Mini-Review

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Gaining Ground Gradually Over 25 Years: GLP-1 Receptor Development as a Successful Weight Loss Target.

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ABSTRACT

Glucagon-like peptide 1 (GLP-1) receptor agonists are effective and safe weight-loss medications, according to recent data from clinical trials. GLP-1 receptor agonists were initially created as medications to lower blood sugar levels in individuals with type 2 diabetes, but advancements in research over the past three decades have shown that they also function by acting on the central nervous system to decrease appetite. The main points of GLP-1 biology and the clinical research demonstrating the GLP-1 receptor signaling system's potential as a weight loss treatment target are outlined in this minireview.

Keywords : obesity, glucagon-like peptide 1, GLP-1 receptor agonists, weight loss

INTRODUCTION

Abbreviations

CNS, central nervous system; fMRI, functional magnetic resonance imaging; GI, gastrointestinal; GLP-1, glucagon-like peptide-1; GLP-1R, glucagonlike peptide-1 receptor; GLP-1RA, glucagon-like peptide 1 receptor agonist; HbA1c, glycated hemoglobin A1c; PBO, placebo; T2DM, type 2 diabetes mellitus.

The seemingly unstoppable increase in obesity rates is a global issue and one of the most significant public health challenges of the twenty-first century. Millions of people's quality and quantity of life are impacted by a variety of comorbidities that are associated with obesity and overweight. Patients often bring weight gain and requests for assistance with weight loss to endocrinologists, and these conversations can often be challenging due to the dearth of effective weight-loss choices.Although food and lifestyle modifications can be helpful, success is elusive and the range of suggested tactics clearly benefits a small percentage of the population.

Bariatric surgery offers a striking illustration of the health advantages of weight loss and has gotten more sophisticated, safe, and successful over time. Nevertheless, given the scope of the obesity epidemic and its now global reach, surgery is invasive, frequently associated with high short-term costs, and not scalable. Up until recently, most legally prescribed medications for weight loss only produced temporary weight loss and showed minimal signs of long-term effects.

The identification and characterization of the glucagon-like peptide 1 (GLP-1) system, which has a physiological function in glucose homeostasis, have occurred within the past few decades. The creation of medications that stimulate the GLP-1 receptor (GLP-1R) has significantly improved the treatment of diabetes. This work's accidental byproduct was the proof that GLP-1 lowers appetite and promotes weight loss. Now, a number of strong clinical studies demonstrate the effectiveness of GLP-1R agonists (GLP-1RA) in the specific treatment of obesity, with effects noticeably stronger than with prior medications and the potential to produce clinically relevant weight reduction for the majority of people receiving treatment. This brief evaluation concentrates on this novel GLP-1RA application.

The Scientific Justification for Focusing on the GLP-1 System in Order to Reduce Weight

The most concrete prospect for targeted weight reduction treatment was presented by the mid-1990s discovery of leptin and its receptor, which united the domains of metabolism and brain. These fascinating findings sparked a surge of investigation that quickly defined the critical central nervous system (CNS) circuits regulating energy balance and nutritional homeostasis. They also offered a tractable point of entry to link systemic metabolism with brain regulation. Reports detailing the effects of glucagon-like peptide 1 (GLP-1), a then rather esoteric peptide produced in the colon, to reduce feeding when injected into the CNS of rodents were almost lost in the flurry of activity surrounding leptin (1). Considering

the past thirty years, it is impossible to dispute the scientific significance of leptin as a physiological mediator and as the driving force behind a revolution in neuroscience.

However, despite early preclinical research' seeming predictions, leptin never materialized as the miracle drug for weight loss. Instead, the GLP-1 system—which was at first less interesting and instructive for CNS function—turned out to produce medications that may have a significant impact on body weight and the clinical correlates of obesity.

The pancreatic islet, the central and peripheral nerve systems, and the gastrointestinal tract are the main elements of the GLP-1 system (2). The preproglucagon gene is only expressed by a tiny subset of hindbrain neurons, certain intestinal mucosal enteroendocrine L-cells, and and the pancreatic islet's α-cells; in each of these cell types, GLP-1 is cleaved from proglucagon. Although the GLP-1 receptor (GLP-1R) is distributed more widely, the vagal afferent neurons and the neurons in the hypothalamus and hindbrain are the main locus for controlling food intake (3). A concept that proposes that GLP-1 produced in the gut promotes satiety through vagal nerve transmission is supported by recent preclinical research (4) and that activation of hindbrain neurons has a parallel, independent effect to limit food intake (5). Nevertheless, deletion of the GLP-1R did not result in obesity in mice, in contrast to the leptin receptor (6, 7), indicating that this system may not be necessary for the control of body weight in a normal manner. Furthermore, despite the fact that the human GLP-1R gene contains a large number of sequence variations, none of them have been conclusively connected to phenotypes related to body weight (8).

Although the broad consensus still holds that GLP-1 produced from the GI tract promotes insulin production via an endocrine mechanism, little is known about how the endogenous peptide affects feeding. GLP-1 from either endogenous or exogenous sources circulates in the brain in a pattern congruent with satiety, according to experimental data from human investigations utilizing functional magnetic resonance imaging (fMRI) (9, 10).Similar research indicates that individuals who have had bariatric surgery may have increased plasma GLP-1 effects on the central nervous system (11). Therefore, it can be argued that GLP-1 is an endocrine component of physiological satiety in humans, even though further research is needed for confirmation and a fuller knowledge of the mechanisms involved.

Pharmacologic agonists of the GLP-1R consistently lower food intake and body weight in preclinical and human investigations, despite preclinical data suggesting that the physiological role of GLP-1 in the control of satiety is auxiliary rather than fundamental. Exendin-4, the first GLP-1 analogue to be produced as a medication, was administered to research subjects, and after a while they regularly reported decreased hunger, a reduction in the amount of food they consumed, and weight loss. Trials using other GLP-1RA reported similar results, with continuous weight loss shown in participants receiving dulaglutide, albiglutide, liraglutide, and exenatide treatments. These pharmaceuticals have substantially greater blood levels than endogenous GLP-1, and it's likely that the central nervous system has a direct role in mediating their effects.Preclinical research indicates that GLP-1RAs not only activate neurons in circumventricular organs that are accessible to circulation, like the hindbrain's region postrema and the midbrain's median eminence, but also make their way to important hypothalamic regions that control eating (12). Exendin-4 alters certain brain activity on fMRI pictures in patterns suggestive of satiety, similar to studies with natural GLP-1 (13), and same results have been reported with other GLP-1RA. When considered collectively, there is compelling evidence that pharmaceutical GLP-1RAs directly decrease appetite and food intake by acting on the brain.

The majority of clinical research on GLP-1RAs has focused on improving and developing this class of drugs for the management of type 2 diabetes (14). But the consistent ability to lower body weight in diabetics participating in clinical trials, along with experimental proof of mechanistic plausibility, provided strong support to move this class of medications forward into studies that expressly aim to reduce body weight in non-diabetic participants.

The outcomes of these trials during the previous few years have been revealed, bringing fresh hope to individuals trying to lower their weight and the negative health effects of obesity.

GLP-1RA Proof-of-Concept Clinical Trials for Non-Diabetic Human Weight Loss : The Food and Drug Administration approved exenatide, the brand-name equivalent of exendin-4, in 2005 for the management of type 2 diabetes. It was used off-label for weight loss very immediately, frequently with unproven dosage schedules, in both diabetics and non-diabetics. Formal research on GLP-1RAs for weight loss, however, was not released until 2009 (15, 16). Using orlistat or an injectable placebo as comparators, a sample of about 600 volunteers with body mass index (BMI) between 30 and 40 and nondiabetic glucose metabolism were randomly assigned to increasing doses of liraglutide in the first report.The two liraglutide dosages (2.4 and 3.0 mg) that were employed in this experiment were higher than the dosages that were previously approved for the treatment of diabetes. The participants treated with ligandilide saw a dose-dependent weight loss throughout the duration of 20 weeks of active treatment, which was higher than that of either control group. Furthermore, rates of nausea were dose-dependent but steadily decreased over the first 10 weeks of treatment. Moreover, the GI symptoms that are the hallmark side effects of GLP-1RA—vomiting, diarrhea,

and nausea—were generally well tolerated and comparable in amount and degree to what was observed in trials of these drugs for the treatment of diabetes.In a follow-up research, 163 patients without diabetes and a mean BMI of less than 40 were randomized to receive either placebo or entreatide (PBO) as part of a 24-week structured lifestyle intervention. In this trial, the standard dose of exenatide resulted in a loss of 5.1 kg from baseline compared to 1.6 kg with PBO. This difference was statistically significant and lasted for one month after the medication was stopped. Notably, the amount of weight lost by participants with diabetes in exenatide trials of glucose reduction was at the higher end of the range for weight loss in this very small study. These two proof-of-concept trials with exenatide and ligarglutide paved the way for larger trials that might yield a more accurate assessment of clinical efficacy.

The Satiety and Clinical Adiposity-Liraglutide Evidence trials, SCALE Obesity and Prediabetes (17) and SCALE Diabetes (18), were the first extensive, long-term studies of a GLP-1RA for weight loss. The multicenter Obesity and Prediabetes trial examined the effectiveness of 3.0 mg of ligarglutide in individuals without diabetes who had a mean body mass index (BMI) of 38.Patients randomly assigned to the liraglutide group dropped 2.8 kg of body weight after 56 weeks, while those in the PBO group lost an average of 8.4 kg.Ninety-two percent of the patients in the liraglutide group had weight loss, with three times as many of them losing more than five percent or ten percent of their initial body weight as those receiving a placebo. 3.0 mg of liraglutide resulted in 6.4 kg of weight reduction compared to 2.2 kg with placebo in the SCALE Diabetes study, which enrolled participants with type 2 diabetes mellitus (T2DM). Additionally, 54% and 25% of participants lost 5% and 10% of their initial body weight, respectively.Similar to liraglutide trials for glucose reduction, the majority of adverse events in both trials were gastrointestinal (GI).

Research Studies Using Semaglutide

The most recent GLP-1RA to be approved and enter clinical use in the US was semaglutide in 2017. Comparable to the file downloaded by guest on July 10, 2024, 2150 from https://academic.oup.com/jcem/article/107/8/2148/6583309 Volume 107, Issue 8 of The Journal of Clinical Endocrinology & Metabolism, 2022 The fatty acyl side chain of liraglutide and semaglutide encourages binding to albumin, increasing the drug's duration in the bloodstream (19). The two medications' pharmacokinetics, however, are different enough that semaglutide, which is administered once weekly, has a significantly longer plasma half-life.Indeed, semaglutide has been shown to be more effective than liraglutide or dulaglutide in reducing glycated hemoglobin (HbA1c) and body weight in clinical trials for glycemic management (20, 21). As a result, semaglutide was quickly introduced into studies looking at weight loss in participants without diabetes. The first of these studies compared semaglutide and liraglutide 3.0 mg given numerous times a day to individuals with BMIs more than 30 kg/m2. (22).Over the course of the 52-week trial, semaglutide doses ranging from 0.05 to 0.4 mg per day resulted in placebo-adjusted weight reduction ranging from 3.7% to 11.5%; all but the lowest dose had higher effects than liraglutide (5.5%).

Adverse effects resembled those reported in the several other GLP-1RA studies

The phase 3 randomized clinical trials of semaglutide for weight loss, specifically aimed at individuals with BMI > 30, include the STEP (Semaglutide Treatment Effect in People with Obesity) program. This program consists of 8 investigations using subcutaneous semaglutide administered over a 68-week period, each with a different subject group or treatment plan. With the exception of STEP 3, all trials had a similar lifestyle component that involved 500 kcal per day of reduced calories and 150 minutes of physical activity per week. The studies, with the exception of STEP 2, were centered on helping adults without diabetes lose weight; STEP 2 enrolled people with type 2 diabetes and a BMI greater than 27.These studies' primary outcomes were typical weight loss trial outcome metrics, such as the percentage of initial body weight dropped in comparison to the placebo and the percentage of participants who lost 5% or 10% or more of their body weight.All told, more than 3700 nondiabetic subjects were enrolled in the STEP trials that have been published so far (trial numbers 1, 3, 4, and 8). Of these, over 75% were women and a comparable proportion were Caucasian, with a mean age of 46 and a starting body weight of about 105 kg.

Over 1900 participants were enrolled in STEP 1 and assigned in a 2:1 ratio to either PBO or semaglutide 2.4 mg weekly (23). Although persons with a diabetes diagnosis were not eligible to enroll, 43% of STEP 1 participants had prediabetes, and over 75% had at least one comorbidity. With a mean change in body weight of 14.9% compared to 2.4% in the PBO group, weight loss with semaglutide was higher than in the SCALE trials. Compared to 31% in the PBO group, more than 80% in the semaglutide group lost at least 5% of their body weight; 70% of them also lost at least 10% of their body weight, and 30% lost at least 20% of their body weight.Semaglutide was associated with a higher frequency of gastrointestinal adverse effects than PBO; however, the majority of these problems were temporary and did not result in the regimen being permanently stopped or study withdrawal being necessary. 2.6% of semaglutide recipients and 1.2% of PBO individuals experienced cholelithiasis; three semaglutide recipients experienced mild acute pancreatitis, two of which were linked

to gallstones; all of them recovered over the trial duration. With a mean PBO-corrected percentage weight loss that was almost double that of other medications in this class, semaglutide appeared to be the most effective GLP-1RA for weight loss based on these findings.The direct within-trial comparison of semaglutide and liraglutide in STEP 8 provided the basis for this conclusion. The mean weight reduction was 6.5% and 15%, respectively (24).Moreover, STEP 1 provided the first indication that a medical intervention potentially result in a body weight loss of more than 10% for the majority of those receiving treatment.

During 68 weeks, a 1:1:1 randomization of almost 1500 T2DM individuals was conducted to determine whether they would get weekly injections of semaglutide 2.4 mg, semaglutide 1.0 mg, or PBO in STEP 2. The mean body weight decreases across the three treatment arms were estimated to be significant, ranging from −9.6% with 2.4 mg and −7% with 1.0 mg of semaglutide to −3.4% with PBO. Additionally, the side effect profile in this cohort was similar to that observed with semaglutide in STEP 1.Notably, semaglutide at the larger dose reduced body weight by about 2.5% while maintaining a similar glycemic drop.Furthermore, the results of the SCALE trials, which showed that the diabetes cohort lost 5.4% and the non-diabetes group lost 8% with liraglutide treatment, are in line with the lower mean reduction in body weight in individuals with diabetes compared to subjects without diabetes studied in STEP 1 (roughly 10% vs. 15%) (18, 25). In contrast to the studies of non-diabetic participants, the cohorts in both trials with T2DM subjects were older, had a higher proportion of males, and used different medications. Nevertheless, this trend in the size of the effect of GLP-1RA on body weight seems consistent, and it is worthwhile to examine further.

As an adjuvant to intense behavioral therapy combined with a planned diet, STEP 3 randomly assigned 611 nondiabetic patients to receive either semaglutide 2.4 mg or PBO (26). During the first eight weeks of the trial, each participant received a low-calorie meal replacement diet; during the full 68-week program, they received intense behavioral treatment. A weekly physical activity requirement of 100 minutes was also given to the participants; this could be increased by 25 minutes every four weeks to a maximum of 200 minutes. At week 68, there was a 10.3% difference in the estimated mean body weight change between semaglutide and PBO, with −16.0% and −5.7%, respectively. Much like in previous STEP studies, 75.3% of patients who received semaglutide lost at least 10% of their body weight. The severity of the lifestyle intervention is attested to by the comparatively high rate of weight loss in the PBO group, with 27.0% of participants losing at least 10% of their starting body weight. The 16% body weight change observed with semaglutide in STEP 3 does not, however, significantly deviate from the outcomes shown with semaglutide in STEP 1, raising the question of how much rigorous lifestyle modification contributes to a strong medication effect.

The purpose of STEP 4 was to evaluate the impact of semaglutide discontinuation following a period of weight reduction therapy in order to determine how it might affect weight maintenance (27). 803 participants in all took 2.4 mg of semaglutide for 20 weeks, during which time they lost about 10% of their initial body weight. Of these, 286 received a weekly PBO for the next 48 weeks, while 535 were subsequently randomly assigned to continue taking semaglutide. Subjects saw changes in lipid profiles linked to weight loss, as well as decreases in blood pressure, HbA1c, waist circumference, BMI, and blood pressure over the 20-week run-in. Following randomization, the semaglutide cohort experienced a further reduction in mean weight of −7.9%, but those who were switched on PBO gained back more than half of the weight they had lost initially.Improved comorbidities related to fat, like blood pressure, also reversed in the cessation group. The continuously treated cohort in STEP 4 had the highest weight loss in the STEP program, with a mean 68-week loss of more than 17% and 40% of treated participants losing more than 20% of their starting body weight. The trial's findings, however, suggest that semaglutide's positive benefits on body weight may need to be maintained over time.

All things considered, the STEP trials offer the clearest illustration of the possibility for medicinal weight loss to yet. Semaglutide outperformed other currently available treatments in terms of weight loss and improved clinically useful obesity correlates like blood pressure, lipid profiles, and glycemia. Over the course of the 68-week studies, semaglutide's effects on weight loss did not diminish, and lengthier trials would be required to ascertain the best course of action.Although experience with other weight reduction interventions suggests that this would be the case, STEP 4 does not make it obvious if patients having a shorter term of therapy would eventually return to their starting body weight. Table 1 lists the completed and continuing STEP studies in summary form. When weight loss is adjusted for exposure to circulating medication, an oral form of semaglutide that has been well examined in individuals with type 2 diabetes has shown weight reduction that is equivalent to the injectable form (28).

GLP-1RA and Weight Reduction in Certain Populations

One of the biggest health care issues in pediatrics is obesity in children and adolescents. Dietary and other lifestyle changes haven't had much of an impact when compared to the constant environmental factors that encourage young

people to maintain a healthy energy balance. A recent study compared the effects of liraglutide and PBO over a 56-week period on 250 adolescents with BMIs greater than 30 (29). There was a considerable reduction in body weight with active treatment, ~ 6% placebo-corrected, even though only 80% of the group receiving liraglutide were able to titrate to the maximal dose of 3 mg.In comparison to the 19% of PBO controls, around 40% of the participants in the liraglutide group lost more than 5% of their initial BMI. These findings imply that young persons react to GLP-1RAs similarly and are consistent with the findings of adult liraglutide studies. The public health is expected to be disproportionately affected by the effective treatment of obesity in young individuals because of their increased exposure to the negative health effects of being overweight.

Although bariatric surgery can help people with T2DM and/or obesity in terms of a number of metabolic markers, less than half of treated patients achieve diabetic regression or a BMI of less than 30 over a five-year period (30). Furthermore, following bypass surgery, 21% to 43% of patients who do experience a remission of type 2 diabetes recur within 3 to 9 years (31). GLP-1RA therapy has been evaluated in patients undergoing sleeve gastrectomy or gastric bypass surgery in order to address the demands of these individuals.Eighty patients with recurrent diabetes and a history of bariatric surgery were randomized to receive either liraglutide 1.8 mg or PBO for a duration of 26 weeks in the GRAVITAS trial (32). When compared to PBO, liraglutide treatment resulted in a 1.22% decrease in HbA1c.

Furthermore, liraglutide-treated participants shed almost 5 kg more weight than the control group (32). These results are somewhat unexpected because endogenous GLP-1 levels are 10–20 times higher in bariatric surgery patients than in healthy individuals. Actually, a frequent theory explaining the metabolic benefit of sleeve gastrectomy and gastric bypass is enhanced signaling via the GLP-1R system. Nonetheless, clinical reactions to GLP-1RA are correlated with drug exposure, and plasma concentrations of GLP-1RAs are at least 100 times higher than circulating levels of native GLP-1 (28). Furthermore, the increased GLP-1 concentrations following bariatric surgery are very temporary and only happen after meals; long-acting GLP-1RAs result in the GLP-1R being continuously stimulated.

Consequences, Open-ended Questions, and Prospects for the Future

The majority of the STEP studies have been completed, which has implications for the physiology, pharmacology, and therapeutic usefulness of GLP-1RAs as well as for their potential as a weight management tool. The GLP-1R signaling pathway seems to have a significant amount of excess capacity from a physiological perspective. Endogenous GLP-1 concentrations seem to operate at the very bottom of an exposure-response curve for which the maximum weight loss threshold has not yet been established.This suggests that further development of GLP-1RAs, especially those that might lessen the typical GI side effects, may enable even higher efficacy and more dose escalation. Pharmacologically speaking, using GLP-1RA to promote weight loss is currently the most popular kind of therapeutic CNS-endocrinology. The main target of this pharmacologic ligand is the brain. It appears likely that pharmacokinetics plays a role in these medications' ability to cause weight reduction, with longer, more consistent exposures producing stronger benefits. Nonetheless, considering the comparable molecular sizes, receptor-binding moieties, and circulatory concentrations of both medications, it is puzzling that liraglutide is not as potent as semaglutide (28, 33). Incretin-based medicines such as GLP-1RAs should be developed further by determining if minute structural variations impact interaction with the GLP-1R or access to important brain locations.

Clinically speaking, patients and their doctors can now look forward to something positive thanks to the introduction of GLP-1RA for weight loss and the significant improvements seen in the STEP studies. With an average weight loss of 10% to 20% over the course of two years, the effects of semaglutide treatment represent a major advancement in the field of pharmacological therapy for obesity. It is crucial to assess the efficacy of semaglutide and comparable treatments within the larger context of clinical practice, as the results of clinical studies typically indicate the medications' ideal performance. Furthermore, the majority of the participants in the STEP program were female and white, and it is yet unclear how the findings will apply to a more diverse population. It's critical to understand what longer treatment periods may entail, given the sustained weight loss from 68 to 104 weeks seen in STEP 4. Other GLP-1RAs that are used for longer than a year are associated with some degree of weight gain, and patients who have had bariatric surgery also tend to exhibit this propensity. Last but not least, the high cost of all GLP-1RAs will prevent them from being widely accessible in the foreseeable future; nonadherence to this class of medication has been linked to cost (34).In this sense, a better distribution of health care resources will be made possible by an understanding of the fixed and adjustable patient traits and behaviors that determine efficacy.

The efficacy of GLP-1R antagonism for weight loss is demonstrated by the STEP trials, in addition to the direct therapeutic advantages of semaglutide. This has given pharmaceutical research, which was already thriving, further momentum. It's possible to create formulations with even

longer half-lives that increase convenience and adherence. Moreover, changes in ligand-receptor interactions may influence downstream signaling and the relative contribution to toxicity balance, according to new studies on the structure and function of GLP-1R and other G-protein coupled receptors. Additionally, combined therapy is being developed.Compared to 2.4 mg of semaglutide alone, co-injection of an amylin agonist with semaglutide resulted in 17% more weight reduction during a 20-week period (35). Furthermore, developments in peptide chemistry have produced multireceptor agonists with potentially increased metabolic impact potency. For instance, the effects of tirzepatide, a dual GLP-1R/glucosedependent insulinotropic polypeptide (GIP) receptor agonist, on weight reduction have been shown to be approximately twice as great as those of semaglutide at 1.0 mg (36).Additional tri-agonists that signal through GLP-1R/GIPR/GcgR or other dual agonists that activate the GLP-1R and glucagon receptor (GcgR) have showed promise in preclinical trials and are being studied in humans. These intriguing findings imply that using the GLP-1R's activity may only be the start of a significant, long-lasting, and scalable advancement in the treatment of obesity. Therefore, the STEP program might only be the beginning.

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