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Review Article

Tirzepatide: the most Effective Drug Therapy for Prevention of type 2 Diabetes

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Abstract

Obesity is a main trigger for development of type 2 diabetes. Tirzepatide is a dual receptor agonist of glucagon-like 1 (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP) and is a potent agent for controlling glycemic control and reducing body weight. Accordingly, tirzepatide was evaluated in addition to lifestyle changes to decrease incidence of type 2 diabetes in obese subjects with obesity and prediabetes in an extension study of the SURMOUNT-1 trial. The latter was a randomized, double-blind trial of 72 weeks to evaluate the effects of tirzepatide on weight reduction in 2,539 participants with obesity; 40% (n=1,032) of those subjects had prediabetes. The authors of SURMOUNT-1 study examined the frequency of new-onset type 2 diabetes in the 1,032 subjects with pre-diabetes from baseline to week 176 and week 193 after a 17-week off tirzepatide or placebo. After 176 weeks, type 2 diabetes was diagnosed in 1.5% (n=4), 2.0% (n=5), 0.4% (n=1), and 13.3% (n=36) in subjects randomized to tirzepatide 5 mg, 10 mg, and 15 mg, and placebo, respectively. At 176 weeks, compared with placebo, risk of type 2 diabetes in the pooled tirzepatide groups, was decreased by 93%; hazard ratio (HR) 0.07, 95% CI, 0.0 to 0.1; P<0.001. This 93% reduction in incidence of type 2 diabetes was superior to that achieved by the maximum doses of the GLP-1 receptor agonists liraglutide (79% reduction) and semaglutide (73% reduction), and by the anti-obesity agent phentermine/topiramate (76% reduction). However, subjects' characteristics in studies evaluating these 4 drugs were different. At 176 weeks, achievement of at least 5% of weight loss resulted in remission of prediabetes to normoglycemia in 96% and 83% of subjects with tirzepatide and placebo, respectively. Weight loss seems to be a main factor leading to prevention of type 2 diabetes in all previous drugs. Other mechanisms such as amelioration of beta-cell function and a decrease in insulin resistance may be involved in case of tirzepatide. Overall, tolerance to tirzepatide was satisfactory. Yet, 12.3% of individuals discontinued tirzepatide 15 mg due to adverse effects versus 5.9% in the placebo group. Gastrointestinal (GI) adverse effects were the main safety issue related to tirzepatide. In summary, tirzepatide is currently the most effective agent for diabetes prevention and reversion to normoglycemia in subjects with obesity and prediabetes. Further studies are needed to examine the long-term efficacy, safety, and cost-effectiveness of tirzepatide for prevention of type 2 diabetes.

Keywords: tirzepatide; weight loss; obesity, prediabetes; diabetes; safety

Introduction

Prevalence of diabetes and prediabetes is rising. From 1999 to 2018, among adults ≥20 years, surveys in the USA showed that age-standardized prevalence of diagnosed diabetes increased from 6.15% to 11.0% and prediabetes from 29.5% to 48.3% [1]. This significant increase in prevalence diabetes and prediabetes is largely attributed to a parallel increase in prevalence of obesity, the principal pathophysiologic driver of type 2 diabetes. In fact, obesity increased from 29.1% to 40.3% from 1999 to 2018 [1]. Prevalence of prediabetes increased from 20.8% to 35.8% among normal weight subjects but increased from 41.8% to 51.2% among individuals with obesity [1]. On the contrary, in the same duration period from 1999 to 2018, number of adults with normal weight decreased from 36.8 to 26.5% [1]. In addition, racial and ethnic minority groups, low-income subjects and those living in food-insecure household were disproportionally impacted by the rising prevalence of diabetes and prediabetes [2]. GLP-1 receptor agonists such as semaglutide and the dual GLP-1/GIP receptor agonist tirzepatide are approved for treatment of type 2 diabetes and obesity [3-6]. Although there are no available studies comparing tirzepatide with high doses of semaglutide (2.0-2.4 mg/week), current data suggest that tirzepatide is more efficacious than semaglutide in terms of glycemic control and weight loss. In a recent network meta-analysis of trials of patients with type 2 diabetes, placebo-adjusted mean weight loss was 9.57 kg with the highest dose of tirzepatide (15 mg/week) versus 4.97 kg with semaglutide (2.0 mg/week) [7]. Moreover, in a propensity score-matching study of a US electronic record health care including overweight or obese subjects with and without diabetes, the difference in percentage weight loss was 6.9% (95% CI, 7.9 to 5.8%) greater with tirzepatide than semaglutide after 12 months of use [8]. Furthermore, in an indirect comparison using placebo as the common comparator, le Roux et al [9] found greater reduction of weight with tirzepatide 10 mg and 15 mg versus semaglutide maximum dose 2.4 mg with mean difference of percentage weight loss of 4.6% and 5.9%, respectively. Tirzepatide was recently evaluated in the SURMOUNT-1 trial to decrease

incidence of type 2 diabetes in obese subjects with prediabetes [10]. The latter is a strong risk factor to develop type 2 diabetes [2]. The purpose of this article is to the efficacy and safety of tirzepatide for prevention or delaying onset of type 2 diabetes.

The surmount-1 trial:

The trial evaluating tirzepatide for diabetes prevention was an extension of the SURMOUNT-1 study [11]. This study was a large (n=2,539) randomized, double-blind, placebo-controlled trial of 72-week duration with the main objective of to compare effects of the 3 tirzepatide weekly doses of 5 mg, 10 mg, 15 mg on weight loss in obese subjects without diabetes [11]. Among the 2,539 subjects participating in the SURMOUNT-1 trial, 1,032 (40%) had obesity and prediabetes, defined glycated hemoglobin (HbA1c) levels in the range 5.7-6.4% [10]. Those 1,032 subjects were followed for 176 weeks (approximately 3.4 years) on tirzepatide or placebo followed a 17-week off-treatment period making total follow-up duration of 193 weeks (3.7 years). The 193-week extension study had 3 key secondary endpoints (no primary endpoints were mentioned), namely: percent change in body weight from baseline to week 176, and onset of type 2 diabetes during the 176-week and 193-week periods [10]. Newly diagnosed type 2 diabetes was compared between the pooled 3 tirzepatide dose-groups versus the placebo group [10]. All participants received lifestyle intervention including counseling sessions with a dietitian, 500-kcal daily deficit and at least 150 minutes of physical activity per week [10].

Results of the extension of SURMOUNT-1 trial:

Weight loss:

At week 176, the mean percent change in body weight was -12.3%, (95% CI, -14.5 to -10.2) with the 5-mg tirzepatide (mean weight reduction 12.4 kg), -18.7% (95% CI, -24.1 to -13.4) with the 10 mg-dose (mean weight reduction, 20.0 kg), and -19.7% (95% CI, -22.1 to -17.3) with the 15-mg dose (mean weight reduction, 21.4 kg) versus -1.3% (95% CI, -4.0 to 1.5) with placebo (mean weight reduction, 0.9 kg) [10]. Placebo-subtracted weight reductions were -11.1%, -17.5% and -18.4%, with 5 mg, 10 mg, and 15 mg tirzepatide. respectively (P<0.001 for all comparisons with placebo). Weight loss reached its maximum at approximately 72 weeks followed by a plateau.

Incidence of type 2 diabetes:

During the 176-week treatment period, type 2 diabetes was diagnosed in 1.3% (10 of 762) and 13.3% (36 of 270) of subjects who received tirzepatide and placebo, respectively (HR 0.07, 95% CI, 0.0 to 0.1; P<0.001) [10]. Analyzed in each tirzepatide group separately, type 2 diabetes was diagnosed in 1.5% (n=4), 2.0% (n=5) and 0.4% (n=1) in subjects randomized to tirzepatide 5 mg, 10 mg, and 15 mg, respectively. Thus, the number needed to treat to prevent once case of type 2 diabetes was 9 [10].

Reversion to normoglycemia from prediabetes:

At week 176, reversion of prediabetes to normoglycemia was achieved in 89.9% to 93.3% of participants across the tirzepatide groups as compared with 58.9% among participants who received placebo [10]. Interestingly, among individuals losing at least 5% of body weight, normoglycemia was attained in 96% and 83% with tirzepatide and placebo, respectively (statistical significance for the difference between tirzepatide and placebo was not reported) [10]. Hence, in obese subjects, the threshold of 5% of weight loss may result in reversion of prediabetes to normoglycemia in vast majority of subjects whether they receive tirzepatide on top of lifestyle changes or lifestyle changes alone (i.e., the placebo group). Meanwhile, among participants who failed to lose 5% of their weight, reversion to normoglycemia from prediabetes occurred in 83% and 49% of participants randomized to tirzepatide and placebo, respectively. These higher remission rates of prediabetes in individuals losing <5% of their weight across the tirzepatide groups suggest that tirzepatide may exert antihyperglycemic effects independent of weight loss. After a 17-week off drug period, i.e., at 193 weeks, reversion to normoglycemia was recorded in 73.7%, 82.1%, 77.7% and 55.9% in the 5-mg, 10-mg, 15-mg, and placebo group, respectively [10].

Effects of stopping tirzepatide:

As mentioned earlier, tirzepatide was stopped at week 176 followed by an observation period of 17 weeks [10]. During the 17 week-off treatment, partial weight regain was found in all tirzepatide groups. Thus, in the tirzepatide 15 mg group, percentage weight loss was reduced from -19.7% to -17.9%, and in the 10 mg-group, from -18.7% to -15.6% [10]. Regarding incidence of type 2 diabetes, 8 among the 762 participants (1.1%) receiving tirzepatide were diagnosed with type 2 diabetes compared to one of the 270 subjects (0.4%) receiving placebo. At the end of the 193 weeks, 2.4% and 13.7% of individuals developed type 2 diabetes in the pooled tirzepatide groups and placebo, respectively: HR 0.12 (95% CI, 0.1 to 0.2) [10].

Effects of tirzepatide on cardiometabolic factors:

At week 176, subjects randomized to tirzepatide had dose-related reductions in HbA1c levels of -0.50 to -0.65% versus -0.14% with placebo (P<0.001) [10]. The maximum reduction in HbA1c values occurred at 48 weeks followed by a plateau to 176 weeks. Systolic blood pressure (SBP) decreased by -5.9 to -8.5 mmHg with tirzepatide versus a minimal rise of 0.2 mmHg with placebo. Diastolic blood pressure (DBP) decreased by -4.2 to -5.9 mmHg with tirzepatide, whereas it decreased by -1.9 mmHg with placebo [10]. Lipid profile showed improvement in pooled tirzepatide groups with -32.4% reduction in triglycerides (versus -4.2% reduction with placebo), -7.9% decrease in low-density lipoprotein cholesterol (LDL-C) (versus 1.5% increase with placebo), and 14.1% increase in high-density lipoprotein cholesterol (versus 2.5% increase with placebo) [10].

Effects of tirzepatide on quality of life:

Scores of physical functions, mental health, bodily pain, general health perception, social function all improved with tirzepatide more than placebo at 176 weeks [10]. Specifically, scoring of the SF-36 physical function ranging from 19.0 to 57.6 (with higher scores indicating better function) was 2.6 (95% CI, 0.0 to 5.3) higher in pooled tirzepatide groups than placebo [10].

Mechanisms of prevention of type 2 diabetes and reversion to normoglycemia by tirzepatide:

Weight loss by tirzepatide was a major factor underlying reduction in development of type 2 diabetes and reversion to normoglycemia [10]. Mediation analysis of the SURMOUNT-1 trial showed that 38.9% of reduction in risk of type 2 diabetes was mediated through percent reduction in body weight. This percentage was raised to 55.2% when considering only participants who did not discontinue tirzepatide or placebo during the trial [10]. However, other mechanisms independent of weight loss may be involved. In a study of patients with type 2 diabetes, Thomas et al [12] found that tirzepatide improved insulin resistance, decreased circulating insulin concentrations and increased adiponenctin levels (a marker of insulin sensitivity). In the latter study, weight loss explained only 21% of improvement in insulin resistance assessed by the homeostatic model [12]. In a post-hoc analysis of a phase 3 trial (SURPASS-2) comparing tirzepatide (5-15 mg) and semaglutide (1 mg) in patients with type 2 diabetes, the authors reported that tirzepatide decreased glucogan levels by 53-55% more than semaglutide (47.7% reduction, P<0.05) [13]. In addition, tirzepatide lowered C-peptide levels by 5.2-6% compared with a 3% increase with semaglutide. Similarly, tirzepatide lowered fasting insulin levels by 8.9 to 20.9% versus an increase of 0.6% with semaglutide (P<0.05) [13]. Hence, these findings suggest that tirzepatide improved islet cell function and insulin sensitivity more than submaximal doses of semaglutide of 1 mg/week. [13]. Recent studies in patients with type 2 diabetes published in abstract form suggest that the GIP receptor agonist component of tirzepatide might improve insulin sensitivity independently of weight loss [14]

Efficacy of tirzepatide for prevention of diabetes as compared with other agents:

Many agents approved for treatment of obesity were evaluated to prevent type 2 diabetes. Table 1 showed the 4 most effective agents in decreasing diabetes incidence [10, 15-17]. Tirzepatide was the most effective with 93% reduction followed by the GLP1 receptor agonist liraglutide, 79% reduction,

the centrally acting phentermine/topiramate, 76% reduction then semaglutide, 73% reduction. Phentermine/topiramate is a combination of 2 centrally acting anti-obesity agents that do not exert any direct antihyperglycemic actions [17]. Orlistat, a gastrointestinal lipase inhibitor, was evaluated in one randomized trial of 4-year duration for diabetes prevention. However, the reduction in incidence of type 2 diabetes was modest; 37.3% reduction compared with placebo [18]. Overall, the degree of diabetes reduction correlates with magnitude of weight loss. However, it should be emphasized that the comparison among these 4 agents is far from being perfect due to important differences in subjects' characteristics such as baseline weight, age, proportions of women (known to respond better than men in terms of weight loss), and duration of intervention [19]. Therefore, no definitive conclusion regarding efficacy of diabetes prevention can be obtained without direct drug comparison.

Agent [reference]	Tirzepatide [10]	Semaglutide [15]	Liraglutide [16]	Phentermine/topiramate [17]
Study name	SURMOUNT-1	SELECT	SCALE	SEQUEL-extension
Subjects	N=1032 with prediabetes and obesity	N=17,604 with obesity and preexisting CV disease, 66% had prediabetes	N=2254 with prediabetes	N=866 with obesity and 80% without diabetes
Age	48	62	47	52
Women	64%	27%	77%	66%
BMI (kg/m2)	38.8	33.3	38.9	36.1
Weight (kg)	107.3	96.7	107.7	102
Glycated hemoglobin	5.7%	5.8%	5.7	6.0%
Follow-up	176-193 weeks.	170 weeks (39.8 months)	160 weeks	108 weeks
Percentage weight loss vs placebo	-18.4% (95% CI, -22.2 to -14.7) at 176 weeks	-8.5% (95% CI, -8.7 to -8.3) at 104 weeks	-4.3% (95% CI, -4.9 to -3.7) at 160 weeks	-10.5 % (CI not reported) at 108 weeks
Incidence of type 2 DM	Pooled tirzepatide vs placebo HR 0.07 (95% CI, 0.0 to 0.1)	Semaglutide 2.4 mg vs placebo HR 0.27 (95% CI, 0.24 to 0.31)	HR 0.21 (95% CI, 0.13 to 0.34)	76% reduction vs placebo

Table 1. Anti-obesity agents for prevention of type 2 diabetes:

Safety of tirzepatide in obese subjects with prediabetes:

Serious adverse events were 13-15% in the tirzepatide groups versus 12% in the placebo group. Adverse effects leading to discontinuation of the study drug occurred in 7.3-12.3% in the tirzepatide groups versus 5.9% in the placebo [10]. GI adverse effects were the most common cause of drug discontinulation (1.6-4.4% with tirzepatide versus 0.4% with placebo [10]. Hypoglycemia (defined as blood glucose levels <54 mg/dl) occurred in 2-3.2% of subjects (n=19) across the 3 tirzepatide groups vs none in the placebo group. Interestingly, frequency of hypoglycemia was not proportional with the dose of tirzepatide (3.2%, 2.3%, and 2.0% with tirzepatide 5 mg, 10 mg, and 15 mg, respectively [10]. Other less common adverse effects were cholelithiasis (2.1-3.6% with tirzepatide versus 1.9% with placebo), and pancreatitis (3 cases with tirzepatide versus 1 case with placebo) [10].

Advantages and limitations of tirzepatide in prediabetes:

Advantages:

When used as adjunctive to lifestyle changes in subjects with prediabetes and obesity, the main advantage of tirzepatide is its high efficacy in decreasing weight coupled with 93% percent reduction in progression to type 2 diabetes [10]. Moreover, remission to normoglycemia was achieved in the vast majority (89.9-93.3%) of subjects after approximately 3 years of treatment. In addition, tirzepatide significantly improved CV risk factors such as blood pressure, dyslipidemia, and HbA1c levels and quality of life [10].

Limitations:

The weight regains shortly after stopping tirzepatide implies long-term and probably lifelong treatment incurring more adverse effects and expenses. In fact, up to 12% of subjects could not tolerate tirzepatide due to adverse effects. Regarding its expense, a cost efficacy analysis has yet to be performed to evaluate the role of tirzepatide in management of prediabetes + obesity. Number of participants in the extension phase of the SURMOUNT-1 trial is overall limited (approximately 250 subjects in each of the 4 groups). In addition, approximately 65% of participants completed the trial of 193 weeks [10]. The effects of tirzepatide on fat free mass (i.e., muscle and bone mass) require further studies to see to what extent weight loss is due to reduction in fat versus fat free mass [20]. While available data suggest that tirzepatide (10-15 mg) may be superior to maximum doses of semaglutide (2.4 mg) in terms of weight loss and diabetes prevention, subjects' characteristics were favorable to more pronounced weight loss with tirzepatide versus semaglutide (young age, more women, and greater degree of obesity at baseline (table 1).

Conclusions and future needs:

Available data suggest that tirzepatide is the most effective pharmacological agent for weight loss and prevention of type 2 diabetes in obese individuals with prediabetes over approximately 3.4 years. Long-term studies are needed to examine the durability of these beneficial effects of tirzepatide. In addition, head-to-head trials comparing maximum effective doses of tirzepatide and semaglutide should be performed not only to confirm superiority of tirzepatide but also to compare its safety and tolerance versus semaglutide. The effects of tirzepatide versus the GLP-1 dulaglutide on CV events and mortality are under evaluation in the randomized SURPASS-CVOT trial [Nicholls 2024]. Although the latter study included patients with type 2 diabetes and high CV risk, its results, if positive, will be provide further reassurance about safety of tirzepatide.

Conflict of interest:

The author has no conflicts of interest to declare.

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