



Dual GLP-1/GIP Agonist Tirzepatide for Diabetes and Obesity: A Review of the Evidence

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Abstract

Background Tirzepatide is a novel dual glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic peptide (GIP) receptors agonist in management of type 2 diabetes mellitus. The aim of this literature review is to comprehensively assess its clinical, biochemical, and safety profiles.

Materials and Methods Search was conducted in several databases including PubMed from drug inception through end of 2022. Publications relevant to tirzepatide including randomized controlled trials, meta-analysis studies, post-hoc analyses, and conference proceedings were identified to examine its profile. Additional necessary references were explored and included as needed.

Results Tirzepatide is a twincretin, acting on both GLP-1 and GIP receptors. Its performance in glycemic control and weight loss was greater than that of GLP-1 receptor agonist or insulin, comparatively. It demonstrated promising positive renal outcomes and was not associated with a higher cardiovascular risk, in addition to favorable effects on lipid, hepatic and blood pressure profiles. Most common adverse events were gastrointestinal side effects and hypoglycemia.

Conclusion Novel dual GLP-1/GIP agonist Tirzepatide shows superior efficacy in glycemic control and weight loss in T2 diabetes mellitus patients. More evidence is needed to explore and compare long-term cardiovascular and renal outcomes reflecting real-world clinical practice.

Keywords

- ▶ tirzepatide
- ▶ GIP/GLP-1 agonist
- ▶ type 2 diabetes
- ▶ weight loss
- ▶ glycemic control
- ▶ incretin

Introduction

Inflicting more than 500 million adults worldwide, diabetes has been an increasingly growing global threat.¹ The chronic progressive course of the disease leads to microvascular and macrovascular complications. The health and social burden

pushed the cause-specific mortality rates by age to a 3% increase in the past two decades.² On a national scale in the United Arab Emirates, the prevalence of diabetes was reported to reach an alarming 16.3%, in contrast to only 9.3% worldwide.³

Despite accelerating developments in diabetes therapeutics and care, many patients with type 2 diabetes still suffer

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complications and are short of reaching treatment goals. In light of detrimental multifaceted consequences, developing new therapies is a necessity. This paved the road for the rise of dual glucose-dependent insulinotropic polypeptide (GIP) and glucagon-like peptide-1 (GLP-1) receptor agonist tirzepatide.⁴

This literature review aims to comprehensively cover the reported clinical efficacy relevant to glycemic control, other metabolic parameters, and the safety profile of this promising novel drug in managing type 2 diabetes mellitus (T2DM). Tirzepatide is available in different dosage forms, 2.5, 5, 7.5, 10, 12.5, and 15 mg. It is administered subcutaneously with a half-life reaching 5 days, thus allowing once-weekly dosing.⁵

Incretin Physiology and Drug Mechanism of Action

In a normal physiological response to the surge of oral carbohydrates and lipid load, the intestinal K cells localized in the duodenum and proximal jejunum secrete GIP. This incretin peptide survives a short half-life of 4 to 7 minutes before being broken down by the dipeptidyl peptidase (DPP)-4 enzyme. In contrast to GLP-1, GIP displays glucagonostatic properties in the state of hyperglycemia while being glucagonotropic in normoglycemic and hypoglycemic states.⁶ As glucagon plays a role in battling hypoglycemia, this glucagonotropic property in hypoglycemic states grants tirzepatide an advantage of lower risk of hypoglycemia and hence safer use.

GLP-1 is an incretin hormone also dedicated to glucoregulatory effects in humans. It is secreted from intestinal enteroendocrine cells in response to nutritional meals to amplify glucose-dependent insulin secretion, enhance β -cell function, inhibit glucagon secretion, and aid in reducing insulin resistance and improving glucose tolerance. It harbors a central effect of suppressing appetite centers in the hypothalamus and delaying gastric emptying. Eventually, it is degraded by intestinal DPP-4 and neutral endopeptidases after a short half-life.⁷

In T2DM, there is a loss of insulinotropic properties of GIP as well as a loss of glucagonostatic properties in the hyperglycemic state (GIP resistance). Evidence demonstrated that administering GIP supraphysiological in T2DM patients fortified the incretin insulinotropic role. Given the glucagon's role in preventing hypoglycemia, the glucagonotropic attribute of GIP is particularly intriguing in managing T2DM.⁶

In T2DM patients, pairing GLP-1 and GIP yielded synergistic effects in considerably enhancing insulin secretion and lowering blood glucose via the insulinotropic and glucagonostatic attributes. These mechanisms paved the road for the development of Tirzepatide. This synthetic peptide stands as a 39-amino acid acting as a dual GIP/ GLP-1 receptor agonist. This twincretin exhibited a GIP receptor affinity similar to native GIP; however, it showed five times less affinity to GLP-1 receptors in comparison to native GLP-1.^{4,6}

Effect on Glycemic Control and HbA1c Reductions

Tirzepatide persistently showed robust improvements in glycemic control across all clinical trials consistent with all

the doses. In comparison to a placebo, all doses yielded more significant hemoglobin A1c (HbA1c) and fasting serum glucose reductions and achieved target HbA1c levels more efficiently^{4,6} (►Table 1 summarizes the results of major randomized controlled trials on tirzepatide.)

Tirzepatide monotherapy was able to achieve HbA1c mean reduction of 1.87% with 5 mg, 1.89% with 10 mg, and 2.07% with 15 mg, in contrast to a rise of mean HbA1c by 0.04% in the placebo group. In addition, 87 to 92% of patients treated with tirzepatide were able to meet target HbA1c of less than 7.0%, 81 to 86% were able to reach HbA1c of 6.5% or less, and 31 to 52% of patients were able to reach HbA1c of less than 5.7%, in contrast to 20%, 10%, and 1% in the placebo group, respectively.⁴

When compared to semaglutide at a dose of 1 mg weekly, tirzepatide was superior at all doses. HbA1c levels in patients treated with tirzepatide trended down by an average of 2.01, 2.24, and 2.3% for 5, 10, and 15 mg, respectively. However, the semaglutide group witnessed an average reduction of 1.86% of HbA1c from baseline only.⁸

Tirzepatide demonstrated superiority compared to insulin degludec with a greater dose-dependent reduction in HbA1c in SUPRASS 3 trials.⁹ A similar trend of significantly improved glycemic control with increased doses was witnessed when added to titrated insulin glargine in patients with type 2 diabetes in comparison to placebo in SUPRASS-5 trials.¹⁰ Importantly, tirzepatide maintained a superior stand with greater reductions in HbA1c in comparison to insulin glargine in patients with type 2 diabetes with a greater cardiovascular risk.¹¹

Effects on Weight Loss

It is no longer sufficient for diabetic drugs to excel in glycemic control only, but it is also demanded to manage obesity. The risk of developing diabetes, dyslipidemia, and cardiovascular complications has been independently associated with visceral fat mass. Hence, remarkable weight loss impacts all body organs.¹² Weight loss of around 5 to 10% manages to mitigate hyperglycemia, dyslipidemia, and hypertension, all of which stand as cardiovascular risk factors. Further weight loss of more than 10% contributes to recovery of obstructive sleep apnea and nonalcoholic steatohepatitis (NASH). An augmented degree of weight loss reaching 15% correlates with remission of diabetes, and even reducing mortality.^{12,13} Weight loss effect of diabetic drugs has grown as a necessity rather than a luxury.

Up to 87 to 97% of patients treated with tirzepatide in the SURPASS trials experienced weight loss in addition to the reduction in HbA1c. This effect was witnessed across all doses of 5, 10, and 15 mg.⁴ Compared to the placebo in SUPRASS-1 trials, tirzepatide monotherapy significantly reduced weight by an average of 7, 7.8, and 9.5 kg with increased doses of 5, 10, and 15 mg, respectively, which correlated with HbA1c changes. These results contrast with only a 0.7 kgs reduction in the placebo group.^{4,14}

This effect was augmented and maintained when compared with semaglutide 1 mg in patients who have been

Table 1 Summary of the major SURPASS program studies

	Comparison		Primary outcome	Inclusion criteria	# of Subjects	Result of primary outcome	Secondary outcomes
SURPASS-1	Monotherapy with tirzepatide 5, 10, 15 vs. placebo	Double-blind RCT	Mean change in (HbA1c) from baseline at 40 weeks	<ul style="list-style-type: none"> Adult ≥ 18 years Type 2 diabetes Inadequately controlled by diet and exercise alone Naive to injectable diabetes therapy 	478	HbA1c reduced by -1.87% (SE 0.09; -20 [1 mmol/mol]) with tirzepatide 5 mg, -1.89% (0.10; -21 [1 mmol/mol]) with tirzepatide 10 mg, and -2.07% (0.10; -23 [1 mmol/mol]) with tirzepatide 15 mg versus +0.04% (SE, 0.11; +0.4 [1 mmol/mol]) with placebo	<ul style="list-style-type: none"> Significant reductions in fasting blood glucose with 5, 10, and 15 mg. Significant reduction in weight of -7.9 kg with 5 mg to -11 kg with 15 mg Increase in pulse rate of 1 to 2 beats per minute with tirzepatide No cases of pancreatitis but pancreatic lipase at 40 weeks were higher in tirzepatide group Single case of pancreatic cancer discovered while evaluating hematuria in the 5 mg group
SURPASS-2	Comparing tirzepatide 5, 10, and 15 mg vs. semaglutide 1 mg	Open-label RCT	The primary end point was the change in the HbA1c in level from baseline to 40 weeks	<ul style="list-style-type: none"> 18 years or older Type 2 diabetes Inadequately controlled with metformin at a dose of at least 1,500 mg per day 	1879	<ul style="list-style-type: none"> HbA1c level was -2.01, -2.24, and -2.30% with 5, 10, and 15 mg of tirzepatide, respectively, and -1.86% with semaglutide; the estimated differences between the 5, 10, and 15 mg tirzepatide groups and the semaglutide group were -0.15 (95% [CI], -0.28 to -0.03; $p = 0.02$), -0.39 (95% CI, -0.51 to -0.26; $p < 0.001$), and -0.45 (95% CI, -0.57 to -0.32; $p < 0.001$) 	<ul style="list-style-type: none"> Weight loss was -1.9, -3.6, and -5.5 kg, respectively; $p < 0.001$ for all comparisons Gastrointestinal and were primarily mild-to-moderate in severity in the tirzepatide and semaglutide groups (nausea, 17–22% and 18%; diarrhea, 13–16% and 12%; and vomiting, 6–10% and 8%, respectively) Serious adverse events were reported in 5 to 7% of the patients who received tirzepatide and in 3% of those who received semaglutide
SURPASS-3	Tirzepatide (5, 10, or 15 mg), or once-daily insulin degludec	RCT, open-label	Mean change from baseline in HbA1c at week 52	<ul style="list-style-type: none"> Aged ≥ 18 years Insulin-naïve type 2 diabetes inadequately controlled (HbA1c 7.0–10.5%) on stable treatment with metformin alone or in combination with an SGLT2 inhibitor for at least 3 months. A BMI of at least 25 kg/m^2. Stable weight (no change outside of 5%) during the previous 3 months <p>Exclusion criteria:</p> <ul style="list-style-type: none"> Type 1 diabetes History of pancreatitis 	1947	<ul style="list-style-type: none"> Mean baseline HbA1c was decreased after 52 weeks of treatment by 1.93% (SE, 0.05), 2.20% (0.05), and 2.37% (0.05) in the tirzepatide 5, 10, and 15 mg groups, respectively, compared with a decrease of 1.34% (0.05) in the insulin degludec group This indicates superiority of tirzepatide 10 and 15 mg versus insulin degludec for the primary efficacy endpoint ($p < 0.0001$ for both doses) 	<ul style="list-style-type: none"> All doses of tirzepatide reduced BMI (by -2.7 to -4.6 kg/m^2) and waist circumference (by -7.1 to -10.9 cm) from baseline at week 52, while insulin degludec increased both parameters Tirzepatide 10 and 15 mg significantly decreased triglycerides and VLDL cholesterol at week 52 to a larger extent than did insulin degludec At week 52, significant decreases in mean systolic

(Continued)

Table 1 (Continued)

	Comparison		Primary outcome	Inclusion criteria	# of Subjects	Result of primary outcome	Secondary outcomes
				<ul style="list-style-type: none"> History of proliferative diabetic retinopathy or maculopathy eGFR of less than 45 mL/min per 1.73 m² 		<ul style="list-style-type: none"> More participants in the tirzepatide groups (82–93%) than in the insulin degludec group (61%) achieved the HbA1c target of less than 7.0% (<53 mmol/mol) at week 52 ($p < 0.0001$ for all tirzepatide doses vs. insulin degludec) 	<ul style="list-style-type: none"> (−4.9 to −6.6 mm Hg) and diastolic (−1.9 to −2.5 mm Hg) blood pressure were observed for tirzepatide; no changes were seen for insulin degludec Mean values of alanine aminotransferase (ALT) and aspartate aminotransferase (AST) concentrations decreased from baseline to week 52 to a greater extent in the tirzepatide groups than in the insulin degludec group The urine albumin-to-creatinine ratio decreased from baseline with tirzepatide 15 mg ($p < 0.0008$) The incidence of severe hypoglycemia and blood glucose less than 54 mg/dL was 1–2% in the tirzepatide groups versus 7% in insulin degludec group
SURPASS-4	Tirzepatide 5, 10, and 15 mg vs. glargine in high risk subjects	Open label RCT	Change in HbA1c from baseline to 52 weeks.	<p>Inclusion criteria:</p> <ul style="list-style-type: none"> Aged ≥ 18 years Type 2 diabetes HbA1c 7.5–10.5% [58–91 mmol/mol], on any of three oral glucose-lowering medications (i.e., metformin, sulfonylurea, or SGLT-2 inhibitor) either alone or in any combination. BMI of 25 kg/m² or more, and stable weight ($\leq 5\%$ fluctuation in either direction) during the previous 3 months. Eligible participants were at high risk for CV events (defined as known coronary, peripheral arterial, or cerebrovascular disease, or aged 50 years or older with either history of chronic kidney disease and an eGFR of less than 60 mL/min per 	3045	<ul style="list-style-type: none"> HbA1c of less than 7.0% (<53 mmol/mol) was achieved in 81–91% of tirzepatide-treated participants versus 51% with glargine HbA1c of 6.5% or lower (<48 mmol/mol) was achieved in 66–81% of tirzepatide-treated participants versus 32% with glargine HbA1c of less than 5.7% (<39 mmol/mol) in 23–43% of tirzepatide-treated participants versus 3% with glargine The composite endpoint of HbA1c of less than 7.0% without weight gain and clinically significant documented symptomatic or severe hypoglycemia was 	<ul style="list-style-type: none"> Tirzepatide dose-dependently reduced bodyweight. At 52 weeks, mean bodyweight changes with tirzepatide were −7.1 kg–8.1% at 5 mg; −9.5 kg–10.7% at 10 mg; and −11.7 kg, −13.0% at 15 mg versus an increase of 1.9 kg with glargine ($p < 0.0001$) Dose-dependent reductions of serum triglyceride (up to −23%), LDL cholesterol (up to −8%) and non-HDL cholesterol (up to −12%) concentrations at 52 weeks with tirzepatide compared with marginal changes with glargine ($p < 0.0001$) There was no increased risk of MACE-4 events for pooled tirzepatide versus glargine, hazard ratio 0.74 (95% CI, 0.51–1.08)

Table 1 (Continued)

	Comparison		Primary outcome	Inclusion criteria	# of Subjects	Result of primary outcome	Secondary outcomes
SURPASS-5	Add on tirzepatide to basal insulin glargine	Open label RCT	Change in HbA1c from baseline to 40 weeks. For doses 10 and 15 mg	<p>1-73 m² or history of congestive heart failure)</p> <p>Exclusion criteria:</p> <ul style="list-style-type: none"> Type 1 diabetes History of pancreatitis 		achieved in 74–88% of tirzepatide-treated participants compared with 13% with glargine	
			Change in HbA1c from baseline to 40 weeks. For doses 10 and 15 mg	<p>Inclusion criteria:</p> <ul style="list-style-type: none"> Adults with type 2 diabetes HbA1c of 7.0% to 10.5% BMI of at least 23 On stable daily dose of glargine (>20 IU/d or >0.25 IU/kg/d) with or without metformin (≥ 1500 mg/d). <p>Exclusion criteria:</p> <ul style="list-style-type: none"> Type 1-diabetes History of pancreatitis History of proliferative diabetic retinopathy or maculopathy eGFR of less than 30 mL/min per 1.73 m² (or <45 mL/min/1.73 m² for patients receiving metformin) hepatitis hypoglycemia unawareness, Gastroparesis, use of any other antihyperglycemic medication in the 3 months before screening 	475	<p>Tirzepatide doses of 10mg and 15mg showed significantly greater change in HbA1c from baseline at week 40 vs. placebo (10 mg: difference, −1.53% [97.5% CI, −1.80% to −1.27%]; $p < 0.001$; 15mg: difference, −1.47% [97.5% CI, −1.75% to −1.20%]; $p < 0.001$).</p>	<ul style="list-style-type: none"> For the efficacy estimand with the 5 mg dose, the corresponding change was −2.23% (difference vs. placebo, −1.30% [95% CI, −1.52% to −1.07%]; $p < 0.001$) Patients receiving tirzepatide, compared with placebo were more likely to achieve body weight loss of 5% (48–72% vs. 6%), 10% (21–42% vs. 1%), and 15% (7–24% vs. 0%) ($p < 0.05$ for all; treatment-regimen estimand)
SURPASS-3 MRI	to compare the effect on LFC of tirzepatide 10 mg and 15 mg dosing groups, versus insulin degludec	Sub-study of SURPASS-3	Mean change from baseline in liver fat content (LFC) at week 52	Same for SURPASS-3	296	<p>LFC decreased significantly from baseline ($p < 0.0001$) in both the pooled tirzepatide group (10 mg and 15 mg) and the insulin degludec group, and this decrease was significantly greater for the pooled tirzepatide group versus the insulin degludec group (−3.38%, 0.83). The ETD value versus insulin degludec was −4.71% (95% CI, −6.72 to −2.70; $p < 0.0001$)</p>	<ul style="list-style-type: none"> All tirzepatide doses significantly reduced the VAT:ASAT ratio from baseline at week 52, whereas no significant change from baseline was observed in the insulin degludec group

Abbreviations: BMI, body mass index; CI, confidence interval; CV, cardiovascular; eGFR, estimated glomerular filtration rate; ETD, Estimated Treatment Difference; HbA1c, hemoglobin A1c; HDL, high-density lipoprotein; LDL, low-density lipoprotein; LFC, liver fat content; RCT, randomized controlled trial; SE, standard error.

concurrently treated with metformin therapy. The SUPRASS-2 clinical trials showed reductions of 7.8, 10.3, and 12.4 kg respective to increased doses correlating with changes in HbA1c.^{8,14} These reductions surpassed the weight loss experienced in the semaglutide 1 mg group of only 6.2 kg. Regardless of the oral diabetic medications used prior, the correlation between HbA1c changes and weight reduction has been significant in those patients.¹⁴

Looking at the effect of semaglutide alone in weight loss, the dose of 2.4 mg achieved an absolute weight loss of around 9.7 kg, corresponding to a 9.6% decrease from starting weight after 68 weeks. The STEP 2 trials demonstrated that 69% of patients were able to achieve 5% weight reduction with semaglutide 2.4 mg, still not attaining the same degree of 78% of patients with tirzepatide. Although there have been no head-to-head comparative studies, data from different studies comparing the proportion of patients achieving weight loss of 10 and 15%, both semaglutide 2.4 mg and tirzepatide 15 mg, yielded similar results, with 46 to 47% and 26 to 27%, respectively.^{13,15}

Effects on Cardiovascular Outcomes

T2DM stands as a potent independent factor doubling the risk of cardiovascular events, namely coronary heart disease, heart failure, ischemic stroke, and vascular death.¹⁶ Tirzepatide has shown a promising impact on various related risk factors, and establishing a clear cardiovascular safety profile is mandatory. A meta-analysis looked deeper into all SUPRASS clinical trials to evaluate the safety profile in T2DM patients with a range of cardiovascular disease risks with a primary objective of time to first occurrence of confirmed MACE-4: four-component major adverse cardiovascular events: cardiovascular death, myocardial infarction, stroke, and hospitalized unstable angina.¹⁷ This data was reported in SUPRASS-4, which was primarily designed to compare tirzepatide to insulin glargine in diabetic patients with high cardiovascular risk, and not a cardiovascular outcome trial.

Tirzepatide showed a hazard ratio of 0.9 (95% confidence interval [CI], 0.50–1.61) for cardiovascular death, 0.76 (95% CI, 0.45–1.28) for myocardial infarction, 0.81 (95% CI, 0.39–1.68) for ischemic stroke, and 0.46 (95% CI, 0.15–1.41) for hospitalized unstable angina. With an overall hazard ratio of 0.8 (95% CI, 0.57–1.11) for MACE-4 outcomes, tirzepatide therapy was not associated with increased cardiovascular risk. In comparison to insulin glargine, degludec, and placebo combined, tirzepatide held a hazard ratio of 0.73 (95% CI, 0.51–1.05) for time to first occurrence of MACE-4 events. Adding events of hospitalized heart failure or coronary revascularization constitutes MACE-6, for which tirzepatide carried a hazard ratio of 0.79 (95% CI, 0.58–1.06).¹⁷ In light of such results, ongoing outcome trials results are awaited to confirm cardiovascular outcomes of tirzepatide at maximum dosage.¹⁸

Cardiovascular benefits of current GLP-1 agonists were inspected in published trials. SUSTAIN 6 clinical trial compared subcutaneous semaglutide to placebo with primary outcome of rate of first occurrence of cardiovascular death,

nonfatal myocardial infarction, or nonfatal strokes. The trial concluded noninferiority of subcutaneous semaglutide with a hazard ratio of 0.74 (95% CI, 0.58–0.95).¹⁹

Similar conclusion was demonstrated by PIONEER 6 clinical trial comparing cardiovascular outcomes of once daily oral semaglutide to placebo. Oral semaglutide proved noninferior to placebo with hazard ratio of 0.79 (95% CI, 0.57–1.11) with a noninferiority margin of 1.8 for upper boundary of confidence interval.²⁰ Oral semaglutide carried a hazard ratio of 0.49 (95% CI, 0.27–0.92) for cardiovascular death, 1.18 for myocardial infarction (95% CI, 0.73–1.9), and 0.74 for ischemic strokes (95% CI, 0.35–1.57).²⁰

Cardiovascular benefit of liraglutide was reported in LEADER clinical trials that compared it to placebo. Liraglutide demonstrated a lower rate of primary outcome than placebo with hazard ratio of 0.87 (95% CI, 0.78–0.97), proving its noninferiority.²¹

A meta-analysis of outcome trials regarding the cardiovascular effects of GLP-1 receptor agonists showed they were able to reduce MACE by 14%, with a hazard ratio of 0.86 (95% CI, 0.80–0.93). Similarly, all-cause mortality decreased by 12%, with hazard ratio of 0.88 (95% CI, 0.82–0.94).²²

Comparatively, a meta-analysis of the pioglitazone cardiovascular profile revealed a reduction in recurrent MACE with relative risk (RR) of 0.74 (95% CI, 0.60–0.92), in myocardial infarction RR of 0.77 (95% CI, 0.64–0.93) and ischemic stroke RR of 0.81 (95% CI, 0.68–0.96). However, pioglitazone did not prove a reduction in all-cause mortality RR of 0.94 (95% CI, 0.81–1.08). Moreover, it was associated with an increased risk of heart failure with RR of 1.33 (95% CI, 1.14–1.54).²³

Effects on Improving Beta Cell Function and Insulin Sensitivity

Homeostatic model assessment (HOMA) 2-B indices were used as an initial assessment to reflect the functional reserve of the pancreatic beta cell function. Tirzepatide at doses of 5, 10, and 15 mg showed a significant increase of HOMA2-B indices ranging from 93 to 163% from baseline, in comparison to 72% with dulaglutide and 1% with placebo.²⁴

The rising metabolic demand for insulin production in T2DM drives pancreatic beta cells into stress, resulting in defective processing of proinsulin. Patients witnessed a significantly decreased degree of change in intact proinsulin levels from baseline, ranging from 28 to 48% across tirzepatide doses 5, 10, and 15 mg when compared to dulaglutide and placebo, where change reached 18% from baseline. A similar trend was seen with proinsulin/insulin and proinsulin/C-peptide ratios, reflecting reduced beta cell stress.²⁴

Moreover, tirzepatide exhibited a decrease in glucose-adjusted glucagon levels by 28 to 36% across doses 5, 10, and 15 mg, whereas the levels increased by 32% with placebo and observed no change with dulaglutide therapy. These changes reflect an improved beta cell function and glucose control.

As hyperinsulinemia strongly correlates with insulin resistance, tirzepatide 10 and 15 mg demonstrated a significantly reduced change in fasting insulin levels by 10% from baseline, reflecting much-reduced insulin resistance.

However, dulaglutide therapy showed an increase of 30% and placebo by 10%.²⁴ Improving insulin resistance with tirzepatide was only partially attributable to weight loss, suggesting additional mechanisms by which tirzepatide enhanced insulin sensitivity, yielding superior glycemic control.

Furthermore, studies have evaluated adiponectin and insulin like growth factor (IGF)-binding proteins 1 and 2, which have been linked to positive responses to diet, weight loss, and bariatric interventions. Tirzepatide therapy with 5, 10, and 15 mg doses yielded notable increments reaching up to 26% in adiponectin, IGF binding protein 1, and IGF binding protein 2 levels. Dulaglutide therapy increased levels by 11% and placebo by 5%.²⁴

Effects on Improving Lipid Profile

Atherogenic dyslipidemia predisposes patients with T2DM to cardiovascular disease risk. This state is reflected by high levels of triglycerides in fasting and postprandial conditions, low levels of high-density lipoprotein (HDL) cholesterol, and elevated levels of low-density lipoproteins (LDL).²⁵ Insulin resistance in T2DM fortifies the root of atherogenic dyslipidemia via increasing very low-density lipoprotein (VLDL) particles. Apolipoprotein C-III (ApoC-III) acts by inhibiting lipoprotein lipase (LPL), the rate-limiting enzyme facilitating the uptake and metabolism of triglycerides.^{26,27}

GLP-1 receptor agonists have demonstrated cardioprotective effects by means of improving glycemic profile, promoting weight loss, blood pressure (BP) reduction, lowering hepatic fat, and renal protection. Furthermore, they have exhibited effects in reducing lipoprotein and chylomicron synthesis, reflecting lower postprandial levels of triglycerides, VLDL, and free fatty acids.²⁸ However, the effect of chronic treatment with GIP receptor agonists on plasma lipid parameters is not investigated. GIP receptor activation may play a role in lipid homeostasis via lipid intake by adipose tissue.²⁷ Following data comparisons have been derived from separate trials, and were not a direct comparison study between drugs.

Tirzepatide displayed a dose-dependent decline in apoB and apoC-III levels. Doses of 5, 10, and 15 mg reduced apoC-III levels by 26, 35, and 46%, compared to only 22% with dulaglutide.²⁷ Triglyceride-lowering drugs such as fenofibrate achieved a reduction of only 20% in apoC-III levels.²⁹

At doses of 10 and 15 mg, triglyceride-rich lipoprotein particles (TRLp) decreased by 77 and 66%, compared to not more than 20% with dulaglutide. These two highest doses reduced triglyceride levels by an average of 31 and 25%, respectively.²⁷ Meanwhile, fenofibrate only achieved a 26% reduction.²⁹ LDLp levels also dropped by 20 and 30%, respectively. Lipoprotein insulin resistance (LPIR) score showed downward trends by 36 and 31% more than dulaglutide and placebo.²⁷

Tirzepatide 15 mg showed similar effects in decreasing LDL-C levels as dulaglutide, reaching 19% in comparison to 17.8%. Tirzepatide decreased non-HDL-C by 16, 21, and 25% for 5, 10, and 15 mg, respectively. Dulaglutide achieved a

decrease of only 18%, whereas the placebo group experienced an increase in non-HDL-C levels. In contrast, dulaglutide did not significantly affect serum LPL or TRLp, LDLp, and LPIR score.²⁷

The dose-dependent decrease in apoC-III levels, independent of change in body weight, seemed to explain best the dose-dependent reduction in triglycerides up to 22.9% of the changes. Tirzepatide exhibited a net improvement in atherogenic lipid profile and insulin sensitivity.²⁷ The fully evident and proven effect of dual GIP and GLP-1 agonism is awaited in upcoming cardiovascular outcomes studies.

Having a close look at the influence of semaglutide on lipid profile, overall performance was positive; however, it runs short in comparison to tirzepatide. Semaglutide 1 mg achieved a reduction in levels of triglycerides, LDL cholesterol, VLDL cholesterol, and total cholesterol by 11.5, 6.4, 11, and 4.8%, respectively.⁸ Despite tirzepatide exceeding these percentages in lipid parameters across all doses, performance was comparable in LDL cholesterol reduction as tirzepatide 15 mg achieved a 5.2% reduction only. HDL cholesterol levels were increased by a range of 7 to 8% with tirzepatide while only reaching a 4.5% increment with semaglutide.⁸

Effects on Biomarkers of Nonalcoholic Steatohepatitis (NASH) and Fibrosis

Patients with T2DM are at twofold risk of developing the nonalcoholic fatty liver disease, potentially progressing with inflammation and hepatocyte injury into NASH, evolving into cirrhosis, hepatic failure, hepatocellular malignancy, and elevated risk of cardiovascular disease.^{30,31} Weight reduction more than or equal to 10% tends to push toward NASH resolution in the majority of patients.³² Hepatic biomarkers were used to reflect the effects of tirzepatide therapy on hepatic profile in T2DM in a post-hoc analysis.³³ Reported data are not from direct head-to-head comparing trials, but rather compilation from various studies.

Elevated aminotransferase (ALT) levels have been linked to higher grades of inflammation and hepatic steatosis. Tirzepatide displayed dose-dependent decreases in levels of ALT significantly greater in comparison to dulaglutide, by -6.8 and -6.4 units/L at doses of 10 and 15 mg, respectively. In the setting of NASH, hepatocyte apoptosis takes place as caspases cleave K-18, yielding elevated plasma levels of K-18. Hence, a reduction in K-18 is associated with a 1.5-fold higher chance of resolution of NASH.³⁴ Tirzepatide therapy witnessed declining levels of K-18, particularly with a dose of 10 mg by -135 units/L, significantly different in comparison to the placebo, yet not different from dulaglutide.³³

Another hepatic biomarker in NASH is Pro-C3. During fibrinogenesis, type III collagen is produced and deposited, yielding a by-product of Pro-C3, reflecting the activity of fibrosis.^{35,36} Treatment with tirzepatide at 15 mg was associated with reduced levels of Pro-C3 by -2.1 ng/mL, significantly different from placebo, yet not from dulaglutide.³³ These changes were similar to those demonstrated in one-stage improvement in fibrosis.³⁴

Overall, higher doses of tirzepatide showed significant improvement in NASH-related biomarkers in T2DM population. This variability could be attributed to changes in body weight (up to 25%) and changes in HbA1c. Although greater changes in body weight were observed in high-dose tirzepatide compared to dulaglutide, the changes in hepatic biomarkers did not change to the same extent.³³

Comparatively, semaglutide was able to achieve a modest positive impact on hepatic parameters with a reduction in levels of ALT by an average of 4 U/L. Fibroscans estimated improvement in liver steatosis and stiffness of 13.4 dB/m and 3.19 kPa, respectively, after semaglutide therapy.³⁷ This is reflected on the hepatic steatosis index and Fibrosis-4 index with a reduction of 2.36 (95% CI, 1.83–2.9) and 0.075 (95% CI, 0.015–0.14) in scoring points, respectively.³⁸

Effects on Systolic Blood Pressure

The effect of tirzepatide on changes in systolic BP was explored across the SURPASS multinational clinical trials with a keen interest in whether the changes are weight loss mediated or independent. There was a significantly notable difference in systolic BP from baseline in tirzepatide therapy, with escalated doses yielding increased reductions in systolic BP readings. Doses of 5, 10, and 15 mg of treatment witnessed up to 5, 6.5, and 11.5 mm Hg reductions by the end of 40 weeks of therapy, respectively.³⁹

The bulk of change observed in systolic BP was attributed to changes in weight loss. However, tirzepatide explained 33 to 57% of independent changes in systolic BP in comparison to insulin glargine in patients with established cardiovascular disease. Moreover, 26 to 73% of weight loss-independent reductions in systolic BP were facilitated by tirzepatide in relation to placebo in patients with the longest duration of diabetes. Hence, the majority of tirzepatide mediated systolic BP reduction was through weight loss, yet there is a variation in the extent of contribution.³⁹

In comparison, patients who have been treated with semaglutide with graduated dose increments experienced reductions in systolic and diastolic BP readings by 9.85 and 5.92 mm Hg, respectively.⁴⁰ This data has been represented from separate studies, not reported by a direct comparative study between tirzepatide and semaglutide.

Effects on Renal Outcomes

Kidney disease is a well-recognized detrimental complication of diabetes. As tirzepatide showed impressive results in glycemic control and weight loss, exploring extended potential renoprotective effects was pertinent. Tirzepatide therapy demonstrated a RR reduction of 42% in collective outcomes relevant to estimated glomerular filtration rate (eGFR) decline more than or equal to 40% from baseline, progression to end-stage renal disease, new onset macroalbuminuria, and renal death.⁴¹

Additionally, tirzepatide had positive effects on stabilizing eGFR and mitigating its decline compared to insulin glargine. Tirzepatide showed less urine albumin creatinine ratio,

which was indifferent to sodium-glucose cotransporter 2 (SGLT2) treatment at baseline. Patients treated with tirzepatide were at lower risk of developing new onset macroalbuminuria in relation to insulin glargine. Tirzepatide promises a great reno-protective role in T2DM patients with high cardiovascular risk, including those using SGLT2 inhibitor drugs.⁴¹

Inspecting data from different studies, semaglutide therapy in patients with T2DM and chronic kidney disease also showed positive renal outcomes. After semaglutide therapy with graduated dose increments, the urine albumin creatinine ratio decreased by 39% at 6 months and 51% after 12 months of therapy in those with baseline macroalbuminuria urine albumin creatinine ratio more than 300 mg/g.³¹ In addition, eGFR remained stable throughout therapy with a nonsignificant increase of 2 mL/min/1.73 m².⁴⁰ Meta-analysis of outcomes of GLP-1 agonists showed a reduction in composite kidney outcomes, including macroalbuminuria, by almost 21%, with a hazard ratio of 0.79 (95% CI, 0.73–0.87).²² SGLT2 inhibitors had shown a risk reduction of about 30% in kidney outcomes across all levels of kidney function; RR of 0.7 (95% CI, 0.54–0.91).⁴² There has not yet been no head-to-head comparison study regarding renal outcomes.

Drug Safety and Tolerability

In light of shared mechanism of action, the dual GIP/GLP-1 agonist tirzepatide shares a side effect profile similar to GLP-1 agonists. Most commonly reported side effects were gastrointestinal complaints, namely nausea, vomiting, and diarrhea. These effects were as prevalent as 23, 32.7, 51%, and reaching 66% in respect to increased doses of 1, 5, 10, and 15 mg. Such side effects were observed in 42.6% of patients treated with dulaglutide, in contrast to 9.8% in placebo group. In addition, around 3.8 to 18.9% of patients report loss of appetite when treated with tirzepatide.^{4,5,43}

These adverse effects of tirzepatide were accountable for drug discontinuation in 5.1% of 5 mg group, 9.1% in the 10 mg group, and 25% in the 15 mg group, displaying a similar dose-dependent fashion. On the other hand, dulaglutide therapy witnessed 11.1% suspension rate. It is suggested that commencing the drug with small starting dose followed by gradual increments is associated with less incidence of adverse events.⁴⁴

In regard to other adverse events, records of hypoglycemia were low across the treatment groups, mostly less than 10% in all doses except for 17.9% in maximum dose group of 15 mg, none of which were severe.^{5,44} Other rarely encountered adverse events reported pancreatitis, cholecystitis, injection site reactions, and hypersensitivity reactions.

Comparing the safety profile of tirzepatide to that of semaglutide, gastrointestinal events remained as the most commonly occurring adverse events. Gastrointestinal adverse events still constituted 57.5% of those with semaglutide 1 mg in STEP2 trials, and 63% of those with dose of 2.4 mg, respectively.¹⁵ Consequently, 6.2% of patients required to prematurely discontinue the therapy with semaglutide 2.4 mg, slightly less than with tirzepatide 15 mg at

6.6%.^{13,15} Clinically significant hypoglycemia was seen in only 0.4% of semaglutide treated patients, in contrast to up to 2% with tirzepatide therapy.⁸ Aforementioned data have been extracted from distinct studies, as no direct comparative trials have been established yet.

Conclusion

The pillar of diabetes care has shifted from a sole “glucocentric” objective to a more exhaustive approach addressing cardiovascular morbidity and mortality. Acknowledging that many diabetic patients are also obese, glucose-lowering medications are developed with the intent of harboring weight loss properties. The coming decade awaits an ideal diabetic medication not only to be efficacious and to carry a low risk of hypoglycemia but also to promote weight loss and exhibit proven cardiovascular benefits.⁵

Despite all the current advancements with recent promising diabetic agents, obese patients with diabetes are still short of meeting optimal glycemic targets. The novel dual GIP/GLP-1 twincretin tirzepatide has shown promising potential with relevant clinical and biochemical outcomes, namely glycemic control, weight loss, favorable lipid profile, and improved inflammatory markers. Coming years may witness dual GIP/GLP-1 agonists as the pillars of therapy in diabetes and weight loss. Ongoing trials such as SURPASS-CVOT and SURMOUNT trials shall establish cardiovascular benefits of tirzepatide as well as explore its efficacy in treating adults with obesity without diabetes, respectively.

Compliance with Ethical Principles

This review falls in compliance with research ethical standards and principles. There has been no human subjects or participants involved.

Authors' Contributions

A.B. conceived the concept of the study and coordinated its design. R.W., T.E., and H.A. performed the literature search, selection of studies and review of the data, drafting the manuscript and editing it. F.R., N.A., and A.B. critically reviewed the manuscript and edited it. R.W. and A.B. supervised the article. All authors read and approved the final manuscript.

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Conflict of Interest

None declared.

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