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Insights into the Efficacy of GLP-1 Agonists and Dual Agonists: Semaglutide and Tirzepatide in Obesity and Type 2 Diabetes

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Abstract

The increasing global prevalence of obesity and type 2 diabetes (T2D) has prompted significant advancements in pharmacological treatments, with glucagon-like peptide-1 (GLP-1) receptor agonists and dual agonists representing key innovations. Semaglutide, a GLP-1 receptor agonist, and tirzepatide, a novel dual agonist targeting both GLP-1 and glucose-dependent insulinotropic peptide (GIP) receptors, have shown remarkable efficacy in improving glycemic control and promoting weight loss.

This review synthesizes the latest clinical evidence on the efficacy and safety of semaglutide and tirzepatide in the management of obesity and T2D, highlighting the findings from recent pivotal trials. In patients with T2D, semaglutide has consistently demonstrated superior glycemic control and weight loss compared to traditional therapies, as evidenced by the SUSTAIN trials [1]. Similarly, tirzepatide has emerged as a more efficacious option, with the SURPASS trials demonstrating greater reductions in HbA1c and more substantial weight loss compared to semaglutide. This positions tirzepatide as a potential first-line therapy for T2D.[2].

Both therapies have shown a favorable safety profile, with gastrointestinal side effects being the most common, and cardiovascular benefits observed in both drug classes. Given their dual mechanism of action, tirzepatide has shown unique potential in addressing both glycemic control and obesity, with emerging evidence supporting its use in non-diabetic patients with obesity [3].This review highlights the potential of these agents to revolutionise the management of obesity and T2D, with tirzepatide emerging as a promising next-generation treatment for metabolic diseases.

Keywords: Semaglutide, tirzepatide, obesity, type 2 diabetes

Introduction

Obesity and type 2 diabetes (T2D) are major global health concerns, with obesity acting as a primary risk factor for the development of T2D. The increasing prevalence of both conditions presents significant challenges for healthcare systems worldwide, leading to high morbidity, reduced quality of life, and rising healthcare costs. While lifestyle interventions remain the cornerstone of treatment, pharmacological therapies have become essential for long-term management.

Incretin-based therapies, specifically GLP-1 receptor agonists like semaglutide, have gained prominence due to their dual effects on glycemic control and weight reduction. Semaglutide, a long-acting GLP-1 agonist, has shown significant clinical efficacy in improving glycemic control and reducing body weight in patients with T2D and obesity [4]. Recently, tirzepatide, a novel dual agonist targeting both GLP-1 and GIP (glucose-dependent insulinotropic peptide) receptors, has demonstrated even greater efficacy, with superior reductions in HbA1c and body weight compared to semaglutide [5].

The objective of this narrative review is to synthesise the most recent evidence pertaining to the mechanisms of action, clinical efficacy, safety profiles and potential therapeutic roles of semaglutide and tirzepatide in the management of obesity and type 2 diabetes.

To ensure a comprehensive and up-to-date synthesis of the literature, a detailed search was conducted using PubMed, Embase, and ClinicalTrials.gov. We used key search terms, including “semaglutide”, “tirzepatide”, “GLP-1 receptor agonist”, “dual agonist”, “obesity”, and “type 2 diabetes”, and identified over 50 peer-reviewed articles, including clinical trials, meta-analyses, and systematic reviews, published in the past 5 years. In the course of our study, a number of pertinent literature sources were subjected to a narrative review in order to extract data concerning the therapeutic outcomes, safety profiles and comparative efficacy of the two therapies under consideration.

The findings from these studies provide insights into the clinical applications of semaglutide and tirzepatide and their place in current treatment algorithms for obesity and T2D.

Mechanisms of action

Semaglutide is a selective GLP-1 receptor agonist that mimics the action of the incretin hormone GLP-1. GLP-1 enhances insulin secretion in a glucose-dependent manner, suppresses glucagon release, slows gastric emptying, and promotes satiety, all of which contribute to improved glucose control and weight loss. By activating the GLP-1 receptor, semaglutide helps regulate blood glucose levels and supports weight reduction, making it an effective treatment for type 2 diabetes and obesity [6].

In contrast, tirzepatide is a dual receptor agonist that targets both GLP-1 and GIP receptors. Like semaglutide, tirzepatide's GLP-1 receptor activity increases insulin secretion and suppresses glucagon release. However, tirzepatide also activates the GIP receptor, which has additional benefits for glucose metabolism. Activation of the GIP receptor enhances insulin sensitivity, improves insulin secretion, and may play a role in reducing ectopic fat accumulation, particularly in the liver and muscles. This dual receptor activation is thought to enhance tirzepatide's efficacy in managing glucose homeostasis and promoting weight loss compared to GLP-1 receptor agonists alone [7].

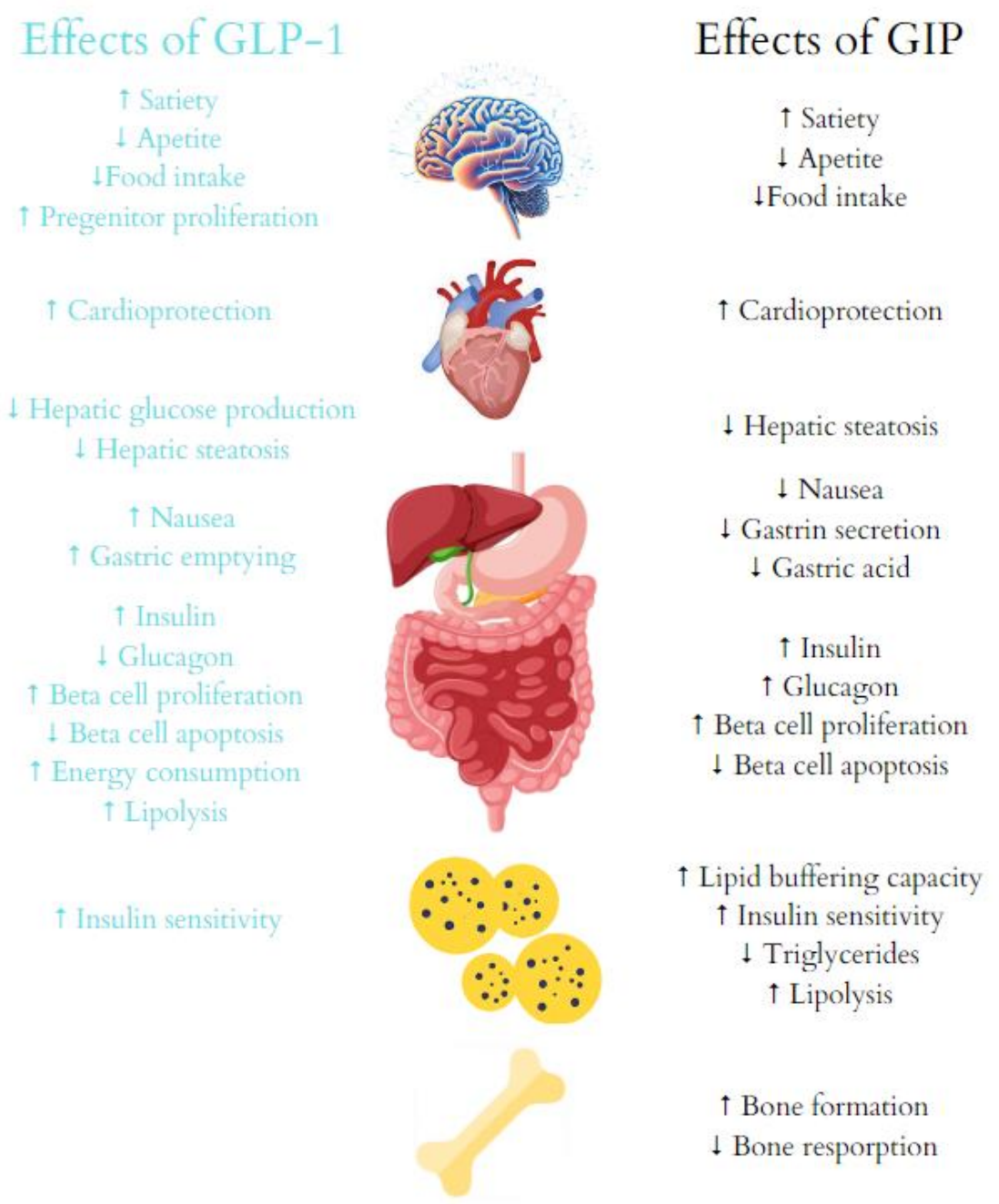

Figure 1. Effects of GLP1/ GIP receptor agonists.

Clinical studies have highlighted significant differences between the two drugs in terms of their effects on insulin sensitivity and glucose control. In the SURPASS-2 study, tirzepatide improved insulin sensitivity by 65.7%, significantly greater than the 37.5% improvement observed with semaglutide. This difference is partly explained by the greater weight loss associated with tirzepatide (average 11.2 kg vs. 6.9 kg with semaglutide), although the improvement in insulin sensitivity per unit weight loss was also greater with tirzepatide. This

suggests that tirzepatide has a more pronounced effect on insulin sensitivity, which may be partially weight-independent, related to its dual receptor action [7].

Both tirzepatide and semaglutide also reduce postprandial glucose and glucagon levels, but tirzepatide leads to a more significant reduction in meal-related insulin secretion compared to semaglutide [8]. This suggests that tirzepatide may improve insulin sensitivity to a greater extent, resulting in less insulin secretion during meals. Furthermore, both drugs have been observed to reduce appetite and ad libitum energy intake in comparison to the placebo [9]. However, no significant differences were noted between the two treatments in this regard.

Clinical efficacy

Semaglutide, a GLP-1 receptor agonist, has been widely studied for its efficacy in the treatment of both obesity and type 2 diabetes (T2D). In the STEP 1 trial, semaglutide 2.4 mg once-weekly led to a mean weight loss of 14.9% over 68 weeks in patients with obesity, a significantly greater reduction compared to the placebo group [1]. The STEP 3 trial further demonstrated that semaglutide resulted in 11.5% weight loss in patients with obesity and comorbidities like hypertension and dyslipidemia [10]. In T2D management, the SUSTAIN 1 trial showed that semaglutide 0.5 mg and 1.0 mg reduced HbA1c by 1.5% to 2.0%, with an associated weight loss of 5-10 kg [11]. In the SUSTAIN 6 trial, semaglutide was associated with a 26% reduction in major cardiovascular events [12]. Semaglutide's dual benefits in glycemic control and weight reduction make it a key therapeutic option for both conditions.

Tirzepatide, a dual GLP-1 and GIP receptor agonist, has been shown to offer superior efficacy compared to semaglutide. In the SURPASS 1 trial, tirzepatide 5, 10, and 15 mg doses led to a mean HbA1c reduction of up to 2.4% and 12.4 kg weight loss [13]. In SURPASS 2, tirzepatide outperformed semaglutide in both HbA1c reduction (1.7% vs. 1.5%) and weight loss (11-12 kg vs. 6-7 kg with semaglutide) [2]. The superior results of tirzepatide are likely due to its dual mechanism of action, which enhances insulin secretion via GLP-1 and improves insulin sensitivity via GIP [14]. Tirzepatide has also shown potential cardiovascular benefits. In the SURPASS 3 trial, tirzepatide reduced the rate of hospitalization for heart failure in patients with T2D and cardiovascular comorbidities [15].

In the management of obesity, tirzepatide has also been demonstrated to be more efficacious. In the SURMOUNT-1 trial, the 5, 10, and 15 mg doses of tirzepatide resulted in a weight loss of 15-22% [16], a significantly higher reduction than the 14.9% weight loss

observed with semaglutide in the STEP 1 trial [9]. These findings serve to highlight tirzepatide's superior efficacy in promoting weight loss, particularly in patients with obesity.

Safety profile

- Common side effects

Both semaglutide and tirzepatide are generally well-tolerated, but their most common side effects are gastrointestinal (GI) in nature, particularly during the initial phase of treatment. These side effects are typically mild to moderate and include nausea, vomiting, and diarrhea. These symptoms often occur as the body adjusts to the medications, as both drugs slow gastric emptying and enhance satiety, which can affect the digestive system.In clinical trials, approximately 30-40% of patients treated with semaglutide reported experiencing nausea, particularly during the dose escalation phase[17]. Similarly, tirzepatide has been associated with gastrointestinal discomfort, with nausea occurring in up to 30% of patients in early treatment phases [13].

Managing these side effects often involves dose titration—starting with a low dose and gradually increasing it to minimize gastrointestinal discomfort. For instance, the semaglutide dosing regimen typically begins at 0.25 mg once weekly for four weeks, then escalates to 0.5 mg, and eventually 1.0 mg [11].Patient education is of paramount importance in managing expectations. It is recommended that patients take the medication at a consistent time each week, avoid high-fat meals, and stay hydrated. In certain instances, a temporary cessation or reduction in dosage may be warranted for patients who experience severe nausea or vomiting.

- Serious Adverse Events

While both semaglutide and tirzepatide are generally safe, there are serious adverse events associated with their use, although they are rare. Pancreatitis is a potential risk, as GLP-1 receptor agonists have been implicated in an increased risk of acute pancreatitis, although this risk remains very low in clinical practice. In the SUSTAIN 6 trial of semaglutide, there was one case of acute pancreatitis among the 3,000+ participants [12]. Similarly, tirzepatide has been linked to a minimal but non-negligible risk of pancreatitis, although it has not been identified as a primary contributor in major clinical trials [13]. Patients with a history of pancreatitis should be closely monitored, and the use of these drugs should be avoided in patients with a history of severe pancreatitis.

Both semaglutide and tirzepatide carry a warning for thyroid tumors. In rodent studies, GLP-1 receptor agonists, including semaglutide and tirzepatide, have been associated with an increased incidence of medullary thyroid carcinoma (MTC) and C-cell hyperplasia [18]. However, the relevance of these findings to humans remains unclear, and no definitive cases of MTC have been reported in human clinical trials. Nevertheless both medications are contraindicated in individuals with a family history of medullary thyroid cancer or those with Multiple Endocrine Neoplasia Type 2 (MEN 2), a rare genetic disorder that predisposes individuals to thyroid cancer [19].

Another potential concern for both semaglutide and tirzepatide is the risk of diabetic retinopathy [20]. In the SUSTAIN 6 trial, semaglutide was associated with a small but significant increase in the risk of diabetic retinopathy complications, particularly in patients with a history of advanced retinopathy [12]. However, the overall risk of severe diabetic retinopathy was low, and the benefits of semaglutide in terms of reducing major adverse cardiovascular events (MACE) outweighed the risks. For tirzepatide, diabetic retinopathy events have not been extensively studied, but the SURPASS trials report a similar pattern, with retinal issues noted but not in significant frequency [2].

Long-term safety concerns include the potential for gastrointestinal adverse events to persist, as well as the need for ongoing monitoring for thyroid and pancreatic risks. For both drugs, regular monitoring for thyroid abnormalities and pancreatic health is recommended. Additionally, patients with a history of diabetic retinopathy should be monitored closely for any progression of eye disease during treatment.

- Cardiovascular safety

The cardiovascular safety of both semaglutide and tirzepatide has been the subject of extensive investigation, with both agents exhibiting notable benefits in this regard.

The SUSTAIN 6 trial of semaglutide was a landmark study that evaluated cardiovascular outcomes in patients with type 2 diabetes at high cardiovascular risk. The trial showed that semaglutide was associated with a 26% reduction in major adverse cardiovascular events (MACE), including heart attack, stroke, and cardiovascular death, compared to placebo [12]. This result led to the approval of semaglutide for reducing cardiovascular risk in patients with T2D.

Tirzepatide's cardiovascular benefits were evaluated in the SURPASS trials, with the SURPASS 3 trial specifically assessing cardiovascular outcomes. In this trial, tirzepatide demonstrated a significant reduction in the risk of cardiovascular events. Although the precise percentage reduction in MACE was not as considerable as that observed with semaglutide, tirzepatide was nevertheless associated with a lower incidence of hospitalisation for heart failure [15]. Furthermore, tirzepatide showed improvements in lipid profiles, including reductions in total cholesterol, LDL cholesterol, and triglycerides, which likely contributed to its cardiovascular benefits [2].

A comparative analysis of the cardiovascular benefits of semaglutide and tirzepatide indicates that both drugs provide a protective effect against cardiovascular disease in patients with type 2 diabetes. Nevertheless semaglutide's 26% reduction in MACE remains one of the strongest outcomes observed for any diabetes medication to date [12]. Tirzepatide has demonstrated favourable cardiovascular outcomes, although the evidence regarding its impact on overall MACE is somewhat less robust. However, it offers additional benefits in heart failure outcomes and lipid management [15].

Discussion

Semaglutide and tirzepatide represent groundbreaking advancements in the treatment of obesity and type 2 diabetes (T2D). Both therapies have demonstrated substantial efficacy in improving glycemic control and promoting weight loss, with tirzepatide emerging as a more potent option due to its dual action on GLP-1 and GIP receptors. This mechanism of action enhances insulin sensitivity, which contributes to greater reductions in HbA1c and more significant weight loss compared to semaglutide [2]. The SUSTAIN and SURPASS trials have consistently shown that semaglutide and tirzepatide offer substantial benefits over traditional diabetes treatments, with tirzepatide showing greater efficacy in both HbA1c reduction and weight loss [12,15].

Despite these promising results, both medications are associated with common gastrointestinal side effects such as nausea, vomiting, and diarrhea, especially during the initial phases of treatment. These adverse events typically subside with dose titration and patient education [21,22]. Serious adverse events, including pancreatitis and thyroid tumors, have been reported in preclinical studies, although human data on these risks remain limited. Both drugs carry warnings regarding the risk of medullary thyroid carcinoma (MTC), and their use is

contraindicated in patients with a family history of thyroid cancer or Multiple Endocrine Neoplasia Type 2 (MEN2) [23].

In terms of cardiovascular outcomes, both semaglutide and tirzepatide have demonstrated cardiovascular benefits in patients with T2D, with semaglutide showing a 26% reduction in major adverse cardiovascular events (MACE) in the SUSTAIN 6 trial [12]. Tirzepatide has also shown promise in reducing hospitalization for heart failure and improving lipid profiles (e.g., reductions in LDL cholesterol, total cholesterol, and triglycerides) [2], although the exact impact on MACE is still under investigation.

The long-term safety and efficacy of these therapies remain areas of active investigation. While current trials have shown benefits over the short term, understanding their sustained effectiveness in real-world settings and across diverse patient populations is crucial for long-term treatment strategies [24]. Furthermore, combination therapies, such as pairing GLP-1 and dual agonists with other medications like SGLT2 inhibitors or metformin, are likely to enhance the therapeutic benefits, addressing a broader range of metabolic dysregulations [25]. The SURPASS-4 and SURPASS-5 trials, exploring tirzepatide in combination with other agents, will provide further insights into the potential of combination therapies [26,27].

Future research should also focus on patient selection to determine which populations would benefit most from semaglutide versus tirzepatide. Personalized treatment approaches, taking into account factors such as obesity severity, insulin resistance, and the presence of comorbidities like cardiovascular disease, will be critical in optimizing therapeutic outcomes [28]. Identifying the ideal candidate for each therapy will help clinicians tailor treatments for maximal efficacy and safety.

In conclusion, both semaglutide and tirzepatide hold immense promise in the treatment of obesity and type 2 diabetes, with tirzepatide particularly standing out due to its dual receptor action. As research progresses, these agents are expected to play a central role in metabolic disease management, particularly with the increasing focus on long-term outcomes, combination therapies, and personalized treatment strategies. With continued investigation into their long-term safety, the future of these therapies looks exceptionally promising in transforming the management of obesity and type 2 diabetes.

Authors' contributions statement

Conceptualization: [AM] [MM] [AO] [KS] [LO] [AMA][JM][NN]

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Funding Acquisition: Investigation: [AM] [MM] [AO] [KS] [LO] [AMA][JM][NN]

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Project Administration: [AM] [MM] [AO] [KS] [LO] [AMA][JM][NN]

Resources: [AM] [MM] [AO] [KS] [LO] [AMA][JM][NN]

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Writing- Review and Editing: [AM] [MM] [AO] [KS] [LO] [AMA][NN]

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