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Tirzepatide A Novel Twincretin for the Treatment of Type 2 Diabetes Mellitus and Obesity

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ABSTRACT:

Therapies based on incretin and employing “glucagon-like peptide-1 receptor agonists (GLP-1RA)” are already well-established in the “treatment of type 2 diabetes (T2D)”. In order to target several metabolic pathways for the “metabolism of carbohydrates, lipids, and proteins, novel dual- or triple-receptor agonists” that bind to the receptors for “glucagon, glucose-dependent insulinotropic polypeptide (GIP), and/or GLP-1” concurrently are being developed. “Dual- and triple-receptor agonists” that act via various receptors and post receptor pathways seem promising for the treatment of type 2 diabetes (T2D) and obesity due to the possibility of additive or synergistic effects. A critical turning point in this process was the recent approval of the first dual-receptor agonist. The “Food and Drug Administration (FDA)” in the US approved tirzepatide, a “GIP/GLP-1” receptor agonist, for once-weekly subcutaneous injections as a T2D treatment in May 2022. A recent approval from the “European Medicines Agency (EMA)”. It has been established that tirzepatide has stronger effects on decreasing these parameters than traditional anti-diabetic medication and that its dose-dependent effects result in clinically meaningful decreases in body weight and glycemic indices. In this article, tirzepatide's potential applications for the treatment of obesity and maybe other T2D comorbidities are summarised together with the present clinical study programme, its findings, and related clinical trial applications.

Keywords: “TIRZEPATIDE, glucagon-like peptide-1 receptor, glucose-dependent insulinotropic polypeptide (GIP), type 2 diabetes”.

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INTRODUCTION:

"Type 2 diabetes (T2D)" prevalence is continually increasing, with distinct incidence increases occurring in various regions of the world, according to the "International Diabetes Foundation (IDF) Diabetes World Atlas", which was published at the end of 2021. By 2045, there will be 783 million affected persons worldwide between the ages of 20 and 79, up from 537 million in 2021, with Europe experiencing the lowest incidence growth (13%) and African countries south of the Sahara experiencing the highest growth (134%). (1). Poor glucose control leads to vascular problems and comorbidities, which shorten lifespan by six years and cause premature mortality (2). Randomized forthcoming examinations have shown a huge decrease in microvascular and macrovascular entanglements in patients with T2D when plasma glucose, pulse, and plasma lipid focuses are brought down towards a typical level (3-15). The goals of T2D treatment have evolved over the past few years, shifting from a primarily "glucocentric" to a "patient-centered," individualized approach that places a greater emphasis on the characteristics and comorbidities of the patient for the purpose of treatment. In 2018, the "American Diabetes Association (ADA)" and the "European Diabetes Association (EASD)" issued joint recommendations for a novel T2D treatment algorithm that is constantly being updated. These recommendations were the initial push for this strategy (16, 17).

Obesity, which is defined as having a body mass index greater than 30 kg/m2, is also on the rise everywhere in the world and is posing challenges for a number of healthcare systems and social structures. This condition's prevalence roughly tripled between 1975 and 2016. In 2016, 650 million individuals worldwide were obese, and by 2020, 39 million children under the age of five were also overweight or obese (18). "Obesity is not only a significant risk factor for type 2 diabetes, but also for other conditions such as osteoarthritis, reflux disease, gallstones, nonalcoholic steatohepatitis (NASH), depression, sleep apnea, and chronic pulmonary disease" (18–22).

The most recent recommendations for treating diabetes and obesity advise using a progressive approach, beginning with lifestyle modifications that encourage people to eat less, move more, and form healthier behaviours. The lifestyle treatments should be assessed, modified, and maintained throughout time in a "informed consent" with the patient regardless of whether additional medical or surgical treatment is started during the course of T2D or obesity (16, 17, 23–25).

THERAPIES BASED ON INCRETINS

"Incretins are hormones that enteroendocrine cells in the mucosa of the gut release following a meal. They contribute to approximately 70% of the physiological postprandial insulin secretion and are potent stimulators of postprandial insulin secretion under hyperglycemic conditions". This phenomenon is described by the so-called incretin effect, which also explains why oral glucose causes euglycemic glucose excursions in comparison to

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intravenous glucose, which causes a lower insulin response (26, 27). The major incretin hormones in humans are the peptides "glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP)". GLP-1 is still able to stimulate insulin release even when GIP loses its insulinotropic effect in T2D with persistent hyperglycemia (28, 29). By concurrently suppressing glucagon secretion and boosting insulin secretion, parenteral injection of therapeutic dosages of GLP-1 can normalise plasma glucose in patients with "type 2 diabetes and hyperglycemia" (30). "Native GLP-1" is not an effective treatment because it is rapidly broken down by the enzyme "dipeptidyl-peptidase-IV (DPP-4)" within minutes (31, 32). The concept of raising GLP-1 concentrations led to the introduction of "synthetic injectable DPP-4 resistant GLP-1 receptor agonists (GLP-1RA) and oral DPP-4 inhibitors as T2D therapeutic treatment options" (31–36). GLP-1RA lowers "body weight and systolic blood pressure" in addition to providing robust and efficient glycemic control. They also slow down gastric emptying and promote satiety through effects on "the central nervous system and have a low risk of hypoglycemia".

However, GLP-1RA therapy is not without its difficulties and drawbacks. Typical at the beginning of treatment are gastrointestinal side effects, most of which are temporary fullness and nausea. They typically subside after a few weeks of long-term therapy and affect 20%–30% of patients. As a result, treatment with GLP-1RA ought to begin at low doses that can be increased (33, 34). In general, compared to long-acting mixes, the gastrointestinal side effects are better defined with more limited acting GLP-1RA. Individual tolerance and the intensity of digestive problems after therapy begins varies (36). GLP-1RA should not be administered to patients who have a history of either acute or chronic pancreatitis, and treatment should be discontinued immediately in the event of any clinical manifestations of acute pancreatitis. Normal GLP-1 RA side effects include a free height in plasma amylase and lipase activity. Treatment can continue in these circumstances. Another contraindication to the usage of GLP-1RA is the presence of medullary thyroid cancer or "multiple endocrine neoplasia type 2 (MEN2)" (33, 34, 36). "GLP-1RAs must be injected subcutaneously on a daily or weekly basis, with the exception of the oral formulation of semaglutide" (33, 34, 36).

"Due to positive results from cardiovascular safety studies that showed a decrease in the combined cardiovascular endpoint three-component major adverse cardiovascular event (MACE-3; cardiovascular death, nonfatal myocardial infarction, and nonfatal stroke) for the GLP-1RA drugs albiglutide, efpeglenatide, dulaglutide, liraglutide, and semaglutide (ages 10–18)".

The GLP-1RA liraglutide has also been authorised for the treatment of obesity at a standard dose that is higher than the normal dose used to treat T2D as a result of the findings of the SCALE study programme (37, 38). (1.2 mg once daily).

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THE DEVELOPMENT OF DUAL- AND TRIPLE-RECEPTOR AGONISTS

The individual pathophysiology of type 2 diabetes and obesity is complex and diverse. Because of the potential for additive or synergistic effects, therapeutic principles acting via various receptors and postreceptor pathways seem appealing. Multiple metabolic pathways for protein, lipid, and carbohydrate metabolism could be influenced simultaneously by this strategy. In a similar vein, the regulation of appetite and energy metabolism could be altered therapeutically (39–41).

THE JUSTIFICATION FOR USING DUAL-RECEPTOR AGONISTS FOR GLP-1 AND GIP

"In healthy volunteers, infusions of GLP-1 and GIP increased insulin secretion together (42). The N-terminal portion of the peptides GLP-1 and GIP share a high degree of amino acid sequence similarity. GLP-1 has a very low affinity for the GIP receptor and vice versa, and they bind to very specific specific receptors (43). GLP-1 and GLP-1/GIP chimeric peptides' affinity for the GLP-1 receptor in insulinoma cell lines was investigated through in vitro receptor binding studies (44, 45). GIP appears to have no such effects, whereas GLP-1 also inhibits appetite and food intake". Going against the norm, many examinations have even recommended that GIP might advance stoutness. GIP did not appear to be a treatment option for T2D or obesity based on these findings (46, 47). The physiological effects of "GLP-1 and GIP on various organ systems" are depicted in detail in Figure 1. In obese people with T2D, GLP-1/GIP chimeric peptides have demonstrated remarkable weight loss and glucose lowering efficacy, and GIP receptor antagonists have been shown in animal studies to induce weight loss. As a result, using both GIP receptor agonists and antagonists in the treatment of obesity may be advantageous (46). There is some proof that agonist-induced internalisation of the two GLP-1 and GIP receptors differs significantly, even though the precise mechanisms underlying these observations are still unclear. The structural alterations in the ligand peptides, similar to those in GIP/GLP-1 dual-receptor agonists, may drastically affect these physiological processes, which may account for why an antagonist can activate while an agonist can block receptor signalling (46–49). The most important patterns of GIP agonism and antagonism's therapeutic effects on preventing obesity and lowering body weight are summarised in Table 1 (49).

"FIGURE 1 Overview of the biological glucose-dependent insulinotropic polypeptide (GIP) and glucagon-like peptide-1 (GLP-1) effects at the organ/tissue level (modified from (47)). The blue arrows depict relevant physiology".

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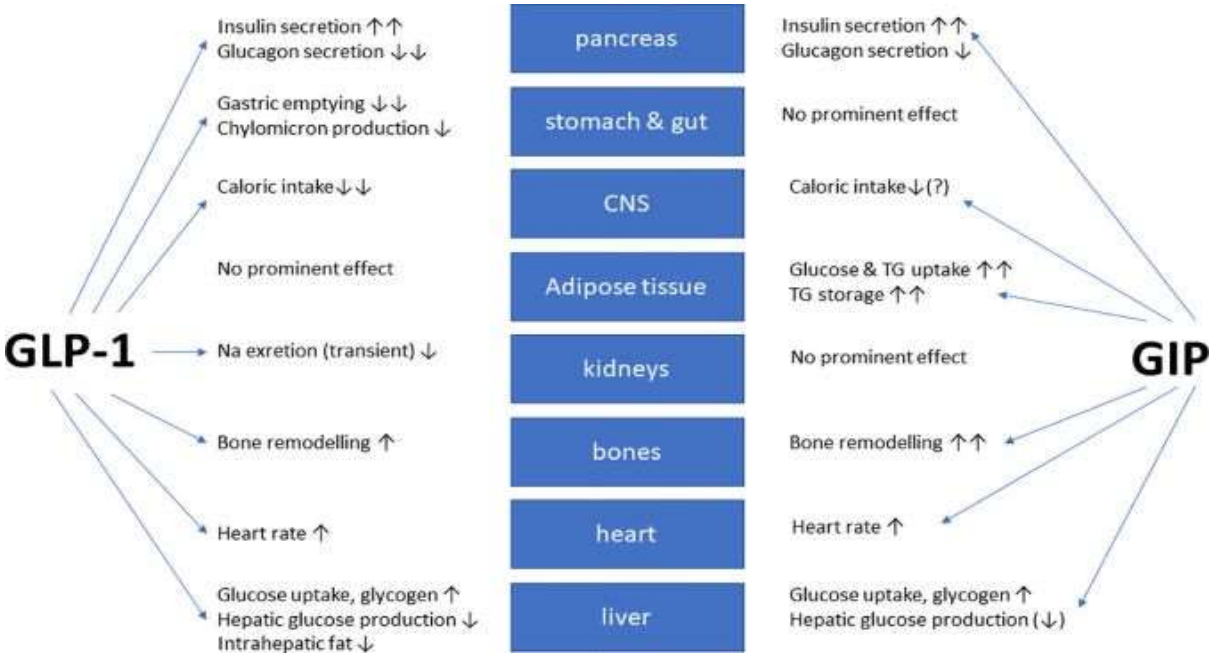

Figure : 1

Table : 1

Experimental approach		Glycemic homeostasis		Body weight/energy household		
Intervention regarding GIP receptor stimulation	Model	Glucose tolerance	Insulin resistance	Body weight	Energy intake	Energy expenditure
Antagonism	Prevention of diet-induced obesity and diabetes	↑	↓	↓↓	(↓)	0
	Treatment of pre-existent obesity and diabetes	↑↑	↓	(↓)	0-(↓)	0
Agonism	Prevention of diet-induced obesity and diabetes	0	0	0	0-(↓)	0
	Treatment of pre-existent obesity and diabetes	↑↑	(↓)	0-(↓)	0-(↓)	0

Prevention of diet-induced obesity: healthy, nonobese animals at baseline receiving experimental treatment while receiving a high-fat diet. Treatment of pre-existing obesity: animals with genetic mutations (ob/ob or db/db mice) causing obesity or high-fat diet-induced obesity at baseline. Agonism summarizes peptide GIP agonists, interventions leading to GIP hypersecretion, or antibody-mediated stimulation of GIP receptors; antagonism summarizes peptide GIP antagonists, interventions against K cells or GIP secretion, or specific antibodies either inactivating circulating GIP or GIP receptors. "(↑), ↑, ↑↑" trend or significant increment in this parameter (weak, intermediate, or strong effect); "(↓), ↓, ↓↓" trend or significant reduction in this parameter (weak, intermediate, or strong effect); 0, no obvious effect. Only patterns that are representative of all published studies in this category have contributed to the conclusions summarized in this table.

"TABLE 1 Effects of GIP receptor agonism or antagonism on glycemic control, body weight, and energy balance in animal models of obesity and diabetes (modified according to Campbell and Nauck)" (47, 49).

THE DEVELOPMENT OF DUAL- AND TRIPLE-RECEPTOR AGONISTS

The individual pathophysiology of type 2 diabetes and obesity is complex and diverse. Because of the potential for additive or synergistic effects, therapeutic principles acting via various receptors and postreceptor pathways seem appealing. Multiple metabolic pathways for protein, lipid, and carbohydrate metabolism could be influenced simultaneously by this strategy. In a similar vein, the regulation of appetite and energy metabolism could be altered therapeutically (39–41).

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The reasoning for double receptor agonists for GLP-1 and GIP

"In sound workers, mixtures of GLP-1 and GIP additively affected the feeling of insulin discharge (42). The N-terminal portion of the peptides GLP-1 and GIP share a high degree of amino acid sequence similarity. GLP-1 has a very low affinity for the GIP receptor and vice versa, and they bind to very specific specific receptors (43). GLP-1 and GLP-1/GIP chimeric peptides' affinity for the GLP-1 receptor in insulinoma cell lines was investigated through in vitro receptor binding studies (44, 45). GIP appears to have no such effects, whereas GLP-1 also inhibits appetite and food intake". Going against the norm, many examinations have even recommended that GIP might advance stoutness. GIP did not appear to be a treatment option for T2D or obesity based on these findings (46, 47). The physiological effects of GLP-1 and GIP on various organ systems are depicted in detail in Figure 1. In obese people with T2D, GLP-1/GIP chimeric peptides have demonstrated remarkable weight loss and glucose lowering efficacy, and GIP receptor antagonists have been shown in animal studies to induce weight loss. As a result, the treatment of obesity may benefit from the use of both agonists and antagonists of the GIP receptor (46). "Although the precise mechanisms behind these findings are still unknown, there is some evidence that agonist-induced internalization of the two GLP-1 and GIP receptors differs significantly. As in GIP/GLP-1 dual-receptor agonists, structural changes in the ligand peptides may significantly alter these cellular processes, which may explain why an antagonist can activate while an agonist can block receptor signaling (46–49). Table 1 (49) provides a summary of the most significant known patterns for the therapeutic effects of GIP agonism and antagonism in preventing obesity and reducing body weight".

IMPROVEMENT, PRECLINICAL, AND EARLY CLINICAL INFORMATION ON THE GIP/GLP-1 RECEPTOR AGONIST TIRZEPATIDE

Tirzepatide (LY3298176), the first drug in this class to receive FDA approval for the treatment of T2D in May 2022 (manufacturer Eli Lilly Comp., Mounjaro® brand), is the GIP/GLP-1 receptor agonist that has received the most attention among those currently in development (53–55). The European Medicines Agency (EMA) recommended that tirzepatide be given marketing authorisation as a T2D medication in a favourable opinion it released in July 2022 (56).

THE GIP/GLP-1 CHIMERIC PEPTIDE PHARMACODYNAMICS

Tirzepatide has a peptide chain length of 39 amino acids. At the side chain of the Lys20 amino acid, the linear peptide is covalently bound to a C20 fatty diacid moiety (57). "The amino acid sequence of tirzepatide is shown in comparison to that of GLP-1, GIP, and the GLP-1RA exendin-4 (exenatide) in Figure 2. The fatty acid side chain, in comparison to other peptides linked to fatty acids (such as the insulins detemir and degludec, the GLP-1RA liraglutide and semaglutide), enables albumin to be bound after subcutaneous injection, slowed enzymatic degradation, and extended biological half-life (57–60). Tirzepatide has a

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high affinity for both GIP (Ki = 0.135, which is comparable to native GIP) and GLP-1 receptors (Ki = 4.23, approximately). 5 times less affinity than for native GLP-1 In vitro flagging examinations exhibited that tirzepatide had the option to enact the GIP receptor with practically identical power to local GIP (57). The GLP-1 receptor's activating power was also demonstrated, but it was 13 times less potent than that of native GLP-1. Tirzepatide was a GLP-1RA with less potency than the GLP-1RA semaglutide. Tirzepatide was able to activate the GIP and/or GLP-1 receptors and induce glucose-dependent insulin secretion in all of the in vitro and in vivo models tested. Tirzepatide administration caused a weight loss in a rodent model of obesity by increasing energy expenditure and reducing food intake (57). Subjects with T2D participated in a phase Ib trial in which they received either 10 mg or 15 mg of tirzepatide once weekly for four weeks. This resulted in a significant drop in fasting plasma glucose concentrations (LSM difference [95% CI]: 49.12 mg/dl [78.14, 20.12] and 43.15 mg/dl [73.06, 13.21] respectively) and weight loss (LSM difference [95% CI: 2.62 kg, or 3.79, 1.45 pounds, and 2.07 kg, or 3.25, 0.88 pounds, respectively; NCT02759107) is the registration number for the clinical trial. In a similar vein, postprandial plasma glucose concentrations and plasma glucagon concentrations were decreased while first- and second-phase insulin secretion and insulin sensitivity were elevated. Similar to the effect seen with GLP-1RA therapy, gastric emptying was delayed The information on insulin emission, insulin awareness, and glucose homeostasis were affirmed in the stage II clinical review (clinical preliminaries enrollment number NCT03131687)" (62). Tirzepatide also improved NASH and biomarkers for cardiovascular risk in the phase II program (63–65).

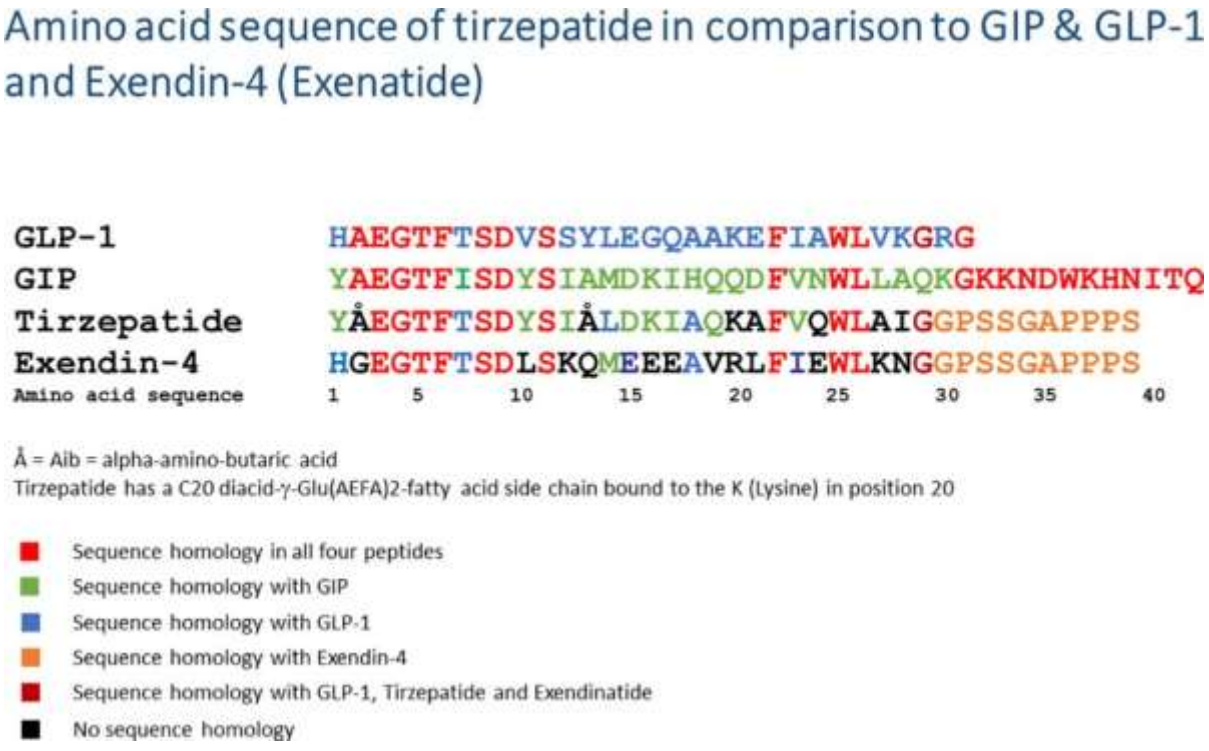

Figure : 2

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"FIGURE 2 Amino acid sequence of tirzepatide in comparison to native GIP, GLP-1, and exendin-4 (exenatide). The amino acid sequences of the peptides are given in a one-letter code starting with the N-terminus on the left side. Å = Aib, alpha-amino-butyric acid; diacid-γ-Glu(AEFA)2, the linker molecule linking a fatty acid side chain with a length of 20 carbon atoms (=C20) to the K (lysine) in position 20; GLP-1, glucagon-like peptide-1; GIP, glucose-dependent insulinotropic polypeptide".

PHARMACOKINETICS

Patients with T2D and healthy volunteers have comparable pharmacokinetics (57). Regardless of the injection site, tirzepatide exposure increases dose proportionally after subcutaneous injection. The bioavailability is 80%, and the time to maximum plasma concentration (tmax) ranges from 8 to 72 hours. After four once-weekly injections, plasma concentrations reach a steady state. Plasma albumin is bound to about 99% of the bioavailable tirzepatide. The tirzepatide peptide backbone is cleaved by proteolysis, the C20 fatty diacid moiety is -oxidized, and amide hydrolysis is used in the metabolic clearance process. The metabolites are eliminated through the feces and urine. It has a half-life of about five days. These pharmacokinetic information permit a once-week by week subcutaneous infusion routine. Age, gender, race, ethnicity, body weight, renal or hepatic function, and body weight have no significant impact on tirzepatide's pharmacokinetics (61). According to the data from the most recent studies, tirzepatide has no effect on CYP enzyme activity or drug transporters. When tirzepatide therapy is started, concomitant oral medications may not be absorbed as quickly or as efficiently; The delayed gastric emptying observed when tirzepatide is administered explains this effect (61). Women who use oral contraceptives should be aware of this effect. In such a situation, women shouldn't just use oral contraception; they should also switch to a completely nonoral contraceptive method or use a barrier contraceptive for four weeks after starting tirzepatide or four weeks after the last dose increase.

THE SURPASS CLINICAL TRIAL PROGRAM'S CLINICAL DATA ON TIRZEPATIDE IN TYPE 2 DIABETES

Early trials with tirzepatide in individuals with T2D from various ethnic populations showed a dose-dependent decrease in HbA1c and other glycemic markers ("clinical trials registration numbers NCT03322631, NCT03131687, and NCT03311724") (66–68). Tirzepatide was found to be similar to dulaglutide (1.5 mg once weekly) in a phase II dose-finding study for lowering body weight and HbA1c (the primary and secondary endpoints, respectively) (66). Comparing GLP-1RA therapy with a stepwise dose escalation that started with a modest beginning dose, it was found that the latter resulted in a decreased incidence of gastrointestinal side effects and better tirzepatide tolerability (67).

Eight studies were launched as part of the phase III clinical program to compare tirzepatide's efficacy and safety to those of a number of other well-established antidiabetic medications in

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T2D when used alone, in combination with metformin as the initial treatment, or with metformin and insulin glargine as the initial treatment. "These studies used a similar design for the doses of tirzepatide, starting with 2.5 mg once a week and increasing by 2.5 mg every 4 weeks until the randomized final treatment doses of 5, 10, or 15 mg were reached. Six global, two Japanese, and one Asian-Pacific study are included in the SURPASS program (69). The characteristics and outcomes of the entire SURPASS study program are summarized in Table 2 (69–74). The remaining studies (SURPASS-6, SURPASS-CVOT, SURPASS-J-mono, and SURPASS-J-combo), as well as the results of the studies SURPASS-1 through SURPASS-5, have been published. The clinical trials for SURPASS-AP-combo (registration numbers NCT04537923, NCT04255433, NCT03861052, NCT03861039, and NCT04093752) have not yet been completed".

TIRZEPATIDE IN TYPE 2 DIABETES: PRELIMINARY CARDIOVASCULAR OUTCOME DATA

"The aforementioned preliminary cardiovascular safety data from the SURPASS-4 study demonstrated that there was no excess cardiovascular risk associated with the treatment (54, 73). The cardiovascular safety of tirzepatide in T2D patients was recently confirmed by a meta-analysis of data from seven double-blind randomized controlled trials with tirzepatide that lasted at least 26 weeks (77). The time it took study participants with T2D receiving tirzepatide to first experience a confirmed MACE-4 (cardiovascular death, myocardial infarction, stroke, and hospitalized unstable angina) was compared to the time it took the control groups receiving different standard therapy in this meta-analysis. A stratified Cox proportional hazards model was used to calculate the hazard ratios (HRs) and confidence intervals (CIs), with trial-level cardiovascular risk serving as the stratification factor and treatment being considered a fixed effect. A total of 7,215 study participants' data were utilized". There were 4,887 patients in the tirzepatide-treated group, and there were 2,328 in the control group. One MACE-4 event occurred for each of the 142 subjects. "The SURPASS-4 trial, which looked at a group of patients with a high risk of cardiovascular disease, had the majority of the MACE-4 patients (n = 109). For MACE-4, the HR for tirzepatide versus standard therapy was 0.80 (95% CI, 0.57–1.11), the HR for cardiovascular death was 0.90 (95% CI, 0.50–1.61), and the HR for all-cause death was 0.80 (95% CI, 0.51–1.25)". All of the subgroups that were looked at showed the same effects, with subjects with type 2 diabetes and a higher risk of cardiovascular disease showing the strongest effects (77). The SURPASS-CVOT study's large cardiovascular event-driven safety trial comparing dulaglutide with tirzepatide is expected to conclude in 2024 (78).

INFORMATION REGARDING TIRZEPATIDE AND FATTY LIVER DISEASE can be found in a substudy of the SURPASS-3 trial that included 296 participants (SURPASS-3 MRI). Throughout the course of the study, changes in liver fat as well as other fat compartments were monitored. "Additionally, a subgroup of the tirzepatide cohort was compared to the insulin degludec comparator subgroup (54, 79). At the outset, the liver fat

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content (LFC) of the tirzepatide group was 15.67%, while that of the insulin degludec group was 16.58%. The pooled tirzepatide 10 and 15 mg groups had a significantly higher mean absolute change at week 52 than the insulin degludec group did (8.09% vs. 3.38%; p < 0.0001; primary destination). In the tirzepatide groups, the reductions in LFC, visceral adipose tissue (VAT) (= 0.29), the transaminase liver enzyme ASAT (= 033), and body weight (p = 034) were all significantly correlated with baseline LFC (p 0.0006) (54, 79). Another study (phase II trial) evaluating the efficacy and safety of tirzepatide in patients with nonalcoholic steatohepatitis (SYNERGY-NASH, clinical trial registration number NCT04166773) is currently conducting additional research on these metabolic effects of tirzepatide on the liver" (54, 80).

The GLP-1RA liraglutide has been approved for the pharmacological treatment of obesity, and other GLP-1RA may also be approved in the future for this indication (39–41, 81).

TIRZEPATIDE IN OBESITY—

"The subsequent clinical study program Additionally, dual- and triple-receptor agonists have the potential to treat obesity (39–41). Treatment with tirzepatide led to significant weight loss in overweight or obese T2D patients (69–76). A clinical study program was launched in response to these findings to investigate the safety and efficacy of tirzepatide in the management of obesity and the treatment of obesity. The global SURMOUNT study program consists of four randomized controlled trials using tirzepatide at doses of 10 and 15 mg in the studies SURMOUNT-2 to SURMOUNT-4 and all three doses, including the 5-mg dose in SURMOUNT-1" (82–85). Each study lasted at least 72 weeks. In the SURMOUNT-1 study, 2,539 people without diabetes were randomly assigned to one of four equally large study arms that received either a placebo or one of the three doses of tirzepatide (five, ten, or fifteen milligrams once weekly) over the course of 72 weeks. The participants were monitored for an additional 52 weeks following a 20-week titration phase. The percentage change in weight from baseline and a body weight reduction of 5% or more were the study's co-primary endpoints at 72 weeks (82). For the coprimary endpoints of percentage body weight reductions from baseline at week 72 and the proportion of patients achieving a 5 percent body weight reduction at week 72, the tirzepatide doses of 10 and/or 15 mg performed better than the placebo. At 72 weeks, the mean body weight reductions from baseline for the treatment-regimen estimand were 15.0%, 19.5%, and 20.9% in the tirzepatide 5, 10, and 15 mg groups, respectively, compared to 3.1% in the placebo group. 85 percent, 89 percent, and 91 percent of patients in the tirzepatide 5, 10, and 15 mg groups experienced a weight loss of less than 5 percent at week 72, in contrast to 35 percent in the placebo group (p 0.001 for all comparisons with placebo). There was a dose-dependent group size of 50% of participants receiving 10 mg tirzepatide and a proportion of 57% in the study arm receiving 15 mg for the secondary endpoint of the proportion of patients achieving a body weight reduction of less than 20%. Tirzepatide treatment was likewise connected with a decrease in midriff perimeter, systolic pulse, fasting insulin and plasma lipid focuses as cardiometabolic risk boundaries.

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The standard 36-item Short Form Health Survey (SF-36)'s physical function parameters also improved (54, 82).

ADVERSE EVENTS WITH TIRZEPATIDE

The adverse events with tirzepatide that were observed in the clinical study program are comparable to those with GLP-1RA therapy. During the first few weeks of treatment, mild to moderate, dose-dependent, and brief gastrointestinal side effects are the most common adverse events. The majority of tirzepatide-related gastrointestinal side effects occurred during the titration phase. The pooled data on the gastrointestinal side effects of T2D therapy versus placebo from the SURPASS-1 to SURPASS-5 studies are summarized in Table 3 37.1%–43.6% of patients in the tirzepatide group and 20.4% of patients in the placebo group experienced gastrointestinal side effects; These side effects caused 3.0%–6.6% and 0.4 percent, respectively, of patients in the respective groups to stop receiving treatment (54). In the aforementioned SURPASS studies, symptom-free elevations of pancreatic enzyme concentrations for lipase and amylase were observed, in comparison to observations made during GLP-1RA treatment. As on account of GLP-1RA, the meaning of this finding which is reversible with cessation of treatment is hazy.

Sinus tachycardia, which is a concomitant increase in heart rate of 15 beats per minute from baseline (4.6%–10.0% vs. 4.3% with placebo), hypersensitivity, including severe reactions (3.2% vs. 1.7%), injection site reactions (3.2% vs. 0.4%), and acute gallbladder disease (0.6% vs. 0%) were additional adverse events observed with tirzepatide treatment (54, 61). It appears that tirzeptide carries no inherent risk of hypoglycemia; In clinical studies, only patients treated with tirzepatide who were also taking insulin and/or oral insulinotropic agents (sulfonylurea) had an increased risk of hypoglycemia (61). The frequency of hypersensitivity reactions and antibody formation during treatment with tirzepatide is comparable to that of GLP-1RA therapy. A black box warning about the risk of thyroid C-cell tumors appears in the US prescribing information for tirzepatide; Patients with multiple endocrine neoplasia type 2 syndromes and those with a personal or family history of medullary thyroid carcinoma should not take tirzepatide (54, 61).

Table : 3

Symptom	Tirzepatide 5 mg (total *n* = 237; % of subjects)	Tirzepatide 10 mg (total *n* = 240; % of subjects)	Tirzepatide 15 mg (total *n* = 241; % of subjects)	Placebo/comparator (total *n* = 235; % of subjects)
Nausea	12	15	18	4
Diarrhea	12	13	17	9
Decreased appetite	5	10	11	1
Vomiting	5	5	9	2
Constipation	6	6	7	1
Abdominal pain	6	5	5	4

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TABLE 3 Pooled gastrointestinal adverse events associated with tirzepatide treatment in the SURPASS 1 and SURPASS 5 studies compared to comparator treatment in type 2 diabetes (54, 70, 75).

CONCLUSIONS:

According to the present study's data, tirzepatide has significantly outperformed the effects of the GLP-1RA dulaglutide and semaglutide on glycemic parameters in patients with T2D (54, 66, 67, 71). There are currently no cardiovascular data on endpoints like MACE-3 or MACE-4, but an early meta-analysis showed that patients with T2D treated with tirzepatide were at least cardiovascularly safe (78, 79). Tirzepatide is likely to be included in the T2D therapy algorithm for patients with obesity and T2D whose therapeutic goals are to normalize glycemia and lose weight until the results of the SURPASS-CVOT trial are available. The American and European Diabetes Associations' current recommendations for the T2D treatment algorithm are currently being revised (17). For obese patients, the updated version may include a 15% weight reduction, highlighting the need for GLP-1RA or tirzepatide treatment to achieve this therapeutic objective. Tirzepatide may be recommended as the first-line treatment in the event that the SURPASS-CV study demonstrates that it is superior to standard treatment. GLP-1RA with cardiovascular benefits continues to be the recommended substance class for obese patients with T2D, pre-existing atherosclerotic vascular disease, or a very high risk for this condition up until that point (17).

Tirzepatide may likewise turn into a significant pharmacological device for the treatment of heftiness assuming information from the Conquer 1 preliminary are affirmed in other clinical examinations (82). As an alternative to various bariatric surgery procedures, the body weight loss observed in this study opens the possibility of a pharmacological treatment for obesity.

According to the data that are currently available, the dual receptor agonist tirzepatide has outperformed the well-established GLP-1 RAs in terms of its ability to lower blood glucose and body weight (54, 66, 67, 71). Mechanistic studies that looked at the proportions of the agonistic properties of the GLP-1 and GIP receptors provide some explanations for these strong effects. Tirzepatide's promising efficacy in a variety of cell models, isolated islets, and perfused pancreas may be due to an imbalance toward the GIP receptor and distinct GLP-1 receptor signaling properties (86). To fully comprehend tirzepatide's molecular action, further mechanistic research will be required.

In the event of a SARS-CoV-2 infection, obesity and type 2 diabetes are significant risk factors for a more severe course of a COVID-19 disease. Obesity, diabetes, and hypertension all increase mortality risk in young and middle-aged patients, as shown by data from the European LEOSS registry and other sources. Adult patients of middle age and younger who had all three of the aforementioned risk parameters had a similar adjusted increased risk of death as nonobese, metabolically healthy patients of older age (56–75 years) (87). COVID-19-related deaths were also included in the SURPASS-4 study. In this study, COVID-19-

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related mortality was less than 1 percent in the insulin glargine and tripeptide arms, with a numerically lower mortality rate in the tirzepatide group (75). There have not yet been any published studies that directly characterize the effects of tirzepatide treatment in patients with T2D, obesity, COVID-19, or long COVID.

In addition, in the absence of obesity and poor metabolic health, elevated CRP levels partially explained the increased risk of COVID-19-related mortality with age. In conclusion, the modifiable risk factors of obesity, diabetes, and high blood pressure raise the risk of COVID-19-related mortality in young and middle-aged patients to levels comparable to those seen in older people.

In conclusion, the FDA recently granted treatment approval for T2D to tirzepatide, the first dual receptor agonist. While the safety profile and incidence of adverse events appear to be comparable, the efficacy in reducing glycemia and body weight is greater than that of GLP-1RAs. There have been no published studies comparing different dual- or triple-receptor agonists. With tirzepatide, there is now one promising GIP/GLP-1 receptor dual agonist that could play a significant role in the treatment plan for T2D and possibly also obesity.

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