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REVIEW

Insights into the Mechanism of Action of Tirzepatide: A Narrative Review

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ABSTRACT

Tirzepatide is the first dual long-acting glucose-dependent insulinotropic polypeptide receptor and glucagon-like peptide-1 receptor agonist indicated for the treatment of type 2 diabetes in adults, for reducing excess body weight and maintaining long-term weight reduction in adults with obesity or overweight and at least one weight-related comorbid condition, and for treating obstructive sleep apnea in adults with obesity. Recent studies found beneficial effects on heart failure with preserved ejection fraction and on metabolic dysfunction–associated steatohepatitis; its effects on cardiovascular outcomes in people with type 2 diabetes, as well as on reducing morbidity and mortality in people with obesity/overweight, remain under investigation. Here, we review the mechanistic activity of tirzepatide and its effect on glycemic control, body weight, the cardiorenal system, and lipid metabolism.

Keywords: Obesity/overweight; Tirzepatide; Type 2 diabetes

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Key Summary Points

Tirzepatide is a first-in-class, single-molecule, dual glucose-dependent insulinotropic polypeptide receptor agonist and glucagon-like peptide-1 receptor agonist.

Tirzepatide is approved for the treatment of diabetes, weight management, and obstructive sleep apnea.

Tirzepatide is under investigation for the treatment of multiple other cardio–kidney–metabolic diseases.

Tirzepatide has pleiotropic effects due to its diverse mechanisms of action on glycemic control, body weight regulation, the cardiorenal system, and lipid metabolism, and is thus hypothesized to provide benefit in many diseases.

INTRODUCTION

Tirzepatide is a long-acting glucose-dependent insulinotropic polypeptide (GIP) receptor agonist (GIPRA) and glucagon-like peptide-1 (GLP-1) receptor agonist (GLP-1RA). It has an amino acid sequence with a C20 fatty diacid moiety (Fig. 1) that enables albumin binding and prolongs the half-life. Tirzepatide selectively binds to and activates both the GIP and GLP-1 receptors, the targets for native GIP and GLP-1 (Fig. 2). The prolonged half-life allows for once-weekly administration in humans [1]. Importantly, GIP receptors (GIPR) and GLP-1 receptors (GLP-1R) are expressed in many organs and tissues in the body and have both overlapping and nonoverlapping expression and function (Fig. 3). It is posited that these variations in expression and function contribute to the unique clinical attributes seen in clinical trials.

The US Food and Drug Administration approved this first-in-class medication for the management of type 2 diabetes (T2D) in 2022 [2], for the reduction of excess weight in adults with obesity or overweight in 2023 [3], and for moderate-to-severe obstructive sleep apnea (OSA) in people with obesity in 2024 [4].

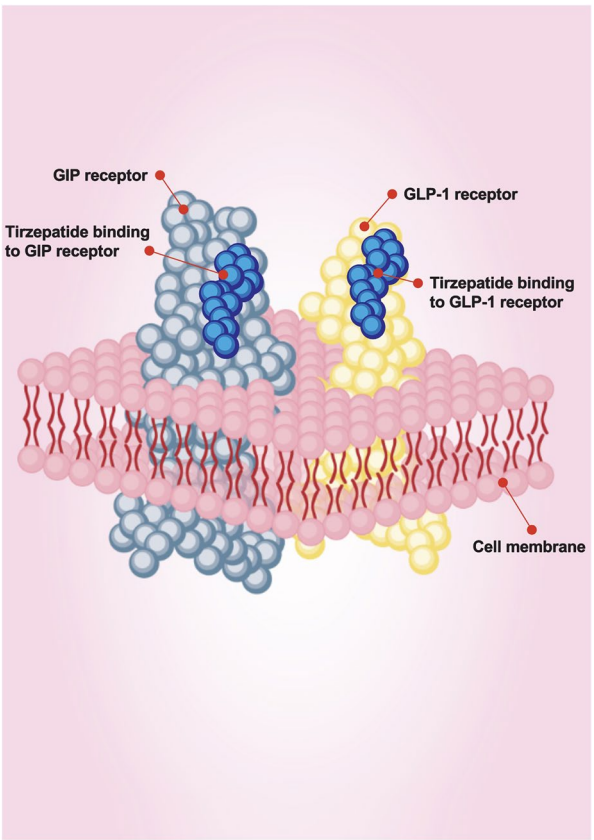


Fig. 2 Tirzepatide binding to GLP-1 and GIP receptors. *GIP* glucose-dependent insulinotropic polypeptide, *GLP-1* glucagon-like peptide-1

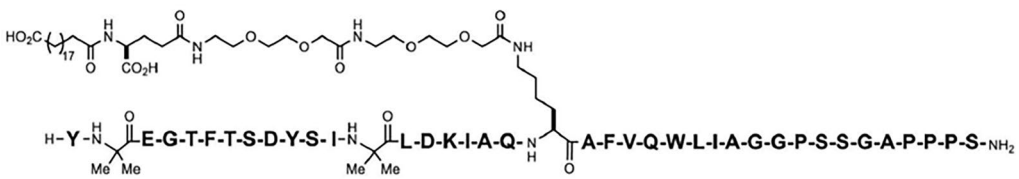


Fig. 1 Diagram showing amino acid sequence with a C20 diacid moiety in tirzepatide

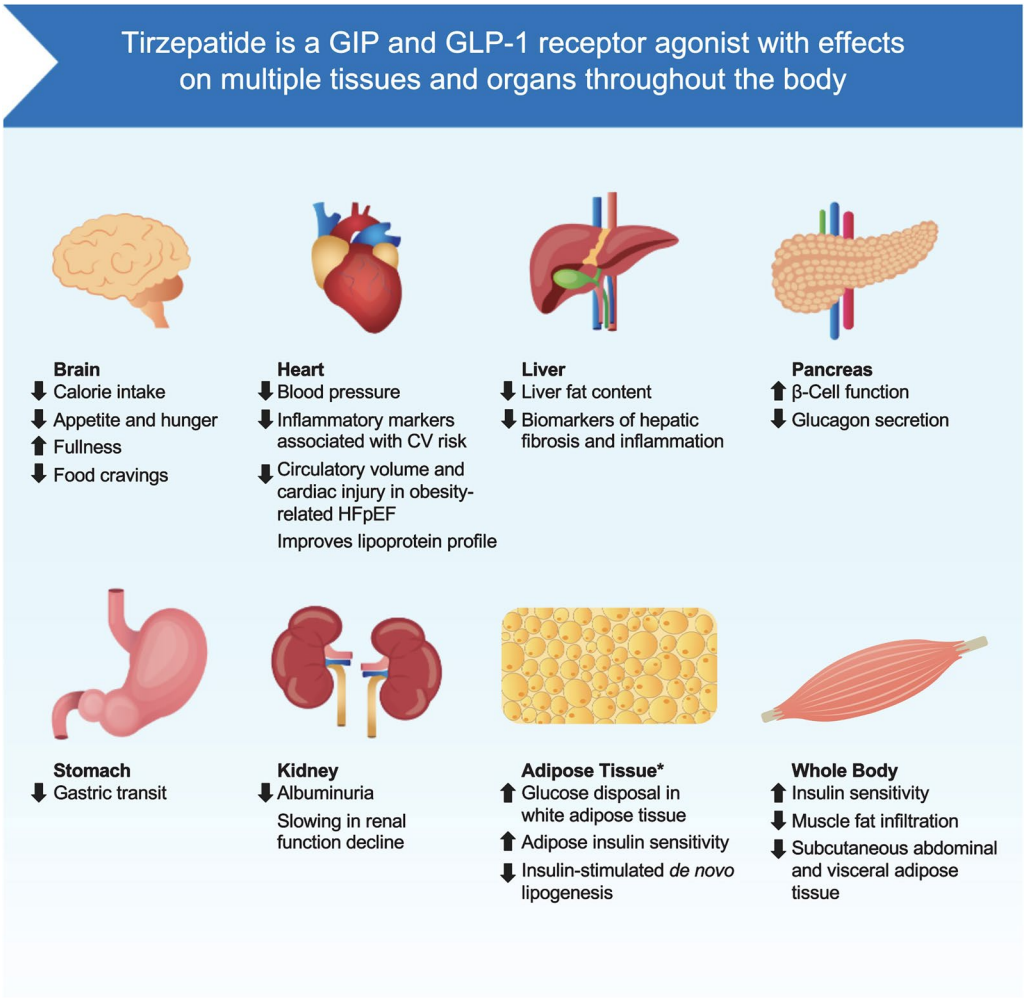


Fig. 3 Tirzepatide exerts beneficial effects on multiple organs and tissues throughout the body. *CV* cardiovascular, *GIP* glucose-dependent insulinotropic polypeptide, *GLP-1* glucagon-like peptide-1, *HFpEF* heart failure with preserved ejection fraction

Furthermore, recent studies show the benefits of tirzepatide in people with metabolic dysfunction–associated steatohepatitis (MASH) [5], in people with heart failure with preserved ejection fraction (HFpEF) and obesity [6], and in people with T2D with established atherosclerotic cardiovascular disease according to a recent press release [7]. Tirzepatide is also under investigation for the reduction of morbidity and mortality in people with obesity and overweight without diabetes (NCT05556512). An overview of major safety and efficacy clinical trials is provided in Tables 1, 2, 3, and 4 to bring context to the mechanistic findings reported herein.

In this review, we provide background on GIP, GLP-1, and tirzepatide molecules and then further examine the evidence from mechanism-of-action studies of tirzepatide. No ethics committee approval was needed as this review only summarizes findings from previously conducted studies with human participants or animals. As this report aims to support clinicians in reviewing major mechanistic studies of the approved molecule tirzepatide, it does not include studies of other GIPRA/GLP-1RAs under investigation. Data from clinical studies were prioritized and, where relevant, specific preclinical studies were discussed.

Table 1 Summary of phase 3 clinical trials in the SURPASS program

	Population	Primary objective	Detailed results
SURPASS-1 [51]	Adults with T2D inadequately controlled with diet and exercise	Change in HbA1c from baseline vs. placebo	HbA1c reduction of 1.9–2.1% vs. an increase of 0.4% (placebo); weight loss of 7.0–9.5 kg vs. 0.7 kg (placebo)
SURPASS-2 [52]	Adults with T2D inadequately controlled with metformin	Change in HbA1c vs. semaglutide 1.0 mg	HbA1c reduction up to 2.0–2.3% vs. 1.9% (semaglutide); weight loss of 7.8–12.4 kg vs. 6.2 kg (semaglutide)
SURPASS-3 [99]	Adults with T2D on metformin ± SGLT2i	Change in HbA1c vs. insulin degludec	HbA1c reduction of 1.9–2.4% vs. 1.3% (degludec); weight loss of 7.5–12.9 kg vs. gain of 2.3 kg (degludec); less hypoglycemia vs. degludec
SURPASS-4 [53]	Adults with T2D inadequately controlled with oral glucose-control medications and high CV risk	Change in HbA1c vs. insulin glargine	HbA1c reduction of 2.4–2.6% vs. 1.4% (glargine); weight loss of 7.1–11.7 kg vs. gain of 1.9 kg (glargine); less hypoglycemia vs. glargine
SURPASS-5 [54]	Adults with inadequately controlled T2D on insulin glargine ± metformin	Change in HbA1c vs. placebo	HbA1c reduction of 2.2–2.6% vs. 0.9% (placebo); weight loss of 6.2–10.9 kg vs. gain of 1.7 kg (placebo); reduced insulin dose requirement
SURPASS-6 [100]	Adults with T2D inadequately controlled with insulin glargine	Change in HbA1c vs. prandial insulin lispro	HbA1c reduction of 2.1–2.5% vs. 1.2% (lispro); weight loss of 6.9–12.0 kg vs. gain of 3.8 kg (lispro); less hypoglycemia vs. lispro
SURPASS-CVOT [7, 88]	Adults with T2D and established CVD	Time to first MACE-3[a] vs. dulaglutide	Risk of MACE-3[a] was 8% lower with tirzepatide vs. dulaglutide (HR = 0.92 [95.3% CI 0.83–1.01]); risk of all-cause mortality was 16% lower with tirzepatide vs. dulaglutide (HR = 0.84 [95.0% CI 0.75–0.94])

For all completed trials, the primary objective of tirzepatide was found to be superior to the comparator. Data presented are for the efficacy estimand unless otherwise noted

CI confidence interval, *CV* cardiovascular, *CVD* cardiovascular disease, *CVOT* cardiovascular outcomes trial, *HbA1c* glycated hemoglobin, *HR* hazard ratio, *MACE* major adverse cardiac events, *SGLT2i* sodium-glucose cotransporter-2 inhibitor, *T2D* type 2 diabetes

[a]MACE-3 comprised CV death, nonfatal myocardial infarction, and nonfatal stroke

Table 2 Summary of phase 3 clinical trials in the SURMOUNT program

	Population	Primary objective	Detailed results
SURMOUNT-1 [55]	Adults with obesity or overweight (no T2D)	Percent change in body weight vs. placebo	16.0–22.5% (16.1–23.6 kg) mean weight loss vs. 2.4% (2.4 kg) (placebo)
SURMOUNT-1 (3-year) [101]	Adults with obesity and prediabetes	Long-term weight loss and delay in progression to T2D	Sustained weight loss over 3 years: 12.7–19.3% vs. 1.3% (placebo) Progression to T2D after 17 weeks off either treatment: 2.4% vs. 13.7% (placebo) (HR = 0.12 [95% CI 0.1–0.2])
SURMOUNT-2 [102]	Adults with obesity or overweight and T2D	Percent change in body weight and percent achieving ≥ 5% weight loss vs. placebo	13.4–15.7% (13.5–15.6 kg) mean weight loss vs. 3.3% (3.2 kg) (placebo) 79–83% achieved ≥ 5% weight loss vs. 32% (placebo) HbA1c ↓ 2.1% vs. 0.5% (placebo, treatment-regimen estimand)
SURMOUNT-3 [103]	Adults with obesity or overweight (no T2D) who lost ≥ 5% body weight after 12-week lead-in	Mean change in body weight vs. placebo after lead-in	21.1% additional weight loss vs. 3.3% weight gain (placebo) after lead-in; 87.5% achieved an additional 5% weight reduction vs. 16.5% (placebo)
SURMOUNT-4 [104]	Adults with obesity or overweight (no T2D)	Maintenance of weight loss after lead-in vs. placebo	20.9% weight loss during 36-week lead-in; mean weight loss of 6.7% vs. 14.8% gain (placebo) from end of lead-in to study end; 93.4% vs. 13.5% (placebo) maintained at least 80% of weight loss to study end
SURMOUNT-5 [105]	Adults with obesity or overweight (no T2D)	Percent change in body weight vs. semaglutide	Mean weight loss of 21.6% (24.3 kg) vs. 15.4% (17.0 kg) (semaglutide) ≥ 15% weight loss: 71.2% vs. 46.0% (semaglutide)

Table 2 continued

	Population	Primary objective	Detailed results
SURMOUNT-MMO [106]	Adults with obesity or overweight (no T2D) with established CVD or increased risk for CVD	Time to first MACE-5[a] vs. placebo	Results pending

For all completed trials, the primary objective of tirzepatide was found to be superior to the comparator. Data presented are for the efficacy estimand unless otherwise noted

CVD cardiovascular disease, *HbA1c* glycated hemoglobin, *MACE* major adverse cardiac events, *MMO* morbidity mortality obesity, *T2D* type 2 diabetes

[a]MACE-5 comprised all-cause death, nonfatal myocardial infarction, nonfatal stroke, unstable angina requiring hospitalization or revascularization, and coronary revascularization

RECEPTOR PHARMACOLOGY

GLP-1 and GIP are hormones secreted by the intestine in response to nutrients; they are also known as nutrient-stimulated hormones. Historically, they have been described as incretin hormones because of their effect on postprandial insulin release, but they exert effects on multiple organs beyond the pancreatic islet.

The GLP-1R is expressed in various tissues, including but not limited to pancreatic β-cells, various cell types of the gastrointestinal tract, neurons throughout the peripheral and central nervous system (CNS), the kidney, the vasculature, and the heart [8–10]. GLP-1R activation improves glucose control via enhanced glucose-stimulated insulin secretion [11–13], slowed gastric emptying [13, 14], and decreased plasma glucagon levels [13].

Both preclinical and clinical studies support that the gastric slowing that occurs with tirzepatide is due to GLP-1R agonism and not related to GIPR agonism [15]. Translational studies have supported a role for GLP-1RA-mediated slowing of gastric emptying in very early improvements in glycemia [16], but such studies have not been completed with tirzepatide. Similar to selective GLP-1RAs, slowing of gastric emptying is greatest with the initial dose of tirzepatide, with this effect diminishing over time [15]. It is hypothesized that the slowing of gastric emptying contributes to some of the more common adverse events that occur with tirzepatide and selective GLP-1RAs (e.g., nausea, diarrhea, and vomiting), as the incidence of these events most commonly coincides with the timing of the early gastric slowing; however, the methods used to investigate such a relationship have been limited [16]. Knop et al. [17] provided clinical evidence that GIPR agonism may enhance the gastrointestinal tolerability of GLP-1RAs. Postmarketing reports of tirzepatide and selective GLP-1RAs suggest an increased risk of retained gastric content at the time of endoscopic procedures and rarer reports of periprocedural aspiration in patients who receive GLP-1RAs [16]. While a direct role for GLP-1RA-mediated slowing of gastric emptying in these events has not been well studied, various clinical recommendations have been proposed to limit patient risk [16].

In both human and experimental animal models, GLP-1RAs reduced food intake and body weight. These effects are likely primarily mediated through actions in various regions of the brain involved in the regulation of appetite and food intake [18], as supported by preclinical studies [19–22], multiple human imaging studies [18], and the GLP-1R expression patterns in the human brain [9, 23].

While both GIPRs and GLP-1Rs are present in the CNS, GIPRs are found in regions of the CNS involved in the regulation of food intake, with an expression pattern that does not fully overlap that of GLP-1R [24–26]. Activation of GIPR-expressing neurons was associated with a reduction in body weight in diet-induced obesity mouse models [27]. Importantly, preclinical

Table 3 Summary of tirzepatide trials for OSA, MASH, and HFpEF

	Population	Primary objective	Detailed results
SURMOUNT-OSA [107]	Adults without diabetes who have obesity and AHI ≥ 15 events/h. Two trials: 1—unable or unwilling to use PAP; and 2—on PAP	Evaluate the effect of tirzepatide on AHI over 52 weeks vs. placebo	Trial 1: AHI reduced by 27.4 events per hour vs. 4.8 events per hour (placebo) Trial 2: AHI reduced by 30.4 events per hour vs. 6.0 events per hour (placebo) Tirzepatide treatment associated with improved secondary outcomes (percent AHI change, body weight, SASHB, hsCRP burden, SBP) vs. placebo
SYNERGY-NASH [5]	Adults with T2D with obesity or overweight and with biopsy-confirmed MASH and fibrosis stage F2 or F3 or cirrhosis (phase 2)	Resolution of MASH without worsening of fibrosis at 52 weeks vs. placebo	MASH resolution without fibrosis worsening in 44–62% vs. 10% (placebo, treatment-regimen estimand). Fibrosis improvement without MASH worsening occurred in 51–55% vs. 30% (placebo, treatment-regimen estimand). Tirzepatide also improved select liver endpoints and body weight
SUMMIT [6]	Adults with HFpEF and obesity	Composite endpoint of CV death and worsening HF-related events and change in KCCQ-CSS vs. placebo	Lower rate of adjudicated composite endpoint, 9.9% vs. 15.3% (placebo, intention to treat) Mean (SD) change in KCCQ-CSS: 19.5 ± 1.2 vs. 12.7 ± 1.3 (placebo, intention to treat)

For all completed trials, the primary objective of tirzepatide was found to be superior to the comparator. Data presented are for the efficacy estimand unless otherwise noted

AHI apnea–hypopnea index (measured by polysomnography and reported in events per hour of sleep), *CV* cardiovascular, *HF* heart failure, *HFpEF* heart failure with preserved ejection fraction, *hsCRP* high-sensitivity C-reactive protein, *KCCQ-CSS* Kansas City Cardiomyopathy Questionnaire clinical summary score (range of 0–100, with higher numbers indicating better quality of life), *MASH* metabolic dysfunction–associated steatohepatitis, *NASH* nonalcoholic steatohepatitis, *OSA* obstructive sleep apnea, *PAP* positive airway pressure, *SASHB* sleep apnea-specific hypoxic burden, *SBP* systolic blood pressure, *T2D* type 2 diabetes

Table 4 Lipid profile changes in tirzepatide SURPASS and SURMOUNT phase 3 trials

Trial	Comparator	Total cholesterol	Triglycerides	VLDL	LDL	HDL	Non-HDL cholesterol
SURPASS-1 [51]	Placebo	↓ 5.5–8.4% vs. ↑ 0.8%	↓ 18.2–21.0% vs. ↑ 4.7%	↓ 17.5–19.8% vs. ↑ 4.3%	↓ 6.7–12.4% vs. ↓ 1.6%	↑ 3.2–7.5% vs. ↓ 3.8%	NR
SURPASS-2 [52]	Semaglutide 1.0 mg	↓ 5.5–6.3% vs. ↓ 4.8%	↓19.0–24.8% vs. ↓ 11.5%	↓ 17.5–23.7% vs. ↓ 11.1%	↓ 5.2–7.7% vs. ↓ 6.4%	↑ 6.8–7.9% vs. ↑ 4.4%	NR
SURPASS-3 [99]	Insulin degludec	↓ 4.3–5.8% vs. ↓ 2.9%	↓ 15.4–26.7% vs. ↓ 12.2%	↓ 14.2–25.2% vs. ↓ 10.6%	↓ 5.7–6.6% vs. ↓ 2.7%	↑ 5.5–10.2% vs. ↑ 1.0%	NR
SURPASS-4 [53]	Insulin glargine 100 U/ml	↓ 5.1–5.6% vs. no change	↓ 16.3–22.5% vs. ↓ 6.4%	↓ 15.7–21.8% vs. ↓ 5.7%	↓ 6.8–8.3% vs. ↑ 1.4%	↑ 6.7–10.8% vs. ↑ 2.9%	↓ 9.9–12.0% vs. ↓ 1.0%
SURPASS-5 [54]	Placebo	↓ 8.8–12.9% vs. ↓ 0.4%	↓ 15.2–24.9% vs. ↓ 6.8%	↓ 15.1–24.1% vs. ↓ 5.5%	↓ 8.9–15.5% vs. ↑ 2.8%	↑ 0.9–2.1% vs. ↑ 1.7%	NR
SURPASS-6 [100]	Insulin lispro 100 IU/ml	↓ 4.0–4.9% vs. ↑ 2.6%	↓ 12.8–22.5% vs. ↓ 0.4%	↓ 12.4–22.2% vs. ↓ 0.6%	↓ 2.4–3.9% vs. ↑ 4.9%	↓ 1.7–↑ 5.6% vs. ↓ 1.1%	↓ 5.9–8.3% vs. ↑ 3.9%
SURMOUNT-1 [55]	Placebo	↓ 4.9–7.4% vs. ↓ 1.1%	↓ 24.3–31.4% vs. ↓ 6.3%	↓ 24.2–31.7% vs. ↓ 5.6%	↓ 5.3–8.6% vs. ↓ 0.9%	↑ 7.0–8.6% vs. ↑ 0.2%	↓ 9.5–13.4% vs. 1.8%
SURMOUNT-2[a] [102]	Placebo	↓ 1.9% vs. ↑ 2.8%	↓ 27.2% vs. ↓ 3.3%	↓ 26.5% vs. ↓ 3.1%	↑ 2.9% vs. ↑ 7.4%	↑ 9.9% vs. ↑ 0.2%	↓ 5.9% vs. ↑ 3.7%
SURMOUNT-3[b] [103]	Placebo	↓ 3.0% vs. ↑ 5.2%	↓ 25.8% vs. ↑ 3.0%	↓ 25.6% vs. ↑ 3.0%	↓ 6.1% vs. ↑ 6.1%	↑ 15.4% vs. ↑ 3.6%	↓ 9.8% vs. ↑ 5.6%
SURMOUNT-4[b] [104]	Placebo	↑ 2.3% vs. ↑ 8.3%	↓ 8.2% vs. ↑ 15.6%	↓ 7.8% vs. ↑ 14.7%	↓ 3.4% vs. ↑ 3.4%	↑ 18.3% vs. ↑ 14.6%	↓ 4.0% vs. ↑ 5.5%
SURMOUNT-5[b] [105]	Semaglutide MTD (1.7 or 2.4 mg)	NR	↓ 34.9 mg/dL vs. ↓ 27.5 mg/dL	↓ 6.8 mg/dL vs. ↓ 5.3 mg/dL	↓ 7.8 mg/dL vs. ↓ 5.9 mg/dL	↑ 5.7 mg/dL vs. ↑ 2.9 mg/dL	↓ 15.6 mg/dL vs. ↓ 12.8 mg/dL

HDL high-density lipoprotein, *LDL* low-density lipoprotein, *MTD* maximum tolerated dose, *NR* not reported, *VLDL* very low-density lipoprotein

[a]Tirzepatide doses 10 mg and 15 mg combined

[b]Tirzepatide maximum tolerated dose, 10 mg or 15 mg

studies demonstrated that the synergistic effect of GIPRAs and GLP-1RAs on body weight requires the GABAergic (GABA refers to gamma-aminobutyric acid) GIPR-expressing neurons in the CNS [21, 28].

In contrast to the GLP-1R, the GIPR is present on adipocytes [29]. The biological activity of GIP in adipocytes has been investigated for some time, and although there is a need for better understanding, GIP is implicated in adipocyte carbohydrate and lipid metabolism through regulation of glucose uptake [30], lipolysis [31], and lipoprotein lipase (LPL) activity [32]. As most studies have been based on short-term GIP exposure, additional research is needed to understand this relationship with chronic GIPR activation that occurs with new and emerging pharmacologic GIPRAs.

Binding and Activity on Human GLP-1R and GIPR

While tirzepatide was engineered from the human GIP molecule, modifications allow it to

bind to both the GIPR and GLP-1R. In receptor-binding studies, tirzepatide demonstrated a high affinity for the GIPR, comparable to that of native GIP, while its affinity for the GLP-1R is approximately 18- to 20-fold weaker than that of native GLP-1 [33]. Furthermore, in signaling studies that used cell lines with recombinantly expressed human GIPR or GLP-1R, tirzepatide stimulated cyclic adenosine monophosphate (cAMP) accumulation by either receptor with potency similar to that of native GIP and approximately 13-fold weaker than that of native GLP-1 [1].

Biased Agonism at the GLP-1R

Tirzepatide displays unique pharmacology and is described as an "imbalanced" agonist. This term applies to the higher affinity and potency of tirzepatide at the GIPR than at the GLP-1R [33]. Upon GLP-1R activation by GLP-1, two pathways are activated: cAMP and β-arrestin. In pancreatic β-cells, activation of the cAMP cascade results in enhanced glucose-stimulated insulin secretion, whereas activation of the β-arrestin pathway results in GLP-1R internalization and degradation [34]. Unlike the native hormone or available selective GLP-1RAs, tirzepatide demonstrates biased agonism toward the cAMP pathway [1], which may optimize the observed metabolic efficacy of GLP-1R agonism. This biased agonism refers to the fact that tirzepatide selectively engages cAMP signaling over β-arrestin recruitment at the GLP-1R, which may augment cellular response via beneficial impact on GLP-1R cell surface trafficking, leading to increased cell surface expression. Mixed findings have been reported for the impact of biased GLP-1R agonism. Previous studies in mice have reported that matched, unbiased agonists are less effective at controlling glucose and body weight than GLP-1RAs with bias similar to that of tirzepatide [35, 36]. Another preclinical study demonstrated similar weight reduction with either a biased or balanced (non-biased) GLP-1RA and similar enhanced weight reduction with both when combined with a GIPRA [37]. The clinical significance of biased dual GIPRAs and GLP-1RAs has not yet been assessed due to the limited existence of such clinically available drugs. At present, research models do not allow investigators to definitively establish the unique contribution of biased GLP-1R agonism with tirzepatide treatment.

GLYCEMIC CONTROL

β-Cell Function and Insulin Secretion

In mechanistic and clinical efficacy trials, tirzepatide has consistently demonstrated benefits in glycemic control. Across the SURPASS clinical development program, tirzepatide demonstrated clinically meaningful and superior glycated hemoglobin (HbA1c) reductions compared not only with placebo but also with multiple active comparators, including a selective GLP-1RA (Table 1). Notably, up to approximately 50% of participants with T2D on the highest dose of tirzepatide achieved normoglycemia, defined as HbA1c < 5.7% (< 39 mmol/mol), for which an improvement in β-cell function would be expected. In a 28-week, phase 1 mechanism-of-action study comparing weekly tirzepatide 15 mg to semaglutide 1.0 mg and placebo, treatment with tirzepatide demonstrated greater improvements in measures of insulin secretion response during a hyperglycemic clamp, including the disposition index, indicative of improved β-cell function in response to a rise in glycemia [38]. Other improvements included increases in first-phase, second-phase, and total insulin secretion rates, all of which were significantly greater with tirzepatide than seen with the selective GLP-1RA semaglutide [38].

Consistent with these findings, tirzepatide-treated participants had significantly decreased fasting levels of intact proinsulin/C-peptide ratio from baseline to as early as 24 weeks, which persisted to week 40, compared with placebo-treated participants in a post hoc, exploratory analysis of the SURPASS-1 trial [39]. Circulating intact proinsulin and proinsulin/C-peptide ratios are markers of pre-proinsulin processing; hence, elevated levels are indicative of β-cell

dysfunction. These results suggest that tirzepatide improves insulin processing in pancreatic β-cells.

Insulin Sensitivity

In addition to improved β-cell function and insulin secretion, tirzepatide treatment is also associated with improvement in insulin sensitivity. Per results from a phase 1 trial, Heise et al. (2022) [38] reported a significant increase in the glucose disposal rate (M-value) during a hyperinsulinemic-euglycemic clamp after 28 weeks of tirzepatide treatment. This was accompanied by reduced postprandial glucose excursions and meal-induced insulin secretion after a mixed meal tolerance test, both reflective of an improvement in whole-body insulin sensitivity [38]. Furthermore, in a post hoc analysis of adult participants with T2D randomized to tirzepatide 15 mg, semaglutide 1.0 mg, or placebo, a greater improvement in insulin sensitivity was seen among participants in the tirzepatide arm than in the semaglutide arm after 28 weeks. Notably, neither weight reduction nor fat mass loss could fully explain the greater improvement in insulin sensitivity associated with tirzepatide treatment compared with that seen with selective GLP-1RA treatment [40]. Preclinical studies in obese mice suggest that tirzepatide may improve insulin sensitivity independently of weight reduction by enhancing glucose disposal in white adipose tissue, an effect mediated by GIPR activation in white adipose tissue [41].

Glucagon Secretion and Hypoglycemia

Insulin resistance also affects α-cell function; α-cells can become resistant to insulin, resulting in inappropriately increased glucagon release that may contribute to the development of hyperglycemia in T2D [42], and both GIP and GLP-1 influence glucagon secretion of pancreatic α-cells. Under normal physiological conditions, postprandial GIP levels are approximately four times that of GLP-1 levels [43]. GIP has important additional functions that are distinct from those of GLP-1. GIP can be both glucagonotropic and insulinotropic in a glucose-dependent manner, stimulating glucagon secretion under hypoglycemic conditions and insulin secretion under hyperglycemic conditions, as evidenced in both human and animal studies [44–48]. However, recent experiments with isolated human islet cells confirm that GLP-1 inhibits glucagon secretion, GIP increases glucagon secretion, and the combination of these two hormones leads to a net-even effect on glucagon secretion [49].

Interestingly, while native GIP and GLP-1 each offset the other's actions on glucagon secretion, resulting in a net-even effect, tirzepatide has an effect similar to that of human GIP alone in isolated islet cells: stimulation of glucagon secretion [49]. However, in clinical trials where the effect of tirzepatide was assessed at the whole-body level and insulin sensitivity was improved, tirzepatide monotherapy for 40 weeks significantly reduced fasting glucose-adjusted glucagon by 37% to 44%, whereas the placebo group experienced an increase in this measure [39]. A phase 1 study found that tirzepatide 15 mg significantly reduced glucagon secretion following a mixed meal tolerance test [38]. Data from a study presented at the 83rd American Diabetes Association Scientific Sessions showed that 12 weeks of treatment with tirzepatide reduced fasting and postprandial plasma glucagon levels in adults with T2D who were also on background metformin [50]. In addition, glucagon response during an insulin-induced hypoglycemic clamp was maintained with tirzepatide 15 mg compared with placebo [50].

Responses of other counterregulatory hormones, including growth hormone and adrenaline, did not differ between tirzepatide and placebo, while increases in cortisol and noradrenaline in response to hypoglycemia were attenuated with tirzepatide 15 mg compared with placebo [50]. During hypoglycemia, insulin secretion was reduced to a greater extent with tirzepatide 15 mg compared with placebo [50]. As presented at the American Diabetes Association's 83rd Scientific Sessions, the changes in counterregulatory response to the insulin-induced hypoglycemic clamp resulted in a statistically significant 4-min delay in hypoglycemia recovery as well as a 3 mg/dl (0.17 mmol/l) lower glucose nadir [50]. Of note, during phase

3 clinical trials in people with T2D (Table 1), the risk of hypoglycemia with tirzepatide as monotherapy or in conjunction with metformin was similarly low as that seen with placebo or semaglutide [51, 52]. The risk of hypoglycemia is increased when tirzepatide is taken in combination with insulin or sulfonylureas [53, 54].

WEIGHT AND APPETITE REGULATION

Tirzepatide contributes to beneficial changes in body composition. In a subgroup of participants from SURMOUNT-1 who underwent dual-energy X-ray absorptiometry at baseline and 72 weeks, the mean reduction in total body fat mass was 33.9% with tirzepatide (doses pooled) compared to 8.2% with placebo, while lean mass decreased by 10.9% with tirzepatide as compared with 2.6% with placebo [55]. Tirzepatide treatment was associated with a fat mass reduction approximately three times greater than that in lean body mass, a ratio similar to that resulting from lifestyle and surgical interventions for weight reduction [55]. Similar changes in body composition were seen as early as 18 weeks of treatment in a mechanistic study [56]. Favorable changes in body composition were also seen in people with obesity and T2D [56, 57].

With newer, highly effective obesity management medications such as tirzepatide and semaglutide, there has been clinical consideration whether some patients could be losing excess lean mass. However, in the SURMOUNT-1 DXA substudy, while the absolute lean mass loss increased, the ratio of fat mass loss to lean body mass loss was similar across tertiles of total body weight reduction at week 72 (≤ 15.3 kg, > 15.3 kg to ≤ 25.9 kg, > 25.9 kg) [58]. Increased weight reduction with tirzepatide treatment has been reported to be associated with greater improvement in physical function [59]. Ideally, future research with obesity management medications will include direct measures of physical function.

Notably, in the SURMOUNT-1 DXA substudy, visceral fat mass was reduced by 40.1% with tirzepatide compared with 7.3% with placebo [58]. Accordingly, in the overall SURMOUNT-1 study, the mean decrease in waist circumference was 18.5 cm with tirzepatide 15 mg [55]. This is relevant, as elevated waist circumference is associated with increased metabolically active visceral adipose tissue (VAT) [60], and during medical weight reduction, greater decreases in waist circumference are associated with greater improvements in cardiometabolic risk factors [61]. Additionally, magnetic resonance imaging (MRI) conducted on a subset of participants from the SURPASS-3 trial showed that, after 52 weeks of treatment with tirzepatide, liver fat content was reduced by 30% or more in 67% to 79% of participants, and VAT volume decreased by 16% to 25% [62]. Similarly, in the SYNERGY-NASH study (Table 3), improvement of at least one fibrosis stage without worsening of MASH was almost doubled with tirzepatide treatment than with placebo [5]. Treatment with tirzepatide was associated with clinically relevant reductions in biomarkers of fibrosis and hepatic inflammation [5]. Ectopic and visceral fat reductions resulting from tirzepatide-induced weight reduction are posited to be particularly relevant to improvements in glycemic control and other cardiometabolic comorbidities and risk factors such as lipid levels and waist circumference [62]. Clinical studies have identified VAT as an important predictor of both OSA [63] and HFpEF [64], and reductions in VAT are associated with improvements in these outcomes [65].

Mechanistic studies of energy balance have been designed to better understand the substantial weight reduction effect of tirzepatide [38, 57]. A phase 1 mechanistic study of people with T2D reported a mean weight change at week 28 of − 11.2 kg among participants assigned to tirzepatide 15 mg as compared with − 6.9 kg for semaglutide 1.0 mg and no change (0 kg) for placebo [38]. When such a magnitude of weight reduction is achieved by caloric restriction alone, increases in appetite caused by weight loss-induced modifications in neuroendocrine hormones that regulate hunger (increased ghrelin), satiety (decreased peptide YY, amylin), and fullness (decreased cholecystokinin) would be expected [66]. However, the effect of tirzepatide on appetite and food intake was assessed in multiple clinical trials, with results indicating

a general improvement in food- and appetite-related assessments, with details provided in Table S1. Table S2 provides additional details on the instruments used to collect food- and appetite-related metrics for these studies.

Both tirzepatide and semaglutide treatment led to similar improvements in fasted and postprandial appetite-related sensations (Table S1) and reduction of food intake at an ad libitum meal (348.4 kcal and 284.1 kcal, respectively; $P=0.187$) [57]. Across studies investigating the impact of tirzepatide treatment on food- and appetite-related assessments (Table S1), tirzepatide treatment was generally associated with reduced overall fasting appetite, including reduced hunger, increased fullness, and reduced prospective food intake compared with placebo, liraglutide, and semaglutide. The effect on satiety varied, depending on experimental design such as length of treatment and the fasted versus non-fasted state. Interestingly, appetite-related sensations were mostly similar to placebo and liraglutide when assessed postprandially after a lunch buffet. Overall, food cravings assessed during fasting also decreased with tirzepatide treatment compared with placebo, including cravings for sweets, high-fat food, carbohydrates, starches, and fast-food fats, while cravings for fruits and vegetables were not impacted by tirzepatide treatment. Reductions of those dimensions were also observed in the non-fasting state, except for high-fat cravings. The improvements in fasting food cravings and appetite score occurred in parallel to the reductions of five sub-scales of food craving (desire, anticipation of positive reinforcement, anticipation of negative reinforcement, lack of control, and hunger scores), and while cognitive restraint remained unchanged by tirzepatide treatment, participants reported reductions in disinhibition and perceived hunger. These changes in components of appetite are suspected to be major contributors to the measured decrease in ad libitum food intake with tirzepatide compared with placebo.

Systemic administration of fluorescently labeled tirzepatide in rodents resulted in labeling of the median eminence, area postrema, and other circumventricular organs in the brain, indicating one route of how tirzepatide may access parts of the brain to exert its effects [67]. Mechanistically, tirzepatide treatment led to activation of brain areas that are known to control appetite and feeding behavior in rodents [67], a finding that is consistent with another GLP-1 analog's (semaglutide) activity in the brain [68]. Preclinical studies show that the central GIPR is essential to the additive effect to reduce food intake with combined GLP-1R and GIPR agonism [21, 27, 28, 67]. Additionally, GIPR agonism in the hindbrain is posited to contribute positively to treatment tolerance, as preclinical studies demonstrate that GIPR agonism in the hindbrain, particularly the area postrema, can attenuate the aversive effects of GLP-1RA by directly suppressing the neural activities underlying aversive behaviors (Fig. 4) [69–71]. Per results of a phase 1 study, a long-acting GIPRA used in combination with a rapidly escalated, selective GLP-1RA demonstrated mild weight loss with reduced gastrointestinal adverse events in participants with or without T2D [17].

In addition to modulation in appetite and food intake, body weight reduction from caloric restriction causes a decrease in energy expenditure beyond what is predicted by the change in body mass. This is known as metabolic adaptation, and it can contribute to weight regain [72]. In a mechanism of action study that aimed to achieve 10% body weight reduction in participants with obesity who were without T2D, tirzepatide was compared to placebo for sleeping and 24-h energy expenditure and respiratory exchange ratio by utilizing metabolic chambers assessed at baseline and after 18 weeks [56]. Tirzepatide did not demonstrate detectable attenuation of weight reduction-induced decreases in sleeping or 24-h energy expenditure, but there was a reduction in respiratory exchange ratio in the tirzepatide treatment arm compared with that in the placebo arm, consistent with an increase in fat oxidation.

Importantly, evidence supporting the hypothesis that tirzepatide targets the physiology of energy balance, including its action on central regulation of food intake, continues to grow. For instance, post hoc analyses from SURMOUNT-1 through SURMOUNT-4 [73] and from across the SURPASS program [74] showed that weight reduction with tirzepatide was neither solely nor fully associated with reported

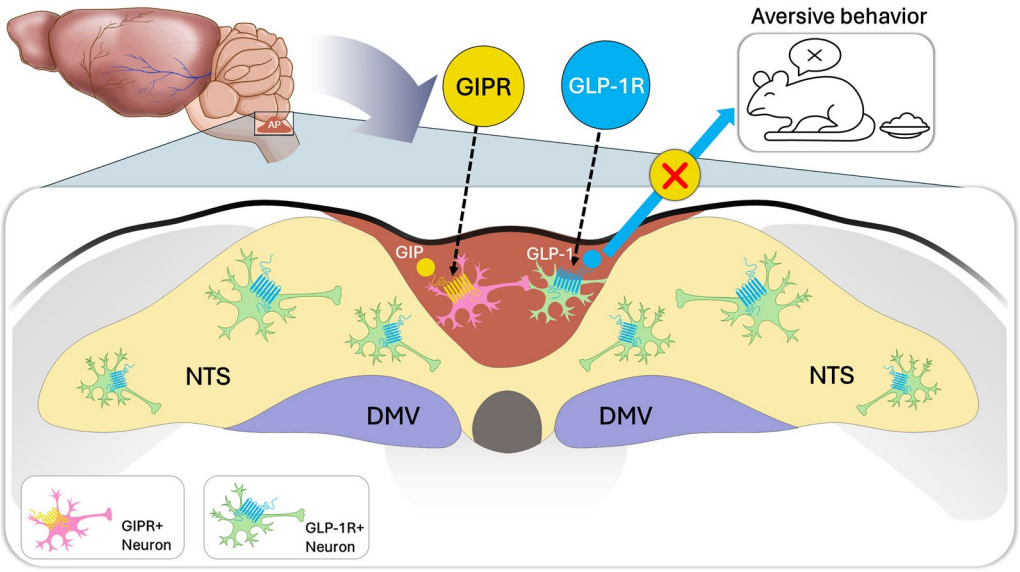


Fig. 4 Brainstem actions by peripherally administered incretins showing that GIPR agonism in the hindbrain, particularly the AP, can attenuate the aversive effects of GLP-1RA by directly suppressing the neural activities underlying aversive behaviors. *AP* area postrema, *DMV* dorsal motor nucleus of the vagus, *GIP* glucose-dependent insulinotropic polypeptide, *GIPR* GIP receptor, *GLP-1* glucagon-like peptide-1, *GLP-1R* GLP-1 receptor, *GLP-1RA* GLP-1R agonist, *NTS* nucleus of solitary tract

gastrointestinal adverse events, challenging the traditional assumption that nausea and vomiting are significant mediators of weight reduction. A 6-week phase 1 study of participants without T2D who had overweight or obesity found reduced activation (estimated from blood oxygen level dependent signal functional MRI) in certain brain regions relevant to appetite regulation in response to high-fat/high-sugar food images among participants assigned to tirzepatide 10 mg as compared with placebo [75]. Overall, preclinical and phase 1 data support that the primary mechanism for weight reduction by tirzepatide is regulation of appetite and decreases in food cravings and food intake, with increased lipid metabolism [76]. However, as mentioned earlier, tirzepatide uniquely binds both the GLP-1R and the GIPR, but only GIPRs are found on human adipocytes [29]. The importance of tirzepatide's action on the GIPR in adipocytes to the medication's ability to promote loss of excess adiposity has not been fully elucidated, and further research is needed.

LIPID METABOLISM

In the SURPASS and SURMOUNT phase 3 clinical trial programs (Tables 1 and 2), treatment with tirzepatide was related to an improvement in the lipid profile, with major decreases in triglycerides (Table 4) that cannot be fully accounted for by reductions in weight alone [77]. The adipocyte is an important site of triglyceride metabolism [29] and is unique in its expression of the GIPR and not the GLP-1R. A recent preclinical study by Regmi et al. [78] showed that tirzepatide is a potent modulator of lipid storage in adipocytes, leading to nutrient storage in the fed state and appropriate nutrient release in the fasted state. In the postprandial state, insulin signaling activates LPL, a key mediator of the intake of triglyceride-derived fatty acids into cells. In human adipocytes, tirzepatide exposure results in an increase in both mRNA expression and LPL activity, as well as increased fatty acid uptake into adipocytes. These findings support the hypothesis that tirzepatide can enhance

dietary lipid metabolism into adipocytes. In the fasting state, adipocytes are crucial to the release of stored nutrients; in human adipocytes, tirzepatide stimulates lipolysis, releasing glycerol into circulation for energy needs [78]. Whether tirzepatide can enhance adipocyte function such that it may be a mechanism of some of the improvements in lipid profiles as shown in clinical studies requires additional investigation.

CARDIORENAL

In 2023, the American Heart Association released an advisory on cardiovascular–kidney–metabolic syndrome due to rising prevalence in conjunction with the growing evidence emphasizing the importance of treatment approaches that counter the complex interplay between metabolic risk factors, including obesity and diabetes, chronic kidney disease, and the cardiovascular system. It was noted that heart failure remained a complication with limited risk-based prevention in clinical practice [79]. The risk of HFpEF increases as body mass index increases [80] and weight loss interventions have been shown to alleviate symptoms in participants with established HFpEF [81–84]. In the SUMMIT trial, Packer et al. (2025) [6] investigated the effect of treatment with tirzepatide on HFpEF (Table 3). After a median follow-up of 104 weeks, treatment with tirzepatide was associated with a significant reduction in the risk of adjudicated death from cardiovascular causes or a worsening heart failure event (hazard ratio (HR) = 0.62; [95% confidence interval (CI) 0.41–0.95]; $P = 0.026$) [6]. Furthermore, after 52 weeks of treatment, the Kansas City Cardiomyopathy Questionnaire clinical summary score (KCCQ-CSS) improved significantly among participants in the tirzepatide arm compared with those in the placebo arm (between-group difference = 6.9 [95% CI 3.3–10.6]; $P < 0.001$), indicating self-reported improvement in quality of life [6]. A secondary mechanistic analysis of the SUMMIT trial found associations between tirzepatide treatment and reductions in circulatory volume and markers of cardiac injury [85].

A cardiac magnetic resonance substudy of the SUMMIT trial showed that tirzepatide treatment led to a placebo-corrected reduction of left ventricular mass by 11 g ([95% CI 4–19 g]; $P < 0.05$), and a placebo-corrected decrease in paracardiac adipose tissue by 45 ml ([95% CI 22–69 ml]; $P < 0.001$ for both). The change in left ventricular mass in the tirzepatide group correlated with changes in body weight ($P < 0.02$) and with changes in left ventricular end-diastolic volume and in left atrial end-diastolic and end-systolic volumes ($P < 0.03$ for all) [86].

Current clinical evidence from a meta-analysis of phase 2 and three studies of tirzepatide in participants with T2D indicates that tirzepatide treatment is not associated with an increased risk of MACE-4, a composite outcome comprising the four outcomes cardiovascular death, nonfatal myocardial infarction, nonfatal stroke, and hospitalization due to unstable angina (HR = 0.80; [95% CI 0.57–1.11]; $P = 0.183$) [87]. The cardiovascular safety and efficacy of tirzepatide in adults with T2D has been assessed in a large phase 3 clinical trial (SURPASS-CVOT) (Table 1) [88]. According to a recent press release, tirzepatide was non-inferior to dulaglutide, an agent with proven cardiovascular prevention benefits, in preventing MACE-3, defined as cardiovascular death, nonfatal heart attack, or nonfatal stroke. Tirzepatide was also associated with a significantly lower risk of all-cause mortality compared with dulaglutide [7].

Thus far, the effect of tirzepatide on cardiovascular risk factors has indicated improvements in lipids, lipoprotein profiles, glucose control, body weight, blood pressure, and several biomarkers of inflammation in adults with overweight or obesity both with and without T2D (Tables 1, 2, 3, 4). The SURPASS-3 MRI substudy also showed reductions in liver fat content, VAT, and abdominal subcutaneous adipose tissue at week 52 [62]. In another exploratory analysis of SURPASS-3 MRI, comparing SURPASS-3 participants with sex- and body mass index-matched virtual control groups, treatment with tirzepatide was related to reduced liver fat content and VAT, but abdominal subcutaneous adipose tissue increased at week 52 among participants from the SURPASS-3 MRI substudy [89]. The authors conclude that this increase in abdominal

subcutaneous fat reflects a more balanced fat distribution pattern with tirzepatide treatment [89].

In a phase 2b trial, tirzepatide treatment was associated in a dose-dependent manner with decreased levels of apolipoprotein (apo) B, apoC-III, large triglyceride-rich lipoprotein particles, and small low-density lipoprotein particles, suggesting a shift towards a less atherogenic lipoprotein profile [77]. A regression analysis suggested that apoC-III level, not body weight or HbA1c (among other variables), was the strongest predictor of changes in serum triglycerides observed with tirzepatide treatment [77]. Post hoc analyses of these data found that several inflammatory markers associated with increased cardiovascular risk, such as high-sensitivity C-reactive protein, YKL-40, intercellular adhesion molecule-1, and leptin, were significantly reduced following 26 weeks of treatment with tirzepatide 15 mg [90]. Post hoc mediation analysis across SURPASS-1 through SURPASS-5 found that decreases in systolic blood pressure (ranging from 1.3 mmHg to 11.5 mmHg across the tirzepatide doses) were primarily mediated through weight loss [91]. Another post hoc analysis of SURMOUNT-1 showed that greater reductions in weight accompanied greater improvements in multiple cardiometabolic risk parameters [92]. In particular, participants experiencing weight reduction of 30% or more also experienced a decrease in mean systolic blood pressure of more than 11 mmHg, while those with weight reduction of less than 10% experienced only a limited effect on blood pressure [92].

Excess adiposity and T2D are independent risk factors for kidney diseases such as acute kidney injury and chronic kidney disease [93, 94]. In a post hoc analysis of SURPASS-4, tirzepatide treatment was associated with a significant reduction in composite renal outcome events (time to first occurrence of at least 40% decline in estimated glomerular filtration rate from baseline, end-stage renal disease, renal-related death, or incident macroalbuminuria) compared with treatment with insulin glargine (HR = 0.58; [95% CI 0.43–0.80]) [95]. Furthermore, participants assigned to tirzepatide had a slower mean rate of decline in estimated glomerular filtration rate over the study period: -1.4 ± 0.2 ml/min/1.73 m^2 body mass per year with tirzepatide compared with -3.6 ± 0.2 ml/min/1.73 m^2 body mass per year with insulin glargine, for a between-group difference of 2.2 ml/min/1.73 m^2 body mass per year [95% CI 1.6–2.8 ml/min/1.73 m^2 body mass per year] [95]. A recent post hoc analysis of the SURPASS-1 through SURPASS-5 clinical trials further supports tirzepatide having a renal-protective action [96]. At the end of 40 or 42 weeks (study time varied by trial), urine albumin-to-creatinine ratio (UACR) was significantly reduced among participants assigned to tirzepatide 5, 10, or 15 mg as compared with those assigned to all pooled comparators (placebo, semaglutide, insulin degludec, and insulin glargine) with adjusted mean percent changes of 19.3% [95% CI 12.5–25.5%], 22.0% [95% CI 15.3–28.1%], and 26.3% [95% CI 20.0–32.0%], respectively, with a greater reduction observed in participants with a UACR ≥ 30 mg/g at baseline [96]. Causal mediation analysis showed both direct and indirect effects of tirzepatide on UACR. The indirect effects, mediated through reductions in HbA1c and body weight, appeared to explain 45.9% [95% CI 20.7–71.0%] of the decrease in UACR associated with tirzepatide relative to the pooled comparator and driven primarily by improved glycemic control, with no statistically significant role for weight reduction. The remaining 54.1% [95% CI 29.0–79.3%] of the effect of tirzepatide on UACR appeared to be direct effects of the pooled tirzepatide doses, with unmodeled variables potentially contributing to some extent [96].

GLP-1R activation can induce proximal tubular natriuresis via inhibition of sodium/hydrogen exchanger isoform 3; this reduces sodium, bicarbonate, and water reabsorption, thereby contributing to improvements in hyperfiltration [97]. A direct effect of tirzepatide at the GIPR in adipose tissue surrounding and within the kidney, such as perirenal fat and intrarenal fat, may favorably affect inflammation known to contribute to kidney dysfunction. Likewise, tirzepatide effects at the GLP-1R, like other specific GLP-1RAs, may improve endothelial function, suppress the renin-angiotensin system, and exert natriuretic effects. Additionally, it is suggested that the beneficial effects of GLP-1RAs on systolic blood pressure may be due to improvements in direct or indirect vasorelaxation of

vascular smooth muscle in the kidneys as well as via endothelial function and natriuresis [98].

The mechanism by which tirzepatide contributes directly to reduced cardiorenal risk is an area that requires additional investigation. In a post hoc analysis of the SUMMIT trial, the decrease in estimated blood volume seen in participants treated with tirzepatide was significantly correlated with decreased blood pressure, lower microalbuminuria, improved KCCQ-CSS, and greater 6-min walking distance [85]. Furthermore, decreased C-reactive protein levels were associated with both reductions in troponin T levels and greater 6-min walking distance. These tirzepatide-related reductions in circulatory volume–pressure overload and systemic inflammation may mitigate cardiorenal end-organ injury in people with HFpEF and obesity [85].

CONCLUSIONS

In conclusion, studies of tirzepatide support that treatment with tirzepatide is associated with countering multiple mechanisms of pathophysiology seen with various cardiometabolic diseases. Tirzepatide has direct effects on insulin secretion, insulin sensitivity, appetite and food cravings, and adipose and lipid metabolism. In addition, several markers of metabolic disturbance are improved with tirzepatide use, including dyslipidemia, elevated blood pressure, and impaired renal function. The dual GLP-1R and GIPR agonism of tirzepatide is a novel therapeutic option for the management of metabolic disorders, including T2D and obesity. Further research will continue to elucidate the mechanistic pathways involved in the clinical efficacy of tirzepatide.

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Declarations

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Ethical Approval. No ethics committee approval was needed as this review only summarizes findings from previously conducted studies with human participants or animals.

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