analysis from the SELECT trial, J. Am. Coll. Cardiol. 84 (2024) 1632–1642, https://doi.org/10.1016/j.jacc.2024.08.007.

[74] M.E. Rinella, B.A. Neuschwander-Tetri, M.S. Siddiqui, M.F. Abdelmalek, S. Caldwell, D. Barb, et al., AASLD Practice Guidance on the clinical assessment and management of nonalcoholic fatty liver disease, Hepatology 77 (2023) 1797–1835, https://doi.org/10.1097/HEP.0000000000000323.

[75] R. Nevola, R. Epifani, S. Imbriani, G. Tortorella, C. Aprea, R. Galiero R, et al., GLP-1 receptor agonists in non-alcoholic fatty liver disease: current evidence and future perspectives, Int. J. Mol. Sci. 24 (2023) 1703, https://doi.org/10.3390/ijms24021703.

[76] L.A. Abushamat, P.A. Shah, R.H. Eckel, S.A. Harrison, D. Barb, The emerging role of glucagon- like peptide-1 receptor agonists for the treatment of metabolic dysfunction-associated steatohepatitis, Clin. Gastroenterol. Hepatol. 22 (2024) 1565–1574, https://doi.org/10.1016/j.cgh.2024.01.032.

[77] European Association for the Study of the Liver (EASL); European Association for the Study of Diabetes (EASD); European Association for the Study of Obesity (EASO), EASL-EASD-EASO Clinical Practice Guidelines on the management of metabolic dysfunction-associated steatotic liver disease (MASLD), J. Hepatol. 81 (2024) 492–542, https://doi.org/10.1016/j.jhep.2024.04.031.

[78] C.R. Andreasen, A. Andersen, T. Vilsbøll, The future of incretins in the treatment of obesity and non-alcoholic fatty liver disease, Diabetologia 66 (2023) 1846–1858, https://doi.org/10.1007/s00125-023-05966-9.

[79] P. Shah, M. White, A. Sievert, A. Conway, A. Kneepkens, G. Sayuk, et al., Semaglutide improves metabolic dysfunction-associated steatohepatitis: A 10-year retrospective study, J. Gastroenterol. Hepatol. Open 8 (2024) e13037, https://doi.org/10.1002/jgh3.13037.

[80] K. Ray, GLP1 agonists and risk of major adverse liver outcomes, Nat. Rev. Gastroenterol. Hepatol. 21 (2024) 218, https://doi.org/10.1038/s41575-024-00911-6.

[81] F. Kanwal, J.R. Kramer, L. Li, Y.-X. Yang, Y. Cao, X. Yu, et al., GLP-1 receptor agonists and risk for cirrhosis and related complications in patients with metabolic dysfunction-associated steatotic liver disease, JAMA Intern. Med. 184 (2024) 1314–1323, https://doi.org/10.1001/jamainternmed.2024.4661.

[82] K. Kim, Y. Lee, J.S. Lee, M.N. Kim, B.K. Kim, S.U. Kim, et al., Incidence of metabolic dysfunction-associated steatotic liver disease and advanced fibrosis and impact of overweight/obesity in elderly population: a nationwide cohort study, J. Gastroenterol. Hepatol. (2024), https://doi.org/10.1111/jgh.16755.

[83] R. Loomba, M.L. Hartman, E.J. Lawitz, R. Vuppalanchi, J. Boursier, E. Bugianesi, et al., Tirzepatide for metabolic dysfunction-associated steatohepatitis with liver fibrosis, N. Engl. J. Med. 391 (2024) 299–310, https://doi.org/10.1056/NEJMoa2401943.

[84] L. Fang, J. Li, H. Zeng, J. Liu, Effects of GLP-1 receptor agonists on the degree of liver fibrosis and CRP in non-alcoholic fatty liver disease and non-alcoholic steatohepatitis: A systematic review and meta-analysis, Prim. Care Diabetes 18 (2024) 268–276, https://doi.org/10.1016/j.pcd.2024.03.005.

[85] A.J. Sanyal, L.M. Kaplan, J.P. Frias, B. Brouwers, Q. Wu, M.K. Thomas, al., Triple hormone receptor agonist retatrutide for metabolic dysfunction-associated steatotic liver disease: A randomized phase 2a trial, Nat. Med. 30 (2024) 2037–2048, https://doi.org/10.1038/s41591-024-03018-2.

[86] N. Reich, C. Hölscher, The neuroprotective effects of glucagon-like peptide 1 in Alzheimer's and Parkinson's disease: an in-depth review, Front. Neurosci. 16 (2022) 970925, https://doi.org/10.3389/fnins.2022.970925.

[87] F. Kong, T. Wu, J. Dai, Z. Zhai, J. Cai, Z. Zhu Z, et al., Glucagon-like peptide 1 (GLP-1) receptor agonists in experimental Alzheimer's disease models: A systematic review and meta-analysis of preclinical studies, Front. Pharmacol. 14 (2023) 1205207, https://doi.org/10.3389/fphar.2023.1205207.

[88] C.T. Hong, J.H. Chen, C.J. Hu, Role of glucagon-like peptide-1 receptor agonists in Alzheimer's disease and Parkinson's disease, J. Biomed. Sci. 31 (2024) 102, https://doi.org/10.1186/s12929-024-01090-x.

[89] M. Monney, F.R. Jornayvaz, K. Gariani, GLP-1 receptor agonists effect on cognitive function in patients with and without type 2 diabetes, Diabetes Metab. 49 (2023) 101470, https://doi.org/10.1016/j.diabet.2023.101470.

[90] W.G. Meissner, P. Remy, C. Giordana, D. Maltête, P. Derkinderen, J.L. Houéto, et al., Trial of lixisenatide in early Parkinson's disease, N. Engl. J. Med 390 (2024) 1176–1185, https://doi.org/10.1056/NEJMoa2312323.

[91] Q.-Q. Wang, X. Yan, T.T. Wang, L.-H. Zeng, Glucagon-like peptide 1 receptor agonists in Alzheimer's disease, Neurochem. J. 17 (2023) 243–246, https://doi.org/10.1134/S1819712423020204.

[92] K. Kalinderi, P. Vasileios, F. Liana, GLP-1 receptor agonists: a new treatment in Parkinson's disease, Int. J. Mol. Sci. 25 (2024) 3812, https://doi.org/10.3390/ijms25073812.

[93] J.K. Snell-Bergeon, G. Kaur, D. Renner, H.K. Akturk, C. Beatson, S.K. Garg, Effectiveness of semaglutide and tirzepatide in overweight and obese adults with Type 1 diabetes, Diabetes Technol. Ther. 27 (2025) 1–9, https://doi.org/10.1089/dia.2024.0328.

[94] W. Wang, Q. Wang, X. Qi, M. Gurney, G. Perry, N.D. Volkow, et al., Associations of semaglutide with first-time diagnosis of Alzheimer's disease in patients with type 2 diabetes: target trial emulation using nationwide real-world data in the US, Alzheimers Dement 20 (2024) 8661–8672, https://doi.org/10.1002/alz.14313.

[95] X. Tan, X. Pan, X. Wu, S. Zheng, Y. Chen, D. Liu, et al., Glucagon-like peptide-1 receptor agonists as add-on therapy to insulin for type 1 diabetes mellitus, Front. Pharmacol. 14 (2023) 975880, https://doi.org/10.3389/fphar.2023.975880.

[96] P. Karakasis, T. Koufakis, D. Patoulias, F. Barkas, A. Klisic, M. Mitrovic, et al., Effects of glucagon-like peptide-1 receptor agonists on glycated haemoglobin and continuous glucose monitoring metrics as adjunctive therapy to insulin in adults with type 1 diabetes: A meta-analysis of randomized controlled trials, Diabetes Obes. Metab. 26 (2024) 6043–6054, https://doi.org/10.1111/dom.15979.

[97] L. Westergaard, L. Alifrangis, S.T. Buckley, H. Coester, T. Klitgaard, N. R. Kristensenet, et al., Pharmacokinetic properties of a once-weekly fixed-ratio combination of insulin icodec and semaglutide compared with separate administration of each component in individuals with Type 2 diabetes mellitus, Clin. Drug. Investig. 44 (2024) 849–861, https://doi.org/10.1007/s40261-024-01405-8.

[98] A. Ali, P.R. Flatt, N. Irwin, Gut-derived peptide hormone analogues and potential treatment of bone disorders in obesity and diabetes mellitus, Clin. Med. Insights Endocrinol. Diabetes 17 (2024) 11795514241238059, https://doi.org/10.1177/11795514241238059.

[99] R. Viggers, N.H. Rasmussen, P. Vestergaard, Effects of incretin therapy on skeletal health in Type 2 diabetes - A systematic review, JBMR 7 (2023) e10817, https://doi.org/10.1002/jbm4.10817.

[100] A. Al Refaie, L. Baldassini, C. Mondillo, E. Ceccarelli, R. Tarquini, L. Gennari L, et al., Glucagon-like peptide-1 receptor agonists and diabetic osteopathy: Another positive effect of incretines? A 12 Months longitudinal study, Calcif. Tissue Int. 115 (2024) 160–168, https://doi.org/10.1007/s00223-024-01240-1.

[ 101] M. Ryan, S. Megyeri, W. Nuffer, J.M. Trujillo, The potential role of GLP-1 receptor agonists in osteoarthritis (online ahead of print), Pharmacotherapy (2025), https://doi.org/10.1002/phar.70005.

[102] H. Bliddal, H. Bays, S. Czernichow, J. Uddén Hemmingsson, J. Hjelmesæth, T. Hoffmann Morville, et al., Once-weekly semaglutide in persons with obesity and knee osteoarthritis, N. Engl. J. Med. 391 (2024) 1573–1583, https://doi.org/10.1056/NEJMoa2403664.

[103] S. Dragonieri, A. Portacci, V.N. Quaranta, P. Carratu, Z. Lazar, G.E. Carpagnano, et al., Therapeutic potential of glucagon-like peptide-1 receptor agonists in obstructive sleep apnea syndrome management: A narrative review, Diseases 12 (2024) 224, https://doi.org/10.3390/diseases12090224.

[104] A. Malhotra, R.R. Grunstein, I. Fietze, T.E. Weaver, S. Redline, A. Azarbarzin, et al., Tirzepatide for the treatment of obstructive sleep apnea and obesity, N. Engl. J. Med. 391 (2024) 1193–1205, https://doi.org/10.1056/NEJMoa2404881.

[105] M. Yu, R. Wang, L. Pei, X. Zhang, J. Wei, Y. Wen, et al., The relationship between the use of GLP-1 receptor agonists and the incidence of respiratory illness: a meta-analysis of randomized controlled trials, Diabetol. Metab. Syndr. 15 (2023) 164, https://doi.org/10.1186/s13098-023-01118-6.

[106] M.K. Klausen, M. Thomsen, G. Wortwein, A. Fink-Jensen, The role of glucagon-like peptide 1 (GLP-1) in addictive disorders, Br. J. Pharmacol. 179 (2022) 625–641, https://doi.org/10.1111/bph.15677.

[107] S. Bettadapura, K. Dowling, K. Jablon, A.W. Al-Humadi, C.W. le Roux, Changes in food preferences and ingestive behaviors after glucagon-like peptide-1 analog treatment: techniques and opportunities, Int. J. Obes. (Lond. ) (2024), https://doi.org/10.1038/s41366-024-01500-y.

[108] E. Kornelius, J.Y. Huang, S.C. Lo, C.N. Huang, Y.S. Yang, The risk of depression, anxiety, and suicidal behavior in patients with obesity on glucagon like peptide-1 receptor agonist therapy, Sci. Rep. 14 (2024) 24433, https://doi.org/10.1038/s41598-024-75965-2.

[109] R. Strumila, A. Lengvenyte, S. Guillaume, B. Nobile, E. Olie, P. Courtet, GLP-1 agonists and risk of suicidal thoughts and behaviours: Confound by indication once again? A narrative review, Eur. Neuropsychopharmacol. 87 (2024) 29–34, https://doi.org/10.1016/j.euroneuro.2024.07.001.

[110] W. Wang, N.D. Volkow, N.A. Berger, P.B. Davis, D.C. Kaelber, R. Xu, Association of semaglutide with risk of suicidal ideation in a real-world cohort, Nat. Med. 30 (2024) 168–176, https://doi.org/10.1038/s41591-023-02672-2.

[111] S. Tempia Valenta, A. Nicastri, F. Perazza, F. Marcolini, V. Beghelli, et al., The impact of GLP-1 receptor agonists (GLP-1 RAs) on mental health: A systematic review, Curr. Treat. Options Psych. 11 (2024) 310–357, https://doi.org/10.1007/s40501-024-00331-y.

[112] R.L. Dubin, S.B. Heymsfield, E. Ravussin, F.L. Greenway, Glucagon-like peptide-1 receptor.

[113] R. Jiao, C. Lin, X. Cai, J. Wang, Y. Wang Y, F. Lv, et al., Characterizing body composition modifying effects of a glucagon-like peptide 1 receptor-based agonist: A meta-analysis, Diabetes Obes. Metab. 27 (2025) 259–267, https://doi.org/10.1111/dom.16012.

[114] F.Y. Hsiao, E.C. Tan, L.C. Meng, Y.C. Lin, H.M. Chen, S.T. Guan, et al., Effect of frailty on effectiveness and safety of GLP-1 receptor agonists versus SGLT2 inhibitors in people with type 2 diabetes in Taiwan: a retrospective, nationwide, longitudinal study, Lancet Healthy Longev. 5 (2024) 100621, https://doi.org/10.1016/j.lanhl.2024.07.004.

[115] R.J. Jalleh, C.K. Rayner, T. Hausken, K.L. Jones, M. Camilleri, M. Horowitz, Gastrointestinal effects of GLP-1 receptor agonists: mechanisms, management, and future directions, Lancet Gastroenterol. Hepatol. 9 (2024) 957–964, https://doi.org/10.1016/S2468-1253(24)00188-2.

[116] Y. Xie, T. Choi, Z. Al-Aly, Mapping the effectiveness and risks of GLP-1 receptor agonists, Nat. Med. (2025), https://doi.org/10.1038/s41591-024-03412-w.

[117] R.F. Kushner, D.H. Ryan, J. Deanfield, A. Kokkinos, C. Cercato, J. Wilding, et al., Safety profile of semaglutide versus placebo in the SELECT study: a randomized controlled trial (online ahead of print), Obes. (Silver Spring) (2025), https://doi.org/10.1002/oby.24222.
[118] M. Cigrovski Berkovic, F. Strollo, Semaglutide-eye-catching results, World J. Diabetes 14 (2023) 424–434, https://doi.org/10.4239/wjd.v14.i4.42.
[119] H. Stevens, M. de la Paz, B. Cooper, R. Bhattacharya, Long-term use of semaglutide and risk of diabetic retinopathy progression, Endocr. Metab. Sci. 15 (2024) 100168, https://doi.org/10.1016/j.endmts.2024.100168.
[120] J.T. Hathaway, M.P. Shah, D.B. Hathaway, S.M. Zekavat, D. Krasniqi, J. W. Gittinger, J.W. Jr, et al., Risk of nonarteritic anterior ischemic optic neuropathy in patients prescribed semaglutide, JAMA Ophthalmol. 142 (2024) 732–739, https://doi.org/10.1001/jamaophthalmol.2024.2296.
[121] J. Grauslund, A.A. Taha, L.D. Molander, R. Kawasaki, S. Möller, K. Højlund, et al., Once-weekly semaglutide doubles the five-year risk of nonarteritic anterior ischemic optic neuropathy in a Danish cohort of 424,152 persons with type 2 diabetes, Int. J. Retin. Vitr. 10 (2024) 97, https://doi.org/10.1186/s40942-024-00620-x.
[122] C.C. Chou, S.Y. Pan, Y.J. Sheen, L.F. Lin, C.H. Lin, H.J. Lin, et al., Association between semaglutide and nonarteritic anterior ischemic optic neuropathy: A multinational population-based study, Ophthalmology (2024) S0161–642000685-7, https://doi.org/10.1016/j.ophtha.2024.10.030.
[123] FDA warns consumers. U.S. Food & Drug Administration, 21 December 2023. ⟨https://www.fda.gov/drugs/drug-safety-and-availability/fda-warns-consumers-not-use-counterfeit-ozempic-semaglutide-found-us-drug-supply-chain⟩.
[124] WHO issues warning. World Health Organization, 24 June 2024. ⟨https://www.who.int/news/item/20-06-2024-who-issues-warning-on-falsified-medicines-used-for-diabetes-treatment-and-weight-loss⟩.
[125] J.J. Neumiller, M. Bajaj, R.R. Bannuru, R.G. McCoy, E.J. Pekas, A.R. Segal, N. A. ElSayed, Compounded GLP 1 and dual GIP/GLP 1 receptor agonists: A statement from the American Diabetes Association, Diabetes Care (2024), https://doi.org/10.2337/dci24-0091.
[126] J.M. Collins, S.K. Singh, T.A. White, D.J. Cesta, C.L. Simpson, L.J. Tubb, et al., Total wash elimination for solid phase peptide synthesis, Nat. Commun. 14 (2023) 8168, https://doi.org/10.1038/s41467-023-44074-5.
[127] N. Alfaris, S. Waldrop, V. Johnson, B. Boaventura, K. Kendrick, F.C. Stanford, GLP-1 single, dual, and triple receptor agonists for treating type 2 diabetes and obesity: a narrative review, eClinical Med 75 (2024) 102782, https://doi.org/10.1016/j.eclinm.2024.102782.
[128] E. Melson, U. Ashraf, D. Papamargaritis, M.J. Davies, What is the pipeline for future medications for obesity? Int. J. Obes. (2024) https://doi.org/10.1038/s41366-024-01473-y.
[129] S. Wharton, T. Blevins, L. Connery, J. Rosenstock, S. Raha, R. Liu, R, et al., Efficacy and safety of oral orforglipron in patients with type 2 diabetes: a multicentre, randomised, dose-response, phase 2 study, N. Engl. J. Med 389 (2023) 877–888, https://doi.org/10.1056/NEJMoa2302392.
[130] J.P. Frias, S. Hsia, S. Eyde, R. Liu, X. Ma, M. Konig M, et al., Efficacy and safety of oral orforglipron in patients with type 2 diabetes: a multicentre, randomised, dose-response, phase 2 study, Lancet 402 (10400) (2023) 472–483, https://doi.org/10.1016/S0140-6736(23)01302-8.
[131] D. Zhu, W. Wang, G. Tong, G. Ma, J. Ma, J. Han J, et al., Efficacy and safety of GLP-1 analog ecnoglutide in adults with type 2 diabetes: a randomized, double-blind, placebo-controlled phase 2 trial, Nat. Commun. 15 (2024) 8408, https://doi.org/10.1038/s41467-024-52353-y.
[132] H. Zhou, L. Ji, X. Song, Y. Zhang, X., Xu X. Li et al., ZT002, a novel ultra long-acting GLP-1 receptor agonist in adults with overweight or obesity: a randomised, placebo-controlled, multiple ascending dose phase 1c study, Diabetologia 67, suppl.1 (20240 abstract 147.
[133] C.W. le Roux, O. Steen, K.J. Lucas, E. Startseva, A. Unseld, A.M. Hennige, Glucagon and GLP-1 receptor dual agonist survodutide for obesity: a randomised, double-blind, placebo-controlled, dose-finding phase 2 trial, Lancet Diabetes Endocrinol. 12 (2024) 162–173, https://doi.org/10.1016/S2213-X.
[134] S.A. Harrison, S.K. Browne, J.J. Suschak, S. Tomah, J.A. Gutierrez, J. Yang J, et al., Effect of pemvidutide, a GLP-1/glucagon dual receptor agonist, on MASLD: A randomized, double-blind, placebo-controlled study, J. Hepatol. 82 (2025) 7–17, https://doi.org/10.1016/j.jhep.2024.07.006.
[135] B. Zhang, Z. Cheng, J. Chen, X. Zhang, D. Liu, H. Jiang H, et al., A phase 2 randomised controlled trial of mazdutide in Chinese overweight adults or adults with obesity. Efficacy and safety of mazdutide in Chinese patients with Type 2 diabetes: A randomized, double-blind, placebo-controlled Phase 2 trial, Diabetes Care 47 (2024) 160–168, https://doi.org/10.2337/dc23-1287.
[136] Roell T. Coskun, T. Kim, L. O'Farrell, J.A. Martin, S. Nason, et al., Characterization of LY3324954 a long-acting glucagon-receptor agonist, Mol. Metab. 91 (2025) 102073, https://doi.org/10.1016/j.molmet.2024.102073.
[137] C.M. Jimenez-Munoz, M. López, F. Albericio, K. Makowski, Targeting energy expenditure-drugs for obesity treatment, Pharm. (Basel) 14 (2021) 435, https://doi.org/10.3390/ph14050435.
[138] J. Rosenstock, J. Frias, A.M. Jastreboff, Y. Du, J. Lou, S. Gurbuz S, et al., Retatrutide, a GIP, GLP-1 and glucagon receptor agonist, for people with type 2 diabetes: a randomised, double-blind, placebo and active-controlled, parallel-group, phase 2 trial conducted in the USA, Lancet 402 (10401) (2023) 529–544, https://doi.org/10.1016/S0140-6736(23)01053-X.
[139] A.M. Jastreboff, L.M. Kaplan, J.P. Frías, Q. Wu, Y. Du, S. Gurbuz, et al., Triple-hormone-receptor agonist retatrutide for obesity - A phase 2 trial, N. Engl. J. Med. 389 (2023) 514–526, https://doi.org/10.1056/NEJMoa2301972.
[140] M.F. Abdelmalek, A. Suzuki, W. Sanchez, E. Lawitz, C. Filozof, H. Cho, E. Baek, J. Choi, S. Baek, A phase 2, adaptive randomized, double-blind, placebo-controlled, multicenter, 52-week study of HM15211 in patients with biopsy-confirmed non-alcoholic steatohepatitis - Study design and rationale of HM-TRIA-201 study, Contemp. Clin. Trials 130 (2023) 107176, https://doi.org/10.1016/j.cct.2023.107176.
[141] M.V. Chakravarthy, F.A. Arguelles-Tello, L.L. Sánchez-Sánchez, W. García Ortiz, M. Elliott, J. Wu, et al., Safety, pharmacokinetics, and pharmacodynamics of CT-388, a signal-biased dual GLP-1/GIP receptor agonist, over 24 weeks in adults with obesity, Diabetologia 67 (l1) (2024) abstract LBA 65.
[142] Viking Therapeutics Press Release, 4 Nov 2024. ⟨https://ir.vikingtherapeutics.com/2024-11-04⟩.
[143] M. Valdecantos, L. Ruiz, C. Folgueira, P. Rada, B. Gomez-Santos, M. Solas, et al., The dual GLP-1/glucagon receptor agonist G49 mimics bariatric surgery effects by inducing metabolic rewiring and inter-organ crosstalk, Nat. Commun. 15 (2024) 10342, https://doi.org/10.1038/s41467-024-54080-w. ⟨⟩.
[144] Amgen. MarTide update, 26 November 2034, ⟨https://investors.amgen.com/static-files/0176d78e-920b-45b3-b9cc-a727e58e80da⟩.
[145] T. Panou, E. Gouveri, D.S. Popovic, N. Papanas, Amylin analogs for the treatment of obesity without diabetes: present and future, Expert Rev. Clin. Pharmacol. (2024) 1–9, https://doi.org/10.1080/17512433.2024.2409403.
[146] J.P. Frias, S. Deenadayalan, L. Erichsen, F.K. Knop, I. Lingvay, S. Macura, S, et al., Efficacy and safety of co-administered once-weekly cagrilintide 2·4mg with once-weekly semaglutide 2.4mg in type 2 diabetes: a multicentre, randomised, double-blind, active-controlled, phase 2 trial, Lancet 402 (10403) (2023) 720–730, https://doi.org/10.1016/S0140-6736(23)01163-7.
[147] Novo Nordisk A/S Company Announcement: CagriSema demonstrates superior weight loss in adults with obesity or overweight in the REDEFINE 1 trial. ⟨https://www.novonordisk.com/news-and-media/news-and-ir-materials/news-details.html?id= 915082⟩.
[148] A. Gasiorek, K. Kirkeby, S. Youbro, et al., Safety, tolerability and weight reduction findings of oral: a novel amylin and glucagon-like peptide-1 receptor co-agonist, in a first-in-human study, Diabetologia 67 (.) (2024) 1, abstract 74.
[149] A.T. Larsen, S.A. Melander, N. Sonne, E. Bredtoft, M. Al-Rubai, M.A.Karsdal, et al., Dual amylin and calcitonin receptor agonist treatment improves insulin sensitivity and increases muscle-specific glucose uptake independent of weight loss, Biomed. Pharmacother. 164 (2023) 114969, https://doi.org/10.1016/j.biopha.2023.
[150] A.T. Larsen, K.E. Mohamed, S.A. Melander, M.A. Karsdal, K. Henriksen, The enduring metabolic improvement of combining dual amylin and calcitonin receptor agonist and semaglutide treatments in a rat model of obesity and diabetes, Am. J. Physiol. Endocrinol. Metab. 327 (2024) E145–E154, https://doi.org/10.1152/ajpendo.00092.2024.
[151] C.M. Rondinone, M.P. Valdecantos, P. Rada, A. Valverde, S. Ghosh, Novel unimolecular tetra-agonist peptides targeting GLP-1, GIP, amylin, and calcitonin receptors with enhanced metabolic benefits in animal models of obesity, Diabetologia 67 (.1) (2024) abstract 81.
[152] A. Ali, D. Khan, V. Dubey, A.I. Tarasov, P.R. Flatt, N. Irwin, Comparative effects of GLP-1 and GLP-2 on beta-cell function, glucose homeostasis and appetite regulation, Biomolecules 14 (2024) 1520, https://doi.org/10.3390/biom14121520.
[153] R.A. Lafferty, P.R. Flatt, N. Irwin, NPYR modulation: Potential for the next major advance in obesity and type 2 diabetes management? Peptides 179 (2024) 179 171256, https://doi.org/10.1016/j.peptides.2024.171256.
[154] F. Sass, T. Ma, J.H. Ekberg, M. Kirigiti, M.G. Ureña, L. Dollet, et al., NK2R control of energy expenditure and feeding to treat metabolic diseases, Nature 635 (2024) 987–1000, https://doi.org/10.1038/s41586-024-08207-0.
[155] G. Chen, W. Kang, W. Li, S. Chen, Y. Gao, Oral delivery of protein and peptide drugs: from non-specific formulation approaches to intestinal cell targeting strategies, Theranostics 12 (2022) 1419–1439, https://doi.org/10.7150/thno.61747.
[156] K. Lin, A. Mehrotra, T.C. Tsai, Metabolic bariatric surgery in the era of GLP-1 receptor agonists for obesity management, JAMA Netw. Open 7 (2024) e2441380, https://doi.org/10.1001/jamanetworkopen.2024.41380.
[157] D. Bataille, C. Gespach, K. Tatemoto, J.C. Marie, A.M. Coudray, G. Rosselin, V, et al., Bioactive enteroglucagon (oxyntomodulin): present knowledge on its chemical structure and its biological activities, Peptides 2 (1981) 41–44, https://doi.org/10.1016/0196-9781(81)90008-5.
[158] A. Pocai, Action and therapeutic potential of oxyntomodulin, Mol. Metab. 3 (2013) 241–251, https://doi.org/10.1016/j.molmet.2013.12.001.