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Journal of Bio-X Research
A SCIENCE PARTNER JOURNAL

REVIEW ARTICLE

Tirzepatide: A Paradigm Shift in the Management of Type 2 Diabetes and Obesity

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Citation: Sonawane RA, Gulave OK, Kale PA, Rasal PB. Tirzepatide: A Paradigm Shift in the Management of Type 2 Diabetes and Obesity. *J. Bio-X Res.* 2026;9:Article 0092. https://doi.org/10.34133/jbioxresearch.0092

Submitted 17 January 2026
Revised 19 May 2026
Accepted 20 May 2026
Published 9 July 2026

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Type 2 diabetes mellitus and obesity represent intertwined chronic disorders that continue to escalate globally despite advances in pharmacotherapy. Current treatment strategies increasingly recognize the need to address both glycemic dysregulation and excess adiposity to meaningfully reduce long-term cardiometabolic risk. While glucagon-like peptide-1 receptor agonists significantly improve outcomes, many patients fail to achieve durable normoglycemia or substantial weight reduction. Tirzepatide is a novel therapeutic agent designed to activate both glucose-dependent insulinotropic polypeptide and glucagon-like peptide-1 receptors within a single molecular framework. By engaging complementary incretin pathways, tirzepatide produces enhanced metabolic effects that extend beyond those observed with selective receptor agonists. Clinical evidence from the SURPASS and SURMOUNT programs has revealed marked improvements in glycemic control, body weight, and multiple cardiometabolic parameters with tirzepatide treatment. This review examines the physiological basis, molecular design, pharmacological properties, and clinical performance of tirzepatide, focusing on its implications for the evolving management of diabetes and obesity. The emergence of dual-incretin agonism represents a meaningful advancement toward integrated metabolic disease control.

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Introduction

The increasing global burden of type 2 diabetes mellitus (T2DM) and obesity represents a major challenge for modern healthcare systems, with projections indicating that diabetes will affect more than 700 million individuals by 2045 [1,2]. These conditions frequently coexist and share underlying pathophysiological mechanisms, including insulin resistance, a dysregulated energy balance, and chronic low-grade inflammation. Their coexistence substantially increases the risk of cardiovascular disease, renal impairment, and premature mortality, underscoring the need for therapeutic strategies that address both glycemic control and excess adiposity in an integrated manner.

Conventional treatment approaches for T2DM have historically followed a stepwise intensification model, beginning with metformin and progressing to additional oral agents or insulin therapy [3,4]. While these treatments are effective at lowering blood glucose levels, they often fail to sustainably reduce weight and may be associated with adverse effects such as hypoglycemia and weight gain [3]. As a result, they do not fully address the broader cardiometabolic risk profile associated with T2DM and obesity.

The development of incretin-based therapies, particularly glucagon-like peptide-1 receptor agonists (GLP-1 RAs), has led to significant advancements in diabetes management [5]. Agents such as liraglutide and semaglutide have been shown to improve glycemic control, induce clinically meaningful weight loss, and reduce cardiovascular risk [6]. Despite these benefits, many patients do not achieve optimal therapeutic outcomes, including normalization of glycemic parameters or substantial weight reduction, which represents a knowledge gap in clinical settings.

Recent advances in metabolic pharmacology have focused on targeting multiple hormonal pathways simultaneously. Dual-incretin receptor agonism, which combines the actions of glucose-dependent insulinotropic polypeptide (GIP) and GLP-1, has emerged as a promising strategy to enhance metabolic outcomes [7–10]. This approach leverages complementary mechanisms, including enhanced glucose-dependent insulin secretion, central appetite regulation, and improved lipid metabolism [11,12].

Despite the success of GLP-1 RAs, long-term glycemic normalization and substantial weight loss remain insufficient in many patients. Furthermore, the comparative mechanistic advantages and clinical efficacy of dual-incretin receptor activation over established therapies have not yet been fully synthesized in the literature.

This review aims to critically examine the physiological rationale, molecular design, pharmacological properties, and clinical performance of tirzepatide as a dual GIP and GLP-1 RA. Importantly, its potential to advance the integrated management of T2DM and obesity and to address persistent gaps in cardiometabolic risk reduction are discussed [13].

Physiology of Incretin Hormones

To understand tirzepatide, the distinct yet complementary roles of the 2 incretin hormones it targets must be examined [14]. GLP-1 is primarily secreted by L-cells in the distal ileum and colon in response to nutrient intake. It enhances glucose-dependent insulin secretion from pancreatic β-cells by increasing intracellular cyclic

adenosine monophosphate (cAMP) and calcium levels while simultaneously suppressing glucagon release from α-cells, thereby reducing hepatic glucose production. Additionally, GLP-1 slows gastric emptying via the "ileal brake" mechanism, which helps regulate postprandial glucose excursions. It also affects the central nervous system by acting on the hypothalamus and hindbrain, promoting satiety and reducing food intake [15].

GIP, on the other hand, is secreted by K cells in the duodenum and proximal jejunum and represents the predominant incretin hormone in healthy individuals [16]. Historically, GIP was considered to have limited therapeutic value in T2DM because of its markedly reduced insulinotropic response under hyperglycemic conditions, a phenomenon often referred to as the "GIP paradox". However, emerging evidence has challenged this view. Specifically, the restoration of normoglycemia has been shown to increase the responsiveness of GIP, and supraphysiological levels of GIP can overcome receptor resistance. Unlike GLP-1, GIP stimulates glucagon secretion during euglycemia, which may provide protective effects against hypoglycemia but does not interfere with GLP-1-mediated glucagon suppression during hyperglycemia. Furthermore, GIP receptors (GIPRs) are widely expressed in white adipose tissue, and GIP signaling increases blood flow in adipose tissue, promotes triglyceride clearance, and supports physiologic lipid storage, potentially reducing ectopic fat accumulation in organs such as the liver and skeletal muscle [17].

Tirzepatide: Drug Overview

Tirzepatide is a groundbreaking 39-amino acid synthetic linear peptide that has been strategically engineered as a novel therapeutic agent for T2DM and chronic weight management. Its importance lies in its unique "twincretin" mechanism, making it the first molecule in its class to function as a dual agonist for both the GIPR and the GLP-1 receptor (GLP-1R) [18]. This dual agonism is achieved through a deliberate molecular architecture that shares structural homology with both native incretin hormones, ensuring the synergistic activation of both pathways. Compared with existing single-receptor agonists, the combined activation of GIPR and GLP-1R offers superior efficacy in terms of glycemic control and weight reduction [19]. The combined effect involves enhancing glucose-dependent insulin secretion from pancreatic β-cells, suppressing inappropriate glucagon release from α-cells, slowing gastric emptying to modulate postprandial glucose levels, and promoting satiety, all of which collectively contribute to significant and sustained weight loss [20]. To transform this potent peptide into a clinically viable, once-weekly injectable medication, 3 critical structural modifications were incorporated to overcome the inherent biological instability and short half-life of native incretin peptides. The first modification involves C-terminal amidation, in which the terminal carboxyl group is converted into an amide. This chemical alteration plays a vital protective role by preventing the degradation of the peptide by carboxypeptidases, thereby extending the integrity of the molecule in vivo [21]. The second key modification involves the substitution of natural amino acids at specific positions, namely, positions 2 and 13, with the nonproteinogenic amino acid aminobisbutyric acid (Aib). The introduction of the Aib residue at position 2 is the principal mechanism that prevents degradation by dipeptidyl peptidase-4 (DPP-4) [22]. DPP-4 is a ubiquitous enzyme that rapidly inactivates native GIP and GLP-1. By sterically hindering the DPP-4 enzyme, this modification dramatically preserves the biological activity of the molecule and extends its effective half-life [23]. Figure 1 illustrates the chemical structure of tirzepatide 1.

The third and arguably most crucial modification for enabling once-weekly dosing is C20 fatty diacid acetylation at lysine 20. A C20 fatty diacid moiety is covalently attached to the lysine residue at position 20 via a specialized hydrophilic linker. This lipophilic fatty diacid is a key element for sustained action, promoting strong, noncovalent, and reversible binding to plasma albumin. Albumin, a large circulating protein, serves as a protective depot for drugs in the bloodstream [24]. This binding achieves 2 critical pharmacological objectives: First, it prevents the rapid renal clearance of tirzepatide, as the large albumin–drug complex is not easily filtered by the kidneys, and second, the slow dissociation of tirzepatide from the albumin depot ensures its sustained release into systemic circulation. This process results in an extended elimination half-life of approximately 5 d, which is the foundational reason why tirzepatide can be conveniently administered via a subcutaneous (SC) injection only once a week [25]. The pharmacological class of tirzepatide is therefore defined as a dual GIP and GLP-1 RA, or "twincretin", and it is commercially available under the trade names Mounjaro for T2DM and Zepbound for chronic weight management, representing a major advancement in metabolic disease therapy [26].

Mechanism of Action

Tirzepatide acts as an imbalanced dual agonist.

GIPR: Full agonist (affinity comparable to that of native GIP)

The action of tirzepatide as a full agonist of the GIPR is critical to its therapeutic efficacy, particularly in the management of T2DM. The term "full agonist" signifies that tirzepatide can elicit the maximum possible biological response from the GIPR, mirroring the effect of the body's naturally occurring GIP hormone. This strong affinity, comparable to that of native GIP, is crucial. GIP is an incretin hormone released by K cells in the gut in response to nutrient ingestion. Its primary role is to potentiate glucose-dependent insulin secretion from pancreatic β-cells. By acting as a full agonist, tirzepatide effectively amplifies this natural signaling pathway. When blood glucose levels increase, tirzepatide binds to the GIPR, stimulating downstream cellular cascades, which ultimately leads to increased insulin release. This mechanism is glucose dependent, which means that the risk of hypoglycemia is inherently low, which is a significant safety advantage. Furthermore, GIPRs are expressed in adipose tissue, bone, and the brain. The activation of these receptors is thought to contribute to the overall metabolic benefits of the drug, potentially by influencing fat metabolism, promoting β-cell proliferation and survival, and modulating appetite and energy expenditure, thereby contributing to weight management. The full agonism property of the drug ensures that the therapeutic dose of tirzepatide robustly and consistently activates the GIPR, thereby maximizing its contribution to glycemic control and its other pleiotropic metabolic effects and distinguishing its action mechanism from that of traditional GLP-1 RAs [18].

GLP-1R: Biased agonist (lower affinity, favoring cAMP signaling over β-arrestin recruitment)

The interaction between tirzepatide and the GLP-1R is characterized by biased agonism, a unique pharmacological property that

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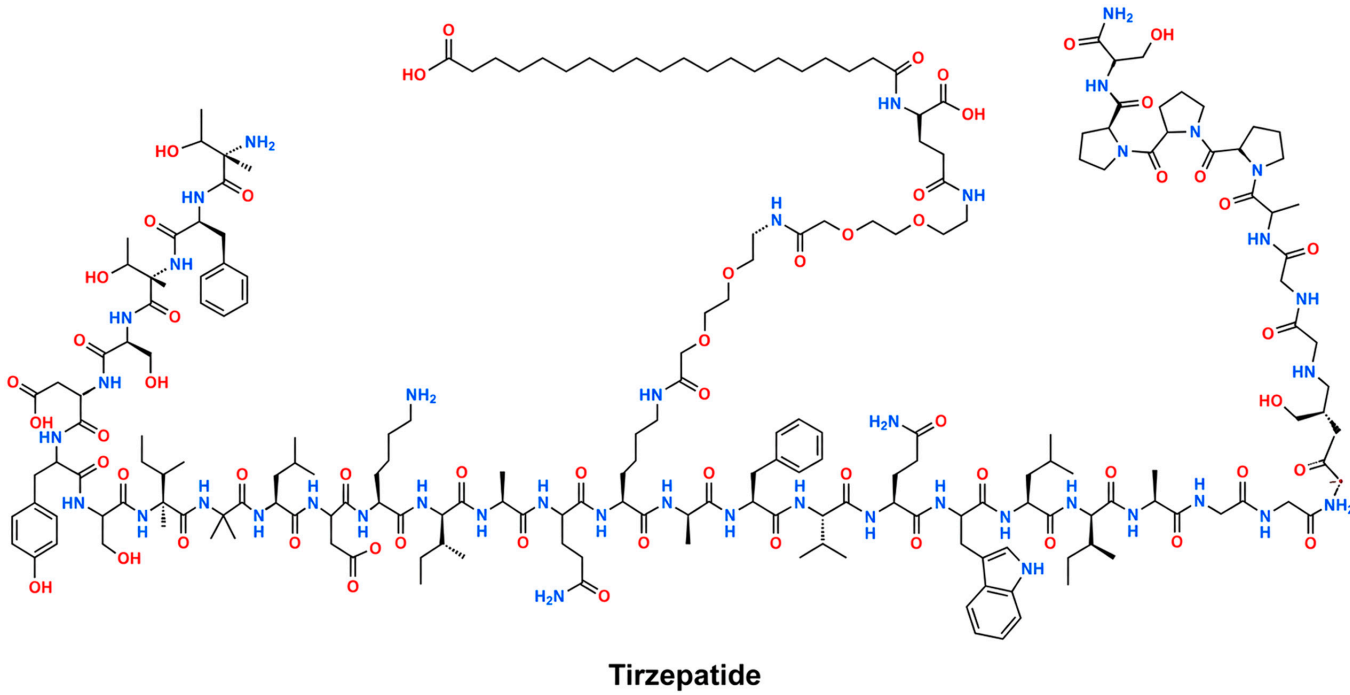


Fig. 1. Structure of tirzepatide.

contributes to its superior efficacy. While tirzepatide is a potent activator of the GLP-1R, its affinity for this receptor is lower than its affinity for the GIPR. The key feature, however, is the "biased" nature of its signaling. Traditional, or unbiased, agonists equally activate all downstream signaling pathways upon receptor binding, typically involving both cAMP generation and β-arrestin recruitment. In contrast, tirzepatide preferentially promotes cAMP signaling. The cAMP pathway is the canonical, beneficial signaling pathway for GLP-1 and is responsible for its core functions, such as increasing glucose-dependent insulin secretion, suppressing glucagon release, slowing gastric emptying, and promoting satiety. By promoting this pathway, tirzepatide maximizes the therapeutic benefits associated with the activation of GLP-1Rs. Conversely, β-arrestin recruitment has been implicated in receptor desensitization (reducing the drug's long-term effectiveness) and potentially mediating some of its adverse effects. By relatively de-emphasizing β-arrestin recruitment, tirzepatide may reduce receptor desensitization, contributing to its sustained efficacy. Furthermore, its side effects, particularly gastrointestinal issues, may be modulated compared with those of agonists that promote a more balanced signaling cascade. Owing to this strategic biased agonism at the GLP-1R, combined with the full agonism at the GIPR, tirzepatide functions as a dual-acting molecule with favorable therapeutic potential for both glycemic control and weight reduction [18], as depicted in Fig. 2.

Pharmacokinetics and Pharmacodynamics

Absorption

The pharmacokinetic effects of this compound begin with its administration via SC injection, a route specifically chosen to achieve systemic drug levels. Following the SC injection, the drug is deposited into the fat layer just beneath the skin and gradually absorbed into the bloodstream. This method offers a balance between patient convenience and predictable drug uptake. A critical measure of this uptake process is the drug's bioavailability, which represents the percentage of the administered dose that successfully reaches systemic circulation in an unchanged form. For this drug, the bioavailability following SC administration is robustly estimated to be approximately 80% [27]. This high bioavailability is a significant pharmacodynamic advantage. This confirms that the vast majority of the administered dose can exert therapeutic effects throughout the body. This high bioavailability ensures consistency between the administered dose and the circulating drug concentration, leading to reliable clinical efficacy across patients [28]. Furthermore, the consistent and high bioavailability is essential for establishing a reliable dosing regimen, as it reduces variability in patient responses and simplifies therapeutic monitoring. The SC route is favored over intravenous (IV) injection for self-administration scenarios and over oral administration, as compounds might degrade in the gastrointestinal tract or exhibit poor intestinal absorption [29].

Distribution and dosing frequency

A notable feature of this drug's profile that profoundly affects patient compliance and treatment convenience is its relatively long elimination half-life of approximately 5 d. The half-life is the fundamental pharmacokinetic parameter that determines how frequently a drug must be administered to maintain therapeutic concentrations. It is defined as the time required for the concentration of the drug in the plasma to decrease by exactly half. An extended half-life, such as the 5-d period of this drug, means that the drug is cleared from the body very slowly. This slow clearance rate is key for a simplified, patient-friendly once-weekly dosing schedule. Compared with drugs that require daily or even multiple daily injections, a once-weekly regimen dramatically reduces the burden on the patient. This decreased frequency is directly associated with a significant increase in patient adherence, as it is much easier for patients to remember and comply with a weekly schedule. The sustained presence of

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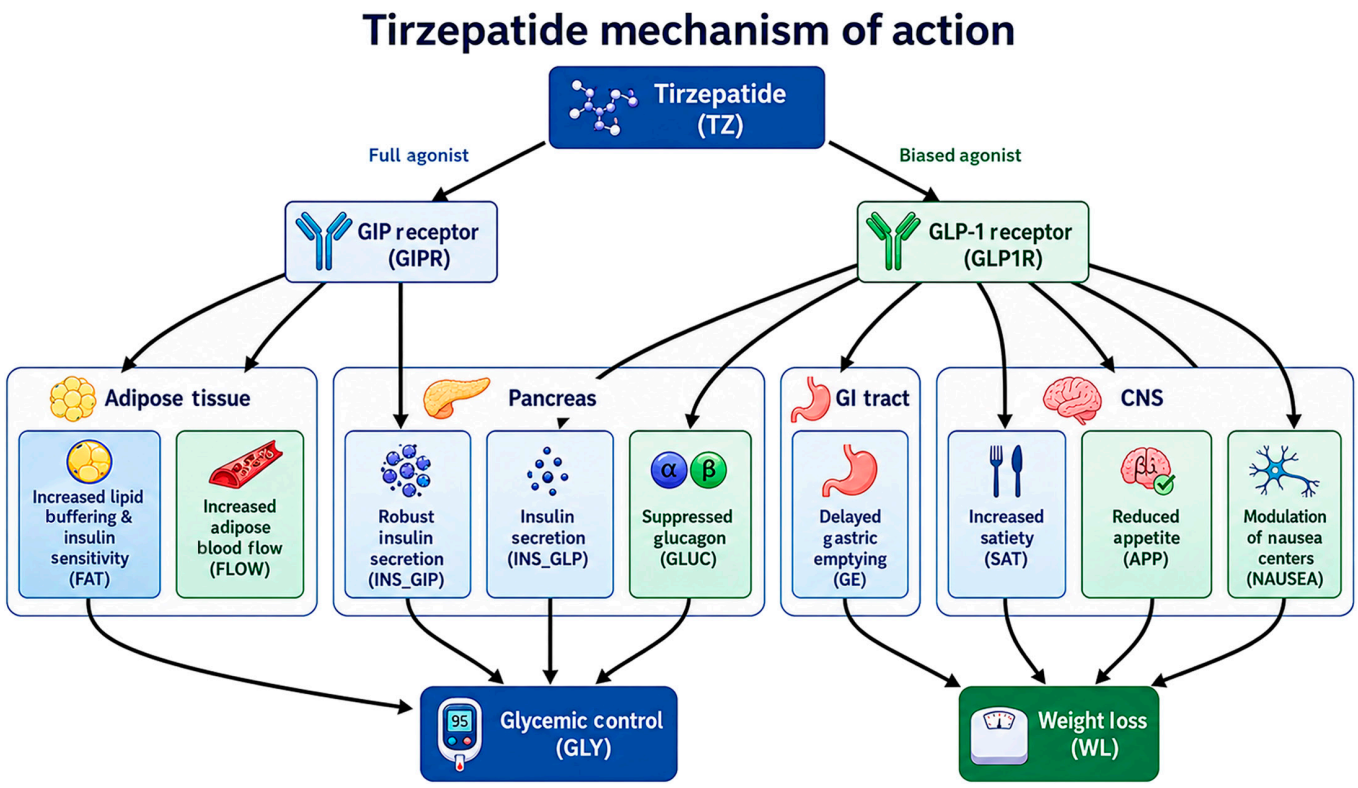


Fig. 2. Mechanism of action of tirzepatide.

the drug in systemic circulation, facilitated by this long half-life, helps ensure that therapeutic drug levels are maintained throughout the week, minimizing concentration fluctuations that can lead to periods of suboptimal drug effects. Thus, the long half-life is a critical design feature that maximizes the therapeutic benefits of the drug while optimizing the practicality of chronic drug therapy [28,30].

Metabolism

The metabolic process, or catabolism, of this drug is highly favorable from a drug–drug interaction (DDI) perspective. The compound is not processed through a complex or variable enzymatic system but rather breaks down primarily via endogenous pathways. Specifically, its breakdown involves 2 main processes: proteolytic cleavage and β-oxidation of the fatty acid chain. Proteolytic cleavage refers to the hydrolysis of peptide bonds, namely, the breakdown of the protein or peptide component of the molecule by naturally occurring proteases in the body. β-Oxidation is a common pathway for the breakdown of fatty acids, which are often incorporated into drug molecules to extend their half-life, as is tirzepatide. This reliance on natural, ubiquitous catabolic processes is a significant clinical advantage because it confirms that there is no significant interaction between this drug and the cytochrome P450 (CYP450) enzyme system. The CYP450 system, which is predominantly located in the liver, is responsible for the metabolism of many therapeutic agents. As a result, drugs that utilize the CYP450 system are highly prone to clinically significant DDIs. When 2 drugs compete for the same CYP450 enzyme or one drug inhibits or induces enzymic activity, the metabolism of the other drug can be dramatically altered, leading to toxicity or reduced efficacy. By bypassing the CYP450 system, this drug minimizes the potential for such complex and often unpredictable DDIs, thus simplifying its co-administration with other necessary medications and enhancing its overall safety profile for polypharmacy patients [28,30].

Excretion

The final stage of the pharmacokinetic process, excretion, involves how the drug and its resulting breakdown products are efficiently removed from the body. For this compound, elimination occurs predominantly via 2 routes: the renal (urine) route and the fecal route. This dual-pathway mechanism is indicative of efficient and robust clearance. The main substances excreted are metabolites generated during the preceding metabolic phase, which involves proteolytic cleavage and β-oxidation of the fatty acid chain. The renal route, which involves excretion through the kidneys and elimination via urine, is the primary mechanism for clearing smaller, water-soluble molecules and metabolites. The fecal route, which involves excretion via bile and subsequent elimination via feces, typically involves larger or more lipophilic (fat-soluble) molecules and their corresponding metabolites. By utilizing both major excretion pathways, the body ensures comprehensive and efficient clearance of this drug and its components. This dual clearance system also provides a degree of redundancy; specifically, if one excretion route is partially impaired (e.g., in patients with mild-to-moderate renal or hepatic impairment), the other route may still contribute significantly to the overall removal of the drug. This balanced clearance mechanism is essential for preventing the accumulation of the drug and its metabolites to toxic levels, thereby contributing to the overall safety and predictability of the drug in clinical settings [28,30].

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Clinical Efficacy

Tirzepatide has consistently demonstrated superior performance in terms of reducing HbA1c levels (by 2.0% to 2.6%) and inducing weight loss (by 15% to 21%) across multiple trials.

Glycemic control: The SURPASS program

The pivotal SURPASS global clinical trial, which investigated the efficacy and safety of tirzepatide across diverse patient populations and treatment regimens, reported groundbreaking results regarding glycemic reduction [31]. The observed reduction in the levels of hemoglobin A1c (HbA1c), a key marker of long-term blood glucose control, was substantial. Notably, across the SURPASS trials, the mean reduction in the HbA1c level ranged from 2.0% to 2.6%. This range often surpassed that achieved by existing first-line and second-line antidiabetic medications, including GLP-1 RAs and basal insulins [32]. Furthermore, one of the most remarkable findings was the high rate of patients who achieved a state of normoglycemia. Specifically, up to 50% of patients treated with the highest dose of tirzepatide (15 mg) reached an HbA1c level of <5.7%. Clinically, this threshold is widely recognized as the nondiabetic range, effectively indicating the remission of biochemical diabetes in these patients. This level of therapeutic efficacy marks a profound shift in T2DM management, moving beyond mere disease control toward the potential for disease reversal [33]. Moreover, while the glycemic control data are compelling, the superiority of tirzepatide is often supported by its additional metabolic benefits, particularly in the context of weight management, which is crucial given the high comorbidity of obesity with T2DM. Tirzepatide consistently induced significant and sustained weight loss, often exceeding 10% to 20% of the baseline body weight of the patients, indicating that tirzepatide represents one of the most effective pharmacologic agents for weight reduction that is currently available for people with T2DM [34].

Weight loss effects

Tirzepatide has demonstrated remarkable efficacy in weight management, positioning it as a potentially transformative pharmacotherapy for obesity. Its distinguishing feature is the extent of weight loss achieved in clinical trials, substantially outperforming existing anti-obesity medications. In robust clinical trials focused on obesity, the highest approved dose of tirzepatide (15 mg) [35] was associated with a mean weight reduction of 20.9% from baseline. This level of efficacy is exceptionally high for a medication. Furthermore, the trial data revealed the further effects of the drug, with more than one-third of the participants successfully losing more than 25% of their initial body weight [36].

This profound weight loss is highly significant because it effectively bridges the gap between conventional pharmacotherapy and the results typically seen with bariatric surgery. Surgical interventions, such as sleeve gastrectomy and gastric bypass, are considered the gold standard for severe obesity and usually result in a total reduction in body weight of 25% to 30% [37]. Tirzepatide can approach this 25% threshold medically and thus represents a powerful, nonsurgical alternative for achieving clinically meaningful and substantial weight reduction, potentially leading to significant improvements in obesity-related comorbidities such as type 2 diabetes (T2D), hypertension, and dyslipidemia [13]. The different pharmacological actions of tirzepatide are depicted in Fig. 3.

Lipid partitioning (the "metabolic sink" effect)

Tirzepatide's unique ability to activate both GIPR and GLP-1R is central to its powerful effects on lipid metabolism, particularly its "metabolic sink" mechanism. Specifically, the activation of GIPRs targets and enhances the function of white adipose tissue (fat cells). This enhancement increases the capacity of SC fat to safely store excess energy, acting as an effective "sink"

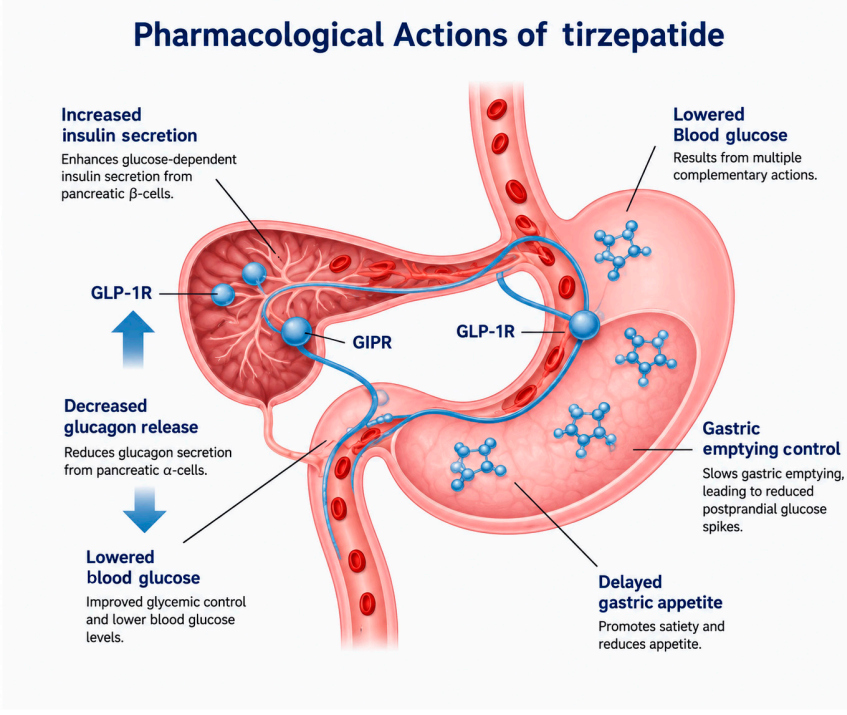


Fig. 3. Pharmacological actions of tirzepatide.

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for circulating lipids [18]. When dietary energy intake exceeds immediate expenditure, this mechanism promotes the uptake and esterification of fatty acids into triglycerides within the SC depot. This is crucial because it reduces the amount of free fatty acids and triglycerides circulating in the blood, thereby preventing a phenomenon known as "lipid spillover". Lipid spillover occurs when fat storage capacity is overwhelmed, resulting in excess fat being deposited ectopically in vital organs such as the liver [which can cause nonalcoholic fatty liver disease (NAFLD)], pancreas, and heart [38]. This ectopic fat deposition is highly toxic, leading directly to cellular dysfunction and severe insulin resistance. By reinforcing the safe storage capacity in SC fat, tirzepatide not only improves lipid profiles (by reducing triglyceride levels) but also fundamentally addresses a core driver of metabolic syndrome and T2D [39].

Anti-inflammatory properties

Chronic, low-grade systemic inflammation is a silent but powerful driver of the progression of nearly all facets of metabolic syndrome, including insulin resistance, NAFLD, and, most importantly, atherosclerotic cardiovascular disease (ASCVD) [40]. Through its dual agonist mechanism, tirzepatide exerts significant anti-inflammatory effects by modulating inflammatory signaling pathways within the body. The activation of incretin receptors on various cell types, including immune cells, leads to the down-regulation of key proinflammatory biomarkers. Clinically significant decreases in the expression levels of markers such as C-reactive protein (CRP), interleukin-6 (IL-6), and tumor necrosis factor-α (TNF-α) have been observed [40]. This reduction in systemic inflammation is not merely a side effect but a critical component of the therapeutic action of tirzepatide. By reducing inflammation, the drug helps to stabilize atherosclerotic plaques, protect the endothelial lining of blood vessels, and mitigate inflammatory stress on metabolic organs. This action provides a critical link between glycemic control and the observed cardiovascular benefits, offering a holistic treatment approach that goes beyond simple blood sugar management to address the underlying pathology of metabolic and cardiovascular diseases [32].

Renoprotection

The kidneys are highly vulnerable to the combined damage caused by chronic hyperglycemia (diabetes) and hypertension. Emerging clinical and established preclinical evidence strongly suggests that owing to its dual agonist effect, tirzepatide significantly protects renal function, a crucial benefit given that diabetic kidney disease is a leading cause of end-stage renal failure. The mechanism of renoprotection is multifaceted. First, the systemic improvements in glucose control and blood pressure—which are hallmarks of tirzepatide therapy—significantly reduce chronic hemodynamic stress on the delicate renal glomeruli [40]. Second, the activation of incretin receptors may directly affect the kidneys. Specifically, the activation of GLP-1Rs can alter renal hemodynamics by modulating afferent and efferent arteriolar tone, which helps to reduce the detrimental intraglomerular pressure (hyperfiltration) that accelerates kidney damage [40]. Furthermore, by reducing systemic inflammation and oxidative stress and potentially having direct antifibrotic effects, tirzepatide may slow the structural decline of the kidney. The clinical manifestation of this protective effect often involves a reduction in albuminuria (the presence of excess protein in the urine), which is a key early marker of kidney damage and a strong predictor of progressive renal decline [41].

Summary of Key Clinical Trials

SURPASS trials (diabetes)

To fully examine the effectiveness and safety of tirzepatide in the treatment of T2DM, the SURPASS clinical trial program was created. In patients with T2DM with different illness durations and use of various background medications, this randomized clinical trial program aimed to compare the safety and effectiveness of tirzepatide with those of a placebo, proven GLP-1 RAs, and basal insulin regimens. The SURPASS clinical trials, which focused on long-term glycemic, weight, and cardiovascular outcomes, provide key evidence that supports the dual activation of GIPR and GLP-1R as the next-generation diabetes treatment approach. The trial results are presented in Table 1.

SURMOUNT trials (obesity)

The SURMOUNT clinical program was designed to directly investigate the weight loss effects of tirzepatide in people with obesity with and without T2D. In these studies, the use of tirzepatide in a chronic weight management paradigm was investigated in a real-world clinical setting. By examining the depth,

Table 1. Results of the SURPASS trials for diabetes

Trial	Comparator	HbA1c reduction	Weight change	Key outcome	References
SURPASS-1	Placebo	−2.07% (15 mg)	−9.5 kg	Superior efficacy as monotherapy in drug-naive patients	[83]
SURPASS-2	Semaglutide 1 mg	−2.30%	−11.2 kg	Head-to-head superiority	[83]
SURPASS-3	Insulin degludec	−2.37%	−12.9 kg	Superior glycemic control with weight loss vs. weight gain with insulin	[84]
SURPASS-4	Insulin glargine	−2.58%	−11.7 kg	Noninferior CV safety in high-risk population; superior glycemia effects	[85]
SURPASS-5	Placebo (add-on)	−2.59%	−10.9 kg	Effective add-on to basal insulin; mitigates insulin-associated weight gain	[86]

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durability, and meaning of weight loss, the SURMOUNT program results support that tirzepatide is a truly transformational pharmacologic agent, with the results remarkably approaching those typically associated with bariatric surgery treatments. The results are provided in Table 2.

Safety and Adverse Effects

Common side effects (nausea, diarrhea, vomiting)

These are the most frequently reported adverse effects associated with this medication, particularly during the initiation of therapy or after dose escalation [42]. The occurrence of nausea, diarrhea, and vomiting is often dose dependent, meaning that these symptoms are more likely to occur at higher doses. They are typically transient, meaning they tend to lessen or resolve as the patient's body adjusts to the drug over time [43]. Managing these common gastrointestinal symptoms often involves starting with a low dose and gradually increasing the dose, taking the medication with food, or using supportive anti-nausea or anti-diarrheal treatments as needed [44].

Serious side effects (pancreatitis, cholelithiasis, hypoglycemia)

While these effects are less common than gastrointestinal issues, they represent more significant health concerns. Pancreatitis (inflammation of the pancreas) is a rare but serious risk and requires immediate medical attention if symptoms such as severe abdominal pain, often radiating to the back, and persistent vomiting occur. Cholelithiasis, or gallstones, is another potentially serious complication linked to changes in gallbladder function, which may manifest as pain in the upper right abdomen [45]. Hypoglycemia (low blood sugar) is rare when this medication is used alone (monotherapy) but is a recognized risk factor, particularly when this drug is combined with other glucose-lowering agents such as sulfonylureas and insulin. Patients, especially those on combination therapy, must be educated on the signs and management of hypoglycemia, such as dizziness, sweating, and confusion, and should carry a source of fast-acting sugar [46].

Boxed warning (thyroid C-cell tumors)

This is the most serious warning assigned to the medication, appearing in a prominent box on the prescribing information, reflecting findings from preclinical studies. This warning indicates an increased risk of thyroid C-cell tumors, including medullary thyroid carcinoma (MTC), in rodents (rats and mice) treated with the drug [47]. Importantly, it remains unclear whether this risk translates to humans. Nevertheless, owing to these findings, the drug is generally contraindicated (should not be used) in patients with a personal or family history of MTC or in patients with multiple endocrine neoplasia syndrome type 2 (MEN 2), which predisposes individuals to MTC. Patients are advised to report symptoms such as a lump in the neck, hoarseness, or difficulty swallowing, which could be signs of a thyroid tumor, to their doctor immediately [48].

Comparison with Other Agents: Why Tirzepatide Is Better

The superiority of tirzepatide over selective GLP-1 RAs, such as semaglutide, is largely attributed to its unique dual-incretin mechanism, which produces synergistic metabolic effects. One of the key advantages is its ability to induce supra-additive insulin secretion. While GLP-1 increases glucose-dependent insulin release, the addition of this GIPR agonist results in a more robust insulinotropic response, particularly restoring early first-phase insulin secretion, which is typically impaired in patients in the initial stages of T2D [18]. In addition to its effects on insulin secretion, tirzepatide plays a significant role in addressing insulin resistance. Unlike traditional GLP-1 RAs, which primarily act through appetite suppression and weight reduction, tirzepatide exerts direct peripheral effects via GIPRs expressed on adipocytes. This leads to greater insulin sensitivity, enhanced lipid handling, and more efficient storage of triglycerides in adipose tissue, thereby reducing ectopic fat deposition. These peripheral metabolic benefits complement the central appetite-suppressing mechanisms of this drug, resulting in more comprehensive therapeutic effects.

Another important factor contributing to the superiority of tirzepatide is its favorable tolerability in addition its high

Table 2. Results of the SURMOUNT trials for obesity

Trial	Population	Mean weight loss (15 mg)	% of patients that achieved >20% loss	Key note	References
SURMOUNT-1	Obesity (no T2D)	−20.9%	~57%	Efficacy approaches that of bariatric surgery benchmarks.	[87]
SURMOUNT-2	Obesity + T2D	−15.7%	~31%	Highest weight loss recorded in a T2D population to date.	[87]
SURMOUNT-3	Intensive lifestyle	−26.6%	N/A	Drug added after lifestyle run-in maximizes total weight loss.	[88]
SURMOUNT-4	Maintenance	−25.3% (Cont.)	N/A	Withdrawal led to significant weight regain (chronic disease).	[89]

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efficacy. Tirzepatide exhibits biased agonist effects at the GLP-1R, favoring intracellular signaling pathways over the receptor itself. This allows the drug to be administered at higher effective doses, yielding substantial weight loss effects while maintaining a tolerability profile comparable to that of less potent agents [18]. Furthermore, tirzepatide offers advantages in terms of glucagon physiology. Unlike GLP-1 RAs alone, which suppress glucagon, the activation of GIPRs helps preserve the glucagon counterregulatory response during hypoglycemia. This may provide a safer profile by reducing the risk of hypoglycemic events, even in the context of improved glycemic control [49]. As summarized in Table 3, these combined mechanisms position tirzepatide as a particularly effective and comprehensive therapeutic option for the management of both diabetes and obesity.

Comprehensive Cardiometabolic and Obesity Management Benefits of Tirzepatide

Cardiovascular and metabolic benefits

Tirzepatide, an innovative dual GLP-1 and GIP RA, profoundly and comprehensively improves various cardiometabolic risk factors that extend well beyond its primary effect on glucose control. Its unique mechanism provides synergistic benefits across multiple organ systems. Specifically, tirzepatide induces a robust and favorable shift in the circulating lipid profile, thereby addressing key components of atherosclerotic risk [26].

Triglyceride reduction

Clinical trial data consistently demonstrate a substantial reduction in serum triglyceride levels, often by up to 25% from baseline. This effect is crucial, as elevated triglyceride levels are an independent risk factor for cardiovascular disease and pancreatitis [50].

Atherogenic particle targeting

In addition to standard lipid panel markers, tirzepatide significantly decreases the levels of pharmacologically stubborn and highly atherogenic particles, specifically ApoC-III (apolipoprotein C-III) and ApoB (apolipoprotein B) [51]. ApoB is a critical marker that represents the total number of atherogenic particles (including low-density lipoprotein, very low-density lipoprotein , and others). Its reduction signifies the diminished burden of circulating particles capable of initiating plaque formation [52]. Additionally, ApoC-III inhibits triglyceride clearance, and its reduction facilitates the more efficient removal of triglyceride-rich lipoproteins (TRLs) [53].

HDL cholesterol enhancement

The increase in high-density lipoprotein (HDL) cholesterol observed with tirzepatide is often more pronounced than that observed with the use of selective GLP-1 RAs alone. This superior impact is largely attributed to the unique effect of the GIP component on lipid metabolism, which is thought to modulate reverse cholesterol transport and lipoprotein lipase activity [32].

The therapeutic benefits extend to consistent and clinically meaningful reductions in systemic blood pressure, which represents a major driver of cardiovascular morbidity. Specifically, patients experience consistent reductions in systolic blood pressure (typically in the range of 6 to 8 mmHg) and diastolic blood pressure (generally 4 to 5 mmHg) [54].

Mechanisms of action

This hemodynamic improvement is multifactorial and mediated by several interconnected pathways. The primary mechanism is the profound and sustained weight loss observed with the use of this drug, which naturally reduces vascular resistance [55]. Additionally, the GIP and GLP-1 components both contribute to enhanced natriuresis (increased sodium excretion) and diuresis via direct and indirect renal effects, reducing the overall fluid volume [56]. Furthermore, the decreased activity of the sympathetic nervous system, a key regulator of blood pressure, contributes to the overall hypotensive effect [57].

Tirzepatide directly affects hepatic manifestations of metabolic dysfunction and is a promising intervention for advanced liver disease. In dedicated studies, such as the SURPASS-3 magnetic resonance imaging (MRI) trial, quantitative imaging demonstrated that tirzepatide significantly reduced liver fat content (LFC) and visceral adipose tissue (VAT). The reduction in LFC directly indicates the improvement in liver steatosis [58]. Moreover, by aggressively reducing ectopic fat stores in the liver and visceral compartment, tirzepatide directly addresses the underlying pathology of metabolic dysfunction-associated steatohepatitis (MASH; formerly known as NASH). This positions it as a leading therapeutic candidate for this rapidly growing and serious hepatic manifestation of metabolic syndrome, offering disease modification functions in addition to weight management [59].

Role in obesity management

Bridging the gap

Historically, the varied obesity treatments presented a significant dichotomy. On the one hand, standard-of-care interventions such as diet, exercise, and traditional pharmacotherapy typically resulted in a modest 5% to 10% reduction in the total body weight. While these effects are beneficial, this level of weight loss was often insufficient to induce profound metabolic health improvements for patients with severe obesity [60]. On the other hand, bariatric surgery (such as Roux-en-Y gastric bypass and sleeve gastrectomy) enabled dramatic and sustained weight loss, often in the range of 25% to 30% or more. However, surgery is invasive, has inherent risks, requires lifelong nutritional and medical follow-up, and is not suitable or desired by all patients.

Table 3. Comparison of tirzepatide with other agents

Drug	Action	Mechanism	HbA1c reduction	Weight reduction
Tirzepatide	Dual GIP + GLP-1	★★★★★	★★★★★	(17, 32)
Semaglutide	GLP-1	★★★★	★★★★	(17, 32)
Liraglutide	GLP-1	★★★	★★★	(17, 32)

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Tirzepatide, marketed as Zepbound for weight management, has fundamentally changed this paradigm. By consistently inducing weight loss in the range of 20% to 25% in clinical trials (e.g., SURMOUNT-1), tirzepatide now represents a crucial middle ground that previously did not exist, thereby addressing a "therapeutic void" [13]. This high-efficacy pharmacotherapy provides a potent, nonsurgical approach for clinically meaningful weight reduction with long-term success rates comparable to those of some surgical procedures. For patients with obesity who are hesitant to undergo an operation or for whom surgery is contraindicated, tirzepatide represents a highly viable and medically potent alternative, effectively making profound weight loss a more accessible treatment goal. The introduction of such a powerful agent broadens the treatment options, allowing for a more personalized and less invasive management strategy for chronic diseases such as obesity [61].

Guideline placement

The profound and clinically significant weight loss induced by tirzepatide, coupled with its primary mechanism as a dual GIP and GLP-1 RA, has necessitated the rapid revision of major clinical practice guidelines [62]. For patients with T2D, the focus of treatment has shifted beyond mere glycemic control to addressing the underlying cardiorenal and metabolic risk factors. As a result, leading professional organizations, including the American Diabetes Association (ADA), the European Association for the Study of Diabetes (EASD), and the American Association of Clinical Endocrinology (AACE), now strongly recommend the preferential use of high-efficacy agents such as tirzepatide for specific patient populations. Specifically, tirzepatide is often recommended as a first-line or early-use agent for patients with T2D who have a "compelling need" for weight loss [32]. This guideline shift reflects the recognition that the magnitude of weight reduction achieved by tirzepatide directly translates into superior control of diabetes, blood pressure, and dyslipidemia beyond what is achievable by less potent glucose-lowering drugs. By explicitly endorsing agents with significant weight-lowering capabilities, the guidelines underscore the pivotal role of obesity treatment in the holistic management of T2D and associated cardiometabolic complications, with high-efficacy pharmacotherapy often recommended as the first-line treatment [63].

Metabolic syndrome reversal

Metabolic syndrome, which involves various conditions, including abdominal obesity, high blood pressure, high blood sugar, and abnormal cholesterol or triglyceride levels, is a major risk factor for cardiovascular disease and T2D. The therapeutic impact of tirzepatide extends far beyond simple weight reduction; the approximately 20% to 25% reduction in total body weight facilitated by this drug is sufficient to induce a profound and often complete reversal of the components of metabolic syndrome [36]. This level of weight loss is associated with several critical health benefits. For instance, the significant reduction in fat mass frequently leads to the reversal of prediabetes and, in many cases, the remission of established T2D. Furthermore, improvements in body composition and the hormonal milieu help normalize blood pressure, often allowing patients to reduce or discontinue antihypertensive medications [64]. Notably, the data from the SURMOUNT-OSA trial specifically demonstrated that tirzepatide treatment was associated with a significant reduction and, in many patients, the resolution of moderate-to-severe obstructive sleep apnea (OSA). By addressing the root cause—excess adipose tissue—of insulin resistance, hypertension, and sleep-related breathing disorders, tirzepatide provides genuine disease-modifying effects, transforming the overall health trajectory and reducing the long-term morbidity and mortality associated with metabolic syndrome [65].

Body composition

A common physiological consequence of any rapid and significant weight reduction, whether through diet, bariatric surgery, or pharmacotherapy, is the concurrent loss of both fat mass and lean mass, which includes muscle. While tirzepatide facilitates substantial weight loss, concerns often arise regarding the preservation of muscle tissue, as the loss of lean mass can have negative long-term effects on strength, metabolism, and functional status [66]. However, clinical data on the effect of tirzepatide on body composition have demonstrated that the ratio of fat mass to lean mass loss is comparable to that observed with other successful weight loss interventions. In other words, while muscle is inevitably lost as part of the overall reduction in weight, the proportion of muscle lost relative to the amount of fat lost is not disproportionately high compared with intensive lifestyle modifications and other anti-obesity medications. Crucially, the maintenance and improvement of lean mass during a period of rapid weight loss can be actively managed. For example, the loss of lean mass can be effectively mitigated with resistance training [67]. Incorporating a regimen of strength or resistance exercises is a key adjunctive strategy that helps patients preserve muscle tissue, maintain their metabolic rate, and increase their functional capacity as their weight is significantly reduced with tirzepatide treatment. This combined approach maximizes the therapeutic benefits of this drug by focusing on favorable body composition changes in addition to total weight loss [68].

Limitations and Challenges

Cost and accessibility

The primary limitation to the widespread adoption of tirzepatide (Mounjaro/Zepbound) is its prohibitive cost. Its high monthly expense results in significant socioeconomic disparities, effectively creating a tiered system of access, with only those with extensive financial resources or comprehensive insurance coverage being able to afford the treatment [69]. This is particularly pronounced for the obesity indication (Zepbound), with many insurance plans still classifying this drug as a lifestyle or cosmetic treatment and often excluding it from coverage. Even with insurance, high deductibles and copays can render the drug unaffordable for the average person [70]. This financial barrier limits the drug's real-world impact, preventing it from reaching the vast majority of people who could benefit from its metabolic advantages. To fulfill its public health potential, affordability should be increased, such as through manufacturer assistance programs or broader insurance mandate changes to classify obesity as a chronic, treatable disease. Without these changes, tirzepatide's profound benefits will remain an exclusive privilege rather than a universally accessible standard of care. This restricted access contradicts the goal of using advanced pharmaceuticals to address widespread health crises such as T2D and obesity [71].

Skeletal muscle loss

A crucial and often underrecognized limitation of tirzepatide therapy is the type of weight lost. Although total body weight

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may be substantially reduced, approximately 20% to 30% of this loss may be derived from lean mass, including skeletal muscle [72]. This phenomenon presents a significant clinical concern, particularly in vulnerable populations such as older adults, individuals with sarcopenia, and those with chronic illnesses. The loss of skeletal muscle can exacerbate frailty, impair physical function, reduce metabolic rates, and increase the risk of falls, disability, and hospitalization, thereby potentially offsetting some of the metabolic benefits of weight reduction. The clinical implications of lean mass loss must be addressed via a proactive and structured management approach. Current evidence supports the integration of targeted lifestyle and nutritional strategies alongside pharmacotherapy. A high-protein diet (generally 1.0 to 1.5 g/kg/d, individualized on the basis of the patient profile) is essential to achieve adequate amino acid availability for muscle protein synthesis [73]. Moreover, regular resistance or strength training exercises should be incorporated, which provide the mechanical stimulus needed to preserve or even increase skeletal muscle mass during periods of caloric deficit.

Additional supportive strategies may include ensuring the adequate intake of key micronutrients such as vitamin D and the implementation of individualized exercise regimens tailored to the age, baseline fitness, and comorbidities of the patient. In high-risk populations, periodic assessments of body composition (e.g., via DXA or bioimpedance analysis) and functional measures (such as grip strength and gait speed) may help guide therapy and monitor outcomes. Despite the clear importance of these interventions, they are not consistently integrated into routine clinical practice. Therefore, a multidisciplinary approach—incorporating physicians, dietitians, and physiotherapists—is strongly recommended to optimize treatment outcomes. The proactive implementation of muscle-preserving strategies should be considered an essential component of tirzepatide therapy, ensuring that weight loss translates into meaningful and sustainable improvements in overall health [68].

Gastrointestinal tolerability ceiling

Despite the generally good tolerability of tirzepatide in clinical trials, a defined subset of patients encounter a "gastrointestinal tolerability ceiling", leading to treatment discontinuation. The most common adverse effects are intractable nausea, vomiting, and diarrhea, which are severe enough to prompt 5% to 10% of users to stop using the medication. These symptoms are primarily related to the drug's mechanism of action, which includes delayed gastric emptying [44]. While this mechanism contributes to satiety and weight loss, it can have serious downstream effects. Delayed emptying complicates standard medical procedures, notably increasing the risk of pulmonary aspiration during anesthesia, as residual stomach contents can be inhaled into the lungs. Furthermore, the altered transit time can interfere with the reliable absorption of concurrently administered oral medications. This can compromise the effectiveness of critical drugs, such as oral contraceptives and specific cardiovascular medications; thus, careful monitoring and potential dose adjustments or alternative formulations are needed. A careful, slow titration schedule is the main strategy to mitigate these side effects; however, for a resistant subset of patients, chronic gastrointestinal distress remains an insurmountable obstacle to continuing this otherwise beneficial therapy [74].

Unknown long-term safety

The long-term safety profile of tirzepatide remains an important area of ongoing evaluation because of its relatively recent introduction and dual-incretin mechanism of action. The drug provides sustained, supraphysiologic stimulation of both GLP-1R and GIPR [75]. While short- and medium-term clinical trials have not reported significant safety concerns, the long-term effects—particularly those of chronic GIPR activation—remain incompletely understood. Potential areas of concern include pancreatic safety (e.g., pancreatitis), thyroid C-cell pathology, and biliary complications such as gallstone formation [76]. To address these uncertainties, structured and long-term post-marketing surveillance is essential. Large-scale, prospective cohort studies and real-world registry-based analyses with extended follow-up durations of at least 5 to 10 years should be performed to evaluate delayed or rare adverse events. Randomized controlled trial extensions and cardiovascular outcome trials (CVOTs) with longer follow-up periods would also provide valuable safety data.

Specific monitoring strategies should include the periodic assessment of the levels of pancreatic enzymes (amylase and lipase), thyroid biomarkers (including calcitonin in clinically appropriate cases), and hepatobiliary parameters through liver function tests and imaging when indicated. Additionally, the levels of metabolic and cardiovascular markers—including HbA1c, lipid profile parameters, renal function parameters, and blood pressure—should be tracked longitudinally to assess both the safety and sustained efficacy of this drug. Moreover, gallbladder-related events and adverse gastrointestinal effects should be systematically monitored during follow-up. Special attention should be given to high-risk populations, including elderly patients, those with preexisting pancreatic or thyroid disorders, and individuals with significant comorbidities. Furthermore, pharmacovigilance systems should prioritize the identification of rare but serious adverse events through global safety databases and real-world evidence platforms. Given that tirzepatide is intended for long-term use in patients with chronic conditions such as obesity and T2D, continuous data collection and transparent reporting are essential. Well-designed longitudinal studies integrating clinical, biochemical, and imaging endpoints are critical to ensure that the substantial therapeutic benefits of tirzepatide are not offset by unforeseen long-term risks [40].

Future Perspectives

Tirzepatide, a dual GIP and GLP-1 RA, has revolutionized incretin-based therapies. As a novel polyagonist, it is the new standard for treating metabolic disorders and is considered the foundational agent for the next generation of highly effective metabolic treatments [77]. The next innovative treatment, namely, triple agonist agents (targeting GIP, GLP-1, and glucagon receptors), exemplified by retatrutide, aims to surpass the effects of dual agonists such as tirzepatide. Adding glucagon stimulates greater energy expenditure and reduces the amount of ectopic fat, especially liver fat, which should enable superior weight loss [10]. Concurrently, oral small-molecule formulations of these agonists should be developed to overcome peptide bioavailability issues. The development of successful oral drugs will eliminate the need for injections, significantly increasing patient adherence and simplifying treatment logistics [78].

Furthermore, the scope of these incretin-based therapies is rapidly expanding beyond the initial indications for T2D and

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obesity. The therapeutic benefits of these treatments are being actively researched for various interconnected cardiometabolic conditions [79]. Key future indications include heart failure with preserved ejection fraction (HFpEF) to address the underlying metabolic dysfunction and inflammation frequently associated with this challenging form of heart failure [80]. Additionally, OSA is addressed primarily through substantial weight loss, which can mechanically resolve airway obstruction [81]. To address chronic kidney disease (CKD), the established cardiorenal protective effects associated with GLP-1 agonists can be leveraged, and their synergistic benefits with GIP and glucagon agonists can be explored [82]. This strategic expansion shifts the focus of medical research from treating individual diseases to the holistic, integrated management of cardiometabolic health. These evolving therapies offer a profound opportunity to address the global epidemics of obesity, diabetes, and cardiovascular disease more effectively and comprehensively [18].

Conclusion

Tirzepatide represents a significant advancement in the management of T2DM and obesity through its dual GIPR/GLP-1R agonism mechanism, which integrates glycemic control with meaningful weight reduction and broader metabolic improvements. In addition to its clinical efficacy, its most important contribution lies in shifting the therapeutic paradigm toward a more comprehensive and mechanism-based approach to metabolic disease, with multiple interconnected pathways addressed simultaneously. Despite these advances, several limitations remain. Concerns regarding the long-term safety of this drug, the sustainability of weight loss, and the potential for lean mass reduction highlight the need for careful patient selection and adjunctive management strategies. In addition, issues related to cost, accessibility, and real-world adherence may influence its broader clinical impact. Future research should focus on long-term outcome studies to better define the cardiovascular benefits, the durability of the metabolic effects, and the safety of the extended use of this drug. Further investigations on combination strategies, personalized treatment approaches, and the role of this drug in related metabolic disorders such as MASH are also essential. In summary, tirzepatide represents an important step toward integrated metabolic care, with the potential to reshape current treatment paradigms. Additional studies and an optimized clinical implementation will determine its ultimate role in improving long-term patient outcomes.

Acknowledgments

Funding: No funding was received for this work.
Author contributions: R.A.S.: Conceptualization, investigation, and writing original draft. O.K.G.: Conceptualization, investigation, and writing original draft. P.A.K.: Resources, data curation, visualization, and formal analysis. P.B.R.: Resources, data curation, visualization, and formal analysis.
Competing interests: The authors declare that they have no competing interests.

Data Availability

All the data generated or analyzed during this study are included in the published article.

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Tirzepatide: A Paradigm Shift in the Management of Type 2 Diabetes and Obesity

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Citation: Sonawane R, Gulave O, Kale P, Rasal P. Tirzepatide: A Paradigm Shift in the Management of Type 2 Diabetes and Obesity. *J Bio-X Res*. 2026;**9**:0092. DOI: 10.34133/jbioxresearch.0092

Type 2 diabetes mellitus and obesity represent intertwined chronic disorders that continue to escalate globally despite advances in pharmacotherapy. Current treatment strategies increasingly recognize the need to address both glycemic dysregulation and excess adiposity to meaningfully reduce long-term cardiometabolic risk. While glucagon-like peptide-1 receptor agonists significantly improve outcomes, many patients fail to achieve durable normoglycemia or substantial weight reduction. Tirzepatide is a novel therapeutic agent designed to activate both glucose-dependent insulinotropic polypeptide and glucagon-like peptide-1 receptors within a single molecular framework. By engaging complementary incretin pathways, tirzepatide produces enhanced metabolic effects that extend beyond those observed with selective receptor agonists. Clinical evidence from the SURPASS and SURMOUNT programs has revealed marked improvements in glycemic control, body weight, and multiple cardiometabolic parameters with tirzepatide treatment. This review examines the physiological basis, molecular design, pharmacological properties, and clinical performance of tirzepatide, focusing on its implications for the evolving management of diabetes and obesity. The emergence of dual-incretin agonism represents a meaningful advancement toward integrated metabolic disease control.
Image

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Journal of Bio-X Research (ISSN 2577-3585) is published by the American Association for the Advancement of Science. 1200 New York Avenue NW, Washington, DC 20005.

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