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Glucagon-Like Peptide 1 Therapy: From Discovery to Type 2 Diabetes and Beyond

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The therapeutic benefits of the incretin hormone, glucagon-like peptide 1 (GLP1), for people with type 2 diabetes and/or obesity, are now firmly established. The evidence-base arising from head-to-head comparative effectiveness studies in people with type 2 diabetes, as well as the recommendations by professional guidelines suggest that GLP1 receptor agonists should replace more traditional treatment options such as sulfonylureas and dipeptidyl-peptidase 4 (DPP4) inhibitors. Furthermore, their benefits in reducing cardiovascular events in people with type 2 diabetes beyond improvements in glycaemic control has led to numerous clinical trials seeking to translate this benefit beyond type 2 diabetes. Following early trial results their therapeutic benefit is currently being tested in other conditions including fatty liver disease, kidney disease, and Alzheimer's disease.

Keywords: Glucagon-like peptide 1; Diabetes mellitus, type 2; Renal insufficiency, chronic

DISCOVERY OF GLUCAGON-LIKE PEPTIDE 1 AS AN INSULINOTROPIC INCRETIN HORMONE

In 1902 Bayliss and Starling [1] described the first gastrointestinal (GI) hormone, secretin, establishing the role of the GI tract as an endocrine organ. The ability to accurately measure serum insulin by radioimmunoassay, allowed the description of the incretin effect, whereby glucose administration into the gut potentiated insulin secretion to a greater extent than equimolar plasma glucose excursions achieved by intravenous infusion.

Glucagon-like peptide 1 (GLP1) belongs to the family of incretin hormones which are released from the GI gastrointestinal tract following nutrient intake, augmenting the glucose-dependent insulin response during hyperglycaemia. The first of these, glucose-dependent insulinotropic polypeptide (GIP), was isolated in 1971 [2]. This review only focusses on the second incretin hormone, namely GLP1.

The insulin-releasing effects GLP1 were described by two groups in 1987 [3,4]. They showed that GLP1 is a peptide hormone derived from the L-cells of the mammalian GI mucosa, which is secreted following the posttranslational cleavage from the pro-hormone, proglucagon. GLP1 is part of several proglucagon-derived peptides including GLP2 as well as additional isoforms of GLP1, such as GLP1(1-36), GLP1(1-37), the truncated form GLP1(7-37) and the arginine-amidated isoforms $GLP1(7\text{-}37)_{amide}$ and $GLP1(1\text{-}36)_{amide}$. In a series of elegant experiments using isolated cell lines, Drucker et al. [5] demonstrated that it was the GLP1(7-37) which induced insulin production via cyclic adenosine monophosphate (AMP). Further-

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more, they demonstrated that GLP1(7-37) increased the insulin mRNA transcription and stimulated its secretion at glucose concentrations of 25 mM but not at 5.5 mM. They also showed that neither GLP1(1-36) or GLP1(1-37) increased cyclic AMP concentrations nor did GLP2 or glucagon induce insulin gene expression. The truncated amide isoform GLP1(7-37)$_{amide}$ also stimulates insulin secretion [3]. These findings established GLP1(7-37) as the proglucagon derived peptide which specifically enhances glucose-dependent insulin secretion in pancreatic β-cells. This was followed by 'first in man' studies which confirmed the insulinotropic effect of GLP1(7-37) and GLP1(7-37)$_{amide}$ [6]. Similar to laboratory cell line experiments, the bioactivities of the extended forms of GLP1 (GLP1(1-36) and GLP1(1-37)) have not been determined. No distinctive physiological action has been clearly attributed to whether GLP1 is amidated or not. Next it was demonstrated that GLP1, in contrast to GIP [7], inhibited glucagon secretion in the perfused pancreas [8] and later in humans [9]. This stimulation was attenuated as plasma glucose decreased which limited the fall to 0.5 to 1 mM. The same group showed that GLP1 inhibited gastric and exocrine pancreatic secretion [10] and also that infusing GLP1 in humans inhibited appetite and food intake [11]. Next it was demonstrated by Nauck et al. [12], that intravenous GLP1 infusion normalised plasma glucose in individuals with longstanding type 2 diabetes. These findings demonstrated the therapeutic potential of GLP1 for the treatment of type 2 diabetes and obesity. Subcutaneous injection of GLP1 was however disappointingly ineffective [13]. The reason for this was demonstrated by Deacon et al. [14] who identified that the protease dipeptidyl-peptidase 4 (DPP4) rapidly degrades GLP1 with an elimination half-life of about 2 minutes [15]. This was soon followed by experiments which demonstrated that GLP1 analogues which are resistant to DPP4 protease inactivation were longer acting than native GLP1, and that inhibition of DPP4 amplified endogenous GLP1's insulinotropic effect [16]. At this stage it was uncertain whether GLP1 therapy could be clinically useful, whether tachyphylaxis would develop and whether there would be safety concerns. Zander et al. [17], infused synthetic GLP1 subcutaneously in a cohort of people with longstanding type 2 diabetes over 6 weeks. No tachyphylaxis was demonstrated, mean hemoglobin A1c (HbA1c) reduced by 1.3% and weight decreased by 2 kg. Clamp studies in this group showed improvements insulin sensitivity and β-cell function. These experiments paved the way for the pharmacological development GLP1 receptor agonists (GLP-1RAs).

DEVELOPMENT OF GLP-1RAs AND PIVOTAL COMPARATIVE EFFECTIVENESS STUDIES IN TYPE 2 DIABETES

Daily GLP-1RAs

The peptide exendin-4 isolated from the saliva of the Gila monster (*Heloderma suspectum*) was serendipitously found to have a high degree of homology to mammalian GLP1 and found to bind and activate GLP1-receptors [18]. Without further modification, the first synthetic exendin-4 (named exenatide) was approved in 2005 (USA) and 2006 (Europe) as a pharmacological GLP-1RA. Its clinical trial programme investigated a twice daily injection regimen.

The first once daily administered GLP-1RA developed was liraglutide. Unlike exenatide, it had high homology with human GLP1. A free fatty side chain enabled albumin binding which serves as a reservoir with an estimated approximately 1% to 2% of liraglutide circulating freely. The elimination half-life of approximately 13 hours made it suitable for once daily administration. The question as to whether this would translate into additional clinical benefit was duly answered in a head-to-head comparative effectiveness study [19]. Liraglutide 1.8 mg reduced the mean HbA1c by 1.12% versus 0.79% for twice daily exenatide 10 μg from a baseline of 8.2%. Mean weight loss was similar (3.24 kg for liraglutide and 2.87 for exenatide). A second once daily GLP-1RA, lixisenatide, gained market authorisation but it was significantly inferior at 20 μg dose to liraglutide 1.8 mg with an estimated treatment difference (ETD) of –0.62% from a mean baseline HbA1c of 8.4% [20]. Such head-to-head comparative studies have commendably continued during the development programmes of other GLP-1RAs, and such studies inform clinical decision-making. Similar head-to-head studies are conspicuously absent in other drug classes such as sodium glucose transport 2 (SGLT2) inhibitors and DPP4 inhibitors and their prescribing is more readily influenced by marketing than by research and development data [21,22].

Weekly GLP-1RAs

The next challenge was to see whether once-weekly GLP-1RAs could provide greater benefits than liraglutide. Exenatide suspended in a microsphere formulation was the first of the once weekly GLP-1RAs to be approved. In its first notable head-to-head trial, 2 mg once weekly exenatide was superior to 10 μg twice daily exenatide (HbA1c ETD 0.4%) with similar weight loss [23].

However, liraglutide 1.8 mg showed a greater reduction in

HbA1c than 2 mg once weekly exenatide (ETD 0.21%) with statistically similar but numerically greater weight loss of 3.6 kg for liraglutide versus 2.7 kg for exenatide [24].

Another successful developmental strategy was to couple modified GLP1 with a large molecule such as albumin (albiglutide) or an immunoglobulin (dulaglutide and efpeglenatide). With slow degradation these compounds have half-lives of approximately a week. The head-to-head comparative studies conducted during their development programmes assessed the progress derived. The Assessment of Weekly AdministRation Dulaglutide in Diabetes (AWARD) 6 trial compared once weekly dulaglutide 1.5 mg to liraglutide 1.8 mg once daily. Dulaglutide was non-inferior to liraglutide with similar HbA1c (–1.42% vs. –1.36%) and weight reductions (–2.9 kg vs. –3.6 kg) [25]. Liraglutide 1.8 mg once daily, however, was superior to albiglutide as assessed by reductions in HbA1c (ETD 0.21%) and weight loss (–2.2 kg vs. –0.6 kg) from a baseline of approximately 92 kg [26].

The most recently developed GLP-1RA was semaglutide. Its structure is similar to that of liraglutide being a modified GLP1 with high homology to human GLP1 attached to a fatty acid. Its longer half-life of about a week is attributed to the greater binding affinity to albumin. It is a much smaller compound approximately 4 kilo-Dalton (kDa) compared to Dulaglutide (which is approximately 63 kDa) and this may explain its superiority over the larger once weekly compounds [27,28]. In head-to-head studies, weekly semaglutide was superior to three GLP-1RAs as assessed by both glycaemic control (the primary endpoint) and weight reduction (a secondary endpoint). The Semaglutide Unabated Sustainability in Treatment of Type 2 Diabetes (SUSTAIN) 3 trial compared weekly semaglutide 1.0 mg to weekly exenatide 2 mg [29]; semaglutide was superior for HbA1c reduction (–1.5% vs. –0.9%) from a baseline of 8.3% and superior for weight reduction (–5.6 kg vs. –1.9 kg) from a baseline of approximately 96 kg. The SUSTAIN 7 trial compared weekly dulaglutide 0.75 mg to semaglutide 0.5 mg (the lower doses of each medicine) and dulaglutide 1.5 mg to semaglutide 1.0 mg (the higher doses) [28]. For both comparisons semaglutide was superior to dulaglutide as measured by HbA1c (ETD 0.4%) and semaglutide had twice the weight loss at the low (–4.6 kg vs. –2.3 kg) and high (–6.3 kg vs. –3.0 kg) doses. The SUSTAIN 10 trial compared liraglutide 1.2 mg to semaglutide 1.0 mg [30]. The investigators chose these doses to reflect the most common prescription pattern in Europe at the time of the study design (liraglutide 1.2 mg) and the most common anticipated pattern (semaglutide 1.0 mg), arguing that this increases the clinical relevance of the results [30]. Semaglutide was superior to liraglutide 1.2 mg in HbA1c (–1.7% vs. –1.0%) and weight reductions (–5.7 kg vs. –1.9 kg) from a baseline of approximately 97 kg.

The SUSTAIN programme also compared injectable semaglutide to sitagliptin, canagliflozin, and insulin glargine. Weekly injectable semaglutide 1.0 mg was superior to sitagliptin for both improved glycaemic control and weight loss (–1.6% vs. 0.5% from baseline 8.1%; –6.1 kg vs. 1.9 kg from baseline 89 kg) [31], to titrated insulin glargine (–1.6% vs. –0.8%; –5.2 kg vs. 1.2 kg) [32] and also to canagliflozin (–1.5% vs. 1.0% from baseline of 8.3%; –5.3 kg vs. –4.2 kg) [33].

Higher doses of existing GLP-1RA

Both semaglutide and dulaglutide were more recently also investigated at higher doses than initially licenced for glucose lowering. The SUSTAIN FORTE compared 2.0 to 1.0 mg of semaglutide once weekly; from a baseline HbA1c of 8.9% the reduction was 2.2% versus 1.9% and the weight loss difference was 6.9 kg versus 6.0 kg (trial product estimand) [34]. The Semaglutide Treatment Effect in People with Obesity (STEP) 2 trial compared semaglutide 2.4 mg and semaglutide 1.0 mg to placebo, demonstrating respective changes in HbA1c (–1.6%, –1.5%) and mean percentage weight reduction (9.6%, 7.0%) [35]. The AWARD-11 trial tested two higher doses of dulaglutide 3.0 and 4.5 mg and compared this to the then highest clinically approved dose of 1.5 mg. The respective HbA1c reductions for the 1.5, 3.0, and 4.5 mg doses from a baseline of 8.6% were –1.52%, –1.71%, and –1.83% [36].

Oral GLP-1RA

Novel technology has allowed for semaglutide to now become available as the first oral GLP-1RA medication through its co-formulation with sodium N-(8-(2-hydroxybenzoyl) amino) caprylate (SNAC) [37]. SNAC increases the local pH in the stomach reducing acid degradation and allowing for transcellular absorption of semaglutide in the stomach (unlike most drugs which are absorbed in the small intestine). The absorption of semaglutide is reduced with excess fluid intake and when taken with food. It should thus be taken in the fasting state (>6 hours after eating) and with minimal fluid (<120 mL). Food and other medications should not be taken for at least 30 minutes following ingestion. The Peptide Innovation for Early Diabetes Treatment (PIONEER) 4 trial compared once daily oral semaglutide 14 mg to liraglutide 1.8 mg [38]. This showed a similar improvement in glycaemic control HbA1c (–1.2% vs. –1.1%) from a baseline of 8.0% with significantly greater weight reduc-

tion (–4.4 kg vs. –3.1 kg). Oral semaglutide 14 mg once a day also showed superior improvements in glycaemic control when compared to empagliflozin 25 mg (–1.3% vs. –0.9%) [39] and sitagliptin 100 mg (–1.3% vs. –0.8%) [40].

SAFETY AND TOLERABILITY

Gastrointestinal

The most frequently reported side-effects of GLP-1RAs are GI with nausea being the most common (occurring in about one in five patients) and diarrhoea and vomiting occurring in about one in 10 patients [41,42]. These side effects are likely due to direct GI effects such a delay in gastric emptying or central activation of GLP1 receptors in the brainstem, such as the area postrema. Fasting subjects can exhibit GI side effects and these can be exacerbated by larger meals and meals with higher fat content which already delay gastric emptying. The GI side-effects occur mostly in the early treatment period (1 to 3 months) and these can be mitigated by dose titration.

GI side effects are dose dependent, but to a lesser degree. In the AWARD-11 trial comparing weekly dulaglutide this was 13.4% (1.5 mg), 15.6% (3 mg); 16.4% (4.5 mg) for nausea and 5.6% (1.5 mg), 8.3% (3 mg), and 9.3% (4.5 mg) for vomiting [36]. In the SUSTAIN FORTE trial GI disorders were 34% and 31% for the 2.0 and 1.0 mg semaglutide doses respectively [34]. Longer acting GLP-1RAs are generally better tolerated than shorter acting GLP-1RAs and tolerability is also influenced by background medication (for example, worse when on metformin and insulin) [41]. The best data from long term adherence in large cohorts are from the placebo controlled cardiovascular outcome trials (CVOTs). These show broadly similar tolerability within the GLP-1RA class. The proportion of patients discontinuing the study drug because of adverse events (AEs) was 11.4% for lixisenatide [43], 9.5% for liraglutide [44], 13.2% for subcutaneous semaglutide [45], 8.6% for albiglutide [46], 11.6% for oral semaglutide [47], and 9.1%, for dulaglutide [48].

It has been suggested that differences exist between populations, with lower rates of GI AEs seen in Japanese compared to Caucasian populations suggesting either differences in pharmacogenetics and/or eating habits [42]. However, more recent analysis of the PIONEER 1–5 and 7&8 trials of oral semaglutide did not show any differences between White, Black/African-American, or Asian subgroups who experienced more than one GI AE [49]. For example, in the PIONEER 2 trial subjects who experienced more than one GI AE on oral semaglutide were White (42%), Black/African American (41%), and Asian (18%) in contrast to the PIONEER 3 study where subjects who experienced more than one GI AE on oral semaglutide were White (34%), Black/African American (34%), and Asian (48%).

GI AEs have hardly any impact on the weight loss effects. This was studied by several mediation analyses [50,51]. GI AEs contributed <0.1 kg to weight loss superiority of semaglutide compared to other GLP-1RAs (weekly exenatide, dulaglutide, and liraglutide) studied in the SUSTAIN 3, 7, and 10 trials. In the SUSTAIN 1–5 trials which compared semaglutide to placebo, sitagliptin, weekly exenatide, and insulin glargine, 0.07 kg of the 2.3 kg weight loss seen on semaglutide 0.5 mg, and 0.5 kg of the overall 6.3 kg for semaglutide 1.0 mg was mediated by nausea/vomiting [51].

Other adverse events

When GLP-1RAs were first introduced there was concern that these agents could increase the risks of pancreatitis, pancreas cancer and medullary thyroid cancer [52]. Since then, these fears have been quelled following numerous large, randomised placebo controlled CVOTs which carefully adjudicated these AEs of special interest. A recent meta-analysis of GLP-1RA CVOTs showed no increased risk for acute pancreatitis or malignancy [53,54].

BENEFITS BEYOND DIABETES

There are numerous reviews discussing the benefits of GLP-1RAs beyond management of glycaemia and for the sake of brevity we therefore discuss these very only briefly.

Weight loss

The weight loss benefits of GLP-1RAs have also been demonstrated in people who do not have diabetes. This has recently been reviewed by several authors [42,55-57] with an in-depth review of the clinical physiology and basic science by Drucker [58]. The most comprehensively studied are liraglutide (Satiety and Clinical Adiposity–Liraglutide Evidence [SCALE] program) and semaglutide (STEP program). Their benefit is such that both have now received market authorisation for the treatment of obesity in numerous countries.

Cardiovascular

The cardiovascular benefits of GLP-1RA therapy demonstrated in CVOTs has led to recommendations from the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD) for this treatment in people with type

2 diabetes who also have established cardiovascular disease (CVD) or at high risk of CVD, irrespective HbA1c target [59]. The cardiovascular benefits of GLP-1RAs and mechanisms by which these are provided, have been recently reviewed by several authors [42,54,56,60,61]. Thus far, the cardiovascular benefits of GLP-1RAs have only been reported in people with type 2 diabetes. This benefit could be expanded to a broader population, and this is being tested in the Semaglutide Effects on Heart Disease and Stroke in Patients With Overweight or Obesity (SELECT) trial which is studying semaglutide in a people who do not have type 2 diabetes but who do have high cardiovascular risk (ClinicalTrials.gov Identifier: NCT03574597) [62].

Renal

GLP-1RA therapies have demonstrated tantalising renal benefits as secondary outcomes in the CVOTs with a reduction of albuminuria (with variations in definitions of either micro- or macroalbuminuria), new onset of albuminuria and a decline in glomerular filtration rate, being reported. These analyses, including their mechanisms, have been recently reviewed [60,63-65] with the most consistent benefit being improvement in albuminuria. Renal specific benefits which have already been tested as primary outcomes for SGLT2 inhibitors require similar testing in GLP-1RAs to validate them. Semaglutide is currently being assessed in a large trial (A Research Study to See How Semaglutide Works Compared to Placebo in People with Type 2 Diabetes and Chronic Kidney Disease [FLOW] study) in a population with type 2 diabetes and chronic kidney disease (CKD) where a composite renal outcome is the primary endpoint (ClinicalTrials.gov Identifier: NCT03819153) [66]. It is also being tested in a group of more advanced kidney disease (stage 4–5 CKD and dialysis dependent end stage kidney disease) (Effect of Subcutaneous Semaglutide on Kidney Transplant Candidacy [RAISE-KT]) (ClinicalTrials.gov Identifier: NCT04741074) [67].

Fatty liver disease

Non-alcoholic fatty liver disease (NAFLD) is associated with visceral obesity and insulin resistance and there is a bidirectional association with type 2 diabetes [68]. The evidence for the potential value of GLP-1RA therapy in NAFLD has accumulated over the past decade and this has been recently reviewed by several authors [69,70]. GLP-1RA therapy has demonstrated improvements in NAFLD as assessed by surrogates such as a reduction in aminotransferase levels [71] and reduction in liver fat content [72]. Randomised controlled trials of liraglutide and semaglutide have now demonstrated benefits on histological endpoints such as resolution of nonalcoholic steatohepatitis and reductions in progression of fibrosis [73,74].

Neurodegenerative diseases

Encouraging results from animal studies have shown that GLP-1RAs improve cognitive performance and synaptic plasticity [75]. This led to pilot studies showing improvements in motor and cognitive function in people with Parkinson's disease [76] and also Alzheimer's disease. The Evaluating the effcts of Liraglutide in Alzheimer's Disease (ELAD) study, a phase 2 double blinded placebo-controlled trial tested the value of liraglutide in people with Alzheimer disease. It showed that liraglutide treated patients performed significantly better than placebo in temporal lobe and whole cortical magnetic resonance imaging volume and cognitive function [77]. Two phase 3 studies (A Research Study Investigating Semaglutide in People With Early Alzheimer's Disease [EVOKE] and A Research Study Investigating Semaglutide in People With Early Alzheimer's Disease [EVOKE] plus) are currently under way, testing the value of oral semaglutide in early Alzheimer's disease (ClinicalTrials.gov Identifier: NCT04777396, NCT04777409) [78,79]. An in-depth review on the pathophysiology, animal studies and clinical trials of the neuroprotective mechanisms of GLP-1RAs was recently published [80].

CONCLUSIONS

The insulinotropic effect of the incretin peptide hormone, GLP1 was described 40 years ago. This led to the development of GLP-1RA therapies which showed clinically impactful improvements from the first twice daily to once weekly injectable and now also as an oral therapy. Comparative effectiveness trials were able to demonstrate improvements with GLP-1RA drug development and the superiority in glycaemic control and weight loss over other glucose lowering drug classes. Subsequently, evidence-based guidelines have recommended their early introduction as well as their use beyond improving glycaemic control for people with type 2 diabetes and high cardiovascular risk. GLP-1RA therapy has already shown tantalizing benefits in several other disease areas, and these are now being rigorously tested in larger clinical trials.

CONFLICTS OF INTEREST

Adie Viljoen has received lecture honoraria and/or, advisory board honoraria and/or, travel support and/or, conducts research

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REFERENCES

1. Bayliss WM, Starling EH. The mechanism of pancreatic secretion. J Physiol 1902;28:325-53.
2. Brown JC, Dryburgh JR. A gastric inhibitory polypeptide. II. The complete amino acid sequence. Can J Biochem 1971;49:867-72.
3. Holst JJ, Orskov C, Nielsen OV, Schwartz TW. Truncated glucagon-like peptide I, an insulin-releasing hormone from the distal gut. FEBS Lett 1987;211:169-74.
4. Mojsov S, Weir GC, Habener JF. Insulinotropin: glucagon-like peptide I (7-37) co-encoded in the glucagon gene is a potent stimulator of insulin release in the perfused rat pancreas. J Clin Invest 1987;79:616-9.
5. Drucker DJ, Philippe J, Mojsov S, Chick WL, Habener JF. Glucagon-like peptide I stimulates insulin gene expression and increases cyclic AMP levels in a rat islet cell line. Proc Natl Acad Sci U S A 1987;84:3434-8.
6. Kreymann B, Williams G, Ghatei MA, Bloom SR. Glucagon-like peptide-1 7-36: a physiological incretin in man. Lancet 1987;2:1300-4.
7. Pederson RA, Satkunarajah M, McIntosh CH, Scrocchi LA, Flamez D, Schuit F, et al. Enhanced glucose-dependent insulinotropic polypeptide secretion and insulinotropic action in glucagon-like peptide 1 receptor -/- mice. Diabetes 1998;47:1046-52.
8. Orskov C, Holst JJ, Nielsen OV. Effect of truncated glucagon-like peptide-1 [proglucagon-(78-107) amide] on endocrine secretion from pig pancreas, antrum, and nonantral stomach. Endocrinology 1988;123:2009-13.
9. Hvidberg A, Nielsen MT, Hilsted J, Orskov C, Holst JJ. Effect of glucagon-like peptide-1 (proglucagon 78-107amide) on hepatic glucose production in healthy man. Metabolism 1994;43:104-8.
10. Wettergren A, Schjoldager B, Mortensen PE, Myhre J, Christiansen J, Holst JJ. Truncated GLP-1 (proglucagon 78-107-amide) inhibits gastric and pancreatic functions in man. Dig Dis Sci 1993;38:665-73.
11. Flint A, Raben A, Astrup A, Holst JJ. Glucagon-like peptide 1 promotes satiety and suppresses energy intake in humans. J Clin Invest 1998;101:515-20.
12. Nauck MA, Kleine N, Orskov C, Holst JJ, Willms B, Creutzfeldt W. Normalization of fasting hyperglycaemia by exogenous glucagon-like peptide 1 (7-36 amide) in type 2 (non-insulin-dependent) diabetic patients. Diabetologia 1993;36:741-4.
13. Ritzel R, Orskov C, Holst JJ, Nauck MA. Pharmacokinetic, insulinotropic, and glucagonostatic properties of GLP-1 [7-36 amide] after subcutaneous injection in healthy volunteers. Dose-response-relationships. Diabetologia 1995;38:720-5.
14. Deacon CF, Nauck MA, Toft-Nielsen M, Pridal L, Willms B, Holst JJ. Both subcutaneously and intravenously administered glucagon-like peptide I are rapidly degraded from the NH2-terminus in type II diabetic patients and in healthy subjects. Diabetes 1995;44:1126-31.
15. Deacon CF, Pridal L, Klarskov L, Olesen M, Holst JJ. Glucagon-like peptide 1 undergoes differential tissue-specific metabolism in the anesthetized pig. Am J Physiol 1996;271 (3 Pt 1):E458-64.
16. Deacon CF, Knudsen LB, Madsen K, Wiberg FC, Jacobsen O, Holst JJ. Dipeptidyl peptidase IV resistant analogues of glucagon-like peptide-1 which have extended metabolic stability and improved biological activity. Diabetologia 1998;41:271-8.
17. Zander M, Madsbad S, Madsen JL, Holst JJ. Effect of 6-week course of glucagon-like peptide 1 on glycaemic control, insulin sensitivity, and beta-cell function in type 2 diabetes: a parallel-group study. Lancet 2002;359:824-30.
18. Eng J, Kleinman WA, Singh L, Singh G, Raufman JP. Isolation and characterization of exendin-4, an exendin-3 analogue, from Heloderma suspectum venom: further evidence for an exendin receptor on dispersed acini from guinea pig pancreas. J Biol Chem 1992;267:7402-5.
19. Buse JB, Rosenstock J, Sesti G, Schmidt WE, Montanya E, Brett JH, et al. Liraglutide once a day versus exenatide twice a day for type 2 diabetes: a 26-week randomised, parallel-group, multinational, open-label trial (LEAD-6). Lancet 2009;374:39-47.
20. Nauck M, Rizzo M, Johnson A, Bosch-Traberg H, Madsen J, Cariou B. Once-daily liraglutide versus lixisenatide as add-on to metformin in type 2 diabetes: a 26-week randomized controlled clinical trial. Diabetes Care 2016;39:1501-9.

21. Hernandez I, Zhang Y. Comparing adoption of breakthrough and "me-too" drugs among medicare beneficiaries: a case study of dipeptidyl peptidase-4 inhibitors. J Pharm Innov 2017;12:105-9.
22. Green AR, Aronson JK, Haddad PM. Examining the 'psychopharmacology revolution' (1950-1980) through the advertising of psychoactive drugs in the British Medical Journal. J Psychopharmacol 2018;32:1056-66.
23. Drucker DJ, Buse JB, Taylor K, Kendall DM, Trautmann M, Zhuang D, et al. Exenatide once weekly versus twice daily for the treatment of type 2 diabetes: a randomised, open-label, non-inferiority study. Lancet 2008;372:1240-50.
24. Buse JB, Nauck M, Forst T, Sheu WH, Shenouda SK, Heilmann CR, et al. Exenatide once weekly versus liraglutide once daily in patients with type 2 diabetes (DURATION-6): a randomised, open-label study. Lancet 2013;381:117-24.
25. Dungan KM, Povedano ST, Forst T, Gonzalez JG, Atisso C, Sealls W, et al. Once-weekly dulaglutide versus once-daily liraglutide in metformin-treated patients with type 2 diabetes (AWARD-6): a randomised, open-label, phase 3, non-inferiority trial. Lancet 2014;384:1349-57.
26. Pratley RE, Nauck MA, Barnett AH, Feinglos MN, Ovalle F, Harman-Boehm I, et al. Once-weekly albiglutide versus once-daily liraglutide in patients with type 2 diabetes inadequately controlled on oral drugs (HARMONY 7): a randomised, open-label, multicentre, non-inferiority phase 3 study. Lancet Diabetes Endocrinol 2014;2:289-97.
27. Lau J, Bloch P, Schaffer L, Pettersson I, Spetzler J, Kofoed J, et al. Discovery of the once-weekly glucagon-like peptide-1 (GLP-1) analogue semaglutide. J Med Chem 2015;58:7370-80.
28. Pratley RE, Aroda VR, Lingvay I, Ludemann J, Andreassen C, Navarria A, et al. Semaglutide versus dulaglutide once weekly in patients with type 2 diabetes (SUSTAIN 7): a randomised, open-label, phase 3b trial. Lancet Diabetes Endocrinol 2018;6:275-86.
29. Ahmann AJ, Capehorn M, Charpentier G, Dotta F, Henkel E, Lingvay I, et al. Efficacy and safety of once-weekly semaglutide versus exenatide er in subjects with type 2 diabetes (SUSTAIN 3): a 56-week, open-label, randomized clinical trial. Diabetes Care 2018;41:258-66.
30. Capehorn MS, Catarig AM, Furberg JK, Janez A, Price HC, Tadayon S, et al. Efficacy and safety of once-weekly semaglutide 1.0mg vs once-daily liraglutide 1.2mg as add-on to 1-3 oral antidiabetic drugs in subjects with type 2 diabetes (SUSTAIN 10). Diabetes Metab 2020;46:100-9.
31. Ahren B, Masmiquel L, Kumar H, Sargin M, Karsbol JD, Jacobsen SH, et al. Efficacy and safety of once-weekly semaglutide versus once-daily sitagliptin as an add-on to metformin, thiazolidinediones, or both, in patients with type 2 diabetes (SUSTAIN 2): a 56-week, double-blind, phase 3a, randomised trial. Lancet Diabetes Endocrinol 2017;5:341-54.
32. Aroda VR, Bain SC, Cariou B, Piletic M, Rose L, Axelsen M, et al. Efficacy and safety of once-weekly semaglutide versus once-daily insulin glargine as add-on to metformin (with or without sulfonylureas) in insulin-naive patients with type 2 diabetes (SUSTAIN 4): a randomised, open-label, parallel-group, multicentre, multinational, phase 3a trial. Lancet Diabetes Endocrinol 2017;5:355-66.
33. Lingvay I, Catarig AM, Frias JP, Kumar H, Lausvig NL, le Roux CW, et al. Efficacy and safety of once-weekly semaglutide versus daily canagliflozin as add-on to metformin in patients with type 2 diabetes (SUSTAIN 8): a double-blind, phase 3b, randomised controlled trial. Lancet Diabetes Endocrinol 2019;7:834-44.
34. Frias JP, Auerbach P, Bajaj HS, Fukushima Y, Lingvay I, Macura S, 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 2021;9:563-74.
35. Davies M, Faerch L, Jeppesen OK, Pakseresht A, Pedersen SD, Perreault L, et al. Semaglutide 2·4 mg once a week in adults with overweight or obesity, and type 2 diabetes (STEP 2): a randomised, double-blind, double-dummy, placebo-controlled, phase 3 trial. Lancet 2021;397:971-84.
36. Frias JP, Bonora E, Nevarez Ruiz L, Li YG, Yu Z, Milicevic Z, et al. Efficacy and safety of dulaglutide 3.0 mg and 4.5 mg versus dulaglutide 1.5 mg in metformin-treated patients with type 2 diabetes in a randomized controlled trial (AWARD-11). Diabetes Care 2021;44:765-73.
37. Buckley ST, Baekdal TA, Vegge A, Maarbjerg SJ, Pyke C, Ahnfelt-Ronne J, et al. Transcellular stomach absorption of a derivatized glucagon-like peptide-1 receptor agonist. Sci Transl Med 2018;10:eaar7047.
38. Pratley R, Amod A, Hoff ST, Kadowaki T, Lingvay I, Nauck M, et al. Oral semaglutide versus subcutaneous liraglutide and placebo in type 2 diabetes (PIONEER 4): a randomised, double-blind, phase 3a trial. Lancet 2019;394:39-50.
39. Rodbard HW, Rosenstock J, Canani LH, Deerochanawong C, Gumprecht J, Lindberg SO, et al. Oral semaglutide versus empagliflozin in patients with type 2 diabetes uncon-

trolled on metformin: the PIONEER 2 Trial. Diabetes Care 2019;42:2272-81.
40. Rosenstock J, Allison D, Birkenfeld AL, Blicher TM, Deenadayalan S, Jacobsen JB, et al. Effect of additional oral semaglutide vs sitagliptin on glycated hemoglobin in adults with type 2 diabetes uncontrolled with metformin alone or with sulfonylurea: the PIONEER 3 Randomized Clinical Trial. JAMA 2019;321:1466-80.
41. Bettge K, Kahle M, Abd El Aziz MS, Meier JJ, Nauck MA. Occurrence of nausea, vomiting and diarrhoea reported as adverse events in clinical trials studying glucagon-like peptide-1 receptor agonists: a systematic analysis of published clinical trials. Diabetes Obes Metab 2017;19:336-47.
42. Nauck MA, Quast DR, Wefers J, Meier JJ. GLP-1 receptor agonists in the treatment of type 2 diabetes: state-of-the-art. Mol Metab 2021;46:101102.
43. Pfeffer MA, Claggett B, Diaz R, Dickstein K, Gerstein HC, Kober LV, et al. Lixisenatide in patients with type 2 diabetes and acute coronary syndrome. N Engl J Med 2015;373:2247-57.
44. Marso SP, Daniels GH, Brown-Frandsen K, Kristensen P, Mann JF, Nauck MA, et al. Liraglutide and cardiovascular outcomes in type 2 diabetes. N Engl J Med 2016;375:311-22.
45. Marso SP, Bain SC, Consoli A, Eliaschewitz FG, Jodar E, Leiter LA, et al. Semaglutide and cardiovascular outcomes in patients with type 2 diabetes. N Engl J Med 2016;375:1834-44.
46. Hernandez AF, Green JB, Janmohamed S, D'Agostino RB Sr, Granger CB, Jones NP, et al. Albiglutide and cardiovascular outcomes in patients with type 2 diabetes and cardiovascular disease (Harmony Outcomes): a double-blind, randomised placebo-controlled trial. Lancet 2018;392:1519-29.
47. Husain M, Birkenfeld AL, Donsmark M, Dungan K, Eliaschewitz FG, Franco DR, et al. Oral semaglutide and cardiovascular outcomes in patients with type 2 diabetes. N Engl J Med 2019;381:841-51.
48. Gerstein HC, Colhoun HM, Dagenais GR, Diaz R, Lakshmanan M, Pais P, et al. Dulaglutide and cardiovascular outcomes in type 2 diabetes (REWIND): a double-blind, randomized placebo-controlled trial. Lancet 2019;394:121-30.
49. Aroda VR, Bauer R, Christiansen E, Haluzik M, Kallenbach K, Montanya E, et al. Efficacy and safety of oral semaglutide by subgroups of patient characteristics in the PIONEER phase 3 programme. Diabetes Obes Metab 2022;24:1338-50.
50. Ahren B, Atkin SL, Charpentier G, Warren ML, Wilding JPH, Birch S, et al. Semaglutide induces weight loss in subjects with type 2 diabetes regardless of baseline BMI or gastrointestinal adverse events in the SUSTAIN 1 to 5 trials. Diabetes Obes Metab 2018;20:2210-19.
51. Lingvay I, Hansen T, Macura S, Marre M, Nauck MA, de la Rosa R, et al. Superior weight loss with once-weekly semaglutide versus other glucagon-like peptide-1 receptor agonists is independent of gastrointestinal adverse events. BMJ Open Diabetes Res Care 2020;8:e001706.
52. Butler PC, Elashoff M, Elashoff R, Gale EA. A critical analysis of the clinical use of incretin-based therapies: are the GLP-1 therapies safe? Diabetes Care 2013;36:2118-25.
53. Abd El Aziz M, Cahyadi O, Meier JJ, Schmidt WE, Nauck MA. Incretin-based glucose-lowering medications and the risk of acute pancreatitis and malignancies: a meta-analysis based on cardiovascular outcomes trials. Diabetes Obes Metab 2020;22:699-704.
54. Nauck MA, Quast DR, Wefers J, Pfeiffer AF. The evolving story of incretins (GIP and GLP-1) in metabolic and cardiovascular disease: a pathophysiological update. Diabetes Obes Metab 2021;23 Suppl 3:5-29.
55. Holst JJ, Jepsen SL, Modvig I. GLP-1: incretin and pleiotropic hormone with pharmacotherapy potential: increasing secretion of endogenous GLP-1 for diabetes and obesity therapy. Curr Opin Pharmacol 2022;63:102189.
56. Pedrosa MR, Franco DR, Gieremek HW, Vidal CM, Bronzeri F, de Cassia Rocha A, et al. GLP-1 agonist to treat obesity and prevent cardiovascular disease: what have we achieved so far? Curr Atheroscler Rep 2022;24:867-84.
57. Taha MB, Yahya T, Satish P, Laird R, Agatston AS, Cainzos-Achirica M, et al. Glucagon-like peptide 1 receptor agonists: a medication for obesity management. Curr Atheroscler Rep 2022;24:643-54.
58. Drucker DJ. GLP-1 physiology informs the pharmacotherapy of obesity. Mol Metab 2022;57:101351.
59. Davies MJ, Aroda VR, Collins BS, Gabbay RA, Green J, Maruthur NM, et al. Management of hyperglycemia in type 2 diabetes, 2022: a consensus report by the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD). Diabetes Care 2022;45:2753-86.
60. Sattar N, Lee MM, Kristensen SL, Branch KR, Del Prato S, Khurmi NS, et al. Cardiovascular, mortality, and kidney outcomes with GLP-1 receptor agonists in patients with type 2 diabetes: a systematic review and meta-analysis of randomised trials. Lancet Diabetes Endocrinol 2021;9:653-62.
61. Berndt J, Ooi SL, Pak SC. What is the mechanism driving

the reduction of cardiovascular events from glucagon-like peptide-1 receptor agonists?: a mini review. Molecules 2021;26:4822.
62. ClinicalTrials.gov. Semaglutide Effects on Heart Disease and Stroke in Patients With Overweight or Obesity (SELECT) [Internet]. Bethesda; U.S. National Library of Medicine; 2022 [cited 2022 Dec 29]. Available from: https://clinicaltrials.gov/ct2/show/NCT03574597.
63. Kristensen SL, Rorth R, Jhund PS, Docherty KF, Sattar N, Preiss D, et al. Cardiovascular, mortality, and kidney outcomes with GLP-1 receptor agonists in patients with type 2 diabetes: a systematic review and meta-analysis of cardiovascular outcome trials. Lancet Diabetes Endocrinol 2019;7:776-85.
64. van Baar MJ, van der Aart AB, Hoogenberg K, Joles JA, Heerspink HJL, van Raalte DH. The incretin pathway as a therapeutic target in diabetic kidney disease: a clinical focus on GLP-1 receptor agonists. Ther Adv Endocrinol Metab 2019;10:2042018819865398.
65. Williams DM, Nawaz A, Evans M. Renal outcomes in type 2 diabetes: a review of cardiovascular and renal outcome trials. Diabetes Ther 2020;11:369-86.
66. ClinicalTrials.gov. A Research Study to See How Semaglutide Works Compared to Placebo in People with Type 2 Diabetes and Chronic Kidney Disease (FLOW) [Internet]. Bethesda: U.S. National Library of Medicine; 2022 [cited 2022 Dec 29]. Available from: https://clinicaltrials.gov/ct2/show/NCT03819153.
67. ClinicalTrials.gov. Effect of Subcutaneous Semaglutide on Kidney Transplant Candidacy (RAISE-KT) [Internet]. Bethesda: U.S. National Library of Medicine; 2022 [cited 2022 Dec 29]. Available from: https://clinicaltrials.gov/ct2/show/NCT04741074.
68. Cariou B. The metabolic triad of non-alcoholic fatty liver disease, visceral adiposity and type 2 diabetes: implications for treatment. Diabetes Obes Metab 2022;24 Suppl 2:15-27.
69. Yabut JM, Drucker DJ. Glucagon-like peptide-1 receptor-based therapeutics for metabolic liver disease. Endocr Rev 2023;44:14-32.
70. Patel Chavez C, Cusi K, Kadiyala S. The emerging role of glucagon-like peptide-1 receptor agonists for the management of NAFLD. J Clin Endocrinol Metab 2022;107:29-38.
71. Cusi K, Sattar N, Garcia-Perez LE, Pavo I, Yu M, Robertson KE, et al. Dulaglutide decreases plasma aminotransferases in people with type 2 diabetes in a pattern consistent with liver fat reduction: a post hoc analysis of the AWARD programme. Diabet Med 2018;35:1434-9.
72. Petit JM, Cercueil JP, Loffroy R, Denimal D, Bouillet B, Fourmont C, et al. Effect of liraglutide therapy on liver fat content in patients with inadequately controlled type 2 diabetes: the Lira-NAFLD Study. J Clin Endocrinol Metab 2017;102:407-15.
73. Armstrong MJ, Gaunt P, Aithal GP, Barton D, Hull D, Parker R, et al. Liraglutide safety and efficacy in patients with non-alcoholic steatohepatitis (LEAN): a multicentre, double-blind, randomised, placebo-controlled phase 2 study. Lancet 2016;387:679-90.
74. Newsome PN, Buchholtz K, Cusi K, Linder M, Okanoue T, Ratziu V, et al. A placebo-controlled trial of subcutaneous semaglutide in nonalcoholic steatohepatitis. N Engl J Med 2021;384:1113-24.
75. Muscogiuri G, DeFronzo RA, Gastaldelli A, Holst JJ. Glucagon-like peptide-1 and the central/peripheral nervous system: crosstalk in diabetes. Trends Endocrinol Metab 2017;28:88-103.
76. Aviles-Olmos I, Dickson J, Kefalopoulou Z, Djamshidian A, Ell P, Soderlund T, et al. Exenatide and the treatment of patients with Parkinson's disease. J Clin Invest 2013;123:2730-6.
77. Edison P, Femminella GD, Ritchie CW, Holmes C, Walker Z, Ridha BH, et al. Evaluation of liraglutide in the treatment of Alzheimer's disease. Alzheimers Dement 2021;17:e057848.
78. ClinicalTrials.gov. A Research Study Investigating Semaglutide in People With Early Alzheimer's Disease (EVOKE) [Internet]. Bethesda: U.S. National Library of Medicine; 2022 [cited 2022 Dec 29]. Available from: https://clinicaltrials.gov/ct2/show/NCT04777396?cond=EVOKE&draw=2&rank=1.
79. ClinicalTrials.gov. A Research Study Investigating Semaglutide in People With Early Alzheimer's Disease (EVOKE Plus) [Internet]. Bethesda: U.S. National Library of Medicine; 2022 [cited 2022 Dec 29]. Available from: https://clinicaltrials.gov/ct2/show/NCT04777409?cond=EVOKE&draw=2&rank=2.
80. Reich N, Holscher C. The neuroprotective effects of glucagon-like peptide 1 in Alzheimer's and Parkinson's disease: an in-depth review. Front Neurosci 2022;16:970925.