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T2DM: Pharmacological Therapies and Clinical Evidence of Combined GIP/GLP-1 Receptor Agonism with Tirzepatide

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ABSTRACT

Diabetes mellitus (DM) is a disease mainly caused by impaired carbohydrate metabolism, resulting in increased blood glucose concentration. Patients with diagnosed diabetes have a higher incidence of atherosclerotic disease, cardiovascular disease, peripheral arterial disease, and cerebrovascular disease. The most recent drug introduced to the Italian market for the treatment of type 2 diabetes mellitus (T2DM) is tirzepatide, marketed under the trade name Mounjaro. It is a long-acting receptor agonist of glucose-dependent insulinotropic polypeptide (GIP) and glucagon-like peptide-1 (GLP-1). Its safety and efficacy were evaluated in five global randomized, controlled, phase 3 studies (SURPASS), which assessed glycemic control as the primary endpoint. Across all studies, treatment with tirzepatide demonstrated clinically significant and sustained reductions in HbA1c compared with placebo or active comparators (semaglutide, insulin degludec, and insulin glargine) for up to one year. The drug's pharmacodynamic profile is characterized by the synergistic activation of two incretins, enabling a combined action on glucose metabolism, appetite, and insulin sensitivity. In conclusion, the introduction of tirzepatide has opened new perspectives toward a personalized, more effective, and patient-centered therapeutic approach.

Keywords

Type 2 diabetes mellitus (T2DM), Tirzepatide, Mounjaro, Glucose-dependent insulinotropic polypeptide (GIP), Glucagon-like peptide-1 receptor agonist (GLP-1 RA), Dual GIP/GLP-1 receptor agonist, Glycemic control.

Introduction

Diabetes mellitus (DM) is a disease mainly caused by impaired carbohydrate metabolism, resulting in increased blood glucose concentration. Patients with diagnosed diabetes have a higher incidence of atherosclerotic disease, cardiovascular disease, peripheral arterial disease and cerebrovascular disease [1]. Insulin, the physiological and pathological target hormone in diabetes, is produced by the endocrine pancreas, which consists of more than one million islets of Langerhans scattered throughout the pancreatic parenchyma.

The five cell types present within the islets produce various hormones:

- Insulin, a hypoglycemic, storage, and anabolic hormone
- Glucagon, a hyperglycemic hormone that activates glycogen stores
- Somatostatin, an inhibitor of secretory cells
- Ghrelin, a peptide that stimulates the release of growth hormone from the pituitary gland
- IAPP (islet amyloid polypeptide), a hormone that modulates insulin secretion, gastric emptying, and appetite regulation [2].

The current classification of DM, based on the underlying pathological condition, includes:

- Type 1 diabetes mellitus
- Type 2 diabetes mellitus

Other forms of diabetes also exist:

- Latent Autoimmune Diabetes in Adults (LADA), characterized

by the presence of markers typical of type 1 diabetes and adult onset.
- Gestational diabetes mellitus (GDM), diagnosed for the first time during pregnancy, particularly in the last trimester. It affects approximately 4–7% of pregnant women, and although most return to normal glucose tolerance after pregnancy, they have a higher lifetime risk of developing type 1 diabetes [2].

Type 1 diabetes mellitus accounts for 5–10% of DM cases and is mainly diagnosed during childhood and adolescence, although it can occur at any age. It is an autoimmune disease characterized by the selective destruction of β cells, resulting in insulin deficiency. It is further classified into immune-mediated (type 1a), the most common form, and idiopathic (type 1b). At diagnosis, most patients have circulating autoantibodies such as anti-glutamic acid decarboxylase 65 (GAD65), insulin autoantibodies (IAA), anti-IA-2 tyrosine phosphatase (ICA512), and anti-zinc transporter 8 (ZnT8) antibodies [2].

Type 2 diabetes mellitus is the most common form, accounting for 90–95% of all cases. Most patients are obese, while non-obese patients typically have fat predominantly distributed in the abdominal region. The disease is caused by tissue resistance to insulin combined with impaired insulin secretion. Insulin resistance may improve with weight loss and/or pharmacological treatment of hyperglycemia but rarely returns to normal. Symptoms vary in severity, and initially patients with T2DM are managed with diet and physical exercise [3].

The diagnosis of diabetes mellitus is based on the American Diabetes Association (ADA) criteria [4].
- HbA1c >48 mmol/mol (6.5%): the proportion of hemoglobin non-enzymatically bound to glucose, reflecting average blood glucose over the previous three months.
- Fasting plasma glucose >126 mg/dL after at least 8 hours of fasting.
- Plasma glucose >200 mg/dL two hours after an oral glucose tolerance test.
- Random plasma glucose >200 mg/dL in a patient with classic symptoms of hyperglycemia, regardless of food intake.

Numerous complications may occur, including both microvascular and macrovascular complications:
- Diabetic retinopathy: closely associated with the severity of hyperglycemia [5]. It is characterized by retinal abnormalities including increased vascular permeability, endothelial cell degeneration, microaneurysm formation, and neovascularization. Initially, hyperglycemia damages retinal capillary integrity by altering vascular permeability, followed by the formation of exudates and edema. Hemorrhages may subsequently lead to ischemic retinal areas [6].
- Diabetic neuropathy: the most common forms are distal symmetric polyneuropathy and autonomic neuropathy. The former is characterized by sensory loss in the lower limbs, whereas the latter affects the autonomic nervous system, causing dysfunction in multiple organ systems [7].
- Diabetic nephropathy: develops in approximately 20–40% of diabetic patients and is one of the leading causes of mortality. Diagnosis is based on serum creatinine measurement, estimated glomerular filtration rate (eGFR), and urinary albumin assessment [8].

Macrovascular complications primarily include atherosclerotic cardiovascular diseases such as coronary artery disease, cerebrovascular disease, and peripheral arterial disease of the lower limbs. It is also important to mention the three major risk factors responsible for metabolic syndrome and involved in the development of atherosclerosis: hyperglycemia, arterial hypertension, and various forms of dyslipidemia. For prevention and management of these complications, annual assessment of all these risk factors is strongly recommended for diabetic patients [9]. Chronic hyperglycemia impairs endothelial vasodilatory function by reducing both endothelial nitric oxide production and the synthesis of vasodilatory and antiplatelet prostaglandins [10].

For type 1 diabetes, insulin therapy is the only available pharmacological treatment. Short- or rapid-acting insulin preparations are administered 30–45 minutes before meals and have a duration of action of 5–8 hours; intermediate-acting insulins last up to 24 hours, while long-acting insulins may remain effective for up to 36 hours.

For type 2 diabetes mellitus (T2DM), numerous pharmacological classes with different mechanisms of action are available, including oral medications. In general, these drugs act by increasing insulin secretion, improving insulin sensitivity, reducing hepatic glucose production, and/or slowing intestinal carbohydrate absorption [2].

Sulfonylureas and meglitinides stimulate insulin secretion by interacting with ATP-sensitive potassium channels in pancreatic β cells. First-generation sulfonylureas (e.g., tolbutamide, chlorpropamide) are metabolized in the liver and may be associated with prolonged hypoglycemia, especially when drug interactions reduce their metabolism. Second-generation sulfonylureas (e.g., glipizide, gliclazide, glimepiride) are more potent and have a more favorable tolerability profile. Meglitinides (e.g., repaglinide, nateglinide) have a rapid onset and short duration of action and are often used in combination with metformin.

Biguanides, represented primarily by metformin (phenformin has been withdrawn from the market), exert their effects mainly in the liver by activating AMP-activated protein kinase (AMPK), thereby reducing hepatic gluconeogenesis and increasing insulin sensitivity. Additional effects include reduced intestinal glucose absorption and modulation of enterocyte metabolism. Metformin is the first-line therapy for T2DM, particularly in obese patients. The most common adverse effects include gastrointestinal disturbances, reduced vitamin B12 absorption, and, rarely, lactic acidosis.

Thiazolidinediones (e.g., pioglitazone, rosiglitazone) improve insulin sensitivity through activation of the nuclear receptor PPAR-γ (peroxisome proliferator-activated receptor gamma), which is expressed mainly in adipose tissue, muscle, and liver. Activation of this receptor regulates the transcription of genes involved in carbohydrate and lipid metabolism. These drugs may be used as monotherapy or in combination with metformin or sulfonylureas. Adverse effects include weight gain, fluid retention, anemia, and hepatotoxicity.

Alpha-glucosidase inhibitors (e.g., acarbose, miglitol) act in the intestine by competitively inhibiting α-glucosidase enzymes, delaying the digestion of complex carbohydrates and reducing postprandial glucose peaks [2].

Among drugs that mimic the effects of incretins or prolong their action are glucagon-like peptide-1 (GLP-1) receptor agonists.

GLP-1 belongs to the incretin family, intestinal hormones released after nutrient ingestion. Food intake stimulates the secretion of numerous intestinal hormones that influence intestinal motility, gastric and pancreatic secretion, gallbladder contraction, and nutrient absorption. Some of these hormones stimulate insulin secretion and are therefore called "incretins". GIP (glucose-dependent insulinotropic polypeptide) is a 42-amino acid peptide secreted by K cells of the jejunum and was the first incretin to be purified. The second identified incretin was GLP-1, which exists in two isoforms and is produced by L cells of the jejunum. Biologically active GLP-1 binds to specific receptors on pancreatic alpha and beta cells, increasing insulin synthesis and secretion while enhancing resistance to apoptosis. Furthermore, it inhibits glucagon secretion in a glucose-dependent manner, delays gastric emptying, and reduces food intake. Drugs in this class include semaglutide, liraglutide, dulaglutide, albiglutide, and exenatide [2].

GLP-1 is rapidly degraded by the enzyme dipeptidyl peptidase-4 (DPP-4). Consequently, an important pharmacological strategy has been the development of DPP-4 inhibitors, which prolong the action of endogenous GLP-1 and GIP. Examples include sitagliptin, linagliptin, alogliptin, and others.

Sodium-glucose co-transporter 2 (SGLT2) inhibitors, also known as gliflozins, are oral antidiabetic agents with insulin-independent glucose-lowering effects. The principal sodium-glucose co-transporters are SGLT1 and SGLT2, whose main physiological role is to reabsorb 100% of filtered glucose in the kidney through a sodium-coupled unidirectional transport mechanism. Examples include dapagliflozin, canagliflozin (also used for heart failure), empagliflozin, ertugliflozin, and others [2].

According to the most recent American Diabetes Association (ADA) guidelines and the ADA/EASD consensus report, the choice of pharmacological therapy for type 2 diabetes should be individualized based on the patient's clinical characteristics, presence of atherosclerotic cardiovascular disease, heart failure, chronic kidney disease, obesity, and risk of hypoglycemia. In this context, GLP-1 receptor agonists and dual GIP/GLP-1 receptor agonists currently represent one of the most effective therapeutic strategies for patients with T2DM.

Clinical Evidence for Tirzepatide

The latest drug introduced to the Italian market for the treatment of T2DM, beginning in February 2025, is tirzepatide, marketed under the trade name Mounjaro. Tirzepatide (Mounjaro) is supplied as a clear, colorless to slightly yellow injectable solution administered via a single-use prefilled pen. Available strengths include 2.5 mg, 5 mg, 7.5 mg, 10 mg, 12.5 mg, and 15 mg in 0.5 mL of solution.

The recommended dosing regimen begins with 2.5 mg once weekly. After four weeks, the dose should be increased to 5 mg once weekly. Subsequently, the dose may be further titrated to 7.5 mg, 10 mg, 12.5 mg, or 15 mg once weekly based on clinical response and tolerability, up to a maximum weekly dose of 15 mg. Mounjaro may be used as monotherapy when metformin is contraindicated or not tolerated, or in combination with other glucose-lowering medications for the treatment of type 2 diabetes mellitus [11].

Tirzepatide is the first dual agonist of the glucose-dependent insulinotropic polypeptide (GIP) receptor and glucagon-like peptide-1 (GLP-1) receptor approved for the treatment of type 2 diabetes mellitus. Receptors for both incretins are expressed in pancreatic α and β endocrine cells, the cardiovascular system, the intestine, the kidneys, and immune cells; GIP receptors are also expressed in adipose tissue. The molecule exhibits high selectivity and affinity for both human receptors, producing pharmacological activation that effectively reproduces the physiological effects of incretins. Its agonist activity at the GIP receptor is comparable to that of the endogenous hormone, whereas its activity at the GLP-1 receptor is lower than that of native GLP-1 while maintaining high clinical efficacy. The pharmacodynamic effects of tirzepatide are mediated through multiple mechanisms involved in the regulation of glucose homeostasis.

Tirzepatide enhances glucose-dependent insulin secretion by increasing pancreatic β-cell sensitivity. In a hyperglycemic clamp study involving patients with type 2 diabetes mellitus, administration of tirzepatide 15 mg increased first- and second-phase insulin secretion by 466% and 302%, respectively, compared with baseline, while no changes were observed in the placebo group. Treatment also improves systemic insulin sensitivity. At the 15 mg dose, the increase in the M-value during the euglycemic-hyperinsulinemic clamp was 63%, whereas no change was observed with placebo. This effect is likely mediated, at least in part, by treatment-induced reductions in body weight and fat mass [11].

Tirzepatide reduces fasting and postprandial glucagon concentrations in a glucose-dependent manner, producing reductions of 28% and 43% in the area under the curve (AUC), respectively, at the 15 mg dose, with no changes in the placebo group.

Delayed gastric emptying has also been observed, resulting in a reduced rate of postprandial glucose absorption; however, this effect tends to diminish over time during treatment.

Efficacy and safety were evaluated in the phase 3 SURPASS 1–5 trials, in which glycemic control was the primary endpoint. Across all studies, tirzepatide produced clinically significant and sustained reductions in HbA1c for up to 52 weeks compared with placebo and active comparators (semaglutide, insulin degludec, and insulin glargine) [11].

Few long-term comparative studies are available to guide the selection of therapy for T2DM, particularly regarding the choice of a second glucose-lowering agent in combination with metformin. The GRADE study examined the relative effectiveness of glucose-lowering drugs from four of the most commonly used classes when added to metformin in achieving and maintaining glycated hemoglobin targets. This multicenter, parallel-group clinical trial, sponsored by the National Institutes of Health and the National Institute of Diabetes and Digestive and Kidney Diseases, enrolled a total of 5,047 participants (19.8% African American and 18.6% Hispanic or Latino) with type 2 diabetes mellitus of less than 10 years' duration, treated with metformin and with HbA1c levels between 6.8% and 8.5% [12].

The trial was conducted during the COVID-19 pandemic; therefore, many visits were performed by telephone, and hemoglobin data were collected using home collection kits. Participants received one of four drugs in addition to metformin:

1. Insulin glargine, administered daily at an initial dose of up to 20 units and subsequently adjusted according to glucose levels.
2. The sulfonylurea glimepiride, administered at doses ranging from 2 mg to 8 mg daily.
3. Liraglutide, a glucagon-like peptide-1 (GLP-1) receptor agonist, initiated at 0.6 mg and increased to 1.8 mg daily depending on side effects.
4. Sitagliptin, a dipeptidyl peptidase-4 (DPP-4) inhibitor, administered at a dose of 100 mg and adjusted according to renal function.

All participants received either immediate-release or extended-release metformin formulations and were evaluated every three months. Thiazolidinediones were excluded because of safety concerns existing at the time the trial was designed, particularly reports of adverse effects such as fluid retention, bone mineral loss, and bladder cancer risk. Sodium-glucose co-transporter 2 (SGLT2) inhibitors were also excluded because they had not yet been approved by the U.S. Food and Drug Administration (FDA) when the study began, and there was insufficient clinical experience with these agents, representing a limitation of the study.

For practical reasons, the trial was conducted as an open-label study, allowing comparison of the efficacy and safety profiles of the four most commonly used glucose-lowering treatments in T2DM. Significant differences emerged in both efficacy and safety among the four treatments. Although the incidence of severe hypoglycemia was low overall, glimepiride was associated with the highest incidence, followed by insulin glargine. Participants treated with liraglutide and sitagliptin experienced weight losses of approximately 3.5 kg and 2.0 kg, respectively, over four years, whereas the insulin glargine and glimepiride groups maintained relatively stable body weight. In conclusion, all four medications added to metformin reduced HbA1c levels. In particular, insulin glargine and liraglutide were more effective in achieving and maintaining HbA1c values below 7.0%, whereas sitagliptin was the least effective treatment [12].

SURPASS 1–5 Studies of Tirzepatide [11]

Monotherapy

In a 40-week, double-blind, placebo-controlled study, 478 patients with inadequate glycemic control despite diet and exercise were randomized to receive tirzepatide 5 mg, 10 mg, or 15 mg once weekly, or placebo. Fifty-two percent of the enrolled patients were men, the mean age was approximately 54 years, and the average duration of diabetes was 5 years. It emerged that the mean HbA1c (%) value over the 40-week period improved with tirzepatide 15 mg, followed by the 10 mg and 5 mg doses, compared with placebo.

Combination therapy with metformin

In a 40-week open-label, active-controlled study, double-blind with respect to tirzepatide dose, 1,879 patients were randomized to receive tirzepatide 5 mg, 10 mg, or 15 mg once weekly or semaglutide 1 mg once weekly, all in combination with metformin. Forty-seven percent of the enrolled patients were men, and the mean age was 57 years.

Combination therapy with metformin, with or without SGLT2 inhibitors

In a 52-week open-label, active-controlled study, 1,444 patients were randomized to receive tirzepatide 5 mg, 10 mg, or 15 mg once weekly or insulin degludec, all in combination with metformin with or without an SGLT2 inhibitor. Patients had a mean diabetes duration of 8 years, a mean age of 57 years, and 56% were men.

Combination therapy with 1–3 oral antidiabetic drugs

Metformin, sulfonylureas, or SGLT2 inhibitors. In an open-label, active-controlled study lasting up to 104 weeks (primary endpoint assessed at 52 weeks), 2,002 patients with type 2 diabetes and increased cardiovascular risk were randomized to receive tirzepatide 5 mg, 10 mg, or 15 mg once weekly or insulin glargine once daily in combination with metformin (95%) and/or sulfonylureas (54%) and/or SGLT2 inhibitors (25%). Patients had a mean diabetes duration of 12 years, a mean age of 64 years, and 63% were men. Patients treated with insulin glargine started at a dose of 10 U/day, which was adjusted using an algorithm targeting a fasting glucose level <5.6 mmol/L. The mean insulin glargine dose at week 52 was 44 units/day.

Combination therapy with titrated basal insulin, with or without metformin

In a 40-week, double-blind, placebo-controlled study, 475 patients with inadequate glycemic control who were using insulin glargine with or without metformin were randomized to receive tirzepatide 5 mg, 10 mg, or 15 mg once weekly or placebo. Patients had a mean diabetes duration of 13 years, a mean age of 61 years, and 56% were men. The estimated median baseline insulin glargine dose was 34 units/day. The median insulin glargine dose at week 40 was 38, 36, 29, and 59 units/day for tirzepatide 5 mg, 10 mg, 15 mg, and placebo, respectively.

The efficacy and safety of tirzepatide in the treatment of type 2 diabetes mellitus, body weight management, and mean HbA1c reduction have been demonstrated by the SURPASS 1–5 studies.

Tirzepatide for Body Weight Reduction

Obesity is a chronic disease associated with high mortality. In a phase 3 study (SURMOUNT-1, clinicaltrials.gov NCT04184622), a double-blind, randomized, placebo-controlled trial conducted from December 2019 to April 2022, 2,539 participants were enrolled. The mean participant age was 45 years, and the majority were women. Participants were randomized in a 1:1:1:1 ratio to receive tirzepatide 5 mg, 10 mg, 15 mg, or placebo, administered subcutaneously once weekly for 72 weeks. Tirzepatide treatment began with a dose of 2.5 mg once weekly (or matching placebo) and was increased by 2.5 mg every 4 weeks until a maintenance dose of 15 mg once weekly was reached. The primary endpoint of the study was the change in body weight after 72 weeks compared with placebo. The study demonstrated that adults with obesity achieved a mean body weight reduction of 19.5% and 20.9% with tirzepatide 10 mg and 15 mg, respectively, compared with a 3.1% reduction in the placebo group [13].

This degree of weight loss is unusually high for an anti-obesity medication compared with results reported in other phase 3 clinical trials. Since tirzepatide is a dual GIP and GLP-1 receptor agonist, a possible additive effect has been hypothesized, resulting from the simultaneous targeting of multiple endogenous nutrient-stimulated hormonal pathways involved in energy homeostasis. A body weight reduction of ≥5% is traditionally considered clinically meaningful because of the associated improvements in metabolic health. In this study, the majority of participants treated with tirzepatide 10 mg and 15 mg reached this threshold (89–91%). Weight reductions of ≥10%, ≥15%, and ≥20% are associated with additional clinical benefits and may be necessary to improve certain obesity-related complications, while also representing relevant therapeutic goals in clinical practice. In this study, the majority of participants achieved these higher targets, with proportions ranging from 78–84%, 67–71%, and 50–57%, respectively, in the 10 mg and 15 mg treatment groups [13].

Comparison Between Tirzepatide and Dulaglutide Cardiovascular Evaluation (SURPASS-CVOT Study)

Among the latest clinical studies conducted in people with type 2 diabetes mellitus, GLP-1 receptor agonists have demonstrated cardiovascular benefits, particularly macrovascular protection through a reduction in major adverse cardiovascular events (MACE: cardiovascular death, myocardial infarction, and stroke) [14]. The true impact of tirzepatide on cardiovascular risk compared with other GLP-1 receptor agonists remains unknown, which justifies the ongoing trial. For this reason, tirzepatide has been and continues to be evaluated in an ongoing randomized, double-blind, active-controlled cardiovascular outcomes trial called SURPASS-CVOT (clinicaltrials.gov, NCT04255433). The study was designed to determine the cardiovascular protective effects of tirzepatide by demonstrating non-inferiority to dulaglutide and evaluating its superiority.

Exclusion criteria included previous pancreatitis, chronic or acute hepatitis, symptoms of other liver diseases, or alanine aminotransferase levels above the normal range. Eligibility required participants to be at least 40 years of age, have type 2 diabetes mellitus, and be receiving glucose-lowering medications. Indeed, 97.3% of participants were receiving antidiabetic therapy, most commonly metformin (81.8%), SGLT-2 inhibitors (30.6%), and sulfonylureas (20.5%). Participants were randomly assigned in a 1:1 ratio (tirzepatide vs. dulaglutide) using an interactive web-based randomization system. The study design involved once-weekly subcutaneous injections of either tirzepatide or dulaglutide. Tirzepatide treatment started at 2.5 mg weekly and was increased by 2.5 mg every 4 weeks until reaching 15 mg, whereas dulaglutide treatment started at 1.5 mg without dose escalation.

The objective of the SURPASS-CVOT study is to evaluate the cardiovascular protective effects of tirzepatide, the first dual GIP/GLP-1 agonist, in individuals with type 2 diabetes and established atherosclerotic cardiovascular disease compared with dulaglutide, since the true impact of tirzepatide on cardiovascular risk relative to other GLP-1 receptor agonists remains unknown [14].

Tirzepatide vs. Semaglutide in the Treatment of Type 2 Diabetes Mellitus

A phase 3 study (SURPASS-2, clinicaltrials.gov NCT03987919), randomized, open-label, parallel-group, active-controlled, and lasting 40 weeks, was conducted from July 2019 to February 2021. A total of 1,878 eligible participants who received treatment were randomized.

Inclusion criteria required glycated hemoglobin levels between 7.0% and 10.5% and inadequately controlled type 2 diabetes despite metformin treatment at a dose of at least 1,500 mg/day. Exclusion criteria included type 1 diabetes, a history of pancreatitis, and macrovascular complications such as proliferative or non-proliferative diabetic retinopathy.

The study was designed to demonstrate the non-inferiority of tirzepatide at doses of 5 mg, 10 mg, and 15 mg compared with semaglutide 1 mg. Patients were randomly assigned in a 1:1:1:1 ratio to receive once-weekly subcutaneous injections of tirzepatide

(5 mg, 10 mg, or 15 mg, double-blind dosing) or semaglutide (1 mg) for 40 weeks.

Tirzepatide treatment began at 2.5 mg once weekly and was increased by 2.5 mg every 4 weeks until the assigned dose was reached. Semaglutide treatment started at 0.25 mg once weekly, with the dose doubled every 4 weeks until reaching 1 mg.

The study showed significantly greater reductions in serum glucose with all tirzepatide doses compared with semaglutide. After 40 weeks, the mean reductions in HbA1c were −2.01%, −2.24%, and −2.30% with tirzepatide 5 mg, 10 mg, and 15 mg, respectively, compared with −1.86% with semaglutide [15].

Tirzepatide vs. Basal Insulin (Insulin Degludec and Insulin Glargine)

The SURPASS-3 and SURPASS-4 studies evaluated the efficacy of tirzepatide compared with insulin degludec and insulin glargine in participants with type 2 diabetes and different glycemic profiles.11 This post hoc analysis of SURPASS-3 and SURPASS-4 aimed to evaluate changes in baseline glycemic parameters after 52 weeks of treatment with tirzepatide (5 mg, 10 mg, or 15 mg) compared with insulin degludec (SURPASS-3) and insulin glargine (SURPASS-4).

The glycemic parameters of interest included fasting serum glucose (FSG), postprandial glucose (PPG), HbA1c, and body weight.16 In both studies, tirzepatide treatment began at 2.5 mg and was increased by 2.5 mg every four weeks until the target dose was reached.

SURPASS-3 enrolled adults with HbA1c values between 7.0% and 10.5% and a body mass index (BMI) of at least 25 kg/m². Participants had never used insulin and were treated with metformin alone or combined with an SGLT-2 inhibitor. They were randomized in a 1:1:1:1 ratio to receive tirzepatide 5 mg, 10 mg, 15 mg, or once-daily insulin degludec (100 units/mL) for 52 weeks. Participants in SURPASS-4 were adults receiving metformin, sulfonylureas, or SGLT-2 inhibitors, with HbA1c values between 7.5% and 10.5%, a BMI of at least 25 kg/m², and established cardiovascular disease or high cardiovascular risk. They were randomized in a 1:1:1:3 ratio to receive tirzepatide 5 mg, 10 mg, 15 mg, or insulin glargine (100 units/mL) for 52 weeks.

Participants in this post hoc analysis were classified into four subgroups based on baseline glucose values:

- Low FSG / Low PPG
- Low FSG / High PPG
- High FSG / Low PPG
- High FSG / High PPG

In conclusion, treatment response varied according to baseline glycemic profile: individuals with elevated PPG experienced greater reductions in postprandial glucose, whereas those with elevated FSG benefited more from reductions in fasting glucose. Nevertheless, treatment proved effective across all subgroups, resulting in overall improvement in glycemic control regardless of baseline FSG/PPG profile [16].

This is the first time a non-insulin medication has demonstrated efficacy comparable to titrated basal insulin in reducing fasting serum glucose levels. Tirzepatide treatment was consistently associated with lower postprandial glucose levels than insulin treatment across all subgroups, leading to greater reductions in HbA1c [16]. Therefore, the mechanisms of action of tirzepatide previously discussed in this paper—including glucose-dependent insulin secretion, reduced glucagon levels, decreased insulin resistance, and delayed gastric emptying—all contribute to reductions in baseline glycemic parameters, body weight, and HbA1c values.

Conclusions

Type 2 diabetes mellitus represents one of the major challenges of modern medicine because of its high prevalence, progressive nature, and significant impact on cardiovascular, renal, and metabolic complications. In recent years, a better understanding of the pathophysiological mechanisms involved in the development of the disease has promoted the introduction of increasingly targeted therapeutic strategies aimed not only at glycemic control but also at reducing cardiovascular risk and improving patients' quality of life.

In this context, tirzepatide represents one of the most significant pharmacological innovations. Thanks to its dual agonism of GIP and GLP-1 receptors, the drug exerts a synergistic effect that improves glycemic control, produces marked body weight reduction, and enhances insulin sensitivity while maintaining an overall favorable safety profile. Evidence from the SURPASS clinical trial program has demonstrated the superiority of tirzepatide over placebo and several major active comparators, both in terms of HbA1c reduction and weight loss, confirming its role as a highly effective therapeutic option for the treatment of type 2 diabetes mellitus.

Despite these particularly promising results, long-term follow-up data are still needed to better define treatment safety, the durability of its metabolic benefits, and its true impact on major cardiovascular outcomes. Ongoing studies, including SURPASS-CVOT, will help clarify the potential role of tirzepatide in cardiovascular prevention and in the management of high-risk patients.

Overall, the available evidence indicates that tirzepatide represents a major advance in the treatment of type 2 diabetes mellitus and reflects the evolution toward an increasingly personalized therapeutic approach aimed at simultaneously addressing hyperglycemia, excess body weight, and cardiovascular risk. The integration of such strategies into clinical practice could significantly improve clinical outcomes and the quality of life of patients affected by this chronic disease.

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