World Journal of Diabetes & Metabolism

OPEN ACCESS

Genesis-WJDM-1(1)-01
Volume 1 | Issue 1 |2026

Interactions of GLP-1, GIP, and GCGR Agonists, Suggesting Potential Treatments for Metabolic Disorders and Obesity

Alber Fares[1*], George Fares[2] and Peter Fares[3]
[1]Professor of Medical Biochemistry and Genetics at Xavier University School of Medicine at Aruba
[2]Intern Pharmacist, Advent Health, East Orlando, Florida, USA
[3]University of Central Florida (UCF), School of Health Science

***Corresponding author:** Alber Fares, Professor of Medical Biochemistry and Genetics at Xavier University School of Medicine at Aruba

Citation: Fares A, Fares G, Fares P. Interactions of GLP-1, GIP, and GCGR Agonists, Suggesting Potential Treatments for Metabolic Disorders and Obesity. World J Diabetes Metab. 1(1):1-32.

Received: July 08, 2026 | **Published:** July 20, 2026

Abstract

The intricate interplay among glucagon-like peptide-1 (GLP-1), glucose-dependent insulinotropic polypeptide (GIP), and glucagon receptors (GCGR) is a focal point in understanding the regulatory networks that govern metabolic homeostasis. These peptide hormones, each with unique receptor-mediated pathways, converge to orchestrate a multifaceted response that influences appetite control, enhances insulin sensitivity, and optimizes energy expenditure. This study explores the combined effects of GLP-1, GIP, and GCGR receptor activation on metabolic parameters critical to maintaining energy balance and glucose homeostasis. Using a comprehensive approach integrating molecular biology, physiology, and nutritional science, we investigated how these receptors collectively modulate appetite, insulin sensitivity, and energy metabolism. Our findings reveal that the synergistic activation of these pathways results in a significant reduction in appetite, improved insulin responsiveness, and increased energy expenditure. These findings suggest potential therapeutic targets for tackling metabolic disorders such as obesity and type 2 diabetes. The study covers GLP-1, GIP, and GCGR receptor pharmacology and therapeutic uses, including FDA-approved treatments and those in development for GLP-1 receptor agonists, dual-action GIP/GLP-1 receptor agonists, and triple-action GLP-1, GIP, and GCGR receptor agonists. The review underscores the importance of a holistic understanding of hormonal interactions in developing effective metabolic interventions.

Keywords

Diabetes mellitus type 2; Glucagon-like Peptide-1 (GLP-1), Glucose-dependent Insulinotropic Polypeptide (GIP), and Glucagon Receptor (GCGR); Hypothalamus; Incretins; Obesity; Satiation; Central nervous system.

Abbreviation

GLP-1: Glucagon-like Peptide-1; GIP: Glucose-dependent Insulinotropic Polypeptide; GCGR: Glucagon receptor; T2DM: type 2 diabetes mellitus; GLP1Rs: GLP-1 receptors; DPP-4: dipeptidyl peptidase-4; GLP-1Ras: GLP-1 receptor agonists; WAT: white adipose tissue; AT: adipose tissue; BAT: while brown adipose tissue; ARC: hypothalamic arcuate nucleus; DMN: the dorsomedial nucleus; cAMP-PKA: AMP-protein kinase A; VMN: the ventromedial nucleus; T2D: type 2 diabetes; POMC: Pro-opiomelanocortin, a vital precursor protein and gene involved in the melanocortin**;** CART: Cocaine- and Amphetamine-Regulated Transcript; MC3: Melanocortin-3 Receptor; MC4R: Melanocortin-4 Receptor; MC3: Melanocortin-3 Receptor; MC4R: Melanocortin-4 Receptor; NPY: Neurons producing neuropeptide Y; AgRP: agouti-related peptide; FDA: U.S. Food and Drug Administration; EMA: European Medicines Agency; GPCRs: G protein-coupled receptors; ALT: alanine aminotransferase.

Introduction

According to [1], maintaining proper glucose metabolism is crucial for health, as failure to manage hypoglycemia or hyperglycemia can lead to severe complications, including microvascular disease leading to death. Glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP) are incretins that regulate insulin secretion in response to glucose intake [2].

Glucagon-like peptide-1 (GLP-1)

Glucagon-like Peptide-1 (GLP-1) is a crucial gastrointestinal hormone derived from proglucagon and secreted by enteroendocrine L cells in the lower intestine. Its secretion is low during fasting and increases two to three times after meals. GLP-1 has a short half-life of about two minutes due to rapid metabolism by dipeptidyl peptidase-4 (Figure 1), resulting in only about 10% reaching systemic circulation. It plays a significant role in clinical medicine with various biological effects [3-6]. GLP-1 exerts various effects through its receptors (GLP1Rs) in multiple organs, notably enhancing insulin secretion, promoting pancreatic β-cell health, and inhibiting glucagon secretion, thereby reducing gluconeogenesis and increasing hepatic glucose storage. It also boosts glucose uptake in muscles and adipocytes while positively influencing cardiovascular function [1].

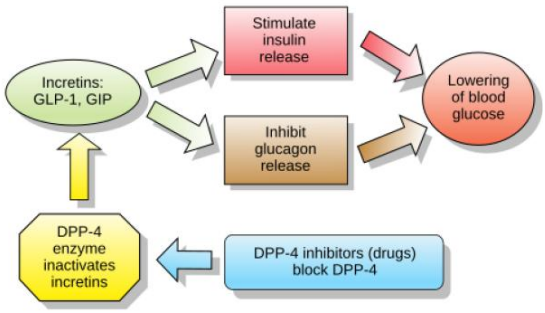

Figure 1: GLP-1 metabolism.

GLP-1 promotes satiety by slowing gastric motility and reducing hunger through its action on specific brain neurons, facilitating weight loss. Moreover, GLP-1 receptor agonists (GLP-1RAs) vary in their

effects on appetite suppression and weight regulation, with some, like semaglutide, having more pronounced effects than others, such as albiglutide. Additionally, GLP-1 helps manage liver metabolism by lowering postprandial glycemia and reducing fatty acid synthesis [4,5,7-17]. (Figure 2, left side in red).

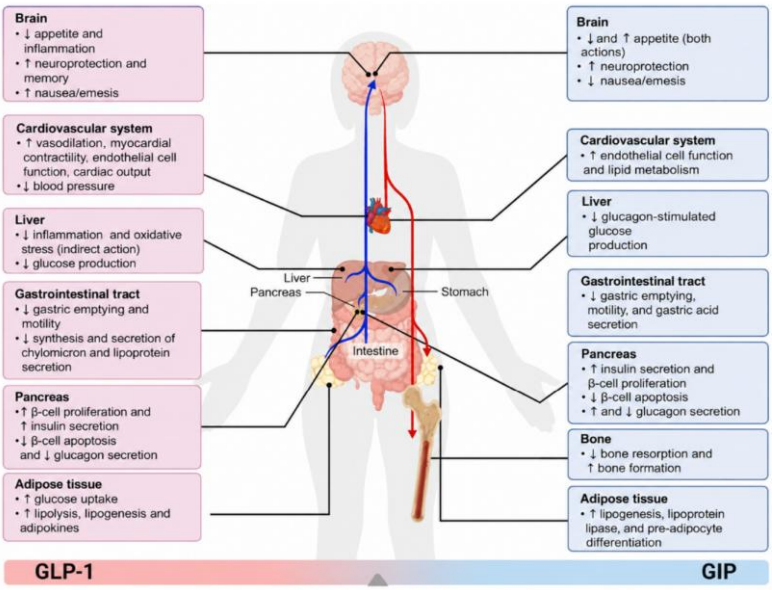

Figure 2: The pleiotropic effects and actions of glucagon-like peptide-1 (GLP-1) in red and glucose-dependent insulinotropic polypeptide (GIP) in blue across various tissues and organs [3].

Glucose-dependent insulinotropic polypeptide (GIP)

Glucose-dependent insulinotropic polypeptide (GIP), released from K-cells in the proximal small intestine, complements GLP-1's insulinotropic effects while promoting lipid storage and enhancing glucose uptake in adipose tissue. The combined action of GLP-1 and GIP receptors increases insulin secretion and peripheral sensitivity, suggesting potential for treating metabolic disorders such as type 2 diabetes. GIP, a 42-amino acid peptide secreted in response to meals, enhances insulin secretion from pancreatic β-cells and is also present in the brain and pancreatic α-cells. It is degraded by dipeptidyl peptidase-4 (DPP-4), leading to an inactive form of the peptide [18-24]. The function of GIP extends beyond the pancreas; Glucose-dependent insulinotropic polypeptide receptor (GIPR) is present in various tissues, including bone, heart, brain, GI tract, and adipose tissue, but not in skeletal muscle or liver. GIP promotes lipid oxidation, enhances blood flow and lipid uptake in adipose tissue, reduces food intake via brain signaling, and aids in weight loss. GIPR agonists are promising for treating type 2 diabetes and may have fewer gastrointestinal side effects than GLP-1R agonists. The improvements in metabolic outcomes associated with GIP may involve interactions with adipose tissue [25-31].

Humans have different types of adipose tissue (AT) that regulate glucose and fatty acid metabolism: white adipose tissue (WAT) stores energy, while brown adipose tissue (BAT) generates heat. Increased BAT activity can protect against weight gain and reduce the risk of metabolic diseases, including type 2 diabetes mellitus (T2DM) and cardiovascular disease. However, it remains uncertain whether BAT

serves as a protective organ in humans.

Dysfunctional AT can impair metabolic health, leading to issues such as insulin resistance and chronic inflammation. Understanding AT's role in energy homeostasis is crucial for developing effective therapeutic treatments [22,32-37].

Glucagon receptors (GCGR)

Glucagon primarily stimulates hepatic glycogenolysis and gluconeogenesis, thereby influencing blood glucose levels in response to dietary composition. It enhances amino acid metabolism, facilitates hepatic lipolysis, promotes cholesterol clearance, and triggers ketogenesis. Glucagon also affects the brain by reducing food intake and regulating blood glucose through the central nervous system, with hypothalamic receptors coordinating glucose production. Additionally, glucagon-induced amino acid catabolism may contribute to muscle wasting and hyperglycemia [38-47]. The glucagon receptor (G-protein) is found in various tissues, including the liver, kidney, intestinal smooth muscle, brain, adipose tissue, heart, pancreatic β cells, and placenta [48]. G protein-coupled receptors (GPCRs) represent the largest and most diverse superfamily of membrane proteins in humans, consisting of over 800 distinct members. These receptors are activated by a wide array of endogenous ligands, including ions, lipids, nucleotides, amines, small molecules, and peptides. They play vital roles in various physiological processes, such as sensory perception, emotional regulation, and metabolic control [49-57].

Due to their significant involvement in health and disease, cardiovascular disorders, neurodegenerative diseases, and metabolic syndromes, GPCRs have become prominent targets for drug development. In fact, over 30% of FDA-approved drugs interact with GPCRs, highlighting their therapeutic significance. GPCRs are categorized into several families (classes A, B, C, and F) based on their sequence homology and domain structure [58-64].

Peptide-binding GPCRs are crucial for regulating essential biological functions like metabolism, immune responses, cardiovascular health, energy balance, pain perception, and reproduction. Peptide ligands, including hormonal, neuropeptides, and regulatory peptides (Figure 3). Activate GPCRs, triggering physiological responses throughout organ systems. Their diverse interactions with GPCRs enable precise control of various processes, indicating significant therapeutic potential for disease management [49].

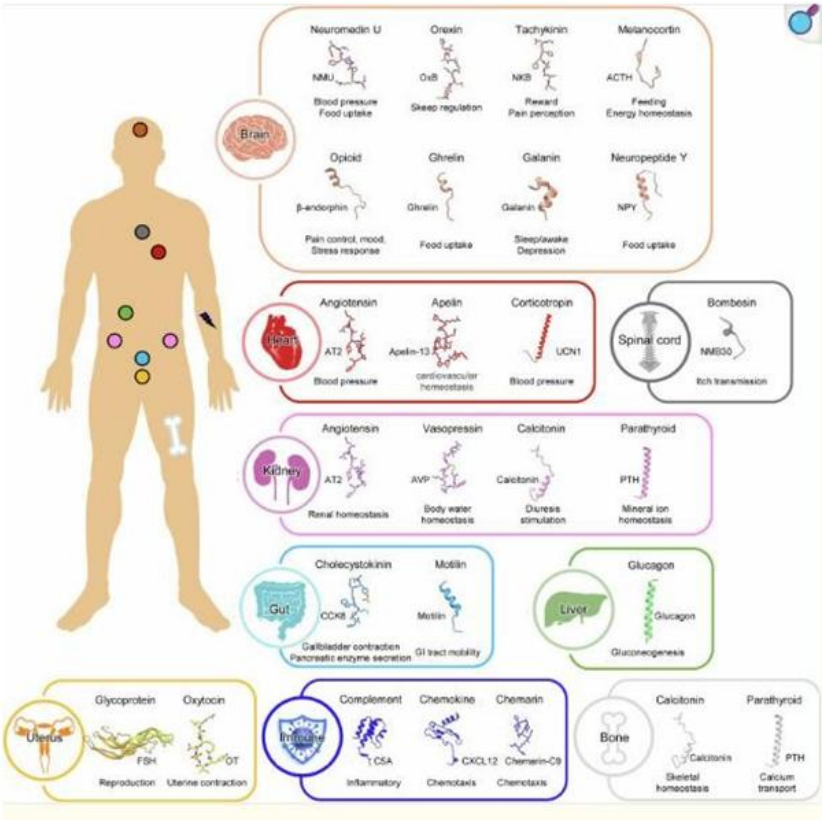

Figure 3: GCGRs are key gut and pancreatic hormones that regulate appetite by signaling nutritional abundance to the brain [49].

Modulating Appetite Control

Obesity not only leads to excess fat but also raises the risk of chronic conditions like type 2 diabetes, cardiovascular disease, and various cancers. Weight loss through diet, exercise, surgery, and medications improves quality of life and positively impacts comorbidities. When paired with lifestyle changes, medications serve as a noninvasive option for initiating and managing weight loss [93-101]. Obesity is the second leading cause of preventable death in the U.S., linked to several comorbidities such as type 2 diabetes, metabolic dysfunction-associated liver disease, cardiovascular disease, and cancer. Initially developed to treat type 2 diabetes, GLP-1, GIP, and GCGR agonists are now also used to treat obesity [128,129].

According to [65], obesity is a major global health issue, defined by Body Mass Index (BMI), with a standard BMI of 18.5 to 24.9 kg/m², and obesity is defined as 30 kg/m² or above (For instance, the ideal weight for a person who is 6 feet tall should not exceed 184 pounds). In 2022, 890 million adults were diagnosed with obesity, a number that has doubled since 1990, resulting in increased health complications related to metabolic disorders [66]. The regulation of body weight involves various gastrointestinal hormones that influence metabolism and weight control. These hormones affect key neural nuclei, like the arcuate nucleus (ARC), via the gut-brain axis [67]. The vagus nerve and bloodstream are crucial for transmitting signals from the gastrointestinal tract to the brain. Nutrient signals and hormones reach the central nervous system via these pathways, influencing metabolic

regulation by traveling along the vagus nerve or crossing the blood-brain barrier [68] (Figure 4).

GLP-1's role in metabolic regulation via the gut-brain axis

The gut-brain axis is the primary pathway through which GLP-1 exerts its effects, promoting insulin secretion, enhancing insulin sensitivity, delaying gastric emptying, reducing appetite, and influencing lipid metabolism [69]. Research has identified glucose-sensitive neurons in the dorsomedial nucleus (DMN) that express GLP-1 receptors and inhibit potassium channels, thereby lowering blood glucose by activating the cAMP-PKA pathway [70]. Other hypothalamic nuclei, such as the ventromedial nucleus (VMN), contain glucose-sensitive neurons: glucose-excited (GE) and glucose-inhibited (GI). GE neurons are activated by high glucose, while GI neurons show decreased activity. Most GLP-1R-expressing neurons are GE, detecting peripheral glucose through ATP-sensitive potassium channels, thus helping regulate glucose homeostasis and energy metabolism by integrating GLP-1 and peripheral glucose signals [71].

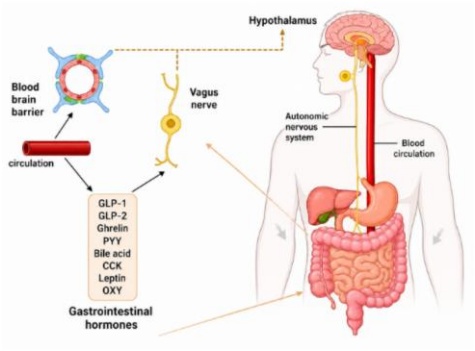

Figure 4: Hormones that regulate metabolism within the gut-brain axis [65].

The gut-brain axis, which involves the vagus nerve, regulates insulin secretion and sensitivity. GLP-1 activates vagal afferents in the nodose ganglion, thereby increasing neuronal activity in the brainstem's solitary nucleus. This is relayed to the hypothalamus, generating efferent vagal signals that innervate the pancreas, gastrointestinal tract, and other organs to regulate insulin secretion [72]. The intracellular signaling pathways related to GLP-1's regulatory effects include cyclic cAMP-PKA and phospholipase C-protein kinase C. These pathways play a crucial role in mediating GLP-1's physiological responses in the central nervous system, affecting insulin secretion and sensitivity [65,73].

Gip's role in human obesity

According to [74], GIP is known as an "obese hormone," with research showing that obese individuals have heightened GIP responses to food and elevated fasting levels. Animal studies indicate that high-fat diets lead to increased GIP production and K cell hyperplasia. GIP also promotes fat accumulation in adipose tissues [75-80]. Direct evidence emerged that GIP acts as an obesogenic signal: mice lacking GIP receptors (GIPR) maintained normal weight on a normocaloric diet but gained less weight and fat on a high-fat diet (HFD), while retaining insulin sensitivity. This suggests that GIPR deficiency may protect against obesity and diet-induced insulin resistance, a concept supported by various

subsequent studies [77].

Current research suggests that inhibiting endogenous GIP or its receptor can combat high-fat diet-induced obesity. Various methods have been studied, including GIP deficiency, K cell ablation, neutralizing antibodies, GIP vaccination, and pharmacological inhibition of GIPR. Additionally, genome-wide association studies have linked GIPR variants to obesity and BMI, with some variants associated with lower BMI. This evidence highlights the significant role of the GIP-GIPR system in the development of obesity [74]. GIP does not promote food intake or fat accumulation; rather, its long-lasting derivatives or transgenic overexpression result in a negative energy balance.

GLP-1/GIP hybrid peptides have shown significant weight loss, outperforming GLP-1 receptor agonists alone. The effectiveness of GIP in reducing food intake depends on central GIPR signaling, allowing weight loss through both GIPR antagonism and agonism. The unclear mechanism behind these findings may involve chronic GIPR agonism leading to desensitization. While desensitization has been observed in adipocytes, its relevance in β-cells and the CNS remains uncertain. Overall, changes in the GIP system substantially affect energy balance [81-91].

The energy balance equation states that weight loss requires energy expenditure to exceed intake. GIP-mediated weight loss may increase energy expenditure, decrease food intake, or both. While the central nervous system (CNS) likely mediates GIP's effects, early studies found that administering GIP directly to the brain does not affect food intake. Despite identifying GIP receptors (GIPR) in the CNS, research on their role in energy balance has been limited. Recent findings have renewed interest in how brain-expressed GIPR may affect energy homeostasis [74,82,92].

GCGR's role in human obesity

GCG regulates metabolic pathways related to lipid, glucose, and amino acid homeostasis primarily through hepatic GCGR signaling, but its use as a monotherapy is limited by hyperglycemic effects. Initial studies on a dual agonist for the glucagon receptor (GCGR) and glucagon-like peptide 1 (GLP1) have shown glucagon's effectiveness in promoting weight loss. A dual GCGR/GLP-1R agonist shows strong weight loss in obese individuals and may be more effective than semaglutide (GLP-1 receptor agonist) alone. It also improves metabolic dysfunction-related steatohepatitis and fibrosis. The mechanism involves increased energy expenditure, lipolysis, and hepatic fat clearance due to GCGR activation, while GLP-1R activation suppresses appetite. Studies indicate that the dual-agonist BI-456908 achieves greater weight loss without adversely affecting glucose control, underscoring the importance of hepatic GCGR signaling in this combined approach [93]. Chronic activation of GCGR by the long-acting agonist IUB288 primarily reduces body weight by decreasing fat mass. Additionally, both acute and chronic GCGR activation enhances liver fibroblast growth factor 21 (FGF21) expressions and secretion, contributing to its antiobesity effects [94-99].

FGF21 has become a promising treatment for obesity and metabolic syndrome, influencing thermogenesis, fatty acid oxidation, glucose metabolism, and body weight. It signals through an FGFR-1c and -3c/β-Klotho complex found in adipose tissue, liver, pancreas, and brain. Initially, the focus was on peripheral actions, but recent evidence indicates that central FGF21 signaling increases energy

expenditure via sympathetic activity and is essential for weight loss in diet-induced obese mice [100-128]. Chronic GCGR signaling promotes weight loss, partly through FGF21 in the liver. The hypothesis suggests that GCGR-stimulated FGF21 signals via central KLB to facilitate this weight loss [94].

GLP-1, GIP, and GCG receptors enhancing insulin sensitivity

[129] the remarkable weight-loss results observed with poly-agonists suggest possible additive or synergistic effects. The distinct effects of GLP-1, GIP, and GCG on energy balance and metabolic function have primarily been assessed in rodent models (Figure 5). GLP-1 reduces food intake by targeting GLP1R in the hypothalamus and brainstem, while enhancing glycemic control by slowing gastric emptying, boosting glucose-stimulated insulin secretion, inhibiting glucagon secretion, and increasing β-cell mass. The role of GIPR agonism in promoting weight loss remains uncertain, as GIP does not influence food intake or energy expenditure. Interestingly, GIPR antagonists have been shown to induce weight loss in mice and non-human primates [130], and ZEPBOUND (tirzepatide), an FDA-approved treatment, fails to induce weight loss in obese Glp1r−/− mice [132].

GIPR agonism may provide metabolic benefits by enhancing glucose-stimulated insulin secretion, improving postprandial adipose tissue blood flow and triglyceride storage, and mitigating weight loss-induced bone loss through decreased bone resorption and increased osteoblast activity. On the other hand, GCGR agonism may facilitate weight loss by lowering food intake, a mechanism supported by rodent studies and mediated via the hepatic vagus nerve. In some models, GCGR agonism has been shown to increase energy expenditure, primarily by activating brown adipose tissue. However, it appears unlikely that chronic GCGR agonist treatment increases energy expenditure in humans. While acute glucagon infusion raises resting energy expenditure, a short-term 72-hour infusion did not alter sleeping, basal, or 24-hour energy expenditure [132].

Nevertheless, glucagon exerts strong influences on hepatic glucose, lipid, and amino acid metabolism. It stimulates hepatic glucose production, which can lower plasma glucose levels, though these effects may be counterbalanced by the positive effects of weight loss. Additionally, glucagon decreases intrahepatic triglyceride content (via increased intrahepatic triglyceride lipolysis, fatty acid oxidation, ketogenesis, and reduced de novo lipogenesis) and lowers plasma LDL-cholesterol concentration (through enhanced hepatic LDL receptor activity) [129].

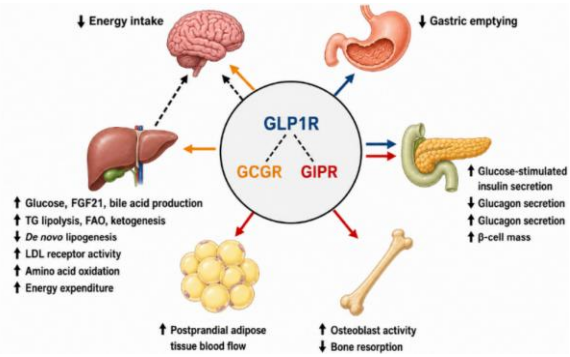

Figure 5: Multi-organ effects of GLP-1 (blue arrows), GIP (orange arrows), and glucagon (red arrows) receptor agonism [129].

Insulin and Glucagon in the Regulation of Glucose Homeostasis

[133] Through its various hormones, especially glucagon and insulin, the pancreas regulates blood glucose levels within a precise range of 4–6 mM. This regulation is achieved through the opposing yet balanced actions of glucagon and insulin, a process known as glucose homeostasis. During sleep or between meals, when blood glucose levels drop, glucagon is secreted by α-cells to stimulate hepatic glycogenolysis. Additionally, glucagon promotes hepatic and renal gluconeogenesis, thereby raising endogenous glucose levels 9 during prolonged fasting. Conversely, insulin release from β-cells is triggered by increased exogenous glucose levels, such as those that follow a meal [134]. Upon binding to its receptor on muscle and adipose tissues, insulin facilitates the insulin-dependent uptake of glucose into these tissues, thereby reducing blood glucose levels by removing exogenous glucose from circulation (Figure 6) [135-137]. Moreover, insulin encourages glycogenesis [138-150], lipogenesis [151,152], and the incorporation of amino acids into proteins [153]. Thus, it acts as an anabolic hormone, in contrast to glucagon's catabolic effects. These two hormones have contrasting effects and collaborate to maintain glucose homeostasis. Insulin is secreted in response to elevated blood glucose levels (hyperglycemia) and lowers blood glucose by prompting cells to take glucose from the bloodstream for energy or storage. Conversely, glucagon is released when blood glucose levels drop (hypoglycemia). It triggers the liver to increase glucose production via glycogenolysis, thereby increasing blood glucose levels [133].

[154] Energy homeostasis is regulated by the brain, which integrates chemical, hormonal, and neural signals from peripheral organs such as adipose tissue, the pancreas, the liver, and the gut, thereby creating the gut–brain axis [155,156] Signals from the periphery, like leptin and insulin, inform the body about energy reserves, while gut factors convey nutrient information, including meal timing, frequency, and composition. Disruptions in these pathways may contribute to unwanted weight gain, obesity, and metabolic disorders such as dyslipidemia, prediabetes, and type 2 diabetes [157]. Glucagon-like peptide-1 (GLP-1) is key to the gut-brain axis and is released during meals for its incretin effects, including boosting insulin secretion and improving post-meal glucose control. Additionally, GLP-1 receptor agonists (GLP-1RAs) influence appetite and energy metabolism by acting on specific brain regions [156].

[158] Systemic blood glucose homeostasis in humans is regulated by GLP-1, a peptide released from intestinal L cells after food intake [128,159]. L cells in the gastrointestinal mucosa act as nutrient sensors, releasing GLP-1 when exposed to sugars, amino acids, and fatty acids [129,160]. GLP-1, released in the intestinal wall, activates enteroenteric reflexes that regulate gastric motility and slow gastric emptying. It also stimulates vagal sensory nerve terminals in the intestinal wall, initiating vagal–vagal autonomic reflexes that affect the endocrine pancreas [161]. Circulating GLP-1 acts as a hormone in the pancreas, enhancing insulin secretion and inhibiting glucagon release. During the postprandial phase, these actions collaborate to effectively lower blood glucose levels.

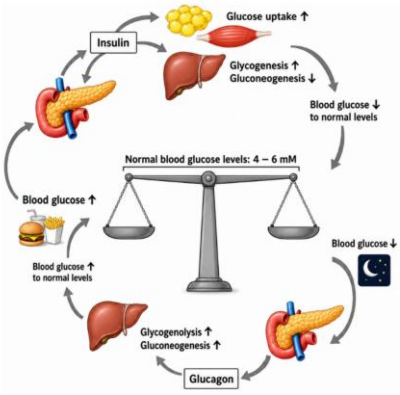

Figure 6: Glucagon and insulin regulate blood glucose levels. When blood glucose is low, glucagon from the pancreas stimulates glycogenolysis to raise blood glucose levels. After eating, insulin is released to facilitate glucose uptake in muscle and fat tissues and promote glycogenesis [133].

After eating, blood glucose levels rise as glucose from food enters the bloodstream, providing energy for various biological functions, then fall during fasting [161]. To stimulate insulin secretion after meals, the body uses two incretin hormones from the intestine: GLP-1 and GIP [7,162]. These hormones, released after eating, stimulate insulin secretion from the pancreas, signaling cells to absorb glucose for energy or storage, thereby reducing post-meal blood glucose spikes.

Incretin-Based Therapies for Obesity Research

[163] The regulation of body weight is primarily mediated by the brain and adipose tissue (Figure 7), which continuously processes information about the body's energy status to regulate food intake, feelings of fullness, and energy balance [67,164,165]. Hormones play a role in the gut-brain-fat communication pathway, including:

- **Adipokines:**
  - Leptin
  - Adiponectin
  - Liver-secreted hormone:
  - Fibroblast growth factor 21 (FGF21)
- **Glucagon:**
  - Produced by pancreatic α cells
- **Gastrointestinal peptides:**
  - Ghrelin
  - Peptide YY (PYY)
  - Cholecystokinin (CCK)
- **Incretins:**
  - Glucagon-like peptide-1 (GLP-1)
  - Glucose-dependent insulinotropic polypeptide (GIP)

These hormones collectively contribute to the intricate communication system between the gut and brain [164].

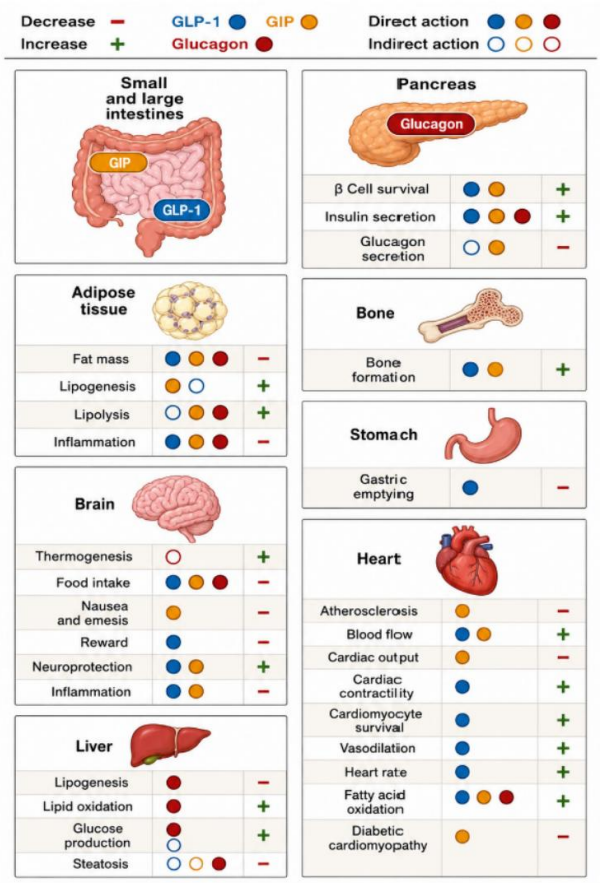

Figure 7: The signaling pathways and metabolic processes affected by endogenous GLP-1, GIP, and glucagon hormones in target tissues [163].

Additionally, enhanced GCGR signaling has been shown to reduce body weight by decreasing food intake [174-176] and increasing energy expenditure [173,176-178], and to influence lipid metabolism by promoting lipolysis and suppressing lipogenesis [179-182]. Furthermore, glucagon can inhibit gastric motility [183] and enhance renal glomerular filtration [184], and it also exhibits significant cardiovascular effects, including increased heart rate, cardiac contractility, and cardiac output [185]. Together, these findings suggest that GCGR agonism may be a promising strategy for treating metabolic diseases associated with obesity, particularly when combined with therapies that mitigate glucagon's immediate glycemic and cardiovascular effects [163].

Examining the role and effects of glp-1 receptor agonists (single agonists) in medicine

A GLP-1R agonist is a peptide analog of GLP-1 that facilitates weight loss. It has been shown to be effective in helping individuals with obesity achieve significant weight reduction when combined with lifestyle modifications, such as reduced caloric intake and increased physical activity, compared with relying solely on lifestyle changes [186]. Peptide-based GLP-1R agonists, including Semaglutide,

lixisenatide, liraglutide, dulaglutide, and exenatide, vary in molecular structure, size, pharmacological properties, efficacy, and safety, offering distinct benefits tailored to individual needs [187]. Non-peptide therapies may present advantages over their peptide counterparts. Typically, peptide-based therapies are large molecular-weight compounds that require injections. In contrast, non-peptide GLP-1R agonists, such as orforglipron, or positive allosteric modulators like V-0219, can be administered orally [188-190]. These non-peptide GLP-1R agonists are currently undergoing clinical trials.

[191] GLP-1 receptor agonists, originally developed for managing type 2 diabetes (DM2), improve glycemic control and promote weight loss. They work by delaying gastric emptying, suppressing appetite, and enhancing feelings of fullness, making them a potential treatment for obesity in both diabetic and non-diabetic individuals [192]. Exenatide, approved by the FDA in April 2005, was the first GLP-1 receptor agonist. It is used as an adjunct to glycemic control in patients with Type 2 diabetes already on metformin, a sulfonylurea, or both [193]. Initial trials of exenatide, administered twice daily, demonstrated both safety and effectiveness, with notable improvements in glycemic control and weight loss among patients with Type 2 diabetes [194,195]. Exenatide evolved into an extended-release formulation, showing positive outcomes for individuals with type 2 diabetes (DM2). Its use expanded to aid weight management in those with obesity or being overweight without diabetes. Long-term studies (up to 6 years) confirmed its safety, sustained glycemic control, moderate weight loss, and a low risk of hypoglycemia [196-200].

Liraglutide was approved for Type 2 Diabetes treatment in January 2010 as an adjunct therapy for glycemic control, following exenatide. A 2009 consensus from the American Diabetes Association and the European Association for the Study of Diabetes recommended GLP-1 receptor agonists for situations where reducing hypoglycemia and promoting weight loss were essential [201]. After observing the encouraging results of liraglutide in managing glycemic levels and promoting weight loss in type 2 diabetes (DM2), a higher-dose formulation (3.0 mg) was specifically developed for weight management. This formulation, known as Saxenda®, received FDA approval for weight loss in individuals with obesity or those who are overweight and experiencing related comorbidities in 2014, followed by approval from the European Medicines Agency (EMA) in 2015 [202-205].

Building on the achievements of exenatide and liraglutide, several additional GLP-1 receptor agonists have been introduced, including dulaglutide, lixisenatide, semaglutide (SMG), and tirzepatide [206-208]. SMG stands out as a promising option for improved glycemic control and weight reduction compared with other GLP-1 receptor agonists [203,209-211]. The benefits include various formulations (subcutaneous and oral), multiple dosing options, a lower risk of cardiovascular events, and substantial research supporting its use in conditions such as hepatic steatosis, sleep apnea, obesity-related heart failure with preserved ejection fraction, and DM2 prevention in prediabetic individuals [212-222]. SMG (Ozempic®) received FDA approval in December 2017 and EMA approval in February 2018 for the treatment of DM2. Later, SMG (Wegovy®) was approved by the FDA in June 2021 and by the EMA in January 2022 for weight management in adults with obesity or those overweight with comorbidities [191].

The weight-lowering effects of SMG involve central and peripheral mechanisms regulating appetite, energy balance, and metabolism (Figure 8). Central effects include GLP-1 stimulation of anorexigenic neurons (POMC and CART) and inhibition of orexigenic neurons (NPY and AgRP) in the hypothalamus. This hormone interaction, influenced by leptin, leads to reduced hunger and increased fullness, supporting sustained weight loss [223,224]. SMG slows gastric emptying, prolongs digestion, and promotes early satiety, reducing calorie intake and postprandial glucose spikes for better metabolic control. Some studies also indicate that GLP-1 receptor agonists may enhance energy expenditure by increasing thermogenesis in brown adipose tissue. [193,225].

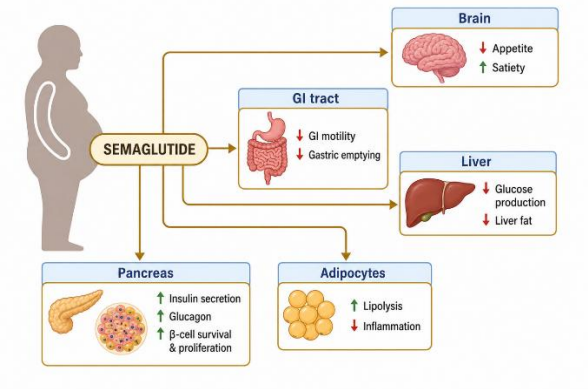

Figure 8: Mechanism of Semaglutide in Managing Obesity [191].

SMG is a modified GLP-1 analog with a half-life of about one week due to amino acid replacements and fatty acid attachment, enhancing its albumin affinity and protecting it from dipeptidyl peptidase-4 (DPP-4) degradation. It is administered weekly via subcutaneous injection at various doses (0.25 mg to 2.4 mg) or taken orally daily (Ribelsus®) in doses of 3 mg, 7 mg, or 14 mg. With 94% amino acid sequence homology to endogenous GLP-1, it effectively mimics its physiological effects, aiding glycemic control and body weight management [207,226].

Current GLP-1 receptor agonists vary in binding affinity, activation dynamics, and effects, impacting clinical outcomes. Short-acting agents such as exenatide and liraglutide mimic natural GLP-1 secretion but require more frequent dosing and have modest effects on glucose and weight. In contrast, long-acting agents such as liraglutide, SMG, dulaglutide, and tirzepatide provide continuous receptor activation, leading to better appetite suppression, improved glycemic control, and more significant weight loss. Notably, SMG at a weekly dose of 2.4 mg showed greater average weight loss than liraglutide, which is approved for weight management [227,228].

Examining the role and effects of glp-1 and gip receptor agonists (dual agonists) in medicine

[229] A thorough understanding of multireceptor agonists is crucial for predicting the effectiveness of drugs for metabolic diseases. Most agonists in development target the GLP-1 receptor while also acting on the GIP and GCG receptors. An ideal drug should combine receptor potency, activate intracellular signaling, and have a pharmacokinetic profile that enhances efficacy beyond that of selective GLP-1R agonists. Tirzepatide, currently in phase 3 trials, serves as a benchmark for future

multireceptor agonists [230,231].

While GIP agonists alone do not appear to slow gastric emptying or have a significant impact on food intake and appetite, the reasons for this are still not fully understood. Tirzepatide stands out as a groundbreaking dual agonist targeting both GLP-1R and GIPR. Nonetheless, the combined action of GLP-1 and GIPR agonists works synergistically, offering greater benefits than GLP-1R agonists used independently [157,232-235]. These dual GLP-1R and GIPR agonists, often referred to as "twincretins," also appear to minimize side effects due to their combined mechanisms of action [235]. The benefits of these dual agonists have spurred research into developing therapies that target multiple mechanisms.

Tirzepatide is an imbalanced dual agonist that prioritizes GIP receptor activity over GLP-1 receptor activity, with equal affinity for GIPR but 5-fold weaker for GLP-1R. This design may enhance effectiveness while reducing gastrointestinal side effects like nausea. Its pharmacological profile enables effective GIPR engagement while minimizing GLP-1-related tolerability issues. Additionally, its C20 unsaturated di-acid acyl chain improves albumin binding, supporting once-weekly dosing [236,237]. Besides convenience, this pharmacokinetic trait may enhance pharmacodynamics, as sustained levels of selective GLP-1R agonists improve clinical efficacy [238,239]. Tirzepatide shows notable effects on glucose management and body weight in studies [88,236,240]. Tirzepatide has strong effects on glucose regulation and body weight, yet its mechanism of action is not fully understood [229].

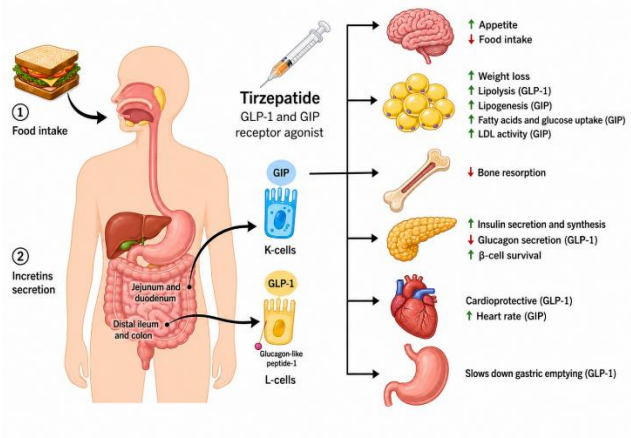

Figure 9: Mechanism of Action for Tirzepatide

According to [241], Tirzepatide offers dosing flexibility, with options ranging from 2.5 mg to 15 mg per 0.5 Ml injection [242]. Its unique molecular structure, consisting of a linear peptide backbone with 39 amino acids and an acyl fatty-chain conjugation, contributes to a favorable pharmacokinetic profile by enhancing albumin binding and extending its half-life [243]. Tirzepatide exhibits a remarkable bioavailability of 81%, with peak plasma concentrations occurring at 48 hours post-administration (with a range of 12–96 hours) [244,245]. Importantly, its half-life of 117 hours (approximately 5 days) supports a once-weekly dosing schedule [136,246]. Although tirzepatide is currently approved solely as an adjunct therapy to improve glycemic control in adults with T2DM, clinical trials have shown

significant reductions in body weight across all dosage groups, along with other notable metabolic improvements [247-249]. The mechanism of action for tirzepatide is depicted in (Figure 9).

Examining the role and effects of glp-1, gip, and gcgr receptor agonists (triple agonists) in medicine

The emergence of GLP-1R, GIPR, and GCGR poly-agonists heralds a new phase in obesity treatment. [250] A groundbreaking therapy that targets all previously discussed molecules is the triple-receptor agonist retatrutide. This synthetic peptide functions as an agonist for the GLP-1, GIP, and CCG receptors (Figure 10). The design of retatrutide enables it to bind specifically to these receptors [251].

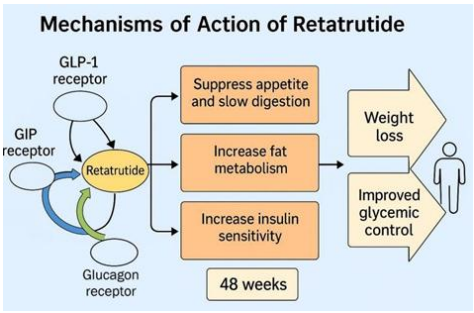

Figure 10: Retatrutide's mechanisms of action.

Retatrutide is a single continuous helix that navigates the receptor's transmembrane domain through its N-terminal segment. Its C-terminus interacts with the extracellular domains of the GLP-1 and GIP receptors. It shows higher potency at the human GIP receptor than at the GLP-1 and glucagon receptors [252]. Retatrutide's action is dose-dependent, reducing gastric emptying, and it has a half-life of 6 days, allowing for weekly dosing. It is mainly metabolized in the liver and does not affect cytochrome P450 enzymes [253]. The effects include significant weight loss and a reduction in HbA1c levels [254]. The most common adverse effects reported are nausea, diarrhea, vomiting, and constipation, leading to many therapy discontinuations, particularly at higher doses. Practical studies indicate that GLP-1RA discontinuation rates can reach 20% to 50% in the first year, with patients often using lower doses than those in clinical trials [255]. Less common adverse effects include a temporary rise in alanine aminotransferase (ALT) levels, increased heart rate, and skin hyperesthesia [256].

The FDA approval process for retatrutide may take several years, as extensive phase 3 trials are expected to continue until 2025 [257]. Preclinical studies showed that retatrutide aids weight loss and improves glycemic control in mice. A trial with a single dose in healthy individuals indicated it is well-tolerated and significantly impacts appetite regulation and weight loss. This meta-analysis aims to assess the safety and effectiveness of retatrutide for weight reduction and better metabolic outcomes in obese individuals [252,258-260].

Experimentation and Limitations

This exploratory observation involved a small number of adult volunteers who independently elected to self-administer retatrutide according to the dosing schedules outlined in (Tables 1 and 2). The

formulation utilized was retatrutide at a concentration of 20 mg/mL. Participants were monitored periodically for changes in body weight, metabolic parameters, tolerability, and adverse events.

Preliminary observations suggested potential improvements in selected metabolic markers and body-weight-related outcomes among some participants. However, these findings should be interpreted with caution due to the exploratory nature of the observation and the absence of a controlled study design.

Several important limitations must be acknowledged. The sample size was small, limiting the generalizability of the findings. Participants were not randomized, and no placebo or comparison group was included. Self-administration may have introduced variability in dosing accuracy, adherence, lifestyle factors, and outcome reporting.

Additionally, the observation period may not have been sufficient to evaluate long-term efficacy, safety, or sustainability of treatment effects. Because retatrutide remains under clinical investigation, the observations reported here should not be considered evidence of clinical efficacy or safety. Further research involving larger, randomized, controlled clinical trials is required to establish the therapeutic benefits, optimal dosing strategies, and long-term safety profile of retatrutide.

Assuming the concentration is:

- 10 mg/mL
- mL = 100 units = 10 mg
- Therefore 1 unit = 0.01 mL = 0.1 mg

Suggested Dosage

Units	25	30	35	40	45	50	55	60	65	70	75	80	85	90	100
mL	0.25	0.30	0.35	0.40	0.45	0.50	0.55	0.60	0.65	0.70	0.75	0.80	0.85	0.90	1.00
mg	2.5	3.0	3.5	4.0	4.5	5.0	5.5	6.0	6.5	7.0	7.5	8.0	8.5	9.0	10

Table 1: Represents the retatrutide dosage and equivalent.

(Table 1) shows the schedule: increases of 0.5 mg every week from 2.5 mg to 10 mg. While the arithmetic is correct, many peptide titration schedules increase more slowly (often every 2–4 weeks) to reduce gastrointestinal side effects. Whether this schedule is appropriate depends on the specific retatrutide protocol, product concentration, and the prescribing clinician's instructions.

Suggested dosage per week:

Week 1-4	Week 1	Week 2	Week 3	Week 4
	25Units	30U	35U	40U
Week 5-8	Week 5	Week 6	Week 7	Week 8
	45 Units	50U	55U	60U
Week 9-12	Week 9	Week 10	Week 11	Week 12
	65 Units	70U	75U	80U

Week 13-16	Week 9	Week 10	Week 11	Week 12
	85 Units	90U	95U	100U
Week 17-onward	100 Units/week			

Table 2: Represents retatrutide weekly dosage.

The potential applications of retatrutide, whether in managing diabetes, obesity, or other metabolic disorders, could revolutionize treatment approaches, offering hope to those who previously had no viable options.

Summary

This review examined the synergistic interactions among glucagon-like peptide-1 (GLP-1), glucose-dependent insulinotropic polypeptide (GIP), and glucagon receptor (GCGR) agonists in regulating appetite, insulin sensitivity, glucose homeostasis, and energy expenditure. The evidence demonstrates that these hormones act through complementary physiological pathways involving the gut-brain axis, pancreatic endocrine function, adipose tissue metabolism, and hepatic energy regulation. GLP-1 primarily enhances insulin secretion, delays gastric emptying, suppresses appetite, and promotes weight loss. GIP contributes to glucose-dependent insulin secretion, improves adipose tissue function, and may enhance the therapeutic effects of GLP-1 when used in combination. GCGR activation increases energy expenditure, promotes lipid oxidation, and supports weight reduction through hepatic and central metabolic pathways.

The review further evaluated the evolution of incretin-based therapies from single-receptor agonists such as semaglutide, to dual agonists such as tirzepatide, and emerging triple agonists such as retatrutide. Clinical and preclinical evidence suggests that multi-receptor agonists achieve greater reductions in body weight and improvements in glycemic control than single-receptor therapies by targeting multiple aspects of metabolic regulation simultaneously. These findings highlight the growing therapeutic potential of combined activation of the GLP-1, GIP, and GCGR receptors for the treatment of obesity, type 2 diabetes mellitus, and related metabolic disorders.

Discussion

The findings of this review support the concept that obesity and type 2 diabetes are multifactorial disorders requiring therapeutic approaches that address several physiological systems simultaneously. While GLP-1 receptor agonists have transformed obesity and diabetes management through appetite suppression and improved glycemic control, their effects may be enhanced when combined with agonism at the GIP and GCGR receptors. The complementary actions of these hormones create a synergistic metabolic response that extends beyond glucose regulation alone.

GLP-1 exerts potent anorectic effects through the hypothalamus and gut-brain axis, leading to reduced caloric intake and improved insulin sensitivity. GIP, once considered primarily an obesogenic hormone, has demonstrated beneficial metabolic effects when combined with GLP-1 receptor activation, including enhanced insulin secretion, improved adipose tissue function, and reduced gastrointestinal adverse

effects. The success of tirzepatide illustrates how dual receptor activation can outperform traditional GLP-1 receptor agonists in achieving weight loss and glycemic improvement.

GCGR agonism introduces an additional therapeutic dimension by increasing energy expenditure, stimulating lipid metabolism, and reducing hepatic fat accumulation. Although glucagon alone may increase glucose production and limit its use as monotherapy, its combination with GLP-1 and GIP receptor agonism appears to offset these limitations while preserving its metabolic benefits. Emerging agents such as retatrutide exemplify this strategy by simultaneously targeting appetite suppression, insulin regulation, and energy expenditure.

Despite the promising outcomes, several challenges remain. Long-term safety, cardiovascular effects, treatment adherence, gastrointestinal tolerability, and cost-effectiveness require further investigation. In addition, the precise mechanisms underlying GIP receptor agonism and its contribution to weight loss remain incompletely understood. Future studies should focus on identifying optimal receptor activation ratios, patient-specific treatment strategies, and long-term clinical outcomes to maximize therapeutic efficacy while minimizing adverse effects.

The findings of this review support the concept that obesity and type 2 diabetes are multifactorial disorders requiring therapeutic approaches that address several physiological systems simultaneously. While GLP-1 receptor agonists have transformed obesity and diabetes management through appetite suppression and improved glycemic control, their effects may be enhanced when combined with agonism at the GIP and GCGR receptors. The complementary actions of these hormones create a synergistic metabolic response that extends beyond glucose regulation alone.

GLP-1 exerts potent anorectic effects through the hypothalamus and gut-brain axis, leading to reduced caloric intake and improved insulin sensitivity. GIP, once considered primarily an obesogenic hormone, has demonstrated beneficial metabolic effects when combined with GLP-1 receptor activation, including enhanced insulin secretion, improved adipose tissue function, and reduced gastrointestinal adverse effects. The success of tirzepatide illustrates how dual receptor activation can outperform traditional GLP-1 receptor agonists in achieving weight loss and glycemic improvement.

GCGR agonism introduces an additional therapeutic dimension by increasing energy expenditure, stimulating lipid metabolism, and reducing hepatic fat accumulation. Although glucagon alone may increase glucose production and limit its use as monotherapy, its combination with GLP-1 and GIP receptor agonism appears to offset these limitations while preserving its metabolic benefits. Emerging agents such as retatrutide exemplify this strategy by simultaneously targeting appetite suppression, insulin regulation, and energy expenditure.

Despite the promising outcomes, several challenges remain. Long-term safety, cardiovascular effects, treatment adherence, gastrointestinal tolerability, and cost-effectiveness require further investigation. In addition, the precise mechanisms underlying GIP receptor agonism and its contribution to weight loss remain incompletely understood. Future studies should focus on identifying optimal receptor activation ratios, patient-specific treatment strategies, and long-term clinical outcomes to maximize therapeutic

efficacy while minimizing adverse effects.

Recommendation

Based on the findings of this review, several important areas warrant further investigation to advance the clinical application of GLP-1, GIP, and GCGR receptor agonists for the management of obesity and metabolic disease.

Future research should focus on elucidating the molecular mechanisms underlying interactions among GLP-1, GIP, and GCGR receptors, optimizing receptor activation ratios, and evaluating the long-term safety and efficacy of multi-receptor agonists. Large-scale clinical trials are needed to establish patient-specific treatment strategies, assess cardiovascular and metabolic outcomes, and determine the cost-effectiveness of these therapies. A deeper understanding of gut–brain–metabolic signaling pathways will facilitate the development of personalized therapeutic approaches and advance next-generation incretin-based treatments for obesity, type 2 diabetes mellitus, and related metabolic disorders.

Conclusion

The collective evidence reviewed in this study indicates that the combined activation of the GLP-1, GIP, and GCGR pathways offers a highly promising strategy for treating obesity, type 2 diabetes mellitus, and other metabolic disorders. These hormones work through interconnected mechanisms that regulate appetite, enhance insulin sensitivity, improve glucose homeostasis, increase energy expenditure, and promote weight reduction. The synergistic effects observed with dual- and triple-receptor agonists suggest that multi-target therapies can provide superior metabolic benefits compared with single-receptor approaches.

Advances in pharmacological development, particularly with agents such as tirzepatide and retatrutide, demonstrate the potential of next-generation incretin-based therapies to reshape the management of metabolic disease. As research continues to clarify the molecular mechanisms and long-term outcomes associated with these treatments, combined agonism of the GLP-1, GIP, and GCGR receptors may become a cornerstone of future therapeutic strategies to address the growing global burden of obesity and diabetes. Ultimately, a comprehensive understanding of hormonal interactions within the gut-brain-metabolic axis will be essential for developing more effective, personalized, and durable interventions for metabolic health.

References

1. Müller TD, Finan B, Bloom SR, D'Alessio D, Drucker D J, Flatt P R, et al. (2019) Glucagon-like peptide 1 (GLP-1). Mol Metab. 30:72-130.
2. Liu QK. (2024) Mechanisms of action and therapeutic applications of GLP-1 and dual GIP/GLP-1 receptor agonists. Front Endocrinol. 15:1431292.
3. Chrysavgis LG, Kazanas S, Bafa K, Rozani S, Koloutsou ME, et al. (2024) Glucagon-like Peptide 1, Glucose-Dependent Insulinotropic Polypeptide, and Glucagon Receptor Agonists in Metabolic Dysfunction-Associated Steatotic Liver Disease: Novel Medication in New Liver Disease Nomenclature. Int J Mol Sci. 25(7):3832.
4. Sandoval D A, D'Alessio DA. (2015) Physiology of proglucagon peptides: Role of glucagon and GLP-

1 in health and disease. Physiol Rev. 95(2):513-48.
5. Holst JJ. (2007) The physiology of glucagon-like peptide 1. Physiol Rev. 87(4): 1409-39.
6. Yabut JM, Drucker DJ. (2023) Glucagon-like Peptide-1 Receptor-based Therapeutics for Metabolic Liver Disease. Endocr Rev. 44(1):14-32.
7. Baggio LL, Drucker DJ. (2007) Biology of incretins: GLP-1 and GIP. Gastroenterology 32(6):2131-57.
8. Zhao X, Wang M, Wen Z, Lu Z, Cui L, et al. (2021) GLP-1 Receptor Agonists: Beyond Their Pancreatic Effects. Front Endocrinol. 12:721135.
9. Pyke C, Heller RS, Kirk RK, Ørskov C, Reedtz-Runge S, et al. (2014) GLP-1 receptor localization in monkey and human tissue: Novel distribution revealed with extensively validated monoclonal antibody. Endocrinology 155(4):1280-90.
10. Laurindo LF, Barbalho SM, Guiguer EL, da Silva Soares de Souza M, de Souza GA, et al. (2022) GLP-1a: Going beyond Traditional Use. Int J Mol Sci. 23(2): 739.
11. Nauck MA, Quast DR, Wefers J, Meier JJ. (2021) GLP-1 receptor agonists in the treatment of type 2 diabetes—State-of-the-art. Mol Metab. 46: 101102.
12. Secher A, Jelsing J, Baquero AF, Hecksher-Sørensen J, Cowley MA, et al. (2014) The arcuate nucleus mediates GLP-1 receptor agonist liraglutide-dependent weight loss. J Clin Invest. 124(10): 4473-88.
13. Gabery S, Salinas CG, Paulsen SJ, Ahnfelt-Rønne J, Alanentalo T, et al. (2020) Semaglutide lowers body weight in rodents via distributed neural pathways. JCI Insight. 5(6): e133429.
14. Nakatani Y, Maeda M, Matsumura M, Shimizu R, Banba N, Aso Y, et al. (2017) Effect of GLP-1 receptor agonist on gastrointestinal tract motility and residue rates as evaluated by capsule endoscopy. Diabetes Metab. 43(5): 430-37.
15. Gutniak M, Ørkov C, Holst JJ, Ahrén B, Efendić S. (1992) Antidiabetogenic effect of glucagon-like peptide-1 (7-36) amide in normal subjects and patients with diabetes mellitus. N Engl J Med. 326(20): 1316-22.
16. Creutzfeldt WOC, Kleine N, Willms B, Ørskov C, Holst JJ, et al. (1996) Glucagonostatic actions and reduction of fasting hyperglycemia by exogenous glucagon-like peptide I (7-36) amide in type I diabetic patients. Diabetes Care. 19(6):580-86.
17. Bifari F, Manfrini R, Cas MD, Berra C, Siano M, et al. (2018) Multiple target tissue effects of GLP-1 analogues on non-alcoholic fatty liver disease (NAFLD) and non-alcoholic steatohepatitis (NASH) Pharmacol Res. 137:219-29.
18. Kagdi S, Lyons SA, Beaudry JL. (2024) The interplay of glucose-dependent insulinotropic polypeptide in adipose tissue. J Endocrinol. 261(3): e230361.
19. Ugleholdt R, Poulsen ML, Holst PJ, Irminger JC, Orskov C, et al. (2006) Prohormone convertase 1/3 is essential for processing of the glucose-dependent insulinotropic polypeptide precursor. J Bio Chem. 281(16):11050-57.
20. Brown JC, Pederson RA. (1970) A multiparameter study on the action of preparations containing cholecystokinin-pancreozymin. Scand J Gastro. 5(6): 537–541.
21. Dupre J, Ross S A, Watson D, Brown J C (1973) Stimulation of insulin secretion by gastric inhibitory polypeptide in man. J Clini Endo and Metabol. 37(5): 826–828.
22. Finan B, Muller T D, Clemmensen C, Perez-Tilve D, DiMarchi R D, Tschop M H (2016) Reappraisal of GIP pharmacology for metabolic diseases. Tren Molec Med. 22(5): 359–376.
23. Kieffer T J, McIntosh C H, Pederson R A (1995) Degradation of glucosedependent insulinotropic polypeptide and truncated glucagon-like peptide 1 in vitro and in vivo by dipeptidyl peptidase IV. Endocrinology 136(8): 3585–3596.
24. Mentlein R, Gallwitz B, Schmidt W E (1993) Dipeptidyl-peptidase IV hydrolyses gastric inhibitorypolypeptide,

glucagon-like peptide-1(7-36) amide, peptide histidine methionine and is responsible for their degradation in human serum. Euro J Biochem. 214(3): 829–835.

25. Seino Y, Fukushima M, Yabe D. (2010) GIP and GLP-1, the two incretin hormones: similarities and differences. J Diab Invest. 1(1-2): 8-23.
26. Beaudry JL, Kaur KD, Varin EM, Baggio LL, Cao X, et al. (2019) Physiological roles of the GIP receptor in murine brown adipose tissue. Molec Metabol. 28:14-25.
27. Hammoud R, Drucker DJ (2022) Beyond the pancreas: contrasting cardiometabolic actions of GIP and GLP1. Nature Reviews. Endocrinology 19: 201-16.
28. Takahashi Y, Fujita H, Seino Y, Hattori S, Hidaka S, et al. (2023) Gastric inhibitory polypeptide receptor antagonism suppresses intramuscular adipose tissue accumulation and ameliorates sarcopenia. J Cach Sarcop Muscle. 14(6): 2703-2718.
29. Tuccinardi D, Watanabe M, Masi D, Gianfrilli D, Manfrini S, et al. (2025) GLP-1 and GIP Beyond Glycaemia: Evolutionary Roles in Energy Optimisation and Organ Protection. Diabetes Metab Res Rev. 41(8): e70108.
30. Borner T, Geisler CE, Fortin SM, Cosgrove R, Alsina-Fernandez J, et al. (2021) GIP Receptor Agonism Attenuates GLP-1 Receptor Agonist-Induced Nausea and Emesis in Preclinical Models. Diabetes. 70(11): 2545-53.
31. McLean BA, Wong CK, Kaur KD, Seeley RJ, Drucker DJ. (2021) Differential importance of endothelial and hematopoietic cell GLP-1Rs for cardiometabolic versus hepatic actions of semaglutide. JCI Insight 6(22): e153732.
32. Choe SS, Huh JY, Hwang IJ, Kim JI, Kim JB. (2016) Adipose tissue remodeling: its role in energy metabolism and metabolic disorders. Front in Endocrin. (Lausanne) 7: 30.
33. Cannon B, Nedergaard J. (2004) Brown adipose tissue: function and physiological significance. Physio Rev. 84(1): 277-359.
34. Becher T, Palanisamy S, Kramer DJ, Eljalby M, Marx SJ, et al. (2021) Brown adipose tissue is associated with cardiometabolic health. Nat Med. 27(1): 58-65.
35. Wibmer AG, Becher T, Eljalby M, Crane A, Andrieu PC, et al. (2021) Brown adipose tissue is associated with healthier body fat distribution and metabolic benefits independent of regional adiposity. Cell Rep Med. 2(7): 100332.
36. Goossens GH, Blaak EE. (2015) Adipose tissue dysfunction and impaired metabolic health in human obesity: a matter of oxygen? Front Endocrinol (Lausanne) 6:55.
37. Hu D, Remash D, Russell RD, Greenaway T, Rattigan S, et al. (2018) Impairments in adipose tissue microcirculation in type 2 diabetes mellitus assessed by real-time contrast-enhanced ultrasound. Cir Cardio Imag. 11(4): e007074.
38. Wewer Albrechtsen NJ, Holst JJ, Cherrington AD, Finan B, Gluud LL, et al. (2023) 100 years of glucagon and 100 more. Diabetologia 66(8): 1378-1394.
39. Elmelund E, Galsgaard KD, Johansen CD, Trammell SAJ, Bomholt AB, et al. (2022) Opposing effects of chronic glucagon receptor agonism and antagonism on amino acids, hepatic gene expression, and alphacells. iScience 25(11): 105296.
40. Kraft G, Coate KC, Winnick JJ, Dardevet D, Donahue EP, et al. (2017) Glucagon's effect on liver protein metabolism in vivo. Am J Physiol Endocrinol Metab. 313(3): E263-E272.
41. Vilstrup H, Hansen BA, Almdal TP. (1990) Glucagon increases hepatic efficacy for urea synthesis. J Hepatol. 10(1): 46-50.
42. Solloway MJ, Madjidi A, Gu C, Eastham-Anderson J, Clarke HJ, et al. (2015) Glucagon Couples Hepatic Amino Acid Catabolism to mTOR-Dependent Regulation of α-Cell Mass. Cell Rep. 12(3): 495-510.
43. Galsgaard KD, Pedersen J, Knop FK, Holst JJ, Wewer Albrechtsen NJ. (2019) Glucagon receptor signaling and lipid metabolism. Front Physiol. 10:413.

44. Gerich JE, Lorenzi M, Bier DM, Schneider V, Tsalikian E, et al. (1975) Prevention of human diabetic ketoacidosis by somatostatin. Evidence for an essential role of glucagon. N Engl J Med. 292(19): 985-9.
45. Inokuchi A, Oomura Y, Nishimura H. (1984) Effect of intracerebroventricularly infused glucagon on feeding behavior. Physiol Behav. 33(3): 397-400.
46. Davidson IW, Salter JM, Best CH. (1957) Calorigenic action of glucagon. Nature. 180(4595): 1124.
47. Thiessen SE, Derde S, Derese I, Dufour T, Vega CA, et al. (2017) Role of Glucagon in Catabolism and Muscle Wasting of Critical Illness and Modulation by Nutrition. Am J Respir Crit Care Med. 196(9): 1131-1143.
48. Charron MJ, Vuguin PM. (2015) Lack of glucagon receptor signaling and its implications beyond glucose homeostasis. J Endocrinol 224(3): R123-30.
49. Kim J, Kim J, Choi C, Bae J, Choi HJ. (2025) Structural insights into GPCR signaling activated by peptide ligands: from molecular mechanism to therapeutic application. Exp Mol Med. 57(7): 1467-1481.
50. Zhang MY, Chen T, Lu X, Lan XB, Chen ZQ, et al. (2024) G protein-coupled receptors (GPCRs): advances in structures, mechanisms, and drug discovery. Signal Transduct Target Ther. 9(1): 88.
51. Stevens RC, Cherezov V, Katritch V, Abagyan R, Kuhn P, et al. (2013) The GPCR Network: a large-scale collaboration to determine human GPCR structure and function. Nat Rev Drug Discov. 12(1): 25-34.
52. Sutkeviciute I, Vilardaga JP. (2020) Structural insights into emergent signaling modes of G protein-coupled receptors. J Biol Chem. 295(33): 11626-642.
53. DeMaria S, Ngai J. (2010) The cell biology of smell. J Cell Biol. 191(3): 443-452.
54. Roper SD, Chaudhari N. (2017) Taste buds: cells, signals and synapses. Nat Rev Neurosci. 18(8): 485-497.
55. Grammatopoulos DK. (2017) Regulation of G-protein coupled receptor signaling underpinning neurobiology of mood disorders and depression. Mol Cell Endocrinol. 449: 82-89.
56. Barella LF, Jain S, Kimura T, Pydi SP. (2021) Metabolic roles of G protein-coupled receptor signaling in obesity and type 2 diabetes. FEBS J. 288(8): 2622-44.
57. Jin C, Chen H, Xie L, Zhou Y, Liu LL, et al. (2024) GPCRs involved in metabolic diseases: pharmacotherapeutic development updates. Acta Pharmacol Sin. 45(7): 1321-1336.
58. Li Y, Li B, Chen WD, Wang YD. (2023) Role of G-protein coupled receptors in cardiovascular diseases. Front Cardiovasc Med. 10: 1130312.
59. Wang J, Gareri C, Rockman HA. (2018) G-Protein-Coupled Receptors in Heart Disease. Circ Res. 123(6): 716-735.
60. Wong TS, Li G, Li S, Gao W, Chen G, et al. (2023) G protein-coupled receptors in neurodegenerative diseases and psychiatric disorders. Signal Transduct Target Ther. 8(1): 177.
61. Huang Y, Todd N, Thathiah A. (2017) The role of GPCRs in neurodegenerative diseases: avenues for therapeutic intervention. Curr Opin Pharmacol. 32: 96-110.
62. Barella LF, Jain S, Pydi SP. (2022) G protein-coupled receptors: Role in metabolic disorders. Front Endocrinol (Lausanne). 13: 984253.
63. Bellmann-Sickert K, Beck-Sickinger AG. (2010) Peptide drugs to target G protein-coupled receptors. Tren Pharma Sci. 31(9): 434-441.
64. Bockaert J, Pin JP (1999) Molecular tinkering of G protein-coupled receptors: an evolutionary success. EMBO J. 18(7): 1723-1729.
65. Liu J, Jing C, Guo Y, Shang Z, Zhang B, et al. (2025) The central signaling pathways related to metabolism-regulating hormones of the gut-brain axis: a review. J Transl Med. 23(1): 648.
66. Qin PP, Wang ZQ, Liu L, Xiong QJ, Liu D, et al. (2025) The association between BMI and postoperative pulmonary complications in adults undergoing non-cardiac, non-obstetric surgery: a retrospective cohort study. Anaesthesia 80(11): 1312-21.
67. Brüning JC, Fenselau H. (2023) Integrative neurocircuits that control metabolism and food intake. Science 381(6665): eabl7398.

68. Li M, Tan HE, Lu Z. (2022) Gut-brain circuits for fat preference. Nature 610(7933): 722-30.
69. Gribble FM, Reimann F. (2021) Metabolic messengers: glucagon-like peptide 1. Nat Metab. 3(2): 142-8.
70. Picard A, Metref S, Tarussio D, Dolci W, Berney X, et al. (2021) Fgf15 Neurons of the Dorsomedial Hypothalamus Control Glucagon Secretion and Hepatic Gluconeogenesis. Diabetes 70(7): 1443-57.
71. Routh VH. (2010) Glucose sensing neurons in the ventromedial hypothalamus. Sens (Basel) 10(10): 9002-25.
72. Sandoval DA, D'Alessio DA. (2015) Physiology of proglucagon peptides: role of glucagon and GLP-1 in health and disease. Physiol Rev. 95(2): 513-48.
73. Suzuki Y, Zhang H, Saito N, Kojima I, Urano T, et al. (2006) Glucagon-like peptide 1 activates protein kinase C through Ca2+ dependent activation of phospholipase C in insulin-secreting cells. J Biol Chem. 281(39): 28499-507.
74. Fukuda M. (2020) The Role of GIP Receptor in the CNS for the Pathogenesis of Obesity. Diabetes. 70(9): 1929-1937.
75. Marks V. (2020) The early history of GIP 1969-2000: from enterogastrone to major metabolic hormone. Peptides 125:170276.
76. Yip RG, Wolfe MM. (2000) GIP biology and fat metabolism. Life Sci. 66(2): 91-103.
77. Miyawaki K, Yamada Y, Ban N, Ihara Y, Tsukiyama K, et al. (2002) Inhibition of gastric inhibitory polypeptide signaling prevents obesity. Nat Med. 8(7): 738-42.
78. Creutzfeldt W, Ebert R, Willms B, Frerichs H, Brown JC. (1978) Gastric inhibitory polypeptide (GIP) and insulin in obesity: increased response to stimulation and defective feedback control of serum levels. Diabetologia 14(1):15-24.
79. Bailey CJ, Flatt PR, Kwasowski P, Powell CJ, Marks V. (1986) Immunoreactive gastric inhibitory polypeptide and K cell hyperplasia in obese hyperglycaemic (ob/ob) mice fed high-fat and high-carbohydrate cafeteria diets. Acta Endocrinol (Copenh) 112(2): 224-29.
80. Polak JM, Pearse AG, Grimelius L, Marks V. (1975) Gastrointestinal apudosis in obese hyperglycaemic mice. Virchows Arch B Cell Pathol. 19(2): 135-150.
81. Killion EA, Lu SC, Fort M, Yamada Y, Véniant MM, et al. (2020) Glucose-dependent insulinotropic polypeptide receptor therapies for the treatment of obesity, do agonists = antagonists? Endocr Rev. 41(1): bnz002.
82. Woods SC, West DB, Stein LJ, McKay LD, Lotter EC, et al. (2020) Peptides and the control of meal size. Diabetologia 20(1): 305-13.
83. Ambati S, Duan J, Hartzell DL, Choi YH, Della-Fera MA, et al. (2011) GIP-dependent expression of hypothalamic genes. Physiol Res. 60: 941-50.
84. NamKoong C, Kim M S, Jang B T, Lee Y H, Cho Y M, Choi H J (2017) Central administration of GLP-1 and GIP decreases feeding in mice. Biochem Biophys Res Commun. 490(2):247-52.
85. Mroz PA, Finan B, Gelfanov V, Yang B, Tschöp MH, et al. (2019) Optimized GIP analogs promote body weight lowering in mice through GIPR agonism not antagonism. Mol Metab. 20:51-62.
86. Zhang Q, Delessa CT, Augustin R, Bakhti M, Colldén G, et al. (2021) The glucose-dependent insulinotropic polypeptide (GIP) regulates body weight and food intake via CNS-GIPR signaling. Cell Metab. 33(4): 833-844.e5.
87. Kim SJ, Nian C, Karunakaran S, Clee SM, Isales CM, et al. (2012) GIP-overexpressing mice demonstrate reduced diet-induced obesity and steatosis, and improved glucose homeostasis. PLoS One 7(7): e40156.
88. Frias JP, Nauck MA, Van J, Kutner ME, Cui X, et al. (2018) Efficacy and safety of LY3298176, a novel dual GIP and GLP-1 receptor agonist, in patients with type 2 diabetes: a randomised, placebo-controlled and active comparator-controlled phase 2 trial. Lancet. 392(10160): 2180-93.
89. Finan B, Ma T, Ottaway N, Müller TD, Habegger KM, et al. (2013) Unimolecular dual incretins maximize

metabolic benefits in rodents, monkeys, and humans. Sci Transl Med. 5(209):209ra151.

90. Nauck MA, Holle H, Kahle M, Tytko A, Deacon CF, et al. (2020) No evidence of tachyphylaxis for insulinotropic actions of glucose-dependent insulinotropic polypeptide (GIP) in subjects with type 2 diabetes, their first-degree relatives, or in healthy subjects. Peptides 125: 170176.
91. Killion EA, Chen M, Falsey JR, Sivits G, Hager T, et al. (2020) Chronic glucose-dependent insulinotropic polypeptide receptor (GIPR) agonism desensitizes adipocyte GIPR activity mimicking functional GIPR antagonism. Nat Commun. 11(1): 4981.
92. Campbell JE. (2021) Targeting the GIPR for obesity: to agonize or antagonize? Potential mechanisms. Mol Metab. 46: 101139.
93. Long F, Challa TD, Efthymiou V, Klug M, Klein T, et al. (2026) Hepatic GCGR is required for the superior weight loss and metabolic effects of a structurally related analogue of the dual GCGR/GLP-1R agonist survodutide in mice. Diabetes Obes Metab. 28(3): 2437-2442.
94. Nason SR, Antipenko J, Presedo N, Cunningham SE, Pierre TH, et al. (2021) Glucagon receptor signaling regulates weight loss via central KLB receptor complexes. JCI Insight. 6(4): e141323.
95. Khaodhair L, McCowen KC, Blackburn GL. (1999) Obesity and its comorbid conditions. Clin Cornerstone. 2(3): 17-31.
96. Blissmer B, Riebe D, Dye G, Ruggiero L, Greene G, et al. (2006) Health-related quality of life following a clinical weight loss intervention among overweight and obese adults: intervention and 24month follow-up effects. Health Qual Life Outcomes 4:43.
97. Fontaine KR, Barofsky I, Andersen RE, Bartlett SJ, Wiersema L, et al. (1999) Impact of weight loss on health-related quality of life. Qual Life Res. 8(3): 275-7.
98. Rothberg AE, McEwen LN, Kraftson AT, Neshewat GM, Fowler CE, et al. (2014) The impact of weight loss on health-related quality-of-life: implications for cost-effectiveness analyses. Qual Life Res. 23(4): 1371-1376.
99. Anderson JW, Konz EC. (2001) Obesity and disease management: effects of weight loss on comorbid conditions. Obes Res. 9 (4): 326S-334S.
100. Ryan DH, Yockey SR. (2017) Weight Loss and Improvement in Comorbidity: Differences at 5%, 10%, 15%, and Over. Curr Obes Rep. 6(2): 187-194.
101. Yanovski SZ, Yanovski JA. (2014) Long-term drug treatment for obesity: a systematic and clinical review. JAMA 311(1): 74-86.
102. Van Gaal L, Dirinck E. (2016) Pharmacological Approaches in the Treatment and Maintenance of Weight Loss. Diab Care. 39(Suppl 2): S260-7.
103. Pocai A, Carrington PE, Adams JR, Wright M, Eiermann G, et al. (2009) Glucagon-like peptide 1/glucagon receptor dual agonism reverses obesity in mice. Diabetes 58(10): 2258-2266.
104. Day JW, Ottaway N, Patterson JT, Gelfanov V, Smiley D, et al. (2009) A new glucagon and GLP-1 co-agonist eliminates obesity in rodents. Nat Chem Biol. 5(10): 749-757.
105. Kim T, Nason S, Holleman C, Pepin M, Wilson L, et al. (2018) Glucagon Receptor Signaling Regulates Energy Metabolism via Hepatic Farnesoid X Receptor and Fibroblast Growth Factor 21. Diabetes 67(9): 1773-1782.
106. Habegger KM, Stemmer K, Cheng C, Müller TD, Heppner KM, et al. (2013) Fibroblast growth factor 21 mediates specific glucagon actions. Diabetes 62(5): 1453-63.
107. Cyphert HA, Alonge KM, Ippagunta SM, Hillgartner FB. (2014) Glucagon stimulates hepatic FGF21 secretion through a PKA- and EPAC-dependent posttranscriptional mechanism. PLoS One 9(4): e94996.
108. Babaknejad N, Nayeri H, Hemmati R, Bahrami S, Esmaillzadeh A. (2018) An Overview of FGF19 and FGF21: The Therapeutic Role in the Treatment of the Metabolic Disorders and Obesity. Horm Metab Res. 50(6): 441-52.
109. Jimenez V, Jambrina C, Casana E, Sacristan V, Muñoz S, (2018) FGF21 gene therapy as treatment for obesity and insulin resistance. EMBO Mol Med. 10(8): e8791.

110. Zhao Y, Dunbar JD, Kharitonenkov A. (2012) FGF21 as a therapeutic reagent. Adv Exp Med Biol. 728: 214-28.
111. Kharitonenkov A, DiMarchi R. (2017) Fibroblast growth factor 21night watch: advances and uncertainties in the field. J Intern Med. 281(3): 233-246.
112. Kharitonenkov A, Shiyanova TL, Koester A, Ford AM, Micanovic R, et al. (2005) FGF-21 as a novel metabolic regulator. J Clin Invest. 115(6): 1627-1635.
113. Geng L, Lam KSL, Xu A. (2020) The therapeutic potential of FGF21 in metabolic diseases: from bench to clinic. Nat Rev Endocrinol 16(11):654-67.
114. Fisher FM, Kleiner S, Douris N, Fox EC, Mepani RJ, et al. (2012) FGF21 regulates PGC-1α and browning of white adipose tissues in adaptive thermogenesis. Genes Dev. 26(3): 271-81.
115. Wanders D, Forney LA, Stone KP, Burk DH, Pierse A, et al. (2017) FGF21 Mediates the Thermogenic and Insulin-Sensitizing Effects of Dietary Methionine Restriction but Not Its Effects on Hepatic Lipid Metabolism. Diabetes. 66(4): 858-867.
116. Potthoff MJ, Inagaki T, Satapati S, Ding X, He T, et al. (2009) FGF21 induces PGC-1alpha and regulates carbohydrate and fatty acid metabolism during the adaptive starvation response. Proc Natl Acad Sci USA 106(26): 10853-58.
117. Markan KR, Naber MC, Ameka MK, Anderegg MD, Mangelsdorf DJ, et al. (2014) Circulating FGF21 is liver derived and enhances glucose uptake during refeeding and overfeeding. Diabetes 63(12): 4057-63.
118. Camporez JP, Jornayvaz FR, Petersen MC, Pesta D, Guigni BA, et al. (2013) Cellular mechanisms by which FGF21 improves insulin sensitivity in male mice. Endocrinology 154(9): 3099-3109.
119. Mashili FL, Austin RL, Deshmukh AS, Fritz T, Caidahl K, et al. (2011) Direct effects of FGF21 on glucose uptake in human skeletal muscle:implications for type 2 diabetes and obesity. Diabetes Metab Res Rev. 27(3): 286-297.
120. Coskun T, Bina HA, Schneider MA, Dunbar JD, Hu CC, et al. (2008) Fibroblast growth factor 21 corrects obesity in mice. Endocrinology 149(12): 6018-27.
121. Ornitz DM, Itoh N. (2015) The Fibroblast Growth Factor signaling pathway. Wiley Interdiscip Rev Dev Biol. 4(3): 215-66.
122. Suzuki M, Uehara Y, Motomura-Matsuzaka K, Oki J, Koyama Y, et al. (2008) betaKlotho is required for fibroblast growth factor (FGF) 21 signaling through FGF receptor (FGFR) 1c and FGFR3c. Mol Endocrinol 22(4): 1006-14.
123. Ogawa Y, Kurosu H, Yamamoto M, Nandi A, Rosenblatt KP, et al. (2007) BetaKlotho is required for metabolic activity of fibroblast growth factor 21. Proc Natl Acad Sci USA 104(18): 7432-7437.
124. Kharitonenkov A, Dunbar JD, Bina HA, Bright S, Moyers JS, et al. (2008) FGF-21/FGF-21 receptor interaction and activation is determined by betaKlotho. J Cell Physiol. 215(1): 1-7.
125. Bookout AL, de Groot MH, Owen BM, Lee S, Gautron L, et al. (2013) FGF21 regulates metabolism and circadian behavior by acting on the nervous system. Nat Med. 19(9): 1147-1152.
126. Fon Tacer K, Bookout AL, Ding X, Kurosu H, John GB, et al. (2010) Research resource: Comprehensive expression atlas of the fibroblast growth factor system in adult mouse. Mol Endocrinol 24(10): 2050-2064.
127. Owen BM, Ding X, Morgan DA, Coate KC, Bookout AL, et al. (2014) FGF21 acts centrally to induce sympathetic nerve activity, energy expenditure, and weight loss. CellMetab. 20(4): 670-677.
128. Beydoun MA, Min J, Xue H, Kaminsky LA, Cheskin LJ. (2020) Has the prevalence of overweight, obesity and central obesity levelled off in the United States? Trends, patterns, disparities, and future projections for the obesity epidemic. Int J Epidemiol 49(3): 810-823.
129. Zhang X, Ha S, Lau HC, Yu J. (2023) Excess body weight: Novel insights into its roles in obesity comorbidities. Semin Cancer Biol. 92: 16-27.
130. Malik IO, Petersen MC, Klein S. (2022) Glucagon-like peptide-1, glucose-dependent insulinotropic

polypeptide, and glucagon receptor poly-agonists: a new era in obesity pharmacotherapy. Obesity (Silver Spring) 30(9): 1718-1721.

131. Killion EA, Wang J, Yie J, Shi SD, Bates D, et al. (2018) Anti-obesity effects of GIPR antagonists alone and in combination with GLP-1R agonists in preclinical models. Sci Transl Med. 10(472): eaat3392.
132. Samms RJ, Christe ME, Collins KA, Pirro V, Droz BA, et al. (2021) GIPR agonism mediates weight-independent insulin sensitization by tirzepatide in obese mice. J Clin Invest. 131(12): e146353.
133. Röder PV, Wu B, Liu Y, Han W. (2016) Pancreatic regulation of glucose homeostasis. Exp Mol Med. 48(3): e219.
134. Komatsu M, Takei M, Ishii H, Sato Y. (2013) Glucose-stimulated insulin secretion: a newer perspective. J Diabetes Investig. 4(6): 511-16.
135. Khan AH, Pessin JE. (2002) Insulin regulation of glucose uptake: a complex interplay of intracellular signalling pathways. Diabetologia. 45(11):1475-83.
136. Kohn AD, Summers SA, Birnbaum MJ, Roth RA. (1996) Expression of a constitutively active Akt Ser/Thr kinase in 3T3-L1 adipocytes stimulates glucose uptake and glucose transporter 4 translocation. J Biol Chem. 271(49): 31372-78.
137. Zisman A, Peroni OD, Abel ED, Michael MD, Mauvais-Jarvis F, et al. (2000) Targeted disruption of the glucose transporter 4 selectively in muscle causes insulin resistance and glucose intolerance. Nat Med. 6(8): 924-928.
138. Sibrowski W, Seitz HJ. (1984) Rapid action of insulin and cyclic AMP in the regulation of functional messenger RNA coding for glucokinase in rat liver. J Biol Chem. 259: 343-46.
139. Kim SY, Kim HI, Kim TH, Im SS, Park SK, et al. (2004) SREBP-1c mediates the insulin-dependent hepatic glucokinase expression. J Biol Chem. 279(29): 30823-30829. Erratum in: J Biol Chem. 279(35): 37210.
140. Aiston S, Hampson LJ, Arden C, Iynedjian PB, Agius L. (2006) The role of protein kinase B/Akt in insulin-induced inactivation of phosphorylase in rat hepatocytes. Diabetologia 49(1): 174-82.
141. Syed NA, Khandelwal RL. (2000) Reciprocal regulation of glycogen phosphorylase and glycogen synthase by insulin involving phosphatidylinositol-3 kinase and protein phosphatase-1 in HepG2 cells. Mol Cell Biochem. 211(1-2): 123-36.
142. Miller T B Jr, Larner J. (1973) Mechanism of control of hepatic glycogenesis by insulin. J Biol Chem. 248(10): 3483-88.
143. Akpan JO, Gardner R, Wagle SR. (1974) Studies on the effects of insulin and acetylcholine on activation of glycogen synthase and on glycogenesis in hepatocytes. Biochem Biophys Res Commun. 61(1): 222-29.
144. Stalmans W, De Wulf H, Hue L, Hers HG. (1974) The sequential inactivation of glycogen phosphorylase and activation of glycogen synthetase in liver after the administration of glucose to mice and rats. The mechanism of the hepatic threshold to glucose. Eur J Biochem. 41(1): 127-34.
145. O'Brien RM, Lucas PC, Forest PD, Magnuson MA, Granner DK. (1990) Identification of a sequence in the PEPCK gene that mediates a negative effect of insulin on transcription. Science 249(4968): 533–537.
146. Streeper RS, Svitek CA, Chapman S, Greenbaum LE, Taub R, et al. (1997) A multicomponent insulin response sequence mediates a strong repression of mouse glucose-6-phosphatase gene transcription by insulin. J Biol Chem. 272(18): 11698-701.
147. Duong DT, Waltner-Law ME, Sears R, Sealy L, Granner DK. (2002) Insulin inhibits hepatocellular glucose production by utilizing liver-enriched transcriptional inhibitory protein to disrupt the association of CREB-binding protein and RNA polymerase II with the phosphoenolpyruvate carboxykinase gene promoter. J Biol Chem. 277(35): 32234-242.
148. Nakae J, Kitamura T, Silver DL, Accili D. (2001) The forkhead transcription factor Foxo1 (Fkhr) confers insulin sensitivity onto glucose-6-phosphatase expression. J Clin Invest. 108(9): 1359-67.
149. Schmoll D, Walker KS, Alessi DR, Grempler R, Burchell A, et al. (2000) Regulation of glucose-6-phosphatase

gene expression by protein kinase Balpha and the forkhead transcription factor FKHR. Evidence for insulin response unit-dependent and -independent effects of insulin on promoter activity. J Biol Chem. 275(46): 36324-33.

150. Lochhead PA, Coghlan M, Rice SQ, Sutherland C. (2001) Inhibition of GSK-3 selectively reduces glucose-6-phosphatase and phosphatase and phosphoenolypyruvate carboxykinase gene expression. Diabetes 50(5): 937-46.
151. Walton PE, Etherton TD. (1986) Stimulation of lipogenesis by insulin in swine adipose tissue: antagonism by porcine growth hormone. J Anim Sci. 62(6): 1584-95.
152. McTernan PG, Harte AL, Anderson LA, Green A, Smith SA, et al. (2002) Insulin and rosiglitazone regulation of lipolysis and lipogenesis in human adipose tissue in vitro. Diabetes 51(5): 1493-1498.
153. Biolo G, Declan Fleming RY, Wolfe RR. (1995) Physiologic hyperinsulinemia stimulates protein synthesis and enhances transport of selected amino acids in human skeletal muscle. J Clin Invest. 95(2): 811-19.
154. Salehi M, Purnell JQ. (2019) The Role of Glucagon-Like Peptide-1 in Energy Homeostasis. Metab Syndr Relat Disord. 17(4):183-91.
155. Nauck MA, Quast DR, Wefers J, Pfeiffer AFH. (2021) The evolving story of incretins (GIP and GLP-1) in metabolic and cardiovascular disease: A pathophysiological update. Diabetes Obes Metab. 23(3:5):29.
156. González-García I, Milbank E, Diéguez C, López M, Contreras C (2019) Glucagon, GLP-1 and Thermogenesis. Int J Mol Sci. 20(14): 3445.
157. Holst JJ, Rosenkilde MM. (2020) GIP as a Therapeutic Target in Diabetes and Obesity: Insight from Incretin Co-agonists. J Clin Endocrinol Metab. 105(8): e2710-6.
158. Nadkarni P, Chepurny OG, Holz GG. (2014) Regulation of glucose homeostasis by GLP-1. Prog Mol Biol Transl Sci. 121:23-65.
159. Calderon G, McRae A, Rievaj J, Davis J, Zandvakili I, et al. (2022) Ileo-colonic delivery of conjugated bile acids improves glucose homeostasis via colonic GLP-1-producing enteroendocrine cells in human obesity and diabetes. Ebio Medicine. 55:102759.
160. Spreckley E, Murphy KG. (2015) The L-Cell in Nutritional Sensing and the Regulation of Appetite. Front Nutr. 2:23.
161. Nakrani MN, Wineland RH, Anjum F. (2024) Physiology, glucose metabolism. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing.
162. Mann E, Sunni M, Bellin MD. (2020) Secretion of Insulin in Response to Diet and Hormones. Pancreapedia: Exocrine Pancreas Knowledge Base.
163. Kusminski CM, Perez-Tilve D, Müller TD, DiMarchi RD, Tschöp MH, et al. (2024) Transforming obesity: The advancement of multi-receptor drugs. Cell 187(15): 3829-3853.
164. Müller TD, Blüher M, Tschöp MH, DiMarchi RD. (2022) Anti-obesity drug discovery: advances and challenges. Nat Rev Drug Discov. 21(3): 201-223.
165. Qiao Y, Zhou F, Mao T, Gao L. (2026) Revitalizing GIP: Therapeutic Potential in Metabolic and Neurodegenerative Disorders. Diabetes Metab Syndr Obes. 19: 559587.
166. Unger RH, Orci L. (1975) The essential role of glucagon in the pathogenesis of diabetes mellitus. Lancet 1(7897): 14-16.
167. Müller WA, Faloona GR, Aguilar-Parada E, Unger RH. (1970) Abnormal alpha-cell function in diabetes. Response to carbohydrate and protein ingestion. N Engl J Med. 283(3): 109-15.
168. Unger RH, Aguilar-Parada E, Müller WA, Eisentraut AM. (1970) Studies of pancreatic alpha cell function in normal and diabetic subjects. J Clin Invest. 49(4): 837-848.
169. Conarello SL, Jiang G, Mu J, Li Z, Woods J, et al. (2007) Glucagon receptor knockout mice are resistant to diet-induced obesity and streptozotocin-mediated beta cell loss and hyperglycaemia. Diabetologia 50(1): 142-150.

170. Lee Y, Wang MY, Du XQ, Charron MJ, Unger RH. (2011) Glucagon receptor knockout prevents insulin-deficient type 1 diabetes in mice. Diabetes 60(2): 391-397.
171. Damond N, Thorel F, Moyers JS, Charron MJ, Vuguin PM, et al. (2016) Blockade of glucagon signaling prevents or reverses diabetes onset only if residual β-cells persist. Elife 5: e13828.
172. Zheng Z, Zong Y, Ma Y, Tian Y, Pang Y, et al. (2024) Glucagon-like peptide-1 receptor: mechanisms and advances in therapy. Signal Transduct Target Ther. 9(1): 234.
173. Billington CJ, Briggs JE, Link JG, Levine AS. (1991) Glucagon in physiological concentrations stimulates brown fat thermogenesis in vivo. Am J Physiol. 261(2 Pt 2): R501-R507.
174. de Castro JM, Paullin SK, DeLugas GM. (1978) Insulin and glucagon as determinants of body weight set point and microregulation in rats. J Comp Physiol Psychol. 92(3): 571-79.
175. Salter JM. (1960) Metabolic effects of glucagon in the Wistar rat. Am J Clin Nutr. 8: 535–539.
176. Geary N, Langhans W, Scharrer E. (1981) Metabolic concomitants of glucagon-induced suppression of feeding in the rat. Am J Physiol. 241(5): R330-R335.
177. Geary N, Smith GP. (1983) Selective hepatic vagotomy blocks pancreatic glucagon's satiety effect. Physiol Behav. 31(3): 391-94.
178. Conceição-Furber E, Coskun T, Sloop KW, Samms RJ. (2022) Is Glucagon Receptor Activation the Thermogenic Solution for Treating Obesity? Front Endocrinol (Lausanne) 13: 868037.
179. Berthet J. (1958) Influence of glucagon and adrenalin on the in vitro synthesis of cholesterol by hepatic tissue. Prog Nucl Energy 6 Biol Sci. 2(3): 179–184.
180. Berthet J. (1959) Some aspects of the glucagon problem. Am J Med. 26(50): 703–714.
181. Hagen JH. (1961) Effect of glucagon on the metabolism of adipose tissue. J Biol Chem. 236: 1023–1027.
182. Lipsett MB, Engel HR, Bergenstal DM. (1960) Effects of glucagon on plasma unesterified fatty acids and in nitrogen metabolism. J Lab Clin Med 56: 342–354.
183. Mochiki E, Suzuki H, Takenoshita S, Nagamachi Y, Kuwano H, et al. (1998) Mechanism of inhibitory effect of glucagon on gastrointestinal motility and cause of side effects of glucagon. J Gastroenterol 33(6): 835-41.
184. Müller TD, Finan B, Clemmensen C, Di Marchi RD, Tschöp MH. (2017) The New Biology and Pharmacology of Glucagon. Physiol Rev. 97(2): 721-66.
185. Parmley WW, Glick G, Sonnenblick EH. (1968) Cardiovascular effects of glucagon in man. N Engl J Med. 279(1): 12-7.
186. Wadden TA, Chao AM, Moore M, Tronieri JS, Gilden A, et al. (2023) The Role of Lifestyle Modification with Second-Generation Anti-obesity Medications: Comparisons, Questions, and Clinical Opportunities. Curr Obes Rep. 12(4): 453-73.
187. Almandoz JP, Lingvay I, Morales J, Campos C. (2020) Switching Between Glucagon-Like Peptide-1 Receptor Agonists: Rationale and Practical Guidance. Clin Diabetes. 38(4): 390-402.
188. Malik F, Li Z. (2022) Non-peptide agonists and positive allosteric modulators of glucagon-like peptide-1 receptors: Alternative approaches for treatment of type 2 diabetes. Br J Pharmacol. 179(4): 511-525.
189. Wharton S, Blevins T, Connery L, Rosenstock J, Raha S, et al. (2023) Daily Oral GLP-1 Receptor Agonist Orforglipron for Adults with Obesity. N Engl J Med. 389(10): 877-88.
190. Decara JM, Vázquez-Villa H, Brea J, Alonso M, Srivastava RK, et al. (2022) Discovery of V-0219: A Small-Molecule Positive Allosteric Modulator of the Glucagon-Like Peptide-1 Receptor toward Oral Treatment for "Diabesity". J Med Chem. 65(7): 5449-5461.
191. Salvador R, Moutinho CG, Sousa C, Vinha AF, Carvalho M, et al. (2025) Semaglutide as a GLP-1 Agonist: A Breakthrough in Obesity Treatment. Pharmaceuticals (Basel) 18(3): 399.
192. Jones LA, Brierley DI. (2025) GLP-1 and the Neurobiology of Eating Control: Recent Advances. Endocrinology 166: bqae167.
193. Bond A. (2006) Exenatide (Byetta) as a novel treatment option for type 2 diabetes mellitus. Baylor Univ Med

Cent Proc. 19(3):281–284.

194. Murphy CE. (2012) Review of the safety and efficacy of exenatide once weekly for the treatment of type 2 diabetes mellitus. Ann Pharmacother. 46(6): 812-21.
195. Nikfar S, Abdollahi M, Salari P. (2012) The efficacy and tolerability of exenatide in comparison to placebo: A systematic review and meta-analysis of randomized clinical trials. J Pharm Pharm Sci. 15(1):1–30.
196. Bonora BM, Avogaro A, Fadini GP. (2019) Effects of exenatide long-acting release on cardiovascular events and mortality in patients with type 2 diabetes: A systematic review and meta-analysis of randomized controlled trials. Acta Diabetol. 56(9): 1051-60.
197. Syed YY, McCormack PL. (2015) Exenatide Extended-Release: An Updated Review of Its Use in Type 2 Diabetes Mellitus. Drugs 75(10): 1141-52.
198. Su N, Li Y, Xu T, Li L, Kwong JS, et al. (2016) Exenatide in obese or overweight patients without diabetes: A systematic review and meta-analyses of randomized controlled trials. Int J Cardiol. 219: 293-300.
199. Genovese S, Mannucci E, Ceriello A. (2017) A Review of the Long-Term Efficacy, Tolerability, and Safety of Exenatide Once Weekly for Type 2 Diabetes. Adv Ther. 34(8): 1791–1814.
200. Henry RR, Klein EJ, Han J, Iqbal N. (2016) Efficacy and Tolerability of Exenatide Once Weekly Over 6 Years in Patients with Type 2 Diabetes: An Uncontrolled Open-Label Extension of the DURATION-1 Study. Diabetes Technol Ther. 18(11):677-86.
201. Nathan DM, Buse JB, Davidson MB, Ferrannini E, Holman RR, et al. (2009) Medical management of hyperglycemia in type 2 diabetes: A consensus algorithm for the initiation and adjustment of therapy: A consensus statement of the American Diabetes Association and the European Association for the Study of Diabetes. Diabetes Care. 32(1):193-203.
202. Alsanea S, Alkofide H, Almadi B, Almohammed O, Alwhaibi A, Alrabiah Z, Kalagi N (2024) Liraglutide's Effect on Weight Management in Subjects with Pre-diabetes: A Systematic Review & Meta-Analysis. Endocr Pract. 30(8): 737-74.
203. Shamim MA, Patil AN, Amin U, Roy T, Tiwari K, et al. (2024) Glucagon-like peptide-1 receptor agonists in adolescents with overweight or obesity with or without type 2 diabetes multimorbidity-a systematic review and network meta-analysis. Diabetes Obes Metab. 26(10): 4302-17.
204. Sun F, Wu S, Guo S, Yu K, Yang Z, et al. (2015) Effect of GLP-1 receptor agonists on waist circumference among type 2 diabetes patients: a systematic review and network meta-analysis. Endocrine 48(3): 794-803.
205. Zhang X, Liu J, Ni Y, Yi C, Fang Y, et al. (2024) Global Prevalence of Overweight and Obesity in Children and Adolescents: A Systematic Review and Meta-Analysis. JAMA Pediatr. 178(8): 800-13.
206. Gurung T, Shyangdan DS, O'Hare JP, Waugh N. (2015) A novel, long-acting glucagon-like peptide receptor-agonist: dulaglutide. Diabetes Metab Syndr Obes. 8: 363-386.
207. Lau J, Bloch P, Schäffer L, Pettersson I, Spetzler J, et al. (2015) Discovery of the Once-Weekly Glucagon-Like Peptide-1 (GLP-1) Analogue Semaglutide. J Med Chem. 58(18): 7370-80.
208. Tall Bull S, Nuffer W, Trujillo JM. (2022) Tirzepatide: A novel, first-in-class, dual GIP/GLP-1 receptor agonist. J Diabetes Complications 36(12): 108332.
209. Ding Y, Shi Y, Guan R, Yan S, Liu H, et al. (2024) Evaluation and comparison of efficacy and safety of tirzepatide and semaglutide in patients with type 2 diabetes mellitus: A Bayesian network meta-analysis. Pharmacol Res. 199: 107031.
210. Shi Q, Wang Y, Hao Q, Vandvik PO, Guyatt G, et al. (2024) Pharmacotherapy for adults with overweight and obesity: a systematic review and network meta-analysis of randomized controlled trials. Lancet. 403(10434): e21-e31.
211. Yao H, Zhang A, Li D, Wu Y, Wang CZ, Wan JY, et al. (2024) Comparative effectiveness of GLP-1 receptor agonists on glycaemic control, body weight, and lipid profile for type 2 diabetes: systematic review andnetwork meta-analysis. BMJ 384: e076410.

212. Qiu M, Ding LL, Wei XB, Liu SY, Zhou HR. (2021) Comparative Efficacy of Glucagon-like Peptide 1 Receptor Agonists and Sodium Glucose Cotransporter 2 Inhibitors for Prevention of Major Adverse Cardiovascular Events in Type 2 Diabetes: A Network Meta-analysis. J Cardiovasc Pharmacol. 77(1): 34-37.
213. García de Lucas MD, Caballero I, Fernández-García JC, Domínguez-Rodríguez M, Moreno-Moreno P, et al. (2023) Influence of chronic kidney disease and its severity on the efficacy of semaglutide in type 2 diabetes patients: a multicenter real-world study. Front Endocrinol (Lausanne) 14: 1240279.
214. Katsuyama H, Hakoshima M, Kaji E, Mino M, Kakazu E, et al. (2024) Effects of Once-Weekly Semaglutide on Cardiovascular Risk Factors and Metabolic Dysfunction-Associated Steatotic Liver Disease in Japanese Patients with Type 2 Diabetes: A Retrospective Longitudinal Study Based on Real-World Data. Biomedicines. 12(5): 1001.
215. Soto-Catalán M, Opazo-Ríos L, Quiceno H, Lázaro I, Moreno JA, et al. (2024) Semaglutide Improves Liver Steatosis and De Novo Lipogenesis Markers in Obese and Type-2-Diabetic Mice with Metabolic-Dysfunction-Associated Steatotic Liver Disease. Int J Mol Sci. 25(5): 2961.
216. Kushner RF, Calanna S, Davies M, Dicker D, Garvey WT, et al. (2020) Semaglutide 2.4 mg for the Treatment of Obesity: Key Elements of the STEP Trials 1 to 5. Obesity (Silver Spring) 28(6): 1050-1061.
217. O'Neil PM, Rubino DM. (2022) Exploring the wider benefits of semaglutide treatment in obesity: insight from the STEP program. Postgrad Med. 134(1): 28-36.
218. Kosiborod MN, Abildstrøm SZ, Borlaug BA, Butler J, Rasmussen S, et al. (2023) Semaglutide in Patients with Heart Failure with Preserved Ejection Fraction and Obesity. N Engl J Med. 389(12): 1069-1084.
219. Kosiborod MN, Petrie MC, Borlaug BA, Butler J, Davies MJ, et al. (2024) Semaglutide in Patients with Obesity-Related Heart Failure and Type 2 Diabetes. N Engl J Med. 390(15): 1394-1407.
220. Schou M, Petrie MC, Borlaug BA, Butler J, Davies MJ, et al. (2024) Semaglutide and NYHA Functional Class in Obesity-Related Heart Failure with Preserved Ejection Fraction: The STEP-HFpEF Program. J Am Coll Cardiol. 84(3): 247-257.
221. McGowan BM, Bruun JM, Capehorn M, Pedersen SD, Pietiläinen KH, et al. STEP 10 Study Group (2024) Efficacy and safety of once-weekly semaglutide 2·4 mg versus placebo in people with obesity and prediabetes (STEP 10): a randomised, double-blind, placebo- controlled, multicentre phase 3 trial. Lancet Diabetes Endocrinol 12(9):631-642.
222. Perreault L, Davies M, Frias JP, Laursen PN, Lingvay I, et al. (2022) Changes in Glucose Metabolism and Glycemic Status with Once-Weekly Subcutaneous Semaglutide 2.4 mg Among Participants with Prediabetes in the STEP Program. DiabetesCare 45(10):2396-2405.
223. Dong Y, Carty J, Goldstein N, He Z, Hwang E, et al. (2021) Time and metabolic state-dependent effects of GLP-1R agonists on NPY/AgRP and POMC neuronal activity in vivo. Mol Metab. 54: 101352.
224. Papakonstantinou I, Tsioufis K, Katsi V. (2024) Spotlight on the Mechanism of Action of Semaglutide. Curr Issues Mol Biol. 46(12):14514-41.
225. van Bloemendaal L, Ten Kulve JS, la Fleur SE, Ijzerman RG, Diamant M. (2014) Effects of glucagon-like peptide 1 on appetite and body weight: focus on the CNS. J Endocrinol 221(1): T1-T16.
226. Donath MY, Burcelin R. (2013) GLP-1 effects on islets: hormonal, neuronal, or paracrine? Diabetes Care 36 (Suppl 2): S145-8.
227. Nauck MA, Petrie JR, Sesti G, Mannucci E, Courrèges JP, et al. Study 1821 Investigators (2016) A Phase 2, Randomized, Dose-Finding Study of the Novel Once-Weekly Human GLP-1 Analog, Semaglutide, Compared With Placebo and Open-Label Liraglutide in Patients With Type 2 Diabetes. Diabetes Care 39(2): 231-41.
228. Davies M, Pieber TR, Hartoft-Nielsen ML, Hansen OKH, Jabbour S, et al. (2017) Effect of Oral Semaglutide Compared with Placebo and Subcutaneous Semaglutide on Glycemic Control in Patients with Type 2 Diabetes: A Randomized Clinical Trial. JAMA 318(15): 1460-1470.
229. Willard FS, Douros JD, Gabe MB, Showalter AD, Wainscott DB, et al. (2020) Tirzepatide is an imbalanced and

biased dual GIP and GLP-1 receptor agonist. JCI Insight 5(17): e140532.
230. Tschöp MH, Finan B, Clemmensen C, Gelfanov V, Perez-Tilve D, et al. (2016) Unimolecular Polypharmacy for Treatment of Diabetes and Obesity. Cell Metab. 24(1): 51-62.
231. Sloop KW, Briere DA, Emmerson PJ, Willard FS. (2018) Beyond Glucagon-like Peptide-1: Is G-Protein Coupled Receptor Polypharmacology the Path Forward to Treating Metabolic Diseases? ACS Pharmacol Transl Sci. 1(1): 3-11.
232. Nauck MA, Quast DR, Wefers J, Pfeiffer AFH. (2021) The evolving story of incretins (GIP and GLP-1) in metabolic and cardiovascular disease: A pathophysiological update. Diabetes Obes Metab. 23(3): 5-29.
233. Al-Zamel N, Al-Sabah S, Luqmani Y, Adi L, Chacko S, et al. (2019) A Dual GLP-1/GIP Receptor Agonist Does Not Antagonize Glucagon at Its Receptor but May Act as a Biased Agonist at the GLP-1 Receptor. Int J Mol Sci. 20(14): 3532.
234. Edholm T, Degerblad M, Grybäck P, Hilsted L, Holst JJ, et al. (2010) Differential incretin effects of GIP and GLP-1 on gastric emptying, appetite, and insulin-glucose homeostasis. Neurogastroenterol Motil. 22(11): 1191-200, e315.
235. Hope DCD, Vincent ML, Tan TMM. (2021) Striking the Balance: GLP-1/Glucagon Co-Agonism as a Treatment Strategy for Obesity. Front Endocrinol (Lausanne) 12:735019.
236. Coskun T, Sloop KW, Loghin C, Alsina-Fernandez J, Urva S, et al. (2018) A LY3298176, a novel dual GIP and GLP-1 receptor agonist for the treatment of type 2 diabetes mellitus: From discovery toclinical proof of concept. Mol Metab. 18:3-14.
237. Andersen A, Lund A, Knop FK, Vilsbøll T. (2018) Glucagon-like peptide 1 in health and disease. Nat Rev Endocrinol 14(7): 390–403.
238. Blevins T, Pullman J, Malloy J, Yan P, Taylor K, et al. (2011) DURATION-5: exenatide once weekly resulted in greater improvements in glycemic control compared with exenatide twice daily in patients with type 2 diabetes. J Clin Endocrinol Metab. 96(5): 1301-10.
239. Wysham C, Blevins T, Arakaki R, Colon G, Garcia P, et al. (2014) Efficacy and safety of dulaglutide added onto pioglitazone and metformin versus exenatide in type 2 diabetes in a randomized controlled trial (AWARD-1). Diabetes Care 37(8): 2159-2167.
240. Ng CD, Divino V, Wang J, Toliver JC, Buss M. (2025) Real-World Weight Loss Observed With Semaglutide and Tirzepatide in Patients with Overweight or Obesity and Without Type 2 Diabetes (SHAPE). Adv Ther. 42(11): 5468-5480.
241. Sara Sokary, Hiba Bawadi. (2025) The promise of tirzepatide: A narrative review of metabolic benefits. Prim Care Diabetes 19(3p): 229-237.
242. Khashayar F, Preeti P. (2024) Tirzepatide - StatPearls - NCBI Bookshelf.
243. Wang L. (2022) Designing a dual GLP-1R/GIPR agonist from tirzepatide: comparing residues between tirzepatide, GLP-1, and GIP, Drug Des. Dev Ther. 16 (2022): 1547–1559.
244. Urva S, Quinlan T, Landry J, Martin J, Loghin C. (2021) Effects of Renal Impairment on the Pharmacokinetics of the Dual GIP and GLP-1 Receptor Agonist Tirzepatide. Clin Pharmacokinet 60(8): 1049-1059.
245. FDA Clinical Pharmacology Review(s) (2022) Center for Drug Evaluation and Research. Application Number: 215866Orig1S000. Tirzepatide.
246. Nieuwlaat R, Wilczynski N, Navarro T, Hobson N, Jeffery R, et al. (2014) Interventions for enhancing medication adherence. Cochrane Database Syst Rev. 2014(11):CD000011.
247. Frías JP, Davies MJ, Rosenstock J, Pérez Manghi FC, Fernández Landó L, et al. (2021) Tirzepatide versus Semaglutide Once Weekly in Patients with Type 2 Diabetes. N Engl J Med. 385(6): 503-515.
248. Dahl D, Onishi Y, Norwood P, Huh R, Bray R, et al. (2022) Effect of Subcutaneous Tirzepatide vs Placebo Added to Titrated Insulin Glargine on Glycemic Control in Patients With Type 2 Diabetes: TheSURPASS-5 Randomized Clinical Trial. JAMA 327(6): 534-545.

249. Rosenstock J, Frías JP, Rodbard HW, Tofé S, Sears E, et al. (2023) Tirzepatide vs Insulin Lispro Added to Basal Insulin in Type 2 Diabetes: The SURPASS-6 Randomized Clinical Trial. JAMA 330(17): 1631-1640.
250. Katsi V, Koutsopoulos G, Fragoulis C, Dimitriadis K, Tsioufis K. (2025) Retatrutide-A Game Changer in Obesity Pharmacotherapy. Biomolecules 15(6): 796.
251. Li W, Zhou Q, Cong Z, Yuan Q, Li W, et al. (2024) Structural insights into the triple agonism at GLP-1R, GIPR and GCGR manifested by retatrutide. Cell Discov. 10(1): 77.
252. Coskun T, Urva S, Roell WC, Qu H, Loghin C, et al. (2022) LY3437943, a novel triple glucagon, GIP, and GLP-1 receptor agonist for glycemic control and weight loss: From discovery to clinical proof of concept. Cell Metab. 34(9): 1234-1247.e9.
253. Ray A. (2023) Retatrutide: a triple incretin receptor agonist for obesity management. Expert Opin Investig Drugs 32(11): 1003-1008.
254. Rosenstock J, Frias J, Jastreboff AM, Du Y, Lou J, et al. (2023) Retatrutide, a GIP, GLP-1 and glucagon receptor agonist, for people with type 2 diabetes: a randomised, double-blind, placebo and active-controlled, parallel-group, phase 2 trial conducted in the USA. Lancet 402(10401): 529-544.
255. Thomsen RW, Mailhac A, Løhde JB, Pottegård A. (2025) Real-world evidence on the utilization, clinical and comparative effectiveness, and adverse effects of newer GLP-1RA-based weight-loss therapies. Diabetes Obes Metab. 27(Suppl 2): 66-88.
256. Jastreboff AM, Kaplan LM, Frías JP, Wu Q, Du Y, Gurbuz S, et al. (2023) Retatrutide Phase 2 Obesity Trial Investigators. Triple-Hormone-Receptor Agonist Retatrutide for Obesity - A Phase 2 Trial. N Engl J Med. 389(6): 514-526.
257. Abdrabou Abouelmagd A, Abdelrehim AM, Bashir MN, Abdelsalam F, Marey A, et al. (2025) Efficacy and safety of retatrutide, a novel GLP-1, GIP, and glucagon receptor agonist for obesity treatment: a systematic review and meta-analysis of randomized controlled trials. Proc (Bayl Univ Med Cent) 38(3): 291-303.
258. Naeem M, Imran L, Banatwala UESS. (2024) Unleashing the power of retatrutide: A possible triumph over obesity and overweight: A correspondence. Health Sci Rep. 7(2): e1864.
259. Sanyal AJ, Kaplan LM, Frias JP, Brouwers B, Wu Q, et al. (2024) Triple hormone receptor agonist retatrutide for metabolic dysfunction-associated steatotic liver disease: a randomized phase 2a trial. Nat Med. 30(7): 2037-2048.
260. Vannesa N (2024) What is retatrutide and is it FDA approved for weight loss?