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How Do GLP-IRA Medications Affect Gut and Brain Hunger Signaling to Allow for Reduction in Weight and Better Glycemic Control in Adults with Obesity and Type 2 Diabetes?

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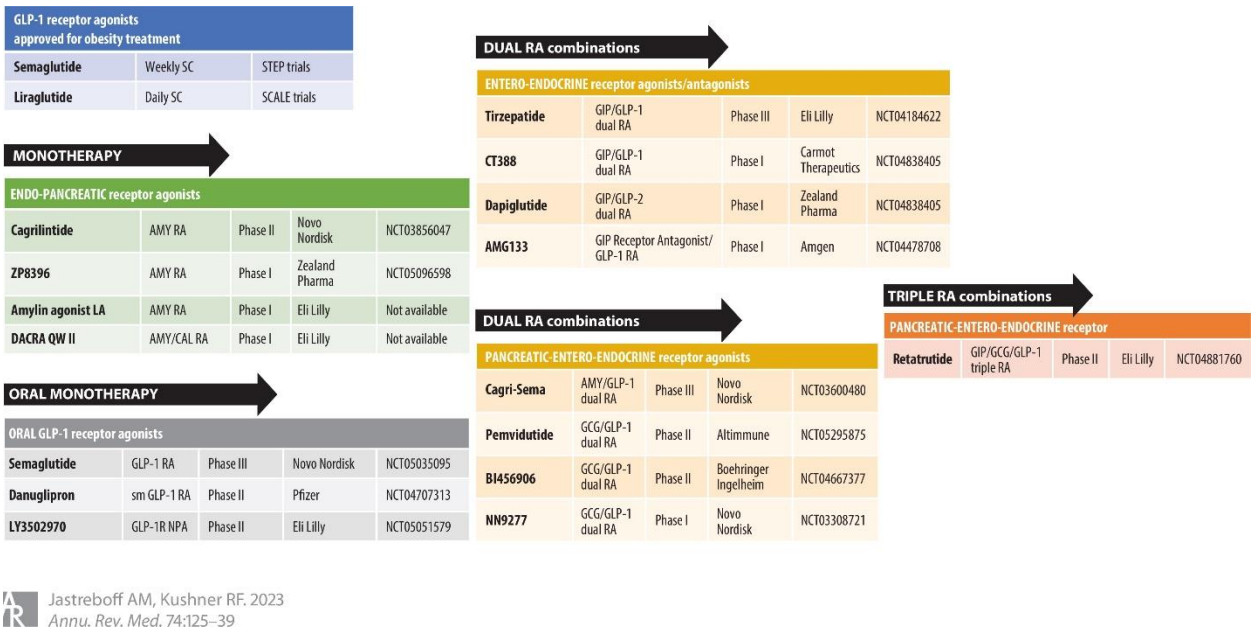
Introduction

Obesity and Type 2 Diabetes Mellitus (T2DM) are two of the most common medical diseases affecting adults in the United States. Recently, advances in medical science have found that glucagon-like peptide one receptor agonists (GLP-1RA) are effective in both day-to-day glycemic control, long-term reduction of hemoglobin A1c (Hgb A1c) and can cause beneficial weight loss in patients with Type 2 diabetes (T2DM) and obesity.

Currently, two of the most prescribed drugs in this class are semaglutide (Ozempic/Wegovy) and tirzepatide (Mounjaro). Both require only once weekly subcutaneous injection, can help with glycemic control, and tend to cause significant weight loss (Frias, 2021). In addition, according to Jastreboff & Kushner (2023), *fourteen* new drugs in this class are being developed that offer even more potential patient benefits. Ten of these drugs have GLP-1 RA as the sole target incretin, while nine target GLP-1 and other incretin hormones, so-called dual or triple agonist peptides. Three oral GLP-1 RA's are being tested, eliminating the need for injections, which can deter patients who do not wish to inject themselves with medication. Phase 3 trials of these oral medications are ongoing; results are expected by the end of 2024. The final four are in early phase 1 development and target amylin and calcitonin receptors. This graphic from Jastreboff & Kushner (2023) is by no means exhaustive, and there are numerous other drugs in development targeting various incretins and other hormone sites:



GLP-1 receptor agonists approved for obesity treatment		
Semaglutide	Weekly SC	STEP trials
Liraglutide	Daily SC	SCALE trials

MONOTHERAPY

ENDO-PANCREATIC receptor agonists				
Cagrilintide	AMY RA	Phase II	Novo Nordisk	NCT03856047
ZP8396	AMY RA	Phase I	Zealand Pharma	NCT05096598
Amylin agonist LA	AMY RA	Phase I	Eli Lilly	Not available
DACRA QW II	AMY/CAL RA	Phase I	Eli Lilly	Not available

ORAL MONOTHERAPY

ORAL GLP-1 receptor agonists				
Semaglutide	GLP-1 RA	Phase III	Novo Nordisk	NCT05035095
Danuglipron	sm GLP-1 RA	Phase II	Pfizer	NCT04707313
LY3502970	GLP-1R NPA	Phase II	Eli Lilly	NCT05051579

DUAL RA combinations

ENTERO-ENDOCRINE receptor agonists/antagonists				
Tirzepatide	GIP/GLP-1 dual RA	Phase III	Eli Lilly	NCT04184622
CT388	GIP/GLP-1 dual RA	Phase I	Carmot Therapeutics	NCT04838405
Dapiglutide	GIP/GLP-2 dual RA	Phase I	Zealand Pharma	NCT04838405
AMG133	GIP Receptor Antagonist/ GLP-1 RA	Phase I	Amgen	NCT04478708

DUAL RA combinations

PANCREATIC-ENTERO-ENDOCRINE receptor agonists				
Cagri-Sema	AMY/GLP-1 dual RA	Phase III	Novo Nordisk	NCT03600480
Pemvidutide	GCG/GLP-1 dual RA	Phase II	Altimmune	NCT05295875
BI456906	GCG/GLP-1 dual RA	Phase II	Boehringer Ingelheim	NCT04667377
NN9277	GCG/GLP-1 dual RA	Phase I	Novo Nordisk	NCT03308721

TRIPLE RA combinations

PANCREATIC-ENTERO-ENDOCRINE receptor				
Retatrutide	GIP/GCG/GLP-1 triple RA	Phase II	Eli Lilly	NCT04881760

Jastreboff AM, Kushner RF. 2023
Annu. Rev. Med. 74:125–39

One injectable triple agonist drug in clinical trials, retatrutide, has been shown in Phase 2 trials to cause patients to lose 24% of their body mass, averaging approximately 58 pounds of weight loss in participants. The drug, on average, reduced systolic blood pressure by 8mmHg, decreased triglyceride levels by 40%, lowered LDL cholesterol by 22%, and eliminated non-alcoholic fatty liver deposits, currently a disease with no treatment or cure in 70% of the patients (Jastreboff, 2023). Retatrutide is now in phase 3 trials with potential indications for T2DM, obesity, cardiovascular disease, obstructive sleep apnea, and osteoarthritis.

While these results are exciting for the future, it begs the question. How do these drugs work? The easy explanation is that these drugs slow gastric emptying and make patients feel full quicker. However, that does not answer how these drugs affect the brain and gut's hunger signaling and reward centers and lead to further cardiometabolic improvements. This paper seeks the answer to that question to empower current and future nurse practitioners, as these medications will only grow in popularity as the benefits become ever more apparent and patient demand increases.

Problem Overview

According to the Center for Disease Control National Diabetes Statistics Report (2020), 34 million adults in the United States, representing approximately 13% of all adults, had diabetes. Obesity is intrinsically intertwined with these diabetic patients, as 61% of all people with diabetes have obesity, defined as a body mass index >30 kg/m^2. In addition, high rates of physical inactivity, hypertension, high cholesterol, and elevated triglycerides were observed in this CDC report on diabetes. Obesity, especially with increased abdominal and visceral fat distribution, is associated with higher levels of triglycerides in the blood and liver and an increased risk of T2DM because it induces beta cell dysfunction and insulin resistance, according to Klein et al. (2022). These are problems that advanced practice nurses (APNs) manage every day, especially in the primary care setting. To highlight this issue in a local context, the author of this paper collected data over three months in the summer of 2023 at a primary care office in Cleveland, Tennessee. 20% of the patients seen in the clinic had diabetes, while 16% were overweight or obese, and a further 4.5% of patients were classified as prediabetic.

Obesity and diabetes have been a national problem in the United States for decades, with multiple causative factors, including easy access to high-sugar, high-fat, and high-calorie foods, significantly associated with fresh food deserts in urban and rural areas (CDC, 2020). A general lack of exercise and sedentary lifestyles can also contribute to the issue. Finally, some people are genetically predisposed toward obesity. These twin diseases have no boundaries and afflict all ages, genders, and socioeconomic statuses. In addition, obesity and diabetes tend to worsen other health conditions such as renal, cardiac, and liver disease, which in turn makes lifestyle modification nearly impossible for many patients (CDC, 2020)

However, a potential solution has started to emerge in the last decade. GLP-1RA drugs can manage both conditions simultaneously. While the first drug in this class, exenatide, was introduced in 2005, it was not until 2017, when semaglutide gained approval by the Food and Drug Administration (FDA), that the true potential of these medications was realized. Patients in the phase 3 trial leading up to semaglutide's approval for T2DM saw an average 9.1-pound weight loss and HgbA1c reduction of 1.5 points (Sorli, 2017) This was followed in 2021 by tirzepatide in the SURPASS-3 trial which showed an average weight loss of 22.8 pounds and HgbA1c reduction of 2.1 points with 78% of patients achieving a HgbA1c of less than 6.5% (Ludvik, 2021). As of the autumn of 2023, numerous other GLP-1RA drugs are in clinical trials, all of which have varying effects on glycemic control and weight loss. Corresponding to these results, the popularity of these drugs has dramatically increased, with semaglutide now approved for weight loss without diabetes and tirzepatide expected to be approved for weight loss by the end of 2023.

This exposes a potentially significant knowledge and practice gap for nurse practitioners as many patients, especially obese patients with or without diabetes, will ask questions or may want to be prescribed one of these medications. Furthermore, due to the half-life of many of these drugs being upwards of 6-10 days, many nurse practitioners in other practice areas need to be aware of these medications. APNs need to understand the mechanism of action, how it may affect appetite, hunger signaling, gastric emptying times, and more. This paper looks to answer many of these questions to allow APNs to understand and explain how these medications work, identify which patients may benefit, and manage potential side effects while allowing weight reduction and glycemic control.

Definition of Terms

Glucagon-like peptide one: An incretin hormone that is mainly secreted by the intestinal L cells in response to ingestion of nutrients and enhances glucose-stimulated insulin secretion while suppressing glucagon secretion in a glucose-dependent manner (Bae et al., 2020). GLP-1 is also synthesized in the brain and distributed throughout the central nervous system (McLean et al., 2021).

Glucose-dependent insulinotropic polypeptide (GIP): The first incretin hormone discovered, produced by intestinal K cells in the upper GI tract after nutrient ingestion, it stimulates insulin release in pancreatic beta cells while suppressing glucagon secretion from pancreatic alpha cells and decreases gastric acid secretion in the stomach. GIP also stimulates bone formation and slows bone resorption (Hammoud & Drucker, 2022).

Incretin: A set of hormones released from the gut after oral ingestion of food that stimulate insulin secretion from the pancreatic beta cells in a glucose-dependent manner. Simply, blood levels of these hormones are low in the fasting state and elevated after food intake (Nauck et al., 2021).

Insulin resistance: A state of reduced responsiveness to insulin targeting tissues to average physiological amounts of insulin and precedes elevated blood glucose levels (Lee et al., 2022).

Purpose Statement/PICO Question

This paper aims to explain how GLP-1 RA drugs work within the brain and gut to affect hunger signaling and food cravings, leading to better glycemic control and weight loss in patients with Type 2 Diabetes and obesity.

Theoretical Framework

Imogene King's Theory of Goal Attainment (TGA) relates directly to the proposed research question. One of the assumptions of TGA is that health professionals have a duty to share information that helps individuals make better-informed decisions regarding their health (Whetsell, 2018). Informing advanced practice nurses (APNs) about how GLP-1 RA drugs work in the brain and gut allows the APN to better explain to patients how these medications work, enables the APN to understand appropriate patients for this drug intervention and allows the APN to teach a patient about this class of drugs so the patient can set realistic goals for their health.

King premised her TGA model on the hypothesis that accuracy in nurse-client interactions increases trust in patient satisfaction and decreases the stress and anxiety of both the provider and the patient. King also posited the reverse is true; if patients cannot receive reliable information and feel the provider isn't able to answer questions thoroughly, then patient stress and anxiety will rise, and it may even devolve into conflict or cognitive dissonance for the patient. This leads directly back to the research question: APNs must be able to provide patients with accurate information, especially on a new class of medications.

Within the TGA, there are four metaparadigms (Whetsell, 2018):

Nursing: A process of action, reaction, and interaction whereby APN and patient share information about their perceptions in each situation. The APN and client then share specific goals, problems, and concerns and explore how to attain the goal.

Health: The life experience of a human being, which includes dynamic stress response while attempting to conform to the internal and external environment. Health requires continuous adjustment of one's resources to achieve physiological stability.

Individuals: Whether healthy or ill, are social beings who are rational and conscious. Humans are open systems that respond and cope with stimuli. Humans gather information and use that to aid in understanding another individual or group, with seven concepts: perception, self, growth, body image, time, personal space, and learning, helping to form a whole person.

Environment: The background for human interactions can be holistic and transformative. The environment is both external to and internal to the individual. Individuals must use energy to bring harmony to their internal and external environments.

Research conducted in Brazil provides insight into how TGA operates. Researchers recruited patients with diabetes for a randomized, quasi-experimental study in Fortaleza, Brazil, over six months. After dividing the patients into a control and intervention group, various goals were set for the intervention group based on King's TGA model. These included removing sugar from the diet, reducing carb consumption, starting physical activity, weight loss, and regular medication use (Araújo et al., 2018). By the end of the six-month timeframe, >75% of the intervention arm had achieved the goals set in place by the research team, while the control group struggled to start physical activity, control carb consumption, or lose weight. The researchers noted that using TGA helped objectively improve the lives of the intervention group (Araújo et al., 2018). This study is limited by a small sample size (N=60) and predominantly female patients (76%); however, it shows the feasibility of using TGA in a similar patient

population as the research question at hand and could provide APNs with insights into how to communicate goals with a patient properly.

SECTION 2: Literature Review

Searches were performed through Google Scholar with a search range from 2015-2023. Key search terms included GLP-1, Obesity, Diabetes, metabolic pathway, and hunger signaling. The search was further narrowed to include literature about brain and gut signaling in the research. Total weight loss and glycemic index were also used to limit the results. The initial results were over 100+ pieces of literature, then narrowed down to approximately 30. In addition to the investigation, two works of literature were provided by Dr. Juan Frias during an interview conducted in August 2023.

Presentation of Literature

Hunger signaling, satiety, and inappropriate hormone response

Hunger and satiety are a complex interplay of various hormones, incretins, intestinal receptors, and vagal nerve responses across the gut-brain axis. This interaction is also different depending on the body composition of the person. In a randomized, single-blinded, crossover study of 29 lean and obese individuals with T2DM, Bae et al. (2020) sought to quantify how brain activation changed in response to visual food cues in these individuals. Past research showed that individuals with obesity and/or T2DM showed differences in functional magnetic resonance imaging (fMRI) scans in the appetite and reward systems of the brain. The study protocol consisted of two interventions with a one-week washout period. After 12 hours of fasting, participants were injected with saline or a short-acting GLP-1RA medication and, after

30 minutes, were placed in an fMRI machine. Researchers showed images of high-calorie food, low-calorie food, and non-food to the study group. Seventy minutes after the fMRI, researchers measured appetite on a visual analog scale and caloric intake in participants who were given access to a buffet of food. After a one-week washout, the study was repeated, and all the participants were switched; those who received the drug first got the placebo, and vice versa.

Before being dosed with the GLP-1RA, results showed that in obese individuals, there was much greater activation of the hypothalamus, pineal gland, and parietal cortex in obese individuals compared to lean individuals when viewing high-calorie food versus low-calorie food ($p < .05$). This was also true when visualizing food vs non-food in the orbitofrontal cortex and visual cortex ($p < .05$) These results show that the central nervous system (CNS) plays a crucial role in hunger signaling. The body uses the hypothalamus for nutrient sensing when eating, signaling hunger and appetite control. At the same time, the orbitofrontal cortex contains some of the central reward circuits in the brain and may relate to craving food (Bae et al., 2020).

After being dosed with a GLP-1RA, the researchers performed the same studies, finding in this subgroup, there was a significant reduction in activation of the hypothalamus and orbitofrontal cortex when viewing food versus non-food objects ($p < .05$). There was no statistically significant difference in calories consumed at the buffet between the placebo and intervention group, however, in the seventeen patients with measurable reduced caloric intake there was a statistically significant difference in brain imaging when viewing high-calorie food versus low-calorie food ($p < .05$). In short, this study showed that brain responses were different between lean and obese individuals with T2DM, that a GLP-1RA drug had measurable changes in brain activation in these individuals and had a potent effect on brain activation in patients with reduced calorie intake after receiving a GLP-1RA (Bae et al., 2020).

This study had some noticeable limitations in that it was a one-time drug administration, studying the immediate effect it has on a patient; in addition, it was a small number of patients. This calls for a larger sample size taken over weeks, if not months, of study to see if these brain activation changes persist. However, if this study is viewed as a pilot study, it provides valuable insight into how these drugs can almost immediately impact a patient's hunger signaling. Moreover, this study offers evidence that dysregulation of brain activation may be a critical factor in developing obesity and T2DM and that GLP-1RA drugs could interrupt that aberrant signaling pathway.

The brain does not just regulate hunger. The stomach and intestines play a role in signaling a person's satiety or hunger. According to Kadough et al. (2019), obesity is defined by increased appetite, altered gut and brain hormone levels, and dysregulated satiety mechanisms. Kadough et al. (2019) hypothesized that compared to a placebo, giving patients the GLP-1 RA liraglutide for 16 weeks would reduce appetite, modify taste preferences, reduce body fat, and alter gastrointestinal hormone levels. Thirty-five participants (17 drug, 18 placebo) were recruited and completed this single-center, double-blind, placebo-controlled randomized control trial. All recruits were obese but otherwise healthy adults. Appetite, taste preference, stomach fullness, satiety, hormone levels, and body fat composition were assessed at the start of the trial and after 16 weeks. To assess satiation, the researchers had participants drink a standardized Ensure drink at a constant 30 milliliters/minute to measure maximum tolerated volume (MTV). A numerical scale was used, with 0 being no symptoms, 3 being typical postprandial fullness, and 5 being unbearable fullness. Participants drank until a score of 5 was reached. A visual analog scale from 1 to 100 was used to assess taste preference, appetite for fatty, salty, savory, or

sweet foods, and satiety. Blood draws assessed hormone levels, and a dual-energy x-ray absorptiometry scan (DEXA) measured body fat composition.

After 16 weeks of treatment, the participants in the liraglutide group had lower MTV, 750ml consumed in the treatment group, versus 1126ml in the placebo group ($p = .054$). Participants also had a much lower appetite for all types of food ($p < .05$) and more reported fullness ($p = .02$) when compared to placebo. Interestingly, plasma GLP-1 was reduced in the treatment group compared to placebo. Finally, there was a significant loss of total body fat on the DEXA scans in the treatment group, with no change in lean body mass ($p = .017$). Average weight loss was 5.8kg with liraglutide compared to 1 kg in the placebo ($p = .003$) (Kadough et al., 2019).

The authors discussed that these findings can be explained in multiple ways. First and most importantly, the increased sensation of fullness can be directly linked to delayed gastric emptying, leaving patients fuller for longer. This, in turn, may affect the brain's feeding centers, reducing appetite. Taste preference alteration in the brain may also lead to decreased calorie intake. Regarding the reduction in GLP-1 levels in the liraglutide group, the researchers proposed that delayed gastric emptying and weight loss decreased endogenous GLP-1 levels. Per the authors, this effect has been seen in other weight loss trials.

When examined in tandem with Bae et al., this study shows that the brain and gut are linked. Because GLP-1 is produced in both regions, medication affecting both areas can correct hunger and appetite signaling. This study had limitations, it did not assess physical activity level, which could account for increased weight loss, and it did not consider the appetite parameters in the middle of the study. Including this could have helped paint a clearer picture of how GLP-1

RA's affect appetite parameters over time. This study did not look at insulin levels or attempt to measure insulin resistance. However, insulin resistance is an essential factor in obesity and diabetes and warrants further investigation.

GLP-1 and insulin resistance in obese diabetics

Insulin resistance is a shared trait of obesity and T2DM. This resistance to insulin can develop even before the acute onset of diabetes or weight gain fully manifest. In the ADDITION-PRO study, a longitudinal cohort of 1462 Danish citizens, Faerch et al. (2015) compared circulating insulin, glucose, and GLP-1 levels during an oral glucose tolerance test. The researchers wanted to see if there was a quantifiable difference in these biomarkers amongst six groups of participants: obese and normal-weight non-diabetics, prediabetics, and diabetic participants. Results of this study revealed that obese non-diabetics had a 20% decrease in GLP-1 levels in response to an oral glucose challenge compared to normal-weight non-diabetics.

Further, among prediabetic and diabetic non-obese patients, GLP-1 response levels were 16-21% lower to a glucose challenge independent of obesity status. Results also showed that women tend to have more GLP-1 impairment than men; however, when accounting for height and weight, this difference was found to be non-significant ($p < .016$). Results also indicated that higher GLP-1 receptor activation responses were associated with better insulin sensitivity and beta-cell function, older age, and a lesser degree of obesity in the participants; this was hypothesized to result from two separate mechanisms of action. First, GLP-1 increases the microvascular surface area of large skeletal muscles, and this may improve insulin's metabolic actions. Second, GLP-1 can preserve and enhance beta cell function and release of insulin in the pancreas while shunting the release of glucagon from pancreatic alpha cells, which allows for a

better insulin response in the body. Finally, for every five-year increase in age, there was an approximate three percent increase in circulating GLP-1 in this study (Faerch et al., 2015).

This shows that alterations in GLP-1 levels are a precursor to T2DM and obesity rather than a consequence of these diseases and further points to dysregulation of metabolism and appetite as the causative agent for both disease states. The obvious implication is that increasing the activation of GLP-1 receptors could treat both diseases. While this study was limited to a single nation, it did include a large number of participants, including some diabetic patients who had not been diagnosed before this study, allowing the researchers access to previously untreated diabetics. Limitations include the age of the study, as no other study has attempted to replicate these findings in humans as of 2023. Other limitations include a lack of generalizability due to a very homogenous patient population and only using oral glucose as a calorie source. Regular meals would be ideal; however, this would be difficult to control due to differences in consumption and calories. This study did not have an intervention arm to see how insulin resistance would vary once patients were treated with medication. Fortunately, numerous studies exist on how GLP-1 RA's affect insulin resistance in human subjects.

As part of a phase 2b study, Thomas et al. (2021) wanted to explore mechanisms for how dual receptor agonist tirzepatide can reduce insulin resistance and increase glycemic control. Tirzepatide (Mounjaro) affects two incretin hormones, GLP-1 and glucose-dependent insulinotropic polypeptide (GIP). To accomplish this, measurements of insulin resistance (IR), beta cell function, and whether weight loss contributes to a reduction in IR after 26 weeks. Three hundred and sixteen subjects were recruited in four countries; inclusion criteria were T2DM with A1c between 7 and 10.5%, with or without metformin use, and a BMI between 23 and 50kg/m^2. Subjects were then randomized (1:1:1:1:1:1) to receive tirzepatide once weekly at

1mg (n=52), 5mg (n=55), 10mg (n=51), or 15mg (n=53) doses, or a separate once weekly GLP-1RA 1.5 mg dulaglutide dose (n=54), or saline placebo (n=51). Fasting blood samples were collected before, during, and after the end of the 26-week study period.

Results showed that along with an increase in pancreatic beta cell function in the tirzepatide groups, there was a marked decrease in Homeostatic Model Assessment for Insulin Resistance (HOMA2-IR) in the 10mg tirzepatide ($p = .004$) compared to placebo and dulaglutide. 15mg of tirzepatide showed a decrease in HOMA2-IR but was not quite significant ($p = 0.63$). High fasting insulin levels in the blood are associated with increased insulin resistance. Fasting insulin levels significantly decreased in the 10mg and 15mg groups compared to placebo ($p = .004$) and dulaglutide ($p = .014$). This shows that the higher dose of tirzepatide improved pancreatic function, decreased fasting insulin levels, and decreased IR. Other markers for IR, such as adiponectin and insulin-like growth factors, were also improved with tirzepatide (Thomas et al., 2021)

Finally, the researchers asked whether the insulin-sensitizing actions of tirzepatide could be explained by weight loss compared to dulaglutide, which only targets GLP-1. Weight loss was only 21% and 13% responsible for the improvement in HOMA2-IR at the 15mg ($p = .014$) and 10mg ($p = .028$) dose groups, respectively. The reduction in fasting insulin and insulin resistance occurred gradually over the first 26 weeks of the study as participants increased the dose of tirzepatide. This suggests that the mechanism of the drug may be primarily responsible for the reduction in fasting insulin and IR, at least in the duration of the study, and helps confirm some of the conclusions reached by Faerch. Namely, improvements in insulin sensitivity seem to reduce metabolic demand on pancreatic beta cells, which in turn helps preserve cell functionality (Thomas et al., 2021).

This study had limitations; these tests were run post hoc in a phase 2b clinical trial with all subjects having blood drawn while fasting, so markers of insulin resistance and beta cell functionality could not be explored after ingesting food. Furthermore, 80% of the participants were on metformin, which could be a potential confounder for insulin sensitivity. The size of the study was small as well, with only 316 participants. The authors know this and call for more extensive phase 3 trials to assess if these findings hold. The trial's design was a strength, especially by comparing tirzepatide to placebo and another GLP-1 RA drug. Apparent differences in HOMA2-IR and fasting insulin were shown in the data analysis. These studies show how systemic issues with GLP-1 and insulin levels can contribute to T2DM and obesity, so how can a nurse practitioner use a GLP-1 RA to correct this problem?

One peptide hormone links the brain and gut

Thomas et al. (2021) found that tirzepatide could improve insulin sensitivity independent of weight loss, which partially explains the mechanism of action of these drugs; there is a noticeable decrease in insulin resistance through various pathways, leading to increased uptake of insulin in the body, contributing to overall glycemic control. However, this brings us back to the question this paper seeks to answer: what GLP-1 RA drugs are doing to reverse, or at least counteract, the effects of dysregulated hunger signaling, food cravings, and abnormal levels of GLP-1 in the bloodstream in obese type 2 diabetic patients. First, we must look at the pancreas and intestines. A literature review by Holst, Andersen, & Gunddal (2022) found GLP-1 is produced by L cells in the duodenum and jejunum in direct response to food ingestion. From there, some GLP-1 is diffused into local capillary beds and immediately degraded by dipeptidyl peptidase 4 **(**DPP-4) enzymes. The bloodstream then takes up what remains to act upon the beta cells in the pancreas, causing increased insulin secretion, decreased glucagon secretion,

increasing beta cell growth, and slowing programmed cell death, further preserving pancreatic function; however, within 5-7 minutes all of the endogenously released GLP-1 has been degraded by enzymatic actions. This explains how GLP-1 RA's improve glycemic response; glucose levels are decreased with less circulating glucagon and more circulating insulin, and the increased insulin levels in the blood allow for lower overall glucose and with the prolonged half-life of GLP-1 RA's, this effect is continuous, even when a person is not ingesting food.

GLP-1 is also taken up by GLP-1 receptor sites throughout the lower stomach and intestines, where it acts directly on these organs, reducing stomach acid production, slowing gastric emptying, and slowing bowel motility. Finally, some GLP-1 activates vagal afferent nerves in the intestines that connect to the brainstem and hypothalamus, signaling to the brain that satiety has been reached and slowing gastric emptying. Essentially, GLP-1 RA's and endogenous GLP-1 act as a hormone-based 'brake' signaling to the brain that further food intake should stop and that satiety has been reached, thereby reducing appetite and intake simultaneously. This may also be the causative reason for the gastrointestinal side effects seen with GLP-1 RAs; high levels of GLP-1 signaling to the brainstem can trigger the area postrema, also known as the brain's vomiting center. However, this effect seems to be transient in many patients, as rapid tolerance to the higher levels of GLP-1 activation is achieved in a matter of days or weeks (Holst, Andersen, & Gunddal, 2022)

The other central area of the body where GLP-1 is produced is in the brain. In a literature review by Chen et al. (2021), two regions in the brainstem were found to make the majority of the nervous system GLP-1. This GLP-1 does not circulate systemically but instead remains in the brain. This review primarily focuses on recent technological advances that have allowed researchers to understand better how GLP-1 acts upon neurons within the brain. With that in

mind, Chen found that GLP-1 activation of neurons in the brainstem and hypothalamus led to a combination of effects, mainly reducing fat intake, appetite, and food intake and decreasing food-motivated behaviors. Even more intriguing, when activation of these sites was blocked, there was an increase in food intake, food-seeking behaviors, and the beginning of weight gain.

With those two literature reviews in mind, the next question to be answered is whether these systems are linked or function independently. Trapp and Brierley (2022) sought this answer in a literature review. The authors found that gut-derived GLP-1 acts as a hormone, binding to receptors, mainly in the digestive system and pancreas, but also affects other organ systems, such as the liver, skeletal muscle, and heart, beyond the scope of this literature review. Within the gut, GLP-1 acts upon vagal afferent neurons, informing the brain of meal status, including satiation, validating what Holst, Andersen, & Gunddal found. However, that mechanism is entirely separate from brain-derived GLP-1, which seems to function more as a neurotransmitter and confirms the finding of Chen et al. with reduction of appetite, food intake, and food-motivated behaviors in areas of the brain that are protected by the blood-brain barrier.

This leads to the role GLP-1 RA drugs have in these two separate systems. These medications primarily act within the digestive system, mimicking the actions of postprandial endogenous GLP-1. However, these drugs also act upon the parts of the brain that are not protected by the blood-brain barrier, such as the area postrema and certain parts of the hypothalamus, providing an explanation for how the medications are so effective at hunger suppression, early satiety and the other benefits described earlier in the review. Without GLP-1 RAs, these systems function independently of each other, each with a role to play in causing diabetes, obesity, or both. With GLP-1 RA's, a link between the two systems is formed that usually may not or only exist for brief periods after heavy food intake. This link allows for the

correction of both systems, leading to better glycemic control and inducing weight loss (Trapp and Brierley, 2022).

These three literature reviews were limited by using a mix of human and animal modeling to gather data. However, given the complexity of the topic and the detailed neuro and digestive anatomy involved, this limitation is inevitable. Sampling brain tissue from live humans would be considered highly unethical and unfeasible. Some animal brain and gut differences could also slightly alter the presented results. That said, the three studies overlap considerably in findings, which gives strength and validity to the findings. Further strengths include that some of the researchers involved in writing these reviews have gone on to design the very GLP-1 RA drugs now being prescribed in clinical practice.

Summary of Literature

This literature review sought an answer to the complex question of obesity and diabetes. First, according to Bae et al. (2020), evidence from fMRI scans shows that in obese individuals, there is a neurological component to obesity, with increased brain activity when viewing food items that were not present in lean individuals. This abnormal signaling was subsequently quelled after administering a GLP-1 RA. Moving to the gut, Kadough et al. (2019) examined how liraglutide would affect appetite, taste preference, stomach fullness, satiety, hormone levels, and body fat composition in a double-blinded placebo-controlled trial. After 16 weeks of treatment, the liraglutide group consumed fewer calories, had less appetite for all foods, and had more fullness and satiety. The intervention group also lost body fat while retaining lean muscle mass. This led the authors to conclude that liraglutide corrected hunger signaling and delayed gastric emptying in the digestive system.

Another contributing factor to obesity and T2DM is insulin resistance and decreased levels of GLP-1 in the bloodstream. Faerch et al. (2015) compared circulating insulin, glucose, and GLP-1 levels during an oral glucose tolerance test of 1462 participants. Results indicated that, especially in obese non-diabetics, GLP-1 levels were 20% lower than in lean non-diabetics, and these altered GLP-1 levels were a precursor to developing diabetes. Furthermore, these low GLP-1 levels persisted in obese diabetic patients, suggesting that dysregulation of gut hormones is a causative factor for both diseases. Thomas et al. (2021) then provided further support for this idea in a trial of tirzepatide in which, over 26 weeks, tracked whether weight loss, the drug, or a combination of both leads to a decrease in insulin resistance and an increase in beta cell functionality. Thomas found that the drug was responsible for the reduction in insulin resistance. Over the study period, participants on the 10mg and 15mg of tirzepatide had improved pancreatic function and decreased insulin levels.

Finally, combining the first two notions, Holst, Andersen, & Gunddal (2022) described the critical roles of gut-produced GLP-1 in acting as a hormonal brake for the gut and brain to stop eating. Loss of gut-derived GLP-1 leads to faster gastric emptying, decreased intestinal motility, increased gastric acid, increased food intake, and higher levels of circulating glucagon, leading to higher fasting glucose levels and impaired insulin uptake. Chen et al. (2021) showed that GLP-1 produced by the brain reduced fat intake, quelling appetite and food intake. Lack of GLP-1 in the brain leads to overeating, increased food seeking, and lack of appetite inhibition. Trapp and Brierley (2022) showed that these two systems function independently but that dysregulation in one leads to obesity and diabetes. GLP-1 RA drugs then act as a bridge that helps correct both systems, leading to weight loss, glycemic control, and many other positive cardiometabolic effects.

SECTION 3: Discussion and Synthesis

The research presented in this paper makes it clear that diabetes and obesity are linked. Each condition potentiates the other, and finding a treatment that attacks the root cause of both diseases has long been a seemingly impossible task. With the arrival of the GLP-1 RA drug class, hope is finally kindled for an effective long-term treatment for both diseases. The review highlighted that abnormal hormone signaling in the brain and gut and altered blood chemistry ultimately lead to both disease states and how GLP-1 RA's can correct hormonal signaling in the brain and gut while also returning insulin, glucose, and other blood levels into a normal range. These medications represent a massive change in practice for all providers. No longer are patients told to try diet and exercise alone; now, patients have medication to act as an adjunct. For some patients who are morbidly obese or have HgbA1c that is >10%, these medications should be the first-line treatment, as the reductions in A1c are more significant than even insulin (El Sayed et al. 2022). Furthermore, this literature review proves that obesity is a disease state worth treating as soon as possible. Obesity is not a moral failing; it does not reflect poor choices or habits on behalf of patients; it is an altered physiological state.

The literature review, when possible, included randomized trials on human subjects as this allows for the most accurate comparison to what providers see daily. In addition, placebo-controlled trials were included as these can help quantify the effect that GLP-1 RA's have. Despite that, some limitations remain; many of these medications are new, and the body of research and data is being built, so considerable knowledge gaps remain. Despite that, many studies were excluded because the amount of data was vast, in-depth, and beyond the scope of this capstone. Indeed, because GLP-1 RA's act on so many organ systems, total reviews of the actions in the liver, kidney, heart, and other areas were not included, and some of these organs

can contribute to obesity, diabetes, or both and are worthy of further exploration. However, many studies excluded from this paper involved testing on rodents and monkeys, which are helpful but must always be considered carefully. In addition, new data is being released almost daily. While this review is accurate for November 2023, it may quickly become outdated as new data, new drugs, and new hormone agonist sites are targeted for future drug development.

As I compiled the data for this capstone project, I was profoundly impacted by how effective these medications are. The author's family has multiple family members on these medications, and all lost considerable amounts of weight after years of trying and failing various diet and exercise regimens. The literature clarified that obesity is a disease, and as advanced practice providers, we need to treat it as such while withholding any judgment on a patient's particular habits. The APN can use King's TGA to set reasonable goals for patients regarding A1c reduction, weight loss, exercise, and other metabolic measures while providing this new tool to reach those goals while becoming healthier.

Implications for Advanced Practice Nursing

As stated, these drugs represent a paradigm shift in how APNs can approach T2DM and obesity. These drugs represent as close to a cure as possible by acting at the source of the disease state. What APNs can do today is to make sure every T2DM patient in the clinic is on one of these drugs. Furthermore, APNs should disseminate the information from this capstone to other providers who may not be up to date on current practices, along with ensuring those providers understand how obesity is a disease state just as much as diabetes is. The APN must advocate for patients and educate other providers. The APN should also use King's TGA; if starting a patient on tirzepatide, goals should be set for HgbA1c, weight, blood pressure, cholesterol, etc. These

goals should represent a moving target; as the patient increases the tirzepatide dose, weight loss and A1c goals can be adjusted. Once those goals are met, the provider and patient should consider the lowest dose of tirzepatide that maintains glycemic control with more appropriate hunger signaling and weight goals.

Another problem exists with these medications that APNs need to advocate for, and that issue is cost. These drugs are all brand names, and the two most prevalent drugs, Ozempic and Mounjaro, will not be generic for about eight years. Monthly costs can be hundreds of dollars if an insurance company does not cover it or the patient lacks insurance. According to El Sayed et al. (2022), GLP-1 RAs are considered first-line medications for the treatment of T2DM by the American Diabetes Association**.** Despite this, many insurance companies are concerned with the cost of the drugs, and as APNs, strong advocacy for insurance coverage and cost control should be considered.

Other issues include the relatively high rate of gastrointestinal side effects that some patients may experience on these drugs. Patients can have nausea, constipation, and diarrhea, especially in the first two to three months of taking these medications. The APN should consider ondansetron for nausea, encourage a high fiber diet to avoid constipation, and for diarrhea should advise patients to avoid fatty foods and should discuss with patients that many of these side effects are worse for the first 90 days and then taper off (Thomas et al. 2021).

The final concern for APNs with these drugs is that many providers and nurses in the hospital are unfamiliar with these drugs. Because gastric emptying is delayed, patients and providers need to have a plan before surgery. Guidelines are still being developed, but concern

exists that in the surgical setting, a higher risk of aspiration, ileus, and post-op constipation is possible for patients on these medications.

Recommendations for Future Research

This capstone sought to explain the effects of GLP-1 RAs on hormone signaling in the brain and gut and the other physiological and metabolic effects accompanying these effects. Future research should focus on other incretins and receptor sites, such as glucagon and fibroblast growth factor-21 receptors. One such drug, tirzepatide, was mentioned as part of a capstone. This drug is considered a dual agonist as it acts on GLP-1 and GIP with synergistic effects noted in current research. Future research needs to focus on maximizing synergy between receptor agonist sites. Retatrutide, mentioned in the introduction, is a triple agonist, acting up GLP-1, GIP, and Glucagon receptors (GCGR). Early phase 2 data show even more weight loss, better glycemic control, lowered cholesterol, reduction in fatty liver disease, and more, as referenced earlier. More research into these dual and triple agonist drugs is needed. Jastreboff & Kushner (2023) noted that most developing medicines target multiple receptor sites. Given some of the other downstream effects on renal function, cardiac function, and liver function, research needs to focus on whether these drugs can reduce morbidity and mortality from heart attack, stroke, chronic kidney disease (CKD), and more. In a hint of this potential, Novo Nordisk announced in a November 2023 quarterly earning call that a trial of semaglutide in patients with chronic renal disease was stopped a year early due to the overwhelmingly positive results in halting the progressive of CKD (Novo Nordisk, 2023). Complete results of that trial are expected in early 2024. Furthermore, in that same earning call, Novo Nordisk announced positive research trial results for heart failure patients and a 20% reduction in major adverse cardiovascular events (MACE) in patients on semaglutide. Tirzepatide, semaglutide, and retatrutide are also being

investigated for the treatment of fatty liver disease, alcohol and substance use disorder, dementia, Parkinson's, obstructive sleep apnea, osteoarthritis, major adverse cardiovascular events and other cardiovascular outcomes, including heart failure, stroke, and myocardial infarction (Novo Nordisk, 2023; Skovronsky & Ricks 2023).

Further research is needed to focus on the long-term effects of these medications on brain signaling as well. If a patient is on one of these drugs long enough, does the brain reset the hunger signaling pathway? Would the patient be able to stop the drug then? Some basic research questions remain: what does maintenance dosing look like once target weight and HgbA1c are met? Most of these drugs have a half-life of six days. Does that mean dosing can be every 10-14 days for maintenance? If research shows a decrease in cardiovascular events, what is the dose schedule for cardiac patients with these medications? What is the dose schedule for a chronic kidney disease patient? Many questions remain, and hundreds of clinical trials worldwide are already seeking answers to many of these questions.

Conclusion

Obesity and Type 2 Diabetes are two diseases that have become all too common in the modern world. The two diseases become intertwined; as obesity worsens, insulin resistance increases. As insulin resistance rises, diabetes develops, causing more adipose tissue growth in a vicious cycle. GLP-1 is an endogenously produced peptide hormone in the brain and intestines, affecting satiety, hunger signaling, and appetite. In patients with obesity and T2DM, GLP-1 and other hunger signaling are often altered. GLP-1 RA drugs can assist in correcting this by allowing for delayed gastric emptying, prolonged satiety, reduced appetite, and modified taste preferences. GLP-1 RA also preserves pancreatic beta cell function, helps with insulin

sensitivity, decreases systemic glucagon release, and induces weight loss, which further reduces HgbA1c and fasting insulin levels. These medications attack the root cause of two disease states simultaneously and, in so doing, can help correct multiple other comorbid diseases that afflict patients daily. APNs now have a powerful tool to use in primary care to support a large majority of patients, and providers should use it as a first-line drug to treat these two diseases. While many questions remain surrounding this class of medications, many of the answers so far could radically change how medicine is practiced. Suppose continued trials of semaglutide, tirzepatide, retatrutide, and many other drugs in this class continue to show further benefits beyond obesity and diabetes. In that case, providers may have a single medication that normalizes HgbA1c, causes substantial weight reduction, reduces blood pressure, reverses hyperlipidemia and fatty liver disease, prevents cardiovascular events, and slows the progression of renal disease. Miracle is perhaps the correct term to describe such a possibility, and providers should be prepared to educate and assist patients in receiving this marvel of modern medicine.

References

Araújo, E., Silva, L., Moreira, T., & et al. (2018). Nursing care for patients with diabetes based on King's Theory. *Brazilian Journal of Nursing*, *71*(3), 1092–1098. https://doi.org/10.1590/0034-7167-2016-0268

Bae, J. H., Choi, H. J., Cho, K. I. K., & et al. (2019, November 4). *Glucagon-like peptide-1 receptor agonist differentially affects brain activation in response to visual food cues in lean and obese individuals with type 2 diabetes mellitus*. Diabetes & Metabolism Journal. https://e-dmj.org/journal/view.php?doi=10.4093%2Fdmj.2019.0018

Centers for Disease Control and Prevention. (2020). National Diabetes Statistics Report 2020. Estimates of diabetes and its burden in the United States. *CDC.gov.* https://www.cdc.gov/diabetes/pdfs/data/statistics/national-diabetes-statistics-report.pdf

Chen, X. Y., Chen, L., Yang, W., & et al. (2021). GLP-1 Suppresses Feeding Behaviors and Modulates Neuronal Electrophysiological Properties in Multiple Brain Regions. *Frontiers in molecular neuroscience*, *14*, 793004. https://doi.org/10.3389/fnmol.2021.793004

El Sayed, N. A., Aleppo, G., & et al. (2022). 9. Pharmacologic Approaches to Glycemic Treatment: *Standards of Care in Diabetes—2023*. *Diabetes Care*, 46(Supplement_1), S140–S157. https://doi.org/10.2337/dc23-s009

Færch, K., Torekov, S. S., Vistisen, D., & et al. (2015). GLP-1 Response to Oral Glucose Is Reduced in Prediabetes, Screen-Detected Type 2 Diabetes, and Obesity and Influenced by Sex: The ADDITION-PRO Study. *Diabetes*, *64*(7), 2513–2525. https://doi.org/10.2337/db14-1751

Financial results and events overview - Novo Nordisk. (2023, Nov 2.). Novo Nordisk. https://www.novonordisk.com/investors/financial-results.html#results2023

Frias, J., Rosenstock, J., Davies, M., & et al. (2021, August 5). Tirzepatide versus Semaglutide Once Weekly in Patients with Type 2 Diabetes. *The New England Journal of Medicine.* https://www.nejm.org/doi/full/10.1056/NEJMoa2107519

Hammoud, R., & Drucker, D. (2022). Beyond the pancreas: contrasting cardiometabolic actions of GIP and GLP1. *Nature Reviews Endocrinology*. https://doi.org/10.1038/s41574-022-00783-3

Holst, J. J., Andersen, D. B., & Grunddal, K. V. (2022). Actions of glucagon-like peptide-1 receptor ligands in the gut. *British journal of pharmacology*, *179*(4), 727–742. https://doi.org/10.1111/bph.15611

Jastreboff, A., Kaplan, L., Frias, J., & et al. (2023, August 10). Triple–Hormone-Receptor Agonist Retatrutide for Obesity — A Phase 2 Trial. *The New England Journal of Medicine.* https://www.nejm.org/doi/10.1056/NEJMoa2301972

Jastreboff, A., & Kushner, R. (2023). New frontiers in obesity treatment: GLP-1 and Nascent Nutrient-Stimulated Hormone-Based Therapeutics. *Annual Review of Medicine*, *74*(1), 125–139. https://doi.org/10.1146/annurev-med-043021-014919

Kadough, H., Chedid, V., Halawi, H., & et al. (2020). GLP-1 Analog Modulates Appetite, Taste Preference, Gut Hormones, and Regional Body Fat Stores in Adults with Obesity. *The Journal of clinical endocrinology and metabolism*, *105*(5), 1552–1563.

Klein, S., Gastaldelli, A., & Yki-Jarvinen, H. (2022, January 4). Why does obesity cause diabetes*? Cell Metabolism.* https://www.sciencedirect.com/science/article/pii/S1550413121006318

Lee, S., Park, S., & Choi, C. S. (2022). Insulin resistance: From mechanisms to therapeutic strategies. *Diabetes & Metabolism Journal*, *46*(1), 15–37. https://doi.org/10.4093/dmj.2021.0280

Ludvik, B., Giorgino, F., Jodar, E., & et al. (2021, August 6). Once-weekly tirzepatide versus once-daily insulin degludec as an add-on to metformin with or without SGLT2 inhibitors in patients with type 2 diabetes (SURPASS-3): a randomized, open-label, parallel-group phase 3 trial. *The Lancet.* https://www.thelancet.com/journals/lancet/article/PIIS0140-6736(21)01443-4/fulltext

McLean, B., Wong, C., Campbell, J., & et al. (2020). Revisiting the Complexity of GLP-1 Action from Sites of Synthesis to Receptor Activation. *Endocrine Reviews*, *42*(2), 101–132. https://doi.org/10.1210/endrev/bnaa032

Nauck, M., Quast, D., Wefers, J., & et al. (2021). The evolving story of incretins (GIP and GLP-1) in metabolic and cardiovascular disease: A pathophysiological update. *Diabetes, Obesity and Metabolism*, *23*(S3), 5–29. https://doi.org/10.1111/dom.14496

Skovronsky, D., & Ricks, D. (2023, November 2). *Quarterly Results | Eli Lilly and Company*. Eli Lilly and Company. Retrieved November 2, 2023, from https://investor.lilly.com/financial-information/quarterly-results

Sorli, C., Harashima, S.-I., Tsoukas, G., & et al. (2017, January). Efficacy and safety of once-weekly semaglutide monotherapy versus placebo in patients with type 2 diabetes (sustain 1): A double-blind, randomized, placebo-controlled, parallel-group, multinational, Multicentre Phase 3A trial. *The Lancet. Diabetes & endocrinology.* https://pubmed.ncbi.nlm.nih.gov/28110911/

Thomas, M. K., Nikooienejad, A., Bray, R., & et al. (2021). Dual GIP and GLP-1 Receptor Agonist Tirzepatide Improves Beta-cell Function and Insulin Sensitivity in Type 2 Diabetes. *The Journal of clinical endocrinology and metabolism*, *106*(2), 388–396. https://doi.org/10.1210/clinem/dgaa863

Trapp, S., & Brierley, D. I. (2022). Brain GLP-1 and the regulation of food intake: GLP-1 action in the brain and its implications for GLP-1 receptor agonists in obesity treatment. *British journal of pharmacology*, *179*(4), 557–570. https://doi.org/10.1111/bph.15638

Whetsell, M., Gonzalez, Y., & Moreno-Fergusson, M. (2018). Models and theories focused on a systems approach. In Butts & Rich (Eds.), *Philosophies and theories for advanced nursing practice* (3rd ed.). Jones & Bartlett Learning

Reference	**Research Question Purpose Objective Hypothesis**	**Patients Population Sample**	**Interventions Identify Independent and Dependent Variables**	**Comparisons**	**Outcomes Findings**	**Level of Evidence and Quality Grade**
Araújo, E., Silva, L., Moreira, T. & et al. (2018). Nursing care for patients with diabetes based on King's Theory. *Brazilian Journal of Nursing*, *71*(3), 1092–1098. https://doi.org/10.1590/0034-7167-2016-0268	To verify the effectiveness of nursing interventions based on Imogene King's Theory of Goal Attainment on improving care for people with diabetes and adherence to treatment.	Patients with Type 2 Diabetes N=60 76% female 30 in the intervention group, 30 in the control group	The intervention group would have researchers set goals for them on physical exercise, weight loss, HgbA1c, carb consumption, and more. The control group would have none.	Rates of physical activity, weight loss, meeting with a nutritionist, reduced glycemic values, reduced carb consumption, and more	After six months,>75% of the intervention arm had achieved goals, while the control group struggled even to start physical activity, control carb consumption, or lose weight. Theory of goal attainment is an excellent way to improve adherence for diabetics.	Randomized, longitudinal quasi-experimental trial. Evidence level II Quality Grade: B
Bae, J. H., Choi, H. J., Cho, K. I. K., & et al. (2020). *Glucagon-like peptide-1 receptor agonist differentially affects brain activation in response to visual food cues in lean and obese individuals with type 2 diabetes mellitus*. Diabetes & Metabolism Journal. https://e-dmj.org/journal/view.ph	How brain activation changed in an fMRI scan in response to visual food cues in obese and lean individuals with Type 2 Diabetes (T2DM)	15 lean and 14 obese patients, all with T2DM N=30	Two interventions with a one-week washout period. After 12 hours of fasting, participants were injected with saline or a short-acting GLP-1RA medication and placed in an fMRI machine. Images of high-calorie food, low-calorie food, and non-foods were shown to the study group. After fMRI, appetite and caloric intake were measured on a visual analog	Brain activation when viewing high vs. low-calorie food vs non-food on placebo and on GLP-1RA Caloric intake at a buffet table after injection with drug or placebo	Obese individuals had greater brain activation compared to lean when viewing high vs low calories ($p < .05$) & when viewing food vs non-food ($p < .05$) when on placebo. Reduction in brain activation	Randomized, single-blinded crossover study. Evidence level I Quality Grade: A

Reference	Research Question Purpose Objective Hypothesis	Patients Population Sample	Interventions Identify Independent and Dependent Variables	Comparisons	Outcomes Findings	Level of Evidence and Quality Grade
p?doi=10.4093%2Fdmj.2019.0018			scale in participants who were given access to a buffet of food. After a one-week washout, the study was repeated, and all the participants were switched.	Obese vs lean patients for all of the above.	and reduction in calories consumed after dosing with drug ($p < .05$).	
Centers for Disease Control and Prevention. (2020). National Diabetes Statistics Report 2020. Estimates of diabetes and its burden in the United States. *CDC.gov.* https://www.cdc.gov/diabetes/pdfs/data/statistics/national-diabetes-statistics-report.pdf	No research question. This is a report produced by the CDC on Diabetes in the United States.	Diabetics in the United States	None	None	13% of all American adults have diabetes, 61% of diabetics are considered obese, and high rates of hypertension, dyslipidemia, and physical activity are seen as well.	Government-sponsored disease report. Evidence level IV Quality Grade: A
Chen, X, Chen, L., Yang, W., & et al. (2021). GLP-1 Suppresses Feeding Behaviors and Modulates Neuronal Electrophysiological Properties in Multiple Brain Regions. *Frontiers in molecular neuroscience*, *14*, 793004.	No research question or hypothesis. Systematic review article on the role of GLP-1 in regulating feeding behaviors and neuronal activities in the brain. The purpose is to provide a background to guide research about GLP-1 feeding inhibition.	None	None	None	Description of recent advances of GLP-1-induced inhibition of feeding behaviors in multiple brain locations within the medulla oblongata, pons, mesencephalon, diencephalon, and telencephalon. GLP-1 suppresses	Systematic review of RCTs without meta-analysis Evidence level I Quality Grade: A

Reference	Research Question Purpose Objective Hypothesis	Patients Population Sample	Interventions Identify Independent and Dependent Variables	Comparisons	Outcomes Findings	Level of Evidence and Quality Grade
https://doi.org/10.3389/fnmol.2021.793004					food intake and induces postsynaptic depolarization of GABAnergic neurotransmitters	
El Sayed, N. A., Aleppo, G., & et al. (2022). 9. Pharmacologic Approaches to Glycemic Treatment: *Standards of Care in Diabetes—2023*. *Diabetes Care*, 46(Supplement_1), S140–S157. https://doi.org/10.2337/dc23-s009	No research question. The purpose of this document is the current American Diabetes Association Standards of Care and clinical practice recommendations and guidelines.	None	None	None	GLP-1 RAs, along with Metformin, are considered the first line for treating T2DM; also, GLP-1 RA use is preferred in patients with renal and cardiovascular co-morbidities.	Clinical practice guidelines from the ADA Evidence level IV Quality Grade: A
Færch, K., Torekov, S. S., Vistisen, D., & et al. (2015). GLP-1 Response to Oral Glucose Is Reduced in Prediabetes, Screen-Detected Type 2 Diabetes, and Obesity and Influenced by Sex: The ADDITION-PRO Study. *Diabetes*, *64*(7), 2513–2525. https://doi.org/10.2337/db14-1751	Is there a quantifiable difference in circulating insulin, glucose, and GLP-1 levels during an oral glucose tolerance test of a large cohort of citizens? The authors wanted to determine if insulin resistance is manifested before the acute onset of diabetes or obesity.	1462 Danish citizens in 6 groups: obese and normal-weight non-diabetics, prediabetics, and diabetic participants	All participants performed an oral glucose tolerance test. Variables were blood levels of insulin, glucose, and GLP-1 levels.	Obese and normal-weight non-diabetics, prediabetics, and diabetic participants	Obese non-diabetics had a 20% decrease in GLP-1 levels in response to an oral glucose challenge compared to normal-weight non-diabetics. In prediabetic and diabetic non-obese patients, GLP-1 response	Longitudinal cohort study Evidence level II Quality Grade: A

Reference	Research Question Purpose Objective Hypothesis	Patients Population Sample	Interventions Identify Independent and Dependent Variables	Comparisons	Outcomes Findings	Level of Evidence and Quality Grade
					levels were 16-21% lower to a glucose challenge independent of obesity status. Higher GLP-1 receptor activation responses were associated with better insulin sensitivity and beta-cell function, older age, and a lesser degree of obesity in the participants.	
Financial results and events overview - Novo Nordisk. (2023, November 2.). Novo Nordisk. https://www.novonordisk.com/investors/financial-results.html#results2023	No research question; this is the third quarter earning call and research update for the company Novo Nordisk	None	None	None	Results from phase 3 semaglutide trials on chronic kidney disease, heart failure with preserved ejection fraction, and reduction in cardiovascular events will soon be published and presented—semaglutide shows positive benefits for all three trials.	Quarterly research update Evidence level V Quality Grade: B

Reference	Research Question Purpose Objective Hypothesis	Patients Population Sample	Interventions Identify Independent and Dependent Variables	Comparisons	Outcomes Findings	Level of Evidence and Quality Grade
Frias, J., Rosenstock, J., Davies, M., & et al. (2021, August 5). Tirzepatide versus Semaglutide Once Weekly in Patients with Type 2 Diabetes. *The New England Journal of Medicine.* https://www.nejm.org/doi/full/10.1056/NEJMoa2107519	Compare the safety and efficacy of once-weekly tirzepatide to semaglutide in Type 2 Diabetics.	1879 patients, mean age 56.6 years	Variables: Tirzepatide 5, 10 or 15mg vs 1mg semaglutide. Primary endpoint change in A1c, secondary endpoint, change in weight	Tirzepatide vs Semaglutide in Type 2 Diabetic patients, change in A1c and weight.	Tirzepatide superior in A1c reduction compared to semaglutide in all doses ($P = .02$) and greater reduction in weight as well ($P < .001$)	International, randomized, open-label, phase 3 trial Evidence level I Quality Grade: A
Hammoud, R., & Drucker, D. (2022). Beyond the pancreas: contrasting cardiometabolic actions of GIP and GLP1. *Nature Reviews Endocrinology*. https://doi.org/10.1038/s41574-022-00783-3	No research question. Review of literature surrounding GLP-1 and glucose-dependent insulinotropic polypeptide (GIP) and actions beyond the pancreas, including liver, adipose tissue, and lipid homeostasis.	None	None	None	GLP-1 and GIP are widely expressed in the body, reduce appetite through signaling receptors in the nervous system, GIP regulate fat and amino acid metabolism, and minimize adipose-related inflammation.	Systematic review of RCTs without meta-analysis Evidence level I Quality Grade: A
Holst, J. J., Andersen, D. B., & Grunddal, K. V. (2022). Actions of glucagon-like peptide-1 receptor ligands in the gut. *British Journal of Pharmacology*, *179*(4),	No research question. A review of the literature on the actions of GLP-1 in the gut, specifically the stomach small and large intestines.	None	None	None	GLP-1 is produced by L cells in the small intestine but is inactivated mainly by enzymes within	Systematic review of RCTs without meta-analysis Evidence level I

Reference	Research Question Purpose Objective Hypothesis	Patients Population Sample	Interventions Identify Independent and Dependent Variables	Comparisons	Outcomes Findings	Level of Evidence and Quality Grade
727–742. https://doi.org/10.1111/bph.15611					minutes of entering the gut. However, it activates vagal afferent nerves and is a brake signal to stop eating. Reduces appetite food intake and slows gastric emptying.	Quality Grade: A
Jastreboff, A., Kaplan, L., Frias, J., & et al. (2023, August 10). Triple–Hormone-Receptor Agonist Retatrutide for Obesity — A Phase 2 Trial. *The New England Journal of Medicine.* https://www.nejm.org/doi/10.1056/NEJMoa2301972	Is retatrutide a safe and effective medication to induce weight loss in an obese population? The study aimed to assess the safety, side effects, and efficacy of retatrutide in obese patients.	338 patients, 51.8% were men, with a BMI of 30 or greater, or BMI of 27 to 30 with one weight-related health condition	Interventions were retatrutide or placebo. The primary independent variable was weight loss. Secondary independent variables were the percentage change in body weight from baseline to 48 weeks and the percentage of patients with reductions of 5%, 10%, 15%, 20% or more in body weight.	Comparisons were ascending doses of retatrutide or placebo randomized in a 2:1:1:1:1:2:2 ratio once weekly for 48 weeks. Those on retatrutide were either on fast or slow ascending dose schedules.	Retatrutide was generally well tolerated at all doses, with fewer side effects in the slow ascending dose group. Weight loss ranged from -8.7% in the 1mg group, -12.9% in 4mg group, -22.8% in 8mg, and -24.2% in 12 mg group. The placebo group lost -2.1%	Phase 2 double-blind, randomized, placebo-controlled trial. Evidence level I Quality Grade: A
Jastreboff, A., & Kushner, R. (2023). New frontiers in obesity treatment: GLP-1 and Nascent Nutrient-Stimulated Hormone-Based Therapeutics.	No research question. A review of current and emerging GLP-1, GIP, and Glucagon agonist medications. This article also previews the	None	None	None	Reviewed current medications such as liraglutide and semaglutide as single agonist medications.	Systematic review of literature without meta-analysis

Reference	Research Question Purpose Objective Hypothesis	Patients Population Sample	Interventions Identify Independent and Dependent Variables	Comparisons	Outcomes Findings	Level of Evidence and Quality Grade
Annual Review of Medicine, *74*(1), 125–139. https://doi.org/10.1146/annurev-med-043021-014919	future of other hormone-based anti-obesity treatment options.				Reviewed tirzepatide as a dual agonist and then checked retatrutide as a triple agonist. Discussed 15+ medications in research trials that act on various receptor sites and the mechanism of action of these new drugs in development.	Evidence level I Quality Grade: A
Kadough, H., Chedid, V., Halawi, H., & et al. (2020). GLP-1 Analog Modulates Appetite, Taste Preference, Gut Hormones, and Regional Body Fat Stores in Adults with Obesity. *The Journal of clinical endocrinology and metabolism*, *105*(5), 1552–1563. https://doi.org/10.1210/clinem/dgz140	Do GLP-1 drugs alter appetite, gut hormones, and taste preferences? Liraglutide would reduce appetite and body fat, modify taste preferences, and change gut hormone levels compared to placebo.	35 obese participants. Seventeen received drugs and 18 placebos.	Liraglutide vs placebo intervention. Measured appetite on a numerical scale of 0-5 and measured taste preferences for food on a 0-100 visual analog scale. Hormone levels via blood draw and body fat composition with a DEXA scan.	Appetite, taste preference, stomach fullness, satiety, hormone levels, and body fat composition were assessed at the start of the trial and after 16 weeks for both the drug and placebo groups.	Participants also had a much lower appetite for all types of food ($p < .05$) and more reported fullness ($p = .02$) when compared to placebo. Significant loss of total body fat on the DEXA scans in the treatment group, with no change in lean body mass ($p = .017$). Average weight loss was 5.8kg with liraglutide	Double-blind, randomized, placebo-controlled trial. Evidence level I Quality Grade: A

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					compared to 1 kg in the placebo (p = .003)	
Klein, S., Gastaldelli, A., & Yki-Jarvinen, H. (2022, January 4). Why does obesity cause diabetes*? Cell Metabolism.* https://www.sciencedirect.com/science/article/pii/S1550413121006318	Why does obesity cause diabetes? The authors sought to explain in the literature review how obesity and body fat cause diabetes and how adequate weight control can prevent both conditions.	None	None	None	A linear relationship exists between body fat amount, BMI, and T2DM. Adipose tissue alterations in beta cell function and insulin resistance are responsible for the development of T2DM; this effect can be reversed with weight loss.	Systematic review of literature without meta-analysis Evidence level I Quality Grade: A
Lee, S., Park, S., & Choi, C. S. (2022). Insulin resistance: From mechanisms to therapeutic strategies. *Diabetes & Metabolism Journal*, *46*(1), 15–37. https://doi.org/10.4093/dmj.2021.0280	In this systematic literature review, the authors sought to explore the mechanism of insulin resistance at a cellular level, including lipid accumulation in the liver and muscle, inflammation, and cellular stressors.	None	None	None	There is no broadly accepted theory of IR. However, evidence supports ectopic lipid deposits to be more strongly related to diabetes than other variables, such as cellular stress and systemic cytokine inflammation. Suppression of	Systematic review of literature without meta-analysis Evidence level I Quality Grade: A

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					lipid synthesis in the liver and stimulating fat oxidation in muscle improves insulin sensitivity and prevents T2DM.	
Ludvik, B., Giorgino, F., Jodar, E., & et al. (2021, August 6). Once-weekly tirzepatide versus once-daily insulin degludec as an add-on to metformin with or without SGLT2 inhibitors in patients with type 2 diabetes (SURPASS-3): a randomized, open-label, parallel-group phase 3 trial. *The Lancet.* https://www.thelancet.com/journals/lancet/article/PIIS0140-6736(21)01443-4/fulltext	Is once weekly dosing of tirzepatide superior to daily dosing of insulin degludec, with or without an SGLT2 inhibitor drug? This study aimed to assess the safety and efficacy of tirzepatide versus standard treatment of T2DM that wasn't controlled with metformin alone.	1437 participants from 122 sites in 13 countries. Tirzepatide groups: N=358 in 5mg, N=360 in 10mg, N=359 in 15mg and N=360 in insulin degludec group. The patient had to be at least overweight by BMI, insulin naïve, and failed metformin therapy.	Interventions were assigned 1:1:1:1, 5mg, 10mg, 15 of tirzepatide, or a titrated daily dose of insulin degludec. The primary endpoint was the non-inferiority of tirzepatide versus insulin degludec measured by the change in HgbA1c. Secondary endpoints of note were change in body weight, patients achieving HgbA1c of <7.0%	Once weekly tirzepatide vs. once-daily insulin degludec with or without an SGLT2 inhibitor in T2DM patients. Compared HgbA1c for all doses of tirzepatide vs. insulin, along with weight loss, and patients with A1c <7.0%	All doses of tirzepatide (5mg, 10mg & 15mg) were superior to insulin in A1c reduction. ($p < .0001$) All doses of tirzepatide reduced weight, while the insulin group gained weight. ($p < .0001$) Lower rates of hypoglycemia with tirzepatide as well (2% vs 7%)	Randomized, open-label, parallel-group phase 3 trial. Evidence level I Quality Grade: A
McLean, B., Wong, C., Campbell, J., & et al. (2020). Revisiting the Complexity of GLP-1 Action from Sites of Synthesis to Receptor Activation. *Endocrine Reviews*, *42*(2), 101–	This literature review examined how GLP-1 is created in the body to receptor activation. This review included gut and brain-derived GLP-1. The authors	None	None	None	GLP-1 is produced in the gut L cells, the hypothalamus, and the brain stem. Authors found it is also	Systematic review of literature without meta-analysis

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132. https://doi.org/10.1210/endrev/bnaa032	wanted to highlight some of the challenges determining the direct vs indirect actions of GLP-1.				produced in the pancreas, affecting insulin and glucagon production. GLP-1 RAs exert actions on multiple cells and tissues that do not express a GLP receptor site.	Evidence level I Quality Grade: A
Nauck, M., Quast, D., Wefers, J., & et al. (2021). The evolving story of incretins (GIP and GLP-1) in metabolic and cardiovascular disease: A pathophysiological update. *Diabetes, Obesity and Metabolism*, *23*(S3), 5–29. https://doi.org/10.1111/dom.14496	This literature review seeks to explain the state of knowledge around GLP-1 and GIP in diabetic patients, along with updated findings on developing GIP/GLP-1 dual agonist medications.	None	None	None	The authors explain that GLP-1 & GIP have an additive effect on insulin secretion. Both are secreted in the gut and pancreas, but the function of pancreatic secretion is still unclear. GIP plays a more significant physiological role than GLP-1; it increases bone remodeling and is neuroprotective and cardiac protective. GIP was thought to be useless for therapeutic drugs,	Systematic review of literature without meta-analysis Evidence level I Quality Grade: A

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					but the success of tirzepatide has shown this to be wrong.	
Skovronsky, D., & Ricks, D. (2023, November 2). *Quarterly Results | Eli Lilly and Company*. Eli Lilly and Company. Retrieved November 2, 2023, from https://investor.lilly.com/financial-information/quarterly-results	There was no research question; this was a quarterly earning call and research update for Eli Lilly Corporation.	None	None	None	Continuing research on tirzepatide and retatrutide for cardiovascular outcomes, morbidity and mortality, NASH, sleep apnea, osteoarthritis, and T2DM	Quarterly research update Evidence level V Quality Grade: B
Sorli, C., Harashima, S.-I., Tsoukas, G., & et al. (2017, January). Efficacy and safety of once-weekly semaglutide monotherapy versus placebo in patients with type 2 diabetes (sustain 1): A double-blind, randomized, placebo-controlled, parallel-group, multinational, Multicentre Phase 3A trial. *The Lancet. Diabetes & endocrinology*. https://pubmed.ncbi.nlm.nih.gov/28110911/	Optimal control of T2DM remains a challenge for many patients. How does once-weekly semaglutide compare to a placebo for the management of HgbA1c and loss of weight? The safety and tolerability of semaglutide were also assessed, and it was thought that semaglutide as a monotherapy would offer superior A1c reduction.	Treatment naïve T2DM with only diet and exercise 30 days before recruitment. A1c of 7-10%. 387 participants in 8 countries. N= 128 0.5mg semaglutide, N=130 1.0 mg of semaglutide, and N=129 in a combined placebo group.	Groups were assigned 2:2:1:1 to receive 0.5mg semaglutide, 1.0mg semaglutide, or two matched dose placebo groups. Dosing was once weekly for all groups. Variables measured were changes in A1c and weight loss. The trial lasted 30 weeks, and labs were measured before, during, and after the trial.	Once weekly semaglutide monotherapy versus placebo in T2DM patients. Weight loss HgbA1c was compared to placebo.	In the semaglutide group, A1c dropped 1.5% in treatment groups ($p < .0001$) No change in the placebo group. Body weight decreased in both the 0.5 and 1mg groups. ($p < .0001$) Side effects were mostly nausea in both treatment groups	Double-blind, randomized, placebo-controlled, parallel-group phase 3a clinical trial Evidence level I Quality Grade: A

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Thomas, M. K., Nikooienejad, A., Bray, R., & et al. (2021). Dual GIP and GLP-1 Receptor Agonist Tirzepatide Improve Beta-cell Function and Insulin Sensitivity in Type 2 Diabetes. *The Journal of clinical endocrinology and metabolism*, *106*(2), 388–396. https://doi.org/10.1210/clinem/dgaa863	How does tirzepatide affect beta cell function and insulin resistance in T2DM patients in a 26-week randomized, double-blind Phase 2b trial? By what mechanism does tirzepatide increase glucose control compared to a single agonist GLP-1RA dulaglutide?	316 subjects with T2DM from 47 sites in 4 countries.	Tirzepatide (1, 5, 10, 15 mg), dulaglutide (1.5 mg), placebo. Analyze biomarkers of beta cell function, insulin resistance with HOMA2-IR, and weight loss contributions to insulin sensitivity.	Tirzepatide (1, 5, 10, 15 mg) versus dulaglutide 1.5 mg versus placebo for beta cell function, HOMA2-IR, and weight loss.	Tirzepatide 10 and 15 mg significantly decreased fasting insulin ($p \leq .033$), and tirzepatide 10 mg significantly reduced HOMA2-IR ($p = .004$). Weight loss ($P \leq .028$) explained only 13% and 21% of improvement in HOMA2-IR with tirzepatide 10 and 15 mg, respectively.	Randomized, double-blind Phase 2b trial. Evidence level I Quality Grade: A
Trapp, S., & Brierley, D. I. (2022). Brain GLP-1 and the regulation of food intake: GLP-1 action in the brain and its implications for GLP-1 receptor agonists in obesity treatment. *British Journal of Pharmacology*, *179*(4),	A systemic review of the literature to discuss the similarities and differences of gut-derived GLP-1 versus brain-derived GLP-1 and whether these systems are independent, linked, or redundant in humans.	None	None	None	Data suggests two sources of GLP-1 are separate. Gut-derived GLP-1 acts as a hormone, and brain-derived acts as a neurotransmitter. However, GLP-	Systematic review of literature without meta-analysis Evidence level I

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557–570. https://doi.org/10.1111/bph.15638					1RA's can act as both as they can access both body parts, bridging the two systems.	Quality Grade: A