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Review

Tirzepatide in Treating Metabolic Disorders

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Abstract: Type 2 diabetes (T2D) and obesity are chronic diseases associated with high morbidity worldwide, seriously threatening people's life and health. Tirzepatide, as a novel glucagon-like peptide 1 receptor (GLP-1R)/glucose-dependent insulinotropic polypeptide receptor (GIPR) dual-targeted agonist, has been proven to be effective in reducing body weight and controlling blood glucose levels in several clinical studies. Therefore, it has been approved by the Food and Drug Administration (FDA) for treating T2D and managing chronic weight in overweight or obese patients, with good therapeutic effects, safety and tolerability. Metabolic dysfunction-associated steatohepatitis (MASH), a metabolic syndrome related to T2D and obesity, is considered an independent risk factor for cardiovascular disease. It can decrease levels of markers associated with MASH and liver fibrosis and even led to the MASH resolution with no fibrosis worsening in treating T2D patients, without increasing the risk of cardiovascular events. The available evidence suggests that it may have potential therapeutic effects on MASH. This review presents a summary of recent preclinical studies and clinical trials on the application of tirzepatide to treat diabetes, obesity, MASH, cardiovascular disease, and kidney disease and reveals the promising prospect of using tirzepatide as a magic bullet in treating metabolic disorders.

Keywords: Tirzepatide; type 2 diabetes; obesity; metabolic dysfunction-associated steatohepatitis

1. Tirzepatide: A Brief Overview

Tirzepatide, a GLP-1R/ GIPR dual-targeted long-acting agonist, is the inaugural dual-incretin agent that has undergone phase 2 and 3 trials [1]. This drug activates multiple hormone receptors and following ingestion of food, it promotes glucagon-like peptide 1 (GLP-1) secretion by L cells in the distal intestine, as well as glucose-dependent insulinotropic polypeptide (GIP) secretion by K cells in the proximal intestine. GLP-1R and GIPR agonists can enhance pancreatic beta cell insulin secretion, thereby improving postprandial blood glucose levels [2]. Additionally, these agonists have been demonstrated to activate receptors in the central nervous system, which in turn, modulate food intake resulting in body weight reduction [3,4].

Tirzepatide has been approved by the FDA for the management of chronic weight issues in adults and for the improvement of glycemia control in T2D adults. This approval was granted following the completion of multiple clinical trials, the results of which demonstrated its good efficacy, safety, and tolerability in treating patients with diabetes and obesity [5]. Moreover, metabolic dysfunction-associated steatotic liver disease (MASLD), which encompasses a spectrum of liver conditions including hepatic steatosis and MASH, was found to have closely associated with T2D, obesity, and a higher risk for developing cardiovascular disease [6, 7]. Studies have shown that tirzepatide can reduce the biomarkers associated with MASH and fibrosis and also achieve significant clinical efficacy in overweight and diabetes in patients with T2D [8].

Given that the initial stage of MASLD is hepatocellular fat accumulation, which is inherently associated with T2D and obesity, we postulate that agents that target potential metabolic disorders, such as obesity and T2D, may potentially treat MASH. In recent years, there has been increased interest in exploring the possible use of tirzepatide in treating MASLD. Furthermore, cardiovascular events are a prevalent complications of diabetes and obesity. Multiple studies have demonstrated that tirzepatide has been found to lower blood pressure, attenuate inflammation, alleviate oxidative stress, reduce cell death and promote autophagy. Additionally, tirzepatide has exhibited cardiovascular safety in clinical trials, indicating that it may be a valuable therapeutic agent in managing cardiovascular disease in the future [9–11]. Key milestones of tirzepatide related studies in cardiometabolic diseases are summarized in Figure 1.

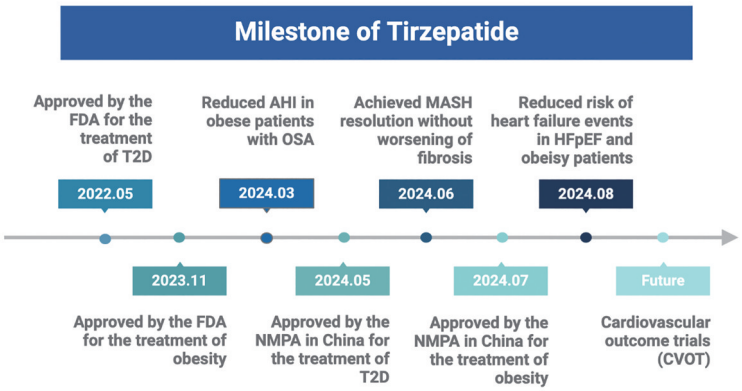

Figure 1. Key milestones of tirzepatide in the treatment of diabetes, obesity and MASH. Abbreviations: AHI, apnea-hypopnea index; CVOT, cardiovascular outcome trials; FDA, the Food and Drug Administration; HFpEF, heart failure with preserved ejection fraction; MASH, metabolic dysfunction-associated steatohepatitis; NMPA, National Medical Products Administration; OSA, obstructive sleep apnea; T2D, type 2 diabetes.

2. Effects and Mechanism of Action of Tirzepatide in Diabetes

Diabetes is a chronic disease that increases the risk of cardiovascular disease, making it a significant public health concern. In 2021, there were 529 million individuals with diabetes globally, 96.0% of whom had T2D, and it is predicted to reach 1.31 billion by 2050 [12]. The current conventional therapeutic agents for diabetes are insulin, metformin, sodium-dependent glucose transporters 2 inhibitors, GLP-1R agonists and DPP4 inhibitors. Besides these, GIPR agonists have only a marginal effect in improving glucose levels. However, the concomitant use of GIPR agonists with GLP-1R agonists may further promote insulin secretion in theory [1].

Recent preclinical research has shown that tirzepatide exerts its effects directly on human and mouse adipocytes, promoting glucose uptake and enhancing insulin signaling to facilitate postprandial glucose clearance by adipose tissue [13]. As a GLP-1R/GIPR dual agonist, tirzepatide has been demonstrated to stimulate glucose effectiveness, defined as the capacity of glucose to be eliminated from blood without altering insulin levels, also known as insulin-independent glucose disposal [14]. Besides, it was uncovered that insulin-independent glucose disposal represents the primary mechanism for lowering glucose levels, analogous to the action of individual GLP-1 or GIP [15].

According to a phase 2 trial, tirzepatide exhibited a dose-dependent reduction in the average level of hemoglobin A1c (HbA1c) compared to baseline (1 mg, −1.06%; 5 mg, −1.73%; 15 mg, −1.94%). The effect was significantly superior to that of the placebo group and the dulaglutide group, with acceptable safety and tolerability [16]. In another randomized, double-blinded, phase 3 trial (SURPASS-1) lasting for 40 weeks, tirzepatide exhibited robust improvement in blood glucose control compared to the placebo group without serious adverse events [17]. Compared to the selective GLP-1R agonist semaglutide, tirzepatide also demonstrated advantages in controlling blood glucose and lowering body weight in T2D patients (SURPASS-2) [18]. One mechanism of action is that tirzepatide enhances β cell responsiveness and improves insulin sensitivity and glucagon suppression, achieving satisfactory glycemic control [19]. In contrast with insulin glargine, another drug for diabetes, insulin glargine and tirzepatide decreased blood glucose in T2D patients

with high cardiovascular event risk. Although the tirzepatide group enhanced the incidence of nausea, diarrhea, and vomiting, they demonstrated satisfactory performance without increasing the risk of cardiovascular death, myocardial infarction, stroke, and unstable angina pectoris (SURPASS-4) [20]. Besides, a phase 3 trial aimed at T2D patients from Asia Pacific region, mainly China, found that the level of HbA1c in participants was significantly reduced and the postprandial blood glucose was close to normal after 40-weeks treatment with tirzepatide, with no significant symptomatic hypoglycemia or severe hypoglycemia (SURPASS-AP-Combo) [21]. Based on evidences obtained from preclinical research and clinical trial, we summarized the mechanisms of action of tirzpatide in the treatment of T2D (Figure 2). In addition to the above effects in T2D patients, tirzepatide was associated with lower hazards of all-cause mortality, adverse cardiovascular events, and acute kidney injury compared to GLP-1R agonists in a retrospective study [22]. It is anticipated that the result of further prospective studies and clinical trials will offer insights into the renal and cardiovascular efficacy of tirzepatide in T2D patients.

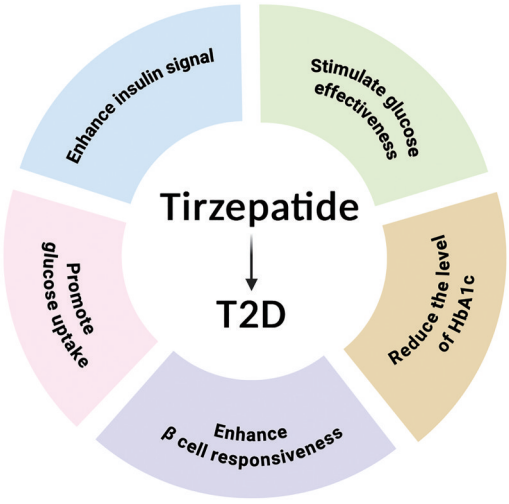

Figure 2. Tirzepatide can effectively treat T2D via multiple mechanisms. For example, it was found to promote glucose uptake and enhance insulin signaling in both mouse models and human adipocytes. It was also observed to improve patients with T2D by stimulating insulin-independent glucose disposal, reducing HbA1c content, enhancing β cell responsiveness, and other beneficial effects. Abbreviations: HbA1c, hemoglobin A1c; T2D, type 2 diabetes.

3. Tirzepatide in Obesity: Preclinical Studies and Clinical Trials

The global prevalence of obesity represents a significant public health challenge. As indicated by the Global Burden of Metabolic Disease, the overall trend of obesity-related mortalities has exhibited a rise from 2000 to 2019, resulting in 5 million deaths occurring in 2019. It has posed a substantial burden on global health [23]. The current mainstay treatment for obesity is lifestyle intervention, which may include dietary intervention and physical exercise. Pharmacological intervention may also be an option, but the effect is limited. Furthermore, weight is more readily regained following the discontinuation of medications than through lifestyle modification. Consequently, the utilization of pharmacological agents in the management of obesity remains a significant challenge [24].

Tirzepide facilitates the alleviation of obesity through the implementation of mechanisms that encompass reducing food intake, increasing energy expenditure and so on (Figure 3). In mouse models of diet-induced obesity, tirzepatide triggered the activation of GIPR and GLP-1R, thereby improving glucose intolerance. Tirzepatide has been demonstrated to lead to decreased food intake and increased fatty acids oxidation during the initial treatment phase (7–10 days). Following a seven-day treatment period, a significant elevation in energy expenditure was observed. Furthermore, the long-term administration of tirzepatide exhibited a dose-dependent reduction in body weight, with a greater reduction than that observed with the GLP-1R agonist alone [25]. Recent studies demonstrated that tirzepatide enhances dietary lipids clearance in human and murine adipocytes. Additionally, it has been shown to synergistically hydrolyze and transport lipid molecules into adipocytes with insulin, without the adverse effect of weight gain [13].

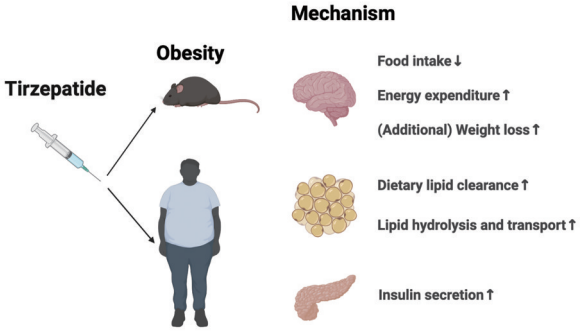

Figure 3. Application of tirzepatide in the treatment of obesity. Its primary mode of action involves lowering food intake and enhancing fatty acid oxidation, thereby promoting weight loss. Additionally, tirzepatide increases the clearance of dietary lipids and facilitates lipid hydrolysis, which contributes to weight reduction. Furthermore, when combined with lifestyle modifications, tirzepatide has been shown to trigger additional weight loss.

In a phase 3 trial (SURMOUNT-1) lasting for 72 weeks, compared to the placebo group, all doses of tirzepatide (5 mg, 10 mg, and 15 mg once weekly) achieved notable and sustained weight loss in obese or overweight patients without diabetes, considered to be the most efficacious weight-loss pharmaceutical agent currently available [26]. Another phase 3 trial (SURMOUNT-3) targeting patients whose body mass index ⩾ 30 or ⩾27 kg/m^2 and are accompanied with obesity-associated complications other than diabetes mellitus, showed that lifestyle intervention supplemented with tirzepatide treatment produced substantial additional weight loss [27]. Moreover, participants were administered the maximum tolerated dose for 88 weeks in the SURMOUNT-4 trial. The trial was conducted in two phases. The initial phase lead-in period, spanning 36 weeks, involved the administration of tirzepatide to all subjects, followed by a double-blinded treatment period of 52 weeks. The results demonstrated that the mean weight change during the double-blinded treatment period was −5.5% in the tirzepatide group (14.0% in the placebo group), indicating that continued treatment of tirzepatide was more effective in sustaining weight loss outcomes, whereas withdrawal of the drug resulted in significant weight rebound [28]. Furthermore, the drug showed good efficacy in managing obesity in T2D patients. The highest dose group (15 mg) demonstrated a mean weight loss of 15.7%, while the placebo group demonstrated an average weight reduction of only 3.3% (SURMOUNT-2) [29]. Besides, in the 15 mg tirzepatide dose group, a mean weight reduction of 17.5% was observed in the overweight or obese Chinese population, with a favorable safety (SURMOUNT-CN) [30]. Compared to semaglutide, both drugs achieved significant body weight reduction. However, tirzepatide exhibited superior efficacy in promoting weight loss in overweight and obese adults [31]. Furthermore, in individuals with sleep apnea and obesity, tirzepatide resulted in weight loss and improved sleep quality (SURMOUNT-OSA) [32].

4. Tirzepatide in MASH: Preclinical Studies and Clinical Trials

MASLD has emerged as the most prevalent chronic liver disease, affecting more than 30% of adults worldwide. Over the past three decades, there has been an increase of nearly 50% in the global prevalence of MASLD [6]. MASH is the progressive form of hepatic steatosis, resulting from the deposition of lipotoxic molecules in the liver. It is related to obesity and diabetes and increases the risk of cardiovascular disease, with the potential for progression to cirrhosis, liver failure, or cancer [6,33]. Previous studies have indicated that GLP-1R agonists promote weight loss and histological regression of nonalcoholic steatohepatitis (NASH), a former term for MASH [34]. Moreover, GLP-1R/GIPR dual agonists demonstrate enhanced efficacy compared to selective GLP-1R agonists in patients with NASH [8].

A recent animal study revealed that tirzepatide can improve various aspects of MASLD. In a murine MASLD model induced by streptozotocin and high-fat diet, tirzepatide attenuated liver fibrosis and reduced hepatic tumorigenesis. However, it only improved tumorigenesis after the onset of advanced fibrosis, but did not improve MASH or fibrosis [35].

Moreover, the primary endpoint of one recent clinical trial was MASH resolution without fibrosis worsening assessed by liver-biopsy results. The results suggested that all doses of tirzepatide notably

achieved the primary endpoint in a dose-dependent effect compared to the placebo group (5 mg, 44%; 10 mg, 56%; 15 mg, 62%; placebo, 10%). Gastrointestinal reactions were the most notable side effects in terms of safety. However, further clinical data are necessary for validating the efficacy and safety of tirzepatide in MASH treatment (SYNERGY-NASH) [36]. In one trial for subjects with T2D, high dose of tirzepatide substantially reduced the levels of triglycerides, total cholesterol, and low-density lipoprotein. Similarly, MASH-related biomarkers, including alanine aminotransferase, aspartate transaminase, and cytokeratin 18 were lowered significantly, suggesting that it can effectively treat MASH [8,21]. Another trial (SURPASS-3) showed that the liver fat content, visceral adipose tissue volume and abdominal subcutaneous adipose tissue decreased following administration of tirzepatide (5 mg, 10 mg, and 15 mg). Moreover, the dose of 10 mg and 15 mg groups exhibited a statistical decrease in liver fat content compared to the ultra-long-acting insulin analogue insulin degludec, at week 52, presenting evidence of novel GLP-1R/GIPR dual agonists in addressing metabolic diseases similar to MASH [37].

5. Tirzepatide in Other Metabolic Disorders: Cardiovascular Disease and Kidney Disease

Obesity and diabetes are significant cardiovascular disease risk factors. Patients with obesity or T2D have an elevated risk of developing a spectrum of cardiovascular conditions, including coronary heart disease, stroke, myocardial ischemia, and cerebral infarction. Recent studies have uncovered that tirzepatide can reduce the levels of biomarkers associated with cardiovascular diseases with good safety and efficacy. For example, the SURPASS-4 clinical trial found that tirzepatide did not increase the risk of cardiovascular diseases, such as cardiovascular mortality, myocardial ischemia and stroke in T2D patients [20]. In the SURMOUNT-1 trial, compared to the placebo group, tirzepatide showed superior improvement in 24-h blood pressure of obese patients, particularly nocturnal systolic blood pressure, which is a more reliable predictor of cardiovascular mortality [38]. Besides, a cardiovascular outcomes trial is currently ongoing to explore the cardiovascular safety and efficacy of tirzepatide in patients with T2D, and the results are awaited [39].

Kidneys play a pivotal role in metabolic regulation, and the accumulation of metabolic substrates places a significant burden on the kidneys, thereby increasing the risk of kidney disease. This highlights the strong association between kidney disease and metabolic disorders. It has been demonstrated that tirzepatide can improve kidney disease through both direct and indirect actions. These include the stimulation of renin-secreting cells, which enhances urinary output and reduces hyperfiltration, as well as indirect actions such as endothelial vasodilation, which in turn lowers blood pressure and improves risk factors of kidney disease [5]. A post-hoc analysis of the SURPASS-4 clinical trial for kidney outcomes in T2D patients demonstrated a significantly reduced annual decline rate of estimated glomerular filtration rate, the urine albumin–creatinine ratio, and the occurrence of composite kidney endpoints in the tirzepatide group versus the insulin glargine group [40]. These studies suggest that tirzepatide may serve as an efficacious treatment for cardiovascular and renal diseases in the future.

6. Concluding Remarks and Future Perspectives

Tirzepatide, as a novel hypoglycemic agent, has favorable efficacy, safety, and tolerability in obesity and T2D treatment with signs of cardiovascular and renal benefits. MASH, a metabolic syndrome closely related to obesity, T2D, and cardiovascular disease, is increasing in prevalence globally. However, only resmetriom, developed by Madrigal Pharmaceuticals, has been approved by the FDA for treating MASH. Moreover, there is growing evidence that tirzepatide may improve hepatic endpoints, with the potential to treat MASH via multiple mechanisms, including lowering the level of hepatic fat content and the risk factors associated with MASH. However, several questions remain to be answered. For example, the long-term efficacy and safety of tirzepatide in MASH resolution have not been examined. Therefore, future studies should investigate the treatment efficacy of MASH with tirzepatide. The molecular mechanism should be further explored in more preclinical studies, as well as the efficacy and safety of tirzepatide be determined in a larger number of MASH patients to provide more information for improving the efficacy of this drug in preventing and treating steatohepatitis. Last but not least, since MASH patients die from cardiovascular events, the cardiovascular outcome trials of tirzepatide in patients with metabolic disorders are warranted.

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