VIA MEDICA
REVIEW ARTICLE
ISSN 2450–7458
e-ISSN 2450–8187

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A Narrative Review on Clinical Evidence of Tirzepatide's Role in Addressing Type 2 Diabetes and Obesity Management

ABSTRACT

Objective: Tirzepatide, a dual glucose-dependent insulinotropic polypeptide receptor (GIPR) and glucagon-like peptide-1 receptor (GLP-1R) co-agonist, was initially approved for type 2 diabetes (T2D), and it later received US Food and Drug Administration (FDA) approval for managing overweight and obesity. This article aims to review the supporting clinical evidence of tirzepatide's role in the treatment of T2D and obesity, shedding light on its potential impact on improving the health outcomes of individuals grappling with these conditions.

Materials and methods: We obtained the clinical evidence from phase 1, 2, and 3 trials comprising the clinical development program for tirzepatide, SURPASS, and SURMONT for our review from the sources such as Google Scholar and PubMed. For studies reporting efficacy measures (e.g., changes in HbA1c levels, weight reduction), descriptive statistics were interpreted. For safety data, incidence rates of adverse events were reported.

Results: Clinical trials across phases 1, 2, and 3 demonstrated that tirzepatide significantly reduced HbA1c levels and induced weight loss in diverse patient populations. The most commonly reported adverse events were gastrointestinal symptoms, including diarrhea (15–20%), nausea (20–30%), vomiting (10–15%), and abdominal pain, which were generally mild to moderate. Less frequent side effects included headache, fatigue, and occasional injection site reactions. Severe adverse events such as pancreatitis (> 1%) and acute kidney injury were rare but required careful monitoring during treatment.

Conclusions: Tirzepatide has shown a favorable safety profile and effective management of T2D and obesity in clinical trials. Current research is assessing its effects on cardiovascular outcomes and chronic kidney disease, which could broaden its therapeutic applications. (Clin Diabetol 2024; 13, 5: 299–306)

Keywords: tirzepatide, diabetes, obesity, SURPASS, SURMOUNT

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Clinical Diabetology 2024, 13; 5: 299–306
DOI: 10.5603/cd.101152
Received: 19.08.2024 Accepted: 19.08.2024
Early publication date: 26.09.2024

Introduction

Type 2 diabetes (T2D) is a metabolic disorder characterized by inadequate insulin production from pancreatic islet beta cells (β-cells) and insulin resistance, where insulin-sensitive tissues such as muscle, adipose, and hepatic tissues fail to respond effectively to insu-

lin [1]. This chronic and progressive disease is marked by elevated blood sugar levels and is often associated with macrovascular disorders (such as coronary artery disease, peripheral artery disease, and stroke) and microvascular complications (diabetic nephropathy, neuropathy, and retinopathy) [2].

T2D is incurable as it disrupts glucose regulation in the body. The number of people diagnosed with diabetes is rapidly increasing. Between 1980 and 2014, there was a four-fold rise in T2D cases, contributing to a 5% increase in T2D-related mortality. As of the end of 2021, the International Diabetes Foundation (IDF) released an atlas highlighting the growing global incidence of T2D. In 2021, 537 million individuals between the ages of 20 and 79 were affected, and it is projected to reach 783 million by 2045. Europe is anticipated to experience the lowest increase in incidence, at 13%, while African countries south of the Sahara are expected to undergo the highest increase, at 134%.

Obesity is identified as a pivotal modifiable risk factor for T2D, leading to the coining of the term "diabesity". The simultaneous increase in T2D and obesity poses a considerable threat to global health. Consequently, the management of type 2 diabetes extends beyond medication to prevent hyperglycemia and optimize metabolic parameters like blood pressure and cholesterol. It also involves nutritional interventions and lifestyle modifications aimed at facilitating weight reduction in certain cases. The surge in type 2 diabetes cases is largely attributed to the escalating prevalence of obesity. Consequently, there is a pressing need to develop innovative treatments for obesity that can directly or indirectly contribute to the effective management of T2D. Although therapeutic drugs, including insulin and various oral medications, that have been integral in managing T2D, they only address symptoms and control blood sugar levels without tackling the underlying cause of the disease [3, 4]. In response, researchers have developed a multitarget agonist 'tirzepatide' with the aim of enhancing the treatment of T2D and obesity [5].

Tirzepatide has been a pioneer for both T2D and obesity. Tirzepatide is a novel dual glucose-dependent insulinotropic polypeptide receptor (GIPR) and glucagon-like peptide-1 receptor (GLP-1R) coagonist, known as Mounjaro® or Tirzepatide, which received approval from the Food and Drug Administration (FDA) on May 13, 2022, for the treatment of T2D. Remarkably, it garnered additional FDA approval for addressing overweight and obesity on November 8, 2023, under a different brand name, Zepbound [6]. Given its dual functionality, tirzepatide is also commonly referred to as 'twincretin'.

This article aims to conduct a thorough review to provide evidence of tirzepatide, encompassing its discovery, pharmacokinetics, pharmacodynamics, safety, and tolerability, and its position in the management of T2D and obesity.

Chemical structure

Tirzepatide (LY3298176), developed by Eli Lilly, is a chimeric peptide characterized by a synthetic linear peptide chain comprising 39 amino acids. It is conjugated to a 20-carbon fatty diacid moiety (eicosanedioic acid), which is attached at the side of the Lys 20 amino acid. The compound has a notable half-life of 5 days [7]. The molecular formula of tirzepatide is C225H348N48O68, and it has a molecular weight of 4813.45. The chemical structure of tirzepatide is represented as (a) in Figure 1, sourced from Pub Chem, Compound CID: 163285897.

Mechanisms of action

The precise mechanism of action of tirzepatide remains undisclosed; however, evidence suggests that it operates through dual actions on the GIP and GLP-1 receptors, leading to weight loss and enhanced glycemic control. Unlike single hormone administration, studies involving simultaneous injection of GIP and GLP-1 demonstrate heightened insulin sensitivity and decreased glucagon activity that aligns with the findings of a previous report [8]. By activating the GIP-1 receptor pathway via either the GLP-1 or GIP receptor, tirzepatide promotes insulin production in response to glucose levels. Tirzepatide exhibits a stronger binding affinity for GIP compared to GLP-1, suggesting that it may mimic the effects of endogenous GIP at the receptor level, thereby potentially attenuating hyperglycemic effects [9].

Tirzepatide exerts its mechanism of action in adipose tissue primarily through the activation of the GLP-1 receptor and modulation of insulin sensitivity. This activation stimulates the breakdown of triglycerides (lipolysis) stored in adipocytes (fat cells) [10]. This results in the release of free fatty acids and glycerol into the bloodstream. By promoting lipolysis, tirzepatide facilitates the utilization of stored fats for energy production, thereby reducing fat accumulation. Enhanced insulin sensitivity in adipose tissue allows for increased glucose uptake, helps to lower blood glucose levels, and improves overall metabolic health. GLP-1 slows gastric emptying and appetite regulation by acting on the central nervous system to reduce appetite and food intake. This effect contributes to weight loss by decreasing hunger, which helps in maintain-

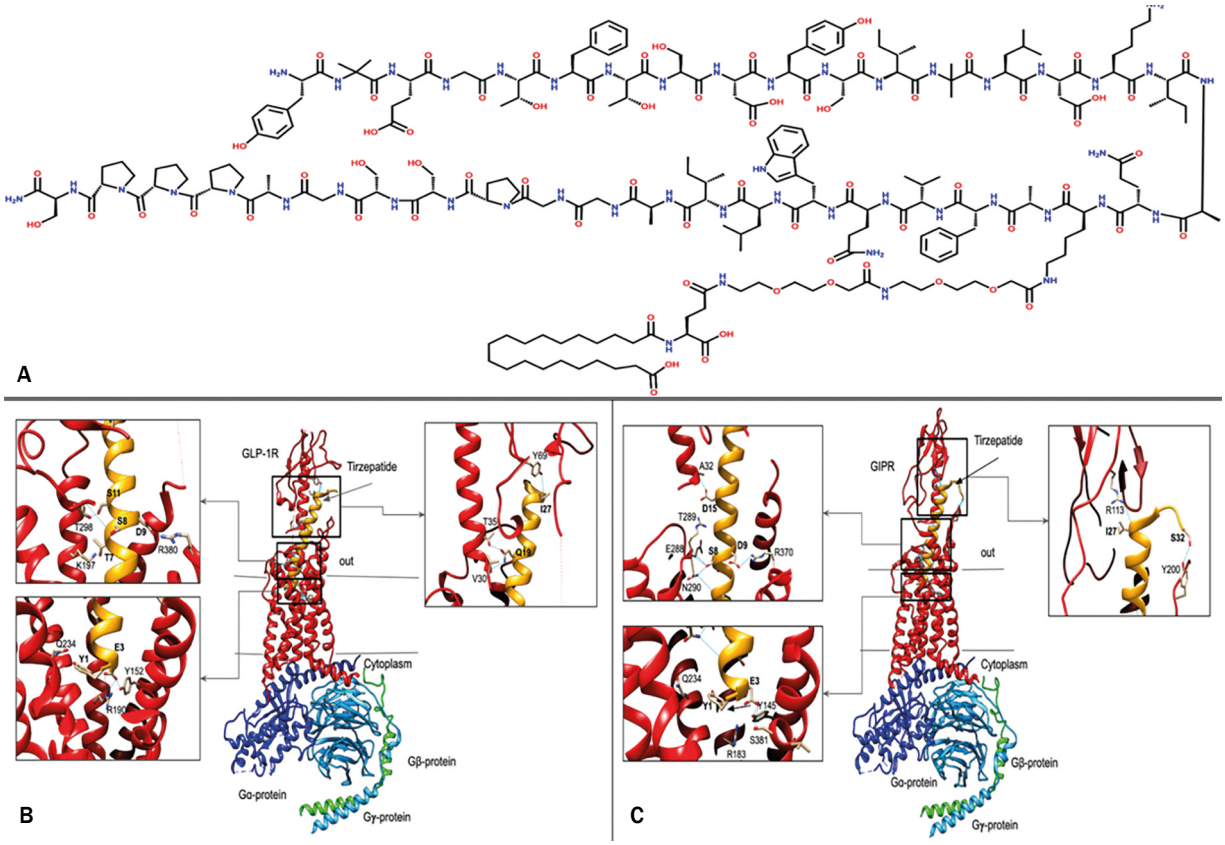

Figure 1. (A.) 2D Structure displaying the amino acid side chains, which are crucial for the biological activity of the peptide and its interaction with receptors; **(B.)** and **(C.)** 3D structures showing the binding sites of the secondary structure that interact with the GLP-1 and GIP receptors
2D/3D — 2-/3-dimensional; GIP — glucose-dependent insulinotropic polypeptide; GLP-1 —glucagon-like peptide-1

ing longer satiety after meals and can contribute to reduced caloric intake. These effects collectively support its role in the treatment of obesity and related metabolic conditions, alongside its established benefits in managing T2D.

Pharmacokinetics of Mounjaro and Zepbound

Tirzepatide, evaluated in clinical trials for both T2D (Mounjaro) and obesity (Zepbound), exhibits similar pharmacokinetic profiles across these conditions. It demonstrates high bioavailability of 80% and reaches peak plasma concentrations (Tmax) between 8 and 72 hours post-administration in both studies. In terms of distribution, tirzepatide shows a steady-state volume of distribution of approximately 10.3 L for T2D and 9.7 L (representing 28.5% of body weight) for obesity, with 99% binding to plasma albumin in both cases.

Metabolically, tirzepatide undergoes breakdown via amide hydrolysis, beta-oxidation of the C20 fatty acid moiety, and proteolytic cleavage of the peptide backbone, a process observed consistently across both studies [11, 12]. Elimination occurs with a population mean clearance of 0.06 L/h for T2D and 0.056 L/h (representing 20.9% of the administered dose) for obesity, yielding a terminal half-life of approximately 5 days in both conditions. The drug is primarily excreted through urine and feces in both studies, highlighting its consistent elimination pathway across different patient groups. These pharmacokinetic characteristics support the use of tirzepatide in both T2D and obesity, indicating its potential efficacy and safety across diverse patient populations.

Clinical evidence from phase 3 clinical trials revealing the impact in T2D in individuals

Several clinical studies have evaluated tirzepatide in patients with T2D, highlighting its efficacy across different populations and dosages.

In phase 3 studies, Frías et al. (2023) [13], using the same dosages of tirzepatide, showed HbA1c reduc-

tions ranging from –2.01% to –2.30%, involving 1879 patients with a mean age of 56.6 years. In 2021, Ludvik et al. [14] investigated tirzepatide in 1437 patients with a baseline HbA1c of 8.17% and age of approximately 57.4 years. In comparison to insulin degludec (1.34%), tirzepatide dosages of 5, 10, and 15 mg showed reductions in HbA1c during a 52-week period, from 1.93% to 2.37%. Del Prato et al. (2021) [15] examined 1995 patients with a mean age of 63.6 years. They found that dosages of 5, 10, and 15 mg resulted in HbA1c reductions ranging from –2.24% to -2.58%. Together, these trials show that tirzepatide can be effective in lowering HbA1c at progressively higher stages of clinical development.

Clinical evidence from phase 3 clinical trials revealing the impact in obesity in individuals

Rosentock et al. (2021) [16] in phase 3 trials observed considerable weight loss ranging from 7.0 kg to 9.5 kg with dosages of 5, 10, and 15 mg in 478 individuals with a mean age of 54.1 years. Using testing doses ranging from 5 mg to 15 mg, 475 patients with a mean age of 60.6 years were evaluated by Dahl et al. (2022) [17], who concentrated on a dose of 5 mg and saw weight loss ranging from 5.4 kg to 8.8 kg. Flaherty et al. (2023) [18] studied 2539 participants with a mean age of 44.9 years, BMI of 38.0 kg/m^2, and initial body weight of 104.8 kg. Over 72 weeks, tirzepatide doses of 5, 10, and 15 mg showed substantial decreases in body weight percentage (–15.0% to –20.9%) compared to placebo (–3.1%). Correspondingly, reductions in waist circumference were noted, ranging from –11.9 cm to –18.5 cm across the tirzepatide doses, indicating significant abdominal fat loss. In another study by Garvey et al. (2023) [19], involving 1514 patients with a mean age of 54.2 years and BMI of 36.1 kg/m^2, tirzepatide at a dose of 10 mg over 72 weeks demonstrated a notable reduction in body weight percentage (–12.8%). Specific changes in waist circumference were not detailed in this study. Together, these findings demonstrate the effectiveness of tirzepatide in promoting significant weight loss and perhaps lowering waist circumference, highlighting its potential as an intervention option for obesity.

SURPASS and SURMOUNT clinical studies

The SURPASS program aimed to assess the efficacy and safety of various anti-diabetic drugs in a larger patient cohort. The study included 6 global trials, 2 Japanese trials, and one Asia Pacific trial. However, it is noted that only Surpass 1-5 have been published according to available information [3].

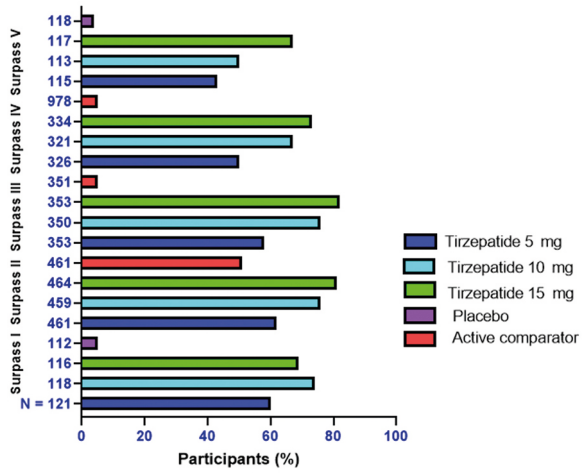

Figure 2. Comparison of tirzepatide with different doses (5, 10, and 15 mg) compared with active comparators/placebo in the SURPASS 1–5 trials
The impact of tirzepatide on achieving 10% weight loss in participants with HbA1c > 7.0% (achieved at baseline) is shown in the graph; HbA1c — glycated hemoglobin

SURPASS-1–5

Tirzepatide was compared to a placebo in SURPASS-1, (n = 478; t = 40 weeks), and the drug significantly lowered HbA1c levels as compared to the placebo. SURPASS-2 (n = 1879; t = 40 weeks) contrasted tirzepatide with the well-known GLP-1 receptor agonist semaglutide. Tirzepatide showed non-inferiority to semaglutide in terms of lowering HbA1c readings. SURPASS-3 (n = 1437; t = 52 weeks) found that tirzepatide significantly lowered HbA1c levels as compared to a placebo. SURPASS-4 (n = 2002; t = 52 weeks) compared insulin degludec and tirzepatide and noted a greater reduction in HbA1c levels with the latter. Tirzepatide was compared with a placebo in SURPASS-5, and the results showed a significant decrease in HbA1c levels as compared to the placebo.

Overall, tirzepatide continuously indicated non-inferiority or superiority to other active comparators such semaglutide or insulin degludec throughout the SURPASS studies, as well as significant decreases in HbA1c levels when compared to placebo and other active comparators (Fig. 2). These results highlight the effectiveness of tirzepatide in enhancing glycemic management.

SURMOUNT 1–4

SURMOUNT is a phase 3, randomized, double blind, placebo-controlled clinical trial program designed to evaluate the efficacy and safety of tirzepatide. In all SURMOUNT studies (SURMOUNT-1 [n = 119 sites; t = 72 weeks], SURMOUNT-2 [n = 77 sites;

Table 1. Adverse Events Observed in Multiple Clinical Trials

Authors name	Phase	Doses of tirzepatide	Decreased appetite	Constipation	Diarrhea	Nausea	Hypoglycemia
Tamer Coskun. et al., 2018 [9]	1	0.5/5/10/15 mg	24	—	10	9	3
Kenichi Furihata et al., 2022 [10]	1	5/10/15 mg	21	16	8	3	—
Ping Feng et al., 2023 [11]	1	2.5 – 10 mg	5	—	6	1	1
		2.5-15mg	8	—	4	4	—
Juan Pablo Frias et al., 2019 [12]	2	1/5/10/15 mg	36	11	49	55	—
Juan Pablo Frias et al., 2023 [13]	2	12 mg	4	1	9	7	2
		15 mg 1st group	6	3	10	11	5
		15 mg 2nd group	8	5	9	10	5
Bernhard Ludvik et al., 2021 [14]	3	5/10/15 mg	102	—	171	207	130
Stefano Del Prato et al., 2021 [15]	3	5/10/15 mg	—	—	119	120	—
Julio Rosentock et al., 2021 [16]	3	5/10/15 mg	—	—	45	52	—
Dominik Dahl et al., 2022 [17]	3	5/10/15 mg	40	23	54	58	58
Ania M. Jastreboff et al., 2022 [20]	3	5/10/15 mg	186	289	398	562	29

*The table presents a summary of tirzepatide-related adverse events from multiple clinical studies. It indicates that gastrointestinal symptoms, such as nausea and diarrhea, are frequently experienced and can change based on the trial's phase and dose. There is no uniform pattern for all side effects, indicating variability in how different participants react to the medication

t = 72 weeks], SURMOUNT-3 [n = 112; t = 72 weeks], and SURMOUNT-4 [significant number of sites for 72 weeks]), tirzepatide had the potential to be used as a weight management treatment, improving metabolic risk variables in people with obesity or overweight. It investigated tirzepatide effects on glycemic control (HbA1c levels) and metabolic risk variables, and focused on patients at high risk of cardiovascular events, assessing its impact when combined with intensive lifestyle intervention.

Safety, adverse event reactions, and precautions

There were no recorded deaths in any of the tirzepatide clinical studies. Short-to medium-term trials have shown a favorable safety profile. A study reported that starting with a lower dose and gradually increasing it can help minimize gastrointestinal discomfort and improve tolerability [20]. Ongoing and future studies will provide more information on the long-term effects and safety of tirzepatide [21]. The gastrointestinal tract was linked to the main adverse events that were noted, including symptoms including diarrhea (15–20%), nausea (20–30%), vomiting (10–15%), constipation, and abdominal pain. Depending on the dosage levels, these side effects ranged in severity from mild to severe. Notably, in a patient receiving 12 mg of tirzepatide, a phase 2 clinical trial revealed 2 very serious side effects: diarrhea and an increased white blood cell count. In SURMOUNT-2, a phase 3 clinical trial involving patients with overweight or obesity with T2D, gastrointestinal events were also documented [22]. Adverse effects that were frequently reported included headaches, minor itching, and cholelithiasis (Tab. 1). Further research over a two-year period showed that tirzepatide (Zepbound and Mounjaro) caused thyroid cell tumors in both male and female rats, including medullary thyroid carcinoma (MTC). As a result, people who have a personal or family history of MTC or multiple endocrine neoplasia syndrome type-2 (MEN2) should not use these medications. Because tirzepatide increases the risk of hypoglycemia, it should also be avoided in patients receiving insulin or insulin secretagogues. Due to severe gastrointestinal side effects that could include acute kidney injury, people with renal impairment or hypersensitivity to tirzepatide or its excipients should also avoid using it. Clinical studies often show cholelithiasis, which calls for more testing and monitoring [23]. Tirzepatide has not been studied in patients with pancreatitis; hence, it is advised to closely monitor patients for pancreatitis symptoms. Additionally, patients with non-proliferative diabetic retinopathy should be properly followed because tirzepatide has not been investigated in this population. Patients who are acting suicidally or who have a history of suicide attempts or active contemplation should not be prescribed Zepbound [24].

Table 2. Summary of Ongoing Trials

Phases	NCT number and study acronym	Location	Conditions	Interventions	Primary outcome measures
1	NCT05696847	United States	Obesity	Tirzepatide & placebo	Number of treatment-emergent adverse events (TEAEs) and serious adverse event(s) (13 weeks)
	NCT05978713	China	Healthy volunteers	Tirzepatide	Pharmacokinetics and AUC 0-∞ of tirzepatide (pre-dose to 30 days post-dose)
2	NCT06037252	Argentina	T2D Obesity	Tirzepatide & placebo	Change in body weight (44 weeks)
	NCT05536804 TREASURE-CKD	United States	Obesity CKD (patients with or without T2D)	Tirzepatide & placebo	Change in kidney oxygenation and blood oxygenation-level dependent magnetic resonance imaging (52 weeks)
3	NCT05963022	China	T2D	Tirzepatide & placebo	Change in HbA1c level (40 weeks)
	NCT06131437	United States	Obesity	Cagrilintide/ semaglutide/ tirzepatide	Change in body weight (72 weeks)
	NCT05691712 SURPASS-CN-INS	China	T2D GMD Metabolic disease	Tirzepatide & placebo	Change in HbA1c level (40 weeks)
	NCT05260021 SURPASS-PEDS	United States	T2D GMD Endocrine system diseases	Tirzepatide (dose 1 and 2) & placebo	Change in HbA1c level (30 weeks)
	NCT06047548 SURMOUNT-MAINTAIN	United States	Obesity	Tirzepatide & placebo	Maintenance and reduction of body weight during a 60-week weight-loss period (112 weeks)
	NCT05556512 SURMOUNT-MMO	United States	Obesity	Tirzepatide & placebo	Time to first occurrence of death, nonfatal myocardial infarction (MI), nonfatal stroke, coronary revascularization, or heart failure events (5 years)
	NCT05963022	United States	T2D	Tirzepatide & placebo	Change in HbA1c level (104 weeks)
4	NCT05553093	China	T2D	Tirzepatide & Insulin glargine	Change of blood sugar level and lipid profiles and brain function through VBM and ASL-fMRI (40 weeks)
	NCT05564039 SURPASS-SWITCH	United States	T2D	Tirzepatide & dulaglutide	Change in HbA1c level (40 weeks)
	NCT06009653 TRZ	United States	Obesity Metabolic disease	Standard care Dietary and behavioral lifestyle Placebo Tirzepatide	Change in body weight (24 and 52 weeks)
	NCT05433584 SURPASS-EARLY	United States	T2D	Tirzepatide & other antihyperglycemic medication	Change in HbA1c level (104 weeks)

ASL-fMRI — arterial spin labelling — functional magnetic resonance imaging; AUC — area under the curve; CKD — chronic kidney disease; GMD — glucose metabolism disorder; HbA1c — glycated hemoglobin; T2D — type 2 diabetes; VBM — voxel-based morphometry

Current clinical trials involving tirzepatide

As of December 16, 2023, Clinicaltrials.gov lists 17 ongoing studies involving tirzepatide, with primary outcomes focusing on changes in body weight and HbA1c levels in patients with T2D, obesity, or overweight [2]. Table 2 shows an overview of the ongoing trials (Tab. 2).

Prospects for tirzepatide in the future

Depending on the outcomes of ongoing trials, regulatory agencies may consider expanding the indications for tirzepatide beyond diabetes and obesity, potentially including other metabolic disorders. The following are some potential future considerations for tirzepatide:

Cardiovascular benefits: Some ongoing trials, such as SURMOUNT-MMO, are evaluating the impact of tirzepatide on morbidity and mortality in obese patients. If tirzepatide demonstrates cardiovascular benefits, it could become a valuable therapeutic option for individuals with diabetes and cardiovascular risk factors [25];

Chronic kidney disease: The TREASURE-CKD trial is exploring the role of tirzepatide in combating chronic kidney disease in patients with obesity. If positive outcomes are observed, tirzepatide may have implications for renal health in individuals with diabetes and obesity [26];

Pediatric obesity: The safety and tolerability of tirzepatide in pediatric obesity participants could pave the way for its use in younger populations, addressing the rising concerns of childhood obesity and related metabolic conditions [27].

It is important to note that the future perspective of tirzepatide will be shaped by continued research, clinical trial results, and regulatory decisions. The evolving landscape of diabetes and obesity management may see tirzepatide playing a crucial role in offering novel treatment options.

Conclusions

Comparative studies have revealed non-inferiority of tirzepatide compared to conventional treatments like semaglutide and insulin degludec, instilling hope for individuals facing challenges in managing their conditions. Although the progress of tirzepatide represents a significant breakthrough in the treatment of T2D and obesity, there are also safety concerns. To mitigate these concerns and ensure patient safety, effective management strategies, careful patient selection, and ongoing monitoring are important. We also think that future directions with the kidney trials and cardiovascular outcomes will determine the potential of tirzepatide for cardio-renal-metabolic disease; however, for people with the established condition or those at high risk, tirzepatide may provide benefits beyond glycemic control. Continued research will define its role in addressing broader metabolic disorders, potentially reshaping therapeutic approaches in the future.

Article information

Authors contribution

Deepalaxmi Rathakrishnan and Amirtha Gnana Sundari contributed to data collection, data screening, drafted the review, and wrote the manuscript. Melina I Sahay contributed to data collection, data screening, and review of manuscript. Sriram DK contributed to the data collection and data screening. Melvin George contributed to the study conception and design, data screening, review of data, and manuscript review. All authors approved the final version to be published.

Funding

The authors did not receive support from any organization for the submitted work.

Acknowledgments

The authors would like to acknowledge Dr. Melvin George, Clinical Research Consultant, for sharing the concept and helping us in drafting this manuscript.

Conflict of interest

The authors declare no conflict of interest.

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