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RETATRUTIDE IN INTERNAL MEDICINE: A NOVEL TRIPLE HORMONE RECEPTOR AGONIST FOR OBESITY, TYPE 2 DIABETES, AND CARDIOMETABOLIC RISK

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ABSTRACT

Obesity and type 2 diabetes mellitus are major chronic diseases associated with cardiovascular, metabolic, hepatic, and renal complications. The development of incretin-based therapies has substantially changed the management of these conditions. Retatrutide is a novel once-weekly triple hormone receptor agonist that simultaneously activates the glucose-dependent insulinotropic polypeptide (GIP), glucagon-like peptide-1 (GLP-1), and glucagon receptors. Unlike currently established incretin therapies, retatrutide combines incretin-mediated effects with glucagon receptor activation, potentially enhancing energy expenditure and lipid metabolism in addition to reducing appetite and food intake. This narrative review aimed to evaluate the current evidence regarding the efficacy, safety, metabolic effects, and potential clinical applications of retatrutide in internal medicine. A literature search was performed using PubMed/MEDLINE and major clinical trial and guideline publications, prioritizing randomized controlled trials, systematic reviews, meta-analyses, and contemporary publications available through August 2026. Phase 2 studies demonstrated substantial, dose-dependent weight loss in adults with obesity, with reductions approaching 24% after 48 weeks at the highest studied dose. In individuals with type 2 diabetes, retatrutide also produced clinically meaningful reductions in glycated hemoglobin and body weight. Improvements in lipid parameters, hepatic steatosis, and other cardiometabolic markers have also been reported. Gastrointestinal adverse events, particularly nausea, diarrhea, and vomiting, represent the most frequent treatment-related adverse effects and appear to be dose dependent. Cardiovascular, renal, and long-term safety outcomes remain under investigation. Recent phase 3 studies have expanded the evidence base, although retatrutide remains an investigational therapy and definitive long-term outcome data are still required. Retatrutide may represent a new generation of pharmacological treatment for obesity and metabolic disease, but its eventual place in clinical practice will depend on the results of ongoing cardiovascular, renal, and long-term safety trials.

Keywords: Retatrutide; Obesity; Type 2 Diabetes Mellitus; GIP; GLP-1; Glucagon; Cardiometabolic Risk; Incretin Therapy.

1 INTRODUCTION

Obesity is a chronic, progressive, and multifactorial disease associated with an increased risk of type 2 diabetes mellitus (T2DM), hypertension, dyslipidemia, cardiovascular disease, metabolic dysfunction-associated steatotic liver disease, chronic kidney disease, and premature mortality. The increasing prevalence of obesity has created a major challenge for internal medicine because effective management frequently requires long-term pharmacological intervention in addition to lifestyle modification.

The development of glucagon-like peptide-1 receptor agonists (GLP-1RAs) substantially changed the pharmacological treatment of obesity and T2DM. More recently, dual glucose-dependent insulinotropic polypeptide (GIP) and GLP-1 receptor agonists have demonstrated even greater effects on body weight and glycemic control. Tirzepatide, for example, established the clinical relevance of simultaneous GIP and GLP-1 receptor activation in obesity and T2DM.

Retatrutide (LY3437943) represents a further development of this therapeutic concept. It is a single-molecule agonist of the GIP, GLP-1, and glucagon receptors, and is therefore classified as a triple hormone receptor agonist. Its mechanism combines the appetite-suppressing and glucose-lowering effects associated with incretin signaling with the metabolic effects of glucagon receptor activation (KATSI et al., 2025).

The first major clinical evidence came from phase 2 studies. In adults with obesity, weekly retatrutide produced dose-dependent weight loss, with the highest dose achieving approximately 24% mean weight reduction at 48 weeks (JASTREBOFF et al., 2023).

More recently, clinical development has progressed to phase 3 trials in obesity and T2DM. A 2026 phase 3 randomized controlled trial in patients with T2DM inadequately controlled by lifestyle intervention demonstrated significant reductions in body weight and glycated hemoglobin with weekly retatrutide compared with placebo (BAJAJ et al., 2026).

Therefore, this study aimed to review the current evidence regarding retatrutide, focusing on its pharmacological mechanism, efficacy in obesity and type 2 diabetes mellitus, metabolic and cardiometabolic effects, safety profile, potential clinical applications, and the limitations of the current evidence.

2 METHODOLOGY

This study was designed as a narrative literature review addressing the current evidence on retatrutide in internal medicine.

A literature search was conducted using PubMed/MEDLINE and publications from major medical journals. Searches were performed using combinations of the terms: “retatrutide,” “LY3437943,” “triple agonist,” “GIP,” “GLP-1,” “glucagon,” “obesity,” “type 2 diabetes,” “weight loss,” “cardiovascular risk,” “metabolic dysfunction-associated steatotic liver disease,” and “chronic kidney disease.”

Publications available through August 2026 were considered, with priority given to randomized controlled trials, phase 1–3 clinical trials, systematic reviews, meta-analyses, mechanistic studies, and contemporary scientific reviews.

The landmark phase 2 trials were included because they established the initial efficacy and safety profile of retatrutide. More recent phase 3 studies and ongoing outcome trials were incorporated to provide an updated perspective on the current stage of clinical development.

Studies were organized according to the following domains:

- Pharmacological mechanism;
- Effects on body weight and obesity;
- Effects on glycemic control;
- Cardiometabolic and hepatic effects;
- Safety and tolerability;
- Potential renal and cardiovascular applications;
- Current limitations and future perspectives.

Because retatrutide remains an investigational medication, published clinical evidence was distinguished from ongoing trials and hypotheses regarding future indications.

3 RESULTS

3.1 Pharmacological mechanism

Retatrutide is a synthetic peptide designed to activate three metabolically relevant hormone receptors: GIP, GLP-1, and glucagon receptors.

GLP-1 receptor activation promotes glucose-dependent insulin secretion, suppresses glucagon secretion, delays gastric emptying, and reduces appetite. GIP contributes to glucose-dependent insulin secretion and may have complementary effects on adipose tissue metabolism.

Glucagon receptor activation produces a distinct metabolic profile. Glucagon can increase energy expenditure, stimulate lipolysis, and promote hepatic substrate utilization. However, excessive glucagon signaling can potentially increase blood glucose, making the combination of glucagon activation with incretin-mediated glucose lowering particularly important.

Retatrutide therefore attempts to combine these complementary pathways within a single molecule.

Preclinical and early clinical studies suggest that the combined activation of these three receptors can produce greater effects on body weight and metabolic parameters than activation of GLP-1 alone (KATSI et al., 2025).

3.2 Effects on body weight

The most prominent clinical effect observed with retatrutide is substantial weight reduction.

In the phase 2 randomized clinical trial published in the New England Journal of Medicine, adults with obesity received weekly retatrutide at different doses or placebo for 48 weeks. Weight reduction was dose dependent, with the highest dose producing approximately 24.2% mean weight loss at week 48 (JASTREBOFF et al., 2023).

This magnitude of weight reduction is clinically important because reductions of 10%, 15%, and 20% or more are associated with progressively greater improvements in obesity-related metabolic complications.

The observed weight loss exceeded that generally seen with earlier generations of anti-obesity pharmacotherapy and placed retatrutide among the most potent pharmacological candidates currently under investigation (JASTREBOFF et al., 2023).

A 2025 analysis focusing on body composition found that retatrutide produced substantial reductions in fat mass, while the proportion of lean mass lost relative to total weight loss was comparable to other contemporary obesity treatments (COSKUN et al., 2025).

These findings are important because the clinical relevance of pharmacological weight loss depends not only on total body weight reduction but also on the preservation of functional lean tissue.

3.3 Retatrutide in type 2 diabetes mellitus

Retatrutide has also demonstrated significant metabolic effects in individuals with T2DM.

In a phase 2 randomized trial involving participants with T2DM, retatrutide produced dose-dependent reductions in HbA1c and body weight. The results supported the transition to phase 3 clinical development (ROSENSTOCK et al., 2023).

More recently, a phase 3 randomized, double-blind, placebo-controlled trial evaluated once-weekly retatrutide monotherapy in adults with T2DM inadequately controlled with diet and exercise.

At 40 weeks, mean body-weight reductions were approximately:

- 11.5% with 4 mg;
- 13.9% with 9 mg;
- 15.3% with 12 mg;

compared with approximately 2% with placebo (BAJAJ et al., 2026).

These findings demonstrate that the effects observed in phase 2 can be reproduced in larger phase 3 populations.

The combination of substantial weight loss and improved glycemic control makes retatrutide particularly relevant to the management of patients with obesity-associated T2DM (BAJAJ et al., 2026).

3.4 Effects on lipid metabolism and cardiometabolic risk

Obesity and T2DM are associated with atherogenic dyslipidemia, insulin resistance, hypertension, and systemic inflammation.

Available retatrutide studies have demonstrated improvements in several cardiometabolic parameters, including lipid profiles and measures of adiposity. Recent analyses have reported reductions in atherogenic lipid-related markers among participants receiving retatrutide.

The potential clinical importance of these changes lies in the possibility that retatrutide may modify several interconnected metabolic risk factors simultaneously.

However, improvements in surrogate markers should not yet be interpreted as proof of cardiovascular event reduction.

Definitive evidence regarding major adverse cardiovascular events, cardiovascular mortality, and long-term survival requires dedicated cardiovascular outcome trials.

3.5 Hepatic effects

Obesity, insulin resistance, and T2DM are major risk factors for metabolic dysfunction-associated steatotic liver disease (MASLD).

Retatrutide has demonstrated promising effects on hepatic fat content and metabolic parameters in exploratory studies.

A phase 2 substudy evaluating participants with obesity and MASLD reported substantial reductions in liver fat following retatrutide treatment. The mean relative reduction in liver fat at 24 weeks reached 82.4% with the 12-mg dose, compared with 0.3% with placebo. These changes were significantly related to changes in body weight, abdominal fat, insulin sensitivity, and lipid metabolism (SANYAL et al., 2024).

These findings suggest that retatrutide may eventually have applications extending beyond weight reduction and glycemic control.

Nevertheless, histological outcomes and long-term effects on fibrosis progression remain important areas for further investigation.

3.6 Potential renal effects

The interaction between obesity and chronic kidney disease is increasingly recognized in internal medicine.

Obesity contributes to CKD through hypertension, insulin resistance, inflammation, glomerular hyperfiltration, and metabolic dysfunction.

Retatrutide may theoretically provide renal benefits through weight reduction and improvement in metabolic risk factors. However, unlike established therapies such as SGLT2 inhibitors, definitive renal outcome evidence for retatrutide is not yet available.

A phase 2b mechanistic trial, TRANSCEND-CKD, was designed to evaluate retatrutide in adults with overweight or obesity and CKD, including participants with and without T2DM. The primary outcome is change in measured glomerular filtration rate, with additional assessments of kidney hemodynamics and renal and perirenal fat (HEERSPINK et al., 2026).

The study included participants with eGFR values between 25 and 75 mL/min/1.73 m^2, making it particularly relevant to the potential future role of retatrutide in patients with obesity and CKD. However, these data remain investigational.

3.7 Safety and tolerability

The adverse-effect profile of retatrutide is predominantly gastrointestinal and resembles that observed with other incretin-based therapies.

The most frequently reported adverse events include:

- nausea;
- diarrhea;
- vomiting;
- constipation;
- decreased appetite;
- abdominal discomfort.

These events tend to be dose dependent and are particularly relevant during dose escalation (JASTREBOFF et al., 2023).

Heart rate increases have also been observed in clinical development, representing an important area for continued cardiovascular surveillance. In the phase 2 obesity trial, dose-dependent increases in heart rate peaked around week 24 and subsequently declined (JASTREBOFF et al., 2023).

Because retatrutide is still investigational, its long-term safety profile has not been fully established.

Potential adverse effects requiring continued evaluation include:

- gallbladder disease;
- pancreatitis;
- persistent changes in heart rate;
- nutritional deficiencies associated with profound weight loss;
- loss of lean mass;
- effects on bone health;
- cardiovascular outcomes;
- renal outcomes;
- long-term gastrointestinal tolerability.

4 DISCUSSION

Retatrutide represents a significant evolution in the pharmacological treatment of obesity and metabolic disease.

The most striking finding is the magnitude of weight loss observed in clinical trials. In the phase 2 obesity trial, the 12-mg dose resulted in approximately 24% weight reduction after 48 weeks, a magnitude that approaches the lower range of weight loss historically associated with some metabolic procedures (JASTREBOFF et al., 2023).

This observation is clinically relevant because obesity treatment has increasingly shifted from the concept of modest weight reduction toward disease modification. A reduction of 20% or more in body weight may substantially influence blood pressure, insulin resistance, dyslipidemia, hepatic steatosis, sleep apnea, and other obesity-related complications.

The pharmacological rationale for retatrutide is also distinctive. GLP-1 receptor activation reduces appetite and improves glucose-dependent insulin secretion, GIP receptor activation provides complementary metabolic effects, and glucagon receptor activation may increase energy expenditure and facilitate lipid utilization (KATSI et al., 2025).

The challenge is balancing these mechanisms. Glucagon receptor activation can theoretically increase glucose concentrations, while GLP-1 and GIP effects counterbalance this tendency. The clinical trials conducted to date suggest that this balance can produce substantial improvements in both weight and glycemic control (JASTREBOFF et al., 2023; ROSENSTOCK et al., 2023).

The results obtained in T2DM are particularly relevant to internal medicine. The 2026 phase 3 trial demonstrated clinically meaningful reductions in both body weight and HbA1c, supporting continued development of retatrutide for metabolic disease (BAJAJ et al., 2026).

Another relevant aspect is body composition. Profound pharmacological weight loss raises the concern that a considerable proportion of weight lost may correspond to lean mass. Current evidence suggests that retatrutide reduces fat mass substantially and that the relative proportion of lean mass loss is not clearly disproportionate compared with other effective anti-obesity therapies (COSKUN et al., 2025).

Nevertheless, clinicians should not interpret a favorable lean-mass ratio as evidence that muscle preservation is guaranteed. Patients undergoing substantial weight loss should receive individualized nutritional counseling and resistance exercise when clinically appropriate.

The hepatic effects are another promising area. The relationship between obesity, insulin resistance, and MASLD creates an opportunity for therapies capable of simultaneously addressing body weight and metabolic dysfunction. Retatrutide's effects on liver fat suggest potential clinical relevance, although long-term histological outcomes remain to be established (SANYAL et al., 2024).

The renal field is similarly promising but still preliminary. TRANSCEND-CKD represents an important step because it directly investigates kidney function and renal hemodynamics in patients with CKD. However, until dedicated outcome trials demonstrate reductions in CKD progression, kidney failure, or cardiovascular mortality, retatrutide should not be considered an established renoprotective therapy (HEERSPINK et al., 2026).

The same principle applies to cardiovascular disease. Improvements in body weight, blood pressure, glycemic control, and lipid parameters are encouraging, but surrogate improvements cannot substitute for cardiovascular outcome evidence.

Therefore, one of the most important clinical considerations is avoiding premature extrapolation of the available evidence. Retatrutide should currently be viewed as a highly promising investigational therapy, rather than as an established replacement for currently approved anti-obesity medications.

The ongoing TRIUMPH program is designed to evaluate retatrutide in several clinically relevant populations, including obesity, obstructive sleep apnea, cardiovascular disease, and osteoarthritis. If positive, these studies could substantially expand the therapeutic role of triple hormone receptor agonism.

CLINICAL IMPLICATIONS FOR INTERNAL MEDICINE

From an internal medicine perspective, retatrutide is particularly relevant because obesity rarely occurs as an isolated condition.

Patients commonly present with combinations of:

- obesity;
- type 2 diabetes mellitus;
- hypertension;
- dyslipidemia;
- metabolic dysfunction-associated steatotic liver disease;
- obstructive sleep apnea;
- cardiovascular disease;
- chronic kidney disease.

A therapeutic strategy capable of simultaneously reducing adiposity and improving multiple metabolic parameters may therefore have considerable clinical relevance.

However, until regulatory approval and definitive outcome data are available, retatrutide should not be incorporated into routine clinical practice as an established therapy.

Future treatment decisions should consider not only the magnitude of weight loss but also:

- Cardiovascular outcomes;
- Renal outcomes;
- Long-term safety;
- Preservation of lean mass;
- Quality of life;
- Durability of weight reduction;
- Effects after treatment discontinuation;
- Cost and accessibility;
- Comparative effectiveness versus semaglutide and tirzepatide.

LIMITATIONS OF THE CURRENT EVIDENCE

- Several limitations must be recognized. First, many of the most impressive data originate from phase 2 trials, which generally have shorter follow-up and smaller populations than definitive cardiovascular and long-term outcome trials.
- Second, retatrutide remains under clinical development, and therefore its long-term safety profile is incompletely characterized.
- Third, improvements in body weight and metabolic biomarkers do not automatically translate into reductions in cardiovascular or renal mortality.
- Fourth, the available studies have primarily evaluated selected populations, and generalizability to frail older adults, patients with advanced multimorbidity, and other underrepresented groups remains uncertain.
- Finally, the magnitude of weight loss raises new questions concerning nutritional adequacy, muscle preservation, bone health, treatment adherence, and the consequences of long-term pharmacological dependence.

FUTURE PERSPECTIVES

The next stage of retatrutide research should focus on clinical outcomes rather than weight reduction alone.

The most relevant questions include whether retatrutide can reduce:

- major adverse cardiovascular events;
- heart failure hospitalization;
- cardiovascular mortality;
- progression of chronic kidney disease;
- development of T2DM in high-risk individuals;
- complications of MASLD;
- obesity-related functional impairment.

The TRANSCEND-CKD program may clarify whether the drug has direct effects on kidney physiology beyond those mediated by weight loss (HEERSPINK et al., 2026).

Likewise, the TRIUMPH program is expected to provide important information regarding obesity-related complications and long-term efficacy.

Comparative studies against established therapies such as semaglutide and tirzepatide will also be important in determining the eventual position of retatrutide within the obesity treatment algorithm.

5 CONCLUSION

Retatrutide is a novel triple hormone receptor agonist targeting GIP, GLP-1, and glucagon receptors and represents one of the most promising developments in contemporary metabolic pharmacotherapy.

Clinical trials have demonstrated substantial, dose-dependent reductions in body weight, with reductions approaching 24% after 48 weeks in adults with obesity. Meaningful improvements in glycemic control have also been observed in patients with type 2 diabetes mellitus, while exploratory studies suggest beneficial effects on lipid metabolism, hepatic steatosis, and other cardiometabolic parameters.

The magnitude of these effects raises the possibility that retatrutide could become an important therapy for obesity and its metabolic complications. Nevertheless, cardiovascular, renal, and long-term safety outcomes remain under investigation.

At present, retatrutide should be considered an investigational therapy rather than an established treatment for routine clinical use. The results of ongoing phase 3 and outcome trials will determine whether its impressive effects on body weight and metabolic parameters translate into reductions in cardiovascular, renal, hepatic, and mortality outcomes.

For internal medicine, retatrutide illustrates the rapid evolution of obesity treatment from simple weight reduction toward comprehensive metabolic disease modification.

STATEMENTS ON COMPLIANCE WITH ETHICAL STANDARDS

Disclosure of conflict of interest

The authors declare no conflicts of interest regarding this manuscript.

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