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# From Scalpel to Syringe: Can Tirzepatide Bridge the Gap Between Pharmacotherapy and Bariatric Surgery?

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## ABSTRACT

This review evaluates whether tirzepatide, a dual GIP/GLP-1 receptor agonist, addresses the historical therapeutic gap between conservative lifestyle modifications and bariatric surgery in obesity management. Based on an analysis of the SURMOUNT trials, real-world data, and pharmacoeconomic models, tirzepatide demonstrates significant clinical efficacy, achieving over 20% total body weight reduction—approaching the outcomes of sleeve gastrectomy under controlled trial conditions. However, real-world effectiveness is frequently limited by high therapy discontinuation rates, contrasting with the anatomically enforced compliance characteristic of surgical interventions. Consequently, rather than rendering metabolic surgery obsolete, tirzepatide modifies current treatment algorithms. It offers demonstrated clinical utility as a neoadjuvant optimization tool prior to surgery, a bridge to solid organ transplantation, and a rescue therapy for post-bariatric weight regain. Ultimately, tirzepatide serves as an effective adjunctive and alternative therapy, complementing rather than replacing surgical interventions in the chronic management of obesity.

**Keywords:** Obesity; Bariatric Surgery; Tirzepatide; Incretins; Weight Regain

## INTRODUCTION

Obesity is currently recognized as one of the most complex, multifactorial, and life-threatening chronic neuroendocrine diseases, reaching the proportions of a global pandemic.[1] Its pathophysiology extends far beyond simple energy balance disorders, encompassing profound dysfunctions of the central nervous system regarding appetite regulation, insulin resistance, chronic low-grade inflammation (adiposopathy), and ectopic lipid accumulation in visceral organs.[2] The systemic consequences of obesity are highly detrimental, with excess adipose tissue acting as a primary driver for the development of type 2 diabetes (T2D), heart failure with preserved ejection fraction (HFpEF), metabolic dysfunction-associated steatotic liver disease (MASLD), and

malignancies.[3-4]

For decades, obesity treatment algorithms have been characterized by a pronounced efficacy gap. On one end of the spectrum were behavioral interventions, dietary modifications, and early generations of anti-obesity medications, which offered only modest and often unsustainable weight reduction in the range of 5% to 10%.[5-6] Such weight loss, while beneficial for reducing cardiovascular risk, rarely allowed for the full remission of advanced metabolic complications. On the other end of the spectrum lay metabolic and bariatric surgery (MBS), including procedures such as Roux-en-Y gastric bypass (RYGB) and sleeve gastrectomy (SG).[7] This surgery provided substantial, long-lasting weight loss of up to 30%, leading to high rates remission of type 2 diabetes and a reduction in overall mortality.[8]

Despite its established efficacy, bariatric surgery remains significantly underutilized. Epidemiological data from the United States and Europe indicate that only about 1% of eligible patients undergo these procedures annually.[4] The barriers are multifaceted: they include patients' fear of irreversible anatomical changes to the gastrointestinal tract, the risk of perioperative complications, systemic healthcare financing deficiencies, and a lack of a sufficient number of highly specialized centers.[3] As a result, millions of patients with severe obesity remained in a therapeutic void—without effective pharmacological options and lacking access to surgical treatment.

However, the therapeutic landscape has undergone a fundamental transformation with the discovery and refinement of incretin-based medications.[1] While early glucagon-like peptide-1 (GLP-1) receptor agonists, such as liraglutide and semaglutide, significantly narrowed the gap between conservative medicine and surgery[9], the introduction of tirzepatide has brought pharmacotherapy to an efficacy level nearly on par with surgical outcomes.[10]

Tirzepatide is an innovative, once-weekly subcutaneous injectable, dual agonist of the glucose-dependent insulinotropic polypeptide (GIP) and GLP-1 receptors. By modulating human physiology in a manner that mimics the polyhormonal response of the body following bariatric surgery, tirzepatide enables weight loss exceeding 20%, representing a historical breakthrough in metabolic medicine.[10]

The primary objective of this review is to critically evaluate whether tirzepatide possesses sufficient clinical, physiological, and pharmacoeconomic potential to serve as a viable bridge between pharmacological treatment and bariatric surgery.

## MATERIALS AND METHODS

A comprehensive narrative review of the contemporary medical literature was conducted to evaluate the evolving role of tirzepatide in obesity management. Relevant literature was identified through searches of major electronic biomedical databases, including PubMed/MEDLINE, Scopus, and Google Scholar, encompassing data available up to April 2026. The search strategy utilized key terms such as 'tirzepatide', 'bariatric surgery', 'metabolic surgery', 'obesity', 'incretin mimetics', and 'weight regain'.

To ensure the high clinical relevance of this review, the selection of sources prioritized high-quality evidence, primarily focusing on phase 3 randomized clinical trials (notably the SURMOUNT clinical program), large-scale retrospective cohort studies providing Real-World Data (RWD), post-hoc analyses, and pharmacoeconomic micro-simulation models. Single case reports without broader clinical context and publications in languages other than English were generally omitted.

### Evolution of Paradigms: From Mechanical Restriction to Neuroendocrine Modulation

The historical perspective on bariatric surgery relied on mechanistic assumptions. Early procedures, such as adjustable gastric banding (AGB) or vertical banded gastroplasty, aimed to physically limit food intake volume, while bypass operations assumed the induction of malabsorption syndrome.[7] The passage of time and advancements in gastroenterological endocrinology have indisputably proven that the success of operations like RYGB or SG does not stem from anatomy alone but from profound alterations in signaling along the gut-brain axis.[11] These surgeries significantly alter the profile of intestinal hormone secretion, leading to a rapid postprandial surge of GLP-1, GIP, peptide YY (PYY), and oxyntomodulin, alongside a pronounced decrease in orexigenic ghrelin concentrations.[12-13]

This paradigm shift became the foundation for the search for "bariatric surgery in a syringe". Researchers hypothesized that if this postoperative hyperincretinemia phenomenon could be pharmacologically replicated, patients would be able to achieve weight reduction analogous to surgery without the need to alter gastrointestinal continuity.[14] Tirzepatide represents a prominent clinical application of this hypothesis to date. Unlike medications based solely on a single receptor pathway, it integrates the action of two key incretin hormones, inducing a powerful synergistic effect.[15]

### Mechanism of Action and Unique Molecular Pharmacology of Tirzepatide

The remarkable clinical efficacy of tirzepatide originates from its unique molecular architecture and highly specific cellular receptor binding profile. Tirzepatide is a synthetic peptide composed of 39 amino acids, featuring structural modifications that protect it from rapid degradation. A key element of the molecule is the addition of a 20-carbon fatty acid diacid moiety, which enables strong,

reversible binding to plasma albumin. This mechanism protects the peptide from glomerular filtration and enzymatic degradation by dipeptidyl peptidase-4 (DPP-4), drastically extending its serum half-life to approximately five days and allowing for convenient once-weekly administration.[16]

In molecular terms, tirzepatide is not a symmetrical dual agonist but exhibits an "imbalanced" or favoring agonism profile. The compound features an affinity for the GIP receptor comparable to endogenous GIP, whereas its affinity for the GLP-1 receptor is approximately five times weaker compared to the natural GLP-1 hormone.[17] This seemingly paradoxical asymmetry plays a crucial role in the drug's efficacy. Cryo-electron microscopy (cryo-EM) and molecular dynamics simulations have revealed that reduced affinity for the GLP-1 receptor leads to biased agonism.[17-18] Consequently, tirzepatide induces less recruitment of beta-arrestin-1, which markedly limits the internalization and desensitization of the GLP-1 receptor. This means the receptor remains active on the cell surface for longer, ensuring a prolonged intracellular response based on cyclic AMP (cAMP) production.[18-19]

The physiological consequences of this dual agonism are multidimensional. The GLP-1 pathway primarily regulates energy balance by slowing gastric emptying, providing early satiety, and directly stimulating satiety centers in the hypothalamus and brainstem.[20] In contrast, GIP modulates metabolic status in a different yet complementary manner. GIP exerts glucagonotropic effects in hypoglycemic and normoglycemic states, protecting the body from dangerous drops in blood sugar. However, under hyperglycemic conditions, GIP acts as a strong glucagonostatic hormone, suppressing glucagon secretion and assisting GLP-1 in restoring glucose homeostasis.[21]

Equally important in the context of weight loss, chronic caloric restriction traditionally triggers mechanisms of metabolic adaptation—the body lowers its resting metabolic rate to defend stored fat reserves, which is a major cause of the weight loss "plateau". Data from preclinical and early clinical studies suggest that tirzepatide mitigates this process. The drug protects against a pronounceddrop in energy expenditure while simultaneously promoting lipid oxidation. A similar phenomenon of increased peripheral tissue insulin sensitivity and energy expenditure modulation is observed in the first months following RYGB surgery, presenting a further argument for considering tirzepatide as a pharmacological analog of bariatric surgery.[22]

**Clinical Efficacy: Analysis of the SURMOUNT Trial Program**

Fundamental evidence for the efficacy of tirzepatide in obesity therapy originates from the global program of multicenter, randomized, double-blind phase 3 clinical trials acronymed SURMOUNT. The SURMOUNT-1 study represented a turning point in the history of obesity treatment. It included

2,539 adult patients with obesity (BMI ≥ 30 kg/m²) or overweight (BMI ≥ 27 kg/m²) with at least one complication (excluding diabetes). Participants assigned to the highest tirzepatide dose group (15 mg weekly) achieved a mean total body weight reduction of 20.9% after 72 weeks of treatment, compared to a mere 3.1% in the placebo group.[10] Strikingly, 57% of patients in the 15 mg group managed to cross the 20% weight reduction threshold—a mark that for decades was considered the exclusive domain of surgical procedures like sleeve gastrectomy.

The SURMOUNT-2 trial encompassed a population historically most resistant to weight-loss interventions: patients with obesity and coexisting advanced type 2 diabetes. Even in this challenging clinical group, patients using 15 mg of tirzepatide achieved an average weight loss of 15.7%.[23]
The SURMOUNT-4 study shed light on the chronic nature of obesity and the necessity of indefinitely continuing pharmacological therapy. Following an initial 36-week lead-in phase where all participants took tirzepatide (achieving an average weight loss of 20.9%), patients were randomized to continue therapy or switch to placebo. Patients continuing the drug managed to lose an additional 5.5% of body weight. Conversely, patients in the placebo group experienced a pronounced and rapid weight regain averaging 14.0%.[24]

Furthermore, the most recent post hoc analysis of the SURMOUNT-4 trial by Zimner-Rapuch et al. demonstrated that within one year of tirzepatide withdrawal, 82% of patients regained 25% or more of their lost weight, and nearly half regained 50% or more. This rapid weight regain was accompanied by a proportional reversal and worsening of previously normalized cardiometabolic parameters.[25] This unequivocally indicates that dual incretins act suppressively on neuroendocrine mechanisms, not curatively. Treatment cessation results in a return to the homeostatic set-point programmed by obesity, highlighting a fundamental difference compared to the permanent anatomical changes induced by bariatric surgery.

**Clinical Efficacy in Trials vs. Real-World Effectiveness**

While randomized clinical trials prove tirzepatide can simulate surgical outcomes, an objective assessment requires verification in daily clinical practice. Restrictive research protocols with rigorous adherence monitoring, free access to costly drugs, and intensive dietary support rarely reflect the realities patients face in standard healthcare systems. Large-scale comparative analyses using Real-World Data (RWD) provide a sobering perspective.

A retrospective comparative effectiveness study analyzing medical records of over 51,000 patients found a stark contrast. After 24 months, bariatric patients achieved a mean total weight loss (TWL) of 24%. In glaring contrast, patients prescribed incretin analogs who remained on therapy for at least a

year achieved approximately 7% TWL.

This immense deviation from the SURMOUNT-1 results stems primarily from adherence rates. Recent real-world analyses, including 2025 reports by IQVIA and HealthVerity, reveal a pronounceddecline in compliance outside strict trial supervision. Only between 10% and 32% of patients with obesity continue incretin therapy 12 months after initiation.[26-27] Additionally, roughly 36% of patients discontinue treatment after filling just the first prescription (the "one & done" phenomenon).[26]

The reasons are numerous: exorbitant and compounding out-of-pocket costs, insurance gaps, repeated supply chain shortages, medication fatigue, and gastrointestinal intolerance. Conversely, bariatric surgery enforces compliance through an imposed anatomical change. Therefore, while tirzepatide successfully bridges the biological gap between pharmacology and the scalpel, the significant adherence gap means that in population analyses, MBS unequivocally remains the most effective form of long-term therapy. These differences are summarized in Table 1.

**Table 1:** Comparison of Modern Pharmacotherapy and Bariatric Surgery in Obesity Treatment

| Clinical Characteristic | Dual Agonism (Tirzepatide) | Metabolic and Bariatric Surgery (RYGB/SG) |
|---|---|---|
| Primary Mechanism of Action | Exogenous stimulation of GIP and GLP-1 receptors | Endogenous incretin hypersecretion and volumetric restriction |
| Reversibility of Intervention | Fully reversible; discontinuation leads to rapid relapse | Permanent, forces lifelong changes to the digestive system |
| Treatment Adherence | Dependent on the patient's weekly willpower and financial ability | Anatomically enforced, largely independent of willpower |
| Efficacy (Clinical Trials) | ~15% to 22% weight loss over 1.5 years | ~25% to 32% sustained over many years |
| Effectiveness (RWD - 2 years) | ~5% to 7% (drastically lowered by high discontinuation rates) | ~24% to 28% in the majority of post-op patients |
| Invasiveness and Complications | Non-invasive therapy (primarily gastrointestinal risks) | Minimally invasive (risks of leaks, bleeding, malnutrition) |

GIP: Glucose-dependent insulinotropic polypeptide; GLP-1: Glucagon-like peptide-1; RYGB: Roux-en-Y Gastric Bypass; SG: Sleeve Gastrectomy; RWD: Real-World Data.

**Cardiometabolic and Multiorgan Protection**

The role of obesity treatment has evolved from mere weight reduction towards preventing irreversible organ damage and reducing cardiovascular mortality. Both bariatric surgery and tirzepatide demonstrate immense end-organ protection potential. In a novel propensity-score matching analysis comprising over 12,000 patients with MASLD, tirzepatide demonstrated highly favorable outcomes compared to surgical patients.[28] The tirzepatide cohort exhibited a lower risk of a composite endpoint encompassing all-cause mortality, major adverse cardiovascular events (MACE), major adverse kidney events (MAKE), and acute liver failure. The incidence rate was 1.9 per 100 person-years in the

tirzepatide group versus 3.5 per 100 person-years in the surgery group (HR 0.47; 95% CI 0.36-0.61). [28]

Furthermore, data from the SUMMIT trial focusing on obesity-related HFpEF provided mechanistic evidence. Cardiac magnetic resonance (CMR) imaging in tirzepatide-treated patients showed an 11-gram reduction in left ventricular mass and a pronounced reduction in epicardial adipose tissue volume.[29-30] This reduction led to the physical reversal of adverse concentric myocardial remodeling characteristic of the obesity-related HFpEF phenotype.[30] These multi-systemic benefits unequivocally position tirzepatide not just as a weight-loss agent, but as a broad cardiometabolic therapeutic.[31]

**Tirzepatide as Neoadjuvant Optimization and Bridge to Transplantation**

Tirzepatide proves to be an exceptionally effective neoadjuvant tool utilized for the physiological optimization of patients bearing extremely high perioperative risk. Severe obesity poses a formidable technical challenge for surgeons. Significant hepatomegaly, combined with excessive intra-abdominal adipose tissue, markedly limits the surgical field and extends operative time. Administering tirzepatide for 3 to 6 months prior to a planned surgery allows for rapid "de-fatting" of internal organs and improvement in cardiorespiratory reserve, bringing the patient from a high-risk zone down to a standard risk profile.

This bridging potential is even more prominent in solid organ transplantation. Due to post-operative complication risks, transplant centers enforce rigorous BMI cut-offs (typically <35 kg/m²). Historically, patients with higher BMIs awaiting kidney or liver transplants were forced to undergo bariatric surgery under conditions of progressive organ failure.[32] Retrospective case series have shown that tirzepatide allowed up to 77.8% of patients with obesity to meet these rigorous qualifying criteria for transplantation, a result bypassing cohorts forced into bariatric surgery.[32]

**Rescue Therapy: Tirzepatide in Weight Regain After Bariatric Surgery**

From a clinical perspective, the most critical "bridge" function of tirzepatide is managing recurrent weight regain (RWG) following bariatric surgery. Over a decade post-surgery, 20% to 40% of patients experience significant obesity recurrence.[33-34] For a long time, managing RWG required invasive revisional surgeries, which carry disproportionately higher complication rates compared to primary operations.[35]

The introduction of tirzepatide has altered this paradigm. In retrospective cohort studies of SG patients with recurrent obesity, initiating tirzepatide resulted in an additional loss of 12.0% to 15.5% of total body weight within just 6 months.[35] Moreover, recent data indicate patients on tirzepatide

achieve weight loss almost identical to those undergoing invasive revisional endoscopic sleeve gastroplasty (R-ESG) at 12 months, avoiding instrumentation altogether. The synergy of both methods is summarized in Table 2.

**Table 2:** Clinical Algorithms for Integrating Tirzepatide with Bariatric Surgery

| Clinical Scenario | Purpose of Tirzepatide Initiation | Expected Clinical Benefits |
|---|---|---|
| Neoadjuvant before surgery | Liver volume reduction, weight loss prior to the procedure | Decreased risk of thromboembolic and surgical complications, shorter operative time |
| Bridge to transplantation | Meeting strict BMI thresholds (e.g., <35 kg/m²) for solid organs | Avoiding risky bariatric surgery in patients with severe end-organ failure |
| Primary alternative | Extremely high anesthetic risk or refusal of invasive treatment | ~20% weight loss while maintaining intact gastrointestinal anatomy |
| Rescue pharmacotherapy (Post-op) | Inhibiting weight regain triggered by metabolic adaptation | 12% - 15% secondary weight loss, avoiding dangerous revisional surgeries |

BMI: Body Mass Index.

**Body Composition Analysis and the Risk of Sarcopenic Obesity**

When comparing incretin medications with surgery, profound changes in body composition must be addressed. Rapid weight loss inherently involves the loss of metabolically important lean body mass (LBM). A sub-study within the SURMOUNT-1 program using dual-energy X-ray absorptiometry (DXA) revealed that patients treated with tirzepatide lost an average of 33.9% of total fat mass but also experienced a 10.9% decrease in lean mass.[36] Proportionally, about 25% of all lost weight was muscle and lean tissue.

While this is a physiological phenomenon consistent with the distribution of losses observed in post-bariatric patients undergoing severe caloric deficits,[37-38] absolute muscle tissue loss raises justified clinical concerns regarding sarcopenic obesity. If pharmacology is to function safely alongside surgery, restrictive resistance training and high-protein nutritional protocols must become an integral component of dual incretin therapy.

**Safety and Tolerability Profile Compared to Surgical Risk**

Adverse events of tirzepatide are predominantly gastrointestinal, mild to moderate in severity, and most frequently occur during the dose-escalation phase (nausea 20-22%, diarrhea 20-21%, vomiting up to 13%).[10,23] Severe incidents, such as acute pancreatitis or medullary thyroid carcinoma, appear exceedingly rare in humans.

Contrasting this with MBS, tirzepatide holds a significant advantage in minimizing acute complication risks. Although surgical mortality is near zero in the laparoscopic era, surgery always carries risks of internal hemorrhage, staple line leaks, internal hernias, or pulmonary embolism.[4] Furthermore, MBS generates lifelong risks of late complications like dumping syndrome and

profound vitamin deficiencies.[3] For thousands of patients fearful of surgical risks, the prospect of treatment via subcutaneous injection becomes undeniably attractive.

However, it must be acknowledged that while the long-term nutritional and anatomical complications of MBS are comprehensively documented over decades, the potential adverse effects of lifelong, uninterrupted dual incretin receptor stimulation remain entirely unknown at this stage.

**Pharmacoeconomics and Cost-Effectiveness Analysis**

The blurring of biological efficacy boundaries pushes the ultimate battle between surgery and modern pharmacology into the realm of health economics. While pharmacotherapy requires lifelong continuation—translating into compounding costs for the purchase of expensive pre-filled syringes—surgery involves a high initial upfront cost followed by drastically lower long-term maintenance expenses. Recent comparative analyses have calculated the financial "break-even point" between these two modalities with striking results. A 2024 study by Docimo et al. demonstrated that the cumulative costs of ongoing use of popular GLP-1 receptor agonists (such as Wegovy or Saxenda) surpass the total flat cost of Roux-en-Y gastric bypass in less than one year, and exceed the cost of sleeve gastrectomy within just nine months. Even when considering the most affordable pharmacological options, cumulative medication costs outpace surgical costs after approximately 1.5 years.[39] Consequently, from a long-term economic perspective, the one-time investment in metabolic surgery strongly dominates the financial burden of chronic incretin administration.

The same trend is observed over shorter timeframes. U.S. insurance database analyses over a two-year horizon revealed that average healthcare costs in the pharmacologically treated group reached $63,483 per patient, compared to $51,794 for bariatric patients.[40-41] Despite high upfront hospital costs, MBS becomes the cheaper solution in just 24 months. These models are outlined in Table 3.

**Table 3:** Overview of Pharmacoeconomic Models in Obesity Treatment

| Comparative Model | Economic Simulation Conclusion | ICER / Costs |
|---|---|---|
| Tirzepatide vs. Lifestyle / Diet | Highly cost-effective compared to no treatment | ~ $57,400 per QALY |
| RYGB Surgery vs. Tirzepatide | Surgery generates more QALYs long-term | Pharmacotherapy is strongly dominated by MBS |
| Total costs over 2 years (MBS) | Costs heavily concentrated at the beginning (surgery) | ~ $51,794 |
| Total costs over 2 years (Pharmacotherapy) | Significant and compounding long-term maintenance costs | ~ $63,483 |

ICER: Incremental Cost-Effectiveness Ratio; QALY: Quality-Adjusted Life Year; RYGB: Roux-en-Y

**Gastric Bypass; MBS: Metabolic and Bariatric Surgery.**

Ultimately, high drug prices and steep capital retention by pharmaceutical companies preclude pharmacotherapy from fully replacing surgery on a macroeconomic level, maintaining a dangerous

inequality gap.

## CONCLUSIONS

The emergence of tirzepatide represents a major advancement in obesity medicine in recent decades. Based on the sophisticated concept of imbalanced dual agonism towards GIP and GLP-1 receptors, this medication precisely replicates the neuroendocrine cascades previously encountered almost exclusively following radical anatomical changes during bariatric procedures.

The efficacy proven in the SURMOUNT clinical trials demonstrates that from a purely biological standpoint, tirzepatide successfully bridges the efficacy gap between conservative management and surgery. However, the simplistic assertion that tirzepatide could entirely consign bariatric operations to history is not reflected in reality. The significant discrepancy between clinical efficacy and real-world effectiveness highlights a fundamental clinical reality: anatomically enforced, lifelong control in RYGB or SG patients still guarantees the longest and most stable remission for a vast patient population. Significant dropout rates from pharmacological treatment due to side effects and exorbitant costs dismantle the thesis that "the syringe has defeated the scalpel." Furthermore, pharmacoeconomic modeling clearly shows that from a decadal perspective, surgical procedures are drastically more cost-effective for healthcare systems.

The key to future success lies in abandoning the antagonism between these two modalities. Surgery and novel incretin molecules must coexist within an integrated clinical algorithm. Tirzepatide represents a perfect "bridge": it functions effectively as a neoadjuvant therapy reducing technical risks in complicated surgeries, provides an excellent primary option for those refusing incisions, and has become a clinically proven rescue alternative for revisional surgeries in challenging cases of postoperative weight regain. Obesity therapy has definitively gained a powerful tool, but it is synergy—not the displacement of surgery—that will define the era of modern metabolic care.

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## DISCLOSURES

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