Review Article

Tirzepatide: Dual GIP/GLP-1 Receptor Agonists, from Molecular to Clinical Practice for Treating Type-2 Diabetes and Obesity

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ABSTRACT

Tirzepatide is a promising drug with dual-acting glucose-dependent insulinotropic polypeptide (GIP) and glucagon-like peptide 1 (GLP-1) receptor activation that has revolutionized the treatment of type 2 diabetes mellitus (T2DM). In phase 3 clinical trials (SURPASS 1-5), tirzepatide has been shown to achieve better glycaemic control in terms of glycosylated hemoglobin reduction (HbA1c) and improved fasting, postprandial glucose levels and weight reduction as compared to placebo and active comparators. The SURPASS 4 clinical trial has shown positive cardiovascular outcomes in people with T2DM with elevated cardiovascular risk. Tirzepatide has acceptable side effects and is well tolerated, with a low risk of hypoglycaemia. Additionally, encouraging results from SURMOUNT trials and ongoing SURPASS-CVOT studies will shed more light on cardiovascular safety in the future. In this review, we have summarized the pharmacology, efficacy, safety, and clinical trials for potential impact for clinical treatment T2DM.

Keywords: *Dual agonist GIP/GLP-1, obesity, tirzepatide, type-2 diabetes*

INTRODUCTION

Diabetes mellitus (DM) remains a major global health problem, with 536.6 million people living with diabetes today.[1] Diabetic patients will spend more on healthcare than non-diabetics and have a 60% higher risk of premature death. Diabetes significantly increases the risk of comorbidities, including myocardial infarction, cardiovascular events, nephropathy, neuropathy, and retinopathy.[2] Obesity and particularly central adipocytes are risk factors for the occurrence of type 2 diabetes mellitus (T2DM), and weight loss can prevent or inhibit the worsening of diabetes, especially the occurrence of cardiovascular risk.[3,4]

Currently, many anti-diabetic drugs focus on weight loss in the diabetes mellitus population. Diabetes medications have advanced at the end of this decade. First, incretin-based, namely DPP4 inhibitors (DPP-4i, gliptins) and glucagon-like peptide-1 receptor (GLP-1Ras) agonists. Second, sodium-glucose cotransporter type 2 inhibitors (SGLT2is, gliflozins). GLP-1 receptor agonists have a special place in the treatment of T2DM patients. Treatment of DM with GLP-1 RA has been included in treatment guidelines by Europe[5], America[6], Indonesia[7], and the French Society of Diabetes (Société francophone du diabète: SFD), an important statement from SFD is that it has placed GLP-1 before insulin treatment after failure with oral drugs.[8]

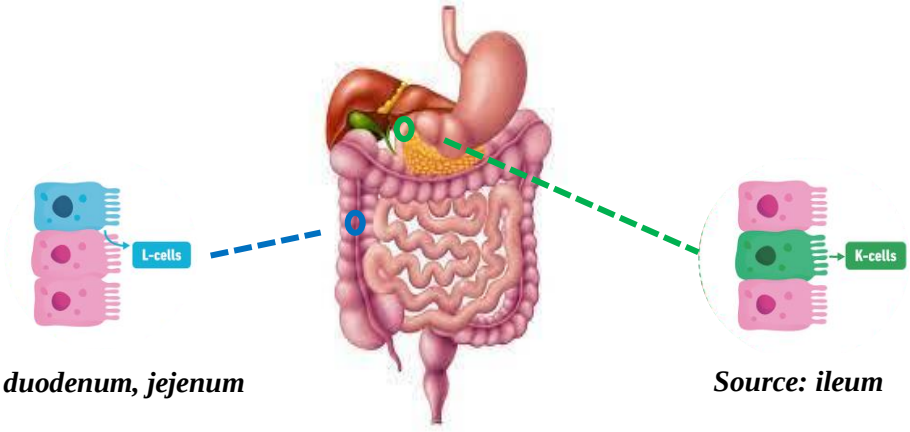
In recent years, GLP1 receptor and glucose-dependent insulinotropic polypeptide (GIP), known as the incretin hormone class, have attracted researchers. GIP can stimulate insulin after meals, lower blood sugar, and make the body more responsive to insulin.[9,10] Furthermore, it can also reduce weight by slowing gastric emptying.[11,12,13] The combination of GLP-1 and GIP has been proposed as a modern option for treating diabetes and obesity.[14] As the early product of dual GIP and GLP1 agonist ("twincretin"), tirzepatide (LY3298176, @ Mounjaro) has been approved by the US Food and Drug Administration since 13 May 2022 to medicate the DM patient, following to its diet and exercise treatment.[15]

This literature review aims to assess the role and clinical evidence of tirzepatide as a GIP/GLP1 dual in treating diabetes and obesity.

Mechanism of Action Tirzepatide for Glucose Haemostasis

Incretin Effect

Combining GIP and GLP-1 agonist in tirzepatide gives the GIP receptors a higher affinity, stabilizing normal glycemic state and weight loss in type 2 diabetes mellitus. Elrick et al, were the pioneers to report that plasma insulin concentration was significantly higher after oral glucose loading compared to parenteral therapy.[16] This phenomenon is known as the "incretin effect," it has been shown that insulin secretion from the pancreas is dominated by 65% of post-meal insulin secretion.[17] Incretin hormones include GLP-1 and GIP. Concentration levels of GLP-1 and GIP are deficient during fasting and increase 15-30 minutes after a meal.[18] Concentration levels of GLP-1 and GIP are deficient during fasting and increase 15-30 minutes after a meal.[19] Post-production, GIP and GLP-1 stimulate pancreatic cell receptors to activate the glucose-dependent insulinotropic response and increase the loss of proper carbohydrate and fat absorption. The incretin produces a brief effect, given that the activated hormones only last one to two minutes after the release before being terminated by the enzyme dipeptidyl peptidase-4 (DPP-4).[19] The effect of incretins is greatly decreased in T2DM patients compared to those without T2DM.[18] Decreased synthesis of incretin hormones in response to feeding (hyposecretion) and loss of insulinotropic action on beta cells[20] are two circumstances that illustrate the decreased effect of incretins in T2DM.[21]



GLP-1	Pancreatic and exopancreatic action	GIP
Appetie ↓ Food intake ↓ Nausea ↑	Brain	Appetie ↓ Food intake ↓ Nausea ↓
Insulin secretion ↑ Glucagon ↓	Pancreas	Insulin secretion ↑ Glucagon ↑
Gastric emptying ↓	Stomach	Gastric acid secretion ↓
Lipolysis ↑	Adipose tissue	Lipogenesis ↑ Lipid buffering capacity ↑
	Bone	Bone resoprtion ↓
Cardioprotection ↑	Heart	
Natriuresis ↑ Diuresis ↑	Kidney	

Figure 1. Mechanism of Action of glucose-dependent insulinotropic polypeptide (GIP) and glucagon-like peptide (GLP-1) in pancreatic and extra-pancreatic. *Adapted from* Rachel S 2023 (22) and André J. Scheena 2023[23]

Complementary effects of GIP and GLP-1

The complementary effects of GIP and GLP-1 can be seen in the illustration of Figure 1. GLP-1 is secreted mainly from L cells in the ileum and colon in response to food entry.[24] Exogenous infusion of GLP-1 persuades the action of lowering multiple glucose, including stimulation of glucose-induced insulin secretion, prolonging gastric emptying time, and inhibiting glucagon secretion in healthy individuals and T2DM patients.[25] Moreover, some reactions, such as decreased food consumption and appetite, are results of exogenous GLP-1 infusion, although it would not directly affect energy expenditure.[26] GLP-1 stimulates insulin secretion after a meal while inhibiting glucagon secretion, which both are sustained by glucose. It also improves satiety through two mechanisms: central (via the hypothalamus) and peripheral (via slow gastric emptying). This mechanism will improve glucose control in T2DM patients, thus bringing several advantages, such as inescapable hypoglycemia and losing weight. GLP1 also positively affects the cardiovascular system and may reduce liver steatosis.[26,27]

GIP is a peptide secreted by K cells in the duodenum and jejenum in response to post-food consumption. In non-diabetic people, GIP provokes insulin secretion without altering glucagon release during hyperglycemia, although GIP increases glucagon release without affecting insulin secretion during hypoglycemia.[28,29] In individuals with T2DM, GIP's ability to stimulate insulin secretion and improve glycemia is impaired, but GIP sensitivity can be regained after improving glycaemic control.[30,31] The central action of GIP may decrease appetite by increasing satiety, leading to weight loss.[32] However, the exact mechanism remains controversial, between the direct and indirect action of GIP through its ability to have an anorectic effect. In peripheral action, GIP benefits body fat and muscle tissue.[33] It can increase lipid storage in white fat tissue and decrease ectopic fat storage in muscle, improving insulin sensitivity.[34]

Tirzepatide: GIP/GLP-1 original unimolecular

The developed dual (or triple) receptor agonist's originality lies in its unimolecular structure, displaying the technological advancement in the field of peptide biotechnology.[35] The chemical structure of tirzepatide is LY3298176. The GIP/GLP-1R unimolecular dual agonist, tirzepatide, is a multifunctional peptide based on the native GIP peptide sequence, designed to bind to both receptors. GIP and GLP-1 combined effect on food consumption and expand in energy expenditure results in body weight loss.[34] tirzepatide is a linear peptide of 39 amino acids conjugated to the fatty diacid moiety C20 through a linker chained to a lysine residue at position 20.[35]

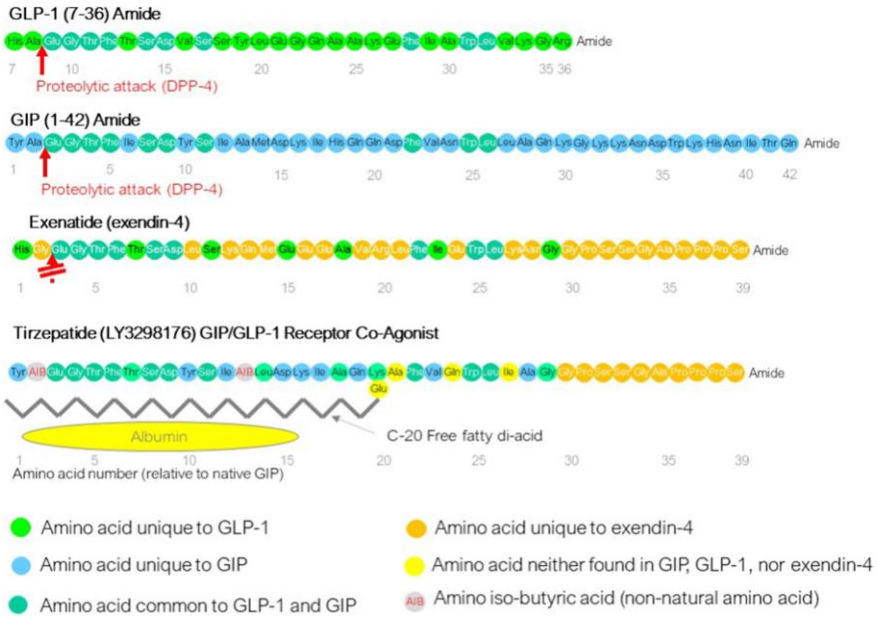


Figure 2. Amino acid sequences of the incretin hormones GLP-1 (glucagon-like peptide-1) and GIP (glucose-dependent insulinotropic polypeptide), the GLP-1 receptor agonist exenatide, and tirzepatide, a GIP/GLP-1 receptor co-agonist.

Colours indicate amino acids in the peptide sequence of tirzepatide which correspond to amino acids in the original primary structure of GLP-1 (green), GIP (blue), shared by both GLP-1 and GIP (blue-green), exenatide (orange). Amino acids not related to any of the parent peptides are shown in yellow. Amino-iso-butyric acid (AIB), a non-natural amino acid, is shown in grey with red letters. The primary amino acid sequence of tirzepatide has been taken from (35); the sequences for human GIP, mammalian GLP-1, and exenatide for comparison are from (36-37).[34]

Figure 2 shows the tirzepatide peptide sequence also accommodates two noncoding amino acid residues at positions 2 and 13 (Aib, a-amino isobutyric acid), and a C-terminus in the center.[38,39] The acylation approach with fatty acids is well known in the field of diabetes as it has been successfully used to extend the duration of insulin and GLP-1 activity, allowing the peptide to bind to albumin, increasing the biological half-life, estimated to be around 116 hours. Therefore, tirzepatide can be used once a week for subcutaneous injection in humans. The molecular weight of tirzepatide is 4810.52 Da.[23]

Clinical Trials for Tirzepatide

Tirzepatide was initially tested in patients with T2DM with lifestyle changes (diet and exercise) or with metformin in phase-2 trials. These trials assessed the effectiveness and safety of increasing doses of tirzepatide from 5 to 15 mg once weekly versus placebo for 12 weeks.[40] and compared to placebo or dulaglutide, a pure GLP-1 analogue, in 26 weeks.[41]

Promising early results in this trial have demonstrated that tirzepatide has been tested in a large study called SURPASS in T2DM patients uncontrolled with various sugar-lowering therapies,[42] including lifestyle alone (SURPASS-1)[43], metformin monotherapy (SURPASS-2)[44], metformin with or without SGLT2i inhibitors (SURPASS-3)[45], combined metformin, SGLT2i and/or sulfonylurea therapy (SURPASS-4)[46], insulin glargine with or without metformin (SURPASS-5)[47] and SURPASS-6[48] (unpublished study). All clinical trials of tirzepatide are reviewed in table 1.

Effects on Glycaemic Outcome

HbA1c effect

The main goal was the HbAc1 level's modification from baseline values. Tirzepatide showed greater dose-dependent reductions in

HbA1c values than placebo, basal insulin, and semaglutide in all SURPASS experiments, even with other glucose-lowering treatments.[23]

In new T2DM subjects, treated only with diet and exercise (SURPASS-1), tirzepatide 5 - 15 mg can increase HbA1c from 1.87% to 2.07% compared to an increase of 0.04% in the placebo group.[43]

In the SURPASS-2 study, subjects with T2DM were treated with tirzepatide 5-15 mg for 40 weeks, and HbA1c successfully dropped from 2.09% to 2.46% compared to the semaglutide 1 mg group at 1.86%.[44] Likewise, In SURPASS-3, tirzepatide 5-15 mg for 52 weeks resulted in HbA1c dropping from 1.93% to 2.37% as opposed to 1.34% drop with insulin degludec.[45] In patients with long-standing T2DM, or more than ten years, and increased cardiovascular risk (SURPASS-4), the use of tirzepatide 5-15 mg can also reduce HbA1c by 2.24% to 2.58% compared to the insulin glargine which boost the HbA1c by 1.44% at 52 weeks.[46]

In the SURPASS-5 study, when tirzepatide was added to those who had received daily glarine insulin, it was found that HbA1 decreased from 2.23% to 2.59% compared to placebo 0.93%, the improvement of HbA1c will be very influential in improving glycemia in insulin use.[47]

Fasting serum glucose (FSG) was lower in the tirzepatide group at all doses and studies (-43.6 to -74.4 mg/dL or -2.4 to -4.1 mmol/L) compared to previous baseline data and compared to placebo, semaglutide 1 mg, and dulaglutide 0.75 mg (J-mono) (Table 1). In the SURPASS-3 study, the depletion in FSG in the tirzepatide group was more significant than that in the insulin degludec; however, in the SURPASS-4 study, only in the tirzepatide 15 mg group was there a significant reduction in fasting blood sugar compared to the insulin glargine group.[45,46]

Constant glucose observation in a subgroup of subjects from the study in SURPASS-3 showed that at all doses of tirzepatide (5, 10, and 15 mg) increased time in range (TIR, 70 to 180 mg/dL or 3. 9 to 10 mmol/L) (TIR increased from 32% to 40% from baseline, attaining an overall 85% to 91% TIR) compared to insulin degludec (TIR increased 22% from baseline, achieving an overall 75% TIR) for 52 weeks after randomization. (A5.70) The tirzepatide group also showed a shorter time below range (<70 mg/dL or <3.9 mmol/L) than the insulin group and reduced glycemia variability.[48]

Effects on Body Weight

Changes in body weight could be seen in the groups in all SURPASS studies.[43-49] In subjects with new-onset T2DM, a 40-week course of 5 to 15 mg of tirzepatide resulted in a weight loss of 7 kg to 9.5 kg compared to a 0.7 kg loss in the placebo group.[44]

In subjects with T2DM, larger body weight was attained in the tirzepatide 5 mg, 10 mg, and 15 mg group (-7.8, -10.3, and -12.4 kg) compared to semaglutide 1 mg (-6.2 kg) in the SURPASS-2 study.[44] In the SURPASS-3 study, the insulin-initiated degludec group lost 2.3 kg after 52 weeks, while the tirzepatide 5-15 mg group lost weight from 7.5 kg to 12.9 kg.[45]

In subjects with long-standing T2DM, subjects who were already on glucose-lowering medications and initiated on insulin glargine (SURPASS-4) were seen to achieve a weight loss of 1.9 kg after 52 weeks compared to a weight loss of 7.1 kg to 11.7 kg in the tirzepatide group.[46] In the SURPASS-5 study, all subjects in the insulin basal glargine and terzipatide group achieved a weight loss of 6.2 to 10.9 kg compared to 1.7 kg in the placebo group.[47]

Table 1. Summary of completed randomized controlled of Tirzepatide versus comparators

Study	Sample size, duration, study design, study site	Participant(s)	Intervention(s)	A1c change from baseline	Body weight change from baseline	Secondary outcome(s)
Rosenstock et al 2021, (SURPASS-1)[43]	N = 478, 40 weeks (between June 2019 and Oct2020) Double blind Placebo controlled (phase 3), 52 sites in 4 countries	≥18 years with type 2 diabetes. HbA1c 7.0-9.5, BMI≥23 kg/m2, and stable weight (±5) during the previous 3 months, uncontrolled with diet and exercise alone (naive to injectable T2DM meds, no oral T2DM meds for prior 3 months)	Tirzepatide 5 mg	-1.75%	-6.3 kg	FSG changes from precedent (5 mg) -39.6 mg/dL, (10 mg) -39.8 mg/dL, (15 mg) -38.6 mg/dL, (placebo) +3.7 mg/dL. Fasting lipids change from precedent cholesterol (15 mg) -8.4%, triglycerides -21%, LDL -12.4%, VLDL -19.8%, HDL +7.5%
			Tirzepatide 10 mg	-1.71%	-7.0 kg	
			Tirzepatide 15 mg	-1.69%	-7.8 kg	
			Placebo once weekly	0.09%	-1,0 kg	
Frías et al 2021 (SURPASS-2)[44]	N = 1,879, 40 Weeks (between July2019 and February, 2021), open label, phase 3, 128 sites in 8 countries	T2DM, mean age = 56.6 years, HbA1C = 7.0% to 10.5%, treatment with metformin for ≥3 months (≥1,500 mg per day), stable body weight ≥3 months, BMI of ≥25 kg/m2	Tirzepatide 5 mg	-2.01%	-7.6 kg	Hypoglycemia less than 54 mg/dL in (5 mg) 0.6%, (10 mg) 0.2%, (15 mg) 1.7%, (semaglutide) 0.4% Fasting lipids change from precedent (15 mg) triglycerides -24.8%, VLDL -23.7%, HDL +7.1%
			Tirzepatide 10 mg	-2.24%	-9.3 kg	
			Tirzepatide 15 mg	-2.30%	-11.2 kg	
			Semaglutide	-1.86%	-5.7 kg	
Ludvik et al 2021 (SURPASS-3)[45]	N =1,444, 52 Weeks (between April 2019 and Jan2021) open label, phase 3, 122 sites in 13 countries	T2DM, ≥ 18 years, insulin naive, HbA1C = 7.0 - 10.5%, stable metformin (≥1,500 mg/day) or metformin and SGLT-2 inhibitor treatment ≥3 months, stable body weight ≥3 months, BMI of ≥25 kg/m2	Tirzepatide 5 mg	-1.85%	-7.0 kg	Hypoglycaemia less than 54 mg/dL in (5 mg) 1.4%, (10 mg), 1.1%, (15 mg) 2.2%, (insulin degludec) 7.3%
			Tirzepatide 10 mg	-2.01%	-9.6 kg	
			Tirzepatide 15 mg	-2.14%	-11.3 kg	
			Insulin degludec	-1.25%	+1.9 kg	
Battelino et al (SURPASS-3 CGM)[48]	Sub-study of SURPASS-3. Interstitial glucose values collected via CGM at baseline, 24 weeks, and 52 weeks	313 patients of SURPASS-3 with normal wake-sleep cycle.		n/a		Proportion of time of CGM values in tight target range (71-140 mg/dL) at 52 weeks: 60%, 72%, 73% vs 48%. Estimated treatment difference of 12%, 24%, and 25% ($P < 0.05$ for all)

Study	Sample size, duration, study design, study site	Participant(s)	Intervention(s)	A1c change from baseline	Body weight change from baseline	Secondary outcome(s)
Gastaldelli et al (SURPASS-3 MRI)[43]	Sub-study of SURPASS-3 MRI at baseline and 52 weeks	296 patients of SURPASS-3 with fatty liver index of at least 60		n/a		For the pooled tirzepatide 10 and 15 mg group compared with insulin degludec, there was a significant reduction in liver fat content ($P <$ 0.0001
Del Prato et al 2021 (SURPASS-4)[46]	N= 2,002, 104 weeks, (between Nov, 2018 and April, 2021) Open label, phase 3 187 sites in 14 countries	T2DM, HbA1C = 7.5% to 10.5%, ≥1-month stable treatment, three oral antihyperglycemic drugs (Metformin, SGLT-2 inhibitors, sulfonylureas), ≥3 months stable treatment, ≥3 months stable body weight, BMI ≥ 25 kg/m2, increased risk of cardiovascular events	Tirzepatide 5 mg	-2.11%	-6.4 kg	+Fasting lipids change from precedent (15 mg) cholesterol -5.6%, triglycerides -22.5%, VLDL -21.8%, HDL +10.8%
			Tirzepatide 10 mg	-2.30%	-8.9 kg	
			Tirzepatide 15 mg	-2.41%	-10.6 kg	
			Insulin glargine	-1.39%	+1.7 kg	
Dahl et al 2022 (SURPASS-5)[47]	N = 475, 40 weeks (between August 2019 and January, 2021) Double-blind, phase 3, 45 sites in in 8 countries	T2DM, 7.0% to 10.5% HbA1C, ≥3 months treatment of insulin glargine U100 (>20 IU/d or >0.25 IU/kg/d) once daily with or without metformin, stable body weight ≥3 months, BMI of ≥23 kg/m2	Tirzepatide 5 mg	-2.11%	-5.4 kg	Hypoglycaemia less than 54 mg/dL in (5 mg) 15.5%, (10 mg) 19.3%, (15 mg) 14.2%, (placebo) 12.5%
			Tirzepatide 10 mg	-2.40%	-7.5 kg	
			Tirzepatide 15 mg	-2.34%	-8.8 kg	
			placebo	-0.86%	+1.6 kg	

Study	Sample size, duration, study design, study site	Participant(s)	Intervention(s)	A1c change from baseline	Body weight change from baseline	Secondary outcome(s)
Inagaki et al 2022 (SURPASS-Jmono)[50]	N = 636, 52 weeks (between May, 2019 and March 2021) Double-blind, phase 3, Japan	T2DM ≥20 Years, HbA1C between 7.0% and 10.0% if OAD is naive, HbA1C = 6.5% to 9% if currently on OAD, BMI of ≥23 kg/m2, stable body weight ≥3 months with no exercise/intensive diet for body weight reduction	Tirzepatide 5 mg	-2.37%	-5.8 kg	FSG changed from precedent (5 mg) -57.9 mg/dL, (10 mg) -64.6 mg/dL, (15 mg) -67.6 mg/dL, (dulaglutide) -31.9 mg/dL. Fasting insulin changes from precedent (5 mg) -1.07 mU/L, (10 mg) -1.87 mU/L, (15 mg) -2.00 mU/L, (dulaglutide) 1.4mU/L. Fasting Cpeptide change from precedent (5 mg) -0.25 ug/L, (10 mg) -0.39 ug/L, (15 mg) -0.37 ug/L, (dulaglutide) 0.01 ug/L
			Tirzepatide 10 mg	-2.55%	-8.5 kg	
			Tirzepatide 15 mg	-2.82%	-10.7 kg	
			Dulaglutide 0,75 mg	-1.29%	-0.5 kg	
Kadowaki et al (SURPASS-Jcombo)[51]	N = 442, 52 weeks, Open label	T2DM, HbA1C between 7.0% and 11.0%, with ≥3 months metformin, sulfonylureas, thiazolidinediones, glinides, SGLT-2 inhibitor or alpha glucosidase inhibitor, BMI of ≥23 kg/m2, stable body weight ≥3 months with no exercise/ intensive diet for body weight reduction	Tirzepatide 5 mg	Not reported ≥1 SAE in patients	-3.8 kg	FSG changed from precedent (5 mg) -58.6 mg/dL, (10 mg) -71.2 mg/dL, (15 mg) -74.4 mg/dL. Fasting insulin changes from precedent (5 mg) 6.2 pmol/L, (10 mg) -4.8 pmol/L, (15 mg) -7.7 pmol/L. Fasting C-peptide change from precedent (5 mg) -0.12 ug/L, (10 mg) -0.28 ug/L, (15 mg) -0.34 ug/L
			Tirzepatide 10 mg		-7.5 kg	
			Tirzepatide 15 mg		-10.2 kg	
			Oral antihyperglycemic oral		-0.5 kg	
Jastreboff et al 2022 (SURMOUNT-1)[52]	N = 2,539, 72 weeks, double blind placebo controlled, phase 3, 119 sites in 9 countries	≥18 years old, BMI ≥ 30 kg/m^2, or ≥27 kg/m^2, or more and at least one weight-related complication. Comorbidities: hypertension, dyslipidemia, obstructive sleep apnea, and cardiovascular disease. History of at least one unsuccessful dietary effort to lose body weight	Tirzepatide 5 mg	Not applicable	-15%	Change in waist circumference from precedent (5 mg) -14.0 cm, (10 mg) -17.7 cm, (15 mg) -18.5 cm. Percentage weight reduction of ≥20% (5 mg, not controlled for type 1 error) 48%, (10 mg) 67%, and (1 5mg) 71% (placebo) 9%
			Tirzepatide 10 mg		-19.5%	
			Tirzepatide 15 mg		-20.9%	
			Placebo, weekly SC		-3.1%	

Outcomes Cardiovascular and Effect of Renal Function

In over two years, tirzepatide's safety and effectiveness were reviewed by comparing it with insulin glargine in subjects at high cardiovascular risk with advanced T2DM.[53] Cardiovascular outcomes were evaluated using four MACE-4 Composites (cardiovascular death, myocardial infarction, stroke, and hospitalization for unstable angina) as the secondary outcome. The tirzepatide group did not have an increased rate of MACE-4 events compared to insulin glargine (hazard ratio [HR], 0.74; 95% confidence interval [CI], 0.51 to 1.08).[53]

In a post-hoc analysis of SURPASS-4 data, a randomized study comparing tirzepatide with insulin glargine in T2DM patients and high cardiovascular risk, it was found that tirzepatide slowed down the decrease in glomerular filtration rate and lowered the ratio of urinary creatinine albumin compared to insulin glargine, after a median of 85 weeks.[54]

Tolerance and Side Effects of Tirzepatide

Hypoglycaemia. The incidence of hypoglycaemia episodes (blood glucose < 70 mg/dL) with tirzepatide has been compared and observed with placebo and GLP-1 Ras. The incidence of hypoglycaemia was lower with 8% to 14% tirzepatide than with insulin 48% degludec, but the same compared with placebo and insulin glargine.[3,42,55]

Gastrointestinal side effects. Nausea was more frequently reported as an adverse effect of tirzepatide compared with placebo (especially at the maximum dose of 15 mg: OR 5.60; 95% confidence interval, 3.12-10.06), followed by vomiting (OR 5.50; 95% CI, 2.40-12.59) and diarrhea (OR 3.31; 95% CI, 1.40-7.85). The incidence of gastrointestinal adverse events was also compared between tirzepatide and two GLP-1 RAs, dulaglutide and semaglutide, except that the incidence of diarrhea was higher at the 10 mg dose of tirzepatide. Note that treatment discontinuation due to intolerance was more frequent at the 15 mg Ttrzepatide dose than the other comparators.[42] Tirzepatide 15 mg was discontinued due to adverse events at 7% versus 3% with placebo in the SURPASS-1 study,[43] 10.8% versus 2.5% with placebo in the SURPASS-5 study,[47] 5.7% versus 2.8% with semaglutide 1 mg in the SURPASS-2 study,[44] 11% versus 1% with insulin degludec in the SURPASS-3 study,[45] and 11% versus 5% with insulin glargine in the SURPASS-4 study.[46]

The incidence of pancreatitis was no more than 1%, and progression to diabetic nephropathy was no more than 2% in all treatments with the tirzepatide group.[41,45,46] This study reported no risk for the above two conditions despite using GLP-1 receptor agonists.

Dosing and Administration

Tirzepatide, mounjaro, is produced as a colourless to slightly yellow transparent solution in an automatic syringe, is used in single doses, and is available in 6 doses, which are 2.5 mg; 2.5 mg; 5 mg; 7.5 mg; 10 mg; 12.5 mg and 15 mg. It is recommended to start this medication at 2.5 mg, subcutaneously (SC) in the abdomen, thigh, or upper arm, and the site should be rotated with each dose. Dose SC once weekly for four weeks to reduce gastrointestinal effects such as nausea and vomiting. The dose may be increased to 5 mg once a week.[52]

Like other GLP-1 agonists, tirzepatide can be administered regardless of meal timing. Dosing can be tolerated if it is as late as four days, but dosing should be skipped if it is more than four days. Patients can also change the day of the week for tirzepatide administration if desired, if the doses are spaced at least three days apart. It is recommended to store tirzepatide-filled syringes in their original containers and the refrigerator, but they can be kept at room temperature for up to 21 days.[52]

Table 2. Tirzepatide Studies Continue to be Carried Out and are Widely Reviewed

Study	Study design	Participant(s)	Start date	Completion date	Primary outcome
SUMMIT (NCT04847557)	Phase 3 study, comparator: placebo	N=700, BMI ≥ 30 kg/m2, diagnosis of stable heart failure (NYHA class II-IV) with LVEF ≥ 50%	April 2021	November 2023	i) A hierarchical composite of all-cause mortality, heart failure event, 6-minute walk test distance (6MWD) and Kansas City Cardiomyopathy Questionnaire Clinical Summary Score ii) Change from baseline in exercise capacity as measured by 6MWD at 52 weeks
SINERGT-NASH (NCT04166773)	Phase 2 study, comparator: placebo	N=196, BMI between 27 and 50 kg/m2 and histologic diagnosis of NASH with stage 2 or 3 fibrosis by liver biopsy	November 2019	December 2023	% of participants with absence of NASH with no worsening of fibrosis on liver histology at 52 weeks
SURMOUNT-OSA (NCT05412004)	Phase 3 study, comparator: placebo	N=412, without diabetes, BMI ≥ 30 kg/m2 and moderate to severe sleep apnoea at the trial screening	June 2022	February 2024	% change from baseline in apnoea-hypopnea index at 52 weeks
SURPASS-SWICTH (NCT05564039)	Phase 4 study, comparator: placebo	N=250 T2DM, BMI ≥ 25 kg/m2 and being on dulaglutide 0.75 mg or 1.5 mg once weekly	December 2022	September 2024	Change from baseline in HbA1c at 40 weeks
SURPASS-CVOT (NCT04255433)	Phase 3 study, comparator: Dulaglutide	N=13.299 with T2DM, BMI ≥ 25 kg/m2 and confirmed atherosclerotic CV disease	May 2020	October 2024	Time to first occurrence of death from CV causes, myocardial infarction or stroke
SURMOUNT-MMO (NCT045556512)	Phase 3 study, comparator: placebo	N=15.000 without diabetes aged ≥ 40 with established CV disease or ≥ 50 (for women ≥ 55) with multiple CV risk factors	October 2022	October 2027	Time to frost occurrence of any composite event of composite (all-cause death, nonfatal myocardial infarction, nonfatal stroke, coronary revascularization or heart failure events)

Table 2. Selected ongoing clinical trials with tirzepatide: (a) SURPASS program and SURMOUNT program; (b) SUR¬MOUNT-MMO, A Study of tirzepatide on the Reduction on Morbidity and Mortality in Adults With Obesity; c) SURPASS-CVOT, A Study of tirzepatide Compared With Dulaglutide on Major Cardiovascular Events in Participants With Type 2 Diabetes; (d) SURPASS-SWITCH, A Study of tirzepatide in Adult Participants With Type 2 Diabetes Switching From Dulaglutide; HbA1c, glycosylated hemoglobin; (d) SYNERGY-NASH, A Study of tirzepatide (LY3298176) in Participants With Nonalcoholic Steatohepatitis (NASH); (e) SURMOUNT-OSA, Obstructive Sleep Apnea Master Protocol GPIF: A Study of tirzepatide in Participants With Obstructive Sleep Apnea; (f) SUMMIT, A Study of tirzepatide in Participants With Heart Failure With Preserved Ejection Fraction and Obesity; NYHA, New York Heart Association; LVEF, left ventricular ejection fraction. CV, cardiovascular; T2DM, type 2 diabetes mellitus; BMI, body mass index, NASH, non-alcoholic steato-hepatitis. *adapted from* Rachel S 2023 (22)

CONCLUSION

Tirzepatide, a uni-molecular dual receptor agonist of GIP/GLP-1, has been subjected to extensive trials in several studies involving large populations, SURPASS, and SURMOUNT. tirzepatide will be one of the future treatments that will be favoured and used as clinical practice guidelines for treating T2DM. tirzepatide has been shown to lower A1c more than other glucose-lowering drugs, more significant weight loss, and similar gastrointestinal incidence as semaglutide. In the future, tirzepatide may become the primary treatment for obesity, including metabolic liver disease, with minimal gastrointestinal effects and at a lower cost.

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