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Tirzepatide - a new drug with great potential in controlling glycemia and body weight

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Abstract

Introduction and Purpose

Type 2 diabetes mellitus (T2DM) and obesity are major global public health challenges associated with increased morbidity, mortality, and reduced quality of life. Despite multiple pharmacological therapies, achieving optimal glycemic control and sustained weight reduction remains difficult in many patients. Tirzepatide, a dual glucose-dependent insulinotropic polypeptide (GIP) and glucagon-like peptide-1 (GLP-1) receptor agonist, has emerged as a promising therapeutic option. The aim of this review is to evaluate the clinical efficacy, safety profile, mechanism of action, and therapeutic potential of tirzepatide in the management of T2DM and obesity.

Methods

A narrative review of current literature, including randomized controlled trials, meta-analyses and European Medicines Agency documentation, was conducted to assess metabolic effects, dosing strategies, adverse events, and long-term implications of tirzepatide therapy.

Results

Clinical trials show significant reductions in glycated hemoglobin (HbA1c), exceeding 2 percentage points in patients with T2DM, and dose-dependent body weight reduction of up to approximately 20% of baseline weight in individuals with obesity. Comparative analyses indicate greater efficacy than selective GLP-1 receptor agonists and basal insulin for glycemic control and weight reduction. The most common adverse events are gastrointestinal and occur mainly during dose escalation. Long-term cardiovascular and renal outcomes remain under investigation.

Conclusions

Tirzepatide represents an important advancement in incretin-based therapy, offering combined metabolic benefits that may modify current treatment algorithms for T2DM and obesity. Although evidence supports high efficacy and acceptable safety, further long-term studies are needed to determine its effects on disease progression, cardiovascular outcomes, and sustained weight management.

Keywords: tirzepatide; type 2 diabetes mellitus; obesity; incretin therapy; GIP/GLP-1 receptor agonist; weight reduction; metabolic disease

1. Introduction

Type 2 diabetes mellitus (T2DM) is one of the most prevalent metabolic diseases and represents a growing global public health problem [1]. In 2019, the disease affected more than 460 million adults worldwide, and projections indicate that this number may increase to approximately 700 million by 2045 [2]. T2DM accounts for over 90% of all diabetes cases [3]. Data from the World Health Organization indicate that in 2022 the condition was diagnosed in approximately 14% of the adult population, with particularly high prevalence observed among older individuals-affecting nearly one in four people over the age of 65 [4,5]. Diabetes belongs to a group of chronic metabolic disorders characterized by persistently elevated blood glucose levels resulting from impaired insulin secretion or abnormal tissue responses to this hormone. This leads to disturbances in carbohydrate, lipid, and protein metabolism [6]. In type 2 diabetes, insulin resistance and chronic hyperglycemia play a key role, making this disease one of the most serious contemporary challenges for healthcare systems worldwide [7]. The disease significantly reduces patients' quality of life, primarily due to the development of numerous chronic complications [8]. Microvascular and macrovascular damage constitutes the main cause of increased morbidity and mortality in this patient population [9]. Type 2 diabetes affects the function of multiple organs, leading, among others, to the development of cardiovascular diseases, retinopathy, nephropathy, and peripheral neuropathy [6]. Prolonged hyperglycemia is considered the primary factor contributing to the development of these complications [10]. Lifestyle-related factors also play a crucial role in the development of T2DM, including excess body weight, lack of physical activity, a sedentary lifestyle, dietary patterns based on foods with a high glycemic index and low fiber content, as well as vitamin deficiencies, tobacco smoking, and alcohol consumption [11]. Obesity is of particular importance, as individuals with chronic obesity have a several-fold higher risk of developing diabetes compared with the general population. Moreover, a substantial proportion of patients with T2DM are overweight or obese, which further increases the likelihood of disease development [12].

The World Health Organization (WHO) defines obesity as a condition in which an excessive accumulation of adipose tissue adversely affects health and well-being. Due to the rapid increase in its prevalence, obesity has been recognized as a "global epidemic" [13]. In 2016, more than 1.9 billion adults were overweight, of whom over 650 million were obese [14]. Most epidemiological studies are based on body mass index (BMI, kg/m^2), with values of 18.5–24.9 considered normal, 25.0–29.9 classified as overweight, and ≥30 defined as obesity [15]. Obesity is further classified into degrees: class I (30.0–34.9), class II (35.0–39.9), and class III (≥40), with class III obesity occurring 50% more frequently in women than in men [16,17]. The high prevalence of obesity represents a significant public health problem, as it is associated with numerous diseases and a reduced life expectancy [18]. The most common conditions comorbid with obesity include:

- dyslipidemia,
- hypertension,
- prediabetes,
- type 2 diabetes,
- obstructive sleep apnea,
- coronary heart disease,
- chronic kidney disease,
- heart failure,
- depression or anxiety [19].

Higher degrees of obesity are also associated with a greater reduction in expected life expectancy: individuals with class III obesity lose an average of 4.3 years of life, those with class II obesity lose 3.2 years, and those with class I obesity lose approximately 2.2 years. Notably, the obesity-related loss of life years decreases with increasing age [20]. Lifestyle modifications remain a safe but often insufficient treatment approach when not accompanied by pharmacological therapy. Modern medications, particularly GLP-1 receptor agonists and dual-action agents such as tirzepatide, have significantly expanded the possibilities for conservative treatment, although their long-term efficacy and safety still require further investigation. The most durable outcomes are achieved with bariatric surgery, which improves health status and prolongs survival but is associated with higher risk, potential complications, and increased costs [21].

2. Tirzepatide as a Potential New Standard of Treatment for Type 2 Diabetes and Obesity

The introduction of tirzepatide into clinical practice has sparked debate as to whether it represents merely another modification of incretin therapy or a qualitatively new phase in the treatment of metabolic diseases [22]. Results from the SURPASS and SURMOUNT clinical trial programs suggest that the scope of this drug’s effects exceeds the current profile of selective GLP-1 receptor agonists [23,24]. Randomized clinical trials have demonstrated reductions in HbA1c exceeding 2 percentage points, as well as significant, dose-dependent weight loss of approximately 20% of baseline body weight in individuals with obesity [23–25]. The magnitude of this reduction approaches that observed after metabolic surgery, thereby significantly altering the position of pharmacotherapy within current treatment algorithms. Importantly, the improvement in glycemic control does not appear to be solely a consequence of weight loss; beneficial effects on β-cell function and tissue insulin sensitivity have also been observed, suggesting a more complex mechanism resulting from the simultaneous activation of GIP and GLP-1 receptors [22]. In comparative analyses, tirzepatide has demonstrated greater efficacy in reducing HbA1c levels and body weight than selective GLP-1 receptor agonists and several other antidiabetic agents [23]. Dual modulation of the incretin axis may therefore represent not only an extension of existing therapeutic strategies but also the advent of a new generation of metabolic treatments. However, it should be emphasized that assessment of the long-term impact on disease progression, as well as on cardiovascular and renal outcomes, requires further investigation and the results of ongoing studies [26].

3. Comparison of tirzepatide with other antidiabetic drugs

Assessing the clinical value of tirzepatide requires its direct comparison to previously used incretin and insulin therapies. The SURPASS-2 study demonstrated that, compared to semaglutide 1 mg, tirzepatide provides greater HbA1c reduction and more pronounced weight loss [24]. Although there are no randomized, head-to-head studies of semaglutide 2.4 mg for the treatment of obesity, a comparison of the SURMOUNT program results with the STEP studies suggests that the magnitude of weight loss with tirzepatide is at least comparable, and in some analyses even greater [25, 27]. Compared to basal insulins such as glargine, tirzepatide allows for better glycemic control with simultaneous weight loss, whereas insulin therapy is usually associated with weight gain [28]. A similar advantage is observed in comparisons with selected GLP-1 agonists, including dulaglutide, particularly in terms of HbA1c and body weight reduction [23]. HbA1c reduction exceeding 2 percentage points is a rare effect of diabetes pharmacotherapy and indicates significant metabolic potential of the drug [29].

4. Indications and dosage

Tirzepatide (Mounjaro®) has been authorized in the European Union following a positive opinion from the European Medicines Agency and a subsequent decision of the European Commission. It is the first dual glucose-dependent insulinotropic polypeptide (GIP) and glucagon-like peptide-1 (GLP-1) receptor agonist, improving glycemic control and promoting weight reduction through a complementary incretin-based mechanism of action [30, 31].

According to the approved EU labeling, tirzepatide is indicated in adults:

- For type 2 diabetes mellitus**: as an adjunct to diet and physical activity in patients with insufficient glycemic control. It may be used as monotherapy when metformin is contraindicated or not tolerated, or in combination with other glucose-lowering agents.
- For weight management**: as part of a comprehensive strategy including a reduced-calorie diet and increased physical activity in adults with obesity (BMI ≥ 30 kg/m²) or overweight (BMI ≥ 27 to < 30 kg/m²) with at least one weight-related comorbidity (e.g., type 2 diabetes, dyslipidemia, hypertension, or obstructive sleep apnea) [30,31].

The dosing regimen of tirzepatide (Mounjaro®) (Tab. 1) according to European Medicines Agency documentation, highlighting that the route of administration and dose-escalation schedule are identical for both approved indications-type 2 diabetes mellitus and obesity/overweight with comorbidities. Treatment is initiated at 2.5 mg once weekly for four weeks, followed by escalation to the minimum therapeutic dose of 5 mg, with further increases of 2.5 mg at intervals of at least four weeks up to a maximum of 15 mg weekly.

Parameter	**Type 2 Diabetes Mellitus**	**Obesity / Overweight with Comorbidities**
Route of administration	Subcutaneous, once weekly	Subcutaneous, once weekly
Initial dose	2.5 mg weekly for 4 weeks (initiation dose)	2.5 mg weekly for 4 weeks (initiation dose)
Minimum therapeutic dose	5 mg weekly	5 mg weekly

Dose escalation	+2.5 mg at ≥4-week intervals	+2.5 mg at ≥4-week intervals
Maximum dose	15 mg weekly	15 mg weekly
Typical maintenance dose	5–15 mg (individualized)	10–15 mg (commonly targeted)
Primary therapeutic goal	HbA1c reduction and glycemic control	Body weight reduction
Additional considerations	Adjust background insulin/SU therapy to reduce hypoglycemia risk	Combine with reduced-calorie diet and increased physical activity

Table 1. The dosing regimen for tirzepatite for the two approved indications

The indications differ primarily in typical maintenance dosing and therapeutic goals: in type 2 diabetes, dosing is individualized to optimize HbA1c reduction and glycemic control while minimizing hypoglycemia risk, whereas in obesity management, higher maintenance doses (10–15 mg weekly) are more commonly targeted to achieve sustained body weight reduction, in combination with lifestyle interventions [30,31]

5. Tirzepatide Adverse Events

The most frequently reported adverse events associated with tirzepatide are gastrointestinal, including nausea, diarrhea, and vomiting. These events are typically mild to moderate in severity and occur predominantly during dose escalation [25,32]. In the SURMOUNT-1 to -4 trials, gastrointestinal adverse events were reported in 27.8–72.8% of tirzepatide-treated participants compared with 12.2–32.5% in placebo groups [33]. The risk of hypoglycemia is low during monotherapy but increases in patients receiving concomitant glucose-lowering agents. In phase II/III trials in type 2 diabetes, hypoglycemia occurred in approximately 3% of the overall population [34], with rates up to 22.6% observed in selected subgroups at higher doses [35,36]. Rare cases of hypersensitivity reactions, including generalized urticaria, pruritus, and injection-site reactions, have been described, with occasional reports of systemic reactions following initial exposure [37,38]. Meta-analyses in individuals with overweight or obesity without diabetes have reported a higher incidence of dizziness compared with placebo [39]. However, due to heterogeneity across studies, the true incidence and causal relationship remain uncertain [40]. Cardiovascular effects include reductions in systolic blood pressure, typically in the range of 4-6 mmHg in randomized trials [41]. Although hypotensive episodes accompanied by compensatory tachycardia have been reported [37], overall blood pressure reduction appears to represent a predictable, dose-dependent response that may exceed changes attributable solely to weight loss in some cases [37,41]. These findings support individualized risk assessment, particularly in patients with low baseline blood pressure or concomitant antihypertensive therapy.

6. Mechanism of Action Tirzepatide

Tirzepatide (LY3298176) is a synthetic 39–amino acid peptide engineered to act as a dual agonist of the glucose-dependent insulinotropic polypeptide (GIP) and glucagon-like peptide-1 (GLP-1) receptors [42].Both receptors are expressed predominantly on pancreatic α- and β-cells, as well as in extra-pancreatic tissues including the gastrointestinal tract, cardiovascular system, adipose tissue, and the central nervous system.Tirzepatide exhibits binding affinity to the GIP receptor comparable to native GIP, while its affinity for the GLP-1 receptor is approximately fivefold lower than that of native GLP-1 [22].This receptor activity profile underlies its combined incretin effects.Structural modification with a C20 fatty diacid moiety enables reversible albumin binding, prolonging systemic exposure and resulting in an elimination half-life of approximately five days, which supports once-weekly administration. The glucose-lowering effects of tirzepatide are mediated through multiple complementary mechanisms, including enhancement of glucose-dependent insulin secretion, suppression of glucagon release, improvement of β-cell function, and delayed gastric emptying, the latter attenuating over time [43,44]. In addition, central and peripheral actions contribute to appetite suppression and reduced energy intake, supporting weight reduction [45].

7. Drug Interactions

Similar to other peptide-based GLP-1/GIP agonists, tirzepatide is not metabolized by common CYP enzymes or transported via typical transporters, making classical pharmacokinetic interactions unlikely. Its primary mechanism of affecting other medications is through delayed gastric emptying, which can reduce Cmax and prolong Tmax of orally administered drugs. In clinical practice, most oral medications do not require dose adjustment, but monitoring is advised for drugs with a narrow therapeutic index (e.g., warfarin, digoxin) or for medications where rapid onset of action is critical [46]. Gastrointestinal adverse effects- such as nausea, diarrhea, and reduced appetite are common and may affect nutritional status, hydration, and the pharmacodynamics of concomitant medications [39]. Real-world use has reported dosing errors, injection-site reactions, and discontinuations due to adverse effects, highlighting the need for careful patient monitoring [47].

8. Contraceptives

Dose adjustment of oral contraceptives is generally not required [48]. However, because Tirzepatide delays gastric emptying, it may affect the rate and extent of absorption of orally administered hormonal contraceptives.This is not a metabolic interaction (e.g.,via CYP enzymes) but rather a result of altered gastrointestinal motility.Given its potential clinical significance-particularly during the initiation of therapy or dose escalation-consideration of additional or non-oral contraceptive methods is recommended [48, 49].

9. Effects on Fertility, Pregnancy, and Lactation

Data on Tirzepatide use during pregnancy are limited.Animal studies have demonstrated adverse effects on reproduction, and therefore Tirzepatide is not recommended for use in pregnant women or in women of childbearing potential who are not using effective contraception. Preclinical studies have not shown direct impairment of fertility caused by Tirzepatide. There is currently insufficient evidence regarding the excretion of Tirzepatide into human breast milk or its potential effects on a nursing infant.Preliminary data suggest that concentrations in milk are very low or undetectable, and absorption by the infant is likely minimal.However, the risk to the breastfed child has not been fully established, and therefore Tirzepatide use during breastfeeding should be approached with caution [48, 49, 50].

10. Tirzepatide and Long-Term Weight Management

Discontinuation of Tiirzepatide therapy in individuals with obesity is associated with a clear trend toward regaining lost body weight in the months following treatment cessation. In many patients, a gradual return of weight and worsening of previously improved metabolic parameters have been observed. These findings suggest that the effects of pharmacotherapy may not be sustained without continued treatment, highlighting the need for a long-term approach to obesity management [51].

Given the increasing use of GLP-1 receptor agonists in the treatment of obesity and diabetes, clinical guidelines should address not only how to initiate and titrate therapy but also provide clear strategies for safely discontinuing treatment and maintaining its long-term benefits [52].

11. Safety and Long-Term Effects

Data from clinical trials and literature reviews indicate that GLP-1 receptor agonists, such as semaglutide, liraglutide, and Tirzepatide, are generally well tolerated and safe when used for several years.The most commonly reported adverse effects involve the gastrointestinal system and are mild to moderate in severity. However, studies with long-term follow-up are lacking, meaning that the extended effects of therapy, including potential loss of muscle mass, impact on the cardiovascular system, and rare adverse events remain largely unknown [53].

12. Conclusion

Tirzepatide represents a significant advancement in the pharmacological management of type 2 diabetes and obesity, offering substantial improvements in glycemic control and clinically meaningful weight reduction. Its dual GIP and GLP-1 receptor agonism may redefine current treatment algorithms, potentially shifting the boundaries between pharmacotherapy and metabolic surgery. In my view, the magnitude of metabolic effects observed to date positions tirzepatide as a promising new standard of care, although confirmation of long-term cardiovascular and renal benefits remains essential.

Author's contribution:

Conceptualization, supervision and project administration- MS

Methodology-MS, FP, MTS

Software, validation, formal analysis, investigation, resources, writing original draft preparation- MS, FP, MTS, AK

Writing review editing and visualization- AK, TS, KS, IH

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