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Metabolic Mastery: Mounjaro's (Trizepatide) Impact on Weight Loss in Type-2 Diabetes Mellitus-What We Know So Far?

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ABSTRACT:

Diabetes mellitus (DM) is a growing epidemic that is causing a significant socioeconomic burden on nations throughout the world. Among all causes of death, obesity ranks fifth globally. The term "twin epidemics" refers to the growing global issue of obesity and diabetes prevalence, particularly in wealthy nations[29]. Adopting healthy behaviours is a challenge for those who suffer from obesity, an illness related to lifestyle. Behavioural and lifestyle variables, such as poor sleep hygiene, bad eating habits, sedentary lifestyles, being overweight, and socioeconomic status, are some examples of modifiable risk factors for obesity. Nonetheless, genetics, macrosomia at birth, gender, ethnicity, and age are non-modifiable risk factors for obesity[8]. Since the standard treatment approaches have serious side effects and have not addressed the disease's underlying causes, new solutions for managing diabetes mellitus are emerging quickly[14]. Therefore, cutting-edge therapeutic strategies are required. Known as a "twincretin," tirzepatide is the only dual agonist of the glucagon-likepeptide-1 (GLP-1) and glucose-dependent insulinotropic peptide (GIP) receptors that is considered a "first-in-class" medication. It can significantly lower blood sugar levels and enhance insulin sensitivity, as well as improve lipid metabolism and reduce body weight by more than 20% [29]. This article outlines essential features of the SURPASS and SURMOUNT trials. It also summarizes the current clinical study program and the respective outcomes and highlights further potential indications for tirzepatide in the treatment of obesity. It emphasizes the as the need for further research to guide future clinical practice.

KEY WORDS:

Obesity, Diabetes mellitus, Tirzepatide, Glucagon-like peptide 1 receptor agonist, Weight loss.

INTRODUCTION:

A major global health concern that impacts millions of people is type 2 diabetes (T2D). The body's improper production or usage of insulin causes high blood glucose (sugar) levels in this progressive and chronic condition [12]. The ongoing global growth in the number of persons with diabetes, particularly type 2 diabetes (T2D), is closely linked to a rise in the prevalence of obesity [20]. An "abnormal or excessive fat accumulation that may impair health" is how the World Health Organisation (WHO) describes obesity [6].Numerous studies

assessing various forms of interventions like differences in lifestyle, medication, bariatric surgery, or a combination of those, with varying designs and done in various settings, showed the potential for remission of type 2 diabetes associated with weight loss [26]. Obesity is linked to an elevated likelihood of experiencing conditions such as diabetes, hypertension, cardiovascular disease, cancer, asthma, hypercholesterolemia, and other significant illnesses. According to research by the Diabetes Prevention Program, every kilogram lost is associated with a 16% decrease in the development of type 2 diabetes. nevertheless, numerous individuals with type 2 diabetes find it taxing to achieve their desired blood glucose levels through diet and exercise alone. Tirzepatide injection is a first-in-class once weekly dual agonist of the glucagon-like peptide-1 (GLP-1) and glucose dependent insulinotropic polypeptide (GIP) receptor that is approved for the treatment of type 2 diabetes (T2D), In addition to being investigated for chronic weight control. It is marketed under the trade name Mounjaro and was approved by the US-FDA on May 13, 2022. It is recommended alongside exercise and diet to improve glycemic control in people with type 2 diabetes. Beginning with this, the "twincretin" era with highly significant and alluring dual therapy choices for diabetes and obesity has commenced [29].

DISCUSSION:

Global prevalence estimates for obesity (at least 15% of adults) and type 2 diabetes (T2D) (>9% of adults) continue to rise. Obesity is a strong risk factor for T2D, and more than two thirds of patients are overweight or obese at the time of diagnosis. Even though reduction in weight can significantly decrease the risk and advancement of T2D and its co-morbidities, sufficient weight loss is notably hard to attain and maintain by changes of lifestyle alone[11]. According to the International Diabetes Federation (IDF), 537 million people worldwide have been diagnosed with the disease, and during the next 25 years, that number is predicted to increase by 50%. A Cross-sectional Research by the Indian Council of Medical Research-India Diabetes (ICMR-INDIAB) found that 7.3% of people in 15 Indian states had diabetes [23].Trizepatide is the first and only approved co-agonist for GLP-1 and glucose-dependent insulinotropic peptide (GIP), developed and manufactured by Eli Lilly and Company[18]. Type 2 diabetes patients do not react, as significantly, to incretin hormones as normal individuals would. Tirzepatide indemnifies for this insufficiency by activating the GLP-1 and GIP receptors in the body. Both hormones are rapidly released after consumption and appear to be controlled by the nervous system. They promote the production of insulin in pancreatic cells in a glucose dependent way. Additionally, GLP-1 prevents the release of pancreatic glucagon and has extra pancreatic effects like directly suppressing appetite and slowing stomach emptying, which enhances the feeling of being full[9]. Once a 12-week intensive lifestyle intervention was completed successfully by programme completers, tirzepatide significantly improved the amount of weight reduction. The baseline body weight was lowered by an average of 6.9%. [6]. In general, tirzepatide's safety profile was comparable to that of the GLP-1 receptor agonist class, and it was well tolerated with a low risk of hypoglycemia when administered without insulin or insulin secretagogues. As a result, data from these clinical trials suggests that tirzepatide presents a novel approach for effectively reducing body weight and glycated haemoglobin in persons with type 2 diabetes [26].

The SURPASS and SURMOUNT trials examined tirzepatide's potential for weight loss and obesity in addition to evaluating its impact on reducing glucose levels. in type2 diabetes patients. These trials highlight the promising efficacy and safety of tirzepatide in managing diabetes, obesity, and weight-related comorbidities.
Tables I and II provide a detailed summary of the SURPASS and SURMOUNT trials [,35,36.]

TRIAL	TRIAL POPULATION	COMPARATOR TREATMENT	FINDINGS
SURPASS-1	Drug-naive individuals with type 2 diabetes.	Placebo.	Tirzepatide was administered at doses of 5, 10, and 15 mg as a weekly subcutaneous injection. The placebo-adjusted reductions in **glycated hemoglobin (HbA1c)** during 40 weeks of treatment ranged from **1.91% to 2.11%** (20.80–23.10 mmol/mol), depending on the tirzepatide dose. Weight reductions ranged from **6.3 to 8.8 kg**. Up to **92%** of participants achieved HbA1c levels below **7.0%** (53 mmol/mol), compared to only **19%** in the placebo group. Up to **52%** achieved levels below **5.7%** (39 mmol/mol).
SURPASS-2	People taking metformin monotherapy.	Semaglutide (GLP-1 receptor agonist)	Tirzepatide at the same three weekly doses (5, 10, and 15 mg) was tested against semaglutide. HbA1c reductions during 40 weeks of tirzepatide treatment were significantly greater than those achieved with semaglutide. Tirzepatide also resulted in significantly greater weight reductions.
SURPASS-3	Individuals taking metformin with or without SGLT2 inhibitor	Insulin degludec	People with type 2 diabetes achieved better glycemic control with tirzepatide than with insulin degludec. Weight loss was observed with tirzepatide .
SURPASS-4	Individulas at increased cardiovascular risk, taking metformin with/without a sulfonylurea or SGLT2 inhibitor	Insulin glargine	Tirzepatide demonstrated statistically significant blood sugar reductions and weight loss in people with type 2 diabetes.
SURPASS-5	People taking insulin glargine	Placebo	Superior **A1C reductions** and **weight reductions** were observed with tirzepatide. Up to 97% achieved A1C below 7%, and up to 62% achieved A1C below 5.7% .

TRIAL	TRIAL POPULATION	COMPARATOR TREATMENT	FINDINGS (WEIGHT LOSS)
SURMOUNT-1	People with obesity (without diabetes).	Tirzepatide at doses of 5, 10, or 15 mg.	Average Reduction: 15.0%, 19.5%, and 20.9%, respectively, compared to 3.1% with placebo.
SURMOUNT-2	Adults with BMI ≥27 kg/m² and type 2 diabetes.	Once weekly tirzepatide (10 mg and 15 mg) for chronic weight management.	Tirzepatide led to superior weight reduction compared to placebo.
SURMOUNT-3	People with obesity or BMI 27 kg/m2 and related comorbidities	Tirzepatide vs. placebo after a 12-week intensive lifestyle intervention lead-in period.	Significant and superior over 72 weeks.
SURMOUNT-4	People with obesity or BMI 27 kg/m2 and related comorbidities	Placebo	The total mean weight loss over 88 weeks reached 26.0%.

OTHER ASSESSMENTS FOR TRIZEPEPTIDES POTENTIAL IN HEALTHCARE

Boye, Kristina S et al[2] performed a study that found that those receiving tirzepatide treatment for type 2 diabetes had improved glycaemic control and weight management outcomes. It explains that comparison to reaching higher HbA1c targets or lower body weight percentage losses, greater improvements in quality of life were associated with obtaining lower HbA1c aims or larger body weight percentage reductions, respectively. Lower HbA1c targets and more weight loss were often associated with the highest QoL ratings. The findings indicated that meeting significant percentage body weight reduction requirements and HbA1c targets is necessary to considerably enhance the overall health-related quality of life (QoL) of people with T2D. Tirazepatide medicine may help a sizable portion of T2D patients achieve these objectives.

Rodriguez, Patricia J et al[1] conducted a comparison of tirzepatide and semaglutide's efficacy in helping obese adults lose weight.The research comprised a total of 41,223 patients who met the criteria for their cohort (32,030 for semaglutide and 9,193 for tirzepatide). When treatment began, the average age of the patients was 52.0 (12.9) years, their average weight was 110 (25.7) kg, 70.5% of them were female, and 51.7% of them had type 2 diabetes. In the first year of therapy, more individuals who took tirzepatide than semaglutide lost weight by at least ≥5% (81.8% vs. 64.6%), ≥10% (62.1% vs. 38.0%), and ≥15% (42.3% vs. 19.3%). Therefore, for 5%, 10%, and 15% of weight loss, the corresponding hazard ratios were 1.76 (1.68 - 1.85), 2.42 (2.25 - 2.59), and 3.04 (2.73 - 3.38). It stated that Patients on tirzepatide saw more fluctuations in their body weight loss percentage at three months.

Gelhorn, Heather L et al[4] investigated the impact on type 2 diabetics' chosen medicines of weight loss and substantial changes in HbA1c. To investigate the Participants (N=620) in the US (N=301) and the UK (N=319) had mean ages of 60.7 and 58.9 years, respectively, and 50.8% and 50.5% of them where female was used. . A drop in HbA1c (26.3%) had the most impact on the preferences of US participants, whereas hypoglycemia (32.8%) had a greater bearing on UK participants.If one could only choose between tirzepatide and semaglutide 1 mg, 95.6% of US customers would probably choose tirzepatide. (5, 10, and 15 mg) as opposed to 4.4%.

Lin, Fei, et al[7] revealed a Systematic review on the safety and effectiveness of tirzepatide for weight reduction.To understand regarding the safety and efficacy, there were 10 trials (12 publications) done. overall, that included 9,873 participants. The tirzepatide group lost a considerable amount of body weight compared to the placebo group: -9.81 kg (95% CI (-12.09, -7.52)), -1.05 kg (95% CI (-1.48, -0.63)), and -1.93 kg (95% CI (-2.81, -1.05), respectively. In a sub-analysis, three tirzepatide dosages—5 mg, 10 mg, and 15 mg—significantly decreased the patients' body weight in relation to placebo, GLP-1 RA, and insulin. Regarding safety, it concluded that the tirzepatide group saw a greater incidence of all adverse events and adverse events that resulted in stopping the study medication.

Author, Place, Journal, Year	AIM OF THE STUDY	CONCLUSIONS
Boye, Kristina S et al, ***USA,*** ***Diabetes Ther*** ***14:1867–1887,*** ***(2023)***	To determine whether various levels of weight loss and/or glycated haemoglobin (HbA1c) decrease are associated with changes in health-related quality of life.	For individuals with T2D, meeting the HbA1c objectives and considerable percentage body weight loss requirements significantly improved the overall health-related quality of life. A significant percentage of T2D patient meet these goals with tirzepatide medication, which lead to an improvement in their quality of life.
Rodriguez, Patricia J et al, ***USA,*** ***medRxiv*** ***2023-11,*** ***(2023)***	To compare weight reduction during therapy with tirzepatide or semaglutide in people who are overweight or obese.	Patients on tirzepatide achieved weight reductions of 5%, 10%, and 15%, as well as bigger weight reductions at 3, 6, and 12 months for obesity or overweight who were started on tirzepatide or semaglutide formulations labeled for T2D. The results held up well to analytical variation and were similar among T2D-stratified groups.
Gelhorn, Heather L et al, ***USA,*** ***Patient Preference and Adherence*** ***793–805,*** ***(2023)***	To measure the treatment preferences of individuals with type 2 diabetes (T2D) between an injectable GLP-1 RA drug profile and a glucose-dependent insulinotropic polypeptide (GIP)/glucagon-like peptide-1 (GLP-1) receptor agonist (RA).	When it comes to pharmaceutical alternatives, patients with T2D are mostly driven by their preferences for weight loss, frequency of hypoglycemia, and lowering of HbA1c. In general, tirzepatide medication profiles are probably preferred by T2D patients above semaglutide 1mg medication profiles.
Lin, Fei, et al, ***BELGIUM,*** ***Plos one*** ***18.5: e0285197,*** ***(2023)***	To investigate the effectiveness and safety of tirzepatide for weight reduction in individuals with obesity and type 2 diabetes mellitus (T2DM).	Tirzeptide is a treatment regimen for weight reduction since it may dramatically lower the weight of patients with type 2 diabetes and obesity.

ONGOING TRIALS ON TRIZEPEPTIDES[34]

TRIAL					STATUS	TRIAL POPULATION	COMPARATOR TREATMENT	OBJECTIVE
SURPASS-6 NCT04537923	Completed, not yet published	People taking insulin glargine, with or without metformin	Insulin lispro	To Assess tirzepatide as an alternative to starting a prandial insulin in people already using a basal insulin to treat type 2 diabetes. The cheif endpoint is change in HbA1c after 52 weeks of treatment.				
SURPASS-CVOT: NCT04255433	Recruiting, estimated study completion in October 2024	People with type 2 diabetes, confirmed atherosclerotic cardiovascular disease, and overweight	Dulaglutide	To assess a three-point major adverse cardiovascular event over an estimated maximum of 54 months.				
SURPASS-EARLY NCT05433584	Recruiting, estimated primary study completion in July 2025	People taking metformin monotherapy	Antihyperglycemic medications	To assess patients in relatively early stages of type 2 diabetes, having elevated HbA1c levels despite metformin treatment.				
SURPASS-SWITCH NCT05564039	Recruiting, estimated primary study completion in June 2024	People taking dulaglutide, with or without other antihyperglycemic medications	Dulaglutide	To assess people already taking dulaglutide and either switch to tirzepatide, or continue with the same medicine. The main endpoint is change in HbA1c between baseline and week 40.				

TRIAL	STATUS	TRIAL POPULATION	COMPARATOR TREATMENT	OBJECTIVE
SURMOUNT-MMO NCT05556512	Recruiting, estimated study completion in October 2027	People with BMI ≥27 kg/m2, without diabetes, but with or at high risk for cardiovascular disease	Placebo	In this event-driven cardiovascular efficacy trial, lasting up to 5 years, participants will be assessed for primary occurrence of nonfatal myocardial infarction or stroke, coronary revascularization, heart failure events, and mortality.
SURMOUNT-OSA NCT05412004	Active, not recruiting, estimated study completion in March 2024	People with obesity but not diabetes, who have obstructive sleep apnea	Placebo	To test whether treatment with tirzepatide can improve obstructive sleep apnea. Subjects will be categorized based on their use of continuous positive airway pressure, and the impact of tirzepatide treatment on the Apnea-Hypopnea Index will be evaluated for a duration of 52 weeks.
SURPASS-PEDS NCT05260021	Recruiting, estimated study completion in December 2027	Children aged 10–17 years with type 2 diabetes taking metformin, insulin, or both	Placebo	To assess children with poorly controlled type 2 diabetes administered with one of two tirzepatide doses or placebo for 30 weeks. The main focus is on the alteration in HbA1c throughout this timeframe. Additionally, there will be continued monitoring in an open-label extension until week 52, during which participants who initially received a placebo will transition to tirzepatide.

CONCLUSION:

In our article we have extensively reviewed the impact of Mounjaro on weight loss and diabetes mellitus. Numerous research studies, observations, and clinical trials have consistently demonstrated enhanced therapeutic outcomes, including weight loss, improved HbA1c levels, and overall quality of life when utilizing the dual incretin agonist-Trizepeptide. Ongoing research is crucial to assess its safety, accessibility, potential drug interactions and user-friendliness which would provide essential data for widespread clinical application and patient usage. Tirzepatide has shown impressive weight loss outcomes, challenging the notion that weight loss goals for individuals with obesity can be solely achieved through diet and exercise. The prospects for peptide therapeutics are promising, and their uptake could be boosted by the development of oral formulations that are easy to administer. It can be expressed optimistically that this is a positive development in the realm of anti-diabetic and anti-obesity medications. Individuals with type 2 diabetes should be able to utilize these technologies to mitigate the consequences of inadequate disease management.

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