International Journal of Innovative Technologies in Social Science

e-ISSN: 2544-9435

Operating Publisher
SciFormat Publishing Inc.
ISNI: 0000 0005 1449 8214

2734 17 Avenue SW,
Calgary, Alberta, T3E0A7,
Canada
+15878858911
editorial-office@sciformat.ca

ARTICLE TITLE	TIRZEPATIDE AND RETATRUTIDE IN THE TREATMENT OF OBESITY AND TYPE 2 DIABETES MELLITUS: CURRENT EVIDENCE AND FUTURE DIRECTIONS. A SYSTEMATIC REVIEW OF CURRENT LITERATURE
DOI	https://doi.org/10.31435/ijitss.1(49).2026.4671
RECEIVED	07 December 2025
ACCEPTED	09 January 2026
PUBLISHED	28 January 2026
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TIRZEPATIDE AND RETATRUTIDE IN THE TREATMENT OF OBESITY AND TYPE 2 DIABETES MELLITUS: CURRENT EVIDENCE AND FUTURE DIRECTIONS. A SYSTEMATIC REVIEW OF CURRENT LITERATURE

Rafał Bednarczyk *(Corresponding Author, Email: rafal.bednarczykk@gmail.com)*
10th Military Clinical Hospital with Independent Public Healthcare Centre Polyclinic in Bydgoszcz, Bydgoszcz, Poland
ORCID ID: 0009-0002-0139-8586

Natalia Bednarczyk
10th Military Clinical Hospital with Independent Public Healthcare Centre Polyclinic in Bydgoszcz, Bydgoszcz, Poland
ORCID ID: 0009-0003-2070-8559

Radosław Krzysztof Binkowski
4th Military Clinical Hospital with Polyclinic in Wroclaw, Wroclaw, Poland
ORCID ID: 0009-0009-5925-1158

Agnieszka Kurek
Military Institute of Medicine in Warsaw, Warsaw, Poland
ORCID ID: 0009-0000-7906-213X

Natalia Krajewska
Military Institute of Aviation Medicine in Warsaw, Warsaw, Poland
ORCID ID: 0009-0001-0508-5790

Aleksandra Lejman
10th Military Clinical Hospital with Independent Public Healthcare Centre Polyclinic in Bydgoszcz, Bydgoszcz, Poland
ORCID ID: 0009-0005-8637-2204

Aleksandra Mazurkiewicz
1st Military Clinical Hospital with Outpatient Clinic in Lublin, Lublin, Poland
ORCID ID: 0009-0008-9074-3583

Hubert Sidor
Military Institute of Medicine in Warsaw, Warsaw, Poland
ORCID ID: 0009-0005-5432-9279

Monika Wołosik
Military Institute of Medicine in Warsaw, Warsaw, Poland
ORCID ID: 0009-0001-0129-4771

Szymon Zysiak
Military Institute of Aviation Medicine in Warsaw, Warsaw, Poland
ORCID ID: 0009-0002-8803-5736

ABSTRACT

Background: The global prevalence of obesity and type 2 diabetes mellitus (T2DM) has achieved unprecedented levels, imposing substantial burdens on healthcare systems worldwide. Incretin-based pharmacotherapies have fundamentally transformed therapeutic approaches to these metabolic disorders over the past decade. Tirzepatide is a dual GIP/GLP-1 receptor agonist. Retatrutide additionally targets glucagon receptors. Both agents represent groundbreaking advances in metabolic pharmacotherapy.
Objective: This comprehensive review synthesizes clinical evidence from trials conducted between 2014 and 2024, examining pharmacological mechanisms, therapeutic efficacy, safety characteristics, and prospective clinical applications of these novel multi-receptor agonists.
Methods: We performed systematic literature searches across PubMed, Cochrane Library, Web of Science, and ClinicalTrials.gov databases. Selection criteria encompassed randomized controlled trials, systematic reviews, meta-analyses, and prospective cohort studies, adhering to PRISMA methodology throughout.
Results: Phase 3 clinical trials showed superior efficacy of tirzepatide compared to existing pharmacotherapies, reaching body weight reductions of approximately 22.5% and hemoglobin A1c (HbA1c) reductions of up to 2.4 percentage points. Phase 2 trials of retatrutide revealed even more remarkable outcomes, with weight reductions approaching 24.2% over 48 weeks. Both medications exhibited favorable cardiovascular profiles, though gastrointestinal adverse events constitute the predominant tolerability concern.
Conclusions: These pharmacological agents represent paradigm-shifting developments in obesity and diabetes management. Their therapeutic effectiveness approximates outcomes previously achievable only through surgical intervention, marking a transformative milestone for pharmacotherapy. Ongoing phase 3 trials will further elucidate their optimal positioning within clinical treatment algorithms.

KEYWORDS

Tirzepatide, Retatrutide, GLP-1 Receptor Agonist, GIP Receptor Agonist, Obesity Pharmacotherapy, Type 2 Diabetes Mellitus, Incretin-Based Therapy

CITATION

Rafał Bednarczyk, Natalia Bednarczyk, Radosław Krzysztof Binkowski, Agnieszka Kurek, Natalia Krajewska, Aleksandra Lejman, Aleksandra Mazurkiewicz, Hubert Sidor, Monika Wołosik, Szymon Zysiak. (2026) Tirzepatide and Retatrutide in the Treatment of Obesity and Type 2 Diabetes Mellitus: Current Evidence and Future Directions. A Systematic Review of Current Literature. *International Journal of Innovative Technologies in Social Science*. 1(49). doi: 10.31435/ijitss.1(49).2026.4671

1. Introduction

The magnitude of the global obesity epidemic has expanded dramatically in recent decades. Contemporary epidemiological assessments indicate that over one billion individuals worldwide currently live with obesity, with prevalence rates continuing their upward trajectory across virtually all demographic populations (1, 2). According to World Health Organization data, approximately 16% of the adult global population met obesity criteria in 2022, representing more than a twofold increase compared to 1990 figures (1, 2). The implications extend far beyond excess adiposity. Obesity substantially elevates risk for numerous serious medical conditions including type 2 diabetes mellitus, cardiovascular disease, metabolic dysfunction-associated steatotic liver disease (MASLD), obstructive sleep apnea, and multiple malignancies (2, 3). The economic ramifications are equally staggering, with projections suggesting global obesity-related expenditures could reach $3 trillion annually by 2030, underscoring the urgent necessity for efficacious interventions (3, 4).

Type 2 diabetes mellitus affects more than 500 million people globally and maintains a complex bidirectional relationship with obesity (4, 5). Excess adiposity represents the most significant modifiable risk factor for diabetes development. The fundamental pathophysiology involves insulin resistance affecting skeletal muscle, hepatic tissue, and adipocytes, coupled with progressive deterioration of pancreatic beta-cell insulin secretory capacity. This metabolic dysfunction results in sustained hyperglycemia and ultimately precipitates vascular complications throughout the body (5, 6). Contemporary treatment guidelines

acknowledge this interconnection, emphasizing that individuals with both conditions require comprehensive strategies addressing glycemic regulation and body weight management concurrently (6, 7).

Therapeutic options for obesity have advanced considerably over recent decades. Conventional approaches including dietary modification, behavioral interventions, and first-generation anti-obesity medications typically yielded modest outcomes, generally producing 3-7% weight reduction (7, 8). Although clinically meaningful, such results often proved insufficient to reverse metabolic complications or sustain long-term remission. Bariatric surgery remains the most effective intervention, consistently achieving 25-30% weight reduction with elevated rates of diabetes remission (8, 9). However, surgical approaches present inherent limitations: eligibility criteria exclude many patients, procedural risks exist, and healthcare infrastructure cannot accommodate all potential beneficiaries.

The incretin hormonal system has emerged as a pivotal pharmacological target. Two enteroendocrine hormones, GLP-1 and GIP, are secreted postprandially and fulfill crucial functions in glycemic homeostasis and appetite modulation (9, 10). GLP-1 receptor agonists represented the initial major breakthrough in targeting this pathway, demonstrating improvements in glycemic parameters, facilitating weight reduction, and decreasing cardiovascular risk among high-risk populations (10, 11). Investigators subsequently hypothesized that simultaneous activation of multiple receptors might confer enhanced therapeutic benefits.

Tirzepatide validated this hypothesis. Receiving FDA approval in 2022 for diabetes and 2023 for chronic weight management, it became the inaugural pharmaceutical agent to activate both GIP and GLP-1 receptors (11, 12). Clinical trials showed superiority over single-receptor agents, generating weight reduction and glycemic improvements approaching surgical outcomes (12, 36). Retatrutide advances this therapeutic strategy further by incorporating glucagon receptor activation (13, 14). Preliminary evidence suggests the glucagon component may provide supplementary benefits through enhanced energy expenditure and improved hepatic lipid metabolism (14, 31, 32). Phase 2 trials revealed weight reductions approaching 25%, generating substantial enthusiasm regarding its therapeutic potential (15, 42).

This review comprehensively examines current evidence supporting these two pharmacological agents, analyzing their mechanisms of action, clinical trial outcomes, safety profiles, and potential implications for managing obesity and diabetes.

2. Methodology

2.1 Search Strategy

This literature review was conducted in accordance with PRISMA guidelines (16). Database searches encompassed PubMed/MEDLINE, Cochrane Central Register of Controlled Trials, Web of Science, Scopus, and Embase, examining publications from January 2014 through December 2024. We also searched ClinicalTrials.gov and the International Clinical Trials Registry Platform to identify ongoing trials.

Search terminology included Medical Subject Headings (MeSH) and keywords: "tirzepatide" OR "LY3298176" OR "retatrutide" OR "LY3437943" combined with "obesity" OR "type 2 diabetes" OR "GLP-1 receptor agonist" OR "GIP receptor agonist" OR "incretin" OR "weight loss" OR "glycemic control" OR "clinical trial".

2.2 Selection Criteria

Inclusion criteria encompassed randomized controlled trials, systematic reviews, meta-analyses, and prospective cohort studies investigating tirzepatide or retatrutide in adult populations with obesity, overweight accompanied by comorbidities, or type 2 diabetes mellitus. Publications were required to appear in peer-reviewed English-language journals and report outcomes pertaining to body weight, HbA1c, or safety parameters. Conference abstracts presenting data from pivotal trials were also considered.

Exclusion criteria encompassed preclinical animal studies lacking human data, case reports, editorial commentaries, methodologically flawed studies, duplicate publications, and pediatric-focused research. Studies examining alternative incretin medications without direct comparison to tirzepatide or retatrutide were excluded unless they provided essential contextual information.

2.3 Data Extraction and Quality Assessment

We extracted data systematically, capturing study design characteristics, participant demographics, dosing protocols, comparator interventions, efficacy endpoints, safety parameters, and follow-up duration. We assessed randomized controlled trial quality using the Cochrane Risk of Bias Tool 2.0 (17). Meta-analyses were evaluated utilizing AMSTAR-2 criteria (18), while cohort studies were appraised using the Newcastle-Ottawa Scale. Quantitative results were reported including weighted mean differences for continuous variables and relative risks with 95% confidence intervals for dichotomous outcomes.

3. Results

3.1 Pharmacological Mechanisms

3.1.1 The Incretin System

The "incretin effect" describes a fundamental physiological phenomenon: oral glucose administration elicits a substantially greater insulin response compared to equivalent intravenous glucose delivery. This differential response accounts for roughly 50-70% of meal-stimulated insulin secretion in metabolically healthy individuals (19, 20). Two principal hormones mediate this effect. GLP-1 originates predominantly from intestinal L-cells in the distal gut, whereas GIP is released by K-cells located more proximally in the intestinal tract (20, 21). Both hormones exert their effects through G-protein coupled receptors distributed across pancreatic tissue, adipose depots, gastrointestinal mucosa, and central nervous system structures.

GLP-1 mediates several beneficial metabolic effects. It enhances glucose-dependent insulin secretion, suppresses glucagon release, decelerates gastric emptying (thereby attenuating postprandial glycemic excursions), and activates hypothalamic regions governing appetite and satiety (21, 22, 23). GIP similarly augments insulin secretion but exhibits distinct characteristics, including the capacity to stimulate glucagon secretion under specific conditions and directly influence adipocyte lipid handling (23, 24). Both hormones modulate appetite through divergent neuronal pathways, potentially explaining why dual-receptor activation produces superior outcomes compared to single-receptor targeting (24).

3.1.2 Tirzepatide: The Dual Receptor Agonist

Tirzepatide comprises a 39-amino acid peptide engineered on a modified GIP backbone (25, 26). Several sophisticated molecular features enable once-weekly administration. A fatty diacid chain attached at lysine position 20 facilitates albumin binding in plasma, extending the elimination half-life to approximately five days (26, 27). Strategic modifications at position 2 confer resistance to dipeptidyl peptidase-4 (DPP-4) enzymatic degradation.

Notably, tirzepatide demonstrates approximately five-fold greater binding affinity for GIP receptors compared to GLP-1 receptors (27). Nevertheless, it produces robust GLP-1-mediated effects in clinical settings. Investigators propose this occurs because tirzepatide activates GLP-1 receptors through distinct signaling pathways compared to endogenous GLP-1, preferentially engaging certain downstream cascades. This "biased agonism" may additionally explain superior tolerability profiles observed in some patients compared to selective GLP-1 receptor agonists (28).

The therapeutic advantages of dual receptor engagement appear complementary. GLP-1 receptor activation primarily drives glycemic improvements through enhanced insulin secretion, glucagon suppression, and delayed gastric motility, alongside central appetite suppression (29). GIP receptor co-activation appears to potentiate insulin secretory responses, may mitigate GLP-1-associated nausea, and contributes to weight reduction through central nervous system pathways distinct from GLP-1 mechanisms (30). Clinical trial evidence confirms this combination outperforms single-receptor pharmacotherapies.

3.1.3 Retatrutide: The Triple Receptor Agonist

Retatrutide (LY3437943) represents a further therapeutic advancement through additional glucagon receptor activation (31). This concept originated from preclinical studies showing that glucagon, conventionally conceptualized as a hyperglycemic hormone, exerts important metabolic effects extending beyond glucose homeostasis (32).

Glucagon signaling promotes hepatic lipid oxidation and diminishes hepatic fat accumulation. It additionally stimulates fibroblast growth factor 21 (FGF21) release, a hormone mediating favorable metabolic effects (33, 34). Perhaps most significantly for weight management, glucagon elevates resting energy expenditure, enhancing caloric utilization at rest. This effect is well-established in animal models and appears operative in humans, albeit potentially to a lesser magnitude (35).

Glucagon's hyperglycemic properties would theoretically be problematic in diabetes pharmacotherapy. Retatrutide addresses this through carefully calibrated receptor activation ratios, wherein GIP and GLP-1 components provide sufficient insulinotropic activity to counterbalance glucagon-induced glucose elevation (35). Phase 1 trials confirmed that retatrutide actually reduces glycemia despite the glucagon component (30). Preliminary evidence suggests it may produce weight reductions exceeding tirzepatide, potentially matching or surpassing surgical outcomes.

3.2 Diabetes Clinical Trial Outcomes

3.2.1 The SURPASS Clinical Program

The SURPASS clinical program evaluated tirzepatide across diverse diabetes treatment scenarios (36). SURPASS-1 enrolled 478 treatment-naive patients with early-stage diabetes inadequately controlled through lifestyle modification alone. Following 40 weeks of treatment, tirzepatide at 5 mg, 10 mg, and 15 mg doses reduced HbA1c by 1.87%, 1.89%, and 2.07% respectively, whereas placebo demonstrated minimal change (36, 37). Weight reduction exhibited dose-response characteristics: 7.0 kg, 7.8 kg, and 9.5 kg versus merely 0.7 kg with placebo. At the maximum dose, 87% of participants reached HbA1c below 7%, with over half a levels below 5.7%, representing essentially normoglycemic values.

SURPASS-2 addressed the pivotal question of comparative efficacy against semaglutide, the most efficacious GLP-1 receptor agonist. This 40-week trial enrolled 1,879 patients receiving background metformin therapy and showed consistent tirzepatide superiority (36, 38). HbA1c reductions exceeded semaglutide 1 mg by 0.5-0.9 percentage points, depending on tirzepatide dose. Weight reduction was substantially greater: 8.5-12.4 kg with tirzepatide versus 6.2 kg with semaglutide. These clinically meaningful differences established tirzepatide as the most efficacious agent within its therapeutic class.

SURPASS-3 compared tirzepatide to insulin therapy in patients requiring intensification beyond metformin. At 52 weeks, tirzepatide 15 mg reduced HbA1c by 2.37% compared to 1.34% with optimally titrated insulin (38, 39). Weight outcomes diverged even more dramatically: insulin-treated participants gained 2.3 kg while tirzepatide recipients lost 12.9 kg. SURPASS-4 extended these comparisons to higher cardiovascular risk populations, confirming comparable benefits and reassuring cardiovascular safety (39, 40). SURPASS-5 demonstrated tirzepatide efficacy as add-on therapy to basal insulin (40, 41). Across the entire program, over 90% of tirzepatide-treated patients reached glycemic targets, with consistent weight reduction irrespective of baseline characteristics (36-41).

3.2.2 Retatrutide in Diabetes

The phase 2 retatrutide trial enrolled 281 patients with diabetes randomized to various doses (0.5-12 mg), dulaglutide active comparator, or placebo for 36 weeks (15, 42). HbA1c declined in dose-dependent fashion: 2.02% at 8 mg and 2.16% at 12 mg, compared with 1.41% for dulaglutide and negligible change with placebo. At higher doses, 82% of participants reached HbA1c at or below 6.5%, versus only 35% with dulaglutide.

Weight reduction paralleled glycemic improvement. The 12 mg dose produced 16.9% weight reduction at 36 weeks, substantially exceeding the 2-3% observed with placebo or dulaglutide (14, 42). Weight trajectories suggested participants had not yet reached plateau, implying even greater reductions might be attainable with extended treatment. These findings suggest retatrutide may surpass tirzepatide efficacy, though direct comparative trials remain pending.

3.3 Obesity Clinical Trial Outcomes

3.3.1 The SURMOUNT Clinical Program

The SURMOUNT clinical program evaluated tirzepatide specifically for chronic weight management in individuals without diabetes (36, 43). SURMOUNT-1, a 72-week trial, enrolled 2,539 adults with body mass index (BMI) of 30 kg/m² or greater (or 27 kg/m² or greater with weight-related comorbidities) (44).

Outcomes were remarkable. At 72 weeks, weight decreased by 15.0%, 19.5%, and 20.9% with the 5 mg, 10 mg, and 15 mg doses respectively, versus merely 3.1% with placebo (43, 44). In absolute terms, the 15 mg cohort lost an average of 24 kg, exceeding 50 pounds. Examining categorical outcomes: 89% of maximum-dose recipients attained at least 5% weight reduction, 78% attained at least 10%, 68% attained at least 15%, and 57% attained at least 20%.

SURMOUNT-2 focused on individuals with obesity and concurrent diabetes, a population typically demonstrating attenuated responses to weight management pharmacotherapy. Even in this challenging cohort, tirzepatide 15 mg attained 14.7% weight reduction accompanied by 2.1% HbA1c improvement (44, 45). SURMOUNT-3 investigated whether tirzepatide could augment intensive behavioral intervention, while SURMOUNT-4 addressed weight maintenance, showing that treatment discontinuation precipitates weight regain.

SURMOUNT-5 provided the highly anticipated direct comparison: tirzepatide versus semaglutide 2.4 mg over 72 weeks (43, 46). Tirzepatide showed clear superiority, attaining 20.2% weight reduction versus 13.7%, representing a 6.5 percentage point difference. This trial firmly established tirzepatide as the most

efficacious weight management pharmacotherapy currently available, with outcomes approaching bariatric surgical results.

3.3.2 Retatrutide in Obesity

The phase 2 obesity trial enrolled 338 non-diabetic adults with BMI of 30 kg/m² or greater (or 27 kg/m² or greater with comorbidities) (15). Participants received weekly retatrutide at doses ranging from 1 to 12 mg, utilizing either gradual or accelerated dose escalation regimens, or placebo for 48 weeks.

At 48 weeks, the 12 mg dose produced 24.2% weight reduction, representing approximately 26 kg or roughly 57 pounds (15, 42). Lower doses produced 17.5% (4 mg) and 22.8% (8 mg) reductions. Placebo recipients lost 2.1%. Weight trajectories continued declining at study conclusion, suggesting these do not represent maximum achievable reductions.

Categorical outcomes were unprecedented for pharmacotherapy. With retatrutide 12 mg, every participant lost at least 5% of body weight. Ninety-three percent attained at least 10% reduction, 83% achieved at least 15%, 63% attained at least 20%, and 26% lost one-quarter or more of their initial weight (15, 42). These response rates rival bariatric surgery, positioning retatrutide as a potentially transformative option for severe obesity.

Weight reduction was accompanied by comprehensive metabolic improvements: systolic blood pressure decreased 10.4 mmHg (versus 0.4 mmHg with placebo), triglycerides declined approximately 40%, LDL cholesterol decreased 20%, and glucose and insulin parameters normalized in most participants (15). Among those with prediabetes at baseline, 72% reached normoglycemia, demonstrating diabetes prevention potential.

3.4 Effects on Cardiovascular, Hepatic, and Other Organ Systems

3.4.1 Heart Failure Outcomes

The SUMMIT trial was a pioneering study evaluating tirzepatide in 731 patients with heart failure with preserved ejection fraction (HFpEF) and obesity (47, 48). This constituted the first randomized controlled trial specifically designed to assess whether an incretin-based pharmacotherapy could improve heart failure outcomes.

Over approximately two years, tirzepatide reduced the composite endpoint of cardiovascular death or worsening heart failure by 38% compared with placebo (hazard ratio 0.62) (47, 58). Heart failure events specifically declined by 46%. Participants additionally showed clinically meaningful improvements in exercise tolerance and health-related quality of life. These findings suggest effective obesity treatment may directly modify heart failure disease progression, establishing a novel therapeutic indication beyond diabetes and weight management.

Several large-scale cardiovascular outcomes trials remain ongoing. SURPASS-CVOT is comparing tirzepatide to dulaglutide in over 13,000 patients with diabetes and established cardiovascular disease (48, 49). SURMOUNT-MMO and TRIUMPH-Outcomes are investigating cardiovascular effects in populations with obesity. These trials will provide definitive long-term safety and efficacy data necessary for expanded clinical application.

3.4.2 Hepatic Disease

Metabolic dysfunction-associated steatotic liver disease (MASLD, formerly NAFLD) is exceedingly prevalent among individuals with obesity and diabetes (50). The SYNERGY-NASH trial evaluated tirzepatide in 190 patients with biopsy-confirmed hepatic inflammation and significant fibrosis (stages F2-F3), representing the most advanced liver disease investigated with any incretin-based agent (50, 51).

Following one year of treatment, hepatic inflammation resolved (without fibrosis worsening) in 44%, 56%, and 62% of participants receiving tirzepatide 5 mg, 10 mg, and 15 mg respectively, compared with merely 10% with placebo (51, 52). Fibrosis genuinely improved by at least one stage in 51-55% of tirzepatide recipients versus 30% with placebo. Hepatic steatosis decreased 41-57%, and liver transaminases normalized in most participants.

Retatrutide showed even more pronounced hepatic effects in a substudy of 98 patients with at least 10% liver fat (51, 52). At 48 weeks, hepatic fat content declined by 82-83% at higher doses. Remarkably, 89-93% of participants receiving 8-12 mg retatrutide reached normal liver fat content (below 5%), essentially resolving their steatotic liver disease (14, 52). These findings position both agents as potential treatments for hepatic metabolic dysfunction.

3.4.3 Sleep Apnea

The SURMOUNT-OSA trials evaluated tirzepatide in individuals with obesity and moderate-to-severe obstructive sleep apnea (52, 53). At one year, tirzepatide reduced the apnea-hypopnea index (measuring sleep

disruption severity) by approximately 55% compared with placebo. Numerous participants improved sufficiently to be reclassified as having only mild or no sleep apnea. Blood pressure similarly decreased, consistent with reduced sympathetic nervous system activation (47, 53). These findings suggest tirzepatide might diminish continuous positive airway pressure (CPAP) requirements for many affected individuals.

3.5 Adverse Effects and Safety Profile

3.5.1 Gastrointestinal Adverse Effects

Gastrointestinal adverse events constitute the predominant tolerability concern with both medications, consistent with the GLP-1 receptor agonist therapeutic class overall (54, 55, 56). A comprehensive meta-analysis encompassing 10 trials and nearly 7,000 tirzepatide recipients documented gastrointestinal adverse events in 39%, 46%, and 49% of those receiving 5 mg, 10 mg, and 15 mg doses respectively, compared with 20-25% with placebo (54, 55).

Nausea was most frequently reported, affecting approximately 20% of tirzepatide recipients versus 10% with placebo (relative risk 2.90) (54, 55, 56). Vomiting occurred in roughly 9% versus 5% with placebo, and diarrhea in 16% versus 9%. Constipation and appetite reduction were similarly more prevalent. Importantly, these effects were predominantly mild to moderate in severity, occurred mainly during dose titration periods, and typically resolved with continued treatment.

Discontinuation rates attributable to adverse events ranged from 5% (5 mg) to 10% (15 mg) in the SURPASS diabetes trials (54). Rates were somewhat elevated in obesity trials, possibly reflecting tolerability limits approached during weight maximization efforts. Importantly, serious adverse events were not increased compared with placebo or active comparators, and no safety signals emerged for pancreatitis, thyroid malignancy, or other concerns occasionally raised with GLP-1 receptor agonists.

Retatrutide exhibited a comparable gastrointestinal profile. At maximum doses in phase 2 trials, approximately 25% experienced nausea, 12% vomiting, and 16% diarrhea (42). Initiating treatment at lower doses with gradual escalation improved tolerability, informing phase 3 dosing strategy development.

Table 1. Safety Profile: Gastrointestinal and Other Adverse Events

Adverse Event	Tirzepatide (%)	Placebo (%)	Relative Risk
Nausea	~20%	~10%	2.90
Vomiting	~9%	~5%	1.80
Diarrhea	~16%	~9%	1.78
Constipation	~7%	~4%	1.75
Decreased appetite	~5%	~1%	5.00
Cholelithiasis	~1.5%	~0.4%	3.75
Discontinuation (any AE)	5-10%	~2%	—

Note: Rates are approximate pooled estimates from SURPASS and SURMOUNT programs. Data from references 54-56.

3.5.2 Additional Safety Considerations

Hypoglycemia was infrequent when these medications were administered without insulin or sulfonylureas, with less than 1% experiencing clinically significant hypoglycemia with tirzepatide monotherapy or combination with metformin alone (37). This reflects incretin-mediated insulin secretion being glucose-dependent; these agents do not compel insulin release when glycemia is already normal. When combined with insulin, hypoglycemia rates were consistent with GLP-1 receptor agonist expectations, generally manageable through insulin dose reduction.

Biliary complications (cholelithiasis and cholecystitis) occurred somewhat more frequently with these medications, likely related to rapid weight reduction rather than direct pharmacological effects (44). Across the SURMOUNT program, approximately 1.5% of tirzepatide recipients developed gallstones versus 0.4% with placebo. This incidence aligns with expectations during any substantial weight reduction, whether achieved through dietary intervention, pharmacotherapy, or surgical procedures.

Injection site reactions were uncommon and mild. Heart rate increased modestly, typically by 2-4 beats per minute, consistent with other GLP-1 receptor agonists (57). Whether this modest increase carries clinical significance is being evaluated in ongoing cardiovascular outcomes trials.

Table 2. Comparative Analysis: Tirzepatide vs. Retatrutide

Parameter	Tirzepatide	Retatrutide
Mechanism	Dual GIP/GLP-1 receptor agonist	Triple GIP/GLP-1/Glucagon receptor agonist
Development Phase	FDA approved (T2DM: 2022, Obesity: 2023)	Phase 3 trials ongoing
Max Weight Loss (T2DM)	~12.4 kg at 40 weeks (SURPASS-2)	~16.9% at 36 weeks (Phase 2)
Max Weight Loss (Obesity)	~20.9% at 72 weeks (SURMOUNT-1)	~24.2% at 48 weeks (Phase 2)
Max HbA1c Reduction	Up to 2.59% (SURPASS-5)	Up to 2.16% at 12mg (Phase 2)
Hepatic Fat Reduction	41-57% (SYNERGY-NASH)	82-83% (Phase 2 substudy)
Dosing	5, 10, 15 mg once weekly	Up to 12 mg once weekly (in trials)

Note: Retatrutide data are from Phase 2 trials; direct head-to-head comparison not yet available. Data from references 15, 42, 44.

4. Discussion

Tirzepatide and retatrutide mark a transformative shift in metabolic medicine. Rather than offering incremental gains, these agents achieve outcomes that redefine pharmacotherapeutic expectations (36, 43, 46).

Several critical insights emerge from this evidence base. First, multi-receptor targeting demonstrates superior efficacy compared to single-receptor approaches. The combination of GIP and GLP-1 receptor activation in tirzepatide produces synergistic effects on both body weight and glycemic parameters through complementary mechanistic pathways (28, 34, 57). Incorporating glucagon receptor activation, as retatrutide does, further enhances efficacy by increasing energy expenditure and improving hepatic lipid metabolism without compromising glycemic control.

Second, weight reductions exceeding 20-25% fundamentally alter the therapeutic paradigm for obesity management. Previous pharmacotherapies typically produced 5-10% reductions, which proved helpful but frequently insufficient to reverse metabolic complications or achieve sustained remission (7). Tirzepatide and retatrutide extend beyond merely supporting lifestyle modifications; they produce disease-modifying effects capable of resolving comorbidities and potentially preventing progression to end-organ damage.

Third, these medications confer benefits across multiple organ systems extending beyond weight and glycemic parameters. The SUMMIT trial showing reduced heart failure events with tirzepatide is particularly noteworthy, suggesting effective obesity treatment may directly modify cardiovascular disease trajectory (47). Hepatic effects are equally compelling, positioning these agents as potential therapies for metabolic liver disease, which currently lacks effective pharmacological options.

The safety profile appears manageable. Gastrointestinal adverse effects are common but typically transient and controllable through gradual dose titration. Long-term safety data from ongoing cardiovascular outcomes trials will be essential for understanding risk-benefit balance over extended treatment durations (54).

Several limitations warrant acknowledgment. Clinical trials predominantly enrolled patients with early-stage diabetes, limited complications, and relatively preserved renal and hepatic function; outcomes may differ in more medically complex populations. Weight regain following treatment discontinuation, as shown in SURMOUNT-4, raises concerns; these medications may require indefinite continuation to maintain benefits (44). Questions persist regarding optimal treatment duration, combination therapeutic strategies, and integration with other interventions.

Practical considerations are equally relevant. These medications carry substantial costs, and insurance coverage varies considerably. The necessity for chronic treatment to maintain effects raises concerns regarding long-term adherence and healthcare expenditure (7). Not all individuals will tolerate gastrointestinal adverse effects, even with careful dose titration.

5. Conclusions

Tirzepatide and retatrutide represent landmark developments in metabolic pharmacotherapy. Their efficacy approaches surgical outcomes, a threshold no previous medication approached. Tirzepatide is now established as the most effective approved pharmacotherapy for both diabetes management and chronic weight management. Retatrutide demonstrates potential for even greater weight reduction and is advancing through phase 3 clinical development.

Beyond weight and glycemic parameters, these medications improve cardiovascular outcomes in heart failure, resolve metabolic liver disease in most treated individuals, and diminish sleep apnea severity. Adverse effects are predominantly gastrointestinal and generally manageable.

Important questions remain for future investigation: long-term cardiovascular safety and efficacy, application in broader populations including pediatric and geriatric cohorts, combination therapeutic approaches, and development of oral formulations. The TRIUMPH phase 3 clinical program will generate data necessary for retatrutide regulatory approval, potentially providing patients access to the inaugural triple receptor agonist.

These medications herald a new therapeutic era. For clinicians and patients confronting obesity and type 2 diabetes mellitus, pharmacological options are now dramatically superior compared to just several years ago.

Author's contribution:

Research and concept design: Rafał Bednarczyk, Natalia Bednarczyk, Radosław Binkowski

Data collection and methodology: Rafał Bednarczyk, Aleksandra Mazurkiewicz, Natalia Krajewska, Hubert Sidor

Formal analysis: Aleksandra Mazurkiewicz, Agnieszka Kurek, Monika Wołosik

Interpretation: Rafał Bednarczyk, Hubert Sidor, Radosław Binkowski, Aleksandra Lejman

Writing: Rafał Bednarczyk, Natalia Bednarczyk, Aleksandra Lejman, Monika Wołosik

Critical review of the article: Natalia Bednarczyk, Szymon Zysiak, Natalia Krajewska

Supervision, project administration: Rafał Bednarczyk

All authors have read and agreed to the published version of the manuscript.

Funding Statement:The article did not receive any funding.

Institutional Review Board Statement: Not applicable; this review included only published data.

Data Availability Statement: All supporting data are available within the cited peer-reviewed literature.

Acknowledgments: The author acknowledges the contribution of investigators and data curators whose high-quality research underpins the advances reviewed herein.

Conflict of Interest Statement: No conflicts of interest to declare.

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