

Tirzepatide: A revolutionary dual-action therapy for type 2 diabetes mellitus and beyond

Abstract

Tirzepatide is a groundbreaking dual agonist of glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP) receptors, offering a transformative approach to managing Type 2 Diabetes Mellitus (T2DM), obesity and now sleep apnoea. Tirzepatide recently approved and marketed in India. This manuscript delves into the clinical efficacy, mechanism of action, and potential impact of Tirzepatide on glycemic control and weight reduction based on recent clinical trials and real-world evidence. With its unique dual-incretin action, Tirzepatide represents a significant advancement in the therapeutic landscape, offering superior outcomes in HbA1c reduction and sustained weight loss compared to traditional therapies.

Keywords: tirzepatide, weight management, hba1c, mounjaro, zepbound

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Introduction

Type 2 Diabetes Mellitus (T2DM) is a chronic metabolic disorder characterized by insulin resistance and hyperglycemia. In India alone, approximately 77 million people suffer from T2DM, with an additional 25 million individuals identified as prediabetic. Obesity, a leading risk factor for T2DM, has emerged as a significant public health concern. Traditional glucose-lowering therapies have shown limited success in addressing both glycemic control and weight management simultaneously. Tirzepatide, a novel dual GIP/GLP-1 receptor agonist, offers a promising solution to this dual challenge.

The burden of diabetes and obesity

Type 2 diabetes mellitus (T2DM) and obesity are interlinked global health challenges, with over 77 million individuals in India diagnosed with T2DM and another 25 million at risk of progression. More than 50% of the diabetic population remains undiagnosed, exacerbating complications. Effective therapies targeting both conditions are urgently needed.¹

Diabetes and obesity are interlinked conditions that significantly increase the risk of cardiovascular disease, renal complications, and other metabolic disorders. Obesity is recognized as a chronic disease with multiple associated complications, including hypertension, dyslipidemia, and obstructive sleep apnea. Evidence suggests that effective weight management can improve overall health outcomes and reduce the incidence of diabetes-related complications.²

Glucose lowering drugs and weight management³

Glucose-lowering drugs play a crucial role in managing Type 2 Diabetes (T2D), with some also aiding in weight reduction. SGLT-2 inhibitors and GLP-1 receptor agonists are particularly beneficial for both glycemic control and weight loss (Figure 1).

The need for innovative pharmacological interventions to manage both conditions has driven the development of incretin-based therapies. Tirzepatide represents a paradigm shift in this context by addressing glycemic control and promoting substantial weight loss.

Dual incretin agonism: Rationale for synergism between GIP and GLP-1

GIP (glucose-dependent insulinotropic polypeptide) and GLP-1 (glucagon-like peptide-1) are physiological incretin hormones—

gut-derived peptides that play a crucial role in glucose homeostasis by stimulating insulin secretion. These hormones exhibit additive effects on insulin secretion, enhancing their overall impact on glucose regulation. Following gastric bypass surgery, the levels of GLP-1 (markedly) and GIP (to a lesser extent) are significantly elevated, contributing to substantial weight loss and the restoration of normoglycemia. Clinical trials investigating a dual GIP/GLP-1 receptor co-agonist have demonstrated notable improvements in glycemic control, with significant reductions in HbA1c and body weight compared to treatment with GLP-1 receptor agonists alone.⁴⁻⁸

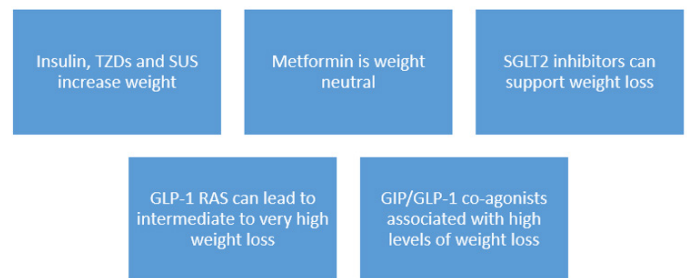


Figure 1 Glucose lowering drugs and weight management.

Mechanism of action

Tirzepatide is a synthetic polypeptide that acts as a dual agonist for GIP and GLP-1 receptors. The drug mimics the physiological effects of these incretin hormones, which play a crucial role in regulating glucose metabolism and appetite (Figure 2).

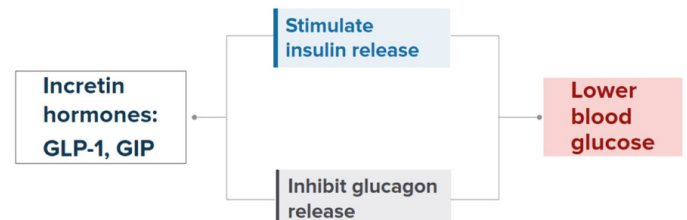


Figure 2 Mechanism of action of GLP-1 and GIP.

Physiological actions of GIP and GLP-1:

- A. GIP (Glucose-dependent insulinotropic polypeptide):**
Enhances insulin secretion in response to meals and promotes lipid metabolism.

B. GLP-1 (Glucagon-Like Peptide-1): Stimulates insulin secretion, inhibits glucagon release, and slows gastric emptying, leading to reduced appetite and food intake.

Tirzepatide: A novel dual GIP and GLP-1 receptor agonist

Molecular attributes⁹

Tirzepatide is a multifunctional peptide derived from the native glucose-dependent insulinotropic polypeptide (GIP) sequence, engineered to bind to both GIP and glucagon-like peptide-1 (GLP-1) receptors. It is a 39-amino acid linear peptide that incorporates a C20 fatty diacid moiety, which enhances its stability and prolongs its duration of action. With a mean half-life of approximately five days, Tirzepatide supports a convenient once-weekly dosing regimen, making it a promising therapeutic option for patients requiring sustained glycemic control.

The dual-incretin action of Tirzepatide leads to:

- 1) Improved glycemic control by enhancing insulin sensitivity.
- 2) Significant weight reduction by suppressing appetite and promoting fat loss.

26-Week Phase 2b Study¹⁰

Tirzepatide (5 mg, 10 mg, and 15 mg) demonstrated significantly lowered HbA1c and body weight compared with placebo or selective GLP-1 RA, dulaglutide 1.5 mg.

Clinical development and trials

The clinical efficacy of Tirzepatide has been extensively studied in the SURPASS (Refer figure 3) and SURMOUNT trial programs.

Trial name	Description
SURPASS-1	Monotherapy Use of Tirzepatide in Adult Patients with Type 2 Diabetes Mellitus
	Tirzepatide Use in Combination with Metformin, Sulfonylureas, and/or SGLT2 Inhibitors in Adult Patients with Type 2 Diabetes Mellitus
SURPASS-2	Add-on to metformin
SURPASS-3	Add-on to metformin with or without SGLT2 inhibitor
SURPASS-4	Add-on to 1-3 oral anti-hyperglycemic agents (metformin, sulfonylurea or SGLT-2 inhibitor)
SURPASS-5	Tirzepatide Use in Combination with Basal Insulin with or without Metformin in Adult Patients with Type 2 Diabetes Mellitus

Figure 3 SURPASS series.

SURPASS clinical trials¹¹⁻¹²

The SURPASS series evaluated the effectiveness of Tirzepatide in patients with type 2 diabetes mellitus (T2DM) across different dosages and patient populations. The trials demonstrated significant reductions in HbA1c levels from baseline to the primary endpoint, highlighting its potent glycemic control. Additionally, Tirzepatide led to unprecedented weight loss, with a substantial proportion of participants achieving more than 5% and even 15% weight reduction. Regarding safety, the most commonly reported adverse events were gastrointestinal in nature, including nausea, vomiting, and diarrhea. These findings underscore tirzepatide's potential as an effective and well-tolerated therapeutic option for T2DM management (Figure 3).

SURPASS program¹¹⁻¹²

A. HbA1c change from baseline to primary endpoint

Summary of the SURPASS trials

The SURPASS program investigates the efficacy of Tirzepatide (TZP) in reducing HbA1c levels across different clinical settings. Below is a breakdown of the primary results from five key SURPASS trials, comparing the efficacy of TZP at varying doses against placebo and active comparators (Figure 4).

Study	Duration	Baseline HbA1c (mmol/mol)	Treatment Regimen	TZP 5 mg	TZP 10 mg	TZP 15 mg	Active Comparator	Placebo
SURPASS-1	40 weeks	7.9 (63)	Monotherapy	-1.87%	-1.89%	-2.07%	N/A	-0.04%
SURPASS-2	40 weeks	8.3 (67)	Add-on to MET	-2.01%	-2.24%	-2.30%	-1.86% (SEMA 1 mg)	N/A
SURPASS-3	52 weeks	8.2 (66)	Add-on to MET or MET + SGLT2i	-1.93%	-2.20%	-2.37%	-1.34% (Insulin degludec)	N/A
SURPASS-4	52 weeks	8.5 (69)	Add-on to MET, SGLT2i, or SU	-2.24%	-2.43%	-2.58%	-1.44% (Insulin glargine)	N/A
SURPASS-5	40 weeks	8.3 (67)	Add-on to insulin glargine ± MET	-2.23%	-2.59%	-2.59%	N/A	-0.93%

Figure 4 Trial overview and HbA1c changes (% HbA1c from baseline).

SURPASS-1: Superiority over placebo. SURPASS-2: Superiority over semaglutide (SEMA) 1 mg. SURPASS-3: Superiority over insulin degludec. SURPASS-4: Superiority over insulin glargine. SURPASS-5: Superiority over placebo when combined with insulin glargine.

Key findings from the trials indicate that tirzepatide demonstrated superiority across all doses compared to both placebo and active comparators in reducing HbA1c levels. The reductions were not only clinically meaningful but also statistically significant, with all p-values being less than 0.001, providing strong evidence of the treatment’s efficacy. These results reinforce Tirzepatide potential as a highly effective therapeutic option for glycemic control in patients with type 2 diabetes mellitus.

B. Weight changes (kg) from baseline.

Key findings from the trials highlight that Tirzepatide demonstrated superior weight reduction compared to both placebo and active comparators across all doses. The weight loss effects were not only clinically significant but also statistically robust, with all p-values being less than 0.001, providing strong evidence of its efficacy in promoting weight reduction. These results underscore Tirzepatide potential as a powerful therapeutic option for both glycemic control and weight management in patients with type 2 diabetes mellitus (Figure 5) (Table 1).

Study	Duration	Baseline Weight (kg)	Treatment Regimen	TZP 5 mg	TZP 10 mg	TZP 15 mg	Active Comparator	Placebo
SURPASS-1	40 weeks	85.9	Monotherapy	-7.0 kg	-7.8 kg	-9.5 kg	N/A	-0.7 kg
SURPASS-2	40 weeks	93.7	Add-on to MET	-8.4 kg	-9.4 kg	-11.2 kg	-5.7 kg (SEMA 1 mg)	N/A
SURPASS-3	52 weeks	94.3	Add-on to MET or MET + SGLT2i	-7.5 kg	-10.7 kg	-12.9 kg	-2.3 kg (Insulin degludec)	N/A
SURPASS-4	52 weeks	90.3	Add-on to MET, SGLT2i, or SU	-7.1 kg	-9.5 kg	-11.7 kg	-1.9 kg (Insulin glargine)	N/A
SURPASS-5	40 weeks	95.3	Add-on to insulin glargine ± MET	-6.2 kg	-8.2 kg	-10.9 kg	N/A	-1.7 kg

Figure 5 Weight changes from baseline from SURPASS 1 to 5.

Table 1 Key efficacy outcomes from surpass trials

Parameter	Results
HbA1c reduction	-2.0% to -2.5%
Proportion achieving HbA1c < 7.0%	80% to 90%
Weight reduction	15% to 20%

Trial overview and adverse events (Prevalence %)

Tirzepatide treatment was associated with higher rates of gastrointestinal side effects, including vomiting, diarrhoea, and nausea, compared to both placebo and active comparators. Among these adverse events, vomiting was most prevalent in the Tirzepatide

15 mg group across all trials. Additionally, diarrhoea incidence increased with higher doses of Tirzepatide, while nausea was more pronounced at elevated doses. These findings suggest a dose-dependent relationship between Tirzepatide and gastrointestinal tolerability, highlighting the need for careful dose titration and patient monitoring (Figure 6).

Study	Duration	Treatment Regimen	TZP 5 mg (%)	TZP 10 mg (%)	TZP 15 mg (%)	Placebo (%)	Active Comparator (%)
SURPASS-1	40 weeks	Monotherapy	10 (Vomiting)	12 (Diarrhea)	15 (Nausea)	5	N/A
SURPASS-2	40 weeks	Add-on to MET	13	17	20	N/A	9 (SEMA 1 mg)
SURPASS-3	52 weeks	Add-on to MET or MET + SGLT2i	14	18	22	N/A	10 (Insulin degludec)
SURPASS-4	52 weeks	Add-on to MET, SGLT2i, or SU	11	15	19	N/A	8 (Insulin glargine)
SURPASS-5	40 weeks	Add-on to insulin glargine ± MET	12	16	21	7	N/A

Figure 6 Trial overview and adverse events (Prevalence %).

SURMOUNT clinical trials

The SURMOUNT trials focused on the use of Tirzepatide for chronic weight management in patients with obesity. The results highlighted long-term weight maintenance and significant reductions in body mass index (BMI).

SURMOUNT-1 Trial of tirzepatide for treatment of obesity¹³

The efficacy summary highlights a steady reduction in body weight over 72 weeks for participants receiving Tirzepatide at doses of 5 mg, 10 mg, and 15 mg once weekly, compared to the placebo group. The data demonstrate a consistent dose-dependent weight loss effect, reinforcing Tirzepatide potential in weight management. Additionally, the confidence intervals are $\pm 95\%$, indicating strong reliability and statistical robustness of the results (Figure 7) (Table 2).

Table 2 SURMOUNT-2: Efficacy¹⁴

Study name	SURMOUNT-2: Efficacy
Baseline Weight	100.7 kg
Mean body weight change at 72 weeks	

Table 2 Continued...

Placebo	-3.3% (-3.2 kg)
Tirzepatide (TZP) 10 mg	-13.4% (-13.5 kg)
Tirzepatide (TZP) 15 mg	-15.7% (-15.6 kg)

The key efficacy results indicate that both Tirzepatide treatment arms demonstrated statistically superior and clinically meaningful weight loss compared to placebo. In the 15 mg treatment arm, participants experienced a mean weight loss of 15.6 kg (34.4 pounds), highlighting the significant impact of the therapy. Additionally, both Tirzepatide treatment arms achieved an average weight loss of approximately 30 pounds or more, reinforcing its potential as an effective option for weight management.

SURMOUNT-3¹⁵

Investigated the effect of Tirzepatide after successful intensive lifestyle intervention in adults with overweight or obesity. Participants who achieved $\geq 5\%$ weight reduction during a 12-week lifestyle program were randomized to Tirzepatide or placebo for 72 weeks. The study found that tirzepatide led to a significant additional mean weight reduction of -18.4% compared to a 2.5% increase with placebo. A high percentage of participants on Tirzepatide (87.5%) achieved an additional $\geq 5\%$ weight loss. The combination of intensive lifestyle

intervention followed by tirzepatide resulted in a total weight change of -24.3%. The most common adverse events with tirzepatide were gastrointestinal and mostly mild to moderate. These findings suggest

that tirzepatide can provide substantial additional weight loss after initial success with lifestyle intervention.

Treatment Regimen	Change in Body Weight (%)	Overall Mean Baseline Weight	Efficacy Estimand
Tirzepatide 5 mg OW	-15	104.8 kg	Significant reduction in body weight compared to placebo
Tirzepatide 10 mg OW	-19.5	104.8 kg	Greater reduction in body weight compared to placebo
Tirzepatide 15 mg OW	-20.9	104.8 kg	Most significant reduction in body weight
Placebo OW	-3.1	104.8 kg	Minimal weight reduction

Figure 7 Change in Body Weight from Baseline to Week 72 (Co-Primary Endpoint).

SURMOUNT-4¹⁶

This phase 3 randomized withdrawal trial evaluated Tirzepatide’s effect on maintaining weight loss in adults with obesity or overweight. After a 36-week open-label lead-in period with once-weekly Tirzepatide (10 or 15 mg), 670 participants were randomized to continue Tirzepatide or switch to placebo for 52 weeks. By week 88, those continuing Tirzepatide had an additional 5.5% weight reduction,

while those on placebo regained 14% of their weight (difference: -19.4%, $P < .001$). Notably, 89.5% of Tirzepatide users maintained at least 80% of prior weight loss vs. 16.6% on placebo. The total weight reduction from baseline was 25.3% with tirzepatide vs. 9.9% with placebo. Mild to moderate gastrointestinal events were the most common adverse effects.

Comparison of GLP-1 receptor agonist in relation to weight loss(Refer figure 8)

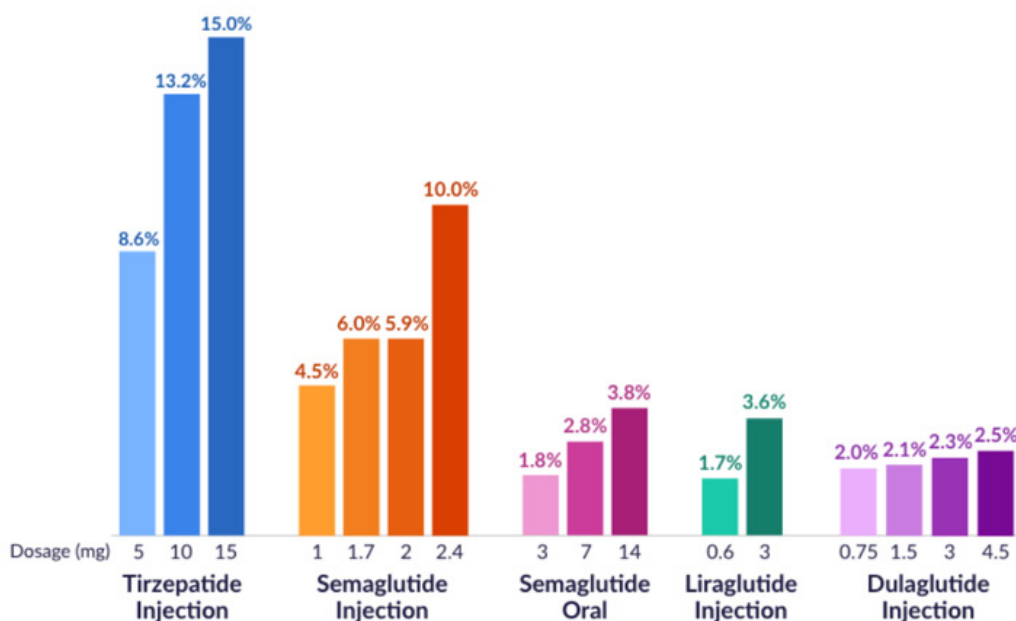


Figure 8 Patients' median weight loss by the peak dosage of the GLP-1 receptor agonist prescribed within the year of starting.¹⁷

Tirzepatide: Approval and Indications

Tirzepatide, marketed under the brand names **Mounjaro** and **Zepbound**, has received regulatory approval in several countries, including the United States, European Union, and India.

Approved indications^{18,19}

- 1) Mounjaro:** Approved for improving glycemic control in adults with T2DM as an adjunct to diet and exercise. (Limitations of Use: Has not been studied in patients with a history of pancreatitis. Is not indicated for use in patients with type 1 diabetes mellitus)
- 2) Zepbound:** Approved for chronic weight management in adults with obesity or overweight conditions accompanied by at least one weight-related comorbidity.

Available as 2.5 mg, 5 mg, 7.5 mg, 10 mg, 12.5 mg, or 15 mg per 0.5 mL in single-dose pen as well as in vial form (Table 3).

Table 3 Dosage recommendations^{18,19}

Dosage	Administration
2.5 mg/week	Starting dose
5 mg/week	After 4 weeks
7.5 to 15 mg/week	Incremental increase based on response

The maximum dosage is 15 mg subcutaneously once weekly. It should be administered at any time of the day, with or without meals. The injection can be given subcutaneously in the abdomen, thigh, or

Table 4 Ongoing clinical trials on tirzepatide for obesity management

Study	Indication	Title	Phase	Patients	Primary Outcome	Primary Completion	Completion
NCT05822830	Obesity	A Study of Tirzepatide (LY3298176) in Participants with Obesity or Overweight With Weight-Related Comorbidities (SURMOUNT-5)	3	700	Percent Change from Baseline in Body Weight	24-Nov	24-Nov
NCT06047548	Obesity	A Study of Tirzepatide (LY3298176) For the Maintenance of Body Weight Reduction in Participants Who Have Obesity or Overweight With Weight-Related Comorbidities (SURMOUNT-MAINTAIN)	3	400	Percent Maintenance of Body Weight (BW) Reduction Achieved During the 60-Week Weight Loss Period	26-May	26-May
NCT06075667	Obesity	A Study of Tirzepatide (LY3298176) Once Weekly in Adolescent Participants Who Have Obesity or Overweight with Weight-Related Comorbidities (SURMOUNT-ADOLESCENTS)	3	150	Percent Change from Baseline in Body Mass Index (BMI)	26-Oct	26-Oct
NCT06439277	Obesity	A Study of Tirzepatide in Adolescents With Obesity and Weight-Related Comorbidities (SURMOUNT-ADOLESCENTS-2)	3	300	Percent Change from Baseline in Body Mass Index (BMI)	27-May	27-Jun
NCT05556512	Obesity	A Study of Tirzepatide (LY3298176) on the Reduction on Morbidity and Mortality in Adults With Obesity (SURMOUNT-MMO)	3	15374	Time to First Occurrence of Any Component Event of Composite (All-Cause Death, Nonfatal Myocardial Infarction (MI), Nonfatal Stroke, Coronary Revascularization, or Heart Failure Events)	27-Oct	27-Oct

upper arm, and it is important to rotate injection sites with each dose to minimize the risk of irritation or tissue damage.

Adverse events and safety considerations^{18,19}

While Tirzepatide has demonstrated remarkable efficacy, it is essential to monitor for potential adverse events. Commonly reported side effects include nausea, vomiting, diarrhea, and reduced appetite. Regular monitoring and appropriate management can help mitigate these effects and enhance treatment adherence. Tirzepatide is not recommended for patients with a history of pancreatitis and is not indicated for use in individuals with type 1 diabetes mellitus. Careful patient selection and monitoring are essential to ensure safe and effective treatment.

On December 20, 2024, the U.S. Food and Drug Administration (FDA) approved Zepbound (tirzepatide) as the first prescription medication for treating moderate to severe obstructive sleep apnea (OSA) in adults with obesity. This approval recommends using Zepbound in conjunction with a reduced-calorie diet and increased physical activity.²⁰

Ongoing clinical trials on tirzepatide for obesity management

The following table provides an overview of the ongoing Phase 3 clinical trials for Tirzepatide in obesity management, highlighting the study identifiers, indications, titles, patient numbers, primary outcomes, and expected completion dates (Table 4).²¹

Ongoing clinical trials on tirzepatide for type 2 diabetes and chronic kidney disease.²¹

The following table outlines the ongoing clinical trials evaluating

Tirzepatide for the management of Type 2 Diabetes (T2D) and Chronic Kidney Disease (CKD). The table summarizes the study identifiers, indications, titles, number of patients, primary outcomes, and estimated completion timelines (Table 5).

Table 5 Ongoing clinical trials on tirzepatide for type 2 diabetes and chronic kidney disease

Study	Indication	Title	Phase	Patients	Primary outcome	Primary completion	Completion
NCT05260021	Type 2 Diabetes	A Study to Evaluate Tirzepatide (LY3298176) in Pediatric and Adolescent Participants With Type 2 Diabetes Mellitus Inadequately Controlled With Metformin or Basal Insulin or Both (SURPASS-PEDS)	3	99	Change From Baseline in Hemoglobin A1c (HbA1c)	24-Aug	25-Feb
NCT04255433	Type 2 Diabetes	A Study of Tirzepatide (LY3298176) Compared With Dulaglutide on Major Cardiovascular Events in Participants With Type 2 Diabetes (SURPASS-CVOT)	3	13299	Time to First Occurrence of Death from Cardiovascular (CV) Causes, Myocardial Infarction (MI), or Stroke (MACE-3)	25-Jun	25-Jun
NCT06037252	Type 2 Diabetes	A Study of Investigational Tirzepatide (LY3298176) Doses in Participants With Type 2 Diabetes and Obesity	2	350	Percent Change From Baseline in Body Weight	26-Jan	26-Oct
NCT05536804	CKD	A Study of Tirzepatide (LY3298176) in Participants With Overweight or Obesity and Chronic Kidney Disease With or Without Type 2 Diabetes (TREASURE-CKD)	2	140	Change From Baseline in Kidney Oxygenation in Participants With or Without T2D [Time Frame: Baseline, Week 52]; Blood Oxygenation-Level Dependent Magnetic Resonance Imaging (BOLD MRI)	26-Jan	26-Feb

Real-world impact and future perspectives

The introduction of Tirzepatide represents a significant advancement in managing Type 2 Diabetes (T2DM) and obesity. Its dual-action mechanism effectively addresses unmet needs by providing both glycemic control and sustainable weight loss. Future research should explore its long-term cardiovascular outcomes, impact on diabetes-related complications, and real-world evidence to validate clinical trial findings.

Conclusion

Tirzepatide represents a novel approach to managing T2DM and obesity, offering superior efficacy in reducing HbA1c levels and achieving substantial weight loss. With its dual-incretin action and favorable safety profile, Tirzepatide is poised to transform the therapeutic landscape for metabolic disorders. Ongoing research and real-world evidence will further solidify its role as a game-changer in diabetes and obesity management.

Acknowledgement

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Conflict of interest

The author declares that conflicts of interest do not exist.

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