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The power of three: Retatrutide's role in modern obesity and diabetes therapy

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ABSTRACT

The increasing prevalence of obesity and type 2 diabetes mellitus has resulted in a significant challenge to public health throughout the globe. It required the development of novel therapeutic approaches. Retatrutide is a groundbreaking triple agonist that targets glucagon receptors, gastric inhibitory polypeptide, and glucagon-like peptide-1. Retatrutide's complex mechanism of action involves a synergistic interaction among these receptors, resulting in increased insulin secretion, improved glucose homeostasis, and refined appetite modulation. Clinical trials in phases 1 to 3 have demonstrated significant efficacy, highlighted by significant reductions in body weight and favorable glycemic control outcomes. Additionally, retatrutide shows promise in mitigating cardiovascular risk factors and addressing metabolic dysfunction-associated steatotic liver disease. However, careful attention is required to delineate its long-term safety profile, explore its potential in special populations, unravel its adjunctive therapeutic roles, and elucidate its mechanisms in pediatric cohorts. As a transformative therapeutic modality, retatrutide represents a beacon of hope, signifying transformative changes in the management landscape of obesity and type 2 diabetes mellitus (T2DM), and warranting continued exploration and refinement in clinical practice. This narrative review examines the therapeutic potential of retatrutide in the management of obesity and T2DM.

1. Introduction

Obesity, characterized by an excessive accumulation of adipose tissue leading to compromised physical and psychosocial well-being, represents a pervasive health crisis across both developed and developing nations, impacting over a third of the world's population alongside individuals classified as overweight (Ng et al., 2014; Stevens et al., 2012). In 2022, obesity posed a significant global burden, with 1 in 8 people affected worldwide (Obesity and overweight, n.d.). The prevalence of overweight adults doubled since 1990, with 2.5 billion adults overweight, including 890 million living with obesity in 2023. Additionally, over 390 million children and adolescents were overweight, with 160 million suffering from obesity (Obesity and overweight, n.d.).

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Abbreviations

αMeL - α-methyl-L-leucine
ALT - alanine aminotransferase
ATP - adenosine monophosphate
BMI - body mass index
cAMP - cyclic adenosine monophosphate
CIM - calorie-intake matched
CNS central nervous system
GCGRA - glucagon receptor agonist
GCGR - glucagon receptor
GE - gastric emptying
GIP(R) glucose-dependent insulinotropic polypeptide (Receptor)
GLP-1(R) - glucagon-like peptide-1 (receptor)
HbA1c - hemoglobin A1c
LF - liver fat
MASLD - metabolic sysfunction-associated steatotic liver disease
NCDs - non-communicable diseases
NEFAs - non-esterified fatty acids
PKA - protein kinase A
T2DM - type 2 diabetes mellitus

Forecasts indicate a concerning trajectory, with an estimated 38% of adults worldwide projected to be overweight and an additional 20% obese by 2030 (Kelly et al., 2008).

Although obesity is commonly defined as excess body weight relative to height, its underlying mechanisms are complex, primarily revolving around increased adiposity or body fat content, which poses metabolic risks beyond mere physical dimensions (Obesity epidemiology and Hu, n.d.). In 2019, an elevated body mass index (BMI) contributed to approximately 5 million deaths attributed to noncommunicable diseases (NCDs), encompassing conditions like cardiovascular diseases, diabetes, cancers, neurological disorders, chronic respiratory diseases, and digestive disorders (GBD 2019 Risk Factors Collaborators, 2020). Furthermore, childhood and adolescent overweight status not only impacts immediate health but also elevates the likelihood and accelerates the onset of numerous NCDs, including type 2 diabetes m ellitus (T2DM) and cardiovascular diseases (Obesity epidemiology and Hu, n.d.). At the beginning of the 21st century, approximately 171 million individuals were believed to be living with T2DM, with projections indicating a surge to 360 million by the year 2030 (McKeigue et al., 1991).

Obesity induces insulin resistance primarily through the increased release of non-esterified fatty acids (NEFAs) (Karpe et al., 2011). Elevated NEFA levels lead to insulin resistance shortly after their acute rise, hampering peripheral insulin uptake and glucose regulation (Jelic et al., 2007; Roden et al., 1996). Moreover, differences in body fat distribution contribute significantly, with central adiposity exacerbating insulin resistance more than peripheral fat deposition (Karpe et al., 2011). Additionally, intra-abdominal fat, being more lipolytic and less responsive to insulin's antilipolytic action, plays a pivotal role in fostering insulin resistance, ultimately predisposing individuals to diabetes (Jelic et al., 2007).

In obese individuals, insulin sensitivity declines, impairing β-cells' ability to modulate insulin release effectively (Boden, 1996). Consequently, insulin-resistant individuals exhibit heightened insulin responses alongside decreased hepatic insulin clearance (Kahn et al., 1993). Failure to maintain glucose homeostasis due to dysregulated insulin secretion can lead to the onset of T2DM. Moreover, prolonged exposure to elevated plasma NEFA levels further exacerbates β-cell dysfunction, disrupting glucose-stimulated insulin secretion pathways and insulin biosynthesis (Kahn, 2001). This interplay between obesity, insulin resistance, and β-cell dysfunction underscores the complex pathophysiology driving diabetes development.

Over recent decades, the elucidation of the gut-brain axis and the pivotal role of gastrointestinal hormones in regulating metabolism, appetite, and glucose homeostasis has opened new avenues for pharmacological intervention (Doggrell, 2023). Various medications for treating obesity have been developed, with notable options including orlistat, phentermine-topiramate, naltrexone-bupropion, liraglutide, and semaglutide, all approved by the Food and Drug Administration (FDA) for long-term use (Chakhtoura et al., 2023; Prescription medications to treat overweight & obesity—NIDDK, n.d.).

Despite advancements, there are still significant unmet needs in obesity and T2DM treatment, notably in the realm of efficacy and side effects (Doggrell, 2023). Existing therapies often fall short of achieving optimal glycemic control for all patients while grappling with burdensome side effects such as weight gain, hypoglycemia, and cardiovascular risks (Doggrell, 2023).

Retatrutide (LY3437943), a novel triagonist that simultaneously activates glucagon-like peptide-1 (GLP-1), glucose-dependent insulinotropic polypeptide (GIP), and glucagon receptors (GCGRs) has been developed and is currently under investigation. Initial findings from preclinical and clinical studies suggest this agent not only potentiates weight loss and improves glycemic control but also offers cardiovascular benefits, challenging the boundaries of what pharmacotherapy can achieve in obesity and T2DM management (Bailey et al., 2024; Jakubowska et al., 2024).

Retatrutide is under Phase III development for obesity, T2DM, and non-alcoholic fatty liver disease (Kaur and Misra, 2024). Phase II trials showed significant weight reduction, with average losses of 17.5% and 24.4% at 24 and 48 weeks, respectively. While promising, further Phase III trials are necessary to validate its efficacy and safety across larger populations.

While retatrutide holds promise in addressing the unmet needs of current therapies, the intricacies of its mechanisms and the full extent of its therapeutic effects remain to be fully understood, underscoring the need for larger and longer clinical trials as well as the establishment of optimal dosing regimens (Doggrell, 2023). This narrative review comprehensively explores the promising potential of retatrutide as a triple agonist for managing both obesity and T2DM, shedding light on its mechanism of action, clinical efficacy, safety profile, and prospects in the realm of metabolic therapeutics.

2. Methodology

This narrative review employed a comprehensive search strategy across multiple electronic databases, including PubMed/MEDLINE, Embase, Cochrane Library, and Scopus, spanning from the inception of

Table 1
Summary Table of methodology for this narrative review.

Methodology steps	Description
Literature search	PubMed, Scopus, Embase, Cochrane Library
Inclusion criteria	• Articles published entirely in English •Emphasis on retatrutide's effects on both diabetes and obesity. •Human and animal studies •Various study designs such as experimental studies, observational studies, systemaytic reviews and meta-analysis.
Exclusion criteria	•Articles published in languages other than English •Unpublished studies
Search terms	Keywords such as "retatrutide", "triple agonist drug"," GIP receptor agonist", "GLP-1 receptor agonist", "glucagon receptor agonist", "diabetes", and "obesity"
Additional search	•Thorough inspection of references mentioned in recent reviews focused on specific diseases through manual examination •Manual search of journal websites •No predefined restriction on the number of studies to be considered

each database to date (Table 1). The search strategy utilized the following key terms: “retatrutide”, “triple agonist drug",” GIP receptor agonist”, “GLP-1 receptor agonist”, “glucagon receptor agonist”, “diabetes”, and “obesity”, ensuring a thorough exploration of human and animal studies focusing on retatrutide’s effects on both diabetes and obesity. Aside from electronic databases, an additional search of reference lists from included studies and journals was conducted to identify articles relevant to our research. The inclusion criteria encompassed various study designs such as experimental studies, observational studies, sytematic reviews and metaanlysis. Studies investigating the efficacy and safety of retatrutide as a triple agonist drug for the treatment of diabetes and obesity, and studies elucidating the mechanism of GIPR, GLP-1R, and GCGRs were considered for inclusion. Only articles published in the English language were included. Unpublished studies and studies published in languages other than English were excluded.

3. Structure and mechanism of action of retatrutide

Retatrutide is a single peptide that consists of 39 amino acids engineered from a GIP peptide backbone to stimulate GLP-1, GIP, and GCGRs (Fig. 1). There are three non-coded amino acid residues [two α-amino isobutyric acids (Aib), and one α-methyl-L-leucine (αMeL)] at positions 2, 20, and 13 of the peptide backbone. Aib2 provides stability from cleavage by dipeptidyl peptidase 4 (DPP4), Aib20 provides optimal GIP activity, pharmacokinetic (PK) profile, and developability, while αMeL13 promotes optimal GIP and glucagon activity. Additionally, a C20 fatty acid moiety is conjugated to the backbone via a linker at the 17 lysine residue position which enables the binding with albumin to extend its PK half-life while maintaining desired pharmacological properties (Coskun et al., 2022).

Retatrutide is a novel peptide drug designed as a triple agonist targeting GLP-1R, GIPR, and GCGR. Structural studies using cryo-electron microscopy (cryo-EM) reveal that retatrutide binds to these receptors with distinct conformational adaptations (Li et al., 2024). It features a continuous helical structure that penetrates the core of the receptor’s transmembrane domain, while its C-terminal segment interacts with extracellular receptor domains (Ng et al., 2014; *Obesity and Overweight*, n.d.). The structural variations observed among GLP-1R, GIPR, and GCGR highlight receptor-specific conformations, which are crucial for retatrutide’s effective binding and activation (Buntz, 2024).

The mechanism of retatrutide surrounds the synergistic effects of its triple agonist abilities at GLP-1Rs, GIPRs, and GCGRs (Fig. 2) (Jastreboff et al., 2023). The incretins, GLP-1 and GIP, promote insulin secretion and glucose lowering in response to oral glucose stimulus (Coskun et al., 2018, 2022). Patients with T2DM may have a blunted response to the incretin effect, leading to hyperglycemia and symptomatic diabetes (Bagger et al., 2011). Mechanistically, the incretin effect increases insulin secretion, delays glucagon secretion, and delays gastric emptying (GE), promoting weight loss, and decreasing hemoglobin A1c (HbA1c) (Coskun et al., 2018).

The GLP-1R is abundant in pancreatic β-cells, the gastrointestinal tract, and the central nervous system (Coskun et al., 2018). GLP-1 is endogenously produced through enzymatic cleavage of proglucagon by prohormone convertase. Production of the peptide is induced via the ingestion of carbohydrates, fats, and glucose (Rocca and Brubaker, 1999). The interaction between GLP-1 and GLP-1R in the pancreas activates adenylyl cyclase stimulating the reduction of adenosine triphosphate (ATP) to cyclic adenosine monophosphate (cAMP) (Zhao et al., 2021). The increase in cAMP activates PKA (protein kinase A) and RAPGEF4 (rap guanine nucleotide exchange factor) (Zhao et al., 2021). Activated PKA closes potassium channels, depolarizing membranes, and activating voltage-gated calcium channels (Zhao et al., 2021). The flow of calcium leads to the generation of action potentials promoting the synthesis of ATP (Zhao et al., 2021). This ATP synthesis is further propagated through PKA-mediated inositol trisphosphate (IP3) release. Increased ATP coincides with the exocytic release of insulin into circulation (Zhao et al., 2021). Moreover, GLP-1Rs have been reported to significantly influence hunger centers in the hypothalamus, suppress appetite, and delay GE.

GIPRs are primarily expressed in pancreatic β-cells and adipose tissue (Coskun et al., 2018). Physiologically, GIP is secreted from the enteroendocrine cells in the small intestine. Oral intake of glucose as well as amino acids and fatty acids are stimuli for GIP secretion. K cells employ sodium-coupled glucose transport channels to release GIP in a glucose dose-dependent fashion (Coskun et al., 2018). GIP acts on G protein-coupled receptors to increase cAMP via the PKA/adenylyl cyclase and phospholipase C pathways. Downstream upregulation of calcium leads to increased insulin release (Defective Glucose-Dependent Insulinotropic Polypeptide Receptor Expression in Diabetic Fatty Zucker Rats | Diabetes | American Diabetes Association, n.d.). Patients with T2DM exhibit lower levels of GIP and/or β-cell resistance to GIP, accounting for a significant reduction of insulin post-oral intake (Coskun et al., 2018; Defective Glucose-Dependent Insulinotropic Polypeptide Receptor Expression in Diabetic Fatty Zucker Rats | Diabetes | American Diabetes Association, n.d.). Activation of GIPR promotes glucose uptake and storage while inhibiting glucagon release (Jastreboff et al., 2023). Additionally, GIPR may influence adipocyte metabolism and lipid accumulation (Jastreboff et al., 2023).

Glucagon is a peptide hormone mainly produced by pancreatic α-cells in response to hypoglycemia. Although the majority of GCGRs are found on hepatocytes, they are also present in the kidneys, gastrointestinal tract, pancreas, and central nervous system (CNS). Activation of GCGRs stimulates lipolysis via activation of hormone-sensitive lipase, inhibits lipogenesis, and increases ketogenesis (Guzman et al., 2017). Furthermore, glucagon promotes satiety, increases energy expenditure, and stimulates insulin secretion (Jastreboff et al., 2023).

GIPRs and GLP-1Rs in cooperation with GCGRs exhibit a synergistically enhanced effect (Turner et al., 1974). Their combined agonism by retatrutide enhances its efficacy in glycemic control and weight loss, surpassing the effects of selective or dual agonists.

4. Pharmacokinetics properties of retatrutide

Retatrutide has a relatively long half-life of approximately 6 days, which supports its administration as a once-weekly subcutaneous injection. This extended half-life is beneficial for maintaining steady plasma levels of the drug, contributing to its sustained effectiveness in reducing body weight and improving glucose levels (Urva et al., 2023). Upon administration, retatrutide is absorbed and distributed efficiently throughout the body, reaching therapeutic concentrations. The drug’s

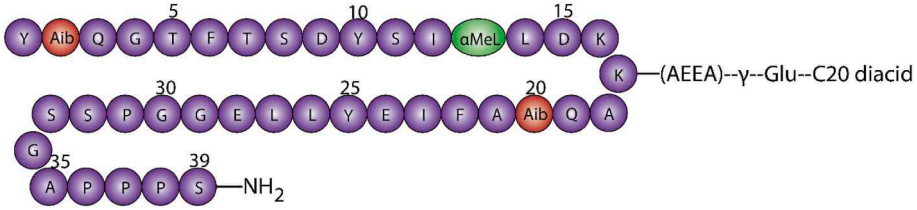

Fig. 1. Structure of retatrutide.

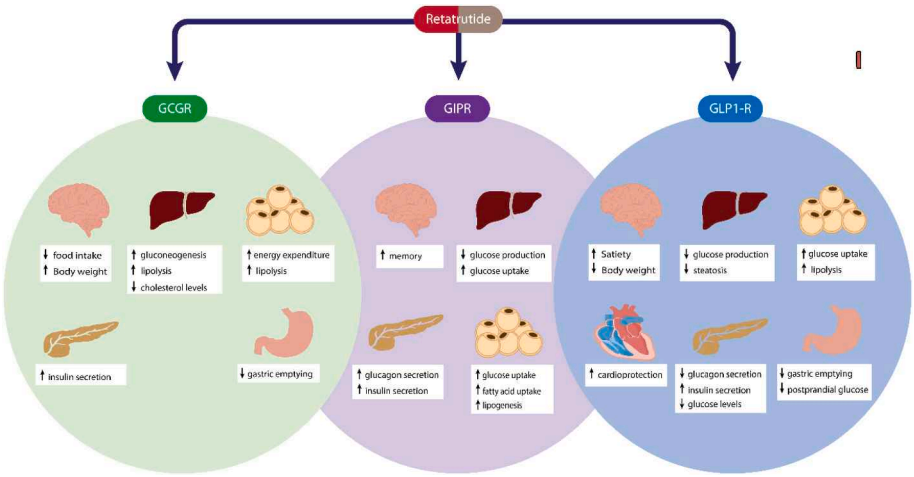

Fig. 2. Mechanism of action of retatrutide.

pharmacokinetics demonstrates dose-dependent effects, with higher doses leading to more substantial reductions in body weight and glycated hemoglobin (HbA1c) levels (Doggrell, 2023). Retatrutide is metabolized primarily in the liver, with excretion pathways yet to be fully elucidated. The drug's metabolism does not involve significant interactions with cytochrome P450 enzymes, which reduces the potential for drug-drug interactions (Ray, 2023).

5. Drug use and adverse effects

Currently, there are no formally established indications for retatrutide as the drug has yet to receive approval from the Food and Drug Administration. Consequently, comprehensive contraindications remain to be determined pending regulatory assessment and approval.

Although retatrutide is still in the experimental phase, several potential clinical uses have been identified for the drug in multiple clinical trials (Jastreboff et al., 2023; Rosenstock et al., 2023; Urva et al., 2022). Due to its triple action as a GIP, GLP-1, and glucagon receptor agonist (GCGRA), it has been investigated in clinical trials to evaluate its effects on obese patients with or without diabetes mellitus. Retatrutide exhibits effectiveness in the treatment of obesity, resulting in substantial weight loss and improved metabolic profiles (Jastreboff et al., 2023). Retatrutide, owing to its capacity for weight reduction and glucose regulation, holds promise for potential benefits in conditions such as cardiovascular diseases and chronic kidney diseases, which share close associations with metabolic dysfunction-associated steatotic liver disease (MASLD). Retatrutide lowers HbA1c levels and induces significant weight loss (Rosenstock et al., 2023). Ongoing investigations like the TRIUMPH phase 3 initiative will investigate the safety and efficacy of retatrutide in the management of chronic weight disorders, obstructive sleep apnea, and knee osteoarthritis among individuals classified as obese or overweight (Study Details, n.d.).

The most commonly reported side effects in a clinical trial by Jastreboff et al. (2023) included gastrointestinal symptoms such as nausea, diarrhea, vomiting, and constipation, which were more common with retatrutide than with a placebo. With retatrutide, the most common adverse event that resulted in treatment discontinuation was gastrointestinal distress (Jastreboff et al., 2023). These events mostly happened during dose escalation, were mild to moderate in severity, more common in higher-dose groups, and somewhat mitigated by using a lower starting dose (2 mg vs. 4 mg) (Jastreboff et al., 2023). Thirteen subjects in the retatrutide groups, with baseline BMIs ranging from 27 to 50.6, showed a decrease in BMI to 22 or less.(Jastreboff et al., 2023). Furthermore, 1% of the subjects experienced temporary elevations of alanine aminotransferase (ALT) levels to over threefold the upper limit of the normal range; heart rate accelerated in a dose-dependent way for 24 weeks and then decreased; and skin hyperesthesia and sensitivity side effects were noted in 7% of the retatrutide subjects (Jastreboff et al., 2023). Retatrutide was not stopped as a result of any of these occurrences, nor were any of them severe, significant, or connected to obvious skin findings (Jastreboff et al., 2023). Supraventricular arrhythmia and cardiac conduction abnormalities have also been observed in some clinical trials (Jastreboff et al., 2023).

Several studies also reported that minimal to intermediate gastrointestinal problems, such as diarrhea, vomiting, nausea, and constipation, are the most common treatment-related side events associated with retatrutide (Rosenstock et al., 2023; Urva et al., 2022). Furthermore, these incidents showed that the dosage was a determining factor (Rosenstock et al., 2023; Urva et al., 2022). In the clinical trial, Rosenstock et al. (2023) reported that 67 subjects in the retatrutide groups had mild-to-moderate gastrointestinal side effects.

6. Physiologic association between retatrutide, incretin, and glucagon receptors

The regulation of body weight through the receptor activity of molecules such as GLP-1Rs, GIPRs, and GCGRs shows significant therapeutic promise. Genetically modified mice models have proven the ability of retatrutide to bind to these receptors and influence nutrient uptake, energy metabolism, and weight loss (Coskun et al., 2022). Investigation of glucose tolerance in GLP-1R-null mice, GIPR-null mice, and wildtype mice exposed to Retatruride showed improved glucose use in all 3 models, proving retatrutide's ability to improve glucose tolerance via both mechanisms (Coskun et al., 2022). This trial further studied glucagon activity by blocking both GIPR and GLP-1R by exposing the GLP-1R-null mice to GIPR monoclonal antagonists (Coskun et al., 2022). Exposure to the triple agonist in this scenario still led to an increased plasma glucose approximately 1 h after dosing (Coskun et al., 2022). Pretreatment of this mouse line with GCGR antibody blocked any glucose increase in the presence of retatrutide, proving the drug's agonism of all three receptors (Coskun et al., 2022). Zhang et al. (2021) examined the physiological effects of GIPR knockout in mice as well, demonstrating that the CNS-specific GIPR knockout effectively protects against diet-induced obesity (DIO). Genome-wide association studies have further corroborated the link between obesity and GIP, spurring interest in further clinical investigations focusing on combination therapies (Zhang et al., 2021).

7. Animal studies investigating the effectiveness of retatrutide in Obesity and diabetes

In a preclinical study by Urva et al. (2023), C57/B16 male obese mice

(Jackson) were used to evaluate the effects of retatrutide (Urva et al., 2023). These mice were individually housed and maintained on a standardized diet (TD95217; Teklad) with ad libitum access to water. Before assessing acute GE, mice were fasted overnight (16 h) and then treated subcutaneously with either a vehicle (10 ml/kg; 40 mM Tris, pH 8), long-acting GCGRA, semaglutide, retatrutide, or a combination of semaglutide and long-acting GCGRA. GE was measured following the administration of 0.5 ml of semi-liquid by oral gavage. Chronic effects of these treatments were also evaluated by administering the compounds daily for 10 days, and monitoring GE delay, body weight, and food intake. Results indicated that while long-acting GCGRA alone did not significantly affect GE, retatrutide caused a dose-dependent delay in GE, similar to semaglutide. The combined treatment of semaglutide and long-acting GCGRA did not statistically differ from retatrutide in terms of GE delay. Over the 10-day period, retatrutide at a dose of 10 nmol/kg significantly reduced body weight, more so than semaglutide, long-acting GCGRA, or their combination. Additionally, retatrutide led to the greatest reduction in food intake. The GE delay observed with retatrutide diminished after the 10-day chronic treatment period. These findings highlight retatrutide's potent effects on body weight reduction and food intake in obese mice, suggesting its potential utility in treating obesity and related metabolic disorders.

To investigate the effects of retatrutide on body weight, energy metabolism, body composition, and hepatic steatosis, Coskun et al. (2022) administered the drug to C57/Bl6 diet-induced obese (DIO) mice. Statistically significant weight reduction at 3 mg dose (1.13 kg at day 8) and greater reductions at 4.5 mg (up to 2.93 kg) and 6 mg (up to 3.52 kg) was seen, which implied that retatrutide significantly reduced body weight in a dose-dependent manner (ED50: 4.73 nmol/kg) and decreased calorie intake. The weight reduction was primarily due to a decrease in fat mass with minimal impact on lean mass, as indicated by the fat mass/lean mass ratio. retatrutide also lowered blood glucose and plasma insulin levels, indicating improved glycemic control and suggesting enhanced insulin sensitivity, similar to effects observed in a different study, with dual GIPR/GLP-1R agonism (Samms et al., 2021). Additionally, retatrutide improved liver health by reducing plasma ALT and liver triglycerides. In a comparative study, retatrutide resulted in greater body weight loss than tirzepatide in obese mice when administered daily at 10 nmol/kg, which correlated with a more significant reduction in calorie intake, potentially explaining the additional weight loss observed with retatrutide (Urva et al., 2022).

Retatrutide increases energy expenditure in obese mice through GCGR engagement. To demonstrate this, experiments were conducted at thermoneutrality (27 °C) by Coskun et al. (2022). Retatrutide at 10 nmol/kg induced a 35% body weight loss within 10 days, compared to 20% in the calorie-intake matched (CIM) group, with significant calorie suppression. Unlike the CIM group, which showed reduced energy expenditure and gradual weight gain, retatrutide-treated mice maintained weight loss by sustaining energy expenditure levels. Retatrutide also resulted in greater fat mass reduction and increased lipid oxidation without affecting locomotor activity. The use of a GCGR antibody antagonist minimized retatrutide's weight loss effect by blocking the increase in energy expenditure, highlighting the role of GCGR agonism in retatrutide's efficacy.

8. Clinical trials and outcomes on retatrutide in Obesity and diabetes

A first-in-human, single ascending dose, phase 1 study was conducted by Coskun et al. (2022) to evaluate the safety and pharmacokinetics of retatrutide. The study included 47 healthy participants in Singapore, with 45 receiving at least one dose of Retatrutide or placebo. Demographic characteristics were comparable across cohorts, although a lower body mass index was noted in the 0.3 mg and 4.5 mg retatrutide groups. Pharmacokinetic analysis revealed that maximum retatrutide concentration was observed within 12–72 h post-dose, and the mean half-life was approximately 6 days, supporting a weekly dosing regimen. The pharmacokinetics of retatrutide appeared nearly dose-proportional, with moderate inter-participant variability. No significant changes in fasting glucose were observed, as expected in non-diabetic individuals. However, dose-related increases in fasting insulin and C-peptide were observed, peaking at 24–48 h and returning to baseline by days 8 and 15, respectively. A decrease in fasting glucagon was noted at higher doses (4.5 and 6.0 mg), consistent with GLP-1R and GCGR target engagement.

Significant reductions in fasting triglycerides and increases in beta-hydroxybutyrate levels were observed, indicating potential GCGR-mediated increases in fatty acid oxidation. Additionally, reductions in gluconeogenic amino acids (alanine, asparagine, serine) were reported. Except for the lowest dose (0.1 mg), retatrutide treatment resulted in dose-dependent decreases in body weight, with the most significant reductions observed at the 4.5 mg and 6.0 mg doses, maintained up to day 43 (Table 2). Higher doses also resulted in reduced appetite, as evidenced by increased appetite visual analog scores. These findings support the potential of retatrutide for weight management and metabolic benefits.

In a phase 1b, double-blind, placebo-controlled, randomized trial, Urva et al. evaluated the safety, pharmacokinetics, and pharmacodynamics of retatrutide, GIP, and GLP-1R, in adults with T2DM and obesity. The study enrolled 72 participants aged 20–70 with HbA1c values of 7.0–10.5% and BMIs of 23–50 kg/m^2. Participants received weekly subcutaneous injections of either retatrutide, placebo, or dulaglutide 1.5 mg over 12 weeks across five ascending dose cohorts. Safety and tolerability were the primary outcomes, with pharmacodynamics and pharmacokinetics as secondary outcomes. Treatment-emergent adverse events (TEAEs) were reported by 63% of retatrutide recipients, with gastrointestinal disorders being the most common. Pharmacokinetics revealed a dose-proportional profile and a half-life of approximately six days. Significant placebo-adjusted reductions in mean daily plasma glucose were observed in the highest retatrutide dose groups: 2.8 mmol/L (3 mg), −3.1 mmol/L (3/6 mg), and −2.9 mmol/L (3/6/9/12 mg). Significant reductions in HbA1c were −1.4% (3 mg), −1.6% (3/6 mg), and −1.2% (3/6/9/12 mg), with a dose-dependent bodyweight reduction up to −8.96 kg in the highest dose group. These findings support the progression of retatrutide to phase 2 trials due to its acceptable safety profile and substantial pharmacodynamic benefits in glucose and body weight reduction (Urva et al., 2022).

Jastreboff et al. (2023) (Jastreboff et al., 2023) spearheaded a phase 2 clinical trial delving into the potential of retatrutide as a therapeutic intervention for combating obesity. The study involved 338 adults with obesity or overweight with weight-related conditions. Participants were given retatrutide once weekly for 48 weeks at various doses or a placebo. Results showed significant reductions in body weight, with the highest dose (12 mg) leading to a 24.2% reduction at 48 weeks. Furthermore, 72% of participants with prediabetes in the retatrutide group achieved normoglycemia as compared to 22% of participants in the placebo group at week 48. Dose-dependent gastrointestinal adverse events were observed but mitigated with lower starting doses.

In a phase 2 trial led by Rosenstock et al. (2023), retatrutide was evaluated in people with T2DM. The study included 281 participants randomized to various doses of retatrutide, dulaglutide, or placebo. Results demonstrated significant reductions in HbA1c levels at 24 weeks, with greater efficacy than placebo and dulaglutide in most doses. Additionally, dose-dependent reductions in body weight were observed at 36 weeks, significantly surpassing placebo and dulaglutide. Mild-to-moderate gastrointestinal adverse events were reported, consistent with GLP-1R agonists. These findings suggest that retatrutide holds promise as both an anti-diabetic and anti-obesity drug, informing its advancement to phase 3 trials.

The latest 48-week phase 2 study by Sanyal et al. (2024), targeting obesity, found that retatrutide, at doses of 8 mg and 12 mg, resulted in weight reductions of 22.8% and 24.2%, respectively. The primary goal of a related substudy was to assess the average relative change in liver

Table 2
Table summary of clinical trials on efficacy of retatrutide in Obesity and T2DM.

Study ID	Trial	Condition	Outcome	Adverse effects
Coskun et al. (2022)	NCT03841630	Obesity	Fasting glucose: No significant change from baseline to day 43 compared to placebo in nondiabetic individuals. - Dose-related increases observed in Fasting Insulin and C-Peptide, peaking at 24 and 48 h post-dose. Levels returned to near baseline by day 8 (insulin) and day 15 (C-peptide). -Body weight: Decreases observed at all dose levels except the lowest (0.1 mg). -Greatest reductions at 3–6 mg doses. -Statistically significant weight reduction at 3 mg dose (1.13 kg at day 8) and greater reductions at 4.5 mg (up to 2.93 kg) and 6 mg (up to 3.52 kg).	Gastrointestinal disorders including vomiting, abdominal distention, and nausea.
Urva et al. (2022)	NCT04143802.	Type 2 Diabetes	Significant decrease in daily plasma glucose at highest doses (3 mg, 3/6 mg, and 3/6/9/12 mg) Significant reduction in sHbA1c at highest doses (−1.4%, −1.6%, and −1.2%) Dose-dependent reduction in bodyweight (up to −8.96 kg in the 3/6/9/12 mg group)	Gastrointestinal disorders (most frequent)
Jastreboff et al. (2023)	NCT04881760.	Obesity	Substantial reductions in body weight after 48 weeks of retatrutide treatment Percentage change in body weight ranged from −7.2% to −24.2%	Gastrointestinal adverse events (most common) Dose-dependent increases in heart rate peaked at 24 weeks and declined thereafter.
Rosenstock et al. (2023)	NCT04867785.	Type 2 Diabetes	Significant reductions in HbA1c with retatrutide at 24 and 36 weeks Bodyweight decreased dose-dependently with retatrutide at 36 weeks Reductions in HbA1c were significantly greater than placebo in most retatrutide groups	Mild-to-moderate gastrointestinal adverse events reported in retatrutide groups Gastrointestinal adverse events included nausea, diarrhea, vomiting, and constipation No reports of severe hypoglycemia or deaths
Sanyal et al. (2024)	NCT04881760.	Metabolic function-associated Steatotic Liver Disease	-Weight reduction at 48 weeks: 22.8% (8 mg) and 24.2% (12 mg) retatrutide. -Mean relative change in liver fat (LF) at 24 weeks: −1 mg: −42.9% −4 mg: −57.0% −8 mg: −81.4% −12 mg: −82.4% -Placebo: +0.3% -Normal LF (<5%) achieved at 24 weeks: −1 mg: 27% −4 mg: 52% −8 mg: 79% −12 mg: 86% -Placebo: 0%	● Serious: 1 participant had acute cholecystitis and vomiting ● Other: Nausea, vomiting, decreased appetite, diarrhea, constipation, hypertension, upper abdominal pain, fatigue, dizziness, dyspepsia, early satiety, increase in lipase levels, upper respiratory tract infections
TRIUMPH-3	NCT05882045	Obesity, cardiovascular disease	● (Ongoing)	● (Ongoing)

fat (LF) at 24 weeks in participants with metabolic dysfunction-associated steatotic liver disease and at least 10% LF. This randomized, double-blind, placebo-controlled trial included 98 participants who were assigned to receive once-weekly subcutaneous injections of retatrutide (at doses of 1, 4, 8, or 12 mg) or a placebo for 48 weeks. At the 24-week mark, the mean relative change in LF was −42.9% for the 1 mg group, −57.0% for the 4 mg group, −81.4% for the 8 mg group, −82.4% for the 12 mg group, and +0.3% for the placebo group (all $P < 0.001$ compared to placebo). Additionally, by 24 weeks, normal LF levels (<5%) were achieved by 27% of participants in the 1 mg group, 52% in the 4 mg group, 79% in the 8 mg group, 86% in the 12 mg group, and 0% in the placebo group. The reduction in LF was closely linked to changes in body weight, abdominal fat, and improvements in metabolic markers associated with better insulin sensitivity and lipid metabolism.

The TRIUMPH-3 (Study Details, n.d.) phase III trial is currently underway, aiming to evaluate the safety and effectiveness of weekly administration of retatrutide in patients with severe obesity and cardiovascular disease. This double-blind, randomized trial began in May 2023 and is expected to enroll 1800 participants to assess the impact of retatrutide thoroughly. The study is anticipated to conclude in November 2025.

9. Comparison of retatrutide with other dual or single receptor agonists

Retatrutide, as a triple agonist, represents a significant advancement in obesity and diabetes therapy compared to dual or single receptor agonists. In preclinical studies, retatrutide has demonstrated superior efficacy at lower doses compared to previous treatments, including dual agonists (GLP-1/GIP or GLP-1/glucagon) and individual agonists (Finan et al., 2015).

When compared to dulaglutide, a GLP-1R agonist, retatrutide showed superior efficacy in both glycemic control and weight loss. After 36 weeks of treatment, retatrutide 12 mg once weekly resulted in up to −2.2% HbA1c reduction, compared to −1.4% with dulaglutide 1.5 mg (Gogineni et al., 2024). The weight loss effects were even more pronounced, with retatrutide 12 mg achieving up to 16.9% weight loss, compared to only 2% weight loss with dulaglutide 1.5 mg (Gogineni et al., 2024).

The magnitude of weight loss achieved with retatrutide (up to 24%) (Jastreboff et al., 2023) is notably higher than that reported for GLP-1R

agonists alone. For instance, liraglutide 3.0 mg/day led to 8.40 kg average weight loss over 56 weeks, while semaglutide 2.4 mg/week led to 15.3 kg average weight loss over 68 weeks in clinical trials (Wang et al., 2023). This suggests that the addition of GCGR and GIPR agonism to GLP-1R agonism in retatrutide may provide additive benefits for weight loss.

Dual agonists targeting GLP-1R and GIPR, such as tirzepatide, have shown promising results in clinical trials. Tirzepatide demonstrated dose-dependent reductions in HbA1c (−1.06% to −1.94%) and significant weight loss (−0.9 kg to −11.3 kg) (Baggio and Drucker, 2021). While these results are impressive, retatrutide's weight loss effects (up to 24%) (Jastreboff et al., 2023) appear to be even more substantial, potentially due to the addition of GCGR agonism.

The balanced activity of all three components (GLP-1, GIP, and glucagon) in retatrutide appears to be crucial for maximal efficacy (Finan et al., 2015). The addition of glucagon activity to the GLP-1/GIP combination enhances weight loss through increased energy expenditure and improved hepatic lipid handling (Finan et al., 2015). This mechanism may explain the superior efficacy of retatrutide compared to dual or single receptor agonists.

In terms of other metabolic improvements, retatrutide has shown marked reductions in waist circumference, blood pressure, and triglycerides (Gogineni et al., 2024). Similar benefits have been observed with GLP-1R agonists and dual GLP-1R/GIPR agonists (Baggio and Drucker, 2021; Wang et al., 2023). However, the magnitude of these improvements appears to be more substantial with retatrutide, particularly in terms of weight loss and waist circumference reduction.

The safety profile of retatrutide appears to be consistent with the known effects of GLP-1R agonism, with gastrointestinal side effects being the most common (Coskun et al., 2022; Gogineni et al., 2024). This is similar to the safety profile of GLP-1R agonists and dual GLP-1R/GIPR agonists (Baggio and Drucker, 2021; Wang et al., 2023). However, the discontinuation rate due to adverse events (up to 17% for retatrutide) (Gogineni et al., 2024) may be higher than what is typically seen with single GLP-1R agonists, possibly due to the triple agonist mechanism.

It's worth noting that GLP-1R agonists and dual agonists have shown benefits beyond glycemic control and weight loss, including potential cardioprotective effects, improvements in cognitive function, and renoprotective effects (Wilbon and Kolonin, 2024). While similar long-term data are not yet available for retatrutide, its mechanism of action suggests it may offer similar or even enhanced benefits in these areas.

In summary, retatrutide demonstrates superior efficacy in weight loss and glycemic control compared to both single GLP-1R agonists and dual GLP-1R/GIPR agonists. The addition of GCGR agonism appears to provide additive benefits, particularly in terms of weight loss and energy expenditure. However, long-term studies are still needed to fully characterize the safety profile and potential additional benefits of retatrutide compared to other agonists. As research continues, retatrutide represents a promising new direction in the treatment of obesity and T2DM, potentially offering more comprehensive metabolic benefits than current single or dual receptor agonists.

10. Comparison of retatrutide with DPP-4 inhibitors

Retatrutide has demonstrated remarkable efficacy in weight loss and glycemic control compared to DPP-4 inhibitors. In clinical trials, retatrutide has shown a dose-dependent reduction in body weight of up to 24% after 48 weeks of treatment (Jastreboff et al., 2023). This is a stark contrast to DPP-4 inhibitors, which are generally considered weight-neutral or, at best, associated with minimal weight loss (Mello et al., 2015). The weight-neutral effect of DPP-4 inhibitors is consistent across various agents in the class, including sitagliptin, vildagliptin, saxagliptin, linagliptin, and alogliptin (Mello et al., 2015).

In terms of glycemic control, retatrutide demonstrated superior efficacy compared to DPP-4 inhibitors. Retatrutide 12 mg once weekly resulted in up to −2.2% HbA1c reduction after 36 weeks of treatment (Gogineni et al., 2024). In comparison, DPP-4 inhibitors typically achieve HbA1c reductions of 0.5%–0.9% compared to placebo (Capuano et al., 2013), with average reductions of 0.6–1.0% and up to 2% in patients with higher baseline levels (Deacon and Holst, 2013). While both classes of drugs show significant improvements in glycemic control, retatrutide appears to offer more substantial HbA1c reductions.

Retatrutide's mechanism of action, which includes GCGR agonism in addition to GIPR and GLP-1R agonism, appears to result in increased energy expenditure along with decreased calorie intake (Coskun et al., 2022). This unique triple-action mechanism potentially leads to more pronounced and durable body weight management compared to DPP-4 inhibitors, which primarily work by increasing levels of active incretins (GLP-1 and GIP) (Crepaldi et al., 2007).

Both retatrutide and DPP-4 inhibitors demonstrate improvements in various cardiometabolic risk factors. Retatrutide treatment led to marked improvements in waist circumference (mean reduction up to −13.2 cm), systolic blood pressure (mean reduction up to −8.8 mmHg), diastolic blood pressure (mean reduction up to −3.9 mmHg), and triglycerides (reduction up to −35%) (Gogineni et al., 2024). DPP-4 inhibitors have also shown potential cardioprotective effects, including lowering blood pressure, improving endothelial function, and improving lipid profiles (Mello et al., 2015). However, the magnitude of these improvements appears to be more substantial with retatrutide.

In terms of safety and tolerability, both drug classes have distinct profiles. Retatrutide's most common side effects were gastrointestinal, including vomiting, abdominal distention, and nausea, with adverse events leading to treatment discontinuation in up to 17% of participants (Gogineni et al., 2024). DPP-4 inhibitors, on the other hand, are generally well-tolerated with an adverse effect profile similar to placebo (Deacon and Holst, 2013). Common adverse events with DPP-4 inhibitors include nasopharyngitis, headache, and urinary tract infections (Capuano et al., 2013). Both classes of drugs have a low risk of hypoglycemia due to their glucose-dependent action (Deacon and Holst, 2013; Gogineni et al., 2024).

One advantage of DPP-4 inhibitors over retatrutide is their oral administration, which may improve compliance compared to injectable therapies like retatrutide (Capuano et al., 2013). Additionally, DPP-4 inhibitors can be used in elderly patients and those with renal impairment, though dose adjustments may be needed for some agents (Deacon and Holst, 2013).

DPP-4 inhibitors have demonstrated efficacy similar to sulfonylureas and thiazolidinediones when used as add-on therapy to metformin (Deacon and Holst, 2013). This positions them as valuable second-line agents in diabetes management. Furthermore, in vitro and animal studies suggest that DPP-4 inhibitors may have the potential to inhibit apoptosis of β-cells and promote their regeneration and differentiation (Crepaldi et al., 2007). This potential for β-cell preservation is a unique aspect not directly addressed in the retatrutide studies. DPP-4 inhibitors have also shown efficacy in maintaining reduced HbA1c levels for up to 1 year and can improve β-cell function and insulin sensitivity (Crepaldi et al., 2007). While these effects are promising, the more pronounced weight loss and glycemic control achieved with retatrutide (Coskun et al., 2022; Gogineni et al., 2024) suggest it may offer superior metabolic benefits. However, long-term studies comparing the effects of retatrutide and DPP-4 inhibitors on β-cell function and durability of glycemic control would be valuable to fully understand their relative benefits.

In conclusion, while both retatrutide and DPP-4 inhibitors offer significant benefits in the treatment of T2DM, retatrutide demonstrates superior efficacy in terms of weight loss and glycemic control. However, DPP-4 inhibitors may still have a valuable role in diabetes management, particularly for patients who prefer oral medications or those at lower risk of obesity-related complications.

11. Future perspectives

Retatrutide has the potential to become the cornerstone of T2DM and sustained weight loss management, given its efficacy, relatively good safety profile as demonstrated by phase 2 trials, and its potential benefits in positively affecting other components of the metabolic syndrome such as high triglycerides, low high-density lipoprotein cholesterol, increased blood pressure, and increased fasting sugars. However, Retatutride's effects in different conditions must be further explored to widen the drug's therapeutic indications. Of particular note is Retatutrides' observed effect on fatty liver disease management. Sanyal et al. (2024) found that Retatutride reversed early-stage fatty liver disease in over 85% of participants. As MASLD is the main cause of chronic liver disease, further research into the efficacy of Retatutride as a curative option for fatty liver disease is necessary.

Future trials are imperative to more fully grasp Retatutride's safety profile as well as long-term treatment effects and potential adverse outcomes. Trials have followed retatrutide use in patients for 48 weeks, however further investigation in patients who continue the regimen for longer periods must be conducted. Effects of retatrutide in special populations such as pregnancy, those undergoing anesthesia, and patients with comorbid conditions must be further investigated for informed clinical decision-making. Childhood obesity is currently one of the most prevalent metabolic disorders. Further research into retatutride as an adjunct therapy for weight loss in adolescents and children could offer valuable insights into addressing this global health change. However, further examination would be necessary before implementation in this demographic.

Studies have demonstrated substantial weight loss, up to 24% of mean body weight, in a significant portion of participants (Jastreboff et al., 2023). Taking this promising effect of retatrutide into account, weight loss goals are expected to improve very significantly, as much as 24%, similar to rates expected in bariatric surgery. This hence, may translate into reduced numbers of patients undergoing this surgical procedure, and its associated costs and complications.

Retatrutide has been reported to be 2.9 times less effective than human glucagon in stimulating GCGRs (Coskun et al., 2022). Moreover, the specific role of GCGR stimulation in retatrutide's mechanism of action for weight loss currently remains unclear. Comparative studies with more dual GLP-1/GIP agonists like tirzepatide could provide valuable insights. This understanding is crucial for optimizing treatment strategies for obesity and T2DM.

Future research should also prioritize direct comparative studies between retatrutide and other established pharmacological agents such as semaglutide and tirzepatide. The current trials primarily use a placebo as a comparator, which limits the understanding of retatrutide's relative efficacy and safety. Given that semaglutide and tirzepatide have demonstrated significant weight loss and glycemic control, and have been compared indirectly with retatrutide, head-to-head trials are essential. These studies will provide critical insights into retatrutide's clinical advantages, optimal usage, and adverse event profile. Addressing this gap is vital for informed clinical decision-making and the strategic positioning of retatrutide in the treatment landscape for obesity and T2DM.

12. Limitations

While extensive efforts were made to ensure a thorough search of the literature, including comprehensive database searches and manual screening of reference lists, there is still a possibility of missing relevant studies. Additionally, restricting the inclusion criteria to articles published in English may introduce language bias and overlook pertinent research published in other languages. Furthermore, the scope of our review was constrained by the limited availability of data on retatrutide, as the existing literature on this novel triple agonist for obesity and diabetes is relatively sparse.

13. Conclusion

In conclusion, the rising prevalence of obesity and T2DM poses a significant global health challenge, with existing therapies often falling short in efficacy and safety. The newly developed triple agonist, retatrutide, presents a promising avenue for addressing these unmet needs. Through its synergistic action, retatrutide has demonstrated significant weight loss, improved glycemic control, and potential cardiovascular benefits in preclinical and clinical studies. However, despite promising results, further research is warranted to unlock the drug's mechanism of action, therapeutic potential, and safety necessitating larger and longer clinical trials. Looking ahead, retatrutide holds the potential to become a cornerstone in the management of obesity, T2DM, and related metabolic disorders, with implications for reducing the burden of these conditions on both individuals and healthcare systems globally.

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Toufik Abdul-Rahman: Writing – review & editing, Writing – original draft, Visualization, Supervision, Data curation, Conceptualization. **Poulami Roy:** Writing – original draft. **Fatma Kamal Ahmed:** Writing – original draft. **Jann Ludwig Mueller-Gomez:** Writing – original draft. **Sarmistha Sarkar:** Writing – original draft. **Neil Garg:** Writing – original draft. **Victor Oluwafemi Femi-Lawal:** Writing – original draft. **Andrew Awuah Wireko:** Writing – review & editing, Writing – original draft. **Hala Ibrahim Thaalibi:** Writing – original draft. **Muhammad Usman Hashmi:** Writing – original draft. **Andrew Sefenu Dzebu:** Writing – original draft. **Sewar Basheer Banimusa:** Writing – original draft. **Aayushi Sood:** Writing – review & editing, Conceptualization.

Declaration of competing interest

Authors wish to declare no conflict of interest.

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Data availability

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

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