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# An update on peptide-based therapies for type 2 diabetes and obesity

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ABSTRACT

Long-acting analogues of the naturally occurring incretin, glucagon-like peptide-1 (GLP-1) and those modified to interact also with receptors for glucose-dependent insulinotropic polypeptide (GIP) have shown high glucose-lowering and weight-lowering efficacy when administered by once-weekly subcutaneous injection. These analogues herald an exciting new era in peptide-based therapy for type 2 diabetes (T2D) and obesity. Of note is the GLP-1R agonist semaglutide, available in oral and injectable formulations and in clinical trials combined with the long-acting amylin analogue, cagrilintide. Particularly high efficacy in both glucose- and weight lowering capacities has also been observed with the GLP-1R/GIP-R unimolecular dual agonist, tirzepatide. In addition, a number of long-acting unimolecular GLP-1R/GCGR dual agonist peptides and GLP-1R/GCGR/GIPR triagonist peptides have entered clinical trials. Other pharmacological approaches to chronic weight management include the human monoclonal antibody, bimagrumab which blocks activin type II receptors and is associated with growth of skeletal muscle, an antibody blocking activation of GIPR to which are conjugated GLP-1R peptide agonists (AMG-133), and the melanocortin-4 receptor agonist, setmelanotide for use in certain inherited obesity conditions. The high global demand for the GLP-1R agonists liraglutide and semaglutide as anti-obesity agents has led to shortage so that their use in T2D therapy is currently being prioritized.

## 1. Introduction

Global prevalence estimates for obesity (at least 15% of adults) and type 2 diabetes (T2D) (>9% of adults) continue to rise, with especial concern for the very high prevalence of obesity (>25% of adults) and T2D (>13% of adults) in several regions of the Americas and Middle East and amongst Pacific island communities [1,2]. Obesity is a strong risk factor for T2D and more than two thirds of patients are overweight or obese at the time of diagnosis. Both obesity and T2D are associated with high susceptibility for many co-morbidities, including non-alcoholic fatty liver, cardiovascular and renal diseases, which are major contributors to the premature mortality [3]. Although weight reduction can substantially reduce the risk and progression of T2D and its co-morbidities, adequate weight loss is notoriously difficult to achieve and maintain by changes of lifestyle alone [4]. The glucose-lowering effect of insulin is associated with weight gain, and most T2D patients have sufficient beta-cell reserve at the time of diagnosis to support near-normal glucose homeostasis if insulin resistance can be relieved by elimination of excess adiposity. Thus, considerable attention is now focussed on other peptide-based interventions that can address both hyperglycaemia and excess adiposity.

Glucagon-like peptide-1 receptor agonists (GLP-1RAs) have proved to be particularly effective as glucose-lowering and weight reducing agents in the management of overweight or obese T2D, and they are now available in most countries as once-daily and once-weekly injectable formulations [(Fig. 1) [5]. They suppress prandial glucose excursions by potentiating nutrient-stimulated insulin secretion, reducing glucagon secretion and delaying gastric emptying, and they facilitate weight loss through a neuronally mediated satiety effect. Accumulated evidence for beneficial cardiovascular effects of these agents has recently elevated their importance in the treatment guidelines, especially for obese T2D patients with atherosclerotic cardiovascular disease [6,7]. Another peptide-based glucose-lowering agent is pramlintide (Symlin), which is an analogue of amylin (islet amyloid polypeptide) with reduced propensity to form amyloid fibrils. This compound has received limited use as an adjunct to insulin, mainly in the USA as a consequence of its ability to reduce glucagon secretion, slow gastric emptying and decrease appetite [8].

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**GLP-1R monoagonists and GLP-1R/GCG-R dual agonists**

Semaglutide HXEGTFTSDVSSYLEGQAAKEFIAWLVRGRG

Pemvidutide HXQGTFTSDYSKYLDEKAAKEFIQWLLQT.NH2 (Lactam:E-16,K-2

NN1177 HXQGTFTSDLSKYLESKRAREFVQWLLKT.$NH_2$

Cotadutide HSQGTFTSDKSEYLDSERARDFVAWLEAGG

BI456906 HΔQGTFTSDYSKYLDERAAKDFIKESA.$NH_2$

GLP-1 HAEGTFTSDVSSYLEGQAAKEFIAWLVKGRG

Glucagon HSQGTFTSDYSKYLDSRRAQDFVQWLMNT

**GIP-R/GLP-1R dual agonists and GIP-R/GLP-1R/GCG-R triple agonists**

Tirzepatide YXEGTFTSDYSIXLDKIAQKAFVQWLIAGGPSSGAPPPS

Retatrutide YXQGTFTSDYSI▼LDKKAQXAFIEYLLEGGPSSGAPPPS.$NH_2$

SAR441255 HXHGTFTSDLSKLKEEQRQXEFIEWLKAaGPPSXKPPPK.$NH_2$

GIP YAEGTFISDYSIAMDKIHQQDFVNWLLAQKGKKNDWKHNITQ

Exendin-4 HGEGTFTSDLSKQMEEEAVRLFIEWLKNGGPSSGAPPPS

**Fig. 1.** A comparison of the primary structures of the long-acting agonists at the GLP-1, glucagon and GIP receptors with the naturally occurring peptides. **X** = α-aminoisobutyric acid, **fx1** = 1-amino-1-cyclobutanecarboxylic acid, fx2 = α-methyl-L-leucine, **a** = D-alanine, K denotes the site of attachment of a fatty acid or fatty di-acid.

## 2. Unimolecular multi-agonist peptides

Peptide therapeutics in development or recently approved for the management of obesity-related T2D are mostly based on the structures of the naturally occurring incretin peptides GLP-1 and glucose-dependent insulinotropic polypeptide (GIP) (Table 1). These hormones offer a relevant portfolio of physiological effects in healthy subjects but their actions, particularly those of GIP, are impaired in T2D. Administration of high supraphysiological doses may be effective in counteracting the reductions in potency and there is evidence that if the hyperglycaemia of T2D is reduced to near normal levels by another therapy (eg GLP-1RA) then the insulin-releasing power of GIP is partially restored [9]. However, the therapeutic potential of GLP-1 and GIP is severely limited by their short half-lives in the circulation. The peptides are rapidly degraded primarily, but not exclusively [10], by dipeptidyl peptidase IV (DPP-IV) in blood and tissues, cleaving at the Ala-2 residue. Thus, increasing the concentrations of circulating GLP-1 and GIP by inhibiting degradation by DPP-IV has been a key approach to the design of viable therapeutic incretins.

Recent studies have noted that the two incretin hormones GLP-1 and GIP appear to exert physiological synergism to produce greater effects when acting together [11]. Accordingly, the design of novel incretin therapies has focussed on multi-agonist synthetic peptides that will interact with the receptors for GLP-1 and GIP to replicate and exaggerate their natural physiological effects [12]. Because glucagon promotes weight loss through its anorexigenic action and its effects on energy expenditure, unimolecular dual agonist peptides that contain amino acid sequences that can interact with the GCG receptor (GCGR) have also been considered in the design of novel peptides for the management of obese T2D patients [13]. The hyperglycaemic effect of GCGR activation can be countered by GLP-1R agonism.

## 3. Design of long-acting analogs

An impetus to the design and development of long-acting analogues of the incretin peptides was provided by the approval in 2005 of the naturally occurring GLP-1RA, exenatide (Byetta) to treat T2D patients [5]. Exenatide is relatively short-acting requiring two subcutaneous (sc) injections per day. Three strategies have been adopted to prepare analogues with substantially longer half-lives in the circulation to enable up to once-weekly administration.

### *3.1. Replacement of the C-terminal carboxylic acid (COOH) by carboxyamide ($CONH_2$) to confer resistance to degradation by carboxypeptidases*

This approach has been employed for the GCGR/GLP-1R dual agonists pemvidutide (ALT-801) [14], NN1177 [15], and BI 456906 [16] and for the GCGR/GLP-1R/GIPR triple agonists retatrutide (LY3437943) [17] and SAR441255 [18].

**Table 1**
GLP-1 receptor agonists available in Europe and North America.

| Drug | $IC_{50}$ (nM) | Approx. $C_{max}$ | Approx. $T_{max}$ | Approx. half-life | Dose | Admin. |
|---|---|---|---|---|---|---|
| **Exenatide** Byetta | 0.55 | 160–250 pg/mL | 2–3 h | 3.5 h | 5 μg<br>10 μg | BD |
| **Exenatide QW** Bydureon | 0.55 | Steady state 300 pg/mL | Steady state 2–6 weeks | Unspecified | 2 mg | QW |
| **Lixisenatide*** Lyxumia | 1.4 | 190 pg/mL (20 μg dose) | 1.2–2.5 h | 2–4 h | 20 μg | OD |
| **Liraglutide** Victoza | 0.11 | 34 nmol/L (1.8 mg/dose) | 10–14 h | 11.6–13 h | 0.6 mg<br>1.2 mg<br>1.8 mg | OD |
| **Dulaglutide* *** Trulicity | Unspecified | 114 ng/mL (1.5 mg dose) | Steady state 2–4 weeks | 4.7 days | 0.75 mg<br>1.5 mg | QW |
| **Semaglutide** Ozempic | 0.38 | 30 nmol/L (1 mg dose) | 1–3 days | 6.2 days | 0.5 mg<br>1.0 mg | QW |
| **Semaglutide** Rybelsus | 0.38 | 40 nmol/L (14 mg dose) | 1 h | 6.2 days | 3 mg<br>7 mg<br>14 mg | Oral |
| **Albiglutide* **** Tanzeum/Eperzan | Unspecified | 4.4 μg/mL (50 mg dose) | 3–5 days | 5 days | 30 μg<br>50 μg | QW |

* Lixisenatide is due to be discontinued in some countries in 2023, * * Dulaglutide comprises GLP-1 covalently linked to an Fc fragment of human IgG4, * ** Albiglutide has not received regulatory approval for clinical use. Cmax, peak plasma/serum concentration; Tmax, time to peak serum concentration. Administration (Admin); OD, once daily; BD, twice daily; QW, once weekly. This table is modified from C.J. Bailey. The current drug treatment landscape for diabetes and perspectives for the future, Clin. Pharmacol. Therap. 98 (2015) 170–184.

### 3.2. Replacement of L-amino acids in the native incretins by unnatural amino acids to confer resistance to proteolytic enzymes, particularly DPP-IV

The Ala-2 residue is replaced by α-aminoisobutyric acid (Aib) in the long-acting GLP-1R agonist, semaglutide [19,20] and in the GLP-1R/GIPR dual agonist tirzepatide [21] as well as in pemvidutide, NN1171, SAR441255 and retatrutide. In BI456906, the Ala-2 residue is replaced by 1-amino-1-cyclobutanecarboxylic acid. Additional resistance of SAR441255 to enzymatic degradation is conferred by additional Aib residues at positions 34 and a D-alanine residue at position 29. In retatrutide, Aib-20 contributes to optimal GIPR activation and α-methyl-L-leucine at position 13 promotes both GCGR and GIPR activation. In pemvidutide, stabilization of the α-helical secondary structure by lactam formation between Glu-16 and Lys-20 also contributes to the agent's longer half-life.

### 3.3. Conjugation of the ε-amino group of a lysine residue to a lipid moiety via a spacer molecule in order to facilitate binding to albumin

A variety of fatty acid and linker molecules have been used for this purpose. In semaglutide, octadecanoic (C-18) diacid is conjugated to the side chain of Lys-20 through a polyethylene glycol (PEG) spacer and a γ-glutamic acid linker resulting in half-life in the circulation of approximately 7 days [19]. Structure-activity studies have shown that conjugation of a fatty diacid rather than palmitate and use of a longer spacer molecule contribute to the longer half-life and improved therapeutic properties of semaglutide compared with the earlier GLP-1RA liraglutide [20]. A C-18 fatty diacid is also used in BI456906 linked by a glycine-serine spacer and in NN1157 linked by a γGlu-γGlu-Ser-Glu-Ser γGlu- γGlu spacer whereas SAR441255 employs palmitate (C-16) linked by two glutamic acid spacers and retatrutide uses a C-20 fatty diacid linked by a Ala-Glu-Glu-Ala- γGlu spacer. Tirzepatide is a single-chain 39 amino acid peptide in which the side chain of a lysine residue is conjugated to a C-20 fatty diacid via a glutamic acid and two (2-(2-aminoethoxy)ethoxy)acetic acid units [21].

The primary structures of the long-acting glucose-lowering and weight-lowering peptides described in this mini-review are compared with the naturally occurring peptides in Fig. 1.

## 4. Oral semaglutide

An oral formulation of the GLP-1R agonist semaglutide (Rybelsus) was approved by FDA in 2019 and by the European Medicines Agency in 2020. This formulation uses the absorption enhancer sodium (N-[8-(2-hydroxybenzoyl)amino]caprylate) (SNAC) to reduce acidity in the stomach in order to protect against enzymatic degradation. The hydrophobic property of SNAC also increases the lipophilicity of semaglutide, which facilitates transcellular absorption across the gastric epithelium [20]. Although oral bioavailability is much lower than by sc injection - hence the much higher dose required (oral 7–14 mg/day versus sc 1–2 mg/week) - tablets do not incur the production requirement of sterile injectable solutions. While oral administration is preferred to sc injection by many patients, the tablets do need patient compliance with regard to administration on an empty (pre-breakfast) stomach. Many other means of peptide administration, such as the use of nanoparticles, peptidase inhibitors and self-emulsifying drug delivery systems (SEDDS), are currently under investigation, and it is anticipated that these could provide convenient and efficient delivery of future peptide medications [22].

## 5. Tirzepatide

In 2022, the first GLP-1R/GIPR dual incretin receptor agonist, tirzepatide (Mounjaro), received regulatory approval for routine clinical use to treat T2D patients and at the time of writing the agent is receiving regulatory assessment for the treatment of obesity or overweight with weight-related comorbidities. Tirzepatide interacts with receptors for GLP-1 and GIP (glucose-dependent insulinotropic polypeptide) and is administered as a once-weekly sc injection. In studies over 40–52 weeks in individuals with T2D, the highest dose (15 mg/week) reduced HbA1c (by 2.5%; 28 mmol/mol) and body weight (by 12.9 kg) [23]. These effects are greater than generally observed with current GLP-1RAs suggesting that the GIP receptor agonism provides extra efficacy. Studies in overweight and obese people who do not have diabetes have indicated that use of tirzepatide (15 mg/week) for 72 weeks can achieve a 20% reduction in body weight [24]. As with GLP-1RAs, tirzepatide lowers plasma glucose and body weight through increased prandial insulin secretion, reduced glucagon secretion, delayed gastric emptying and a satiety effect. The relative contributions of the agonist effects at the GLP-1R and GIPR have yet to be clearly defined. Tirzepatide has a similar binding affinity for GIPR as GIP but a lesser binding affinity for GLP-1R than GLP-1 to approximate to the relative physiological balance of the incretin effect generated by the normal plasma concentrations of the hormones [5,21].

## 6. Efficacy studies with other unimolecular multi-agonist peptides

Preclinical studies have been undertaken with several novel single-chain peptides that interact with receptors for incretin and other glucoregulatory hormones to assess their potential for the management of obese or overweight T2D patients [25]. Among these, the long-acting GLP-1R/GCGR dual agonists NN1177 [15] and LY3305677 (mazdutide), an acylated analogue of oxyntomodulin [26], as well as the GIPR/GCGR/GLP-1R receptor triagonist retatrutide (LY3437943) [27] have entered clinical trials. In a phase-1b study, once-weekly sc administration of retatrutide (up to 12 mg) to T2D patients for 12 weeks was efficacious in producing reductions in glucose concentrations, decreased HbA1c by 1.2% and body weight by 8.9 kg and showed an acceptable a safety profile not dissimilar to GLP-1RAs [27]. Preliminary studies with the similar triagonist SAR441255, an analogue based upon the structure of exendin-4, in healthy human subjects also demonstrated beneficial effects on weight loss and glycaemic control while buffering the diabetogenic risk of chronic GCG receptor agonism [18,28].

A potential beneficial drug interaction has been suggested by recent evidence that inhibition of the enzyme neprilysin (formerly known as endopeptidase 24.11) by the antihypertensive agent sacubitril alongside a DPP-IV inhibitor can increase active plasma GLP-1 concentrations in patients with obesity and T2D [10]. Thus, neprilysin inhibition might provide additional protection against degradation of therapeutically relevant peptides containing GLP-1 sequences. However, neprilysin inhibition also protects against degradation of glucagon and the resulting hyperglucagonaemia may have been responsible for the observed worsening glucose tolerance. Future studies are necessary to analyze the complex balance of these possible effects for molecules possessing GLP-1R and GCGR agonist properties.

## 7. Anti-obesity peptides

In addition to the weight-reducing effects of the peptides described above, several other peptides are under investigation specifically for

| | |
|---|---|
| Amylin | KCNTATCATQ RLANFLVHSSNNFGAILSSTNVGSNTY.$NH_2$ |
| Pramlintide | KCNTATCATQ RLANFLVHSSNNFGPILPPTNVGSNTY.$NH_2$ |
| Cagrilintide | **K**CNTATCATQ RLAEFLRHSSNNFGPILPPTNVGSNTP.$NH_2$ |

**Fig. 2.** A comparison of the primary structure of cagrilintide with naturally occurring amylin and the proline-substituted analogue pramlintide. **K** denotes the site of attachment of a C-20 fatty di-acid via a γ-glutamyl spacer. Amino acid residues that differ from amylin are shown as shaded.

weight management. Cagrilintide is a long-acting acylated amylin analogue whose primary structure is shown in Fig. 2. Cagrilintide contains the proline-substitutions ($Pro^{25}$, $Pro^{28}$ and $Pro^{29}$) found in the analogue pramlintide that inhibit the formation of amyloid fibrils and the substitution $Tyr^{37} \rightarrow$ Pro to increase potency. In addition, the peptide contains the substitutions $Asn^{14} \rightarrow$ Glu which prevents deamination and $Val^{17} \rightarrow$ Arg to increase solubility at physiological pH and form a helix-stabilizing salt-bridge with $Glu^{14}$, and attachment of a C-20 fatty diacid via a γ-glutamyl spacer to increase duration of action by binding to albumin [29]. During a 26-week study in obese or overweight people, once weekly sc injection of cagrilintide (0.3 – 4.5 mg/week) reduced body weight by 6.4–11.5 kg compared with 3.3 kg weight loss with placebo [30]. When obese or overweight people received cagrilintide (4.5 mg/week) in combination with semaglutide (2.4 mg/week) there was a 15.4% reduction in body weight at 20 weeks [31], and in a 32 week study in obese or overweight people with T2D, a combination of cagrilintide with semaglutide (each 2.4 mg/week) was associated with reductions in body weight (by 15.6%) and HbA1c (by 2.18%) [32].

Other potential anti-obesity peptides receiving detailed evaluation include the GCG-R/GLP-1R agonists pemvidutide and BI 456906 and the triple GIPR/GCGR/GLP-1R agonists retatrutide (LY3437943) and SAR441255. In a phase 1 trial using healthy volunteers (NCT03841630), a single dose of retatruitide resulted in significant weight loss that persisted for up to 43 days. The safety and tolerability of the agent was comparable to that of other incretin-related peptides and its pharmacokinetic profile was consisted with once-weekly sc administration [17,33]. As well as improving glycaemic control in T2D patients, the GLP-1R/GCGR dual agonist cotadutide (100–300 ug/day by once-daily sc injection) has shown weight-lowering efficacy in non-diabetic individuals [34–36]. This agent is currently under investigation as a possible treatment for fatty liver disease, and other incretin-based weight-lowering peptides are anticipated to receive similar investigation.

Another approach to reducing adiposity is the fully human monoclonal antibody, bimagrumab (BYM338) which blocks activin type II receptors and is associated with growth of skeletal muscle. Administered by infusion (10 mg/kg up to 1200 mg) every 4 weeks for 48 weeks this antibody reduced body weight by 6.5% (5.9 kg) with a decrease in fat mass of 20.5% (7.5 kg) and a small increase in lean mass in obese or overweight people with T2D [37]. It has been long since known from studies in obese rodents that administration of GIPR antogonists has a beneficial effect on preferential oxidation of fat and clearance of triacylglycerol deposits from liver and muscle [38]. In this light, a recent phase 1 study in obese, non-diabetic individuals (NCT04478708) demonstrated that AMG-133, an antibody that blocks GIPR to which are conjugated two modified GLP-1 peptides that activate GLP-1R, displayed an effective weight-reducing action. Subcutaneous injection of AMG-133 was associated with a 14.5% reduction in body weight after 12 weeks at the highest dose tested [39].

The cyclic melanocortin-4 receptor agonist setmelanotide (Ac-Arg-Cys-D-Ala-His-D-Phe-Arg-Trp-Cys.$NH_2$) is used to lose weight and maintain weight in individuals who are obese due to certain inherited conditions including deficiencies in proopiomelanocortin (and therefore melanocyte-stimulating hormone), proprotein convertase subtilisin/kexin type 1 or the leptin receptor. With precision medicine in mind, small-scale studies of hypothalamic obesity have shown that setmelanotide injection can reduce body weight by more than 20% [40] but at this time the agent is not indicated for weight management in the general patient population.

## 8. Agents addressing fatty liver disease

Non-alcoholic fatty liver disease (NAFLD) and its progression to non-alcoholic steatohepatitis (NASH) and cirrhosis have shown favourable responses to GLP-1RA therapy [41–43]. These responses have included a decrease in liver fat content, reductions of hepatic inflammation and liver enzymes, as well as improved liver histology without worsening of fibrosis. Several studies are currently in progress to provide more detailed information about the effects of GLP-1RA therapy on NAFLD and NASH. Glucagon can reduce liver fat but the liver– alpha cell axis is disturbed by protracted exposure to excess glucagon so that enhancing glucagon secretion causing glucagon resistance limits the effects of the peptide on the liver. However, the GLP-1R/GCGR dual agonist cotadutide (100–300 ug/day by once-daily sc injection) has shown weight-lowering efficacy in non-diabetic individuals and also improved glycaemic control in T2D patients [34–36]. This agent is currently under investigation as a possible treatment for fatty liver disease, and other incretin-based dual agonist and triple agonist peptides are anticipated to be similarly investigated.

## 9. Shortage of glucagon-like peptide-1 receptor agonists

Although GLP-1RAs are used less than the other main classes of glucose-lowering therapies, possibly due in part to higher cost and to the need for injections, global demand has increased faster than current supply for several of these agents [44]. This may reflect the recent regulatory approvals for use of high doses of liraglutide (Saxenda) and semaglutide (Wegovy) for weight lowering in the treatment of obesity [45,46]. However, the manufacturers have limited promotion of the anti-obesity indications in order to prioritise supplies for the treatment of diabetes. A further contributory factor may be the introduction of the oral formulation of semaglutide (Rybelsus) which also requires high doses of the peptide. The shortages have prompted various recommendations to delay the initiation or slow the dose titration of GLP-1RA therapies for new patients or consider at least temporary use of alternative therapies [47].

The GLP-1RAs in short supply are produced in part by recombinant DNA (rDNA) technology using yeast or CHO cells which limits the speed of commercial adaptation to meet demand. Development in the future of large-scale chemical synthesis methods for therapeutic peptides of amenable size could enable faster responsiveness to demand [48]. Indeed, the US Food and Drug Administration (FDA) has recently adopted an abbreviated new drug application (ANDA) process to facilitate approval of synthetic peptides if previously approved for rDNA production. The process is based on proof of bioequivalence and does not require new preclinical or clinical studies [49].

## 10. Conclusion

To address the increasing prevalence of overweight, obesity and T2D, recent attention has focused on the use of GLP-1RAs - some of which are presently in short supply - and on the development of multi-agonist incretin-based peptides. The newly approved GIPR/GLP-1R dual agonist, tirzepatide, as well as a combination of the GLP-1R agonist semaglutide with the long-acting amylin analogue cagrilintide, have shown particularly high glucose-lowering and weight-lowering efficacy in T2D patients The opportunities for peptide therapies are encouraging and their adoption may be enhanced if facile administration with oral formulations can be developed. One may optimistically write that a much-needed new era in anti-diabetic and anti-obesity therapeutics has begun.

## Author contributions

All authors contributed to the writing of this review.

## 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 and have served as advisor to several pharmaceutical companies.

## Data Availability

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

## References


[1] World Obesity Atlas 2022. https://s3-eu-west-1.amazonaws.com/wof-files/World_Obesity_Atlas_2022.pdf Accessed 7 November 2022.

[2] International Diabetes Federation Diabetes Atlas 2021. IDF_Atlas_10th_Edition_2021.pdf https://diabetesatlas.org/ Accessed 7 November 2022.

[3] K. Iglay, H. Hannachi, P.J. Howie, J. Xu, X. Li, S.S. Engelet, et al., Prevalence and co-prevalence of comorbidities among patients with type 2 diabetes mellitus, Curr. Med. Res. Opin. 32 (2016) 1243–1252, https://doi.org/10.1185/03007995.2016.1168291.

[4] A.B. Evert, M.J. Franz, Why weight loss maintenance is difficult, Diabetes Spectr. 30 (2017) 153–156, https://doi.org/10.2337/ds017-0025.

[5] M.A. Nauck, D.R. Quast, J. Wefers, J.J. Meier JJ, GLP-1 receptor agonists in the treatment of type 2 diabetes – state-of-the-art, Mol. Metab. 46 (2021) 1–26, https://doi.org/10.1016/j.molmet.2020.101102.

[6] M.J. Davies, V.R. Aroda, B.S. Collins, R.A. Gabbay, J. Green, N.A. Maruthur, et al., Management of hyperglycaemia in type 2 diabetes, 2022. A consensus report by the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD), Diabetologia 65 (2022) 1925–1966, https://doi.org/10.1007/s00125-022-05787-2.

[7] L. Blonde, G.E. Umpierrez, S.S. Reddy, A. Vella, P. Vellanki, et al., American Association of Clinical Endocrinology Clinical Practice Guideline: Developing a diabetes mellitus comprehensive care plan - 2022 update, Endocr. Pract. 26 (2022) 923–1049, https://doi.org/10.1016/j.eprac.2022.08.002.

[8] M.C. Riddle, K.C. Yuen, T.W. de Bruin, K. Herrmann, J. Xu, P. Ohman, et al., Fixed ratio dosing of pramlintide with regular insulin before a standard meal in patients with type 1 diabetes, Diabetes Obes. Metab. 17 (2015) 904–907, https://doi.org/10.1111/dom.12504.

[9] J.J. Holst, M.M. Rosenkilde, GIP as a therapeutic target in diabetes and obesity: insight from incretin co-agonists, J. Clin. Endocrinol. Metab. 105 (2020) e2710–e2716, https://doi.org/10.1210/clinem/dgaa327.

[10] N.J. Wewer Albrechtsen, A. Møller, C. Martinussen, L.L. Gluud, E.B. Rashu, M. M. Richter, et al., Acute effects on glucose tolerance by neprilysin inhibition in patients with type 2 diabetes, Diabetes Obes. Metab. 24 (2022) 2017–2026, https://doi.org/10.1111/dom.14789.

[11] M.C. Pelle, M. Provenzano, I. Zaffina, R. Pujia, F. Giofrè, S. Lucà, et al., Role of a dual glucose-dependent insulinotropic peptide (GIP)/glucagon-like peptide-1 receptor agonist (twincretin) in glycemic control: from pathophysiology to treatment, Life (Basel) 12 (2022) 29, https://doi.org/10.3390/life12010029.

[12] M.H. Tschop, B. Finan, C. Clemmensen, V. Gelfanov, D. Perez-Tilve, T.D. Muller, et al., Unimolecular polypharmacy for treatment of diabetes and obesity, Cell Metab. 24 (2016) 51–62, https://doi.org/10.1016/j.cmet.2016.06.021.

[13] S. Del Prato, B. Gallwitz, J.J. Holst, J.J. Meier, The incretin/glucagon system as a target for pharmacotherapy of obesity, Obes. Rev. 23 (2022), e13372 org/10.1111/obr.13372.

[14] J.J. Nestor, D. Parkes, M. Feigh, J.J. Suschak, M.S. Harris, Effects of ALT-801, a GLP-1 and glucagon receptor dual agonist, in a translational mouse model of non-alcoholic steatohepatitis, Sci. Rep. 12 (2022) 6666, https://doi.org/10.1038/s41598-022-10577-2.

[15] M. Friedrichsen, L. Endahl, F.F. Kreiner, R. Goldwater, M. Kankam, S.Toubro et al., Glucagon/GLP-1 receptor co-agonist NNC9204–1177 reduced body weight in adults with overweight or obesity but was associated with safety issues, Pre-print version posted June 3, 2022. doi.org/10.1101/2022.06.02.22275920doi:medR.

[16] T. Zimmermann, L. Thomas, T. Baader-Pagler, P. Haebel, E. Simon, W. Reindl, et al., BI 456906: discovery and preclinical pharmacology of a novel GCGR/GLP-1R dual agonist with robust anti-obesity efficacy, Mol. Metab. 7 (2022), 101633, https://doi.org/10.1016/j.molmet.2022.101633.

[17] T. Coskun, S. Urva, C. Roell, H. Qu, C. Loghin, J.S. Moyers JS, et al., LY3437943, a novel triple glucagon, GIP, and GLP-1 receptor agonist for glycemic control and weight loss: from discovery to clinical proof of concept, Cell Metab. 34 (2022) 1234–1247, https://doi.org/10.1016/j.cmet.2022.07.013.

[18] M. Bossart, M. Wagner, R. Elvert, A. Evers, T. Hübschle, T. Kloeckener, et al., Effects on weight loss and glycemic control with SAR441255, a potent unimolecular peptide GLP-1/GIP/GCG receptor triagonist, e10, Cell Metab. 34 (2022) 59–74, https://doi.org/10.1016/j.cmet.2021.12.005.

[19] L.B. Knudsen, J. Lau J, The discovery and development of liraglutide and semaglutide, Front. Endocrinol. (Lausanne) 10 (2019) 155, https://doi.org/10.3389/fendo.2019.00155.

[20] J. Lau, P. Bloch, L. Schäffer, I. Pettersson, J. Spetzler, J. Kofoed, et al., Discovery of the once-weekly glucagon-like peptide-1 (GLP-1) analogue semaglutide, J. Med. Chem. 58 (2015) 7370–7380, https://doi.org/10.1021/acs.jmedchem.5b00726.

[21] T. Coskun, K.W. Sloop, C. Loghin, J. Alsina-Fernandez, S. Urva, K.B. Bokvist, et al., LY3298176, a novel dual GIP and GLP-1 receptor agonist for the treatment of type 2 diabetes mellitus: From discovery to clinical proof of concept, Mol. Metab. 18 (2018) 3–14, https://doi.org/10.1016/j.molmet.2018.09.009.

[22] A.T. Zizzari, D. Pliatsika, F.M. Gall, T. Fischer, R. Riedl, New perspectives in oral peptide delivery, Drug Discov. Today 26 (2019) 1097–1105, https://doi.org/10.1016/j.drudis.2021.01.020.

[23] C. De Block, C. Bailey, C. Wysham, A. Hemmingway, S.E. Allen, J. Peleshok, 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.

[24] A.M. Jastreboff, L.J. Aronne, N.N. Ahmad, S. Wharton, L. Connery, et al., Tirzepatide once weekly for the treatment of obesity, N. Engl. J. Med 387 (2022) 205–216, https://doi.org/10.1056/NEJMoa2206038.

[25] E. Jiménez-Martí, G. Hurtado Genovés, M. Aguilar-Ballester, S. Martínez-Hervás S, H. González Navarro, Novel therapies for cardiometabolic disease: recent findings in studies with hormone peptide-derived G protein coupled receptor agonists, Nutrients 14 (2022) 3775, https://doi.org/10.3390/nu14183775.

[26] H. Jiang, S. Pang, Y. Zhang, T. Yu, M. Liu, H. Deng, et al., A phase 1b randomised controlled trial of a glucagon-like peptide-1 and glucagon receptor dual agonist IBI362 (LY3305677) in Chinese patients with type 2 diabetes, Nat. Commun. 13 (2022) 3613, https://doi.org/10.1038/s41467-022-31328-x.

[27] S. Urva, T. Coskun, M.T. Loh, Y. Du, M.K. Thomas, S. Gurbuz S, et al., LY3437943, a novel triple GIP, GLP-1, and glucagon receptor agonist in people with type 2 diabetes: a phase 1b, multicentre, double-blind, placebo-controlled, randomised, multiple-ascending dose trial, S0140-6736, Lancet 27 (22) (2022) 02033–02035, https://doi.org/10.1016/S0140-6736(22)02033-5.

[28] E. Araki, M. Sakaguchi, K. Fukuda, T. Kondo, Potential of a glucagon-like peptide-1 receptor/glucose-dependent insulinotropic polypeptide receptor/glucagon receptor triagonist for the treatment of obesity and type 2 diabetes, J. Diabetes Investig. 13 (2022) 1958–1960, https://doi.org/10.1111/jdi.13896.

[29] T. Kruse, J.L. Hansen, K. Dahl, L. Schäffer, U. Sensfuss, C. Poulsen, et al., Development of cagrilintide, a long-acting amylin analogue, J. Med. Chem. 64 (2021) 11183–11194, https://doi.org/10.1021/acs.jmedchem.1c00565.

[30] D.C. Lau, L. Erichsen, A.M. Francisco, A. Satylganova, C.W. le Roux, B. McGowan B, et al., Once-weekly cagrilintide for weight management in people with overweight and obesity: a multicentre, randomised, double-blind, placebo-controlled and active-controlled, dose-finding phase 2 trial, Lancet 398 (10317) (2021) 2160–2172, https://doi.org/10.1016/S0140-6736(21)01751-7.

[31] L.B. Enebo, K.K. Berthelsen, M. Kankam, M.T. Lund, D.M. Rubino, A. Satylganova, et al., Safety, tolerability, pharmacokinetics, and pharmacodynamics of concomitant administration of multiple doses of cagrilintide with semaglutide 2·4 mg for weight management: a randomised, controlled, phase 1b trial, Lancet 397 (10286) (2021) 1736–1748, https://doi.org/10.1016/S0140-6736(21)00845-X.

[32] Novo Nordisk company announcement, August 2022. Novo Nordisk successfully completes phase 2 trial with CagriSema in people with type 2 diabetes https://www.novonordisk.com/news-and-media/news-and-ir-materials/news-details.html?id=131155, Accessed 13 November 2022.

[33] ClinicalTrials.gov. A study of LY3437943 in participants with type 2 diabetes. https://clinicaltrials.gov/ct2/show/NCT04867785, Accessed 14 November 2022.

[34] V.E.R. Parker, D. Robertson, T. Wang, D.C. Hornigold, M. Petrone, A.T. Cooper, et al., Efficacy, safety, and mechanistic insights of cotadutide, a dual receptor glucagon-like peptide-1 and glucagon agonist, J. Clin. Endocrinol. Metab. 105 (2020) 803–820, org/10.1210/clinem/dgz047.

[35] M.M. Ali, A. Hafez, M.S. Abdelgalil, M.T. Hasan, M.M. El-Ghannam, O.M. Ghogar, et al., Impact of cotadutide drug on patients with type 2 diabetes mellitus: a systematic review and meta-analysis, BMC Endoc. Disord. 22 (2022) 113, https://doi.org/10.1186/s12902-022-01031-5.

[36] R. Nahra, T. Wang, K.M. Gadde, J. Oscarsson, M. Stumvoll, L. Jermutus, et al., Effects of cotadutide on metabolic and hepatic parameters in adults with overweight or obesity and type 2 diabetes: a 54-week randomized phase 2b study, Diabetes Care 44 (6) (2021) 1433–1442, https://doi.org/10.2337/dc20-2151.

[37] S.B. Heymsfield, L.A. Coleman, R. Miller, D.S. Rooks, D. Laurent, O. Petricoul, et al., Effect of bimagrumab vs placebo on body fat mass among adults with type 2 diabetes and obesity: a phase 2 randomized clinical trial, JAMA Net. Open 4 (2021), e2033457, https://doi.org/10.1001/jamanetworkopen.2020.33457.

[38] N. Irwin, P.R. Flatt, Evidence for beneficial effects of compromised gastric inhibitory polypeptide action in obesity-related diabetes and possible therapeutic implications, Diabetologia 52 (2009) 1724–1731, https://doi.org/10.1007/s00125-009-1422-8.

[39] ClinicalTrials.gov. Single and multiple ascending dose study of AMG 133 in participants with obesity. Available at: https://clinicaltrials.gov/ct2/show/NCT04478708, accessed December 30 2022.

[40] National Institute for Health Care Excellence Guidance. Setmelanotide for treating obesity caused by LEPR or POMC deficiency. NICE 2022, https://www.nice.org.uk/guidance/hst21, accessed 14 November 2022.

[41] R.K. Vincent, D.M. Williams, M. Evans, A look to the future in non-alcoholic fatty liver disease: are glucagon-like peptide-1 analogues or sodium-glucose co-transporter-2 inhibitors the answer? Diabetes Obes. Metab. 22 (2020) 2227–2240, https://doi.org/10.1111/dom.14196.

[42] A. Mantovani, G. Petracca, G. Beatrice, A. Csermely, A. Lonardo, G. Targher, Glucagon-like peptide-1 receptor agonists for treatment of non-alcoholic fatty liver disease and non-alcoholic steatohepatitis: an updated meta-analysis of randomized controlled trials, Metabolites 11 (2021) 73, https://doi.org/10.3390/metabo11020073.

[43] C. Gar, S.J. Haschka, S. Kern-Matschilles, B. Rauch, V. Sacco, C. Prehn, et al., The liver–alpha cell axis associates with liver fat and insulin resistance: a validation study in women with non-steatotic liver fat levels, Diabetologia 64 (2021) 512–520, https://doi.org/10.1007/s00125-020-05334-x.

[44] C.J. Bailey, Why are GLP-1 receptor agonists in short supply?, Brit. J. Diabetes 2022 in press.

[45] Saxenda product label. https://www.medicines.org.uk/emc/product/2313/smpc#gref Accessed 13 November 2022.

[46] Wegovy product label. https://www.ema.europa.eu/en/documents/product-information/wegovy-epar-product-information_en.pdf Accessed 13 November 2022.
[47] H. Beba, C. Ranns, C. Hambling, J. Diggle, P. Brown, PCDS consensus statement: A strategy for managing the supply shortage of the GLP-1 RAs Ozempic and Trulicity. Diabetes & Primary Care 2022, 24 (5). Available on-line at https://diabetesonthenet.com/wp-content/uploads/PCDS-GLP-1-RA-shortage-statement-1.pdf, accessed 7 November 2022.
[48] M.O. Frederick, R.A. Boyse, T.M. Braden, J.R. Calvin, B.M. Campbell, S.M. Changi, et al., Kilogram-scale GMP manufacture of Tirzepatide using a hybrid SPPS/LPPS approach with continuous manufacturing", Org. Process Res. Dev. 25 (2021) 1628–1636, https://doi.org/10.1021/acs.oprd.1c00108.
[49] U.S. Food & Drug Administration. ANDAs for certain highly purified synthetic peptide drug products that refer to listed drugs of rDNA origin. Guidance for Industry, 2021, https://www.fda.gov/regulatory-information/search-fda-guidance-documents, accessed 10 November 2022.