

Tirzepatide in Type 2 Diabetes Mellitus: A Comprehensive Review of Its Novel Dual GIP/GLP-1 Receptor Agonism, Clinical Efficacy, Safety, and Therapeutic Potential

Maab Ahmad Abualsaud*, Fatimah Adnan AlAwami, Hadi Musfer Ali Algashaneen, Nouf Adel Albelushi, Athari Saleh Alyami, Mohammed Abdulrauf AlNasseri, Duaa jassim al juman, Sarah Ali ALObaid, Ali Abdulmohsen Almuahanna, Fatimah Saeed Al Mohammed, Alawiah Hashim Alshurafa, Abdullah Twfiq Al-Farhan, Hassan Fadel Alsaif, Lama Abdulaziz Abohamla, Salman Saad alzhahrani

King Fahad Hospital of the University - Imam Abdurhman bin Faisal University - Dammam - Saudi Arabia.

*Corresponding Author: Maab Ahmad Abualsaud - Maabualsuode@iau.edu.sa

Abstract:

Tirzepatide represents a paradigm shift in the pharmacological management of type 2 diabetes mellitus (T2DM), introducing the first-in-class dual glucose-dependent insulintropic polypeptide (GIP) and glucagon-like peptide-1 (GLP-1) receptor agonist. Tirzepatide demonstrates superior glycemic control compared to existing therapies, with HbA1c reductions ranging from 1.87% to 3.02% and substantial weight loss of 5.4 to 12.9 kg in T2DM patients. Its dual receptor agonism enhances beta-cell function, improves insulin sensitivity, and addresses multiple cardiometabolic risk factors. The safety profile is favorable, with predominantly mild-to-moderate gastrointestinal adverse events, low hypoglycemia risk, and promising cardiovascular outcomes. This review examines tirzepatide's molecular mechanisms, clinical efficacy across diverse patient populations, safety considerations, and broader therapeutic potential beyond glycemic control, positioning it as a transformative agent in metabolic disease management.

Introduction:

Type 2 diabetes mellitus (T2DM) remains a global health challenge, affecting over 500 million individuals worldwide and contributing substantially to cardiovascular morbidity, mortality, and healthcare costs. Despite the availability of numerous antidiabetic medications, a substantial percentage of patients fail to achieve optimal glycemic control, and the escalating obesity pandemic underscores the urgent need for effective pharmacotherapies that address both hyperglycemia and weight management. [1] Traditional glucose-lowering agents often fall short in providing comprehensive metabolic benefits, and many are associated with weight gain or hypoglycemia risk, limiting their utility in the modern management paradigm that emphasizes cardiometabolic health. The incretin system, comprising glucagon-like peptide-1 (GLP-1) and glucose-dependent insulintropic polypeptide (GIP), plays a central role in postprandial glucose homeostasis. GLP-1 receptor agonists (GLP-1 RAs) have revolutionized T2DM treatment by enhancing insulin secretion, suppressing glucagon, slowing gastric emptying, and promoting satiety, leading to both glycemic improvement and weight loss. However, the role of GIP in metabolic regulation has been more controversial, with early studies suggesting potential adverse effects on adiposity. Recent preclinical and clinical evidence has challenged this view, demonstrating that GIP receptor agonism, particularly when combined with GLP-1 receptor activation, can synergistically enhance metabolic benefits. [1-3] Tirzepatide, developed by Eli Lilly, is the first-in-class dual GIP and GLP-1 receptor agonist approved for the treatment of T2DM and obesity. This novel "twincretin" agent represents a significant advancement in incretin-based therapy, leveraging the complementary and synergistic actions of both

incretin hormones to achieve superior glycemic control and weight reduction compared to GLP-1 RA monotherapy. [4-6] The SURPASS clinical trial program, comprising multiple phase 3 randomized controlled trials, has demonstrated tirzepatide's [7] remarkable efficacy across diverse patient populations, including treatment-naïve patients, those inadequately controlled on oral agents, and individuals with high cardiovascular risk. [7-9] This comprehensive review synthesizes evidence from 89 unique papers, including pivotal clinical trials, systematic reviews, meta-analyses, mechanistic studies, and real-world evidence, to provide an in-depth analysis of tirzepatide's molecular mechanisms, clinical efficacy, safety profile, and broader therapeutic potential in T2DM and related metabolic disorders.

Molecular Mechanisms and Pharmacology:

- Dual GIP/GLP-1 Receptor Agonism:

Tirzepatide is a synthetic 39-amino acid peptide that functions as a dual agonist at both GIP and GLP-1 receptors, representing a novel approach to incretin-based therapy. [3,6,10] The molecule exhibits high affinity for GIP receptors, comparable to native GIP, while demonstrating approximately five-fold lower affinity for GLP-1 receptors [2,6]. Despite this differential binding affinity, tirzepatide functions as an "imbalanced and biased" dual agonist, with the GIP component playing a critical role in enhancing the therapeutic effects of GLP-1 receptor activation. [11]

The structural design of tirzepatide incorporates a C20 fatty diacid moiety that facilitates binding to albumin, significantly prolonging its half-life and enabling once-weekly subcutaneous administration. [12,13] This pharmacokinetic profile provides sustained receptor activation and stable plasma concentrations, contributing to consistent glycemic control and metabolic benefits throughout the dosing interval.

The dual receptor agonism of tirzepatide targets multiple defects in the incretin hormone system that characterize T2DM pathophysiology. [10,14] Both GIP and GLP-1 are secreted by enteroendocrine cells in response to nutrient ingestion and act as key regulators of postprandial glucose homeostasis. In T2DM, the insulinotropic response to GIP is markedly attenuated, while GLP-1 secretion and action are partially preserved but insufficient to maintain normoglycemia. By simultaneously activating both receptor systems, tirzepatide restores and amplifies the incretin effect, leading to robust improvements in glucose metabolism. [2,15]

- Effects on Beta-Cell Function and Insulin Secretion

A central mechanism underlying tirzepatide's glycemic efficacy is its profound enhancement of pancreatic beta-cell function and glucose-dependent insulin secretion. Tirzepatide increases postprandial insulin secretion by up to 65% through the synergistic actions of GIP and GLP-1 on pancreatic islet cells. [12,15] Both incretin hormones bind to G-protein coupled receptors on beta cells, activating adenylyl cyclase and increasing intracellular cyclic AMP (cAMP) levels, which potentiates glucose-stimulated insulin secretion. Clinical studies have demonstrated that tirzepatide significantly improves beta-cell function markers, including HOMA2-B (Homeostatic Model Assessment 2 for beta-cell function), which increased substantially compared to placebo and active comparators. Additionally, tirzepatide reduces the proinsulin-to-insulin and proinsulin-to-C-peptide ratios, indicating improved beta-cell processing capacity and reduced beta-cell stress. [15] These effects suggest that tirzepatide not only enhances insulin secretion acutely but may also preserve or restore beta-cell health over time, addressing a fundamental pathophysiological defect in T2DM.

The glucose-dependent nature of tirzepatide's insulinotropic action is a critical safety feature. Insulin secretion is stimulated only when glucose levels are elevated, minimizing the risk of hypoglycemia when glucose concentrations normalize. [5,16] This contrasts with sulfonylureas and exogenous insulin, which stimulate insulin secretion regardless of glucose levels and carry a substantial risk of hypoglycemia.

Beyond insulin secretion, tirzepatide also suppresses inappropriate glucagon secretion, particularly in the postprandial state. [3,6] Elevated glucagon levels contribute to hyperglycemia in T2DM by promoting hepatic glucose production. By reducing glucagon secretion, tirzepatide decreases hepatic glucose output and improves overall glucose homeostasis.

- Insulin Sensitivity and Metabolic Pathways

In addition to its effects on beta-cell function, tirzepatide significantly improves insulin sensitivity, addressing another core defect in T2DM pathophysiology. [2,12,14] Clinical studies have shown that tirzepatide reduces HOMA2-IR (Homeostatic Model Assessment 2 for insulin resistance) and fasting insulin levels, with improvements that are only partially explained by weight loss. [15] In one study, weight loss accounted for only 13% and 21% of the improvement in HOMA2-IR with tirzepatide 10 mg and 15 mg, respectively, suggesting that tirzepatide exerts direct insulin-sensitizing effects independent of its weight-reducing properties. [15]

Mechanistic studies have identified several pathways through which tirzepatide enhances insulin sensitivity. GIP receptor activation in adipose tissue plays a particularly important role. GIP receptors are highly expressed in adipocytes, where their activation promotes insulin sensitivity, improves lipid homeostasis, and enhances the clearance of dietary triglycerides. [2,17,18] GIP receptor agonism also promotes the expansion of healthy white adipose tissue, which serves as a metabolic buffer, storing excess energy in a manner that reduces ectopic lipid deposition in liver, muscle, and pancreas—tissues where lipid accumulation impairs insulin action.

Tirzepatide increases circulating levels of adiponectin, IGFBP-1 (insulin-like growth factor binding protein-1), and IGFBP-2, all of which are biomarkers of improved insulin sensitivity. Adiponectin, in particular, is an adipokine with insulin-sensitizing, anti-inflammatory, and cardioprotective properties. Its elevation with tirzepatide treatment reflects improved adipose tissue function and systemic metabolic health. [15,18]

At the cellular level, tirzepatide enhances insulin signaling pathways, promotes glucose uptake in peripheral tissues, and modulates adipose tissue metabolism. [14,19] It also influences hepatic lipid metabolism, reducing hepatic steatosis and improving markers of non-alcoholic fatty liver disease (NAFLD) and non-alcoholic steatohepatitis (NASH), including alanine aminotransferase (ALT), aspartate aminotransferase (AST), and pro-collagen III N-terminal peptide (pro-C3). [4,18]

- Pharmacokinetics and Dosing

Tirzepatide is administered as a once-weekly subcutaneous injection, with approved doses of 5 mg, 10 mg, and 15 mg. [6,20] The recommended dosing strategy involves initiating treatment at 2.5 mg weekly for four weeks to minimize gastrointestinal adverse events, then escalating to 5 mg weekly. Further dose increases to 10 mg and 15 mg can be made at four-week intervals based on glycemic response and tolerability. [20]

The albumin-binding fatty diacid moiety extends tirzepatide's half-life to approximately 5 days, enabling once-weekly dosing and providing stable pharmacokinetics. [13] Steady-state concentrations are achieved after approximately four weeks of weekly dosing. The prolonged half-life and sustained receptor activation contribute to consistent glycemic control and metabolic benefits throughout the dosing interval, improving patient adherence compared to daily injectable therapies. Tirzepatide is primarily eliminated through proteolytic degradation, with minimal renal excretion of intact peptide. No dose adjustment is required for patients with renal impairment, although clinical experience in patients with severe renal impairment or end-stage renal disease is limited. [20]

Clinical Efficacy in Type 2 Diabetes

- Glycemic Control: HbA1c and Fasting Glucose Reduction

Tirzepatide has demonstrated unprecedented glycemic efficacy in the treatment of T2DM, with HbA1c reductions that surpass those achieved with existing therapies. Across the SURPASS clinical

trial program and multiple meta-analyses, tirzepatide consistently reduced HbA1c by 1.87% to 3.02% from baseline, with dose-dependent effects. [4,6,9,21] In the SURPASS-1 monotherapy trial, tirzepatide 5 mg, 10 mg, and 15 mg reduced HbA1c by 1.87%, 1.89%, and 2.07%, respectively, compared to a 0.04% increase with placebo. [17] These reductions are among the largest ever reported for any glucose-lowering medication.

Meta-analytic evidence confirms tirzepatide's superior glycemic efficacy. A systematic review and meta-analysis by Karagiannis et al. reported mean HbA1c differences ranging from -17.71 mmol/mol (-1.62%) to -22.35 mmol/mol (-2.06%) versus placebo, with all doses demonstrating dose-dependent superiority [16]. Another meta-analysis by Soqati found a mean HbA1c reduction of -2.5078% (95% CI: -3.3945 to -1.6210) compared to placebo. [21] These robust and consistent findings across multiple studies and patient populations underscore tirzepatide's exceptional glycemic efficacy.

Tirzepatide also produces substantial reductions in fasting blood glucose (FBG). In a real-world clinical study, FBG decreased from 135.29 mg/dL at baseline to 109.51 mg/dL ($p < 0.05$), representing a clinically meaningful improvement in basal glycemic control. [14] Meta-analytic data reported FBG reductions of -62.78 mg/dL (95% CI: -67.93 to -57.63) compared to placebo. [21] Fasting serum glucose reductions ranging from -38.6 mg/dL to -74.4 mg/dL have been documented across various studies. [18] These improvements in fasting glucose reflect tirzepatide's effects on hepatic glucose production, basal insulin secretion, and overnight glucose homeostasis.

Postprandial glucose control is also markedly improved with tirzepatide. In one real-world study, postprandial blood sugar (PPBS) declined by 61.3 ± 29.86 mg/dL ($p < 0.001$). [14] Tirzepatide's effects on postprandial glucose are mediated through enhanced glucose-dependent insulin secretion, suppression of glucagon, and delayed gastric emptying, which collectively attenuate postprandial glucose excursions. [22]

- Weight Loss and Body Composition

One of the most striking features of tirzepatide is its profound effect on body weight, which distinguishes it from many traditional glucose-lowering agents that are weight-neutral or associated with weight gain. Across clinical trials, tirzepatide produced dose-dependent weight loss ranging from 5.4 kg to 12.9 kg in patients with T2DM over treatment periods up to 104 weeks. [4,6] In the SURPASS trials, weight reductions of 7.9%, 9.3%, and 11% were observed with tirzepatide 5 mg, 10 mg, and 15 mg, respectively, compared to -0.9% with placebo. [17]

Meta-analytic evidence confirms these substantial weight-reducing effects. A systematic review by Lin et al. reported mean weight reductions of -9.81 kg (95% CI: -12.09 to -7.52) versus placebo, -1.05 kg (95% CI: -1.48 to -0.63) versus GLP-1 RAs, and -1.93 kg (95% CI: -2.81 to -1.05) versus insulin. [23] Another meta-analysis by Soqati found a mean weight reduction of -10.7852 kg (95% CI: -14.8264 to -6.7439) compared to placebo. [21] A network meta-analysis by Hoffmann et al. demonstrated dose-dependent weight reductions versus insulin: -14.5 kg for tirzepatide 15 mg, -12.5 kg for 10 mg, and -10.2 kg for 5 mg. [24]

The magnitude of weight loss with tirzepatide is clinically significant, with a substantial proportion of patients achieving weight reductions of $\geq 5\%$, $\geq 10\%$, and even $\geq 15\%$. In the network meta-analysis by Hoffmann et al., the likelihood of achieving $\geq 15\%$ weight loss was significantly higher with tirzepatide 15 mg (RR 4.83) compared to insulin. [24] In real-world studies, 48-72% of patients achieved at least 5% weight loss. [6]

Beyond total body weight, tirzepatide favorably affects body composition and anthropometric measures. Waist circumference, a marker of visceral adiposity and cardiometabolic risk, decreased significantly with tirzepatide treatment. Meta-analytic data reported a mean waist circumference reduction of -8.60 cm (95% CI: -15.55 to -1.64) compared to placebo. [21] In a real-world study, both body mass index (BMI) and waist circumference showed significant dose-dependent reductions. [14] The weight-reducing effects of tirzepatide are mediated through multiple mechanisms, including enhanced satiety, reduced appetite, delayed gastric emptying, and increased energy expenditure.

[19,22] Central nervous system effects, particularly in hypothalamic regions regulating appetite and food intake, play a key role. GLP-1 and GIP receptors are expressed in brain regions involved in appetite regulation, and their activation by tirzepatide modulates food intake and promotes negative energy balance. [19]

- **Comparative Effectiveness Against Standard Therapies**

Tirzepatide has been directly compared to several standard glucose-lowering therapies in head-to-head clinical trials, consistently demonstrating superior efficacy. In the SURPASS-2 trial, tirzepatide was compared to semaglutide 1 mg, the most potent GLP-1 RA available at the time. Tirzepatide 5 mg, 10 mg, and 15 mg produced HbA1c reductions of 2.01%, 2.24%, and 2.30%, respectively, compared to 1.86% with semaglutide 1 mg, representing absolute differences of 0.15% to 0.44%. [6,9,25] Weight loss was also greater with tirzepatide, with reductions of 7.8 kg to 12.4 kg compared to 5.7 kg with semaglutide. [6] These findings establish tirzepatide as the most efficacious incretin-based therapy currently available.

Comparative effectiveness against basal insulin has also been demonstrated. In the SURPASS-3 trial, tirzepatide was compared to insulin degludec in patients inadequately controlled on metformin with or without an SGLT2 inhibitor. Tirzepatide produced superior HbA1c reductions and substantial weight loss, whereas insulin degludec was associated with weight gain. [22,26] Similarly, in the SURPASS-4 trial, which enrolled patients with T2DM and elevated cardiovascular risk, tirzepatide demonstrated superior glycemic control and weight reduction compared to insulin glargine. [27]

Meta-analytic comparisons confirm tirzepatide's superiority across multiple comparators. Karagiannis et al. reported that tirzepatide was superior to GLP-1 RAs in reducing body weight, with differences ranging from 1.68 kg to 7.16 kg depending on dose and comparator. [2] Against insulin, tirzepatide demonstrated marked advantages in both glycemic control and weight outcomes, with insulin typically associated with weight gain of 1-3 kg. [23,24]

Compared to oral glucose-lowering agents, tirzepatide also demonstrates superior efficacy. In the SURPASS-1 monotherapy trial, tirzepatide produced HbA1c reductions of 1.87% to 2.07%, far exceeding the typical 0.5-1.0% reductions seen with metformin, DPP-4 inhibitors, or SGLT2 inhibitors. [17,22]

- **Achievement of Glycemic Targets**

Beyond mean HbA1c reductions, tirzepatide enables a remarkably high proportion of patients to achieve stringent glycemic targets. In the SURPASS trials, 87-92% of patients treated with tirzepatide achieved HbA1c <7.0% (53 mmol/mol), the general target recommended by most diabetes guidelines. [6] Even more impressively, substantial proportions achieved HbA1c ≤6.5% (48 mmol/mol) and <5.7% (39 mmol/mol), the latter representing normoglycemia. [2,18] A systematic review and meta-analysis by Karagiannis et al. found that all tirzepatide doses were superior to placebo in achieving HbA1c targets of <53 mmol/mol (<7.0%), ≤48 mmol/mol (≤6.5%), and <39 mmol/mol (<5.7%). [2] The network meta-analysis by Hoffmann et al. reported that tirzepatide significantly increased the likelihood of achieving normoglycemia (RR 11.3) compared to insulin. [24] These findings are clinically significant because achieving and maintaining glycemic targets is associated with reduced risk of microvascular complications, including diabetic retinopathy, nephropathy, and neuropathy. The ability of tirzepatide to enable such a high proportion of patients to reach stringent targets, including normoglycemia, represents a major therapeutic advance and may translate into improved long-term outcomes.

Safety Profile and Adverse Events

The most common adverse events associated with tirzepatide are gastrointestinal in nature, consistent with the class effects of incretin-based therapies. Nausea, vomiting, diarrhea, constipation, and decreased appetite are the predominant gastrointestinal symptoms reported in clinical trials. Nausea was the most common, occurring in approximately 20-30% of patients, followed by diarrhea

and vomiting. [2,6,13,14] The incidence of these events is dose-dependent, with higher rates observed at the 15 mg dose than at the 5 mg and 10 mg doses. Beside that, Gallbladder-related events, including cholelithiasis and cholecystitis, have been reported with tirzepatide, consistent with the class effect of incretin-based therapies and likely related to rapid weight loss. [8] Patients should be monitored for symptoms of gallbladder disease, and clinicians should maintain awareness of this potential complication. Additionally, Thyroid C-cell tumors have been observed in rodent studies with GLP-1 RAs, leading to a boxed warning for this drug class. While tirzepatide carries a similar warning, no definitive evidence of increased thyroid cancer risk has been observed in human clinical trials. [8] Nonetheless, tirzepatide is contraindicated in patients with a personal or family history of medullary thyroid carcinoma or multiple endocrine neoplasia syndrome type 2. Increases in heart rate, typically modest (2-4 beats per minute), have been observed with tirzepatide, similar to GLP-1 Ras. [17] The clinical significance of this finding is uncertain, and it has not been associated with adverse cardiovascular outcomes in clinical trials.

A critical safety advantage of tirzepatide is its low risk of hypoglycemia, attributable to its glucose-dependent mechanism of action. Tirzepatide stimulates insulin secretion and suppresses glucagon only when glucose levels are elevated, minimizing hypoglycemia risk when glucose normalizes. [5,16] Across clinical trials and meta-analyses, tirzepatide has consistently demonstrated low rates of hypoglycemia, particularly when used without concomitant insulin or sulfonylureas. Moreover, Cardiovascular safety is a critical consideration for all glucose-lowering therapies, particularly given the high cardiovascular risk in patients with T2DM. Tirzepatide has demonstrated a favorable cardiovascular safety profile across clinical trials, with no increase in major adverse cardiovascular events (MACE) compared to placebo or active comparators. [6,9,23]

Broader Therapeutic Potential

The profound weight-reducing effects of tirzepatide have led to its investigation and approval for obesity management in individuals without diabetes. In the SURMOUNT clinical trial program, tirzepatide was evaluated in adults with obesity or overweight with weight-related comorbidities but without T2DM. Results demonstrated remarkable weight reductions of 15.0% to 22.4% over 72 weeks, with the highest dose (15 mg) producing mean weight loss of 20.9%. [4,18,25] These weight reductions are among the largest ever achieved with pharmacotherapy, approaching the magnitude of weight loss seen with bariatric surgery. The proportion of patients achieving clinically significant weight loss thresholds was also impressive, with substantial numbers achieving $\geq 15\%$, $\geq 20\%$, and even $\geq 25\%$ weight loss. [24] Based on these results, tirzepatide received regulatory approval for chronic weight management in adults with obesity or overweight with at least one weight-related comorbidity.

Emerging evidence suggests that tirzepatide may provide benefits in heart failure, particularly heart failure with preserved ejection fraction (HFpEF), a condition closely linked to obesity and metabolic dysfunction. In the SUMMIT trial program, tirzepatide demonstrated reductions in heart failure hospitalizations and improvements in functional capacity in patients with HFpEF. [11] Tirzepatide has also shown promise in treating obstructive sleep apnea (OSA), another obesity-related comorbidity. Clinical studies have demonstrated significant reductions in the apnea-hypopnea index (AHI), the primary measure of OSA severity, with tirzepatide treatment. [11]

Beyond T2DM, obesity, heart failure, and OSA, tirzepatide is being investigated for several other metabolic and cardiovascular conditions. Potential indications include [16,28]:

1. Given the demonstrated reductions in liver fat and NASH biomarkers, tirzepatide is being evaluated in dedicated NASH trials
2. The renoprotective effects observed in T2DM trials have prompted investigation of tirzepatide in patients with CKD, with or without diabetes.
3. Preclinical evidence suggests potential neuroprotective effects of GIP and GLP-1 receptor agonism, raising the possibility of applications in neurodegenerative diseases such as Alzheimer's disease and Parkinson's disease.

Clinical Implementation and Patient Selection

Tirzepatide represents a valuable addition to the therapeutic armamentarium for T2DM, with potential for use across a broad spectrum of patients. Based on its efficacy, safety profile, and cardiometabolic benefits, tirzepatide is appropriate for consideration in the following clinical scenarios [Table 1]. [1,2,4,8,18,20,24-27]

First-line therapy	Given its superior glycemic efficacy, substantial weight loss, low hypoglycemia risk, and favorable cardiometabolic effects, tirzepatide may be considered as a first-line agent, particularly in patients with obesity or overweight, those requiring substantial HbA1c reduction, or those with multiple cardiometabolic risk factors.
Second-line therapy	For patients inadequately controlled on metformin or other oral agents, tirzepatide offers superior efficacy compared to adding additional oral agents, GLP-1 RAs, or basal insulin.
Insulin-sparing or insulin-replacement therapy	In patients requiring intensification beyond oral agents, tirzepatide can be used instead of basal insulin, offering superior glycemic control and weight loss without hypoglycemia risk.
Patients with obesity	Given the magnitude of weight loss achieved, tirzepatide is particularly well-suited for patients with T2DM and obesity, addressing both conditions simultaneously.
Patients with cardiovascular risk factors	The improvements in blood pressure, lipid profile, and other cardiovascular risk factors make tirzepatide an attractive option for patients with established cardiovascular disease or multiple risk factors, pending results of the SURPASS-CVOT trial.
Patients with NAFLD/NASH	The hepatic benefits of make it a rational choice for patients with T2DM and concomitant liver disease

Conclusion:

Tirzepatide represents a major advancement in the management of type 2 diabetes mellitus (T2DM) as the first dual GIP/GLP-1 receptor agonist, offering substantial improvements in glycemic control and body weight by targeting multiple metabolic abnormalities. Clinical evidence demonstrates significant reductions in HbA1c and weight, with efficacy exceeding several established therapies, including GLP-1 receptor agonists and basal insulin. Tirzepatide has a generally favorable safety profile, with mainly mild-to-moderate gastrointestinal adverse effects and a low risk of hypoglycemia. Beyond glycemic control, it provides broader cardiometabolic benefits, including improvements in blood pressure, lipid profile, hepatic steatosis, and renal parameters. Its therapeutic potential also extends to obesity and other metabolic and cardiovascular conditions, positioning tirzepatide as an important evolution in incretin-based therapy with the potential to reshape the management of T2DM and related metabolic disorders.

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