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The Dual-Agonist Advantage: Comparing Tirzepatide (GIP/GLP-1) Efficacy Against Single GLP-1 RAs (Semaglutide) in T2DM

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Abstract

This narrative review explores the therapeutic shift in Type 2 Diabetes Mellitus (T2DM) management from single-receptor agonists to dual-agonist therapies. While selective GLP-1 receptor agonists like semaglutide have served as a primary treatment standard for metabolic control, the emergence of tirzepatide a "Tw incretin" targeting both GIP and GLP-1 receptors-presents a new clinical advantage. By simultaneously activating these distinct metabolic pathways, tirzepatide achieves a synergistic effect that enhances insulin secretion and improves adipose tissue regulation beyond the capabilities of single-hormone agents. Clinical comparisons indicate that tirzepatide provides superior reductions in blood glucose and body weight, helping a greater proportion of patients achieve near-normal metabolic levels. Furthermore, the dual-agonist profile shows promising improvements in cardiovascular markers and lipid metabolism with a safety profile characterized primarily by transient gastrointestinal side effects. This paper synthesizes the mechanistic benefits of dual agonism and evaluates its potential to redefine the gold standard for intensive T2DM therapy.

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Introduction

The global burden of Type 2 Diabetes Mellitus (T2DM) continues to rise, with an estimated 537 million adults affected-representing roughly 10.5% of the world's adult population [1,2]. The necessity to develop more effective therapeutic strategies for such a complex disease cannot be overstated. For much of the latter half of the 20th century, particularly from the 1970s through the 1990s, T2DM management was predominantly glossocentric, targeting stabilization of glycaemic indices such as fasting plasma glucose, urine glucose, and later HbA1c [3,4]. Modern treatments not only focus on glycaemic control but also on weight management and the reduction of cardiovascular risks [5]. A key element in this modern approach is utilizing the effect of incretin, an insulinotropic response activated by gut hormones after oral glucose intake. Therapies such as semaglutide, a single-agonist that targets the Glucagon-like Peptide-1 (GLP-1) receptor, has been labelled as the gold standard treatment class for many years. These agents effectively lower HbA1c by stimulating glucose-dependent insulin secretion, suppressing glucagon, and slowing gastric emptying to increase satiety [6].

Tirzepatide is the first approved agent that can target both GLP-1 and Glucose-dependent Insulinotropic Polypeptide (GIP) receptors. Activating both receptors simultaneously generates a synergistic effect and is believed to have a superior therapeutic outcome compared to using either hormone alone. GIP and GLP-1 have overlapping but distinct properties on insulin and glucagon secretion. However, GIP is more pronounced in regulating adipose tissue and bone metabolism [7].

Although tirzepatide has demonstrated greater efficacy in glycemic and weight management in clinical trials, several key aspects remain unclear in the current literature [8]. A detailed explanation of the specific benefits and mechanisms of dual agonism is much needed as most literature focuses on general outcomes. The purpose of this review is to synthesize existing knowledge on "dual-agonist advantages", verifying if combined action is more beneficial than single action agent.

What is GIP and GLP-1 and How Do They Work?

Glucose-dependent insulinotropic polypeptide (GIP) and peripheral glucagon-like peptide-1 (GLP-1) are incretins released from the gastrointestinal tract (GIT) in response to oral glucose or nutrient intake, while central GLP-1 is produced by brainstem neurons independently of gut stimuli. Both hormones collectively mediate the incretin effect, GIP is secreted from K-cells located in the duodenum and proximal jejunum, whereas peripheral GLP-1 is secreted from L-cells found in the distal ileum and colon. The plasma half-life of endogenous GIP (1-42) is limited by dipeptidyl peptidase-4 (DPP-4) to approximately 7 minutes, an enzyme that degrades GIP into an inactive molecule GIP (3-42). Native GLP-1 is also vulnerable to DPP-4, and is broken down within minutes upon contact with the enzyme [9-11]. Neural stimulation also plays a role in peripheral GLP-1 secretion, which can be explained by the morphology of the L-cells. These L-cells have two surfaces, with the apical surface sensing nutrients and the basolateral surface involving neural and endocrine signaling through vascular activity [11].

Once both incretins enter the circulation, they bind to their distinct class B G protein-couple receptors (GPCR), GIPR and GLP-1R, to activate G protein-mediated signalling cascades. G is the major G protein that is coupled by both GPCRs, leading to stimulation of adenylate cyclase. Afterwards, increasing intracellular cyclic adenosine monophosphate (cAMP) initiates protein kinase A (PKA) and exchange protein directly activated by cAMP 2 (EPAC2). This signalling pathway facilitates glucose-dependent insulin secretion by promoting β-cell membrane depolarization, calcium influx, and insulin granule exocytosis. These shared Gs-cAMP-PKA/EPAC2 cascades not only drive acute insulin release but also underpin longer-term β-cell preservation, providing a mechanistic foundation for dual GIPR/GLP-1R agonism in agents like tirzepatide, which elicits synergistic cAMP elevation in β-cells beyond either incretin alone.

Moreover, GIP and peripheral GLP-1 share common actions that are beneficial for pancreatic β-cell. They support β-cell survival, reduce apoptosis, and enhance proliferation by activating the CREB, Akt/PKB, and ERK pathways [12]. For instance, GIP binding to GIPR elevates cAMP/PKA to phosphorylate nuclear

CREB and activate Akt/PKB, which phosphorylates.

Foxo1 to downregulate pro-apoptotic Bax and suppress mitochondrial Bad/Beimel translocation via p38 MAPK/JNK inhibition under glucolipotoxicity or ER stress conditions. Similarly, GLP-1 activates Akt/PKB (often PI3K-dependent) to upregulate anti-apoptotic Bcl2/IAP2 via NFKB and reduces ER stress in human islets, while both incretins induce cyclin D1 transcription to promote G1/S-phase progression through PKA/MEK and EGFR transactivation. These overlapping protective effects expand β-cell mass, countering the progressive dysfunction in type 2 diabetes, and synergize in dual agonists like tirzepatide to improve HOMA2-B-derived β-cell function by 93–163% [13].

Although possessing these protective characteristics, they differ in glucagon regulation. GLP-1 inhibits glucagon secretion in a glucose-dependent manner, via direct effects on pancreatic alpha cells and indirect effects through somatostatin release from delta-cells. A small portion of GLP-1R found on pancreatic alpha cells are responsible for the direct effect. Shortly after the activation of PKA by GLP-1R, voltage gated calcium channels are suppressed in order to down regulate glucagon exocytosis. On the other hand, GIP raises glucagon secretion mainly during fasting or hypoglycemia, owing to an increased GIPR gene promoter activity that makes alpha cells more sensitive to GIP [10,14]. This glucose-contextual divergence GIP stimulating α-cells at low glucose while GLP-1 suppresses across hyperglycaemia allows dual agonism to balance glucagon appropriately, avoiding hyperglucagonemia in fed states while preserving counter regulation during hypoglycaemia [10,13,15].

In terms of energy and satiety modulation, GLP-1 coordinates peripheral and central systems to delay gastric emptying, suppress food intake, and amplify satiety sensation. The peripheral system communicates with the central system via the vague nerve, specifically vagal afferent in the nodose ganglion that activate nucleus tractus solitarius (NTS) neurons in the brainstem [16]. Subsequently, the hypothalamus and brainstem the “command center” and “vital center” known for their role in appetite control integrate the effect of GLP-1. Early satiety reduces meal size and total caloric intake, which ultimately favors weight loss. Besides, central GLP-1 targets the mesolimbic reward system, insular cortex, and putamen to facilitate the hedonic control of food intake [17]. This impact is mostly relevant in obese patient, where dysregulated reward-based food consumption contributes heavily on excessive caloric increase [18].

Historically, the role of GIP was understood to promote postprandial lipid uptake and triglyceride storage in adipocytes, but recent studies demonstrated that GIP also participates in appetite regulation [19,20]. Resembling GLP-1’s effect on appetite, GIP has its receptors widely distributed in regions of the central nervous system which are crucial for appetite and energy balance. These command centers for metabolic regulation that GIPRs strategically distributed in are the paraventricular hypothalamus (PVH), arcuate hypothalamus (ARH), and dorsomedial hypothalamus (DMH) [10,11,21].

DPP-4 inhibitors prevent the rapid enzymatic degradation of endogenous GLP-1 and GIP which extends their hormonal activity. Conversely, GLP-1R agonist therapies (GLP-1RAs), such as semaglutide and tirzepatide, are pharmacologically modified analogs resistant to DPP-4.

In subjects with obesity and T2DM, the secretion and activity of endogenous GLP-1 are decreased, while GIP remains partially active with diminished β-cell insulinotropic function and preserved glucagon tropic and adaptogenic effects [22]. These complementary yet divergent properties of GIP and GLP-1 provide a robust pathophysiological foundation for drug development. This mechanistic diversity explains why dual receptor agonists are able to enhance the quality of T2DM management [10,15].

Pharmacology of Tirzepatide and Semaglutide

Semaglutide on the other hand has a half-life around 7 days (approximately165-186 hours), which also enables once weekly subcutaneous injection [22-25]. This slightly longer half-life comparing to Tirzepatide is achieved through fatty acid acylation and stable albumin binding. At the receptor level, tirzepatide presents an unbalanced dual-agonist profile [26]. Binding and functional studies indicated that tirzepatide parallels endogenous GIP’s affinity at GIPR while exhibiting

5-fold lower affinity at GLP-1R compared to native GLP-1. This GIPR-biased property maximizes the benefits of GIP while maintaining moderate GLP-1 effects for superior metabolic outcomes [22-25].

Concurrent GIPR/GLP-1R activation promotes glycaemic control by eliciting the first and second phases of glucose-stimulated insulin secretion and suppressing inappropriate glucagon secretion. Furthermore, tirzepatide showed its benefits on β-cell processing capacity and insulin sensitivity/resistant are beyond what selective GLP-1 receptor agonists achieve. Both agents allow once-weekly subcutaneous injection while tirzepatide has a starting dose of 2.5mg for the first 4 weeks [22,25,27]. After the initial period, the dosage is raised to 5mg once weekly and a maximum of 15mg weekly dose if additional glycemic management is required. Semaglutide follows a similar titration pattern, starting at 0.25 mg once weekly for 4 weeks, increasing to 0.5 mg, and may be further titrated up to 2 mg weekly if needed.

Pharmacokinetic studies in healthy individuals and T2DM patients show tirzepatide exhibits dose-proportional concentrations across a wide range [27,28]. Tirzepatide reaches its Tax around 8-72 hours post subcutaneous administration with approximately 80% absolute bioavailability. The steady state was achieved after about 4 weeks of weekly dosing. The compound is metabolized through proteolytic degradation of the peptide backbone and β oxidation of its fatty acid side chain. Its primary elimination route is via urine and faces with no unchanged parent drug detected. Semaglutide demonstrates comparable traits: dose-proportional PK, Tax of 1-3 days (24-72 hours), 89% bioavailability, steady-state in 4-5 weeks, identical metabolism (proteolytic cleavage and beta-oxidation of fatty acid side chain), and elimination via urine (~3% unchanged) and faces [29-31].

Neither drug's pharmacokinetics is significantly influenced by age (18-80+ years), gender, race/ethnicity, body weight (within 40-160 kg studied ranges), mild-moderate renal/hepatic impairment, or upper GI disease. Dedicated studies confirm no clinically meaningful changes even in ESRD patients on dialysis (eGFR <15, n=8), though data for non-dialysis severe renal impairment (eGFR 15-30 mL/min/1.73 m²) and severe hepatic impairment (Child-Pugh C) remain more limited, with no dose adjustment recommended, though caution/monitoring is advised in ESRD [32,33].

Head-to-Head Efficacy Comparison in SURPASS-2

SURPASS-2 was a trial designed to compare the clinical outcomes of semaglutide (1.0mg once weekly) and tirzepatide (5mg, 10mg, and 15mg once weekly) in T2DM patients(8). The trial concluded that tirzepatide, at all dosages, outperformed semaglutide in glycemic control over a 40-week period. The three groups that received tirzepatide showed a dose-dependent reduction in HbA1c by 2.01%, 2.24%, and 2.30%, with their original mean baseline HbA1c of 8.3%. In contrast, semaglutide was only able to achieve a 1.86% reduction in HbA1c. These results were statistically significant with a p-value of less than 0.02 across all dose comparisons. It is worth noting that when SURPASS-2 trial was conducted, 1.0 mg once weekly was the highest maintenance dose approved for T2DM glycemic control, whereas semaglutide is now available at 2.0mg once weekly for the same purpose [34].

Tirzepatide provided numerically and statistically greater reductions in HbA1c than semaglutide. Tirzepatide accomplished a treatment difference by 0.15% at the lowest dose, 0.39% at the mid-dose, and 0.45% at the highest dose [35]. All three tested doses of tirzepatide were not only non-inferior but statistically superior to semaglutide in regard to glycemic regulation. To establish the superiority of tirzepatide, a subgroup analysis was conducted among Hispanic and Latino participants [36]. Reductions in HbA1c were significantly greater for all tirzepatide doses compared with semaglutide (all $p \leq 0.027$), and the gap in efficacy remained consistent while the highest tirzepatide dose reached even more pronounced reductions, including a treatment difference of –0.54% in HbA1c ($p \leq 0.027$) and substantially greater weight loss (–10.5 kg vs –5.6 kg, $p<0.001$).

Holding the position of superior glycaemic control over semaglutide, tirzepatide enables patients to reach both standard and intensive glycaemic targets more efficiently [8]. With the traditional clinical goal of HbA1c <7.0% for T2DM management, tirzepatide had an achievement rate of 82% with the 5mg dose and 86% at both the 10 mg and 15 mg doses [37].

On the other hand, 75% to 79% of participants on semaglutide 1.0 mg achieved this clinical goal. Here, a dose-dependent relationship is again established, with tirzepatide consistently outpacing semaglutide in clinical efficacy [8]. Normoglycemia, or euglycemia, is defined as an HbA1c level below 5.7%. This ideal therapeutic goal was achieved in 27% to 51% of patients treated with tirzepatide, whereas 19% of patients on semaglutide reached euglycemia ($p < 0.001$). Tirzepatide enabled nearly half of the patients on the 15 mg dose to regain euglycemia, providing a solid proof of the potent synergistic effect of dual receptor agonism in restoring metabolic balance [8].

Regarding the safety profile of tirzepatide and semaglutide, both demonstrated excellent profiles with respect to clinically significant hypoglycemia (blood glucose levels below 54 mg/dL). The incidence of such events remained remarkably low across all cohorts, occurring in 0.6%, 0.2%, and 1.7% of patients in the tirzepatide 5 mg, 10 mg, and 15 mg groups, respectively, compared to just 0.4% in the semaglutide 1.0 mg group(8). Even though the highest dose of tirzepatide (15 mg) showed nearly a 4-fold higher risk than semaglutide, none of the episodes required third-party assistance. Compared to insulin and sulfonylurea therapies, these hypoglycemic incidents occurred far less frequently [38,39]. Insulin glargine showed 13.5-16.6% events in SURPASS-4 while sulfonylureas had around 20-30% severe events yearly in UKPDS 10-50 times higher than tirzepatide or semaglutide [40,41]. This modest increase in events seen with higher-dose tirzepatide remains a clinically acceptable compromise, considering its superior effects on both glycaemic control and weight reduction, and its glucose-dependent mechanism of action [8].

It is crucial to mention that the participants in the SURPASS-2 trial had a mean diabetes duration of 8.6 years. A relatively short diabetes duration can indicate significantly preserved β-cell function in many participants. This specific population made high rates of normoglycemia (HbA1c <5.7%) achievable, as a prolonged history of disease correlates with β-cell exhaustion [42].

Moreover, all participants were on a stable background of metformin monotherapy. This allowed researchers in the SURPASS-2 trial to isolate the glucose dependent mechanisms of tirzepatide and semaglutide [8]. This uniform background eliminated confounding variables from other medications and explains the exceptionally low hypoglycemia rates reported across all arms. While these characteristics make the results highly generalizable to the typical patient failing first-line metformin therapy, caution should be used when extrapolating these impressive findings particularly the rates of normoglycemia to more complex clinical scenarios, such as patients with advanced diabetes duration (>15 years) or those already requiring insulin therapy [8].

Comparative Weight Management and Cardiometabolic Outcome

Obesity is one of the strongest risk factors for T2DM, accounting for 60% to 90% of T2DM cases [43]. Beyond tirzepatide's potent glyceric effect, it also demonstrated a significant dose dependent advantage over semaglutide in terms of total weight reduction. From a mean baseline body weight of 93.7kg, participants who underwent semaglutide therapy experienced an average weight loss of 6.7% (approximately 5.7 kg). Tirzepatide achieved mean wight reduction of 7.6 kg (7.8%), 9.3 kg (9.8%), and 11.2 kg (11.4%) according to the 5 mg, 10mg, and 15 mg dosage groups. In this trial, the lowest dose of tirzepatide outperformed the standard dose of semaglutide, with the 15mg dose exerting nearly double the weight loss of semaglutide [8].

An analysis of patients reaching specific weight loss milestones was conducted to further illustrate the clinical impact of both agents in the SURPASS-2 trial. Approximately 65% to 80% of participants across the three doses of tirzepatide achieved the clinically significant threshold of 5% weight loss, compared to 54% for semaglutide. The 15% weight loss benchmark was accomplished by 36% of the 15 mg tirzepatide group and 8% of the semaglutide group. Moreover, a composite "triple goal" reaching an HbA1c of $\leq 6.5\%$, $\geq$ 10% weight loss, and without severe hypoglycemia was met by 32% to 60% of tirzepatide-treated patients, compared to just 22% of those treated with semaglutide [25].

Beyond weight and glycemic control, tirzepatide also demonstrated a robust influence on cardiovascular and metabolic markers [8]. Systolic blood pressure decreased by 4.8 to 6.5 mmHg across the tirzepatide

doses, a more pronounced drop than the 3.6 mmHg reduction seen with semaglutide. Additionally, tirzepatide led to greater reductions in triglycerides and very-low-density lipoprotein (VLDL), while simultaneously increasing High-density lipoprotein (HDL). Interestingly, while both drugs had minimal and comparable effects on LDL cholesterol, the superior impact of tirzepatide on the broader lipid panel suggests a more comprehensive improvement in insulin sensitivity and metabolic health [8].

The mechanistic foundation for this superior performance likely lies in the synergistic interplay between GLP-1 and GIP receptor agonism. In addition of GLP-1's role in appetite suppression and delayed gastric emptying, GIP incorporated its ability in fat deposition and energy expenditure regulation [27].

Adverse Events and Patient Experience

Tolerability is a major concern in drug selection for all patients; it is also crucial to note down any adverse events after drug administration. In case of tirzepatide, gastrointestinal related adverse effects were the most frequently observed following a clear dose-dependent trajectory. For the 10 mg and 15 mg doses of tirzepatide, nausea was reported in approximately 19–20% and 22% of participants, respectively. The semaglutide group showed a relatively lower incident rate of 18%. Diarrhea occurred in 12% of those with semaglutide, whereas 14–15% of those on the 10 mg dose and 16% on the 15 mg dose of tirzepatide. Rates of vomiting followed a similar pattern, affecting roughly 8% of patients on tirzepatide 10 mg and 10% on the 15 mg dose, compared to 8% in the semaglutide cohort. Despite these figures, the overall incidence of gastrointestinal distress was remarkably similar between the two therapies, with 40–46% of all tirzepatide-treated patients experiencing at least one such event versus 41% for semaglutide [8].

Generally, most complications reported fell into the category of mild-to-moderate in terms of severity and were concentrated during the initial dose-escalation phase. Less than 3% of participants discontinued tirzepatide specifically due to nausea, vomiting, or diarrhoea. While severe gastrointestinal events were exceptionally rare and typically transient, a clear dose- dependent pattern was observed in overall tolerability. Discontinuation rates due to adverse events were higher among patients receiving tirzepatide recorded at 3.0% to 4.3% for the 5 mg dose, 4.0% to 7.1% for the 10 mg dose, and 6.2% to 8.5% for the 15 mg dose compared to a 3.0% to 4.1% rate in the semaglutide group. Despite the 15 mg dose showing approximately twice the discontinuation rate of semaglutide, the low absolute numbers and generally manageable symptoms support a favourable safety profile for tirzepatide, notwithstanding the marginally higher gastrointestinal burden at peak doses [8].

In addition to gastrointestinal effects, the broader safety profile of these therapies includes rare but clinically relevant concerns such as pancreatitis, gallbladder disorders, and hypersensitivity. Pancreatitis rates remain exceptionally low across the board, with occurrences reported in <1% of participants for both medications. Meta-analyses of tirzepatide indicate no statistically significant increase in pancreatitis risk compared to control groups (RR 1.46, 95% CI 0.59-3.61), including basal insulin, selective GLP-1RAs (dulaglutide/semaglutide), and placebo(44).Cases involving semaglutide were typically associated with a prior history of biliary disease or gallstones. Similarly, severe allergic reactions and systemic hypersensitivity are uncommon. While minor injection site reactions were noted in approximately 1.9% to 4.5% of tirzepatide users-a rate slightly higher than the 0.2% observed with semaglutide-documented instances of anaphylaxis or angioedema remain isolated case reports rather than frequent trial outcomes [8].

A more distinct differentiation between the two agents emerges regarding gallbladder health. While the incidence of gallbladder-related disorders remains generally low, meta-analyses suggest that semaglutide may carry a higher risk, with a 2.6-fold increase in the likelihood of cholelithiasis compared to placebo. In the STEP trials, gallbladder events occurred in up to 3.0% of semaglutide patients, whereas tirzepatide showed no significant biliary risk in comparable systematic reviews. Specifically, cholelithiasis rates for tirzepatide remained below 1.4% across all doses, which is nearly identical to placebo levels. This risk for both drugs appears to be a function of dose and the velocity of weight loss rather than a direct toxic effect, suggesting that patients achieving rapid metabolic changes should be monitored for biliary symptoms regardless of their assigned therapy [8].

Discussion

The comparative analysis provided in this narrative review underscores a significant evolution in the pharmacological management of Type 2 Diabetes Mellitus (T2DM). The transition from selective GLP-1 receptor agonists, like semaglutide, to dual GIP/GLP-1 receptor agonists, such as tirzepatide, represents a move toward more comprehensive metabolic restructuring. The primary finding of this synthesis is that tirzepatide's "Tw incretin" mechanism which simultaneously leverages the insulinotropic and glucagon tropic properties of GIP alongside the potent anorexigenic effects of GLP-1 consistently outperforms the previous "gold standard" in available comparative data on both glyceric control and weight reduction.

The clinical superiority of tirzepatide, as evidenced by the SURPASS-2 trial data, is particularly striking in its ability to achieve normoglycemia (HbA1c <5.7%) in nearly half of patients on the 15 mg dose—a milestone previously difficult with single-agonist therapies. Achieving an HbA1c below 5.7% in nearly half of the patients on the 15 mg dose is a milestone that was previously difficult to reach with single-agonist therapies. This level of glycemic normalization carries profound long-term implications, including potential T2DM remission trajectories and substantial microvascular risk reduction (retinopathy, nephropathy, neuropathy), as evidenced by UKPDS legacy effects where each 1% HbA1c lowering yields 21-37% relative risk reductions [45-47]. This suggests that the GIP component of tirzepatide does not merely serve as a supplementary hormone but acts synergistically to enhance insulin sensitivity and β-cell processing capacity beyond the scope of GLP-1 activation alone. Furthermore, the dose-dependent nature of these results indicates that tirzepatide allows for a highly tailorable treatment approach, where the 5 mg dose can match or exceed the efficacy of semaglutide 1.0 mg, while higher doses push the boundaries of metabolic restoration.

Weight management remains a cornerstone of T2DM therapy, and the data presented here confirms that tirzepatide offers a distinct advantage in this domain. The 15 mg dose achieving nearly double the weight loss of semaglutide 1.0 mg (11.4% vs 6.7%) highlights the importance of GIP in regulating adipose tissue metabolism and central energy balance. This weight-loss efficacy is coupled with superior improvements in systolic blood pressure and lipid profiles specifically triglycerides and VLDL suggesting tirzepatide provides a more robust cardioprotective and insulin-sensitizing environment than selective GLP-1 RAs, though definitive cardiovascular outcome data directly comparing tirzepatide and semaglutide remain unavailable to date. However, this increased potency necessitates a careful evaluation of tolerability. While the gastrointestinal adverse event profiles are remarkably similar in nature (primarily mild-to-moderate nausea and diarrhea), tirzepatide does carry a marginally higher burden at peak doses. The doubling of discontinuation rates at the 15 mg dose (8.5% compared to 4.1% for semaglutide) is a critical consideration for clinicians. Nevertheless, the fact that less than 3% of patients are discontinued specifically due to GI distress suggests that these symptoms are largely manageable with proper titration. Moreover, the potentially lower biliary risk associated with tirzepatide despite more rapid weight loss provides an additional safety incentive for its use.

Ultimately, while the SURPASS-2 population represented an ideal "sweet spot" of patients with preserved β-cell function, the findings suggest that dual-agonist therapy is redefining the therapeutic ceiling for T2DM. Tirzepatide's ability to "normalize" metabolic markers rather than just "manage" them marks a paradigm shift toward intensive, early intervention that could potentially alter the long-term trajectory of the disease.

Gaps in the literature and future directions

Despite the robust clinical outcomes demonstrated by tirzepatide and semaglutide, several critical literature gaps persist, particularly regarding the "GIP receptor paradox" and the precise mechanistic contribution of dual agonism in humans. Current research indicates that tirzepatide improves insulin sensitivity through weight-independent pathways-estimated to account for nearly 30% of its glycaemic effect—yet tissue-specific studies in human adipose and central nervous system (CNS) tissues are needed to confirm if these effects stem from direct GIP receptor activation or functional antagonism [48,49]. Furthermore, while real-world data from 2025 suggests comparable cardiovascular protection (HR 1.06), a significant evidence

gap remains as no randomized, head-to-head trial has directly assessed long-term major adverse cardiovascular events (MACE) between tirzepatide and semaglutide; results from SURPASS-CVOT only compare tirzepatide to dulaglutide, leaving the question of incremental dual-agonist cardio protection unanswered [50]. Future research directions must prioritize 3–5-year durability studies to track β-cell preservation, stratified analyses to identify "responder phenotypes" based on baseline insulin resistance, and mechanistic investigations into why tirzepatide appears to carry a lower biliary risk (2.6-fold lower cholelithiasis rates vs semaglutide in obese adults from SURMOUNT/STEP trials) despite achieving more rapid weight loss than semaglutide [51,52].

Conclusions

In summary, the findings from the SURPASS-2 trial underscore a significant shift in the management of type 2 diabetes, positioning dual-agonist therapy as a robust advancement over traditional single-agonist approaches. By simultaneously targeting GIP and GLP-1 receptors, tirzepatide achieves a synergistic metabolic restructuring that consistently outperforms semaglutide in both glycaemic reduction and substantial weight loss. While the dual-agonist profile introduces a slightly higher frequency of gastrointestinal side effects and treatment discontinuation at peak doses, these events remain largely manageable and are offset by the medicine's superior ability to restore normoglycemia in nearly half of the high-dose cohort. Ultimately, while further research into long-term cardiovascular outcomes and specific responder phenotypes is necessary, the current evidence suggests that tirzepatide offers a highly effective, clinically tolerable option for patients who require more intensive metabolic intervention than selective GLP-1 receptor agonists can provide.

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