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Recent advances in peptide-based therapies for obesity and type 2 diabetes

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ABSTRACT

Options for the treatment of type 2 diabetes mellitus (T2DM) and obesity have recently been expanded by the results of several large clinical trials with incretin-based peptide therapies. Most of these studies have been conducted with the glucagon-like peptide-1 (GLP-1) receptor agonist semaglutide, which is available as a once weekly subcutaneous injection and once daily tablet, and the once weekly injected dual agonist tirzepatide, which interacts with receptors for GLP-1 and glucose-dependent insulinotropic polypeptide (GIP). In individuals with T2DM these therapies have achieved reductions of glycated haemoglobin (HbA1c) by > 2% and lowered body weight by > 10%. In some studies, these agents tested in non-diabetic, obese individuals at much higher doses have lowered body weight by > 15%. Emerging evidence suggests these agents can also offer cardio-protective and potentially reno-protective effects. Other incretin-based peptide therapies in early clinical development, notably a triple GLP-1/GIP/glucagon receptor agonist (retatrutide) and a combination of semaglutide with the amylin analogue cagrilintide (CagriSema), have shown strong efficacy. Although incretin therapies can incur adverse gastrointestinal effects these are for most patients mild-to-moderate and transient but result in cessation of treatment in some cases. Thus, the efficacy of new incretin-based peptide therapies is enhancing the opportunity to control body weight and blood glucose and improve the treatment of T2DM and obesity.

1. Introduction

The prevalences of obesity and diabetes continue to escalate alarmingly and to impair health outcomes for over a billion people worldwide. Globally about 15% of adults are obese (body mass index (BMI) > 30 kg/m^2) and an additional 25% are overweight (BMI 25 - <30 kg/m^2) [1]. Type 2 diabetes mellitus (T2DM), which accounts for 90% of all diabetes, affects about 9% of adults globally and over 15% of adults in some regions [2]. The links between obesity and T2DM are well recognised, particularly the effects of excess visceral adipose tissue and disturbances of lipid metabolism in the pathogenesis of T2DM, and the shared cardio-renal complications and other associated morbidities [3].

All guidelines for the management of obesity and T2DM are underpinned by lifestyle measures (principally reduced-calorie diet and increased physical activity): a sustained 5% reduction in body weight can reduce the onset and severity of T2DM and cardio-renal diseases, while long-term weight reductions of 10–15% can often facilitate remission of T2DM and deliver a spectrum of additional health benefits [4,5]. However, achieving and maintaining these clinically meaningful amounts of weight loss are particularly difficult for individuals with T2DM because weight loss improves insulin sensitivity which favours weight gain [6]. Thus, adding pharmacotherapies with both weight-lowering and blood glucose-lowering properties provides a desirable approach to the management of obesity and T2DM [7]. In this respect several peptide-based therapies have come to the fore: the glucagon-like peptide-1 receptor agonists (GLP-1RAs) are well established for use in T2DM, and some are now being introduced at high dose to exploit their weight-lowering properties for the management of obesity. Combination of a GLP-1RA with an amylin analogue (Cagrilintide) is under investigation to enhance weight lowering, and various synthetic unimolecular peptides that interact with receptors for GLP-1, glucose-dependent insulinotropic polypeptide (GIP) and/or glucagon (GCG) are showing potent weight-lowering and glucose-lowering properties [8–10]. The primary structures of the peptide-based therapeutic agents described in this review are shown in Fig. 1.

We are reminded that GLP-1RAs mimic the effects of the incretin hormone GLP-1, notably to potentiate prandial insulin release, reduce glucagon secretion, delay gastric emptying and reduce appetite. These

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effects combine to promote weight loss and improve glycaemic control in obesity and T2DM [10]. The other recognised incretin hormone, GIP, exerts a greater potentiation of prandial insulin release than GLP-1 in non-diabetic individuals, but the effectiveness of GIP is much diminished in T2DM, although it is partially restored if the hyperglycaemia is concurrently addressed by other glucose-lowering agents. However, GIP can increase glucagon concentrations and increase adipose deposition. Hence GIP was not favoured as a therapeutic template molecule for the treatment of obese T2DM [11]. Moreover, early preclinical studies noted that GIPR antagonism (as well as GIPR agonism) can lower blood glucose and impair weight gain, raising the possibility that suppression of GIP activity might offer therapeutic benefits in obese T2DM[12]. The potential value of GIPR agonism was reconsidered when clinical studies with synthetic unimolecular multi-agonist peptides that exert agonism at both GIPR and GLP-1R greatly augmented glucose-lowering and weight-lowering efficacy compared with GLP-1R agonism alone [10, 11]. However, there is evidence to suggest that this could be due to so-called 'biased agonism' in which the novel conformation of a synthetic peptide can enhance GLP-1R agonism by reducing internalisation of GLP-1R. At the same time the effect of GIPR agonism is reduced by increased internalisation and degradation of GIPR, basically creating a direct or functional antagonism of the GIPR [13].

Regarding triple GIPR/GLP-1R/GCGR agonists such as retatrutide, the inclusion of a GCGR moiety may seem counter intuitive given that a key action of GCG is to raise blood glucose by increasing hepatic glucose output [14]. Also, GCG can increase insulin secretion where adequate beta-cell function persists, and although this will help to counter hyperglycaemia it can also favour weight gain. Overall however, GCG promotes weight loss due to its anorexigenic effect and by increased energy expenditure, while the hyperglycaemic effect of endogenous GCG can be countered by the GLP-1RA effect. Further synthetic unimolecular combinations based on other hormonal peptides are at early stages of development and reviewed elsewhere [14].

During the past two years, there has been a marked expansion in the development of new incretin-based peptide therapies and their clinical application in the management of obesity and T2DM. Consequently, this

GLP-1R monoagonists

Semaglutide H**X**EGTFTSDVSSYLEGQAA**K**EFIAWLVRGRG

GLP-1R/GCGR dual agonists

Pemvidutide H**X**QGTFTSDYSKYLDE**K**AAKEFIQWLLQT.NH2 (Lactam:E-16,K-20)

Survodutide H**Δ**QGTFTSDYSKYLDERAAKDFI**K**ESA.NH_2

Mazdutide H**X**QGTFTSDYSKYLDEKKA**K**EFVEWLLEGGPSSG.NH_2

GIPR/GLP-1R dual agonists

Tirzepatide Y**X**EGTFTSDYSI**X**LDKIAQ**K**AFVQWLIAGGPSSGAPPPS

GIPR/GLP-1R/GCGR triple agonists

Retatrutide Y**X**QGTFTSDYSI**▼**LDK**K**AQ**X**AFIEYLLEGGPSSGAPPPS.NH_2

SAR441255 H**X**HGTFTSDLSKL**K**EEQRQ**X**EFIEWLKA**a**GPPS**X**KPPPK.NH_2

Amylin analog and dual amylin/calcitonin receptor agonists (DACRA)

Cagrilintide **K**CNTATCATQRLAEFLRHSSNNFGPILPPTNVGSNTP.NH_2

KBP-066 Ac-CSNLSTC**X**LGRLSQDLHRLQTYP**K**TDVGANAP.NH_2

Melanocortin-4 receptor agonist

Setmelanotide AcRC**a**H**f**RWC.NH_2

X = α-aminoisobutyric acid, **Δ** = 1-amino-1-cyclobutanecarboxylic acid, **▼** = α-methyl-L-leucine, **a** = D-alanine, **f** = D-phenylalanine, **K** denotes the site of attachment of a fatty acid or fatty di-acid.

Fig. 1. Primary structures of peptide-based agents for obesity and T2DM therapy described in this review.

article aims to update our previous review of this topic published in the journal [11] by focusing on recent laboratory studies and clinical trials that utilise such agents.

2. Peptide-based therapeutics to address obesity

A high dose of the GLP-1RA liraglutide (3 mg once daily by subcutaneous injection; *Saxenda*) has been approved since 2014 as an adjunct to a reduced-calorie diet and exercise for weight management in adults with obesity or overweight with weight-related co-morbidities. Several randomised clinical trials have shown that this dose of liraglutide is associated with reductions in body weight of about 5 kg over periods of 6–12 months in individuals without or with T2DM [15]. This has encouraged further consideration of peptide therapies for the management of overweight and obesity, and recent key clinical trials to measure weight loss efficacy are listed in Table 1. In all these trials participants were asked to follow a calorie-reduced diet and undertake appropriate physical activity.

2.1. STEP trials

The STEP trial programme assessed the effect of a high dose of the GLP-1RA semaglutide (2.4 mg once weekly by subcutaneous injection: *Weygovy*) and typically noted about a 15% reduction in body weight during treatment periods up to 2 years in overweight and obese adults who did not have T2DM (STEP-1, 3, 4, 5, 8) [16–23]. Similar efficacy was achieved with 2.4 mg once weekly injections in adolescents with comorbidities (STEP Teens) and with a high dose (50 mg once daily) of the oral formulation of semaglutide in adults (OASIS-1) [24,25].

[24,25]. However, weight loss was less amongst obese individuals with T2DM (eg 9.6% weight loss with the 2.4 mg once weekly injected semaglutide in STEP-2) for likely reasons described above [17,24,25]. A one-year study with injected semaglutide (2.4 mg once weekly) has noted reduced symptoms (such as fatigue, dyspnoea and oedema) and improved physical capacity in obese patients with heart failure with preserved ejection fraction (STEP-HFpEF) [26]. Additionally, a 40 week study (SELECT) in overweight and obese people with cardiovascular (CV) disease found that injected semaglutide (2.4 mg once weekly) was associated with a 20% reduction of adverse CV events (3-point MACE: CV death, non-fatal myocardial infarction and non-fatal stroke) [27,28].

The main tolerability issue with GLP-1RAs is initial nausea and vomiting which appear to be linked to delayed gastric emptying. These adverse effects were reported in up to about 40% of people receiving injected semaglutide (2.4 mg once weekly) in the STEP trials reported to-date [29]. However, these were typically considered to be mild-to--moderate in severity, mostly resolved after 1–3 months of treatment and were responsible for discontinuation of treatment in $< 5\%$ of participants. Thus, these gastro-intestinal (GI) adverse effects could not have made a long-term contribution to the weight loss. Initial GI adverse effects were reported for about 80% of participants receiving the high dose oral (50 mg once daily) semaglutide formulation, but these also diminished with time as seen with the once weekly injected formulation.

High dose injected semaglutide (2.4 mg once weekly) is currently approved in the UK, Europe, and North America for weight management of obesity and overweight (the latter with $\geq$1 wtrelated comorbidity) as an adjunct to a calorie-reduced diet and increased physical activity. The ongoing OASIS trial programme is assessing the weight-lowering efficacy of oral semaglutide (50 mg once daily) in East Asian populations and providing addition data for regulatory approval similar to the injected formulation.

2.2. SURMOUNT trials

The design of the SURMOUNT trial programme with the synthetic dual GLP-1R/GIPR agonist tirzepatide shows many similarities with the STEP programme [30]. A high dose of tirzepatide (15 mg once weekly by subcutaneous injection: *Mounjaro* and *Zepbound*) typically reduced body weight by about 20% during treatment periods up to 2 years in overweight and obese adults who did not have T2DM (SURMOUNT-1 and 3) [31,32]. Weight loss was less (14.7% in SURMOUNT-2) for overweight and obese individuals with T2DM [33]. To minimise initial GI adverse effects the dose of tirzepatide was increased gradually in all of the SURMOUNT clinical trials starting at 2.5 mg and increasing by 2.5 mg every 4th week up to the required maintenance dose. Initial GI adverse effects were reported by about 30% of participants: these were mostly mild-to-moderate in severity and diminished quickly, contributing to discontinuation of treatment in $< 8\%$ of participants. A gradual escalation of dose as used with tirzepatide is generally recommended for other incretin-based peptide therapies. Small meals should be consumed slowly with adequate fluids, and temporary lowering of dose or temporary suspension of therapy should be considered if GI adverse effects do not remit [34].

Several large randomised clinical trials are ongoing in the SURMOUNT programme to determine the weight-lowering efficacy of tirzepatide in overweight and obese children, East Asian populations, people with obstructive sleep apnoea and people with preserved ejection fraction heart failure [30]. A long-term study in overweight and obese adults is also in progress to assess the effect of tirzepatide on major adverse CV events. Tirzepatide has recently been approved by FDA (November 2023) for weight management of obese and overweight individuals and is being evaluated by other regulatory authorities.

2.3. Other anti-obesity studies

Some further potential anti-obesity therapies are advancing in clinical development. Of particular note, the synthetic triple GLP-1R/GIPR/GCGR agonist peptide retatrutide (12 mg once weekly by subcutaneous injection) achieved a weight reduction of 24% during a 48 week study in overweight and obese individuals [35]. Other unimolecular multi-agonist peptides designed primarily for weight lowering have yet to report the results of large (phase 3) randomised trials [36]. Among these are peptides based on the hormone oxyntomodulin, notably the dual GLP-1/GCGR agonists survodutide (BI-456906), pemvidutide (ALT-801) and mazdutide (IBI362 and LY3305677) which have shown promising anti-obesity effects in initial clinical studies [36,37]. Some other dual GLP-1/GCGR agonists have not been continued as potential anti-obesity agents (eg cotadutide and NN-1177) but may be considered for treatment of fatty liver [38]. The triple GLP-1R/GIPR/GCGR agonist efocipegtrutide (HM15211) and the fibroblast growth factor (FGF21) analogue LY2405319 may also be considered for treatment of fatty liver. Peptide tyrosine tyrosine (PYY) is known to exert a strong anorectic effect and initial clinical studies are in progress with long-acting PYY analogues alone and in combination with a GLP-1RA for the treatment of obesity [39].

The satiety-inducing and glucagon-reducing effects of the pancreatic hormone amylin are well recognised, and the amylin analogue pramlintide continues to receive limited clinical use as a prandial adjunct to insulin therapy [40]. A closely related long-acting amylin analogue, cagrilintide has recently been shown to reduce body weight by about 10% at doses of 2.4 mg and 4.5 mg injected subcutaneously once weekly during a 26-week study in overweight and obese individuals [41,42]. Combination of cagrilintide with semaglutide (*CagriSema*) is now being considered (REDEFINE programme) for the treatment of overweight and obesity with and without T2DM. Other long-acting amylin analogues and a unimolecular dual amylin/calcitonin receptor agonist (*DACRA*) are receiving initial clinical scrutiny as candidate anti-obesity agents [43,44].

Although various other peptide-based approaches to weight loss continue to receive investigation, their potential clinical utility remains limited [45]. The anorexigenic effect of leptin analogues is quickly diminished by the development of leptin resistance such that use of metreleptin is limited to replacement therapy for individuals with

Table 1
Recent clinical trials designed primarily to assess the efficacy of weight-lowering peptide-based therapies in overweight (BMI 25-<30 kg/m^2) and obese (BMI ≥30 kg/m^2) individuals. STEP 1–6, STEP-teens, SURMOUNT 1–4 and studies with retatrutide and cagrilintide were principally assessing weight loss, whereas STEP-HFpEF and SELECT were assessing cardiovascular protection.

Trial name and agent tested	Design, number, duration, development phase	Body mass index, BMI (kg/m^2) required for inclusion	Baseline mean body weight (kg) and BMI (kg/m^2)	Outcome: change in body weight (% reduced vs baseline)	Reference
STEP-1 Semaglutide 2.4 mg SC inject, Qw	RDBPC N = 1961 68 wks Phase 3	BMI ≥ 30 or BMI > 27-< 30 *	105.3 kg BMI 37.9	At 68 wks Sema − 14.9% Pbo − 2.4%	[16]
STEP-2 Semaglutide 2.4, 1.0 mg SC inject, Qw	RDBPC N = 1210 68 wks Phase 3	BMI ≥ 30 or BMI > 27-< 30 + T2DM	99.8 kg BMI 35.7 HbA1c 8.1%	At 68 wks Sema 2.4 mg − 9.6% Sema 1.0 mg − 6.9% Pbo − 3.4%	[17]
STEP-3 Semaglutide 2.4 mg SC inject, Qw	RDBPC N = 611 68 wks Phase 3	BMI ≥ 30 or BMI ≥ 27-< 30 * + intensive behavioural therapy[a]	105.8 kg BMI 38.0	At 68 wks Sema − 16.0% Pbo − 5.7	[18]
STEP-4 Semaglutide 2.4 mg SC inject, Qw	RDBPC N = 803 68 wks Phase 3	BMI ≥ 30 or BMI > 27-< 30 * + 20 wk lead in on 2.4 mg sema	107.2 kg BMI 38.4	At 68 wks Sema − 17.4% Pbo − 5.0%	[19]
STEP-5 Semaglutide 2.4 mg SC inject, Qw	RDBPC N = 304 104 wks Phase 3	BMI ≥ 30 or BMI > 27-< 30 *	106.0 kg BMI 38.5	At 104 wks Sema − 15.2% Pbo − 2.6%	[20]
STEP-6 Semaglutide 2.4, 1.7 mg SC inject, Qw	RDBPC N = 401 68 wks Phase 3	East Asian BMI ≥ 27 with comorbidities + /- T2DM	87.5 kg BMI 31.9	At 68 wks Sema 2.4 mg − 13.2% Sema 1.7 mg − 9.6% Pbo − 2.1%	[21]
STEP-8 Semaglutide 2.4 mg SC inject, Qw vs liraglutide 3.0 mg SC inject, od	H2H[b] N = 338 68 wks Phase 3	BMI ≥ 30 or BMI ≥ 27-< 30 *	104.5 kg BMI 37.5	At 68 wks Sema − 15.8% Lira − 6.4% Pbo − 1.9%	[22]
STEP HFpEF Semaglutide 2.4 mg SC inject, Qw	RDBPC N = 529 52 wks	HFpEF (LVEF ≥45%; NYHA class II–IV HF symptoms); BMI ≥ 30 kg/m^2	105.1 kg BMI 37.0 LVEF 57% KCCQ-CSS 58.9	At 52 wks Sema improved KCCQ-CSS score Wt change Sema − 13.3% Pbo − 2.6%	[26]
STEP Teens Semaglutide 2.4 mg SC inject, Qw	RDBPC N = 201 68 wks	Adolescents (12-18 yr) BMI ≥ 85th percentile with comorbidities	107.5 kg BMI 37.0 (131.8% above 95th percentile)	At 68 wks BMI change Sema − 16.1% Pbo − 0.6%	[24]
SELECT Semaglutide 2.4 mg SC inject, Qw	RDBPC N = 17,604 40 wks	BMI > 27 Established CV disease, no diabetes	96.6 kg BMI 33.3	At 40 wks 3-pt MACE events Sema 6.5% Pbo 8.0% Ie, sema reduced events by 20% (HR 0.80, 95%CI 0.72-0.90)	[28]
OASIS-1 Semaglutide 50 mg Oral, od	RDBPC N = 667 68 wks	BMI > 30 or BMI > 27-< 30 *	105.4 kg BMI 37.5	At 68 wks Sema 50 mg − 15.1% Pbo − 2.4%	[25]
SURMOUNT-1 Tirzepatide 5, 10, 15 mg SC inject, Qw	RDBPC N = 2539 72 wks Phase 3	BMI > 30 or BMI > 27-< 30 *	104.8 kg BMI 38.0	At 72 wks TZP 5 mg − 15.0% TZP 10 mg − 19.5% TZP 15 mg − 20.9% Pbo − 3.1%	[31]
SURMOUNT-2 Tirzepatide 10, 15 mg SC inject, Qw	RDBPC N = 938 72 wks Phase 3	>BMI 27 kg/m2 with T2DM HbA1c 7-10%	100.7 kg BMI 36.1 kg/m HbA1c 8.02%	At 72 wks TZP 10 mg − 12.8% TZP 15 mg − 14.7% Pbo − 3.2%	[32]
SURMOUNT-3 Tirzepatide 10, 15 mg SC inject, Qw	RDBPC N = 579 72 wks Phase 3	≥ 30 or ≥ 27-< 30 * kg/m2 with intensive lifestyle lead in	102.5 kg BMI 36.1 after lead in	At 72 wks Both doses combined for this analysis TZP − 18.4% Pbo + 2.5%	[33]
SURMOUNT- 4 Tirzepatide 10, 15 mg SC inject, Qw	RDBPC N = 670 52 wks Phase 3	≥ 30 or ≥ 27-< 30 * kg/m2 with 36 wk lead in on TZP 10 or 15 mg	107.3 kg reduced by 21.1% after 36-week t lead in with TZP	At 88 wks Both doses combined for this analysis of weight loss versus 36 wk lead in TZP − 6.7% Pbo + 14.8%	Full paper awaited[c]

(*continued on next page*)

Table 1 (*continued*)

Trial name and agent tested	Design, number, duration, development phase	Body mass index, BMI (kg/m^2) required for inclusion	Baseline mean body weight (kg) and BMI (kg/m^2)	Outcome: change in body weight (% reduced vs baseline)	Reference
Retatrutide 1-12 mg SC, Qw	RDBPC N = 338 48 wks Phase 2	BMI > 30 or BMI > 27-< 30 *	BMI 37.3	At 48 wks Ret 1 mg − 8.7% Ret 4 mg − 17.1% Ret 8 mg − 22.8% Ret 12 mg − 24.2% Pbo − 2.1%	[35]
Cagrilintide 0.3, 0.6, 1.2, 2.4, 4.5 mg SC, Qw	RDBPC N = 706 26 wks Phase 2	BMI > 30 or BMI > 27-< 30 *	107.4 kg BMI 37.8	At 26 wks Cag 0.3 mg − 6.0% Cag 0.6 mg - 6.8% Cag 1.2 mg − 9.1% Cag 2.4 mg − 9.7% Cag 4.5 mg − 10.8% Pbo − 3.0% Lira 3 mg − 9.0%	[42]

BMI, body mass index kg/m^2; Cag, cagrilintide; CI, confidence interval; CV, cardiovascular; H2H, head-to-head comparison; HR, hazard ratio; KCCQ-CSS, Kansas City Cardiomyopathy Questionnaire-Clinical Summary Score; Lira, liraglutide; LVEF, left ventricular ejection fraction; MACE, major adverse cardiac event (cardiovascular death, non-fatal myocardial infarction or non-fatal stroke); Pbo, placebo; RDBPC, randomised, double-blind, placebo-controlled; Qw, once weekly, Ret, retatrutide; SC, subcutaneous; + comorbidity, with an obesity-related morbidity excluding diabetes; od, once daily; T2DM, type 2 diabetes mellitus; Sema, semaglutide; TZP, tirzepatide, wks, weeks; Wt, body weight kg.

* BMI > 27-< 30 with comorbidity/complication that does not include diabetes

[a] intensive behavioural therapy involves a low-calorie diet (1000-1200 kcal/day for 8 weeks and 1200-1800 kcal/day thereafter) plus a physical activity programme (100 min/week for 4 weeks and gradually increasing 200 min/week).

[b] H2H head-to-head open label comparison of semaglutide (Qw) versus liraglutide (od) with a separate double-blinded placebo group for each therapy (placebo data pooled).

[c] Full publication of SURMOUNT-4 trial awaited.

SURMOUNT-3 population included participants with ≥ 1 obesity-related complication (excluding diabetes) and required participants to achieve ≥ 5.0% weight reduction during a 12-week intensive lifestyle lead in.

SURMOUNT-4 complications excluded diabetes, and all participants received open label tirzepatide subcutaneously once weekly up to 10 mg or 15 mg for 36 weeks lead in as an adjunct to a reduced-calorie diet and increased physical activity. By 36 weeks there was 21.1% mean weight loss. Then participants were randomised to either continue tirzepatide or placebo once weekly during a 52-week double-blind period.

congenital or acquired leptin deficiency [46]. Direct activation of the hypothalamic melanocortin-4 (MC4) satiety signalling pathway with the MC4R agonist setmelanotide has produced marked weight loss during small clinical studies of severely obese individuals with pro-opiomelanocortin (POMC) deficiency and other rare congenital conditions that disrupt the MC4 signalling pathway [47]. Although the orexigenic hormone ghrelin is a potentially attractive anti-obesity target, peptide-based interventions to inhibit ghrelin receptor activity have not provided sufficient efficacy to encourage further clinical development [48].

3. Peptide-based therapeutics to address T2DM

3.1. SUSTAIN and PIONEER trials

Although injected GLP-1RAs have been used to treat T2DM since 2005, the most recent addition to the class, semaglutide, has shown particularly strong glucose-lowering efficacy, and its availability as a once daily oral formulation as well as a once weekly subcutaneous injection has increased usage options [11,49]. The glucose-lowering efficacy of injected semaglutide (*Ozempic,* 0.5 and 1 mg once weekly) in T2DM has been assessed in the SUSTAIN trial programme and approved for the treatment of overweight and obese T2DM in 2017 in the USA and 2018 in Europe [50,51]. As reviewed elsewhere, randomised controlled phase 3 trials with injected semaglutide (1 mg once weekly) generated reductions of HbA1c by about 1.5% and body weight by about 4–6 kg over periods up to a year [50]. After these trials were conducted a higher dose of injected semaglutide (2 mg once weekly) was tested and produced slightly greater reductions of HbA1c (by 2.2%) and body weight (by 6.9 kg) at 40 weeks, and the 2 mg dose is now approved (2022) for routine treatment of T2DM [52].

The initial oral formulations of semaglutide (*Rybelsus,* up to 14 mg once daily) studied during the PIONEER trial programme in overweight and obese T2DM patients produced similar or slightly lesser reductions of HbA1c and body weight compared with the 1 mg once weekly injected formulation [53]. However, stronger oral formulations of semaglutide (up to 50 mg once daily) have recently been shown to reduce HbA1c by 2.0% and body weight by 8.5 kg during a 68-week trial in obese T2DM patients [54]. The CV safety of injected and oral semaglutide in T2DM was confirmed with the SUSTAIN-6 and PIONEER-6 trials [55], and initial GI adverse events (generally mild-to-moderate in severity) occurred in about 40% of participants but resulted in < 9% discontinuations. Semaglutide, like other GLP-1RAs, does not cause clinically significant hypoglycaemia (blood glucose <3 mmol/L) when used alone and such events were uncommon (≤2% of participants) when semaglutide was added to sulphonylurea or insulin therapy [56].

3.2. SURPASS trials

The dual GLP-1R/GIPR agonist tirzepatide was approved in 2022 for treatment of overweight and obese T2DM. The efficacy of tirzepatide (5, 10 and 15 mg once weekly subcutaneous injection: *Mounjaro*) was assessed in the SURPASS trial programme which showed greater glucose-lowering and weight-lowering effects than semaglutide and other GLP-1RAs [57–62]. In overweight or obese T2DM populations tirzepatide at 15 mg once weekly reduced HbA1c by about 2% and body weight by about 10–12 kg during periods up to 40 weeks as detailed in Table 2. Moreover, about 90% of participants taking 15 mg tirzepatide in the clinical trials achieved HbA1c values < 7.0%, and about half achieved normal non-diabetic values (HbA1c <5.7%) [63]. Tirzepatide also produced greater glucose-lowering effects than basal insulin therapy (SURPASS-3/4) or additional prandial insulin (SURPASS-6), and was effective as add-on to basal insulin therapy (SURPASS-5). The SURPASS trials, like the SURMOUNT trials, gradually escalated the dose of tirzepatide to minimise initial GI adverse effects: these effects occurred in up to 40% of participants, but mostly resolved quickly and caused few discontinuations of treatment. The only episodes of clinically significant hypoglycaemia with tirzepatide were reported for up to 2%

Table 2
Recent clinical trials designed primarily to assess the glucose-lowering efficacy of peptide-based therapies in type 2 diabetes individuals who are overweight (BMI 25-<30 kg/m^2) or obese (BMI ≥30 kg/m^2).

Trial name and agent tested	Design, number, duration, Develop-ment phase	Background therapy	Baseline mean HbA1c (%), BMI (kg/m^2) and/or body weight (kg)	Outcome: changes in HbA1c (%) and body weight (kg versus baseline	Reference
SURPASS-1 Tirzepatide 5, 10, 15 mg SC inject, Qw	RDBPC N = 478 40 wks Phase 3	Diet & exercise only	HbA1c 7.9% BMI 31.9	At 40 wks Change in HbA1c and wt 5 mg −1.87% −7.0 kg 10 mg −1.89% −7.8 kg 15 mg −2.07% −9.5 kg Pbo +0.04% −0.7 kg	[57]
SURPASS-2 Tirzepatide 5, 10, 15 mg vs 1 mg semaglutide	ROL N = 1878 40 wks Phase 3	Metformin	HbA1c 8.2% BMI 34.2	At 40 wks Change in HbA1c and wt 5 mg −2.01% −7.8 kg 10 mg −2.24% −10.3 kg 15 mg −2.30% −12.4 kg Sema −1.86% −6.2 kg	[58]
SURPASS-3 Tirzepatide 5, 10, 15 mg vs insulin degludec titrated to FBG <90 mg/dL	ROL N = 1444 52 wks Phase 3	Metformin ± SGLT2i	HbA1c 8.1% BMI 33.5	At 52 wks Change in HbA1c and wt 5 mg −1.93% −7.5 kg 10 mg −2.20% −10.7 kg 15 mg −2.37% −12.9 kg Insulin −1.34% +2.3 kg	[59]
SURPASS-4 Tirzepatide 5, 10, 15 mg vs insulin glargine titrated to FBG <100 mg/dL	ROL N = 1995 52 wks Phase 3	Any combin-ation of metformin, SGLT2i and/or SU	HbA1c 8.5% BMI 32.6	At 52 wks Change in HbA1c and wt 5 mg −2.24% −7.1 kg 10 mg −2.43% −9.5 kg 15 mg −2.58% −11.7 kg Insulin −1.44% +1.9 kg	[60]
SURPASS-5 Tirzepatide 5, 10, 15 mg	RDBPC N = 475 40 wks Phase 3	Insulin glargine ± metformin	HbA1c 8.3% BMI 33.4	At 40 wks Change in HbA1c and wt 5 mg −2.11% −5.4 kg 10 mg −2.40% −7.5 kg 15 mg −2.34% −8.8 kg Pbo −0.86% +1.6 kg	[61]
SURPASS-6 Tirzepatide 5, 10, 15 mg Vs prandial insulin lispro	ROL N = 1428 52 wks Phase 3	Insulin glargine + metformin	HbA1c 8.8%	At 52 wks Change in HbA1c and wt TZP pooled cohort analysis TZP −2.1% −9.0 kg Insulin −1.1% +3.2 kg	[62]
Retatrutide 0.5-12 mg SC, Qw	RDBPC N = 281 36 wks Phase 23	Diet & exercise ± metformin	HbA1c 8.2% BMI 35.0	HbA1c change at 24 wks Wt change at 36 wks 0.5 mg −0.43% −3.3 kg s4mg −1.39% −7.2 kg f4mg −1.30% −10.3 kg s8mg −1.99% −16.4 kg f8mg −1.88% −16.1 kg 12 mg −2.02% - 17.1 kg Pbo −0.01% −3.2 kg Dula −1.41% −1.9 kg	[65]
CagriSema Cagrilintide 2.4 mg Semaglutide 2.4	RDB N = 92 32 wks Phase 2	BMI >27	Wt 105.7 kg BMI 35.5	At 32 wks Change in HbA1c and wt CagSem −2.2% −15.6 kg Sem −1.8% −5.1 kg Cag −0.9% −8.1 kg	[66]

BMI, body mass index kg/m2; Cag, cagrilintide; CagSem, CagriSema (combination of 2.4 mg cagrilintide and 2.4 mg semaglutide); Dula, dulaglutide; HbA1c, glycated haemoglobin; Pbo, placebo; ROL, randomised, open label; Dula, dulaglutide 1.5 mg; s, slow dose escalation; f, fast dose escalation; Sema. Semaglutide; SGLT2i, sodium-glucose cotransporter-2 inhibitor; SU, sulphonylurea; vs, versus; wt, body weight in kg.

of participants who received it as add-on to sulphonylurea or basal insulin [64].

3.3. Trials with other glucose-lowering peptides

A phase 2 trial assessed the effect of the triple GLP-1R/GIPR/GCGR agonist retatrutide (up to 12 mg once weekly by subcutaneous injection) in overweight and obese type 2 diabetes and found that the 12 mg dose reduced HbA1c by 2.02% at 24 weeks and body weight by 17.1 kg at 36 weeks [65]. There were no reports of severe hypoglycaemia, and although up to 40% of participants experienced initial GI adverse effects these were usually mild-to-moderate and temporary. Preclinical studies have noted the glucose-lowering efficacy of various other unimolecular peptides with agonist effects at multiple receptors. These are considered elsewhere and the results of clinical studies are awaited [11,14].

A recent 32-week phase 2 study in overweight and obese T2DM found that a combination of semaglutide with cagrilintide in the same once weekly subcutaneous injection (each at a dose of 2.4 mg: *CagriSema*) produced similar effects to the 15 mg dose of tirzepatide. The *CagriSema* reduced HbA1c by 2.2% and body weight by 15.6% while incurring no significant hypoglycaemia and mild-to-moderate GI adverse events (in 68% of participants) that mostly diminished quickly [66].

Consistent with the concept of biased agonism and with the glucose-lowering and weight-lowering effects of GIPR antagonism in animal models, a bispecific molecule has been generated that links a GIPR antagonist antibody with a GLP-1RA (AMG 133) [67]. Once monthly subcutaneous injection of this molecule has recently proceeded into

clinical trial.

4. Peptides to address diabetes co-morbidities

Although all forms of diabetes carry a strong risk of microvascular complications, T2DM and obesity are each associated with increased risk of cardiovascular disease, a chronic deterioration of renal function, various cancers and possibly altered cognitive function. Nevertheless, sustained weight reduction can help to defer the onset and reduce the progression of these co-morbidities [68–71]. The 'cardiovascular outcome trials' with GLP-1RAs have generally shown protective effects against major adverse cardiovascular events, but different members of the class have exerted different effects on CV deaths, non-fatal myocardial infarction and non-fatal stroke as well as improving heart failure prognosis in some studies [72–74]. Intricate sub-group analyses of data generated during the trials suggest that the cardio protective effects are not fully explained by weight loss, glucose-lowering, reductions in blood pressure, a natriuretic effect or an improved lipid profile. Receptors for GLP-1 are expressed in the myocardium and vascular walls and there is evidence that GLP-1RAs may act to reduce local inflammation and oxidative stress to assist in the protection against atherosclerotic disease [75]. Less favourable may be the increase in heart rate that often accompanies use of GLP-1RAs, but earlier concerns about pancreatitis have not been confirmed in the large CV outcome trials [76].

Many of the cardiovascular outcome trials and other recent trials with incretin-based peptides have monitored renal function and shown a reno-protective effect of these treatments associated mainly with a reduction in the onset and severity of albuminuria [77–80]. Indeed, a randomised phase 3 trial (FLOW) investigating the effect of injected semaglutide (1 mg once weekly) in people with T2DM and chronic kidney disease has been terminated early (October 2023) after an interim data analysis showed significant efficacy. Another ongoing trial (REMODEL) in people with T2DM and chronic kidney disease is examining mechanistic aspects of the effect of injected semaglutide on kidney structure and function [81]. Trials are also being conducted to examine the renal effects of oral semaglutide and tirzepatide. The beneficial influence of GLP-1RA-associated therapies on kidney function is likely to reflect many of the treatment effects including reductions in blood pressure, weight and glycaemia as well as reductions of inflammation and oxidative stress.

Several incretin-based peptide therapies have been reported to offer clinically significant benefits to reduce liver fat, improve bone quality and counter some neurodegenerative disorders [82]. Studies are underway to investigate whether such effects apply to semaglutide [82–84]. A lingering concern about synthetic peptides is the risk of developing neutralising antibodies. Evidence from studies with GLP-1RAs and preliminary findings during trials with tirzepatide indicate that although a small percentage of recipients develop anti-drug antibodies, these have not affected the pharmacokinetics or therapeutic efficacy of these agents [85].

5. Conclusion

Many large clinical studies have recently reported the effects of incretin-based peptide therapies in people with obesity and/or T2DM. The peptides used in these studies include the GLP-1RA semaglutide, the dual GLP-1R/GIPR agonist tirzepatide and the GLP-1R/GIPR/GCGR agonist retatrutide. The studies have consistently confirmed that substantial weight-lowering efficacy (over 15% weight loss in some studies in obese individuals without T2DM) and glucose-lowering efficacy (about a 2% reduction in HbA1c in individuals with T2DM in some studies) are achievable with sustained therapy. Cardio-protective and reno-protective effects have also been evident as well as reductions in fatty liver. However, on the negative side, GI adverse effects are commonplace with these therapies and although these are usually temporary they may be sufficiently debilitating to result in temporary or permanent discontinuation of treatment in up to 10% of recipients. Once the desired weight loss and/or glycaemic control is achieved a life-time maintenance dose will generally be required to prevent weight regain. Effects of treatment over many years have yet to be seen with newer therapies and, while potential long-term benefits to bone health [86] and cognitive function [87] have been proposed, there are also possible unwanted reductions in lean body mass and inappropriate consequences when used for cosmetic purposes in individuals who are not seriously overweight [88]. Overall, recent results of studies with the newer incretin-based peptide therapies for control of body weight and blood glucose have shown particularly beneficial properties for the treatment of obesity and T2DM.

CRediT authorship contribution statement

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

Declaration of Competing 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.

Data availability

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

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