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REVIEW

Tirzepatide: Does the Evidence to Date Show Potential for the Treatment of Early Stage Type 2 Diabetes?

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Abstract: Tirzepatide is a novel "twincretin" with glucagon-like peptide 1 and glucose-dependent insulinotropic polypeptide receptor agonist activity, which was recently approved by the Food and Drug Administration for the treatment of type 2 diabetes mellitus. In this review, we discuss preclinical and mechanistic human studies, which demonstrate improvements in insulin sensitivity and beta-cell function with the use of tirzepatide, as compared to placebo and glucagon-like peptide 1 receptor agonists. We then discuss SURPASS trials 1–5, which evaluated the safety and efficacy of tirzepatide for type 2 diabetes mellitus as either monotherapy or combination therapy with other antidiabetic agents. The magnitude of tirzepatide's effects and the efficacy relative to other anti-diabetes medications on weight, glycemic control, and beta-cell function may prove beneficial for the treatment of early type 2 diabetes mellitus. Further studies, including data on cardiovascular outcomes and long-term safety, will continue to elucidate the role of tirzepatide in the treatment algorithm of type 2 diabetes mellitus.

Keywords: tirzepatide, type 2 diabetes mellitus, obesity, SURPASS trials, glucagon-like peptide 1 receptor agonists, glucose-dependent insulinotropic polypeptide receptor agonist, "twincretin"

Background

There is a rising global impact of type 2 diabetes mellitus (T2DM), with an estimated 6.28% prevalence, as of 2017, and an expected continued upward trend in cases.[1] Based on National Health Interview Survey data, there are 21 million adults in the United States with T2DM.[2] Obesity, specifically visceral adiposity, is known to be a major risk factor for the development of insulin resistance and T2DM, and an estimated 90% of people in the United States with T2DM have overweight or obesity.[3] T2DM is also strongly associated with cardiovascular disease. The onset of T2DM is influenced by both genetic and environmental factors, and results from the combination of insufficient insulin secretion by pancreatic islet beta (ß)-cells and peripheral insulin resistance in the skeletal muscle, adipose tissue, and liver.[4] Insulin is essential for glucose uptake and utilization, as well as for promoting lipogenesis and preventing gluconeogenesis, glycogenolysis, lipolysis, and protein breakdown. The pathogenesis of T2DM is thought to begin with insulin resistance, increasing the demand on pancreatic ß-cells.[5] At the initial stage, patients can achieve normoglycemia through increased insulin secretion. Over time, the ß-cells are unable to compensate, leading to hyperglycemia and overt T2DM. ß-cell dysfunction is thought to derive from metabolic and oxidative stress, occurring from excess free fatty acids and hyperglycemia.[4] When T2DM is diagnosed, around 40–50% of ß-cell function is already lost, from reductions in both ß-cell mass and ß-cell functionality. As such, there is clinical interest in addressing insulin resistance and ß-cell dysfunction earlier in the disease course, as this may result in improved diabetes remission.[6]

Given that obesity is the key pathophysiologic driver of T2DM, pharmacotherapies that target weight-loss and hyperglycemia may be useful for the management of prediabetes or early T2DM. Incretins, which stimulate insulin

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secretion in a glucose-dependent manner by increasing cyclic AMP (cAMP) activity in ß-cells, have become important clinical targets for T2DM. Both glucose-dependent insulinotropic polypeptide (GIP) and glucagon-like peptide 1 (GLP-1) have low concentrations in fasting humans, with a rise after nutrient intake.[7,8]

GLP-1 receptor agonists (GLP-1Ra) are approved to treat T2DM and obesity. These medications act through the GLP-1R, a G protein-coupled receptor (GPCR) expressed in pancreatic ß-cells, the gastrointestinal tract, and neurons throughout the nervous system. The anti-hyperglycemic effects of GLP-1R agonists are mediated by glucose-stimulated insulin secretion and decreased plasma glucagon, as well as delayed gastric transit time. These medications also activate anorexigenic pathways, resulting in decreased body weight.[9] There is growing evidence that GLP-1Ras delay progression of T2DM. The Restoring Insulin Secretion Adult Medication Study compared ß-cell function in patients with impaired glucose tolerance or T2DM <12 months duration on 12 months of metformin, 3 months of insulin glargine followed by 9 months of metformin, 12 months of liraglutide combined with metformin, or 12 months of placebo. The three treatment arms resulted in improvement in glucose-stimulated insulin secretion, which was most apparent in the liraglutide-metformin group, though the effect dissipated within 3 months of treatment cessation.[10] In a 3-year study on subjects with prediabetes with a BMI ≥30 kg/m^2 or ≥27 kg/m^2 with hypertension and/or dyslipidemia, liraglutide resulted in more weight-loss and delayed progression to T2DM, as compared to placebo.[11] Of the available GLP-1Ras, subcutaneous weekly semaglutide 1mg weekly is the most effective for the management of T2DM, in terms of weight reduction and improvements in glycemic control.[12] At this time, semaglutide has not been evaluated in delaying progression to T2DM.

In terms of GIP as a pharmacologic target, GIP is secreted by K cells in response to food. GIP activity in the pancreas is also mediated through a GPCR and cAMP accumulation. GIP receptor (GIPR) knockout mice have impaired oral glucose tolerance, secondary to reduced insulin secretion. GIPRs are also found in adipocytes and associated with fatty acid intake, glucose uptake, and fatty acid synthesis. Post-prandial GIP levels are 4-fold higher than GLP-1 under normal conditions. Of note, GIP is glucagonotropic and insulinotropic, depending on the glucose homeostasis.[13,14] There has not been evidence of differences in the nutrient-induced secretion of GIP in T2DM, compared to healthy subjects. However, there is likely GIP resistance in T2DM, given that elevated GIP concentrations do not lead to significant insulin secretion.[7] Normalization of blood glucose appears to restore the incretin effect of GIP.[15] GIP is thought to be responsible for a greater incretin effect after oral glucose, though GLP-1 likely has an additive effect.[7,8]

Tirzepatide

Tirzepatide, LY3298176, is a fatty-acid modified peptide of dual GIP and GLP-1 receptor agonist activity. The chemical structure is a 39 amino acid linear peptide, which allows for albumin binding to administer once weekly and resists dipeptidyl-peptidase 4 (DPP4) break-down.[7,13] Tirzepatide has unbalanced dual agonism in favor of the GIPR, over the GLP-1R. The molecule binds the GLP-1R with a 5-fold weaker affinity and a 20-fold lower potency in cAMP accumulation, than native GLP-1. However, there is a signaling bias towards the cAMP pathway over ß-arrestin recruitment. At the GIPR, tirzepatide demonstrates full agonism and equipotency to native GIP at ß-arrestin recruitment. Given that GPCR internalization is mediated by the arrestin pathway, tirzepatide results in less internalization of the GLP-1R, compared to native GLP-1 (about 40% of what would be expected). Alternatively, the internalization of GIP-1R with tirzepatide is equivalent to that of GIP. This may explain why tirzepatide requires lower GLP-1R activation than semaglutide (long-acting GLP-1Ra) with greater glucose and weight control.[16]

Preclinical and Mechanistic Studies

Data indicates tirzepatide has a greater effect on insulin secretion and glucose modulation, than GLP-1Ras. Using a cell-line with both GIP and GLP-1 receptors (human pancreatic ß-cells), cAMP accumulation with tirzepatide was higher than that for GLP-1 or GIP alone. Comparatively, in human adipocytes with only GIP receptors, cAMP accumulation was similar to that of native GIP. In terms of glucose response, tirzepatide improved glucose excursions similarly to semaglutide and a DPP-4 resistant GIP analog in mice lacking the GIPR or GLP-1R, respectively. In wild-type mice, GLP-1R blockade minimized the glucose-lowering effect of semaglutide but had a minimal effect on tirzepatide, indicating that tirzepatide can improve glucose-dependent insulin secretion through the GIPR or the GLP-1R. In terms of body weight, administration of a long-acting GIPRa did not have an impact on body weight or body composition in the

mice model. Chronic treatment with tirzepatide resulted in a dose-dependent decrease in body weight, more pronounced than that of semaglutide alone, which was driven mainly by loss in fat mass. There also appeared to be a reduction in mice food intake during the first 7–10 days of treatment, causing more fat oxidation. There was a small but significantly greater energy expenditure noted 7 days after treatment in mice given tirzepatide, but not in mice treated with semaglutide.[13]

There is also evidence that the dual agonism of tirzepatide improves ß-cell function and insulin resistance, more than GLP-1Ras alone. In preclinical studies, GLP-1 has been shown to improve ß-cell proliferation and reduce ß-cell apoptosis, through signal transduction pathways. There is an indirect improvement in ß-cell survival, through reduced glucotoxicity. GIP has also been shown to improve ß-cell function and survival.[17] The GIP component of tirzepatide works in white and brown adipose tissue (WAT and BAT, respectively), and is thought to improve the clearance of dietary triglycerides (TG) and the long-term storage of lipids. Using high-fat diet-fed obese insulin-resistant mice, 14 days of tirzepatide reduced circulating TG levels and free fatty acids, and lowered hepatic fat content. Tirzepatide also improved systemic insulin sensitivity, with enhanced insulin-stimulated glucose deposition in skeletal muscle and adipose tissue. With GLP-1Ra, the insulin sensitizing effect has been shown to result mainly from weight-loss. Comparatively, the weight-loss effect of tirzepatide represented only 70% of the improvement in insulin sensitivity. Using GLP-1R knockout mice, tirzepatide resulted in improvements in insulin sensitivity, even without weight-loss, demonstrating that the weight-independent effects on insulin sensitivity are mediated via GIPR agonism. Looking at metabolic analysis, tirzepatide and long-acting GIPRa-induced genes are involved in the breakdown of glucose, lipids, and branch-changed amino acids in BAT, which may explain the improvements in peripheral insulin sensitivity. Notably, this effect was not observed in the rodent skeletal muscle or WAT.[18]

In terms of human subject research, a post-hoc analysis of 316 subjects with T2DM on tirzepatide showed improvements in ß-cell function and insulin resistance at 26 weeks, compared to placebo and dulaglutide 1.5 mg weekly. The authors calculated homeostatic model assessment indices for both ß-cell function and insulin resistance (HOMA2-B and HOMA2-IR, respectively). All three doses of tirzepatide (5, 10, and 15 mg), as well as dulaglutide, resulted in improved HOMA2-B as compared to placebo. HOMA2-IR was decreased with tirzepatide 10mg, compared to both placebo and dulaglutide. Weight-loss with tirzepatide 10 and 15 mg only accounted for 13% and 21%, respectively, of the decreases found in HOMA2-IR. Higher levels of adiponectin and IGF binding proteins (IGFBP-1 and IGFBP-2) are known indicators of improved insulin sensitivity. Adiponectin levels increased significantly at 26 weeks from between 12% and 26% with tirzepatide 5, 10, and 15 mg, though by 11% with dulaglutide. IGFBP-1 levels at 26 weeks were higher for tirzepatide 5 and 15 mg, as compared to dulaglutide. IGFBP-2 levels were also noted to be significantly higher for tirzepatide 10 and 15 mg doses, as compared with dulaglutide.[19] Semaglutide 0.5 and 1 mg dosing have also been found to result in improvements in insulin sensitivity (by HOMA-IR) at 52 weeks of treatment in patients with T2DM, though the majority of these improvements were attributed to weight-loss.[20]

As expected with improvements in insulin sensitivity, fasting insulin levels decreased at 26 weeks with tirzepatide 10 and 15 mg treatment, compared to both placebo and dulaglutide 1.5mg. Tirzepatide 5, 10, and 15 mg also resulted in reduced glucose-adjusted glucagon levels (percent change), as compared to tirzepatide 1mg, dulaglutide, and placebo.[19] Although the mechanism of dysregulated glucagon secretion in T2DM is not fully elucidated, elevated fasting glucagon levels contribute to hyperglycemia in diabetes progression.[21] Of note, a study of subcutaneous semaglutide 0.5 and 1mg weekly in subjects with T2DM did not show a difference in fasting insulin or glucagon levels, compared to placebo.[22]

To further evaluate improvements in ß-cell function with tirzepatide, proinsulin levels, as well as intact proinsulin/insulin and intact proinsulin/C-peptide ratios, were evaluated.[19] In the early stages of T2DM, ß-cells produce increased proinsulin, the insulin precursor, to keep up with the increased demand for insulin production. Proinsulin is prone to misfolding, and impaired proinsulin to insulin conversion contributes to ß-cell dysfunction.[23] Increased fasting proinsulin and proinsulin/insulin ratios have also been shown to predict the progression of T2DM.[24] As compared to baseline at 26 weeks, intact proinsulin significantly decreased from between 28% and 48% with tirzepatide 5, 10, and 15mg, though did not change significantly for tirzepatide 1 mg or dulaglutide and increased with placebo. Intact proinsulin/insulin ratios decreased by 26% for tirzepatide 5 mg and 37% for tirzepatide 10 mg at 26 weeks. The absolute change from baseline was also significantly different for tirzepatide 10mg and 15mg, compared to dulaglutide. There were also significant

decreases in intact proinsulin/C-peptide ratios for the various tirzepatide doses at 26 weeks.[19] These changes suggest that tirzepatide results in decreased ß-cell stress, as compared to placebo and dulaglutide. There are no direct comparisons between semaglutide and tirzepatide on ß-cell function. However, fasting proinsulin levels and proinsulin/insulin ratios were also significantly reduced with semaglutide 0.5 and 1 mg, as compared to placebo, in a study of patients with T2DM.[22]

It has also been established that delayed gastric emptying is partially responsible for the effect of long-acting GLP-1Ra on glycemic control. In this vein, the impact of tirzepatide on gastric emptying has also been evaluated in preclinical and clinical models. In male mice with diet-induced obesity, semaglutide and tirzepatide inhibited gastric emptying, though long-acting GIPRa had no effect. Increasing concentrations of GIPRa with GLP-1Ra did not result in a further delay in gastric emptying. Tirzepatide and long-acting GLP-1Ra also did not differ in the effect on gastric emptying, indicating that GLP-1R agonism is primarily responsible for the delayed gastric emptying seen with tirzepatide. After 2 weeks of treatment, the effect of delayed gastric emptying dissipated.

In human studies, the effect of tirzepatide on gastric emptying was similar to that of dulaglutide in healthy participants. In participants with T2DM, a gastric emptying delay was seen after the initial dose of tirzepatide 5 mg, with tachyphylaxis after four doses. With the dose-escalation protocol (5/5/10/10 or 5/5/10/15 mg), the gastric emptying delay also diminished over time, but remained apparent following the last dose.[17] The overall evidence suggests that tirzepatide has a similar effect on gastric emptying as long-acting GLP-1Ras.

Tirzepatide: Clinical Efficacy and Safety

Phase III (SURPASS) Trials

The SURPASS clinical trials assessed the safety and efficacy of tirzepatide as either monotherapy or combination therapy with other antidiabetic agents (metformin, sulfonylureas (SU), sodium-glucose cotransporter 2 inhibitors (SGLT2i), and insulin).[25–29] These trials include six global, one Asia Pacific and two Japanese studies. The primary endpoint for the trials was the change in glycated hemoglobin (HbA1c) from baseline. The secondary endpoints included change in body weight, change in fasting serum glucose, percentage of participants achieving HbA1c targets of <7%, <6.5% and <5.7%, percentage of participants achieving weight loss of >5%, >10% and >15%, and rate of hypoglycemia.

In this section, we review five of the six international trials with respect to improvement in HbA1c, improvement in fasting and postprandial serum glucose, safety, and tolerability profile, and its effectiveness as a weight loss agent in people with diabetes. The phase three trials were designed similar to the phase two trials for dose escalation, with a starting dose of 2.5mg weekly for initial 4 weeks, then dose increments of 2.5mg every 4 weeks until reaching a maintenance dose of 5, 10 or 15mg. The baseline characteristics, primary and some secondary endpoints are summarized in Table 1.

Glycemic Control in T2DM

Effect on HbA1c

SURPASS 1 was a 40-week double-blind, randomized placebo-controlled trial that included 478 participants with T2DM who had inadequate glycemic control on lifestyle changes alone. Participants were naïve to injectable diabetes therapy and were not on any oral antihyperglycemic agent for 3 months prior to the study. The proportion of participants who achieved HbA1c targets of <7% and <6.5% was higher in all tirzepatide groups, 87–92% and 81–86%, respectively. The placebo-adjusted- HbA1c reductions ranged from 1.91% to 2.11% on 40 weeks with the treatment drug. An interesting observation was that the mean duration of diabetes was shorter in SURPASS 1 as compared to the other published SURPASS trials (4.7 years vs >8 years) with 79% participants having an HbA1c <8.5%. As such, this population had "early stage T2DM" with relatively preserved ß-cell function. HbA1c reduction plateaued at 20 weeks but weight-loss continued until the end of the trial.[25]

SURPASS 2 was an open-label 40-week trial including 1879 participants who were randomized to receive tirzepatide at doses 5mg, 10mg, 15 mg vs semaglutide 1 mg. Tirzepatide was superior to semaglutide for glycemic control in T2DM participants on monotherapy with metformin showing HbA1c reductions from 2.01 to 2.3% with

Table 1 Overview of SURPASS Trials (25–29)

SURPASS	Inclusion Criteria	N	Duration (Weeks)	Mean Duration of T2DM (Years)	Mean Baseline HbA1c (%)	Treatment Groups (N)	Change in Mean HbA1c	Change in Mean Body Weight (%)	Overall Treatment Discontinuation n (%)
1	Naive to injectable ADAs	478	40	4.7	7.9	TZP 5mg (121) TZP 10mg (121) TZP 15 mg (121) Placebo (115)	−1.87 −1.89 −2.07 +0.04	−7.9 −9.3 −11 −0.9	7 (5.7) 9 (7.4) 18 (14.8) 16 (13.9)
2	T2DM inadequately controlled on metf	1879	40	8.6	8.2	TZP 5mg (471) TZP 10mg (469) TZP 15mg (470) Semaglutide 1 mg (469)	−2.09 −2.37 −2.46 −1.86	−8.5 −11 −13.1 −6.7	19 (4) 27 (5.7) 24 (5.1) 26 (5.5)
3	Insulin naive, metf or metf and SGLT2i	1444	52	8.4	8.1	TZP 5mg (359) TZP 10mg (361) TZP 15mg (359) Insulin Degludec (365)	−1.93 −2.20 −2.37 −1.34	−8.1 −11.4 −13.9 +2.7	26 (7.2) 40 (11) 19 (5.2) 34 (9.3)
4	Increased risk of CVD	2002	52	10.5	8.5	TZP 5mg (329) TZP 10mg (330) TZP 15mg (338) Insulin Glargine (1005)	−2.24 −2.43 −2.58 −1.44	−8.1 −10.7 −13.0 +2.2	21 (6.3) 11 (3.3) 9 (2.6) 52 (5.1)
5	Insulin dependent T2DM	475	40	13.3	8.3	TZP 5mg (116) TZP 10mg (119) TZP 15mg (120) Placebo (120)	−2.23 −2.59 −2.59 − 0.93	−6.6 −8.9 −11.6 +1.7	7 (6) 4 (3.3) 10 (8.3) 3 (2.5)

Abbreviations: ADA, antidiabetic agents; T2DM, Type 2 diabetes mellitus; Metf, metformin; SGLTi, sodium-glucose co-transporter 2 inhibitors; TZP, Tirzepatide; CVD, cardiovascular disease.

incremental doses of 5 mg to 15mg as compared to HbA1c reduction of 1.86% with semaglutide 1mg. In further subgroup analysis, for participants with HbA1c greater than 8.5%, the lowering of HbA1c was –3.22 percentage points with tirzepatide 15mg vs –2.68 percentage points with semaglutide 1 mg.[26]

The SURPASS 3 was an open label, parallel group, multicenter, multinational, 52-week trial, to assess noninferiority of tirzepatide at doses of 10mg and 15mg versus insulin degludec. Participants were insulin-naïve and were treated with metformin or combination of metformin and SGLT2i (65% vs 32% respectively) for 3 months prior to screening. This was the first study that looked at efficacy of tirzepatide in participants with inadequate glycemic control on multiple oral antihyperglycemic medications and who required intensification of regimen with an injectable treatment. Mean baseline HbA1c decreased by 1.93–2.27% with tirzepatide 5–15 mg, compared with a decrease of 1.34% in the insulin degludec group. Non-inferiority as well as superiority of tirzepatide for doses 10mg and 15mg versus insulin degludec was achieved for primary efficacy endpoint. Notably, no differences were seen in HbA1c reduction at week 52 in the subgroup of participants on metformin plus SGLT2i versus those on metformin alone.[27]

SURPASS 4 was a 52-week, open label, parallel group, multinational Phase 3 trial that assessed the efficacy and safety of tirzepatide vs insulin glargine in 2002 participants. Participants had T2DM with significant cardiovascular risk factors and were inadequately controlled on oral antihyperglycemic agents. Cardiovascular safety was a particular focus of this trial. Further, it included participants on SUs which was excluded as a concomitant medication in SURPASS 1–3. The duration of this study was the longest as compared to the other studies; after an initial treatment period of 52 weeks of treatment there was a variable period up to 52 weeks to observe cardiovascular outcomes. Cardiovascular risk comparators were defined with 4-point MACE (cardiovascular death, myocardial infarction, stroke and hospitalization for unstable angina), transient ischemic attack, coronary revascularizations and hospitalization for heart failure. Of note, the trial was not powered to evaluate differences in incidence of 4-point MACE in tirzepatide vs insulin glargine.

At 52 weeks, mean HbA1c changes with tirzepatide were –2·24% for 5 mg, –2·43% for 10 mg, and –2·58% for 15 mg, versus –1·44% with glargine. Non inferiority as well as superiority of tirzepatide 10 mg and 15 mg versus

glargine for HbA1c change from baseline to week 52 was achieved ($p < 0{\cdot}0001$ for both doses). Tirzepatide 5 mg was also superior to glargine, with an estimated treatment difference of –0·80%. The reductions in HbA1c observed for tirzepatide at 52 weeks were maintained after 78 weeks and 88 weeks of treatment with no increase in cardiovascular risk.[28]

SURPASS 5 was a 40-week, phase 3, randomized, double blind, parallel, multicenter, placebo- controlled study that evaluated the safety and efficacy of tirzepatide at doses 10 and 15mg added to insulin glargine in 475 participants with insulin-dependent T2DM with or without background metformin use. The treatment period consisted of an initial 4-week insulin glargine stabilization period followed by a 36-week insulin titration period. To minimize the risk of hypoglycemia, participants were kept on a fixed dose of insulin glargine in the initial 4-week period and participants with an initial HbA1c <8.0% at randomization were required to reduce dose of glargine by 20%. At week 40, the mean HbA1c change from baseline was similar as demonstrated in the other tirzepatide trials (SUPRASS 1–4), 2.40% with 10-mg tirzepatide and 2.34% with 15-mg tirzepatide vs 0.86% with volume matched placebo.[29]

Although there was significant heterogeneity, a recent meta-analysis of the 7 available randomized controlled trials on tirzepatide for T2DM, including SURPASS 1–5, demonstrated that all 3 doses of tirzepatide (5mg, 10mg, and 15mg) demonstrated superior HbA1c lowering as compared to placebo, basal insulin, and GLP-1Ras. Specifically, as compared to dulaglutide 1.5 mg and semaglutide 1 mg, tirzepatide 5, 10, and 15 mg resulted in a HbA1c reduction of 0.29%, 0.65%, and 0.92%, respectively.[30]

Effect on Fasting and Postprandial Serum Glucose

SURPASS 1 showed improvement in fasting glucose as early as 4 weeks in the treatment group. Estimated mean treatment differences vs placebo were –56.5 to –62.1 mg/dL with tirzepatide at 40 weeks. Similarly, postprandial glucose profiles improved as early as 12 weeks, values ranged from –61 to –65 mg/dL with tirzepatide vs –11mg/dL with placebo.[25] The improvement in postprandial glucose elucidates the glucose-dependent insulin secretion seen with tirzepatide and is unlikely related to slowed gastric emptying given the improvement in postprandial glucose persisted at 40 weeks, by which time the transient effect of delayed gastric emptying has waned.[17]

Similarly, in SURPASS 2, greater reductions in fasting and 2-hour postprandial blood glucose were observed with all doses of tirzepatide when compared to semaglutide 1mg.[26]

In SURPASS 3, although fasting serum glucose (FSG) improvement was similar in tirzepatide vs insulin degludec, notably, the effect of tirzepatide on FSG was apparent in all the treatment groups as early as week 2, suggesting that even the starting dose of 2·5 mg of tirzepatide is efficacious for hyperglycemia. All three treatment doses of tirzepatide were superior to insulin degludec in reducing 2-h post-meal serum glucose at week 52 with all mean postprandial values remaining below the normal glucose level of 7·8 mmol/L (140 mg/dL).[27]

When comparing tirzepatide to insulin glargine, the improvement in fasting glucose was similar in SURPASS 4. The lower mean seven point SMBG levels with tirzepatide vs insulin glargine may be attributed to better postprandial control of glucose similar to the other three tirzepatide trials.[28]

In SURPASS 5, tirzepatide added to insulin glargine, significantly reduced mean FSG by −58.2 mg/dL for the 5-mg dose, −240 mg/dL for the 10-mg dose, and −62.6 mg/dL for the 15-mg dose, compared with −39.2 mg/dL for placebo at week 40.[29]

Effect on Body Weight

All doses of tirzepatide were superior to placebo for body weight loss. Estimated mean treatment differences versus placebo were –6.3 kg (95% CI –7.8 to –4.7) to −8.8 kg (–10.3 to –7.2) with tirzepatide (all $p < 0.0001$). The action of tirzepatide on body weight was dose dependent and started as early as week 4 and did not plateau at week 40. A greater proportion of participants had body weight reductions of 5% or greater (67–78%), 10% or greater (31–47%) and 15% or greater (13–27%) with tirzepatide vs 14%, 1% and 0% with placebo.[25]

Tirzepatide was superior to semaglutide at all doses, with estimated treatment differences of −1.9kg (95% CI, −2.8 to –1.0) with tirzepatide 5mg, −3.6kg (95% CI, −4.5 to –2.7) at tirzepatide 10mg and –5.5kg (95% CI, −6.4 to –4.6) at tirzepatide 15mg ($p < 0.001$ for all comparisons). The percentage of participants achieving >5% body weight loss was higher for all doses of tirzepatide when compared to semaglutide (65–80% vs 54% respectively).[26]

When comparing tirzepatide to daily insulin degludec in SURPASS 3, the tirzepatide group lost an average of 7.5–12.9 kg compared to an average of 2.3 kg weight gain in the insulin degludec group. A higher proportion of participants in the tirzepatide groups than in the insulin degludec group achieved the composite endpoints of the HbA1c targets of <7·0% (80–92% vs 15%) or <6·5% (69–86% vs 12%) without weight gain and without clinically significant documented symptomatic hypoglycemia or severe hypoglycemia at week 52 ($p < 0·0001$ for all tirzepatide doses vs insulin degludec). Body weight reduction started at week 4 and continued at week 52 without reaching a plateau in this study. The longer duration of the study perhaps also resulted in the highest decrease in body weight (12.9kg) observed amongst all tirzepatide trials.[27]

All tirzepatide doses demonstrated superiority to glargine with estimated treatment differences of –9·0 kg (95% CI –9·8 to –8·3) at 5 mg, –11·4 kg (–12·1 to –10·6) with 10 mg, and –13·5 kg (–14·3 to –12·8) with 15 mg (all $p < 0·0001$). Even with a more complex diabetic group in this study, bodyweight reductions of 5% or more were achieved in 63–85% of tirzepatide-treated participants versus 8% with glargine.[28]

When tirzepatide was used in combination with insulin glargine, the mean body weight change from baseline was lower when compared with studies without background insulin glargine use, with –5.4kg with 5 mg tirzepatide, −7.5kg with 10mg tirzepatide and –8.8kg with 15mg tirzepatide vs 1.6kg with placebo. At week 40, the mean percent change from baseline in insulin dose was 13.0% for 5-mg tirzepatide, 8.1% for 10-mg tirzepatide,-11.4% for 15-mg tirzepatide, and 75.0% for placebo. The proportion of people who achieved >5% body weight loss ranged from 47.9 to 71.6% with tirzepatide 5–15mg, respectively. This was significant given weight gain associated with insulin use. Participants on 15mg tirzepatide also required less basal insulin.[29]

As expected, these findings were confirmed in the meta-analysis, showing a dose-dependent reduction in body weight with tirzepatide, as compared to placebo, basal insulin, and GLP-1Ras.[30]

Safety and Tolerability of Tirzepatide

The most frequent side effects with tirzepatide vs placebo were related to the gastrointestinal system including nausea (12–18% vs 6%), diarrhea (12–14% vs 8%) and vomiting (2–6% vs 2%).[25] Of note, when comparing tirzepatide to semaglutide, gastrointestinal specific side effects were similar: nausea 17.4 vs 22.1%, diarrhea 11.5 vs 16.4%, and decreased appetite 5.3 to 8.9%.[26] Notably, throughout all studies, the gastrointestinal side effects were mild to moderate in severity and occurred only during the dose-escalation period.[25–29]

Hypoglycemia <70mg/dL was seen in 6–7% participants on tirzepatide vs 1% on placebo.[25] In the SURPASS 2 trial, clinically significant hypoglycemic events were higher at the highest dose of tirzepatide (1.7% at 15mg) as compared to semaglutide 1mg (0.4%).[26] The incidence of severe hypoglycemia and blood glucose less than 54 mg/dL was 1–2% in the tirzepatide groups versus 7% in the insulin degludec group.[27] Notably, the total number of hypoglycemic events was lower with tirzepatide compared with glargine, with nearly all events on tirzepatide occurring in participants using SUs at baseline.[28] In the meta-analysis, hypoglycemia <70mg/dL was not different between tirzepatide and placebo, and was increased with basal insulin, as compared to all 3 doses of tirzepatide.[30]

Near normalization of glucose concentration without the added risk of increasing hypoglycemia as seen with tirzepatide will be valuable in reducing risk of long-term complications in patients with diabetes.

There were no cases of pancreatitis in the placebo or tirzepatide arms of SURPASS 1.[25] When comparing risk of pancreatitis with tirzepatide versus semaglutide, there were 2 cases each with tirzepatide 10mg and 15mg as compared to 3 cases in the semaglutide group. Moreover, these cases were mild in nature. There were 4 cases in each tirzepatide dose group with cholelithiasis as compared to 2 cases in the semaglutide group.[26] There were no reported cases of medullary thyroid cancer in any of the tirzepatide trials.[25–29]

Other Significant Tirzepatide Trials in Development Affecting Early T2DM

SURPASS 6 is a randomized, phase 3, open label trial comparing the addition of tirzepatide versus multiple daily injection insulin regimen in participants with inadequately controlled T2DM on insulin glargine. The SURMOUNT 1 trial is a multicenter, double blind, parallel, placebo-controlled trial comparing the efficacy and safety of tirzepatide to placebo in adults without T2DM who are obese or overweight with comorbidities (hypertension, dyslipidemia,

obstructive sleep apnea or cardiovascular disease). The trial randomized 2539 participants with the primary endpoint of percentage of participants achieving >5% body weight reduction at 72 weeks compared to placebo. Participants taking tirzepatide achieved average weight reductions of 15% (95% CI −15.9 to −14.2) on tirzepatide 5mg, 19.5% (95% CI −20.4 to −18.5) on 10mg tirzepatide and 20.9% (95% CI −21.8 to −19.9) 15mg tirzepatide compared to placebo of 3.1%. Notably, 85.1%–90.9% of people taking tirzepatide achieved at least 5% body weight reductions compared to 34.5% of those taking placebo. An important evaluation of SURMOUNT 1 with regard to early diabetes is that the participants who had prediabetes at baseline will remain enrolled for an additional 104 weeks of treatment following the initial 72-week completion date. This will evaluate the progression to T2DM at three years of treatment with tirzepatide compared to placebo.[31]

Conclusion/Commentary

T2DM is a chronic and complex disease with microvascular and macrovascular complications. Over the past two decades, the management of T2DM has shifted from a glucocentric to a multisystem approach. Novel treatments for T2DM management focus on efficacy in glycemic control, prevention of hypoglycemia, weight loss properties, and reduction in the incidence of micro- and macrovascular complications. The newer treatments with GLP-1Ras and SGLT2i have favorable results for glycemic control, but some participants with concomitant obesity and T2DM still are in need of better therapy. Overall, data suggest that tirzepatide is a safe and effective glucose-lowering and weight-reducing agent. The near-normalization of HbA1c with low risk of hypoglycemia indicates an optimized incretin effect with dual agonism of GLP-1 and GIP. Preclinical and clinical data indicate tirzepatide improves insulin sensitivity through weight-loss, as well as weight-independent mechanisms. There is also evidence that tirzepatide improves ß-cell function and peripheral insulin resistance, more than GLP-1Ras alone, though preclinical comparisons between the most effective GLP-1Ra (semaglutide) and tirzepatide have not been performed. The SURPASS 2 trial further demonstrated superiority of tirzepatide to semaglutide in terms of both body weight and HbA1c reduction.

The SUPRASS trials have established tolerability and short-intermediate-term safety of tirzepatide. Further, SURPASS 4, which included subjects with baseline increased cardiovascular risk, demonstrated no increase in MACE-4 events (cardiovascular death, myocardial infarction, stroke, and hospitalized unstable angina) for tirzepatide versus glargine, hazard ratio 0·74 (95% CI 0·51 to 1·08).[28] A pooled meta-analysis of 7215 randomized participants (4887 on tirzepatide for at least 26 weeks) with T2DM demonstrated that 142 participants on tirzepatide had one or more MACE-4 event. Of note, 109 of the events were in subjects of SURPASS 4. There was no increase in MACE-4 events in the subjects on tirzepatide versus those on the comparators (placebo, insulin degludec, insulin glargine, semaglutide and dulaglutide), hazard ratio 0.80 (95% CI 0.57 to 1.11). There was also no increase in cardiovascular death or all-cause mortality.[32] Another brief meta-analysis evaluated the mean difference in systolic and diastolic blood pressure (SBP and DBP) with dual GIPR and GLP-1R agonists compared to placebo or active comparators (insulin degludec, insulin glargine, liraglutide, or dulaglutide) in 5060 subjects with T2DM, finding a significant decrease in SBP by 3.6 mm Hg (95% CI −5.54 to −1.65) and DBP by 1.29 mm Hg (95% CI −2.30 to −0.28) with the dual agonism.[33] The SURPASS CVOT trial (tirzepatide vs dulaglutide) will continue to elucidate the definitive impact of tirzepatide on cardiovascular outcomes in participants with advanced/complicated T2DM and illuminate the long-term safety of tirzepatide. In addition, the extended SURMOUNT 1 trial will provide important insights on the long-term use of tirzepatide in individuals with prediabetes.

In summary, as seen in the preclinical, early clinical, and SURPASS trials, the novel GLP-1 and GIP "twincretin" tirzepatide has been shown to be efficacious and safe in treatment of patients with early as well as advanced T2DM. The exact position of tirzepatide in the treatment algorithm of T2DM will be determined by cardiovascular outcomes and long-term safety data as well as other factors such as cost.

Disclosure

Dr Razzaki is a medical advisor for Measured. Drs. Weiner and Shukla report no conflicts of interest in this work.

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