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Efficacy and Safety of Tirzepatide in the Treatment of Obesity in Adults: A Comprehensive Review

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ABSTRACT

Obesity is one of the most serious health challenges of the modern world, associated with an increasing incidence and serious health consequences, including cardiovascular diseases and type II diabetes. Pharmacotherapy of obesity is developing rapidly, and tirzepatide, an agonist of GIP and GLP-1 receptors, is emerging as a promising solution. In the SURMOUNT and SURPASS clinical trials, tirzepatide was shown to effectively reduce body weight and improve metabolic parameters in diabetic and non-diabetic patients, surpassing other available therapies, such as semaglutide in terms of efficacy. Tirzepatide not only promotes weight loss but also helps maintain the effects achieved and reduces cardiovascular risk, making it an important tool in the treatment of obesity. Its clinical benefits are further enhanced by the introduction of intensive lifestyle interventions before starting therapy. In summary, tirzepatide is an innovative approach to the treatment of obesity, offering promising long-term effects while maintaining a favorable safety profile.

Keywords: Tirzepatide, obesity treatment, pharmacotherapy, GLP-1 and GIP analogs, cardiovascular risk, lifestyle interventions, SURMOUNT, SURPASS

Introduction

The World Health Organization (WHO) defines obesity as a disease characterized by abnormal or excessive fat accumulation that negatively affects health. It is diagnosed when a patient's body mass index (BMI) reaches 30.0 kg/m² or more. The prevalence of obesity has increased significantly in recent years, with approximately 16% of adults worldwide being classified as obese in 2022—double the number in 1990 (1). This increase is alarming because obesity is a

significant risk factor for various health problems, including cardiovascular disease, some types of cancer, type 2 diabetes, chronic obstructive pulmonary disease, and severe cases of COVID-19, which are among the leading causes of death worldwide (2–4).

One of the first interventions in the treatment of obesity is the use of non-pharmacological methods, such as diet, psychotherapy, and increased physical activity (5). Appetite control involves the coordinated action of several systems: the satiety and hunger center in the hypothalamus, the mesolimbic system, the prefrontal cortex responsible for controlling food choices, as well as centrally acting mediators from adipose tissue, the pancreas, the intestines, and other organs. In the case of people suffering from obesity, we are dealing with a weakened effect of the previously mentioned mediators, and cognitive functions located in the prefrontal cortex have difficulty in opposing dysregulated appetite mechanisms, which is associated with a more significant challenge in maintaining a healthy body weight (6). It turns out that only <20% of people undergoing lifestyle interventions manage to lose $\geq 15\%$ of their initial body weight, which will affect the optimal control of obesity complications and cardiovascular risk, and within a year of the intervention, they regain as much as 1/3 of the lost body weight, with this tendency increasing over time. This is associated with a disproportionate loss of body weight and the energy expenditure of the patient's body (7).

In obese individuals who have not achieved satisfactory results with dietary treatment or increased physical activity, it is possible to use pharmacological treatment based on drugs aimed at enhancing the feeling of satiety and suppressing appetite (6). This treatment can also be used in obese patients with significantly increased cardiovascular risk, class I obesity (BMI ≥ 30 kg/m²), adults with BMI 27-29.9 kg/m² and ≥ 1 comorbidity associated with abnormal body weight, or in individuals eligible for bariatric surgery (8,9).

Pharmacological treatment of obesity has been the fastest-developing strategy for dealing with obesity in recent years (10). Currently, the following drugs are registered in Europe by the European Medicines Agency (EMA): orlistat, a preparation consisting of naltrexone hydrochloride and bupropion hydrochloride, liraglutide, semaglutide, and tirzepatide (9).

Orlistat, the oldest of the registered drugs, is a strong, specific, irreversible inhibitor of pancreatic and gastric lipases. Its action is based on inhibiting the breakdown of triglycerides to free fatty acids, significantly reducing the absorption of fats supplied with food (11). However, it does not affect the mechanisms of regulating hunger and satiety (9).

The next registered drug was Naltrexone/Bupropion, whose mechanism leading to weight loss has not been fully understood. It is assumed that it is related to the synergistic effect of naltrexone – an opioid receptor antagonist, together with bupropion – a non-selective

dopamine and noradrenaline reuptake inhibitor and an antagonist of nicotinic acetylcholinergic receptors, which leads to an anorectic effect associated with long-term activation of anorexigenic neurons in the hypothalamus. It promotes the feeling of satiety, reduces food intake, and increases the body's energy expenditure (12,13).

Liraglutide and semaglutide are analogs of glucagon-like peptide (GLP-1), but due to peptide modification, they act longer than the one naturally occurring in the body. These are drugs previously used in the treatment of type II diabetes, but during clinical trials, their simultaneous effect on promoting body weight loss was observed (14). GLP-1 analogs stimulate insulin secretion from pancreatic cells in response to elevated postprandial glucose levels, inhibit glucagon production, and delay gastric emptying. Experimental studies have shown that both analogs provide effective glycemic control, increase the feeling of satiety and postprandial fullness, and reduce the feeling of hunger, which directly translates into reduced food consumption (15,16). GLP-1 analogs are well tolerated; gastrointestinal disorders are the most common side effects. They are administered as a subcutaneous injection (17).

The latest drug used in the treatment of obesity, approved by the EMA in 2023, is Tirzepatide, which has been allowed to be used in patients with type II diabetes for glycemia control for a year now (18). Since this drug has only been used for a few years, this review will focus on the mechanisms and effects of its action, its systemic effects, potential additional benefits, and its safety.

Methods

A systematic search of the PubMed database was performed, focusing on studies published in the last 5 years. The search strategy used relevant keywords related to tirzepatide and obesity. Studies were included if they provided key information on the use of tirzepatide in the treatment of obesity in the adult population. The most relevant articles were selected.

Tirzepatide – characteristics and drug target

Tirzepatide is the first synthetic peptide consisting of 39 amino acids, called "twincretin". It shows structural similarity to incretin hormones GIP (glucose-dependent insulinitropic peptide) and GLP-1 (glucagon-like peptide) (Figure 1).

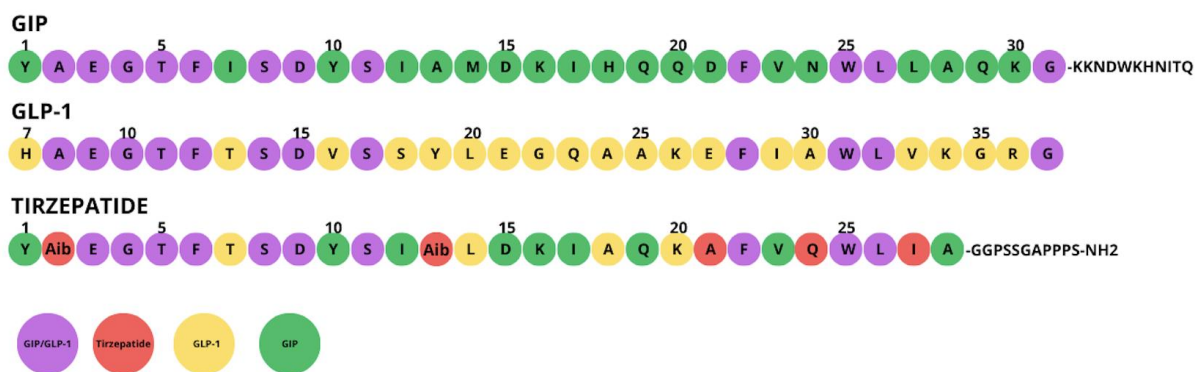


Figure 1. Structural similarity between GIP, GLP-1 and Tirzepatide (19).

Due to the presence of additional amino acid residues of α -aminoisobutyric acid (Aib) in positions 2 and 13, it becomes resistant to the action of the enzyme dipeptidyl peptidase IV (DPP-4), which is responsible for the breakdown of natural incretins. This is associated with the extended half-life of tirzepatide to 6 days, thanks to which it can be administered by subcutaneous injection once a week (20,21). Due to its characteristic structure, tirzepatide simultaneously exerts an agonistic effect on the GIP receptors, to which it shows a greater affinity, and on GLP-1, on which it affects approximately 5 times weaker than the natural incretin found in the body (22–25).

GIP and GLP-1 are incretin hormones responsible for stimulating pancreatic cells to release insulin in response to a postprandial increase in blood glucose, thanks to which they participate in the regulation of glucose homeostasis. GIP is also responsible for inhibiting the activity of gastric secretion, inhibiting lipolysis, and promoting lipogenesis. GLP-1, on the other hand, also exhibits an inhibitory effect on glucagon release, slows gastric emptying, and induces a feeling of satiety (24).

In recent years, when GLP-1 agonist drugs were successfully used in the treatment of type II diabetes, the role of GIP was considered insignificant due to the lack of significant clinical effects in human studies. However, the recent discovery of the greater efficacy of tirzepatide, a GIP/GLP-1 receptor coagonist, in controlling glycemia and body weight compared to GLP-1 agonists has renewed interest in GIP (26). Due to the simultaneous action of tirzepatide on both GIP-1 and GIP receptors, it seemed that this drug could lead to better clinical outcomes in patients with both glycemia and body weight control, and several clinical trials were conducted.

Tirzepatide in the treatment of obesity in non-diabetic individuals – SURMOUNT-1

The multicenter, double-blind, randomized, placebo-controlled SURMOUNT-1 study examined the efficacy and safety of tirzepatide in adults with a BMI ≥ 30 kg/m², as well as in patients with a BMI ≥ 27 kg/m² who had one or more obesity-related complications, including hypertension, dyslipidemia, obstructive sleep apnea, or cardiovascular disease. Participants were also required to have had at least one failed nutritional intervention for obesity. The study was ineligible for individuals with diabetes, previous or planned bariatric surgery, treatment with another antiobesity drug within the last 90 days, or a weight gain of more than 5 kg in the last 90 days before the study.

Patients were assigned to four groups in a 1:1:1:1 ratio, including three that received tirzepatide at different doses: Group One – 5 mg, Group Two – 10 mg, and Group Three – 15 mg. Group Four received a placebo. Each participant received a subcutaneous injection once a week for 72 weeks.

The primary endpoints were the percentage change in body weight from baseline to week 72 and a reduction in body weight of 5% or more at week 72. Secondary endpoints included a reduction in body weight of $\geq 10\%$, $\geq 15\%$, and $\geq 20\%$ at week 72, a change in body weight from baseline, and a change in waist circumference, systolic blood pressure, fasting insulin and lipids, and physical function at week 72 from baseline.

In the SURMOUNT-1 study, a statistically significant ($p < 0.001$) greater mean weight loss was demonstrated for all tirzepatide doses compared to placebo, $\geq 15\%$ for the 5 mg dose, $\geq 19.5\%$ for the 10 mg dose, $\geq 20.9\%$ for the 15 mg dose, and $\geq 3.1\%$ for placebo. The percentage of participants who lost $\geq 5\%$ of their body weight at week 72 was 85%, 89%, and 91% for the 5 mg, 10 mg, and 15 mg tirzepatide doses, respectively, compared to 35% of participants in the placebo group ($p < 0.001$ for all comparisons with placebo). A weight loss of $\geq 5\%$ is considered the threshold for clinically significant improvement in metabolic health (25).

A reduction in body weight of $\geq 10\%$, $\geq 15\%$, and $\geq 20\%$ during treatment was achieved in more patients with all three doses of the drug compared to placebo ($p < 0.001$). Patients whose body weight decreased by $\geq 25\%$ from the initial value constituted 15%, 32%, and 36%, respectively, with doses of 5 mg, 10 mg, and 15 mg, while with placebo, this percentage was only 1.5% (Table 1).

In the case of patients treated with Tirzepatide, there was a significant improvement in waist circumference, systolic and diastolic blood pressure, fasting insulin level, physical fitness, lipid profile, and in patients with prediabetes at the beginning of the study, glycemia level normalized (21).

	Tirzepatide			Placebo (n = 643)
	5 mg (n = 630)	10 mg(n = 636)	15 mg (n = 630)	
Average weight loss [%]	- 15%	- 19,5%	- 20,9%	- 3,1%
Percentage of participants who achieved $\geq 5\%$ weight loss	85%	89%	91%	35%
Percentage of participants who achieved $\geq 25\%$ weight loss	15%	32%	36%	1,5%

Table 1. Comparison of Weight Loss Outcomes in Patients Receiving Tirzepatide and Placebo after 72 Weeks of Study

Tirzepatide in the treatment of obesity in people with diabetes – SURMOUNT 2

Another study from the SURMOUNT series confirmed the reports from the previous publication on the effectiveness of tirzepatide in reducing body weight, this time in a group of people struggling with diabetes. The study compared the following doses of the drug with placebo: 10 mg and 15 mg. The average body weight of patients decreased by 12.8% and 14.7%, respectively, at doses of 10 mg and 15 mg, compared with placebo -3.2%. The threshold for clinically significant improvement in metabolic health, i.e., a loss of $\geq 5\%$, was achieved by more participants, 79-83% of those treated with Tirzepatide compared to 32% of those treated with placebo ($p < 0.001$).

	Tirzepatide		Placebo (n = 315)
	10 mg (n = 312)	15 mg (n = 311)	
Average weight loss [%]	-12,8%	-14,7%	-3,2%
Percentage of participants who achieved $\geq 5\%$ weight loss	79,2%	82,8%	32,5%
Percentage of participants who achieved $\geq 10\%$ weight loss	60,5%	64,8%	9,5%

Percentage of participants who achieved $\geq 15\%$ weight loss	39,7%	48%	2,7%
Percentage of participants who achieved $\geq 20\%$ weight loss	21,5%	30,8%	1%
Percentage of participants who achieved $\geq 25\%$ weight loss	9%	15,5%	0,3%

Table 2. Percentage reduction in body weight in diabetic patients treated with Tirzepatide at a dose of 10 mg, 15 mg compared with placebo after 72 weeks of the study

Tirzepatide is effective in reducing patients' body weight by a greater percentage than the defined threshold of clinically significant improvement in metabolic health ($\geq 5\%$). This may contribute to additional clinical benefits by reducing the risk of cardiovascular disease, improving quality of life, or stabilizing diabetes. This study, in comparison with the previous one, also showed that weight loss in obese patients with diabetes is more difficult than in patients without diabetes (27).

Tirzepatide as an adjunct to intensive lifestyle intervention – SURMOUNT-3

The study aimed to determine whether introducing tirzepatide treatment in patients undergoing intensive lifestyle intervention would be associated with an additional, significant clinical effect in terms of weight loss and its maintenance later. Intensive lifestyle intervention was associated with the use of a reduced-calorie diet (1200-1500 kcal per day), physical activity (≥ 150 min per week), frequent behavioral counseling (≥ 14 sessions over 6 months) and resulted in a reduction of initial body weight by 5-8% with an accompanying improvement in well-being. Only people who effectively responded to the introduced 12-week intervention before randomization by losing $\geq 5\%$ of their initial weight were included in the study.

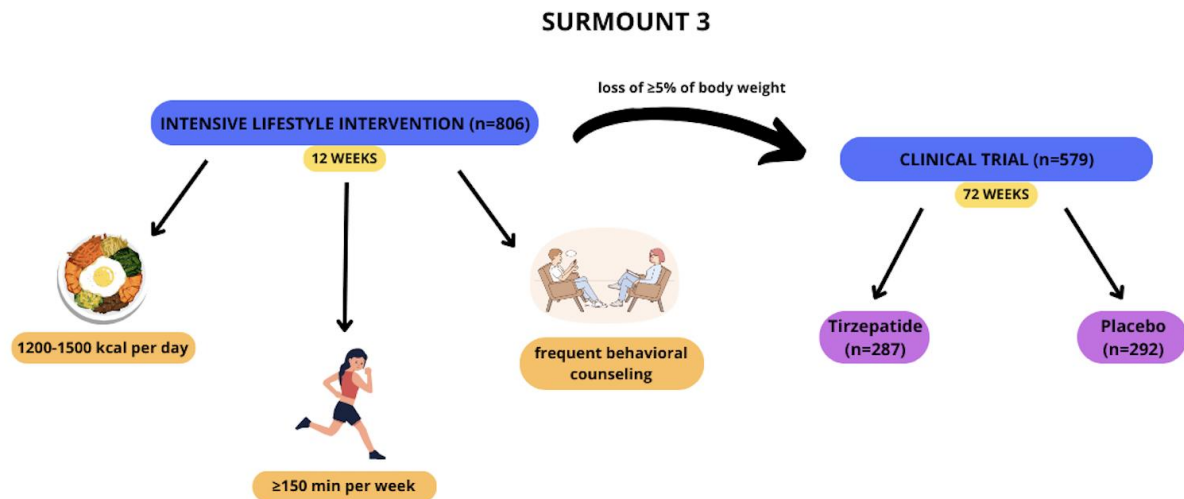


Figure 2. Flow chart of the SURMOUNT-3 study

During the experiment, a placebo and tirzepatide at the maximum tolerated dose (MTD) were used, with most patients receiving a dose of 15 mg. At 72 weeks of treatment, the mean weight loss was 18.4% and 2.5% for tirzepatide MTD and placebo, respectively. Including the 12-week pre-study intervention, the mean weight loss was -24.3% for tirzepatide compared with placebo, with a mean weight loss of 4.5%. The difference in BMI at 72 weeks was 7.7 kg/m² for tirzepatide and 1.2 kg/m² for placebo. Including the intervention period, the baseline and final BMI differences were 10.4 kg/m² and 1.4 kg/m², respectively. With MTD, 87.5% of subjects lost an additional $\geq 5\%$ of their body weight compared with 16.5% of placebo-treated subjects. In week 72 of the study, as many as 94% of patients in the tirzepatide group maintained $\geq 80\%$ of weight loss in the 12-week preparatory period. In comparison, this value was only 43.8% in the placebo group. The change in waist circumference with the drug after the randomization period was better than with placebo, respectively -14.6 cm and -0.2 cm. All the above-mentioned differences in the results were statistically significant ($p < 0.001$).

In addition to effectively maintaining the body weight already lost in the preparatory period, tirzepatide also influenced additional weight loss. The study showed a beneficial effect of the 12-week preparatory period, including intensive intervention in the patient's lifestyle before the introduction of pharmacological treatment, which was associated with a total higher mean percentage weight loss compared to the SURMOUNT-1 study, where such intervention was not used (28).

	Study period (72 weeks)		Preparation period (12 weeks) + study period (72 weeks)	
	Tirzepatide MTD	Placebo	Tirzepatide MTD	Placebo
Average weight loss [%]	-18,4%	-2,5%	-24,3%	-4,5%
Change in BMI value	-7,7 kg/m ²	-1,2 kg/m ²	- 10,4 kg/m ²	- 1,4 kg/m ²

Table 3. Comparison of mean percentage of body weight loss and BMI over the 72-week study period and the study period including the 12-week run-in period in the tirzepatide and placebo groups

Tirzepatide treatment to maintain weight loss – SURMOUNT – 4

The results of randomized studies have shown that patients tend to gain weight and regain previously lost weight after discontinuing pharmacological treatment of obesity (29,30). Other drugs in the pharmacotherapy of obesity, such as naltrexone/bupropion, phentermine/topiramate, or orlistat, helped patients maintain the weight loss they achieved. Therefore, the SURMOUNT-4 study decided to check whether tirzepatide can also be used in this area.

For this purpose, patients were qualified for treatment with tirzepatide at the maximum tolerated dose (MTD) for a run-in period of 36 weeks. Then randomization was performed, dividing them into two study groups for the next 52 weeks: the first receiving the drug and the second giving the placebo.

The key assumptions of the study were to check the percentage change in the participants' body weight from randomization to week 88 of the experiment and to assess their ability to maintain at least 80% of the lost body weight during the run-in period. In addition, the time it took for patients who lost $\geq 5\%$ of their initial weight during the run-in period to regain more than 95% of their initial weight was analyzed. Changes in absolute body weight and waist circumference were also assessed between weeks 36 and 88 of the study. Secondary measures included the percentage of participants who achieved weight loss thresholds of $\geq 5\%$, $\geq 10\%$, $\geq 15\%$, and $\geq 20\%$ from study entry (weeks 0-88) and the percentage who lost $\geq 25\%$ of their body weight during the same period.

During the run-in period, the mean percentage change in body weight among participants was 20.9%, with a reduction in BMI of 8.0 kg/m² and waist circumference of 17.8

cm. At the end of the study, at week 88, the mean percent change in body weight for patients receiving tirzepatide MTD was -5.5%, compared with +14% for placebo ($p<0.001$). The absolute change in body weight and waist circumference for the tirzepatide MTD group was -4.7 kg and -4.3 cm, respectively, and for the placebo group, +11.1 kg and +7.8 cm, respectively ($p<0.001$). Analysis of patient weight change over the weeks showed that continued tirzepatide treatment reduced the risk of regaining more than 95% of the initial body weight by approximately 98% compared with placebo in patients who had lost $\geq 5\%$ of their body weight during the run-in period ($p<0.001$). At week 88, a significantly more significant percentage of patients receiving tirzepatide maintained at least 80% of their body weight loss, compared with placebo, 89.5%, and 16.6%, respectively ($p<0.001$). A significantly greater proportion of participants who continued to receive tirzepatide compared with placebo achieved weight loss thresholds of $\geq 5\%$ (97.3% vs. 70.3%), $\geq 10\%$ (92.1% vs. 46.2%), $\geq 15\%$ (84.1% vs. 25.9%), $\geq 20\%$ (69.5% vs. 12.6%), $\geq 25\%$ (54.5% vs. 5.0%) from week 0 to week 88 (all $p<0.001$). Only 9.9% of patients assigned to placebo maintained significant weight loss at 1 year.

The results of the SURMOUNT-4 study underscore the value of tirzepatide in maintaining weight loss in obese and overweight patients, with continued benefits in terms of cardiovascular risk. This highlights the importance of obesity, a chronic disease requiring long-term treatment (31).

	Tirzepatide MTD (n=335)	Placebo (n=335)
Change in body weight (36-88 week) [%]	-5,5%	+14%
Change in body weight (36-88 week) [kg]	-4,7kg	+11,1kg
Change in waist circumference (36-88 week) [cm]	-4,3cm	+7,8cm
<i>Patients who maintained at least 80% of their lost body weight during the initial 36 weeks at week 88 [%]</i>	89,5%	16,6%

Table 4. Clinical outcome in patients receiving Tirzepatide compared with placebo during the SURMOUNT-4 study period

Tirzepatide vs. semaglutide

Both tirzepatide and semaglutide have agonist activity at GLP-1 receptors, while tirzepatide also affects GIP receptors. Therefore, the clinical effect of both drugs was compared in the studies to answer whether the additional effect of tirzepatide affects its greater efficacy in the treatment of obesity. It turned out that the use of tirzepatide at a dose of 5 mg compared with semaglutide at a dose of 0.5 mg for one year is associated with significantly increased weight loss in patients, $\geq 5\%$ (81.8% of patients for tirzepatide vs. 62.1% for semaglutide), $\geq 10\%$ (62.1% vs. 37.1%) and $\geq 15\%$ (42.3% vs. 18.1%). The percentage of body weight loss during treatment was significantly greater in patients receiving tirzepatide after 3, 6, and 12 months compared to patients receiving semaglutide [33]. Thomas Karagiannis et al., in another study, proved that tirzepatide in doses of 15 mg, 10 mg, and 5 mg showed greater efficacy in reducing body weight compared to semaglutide in doses of 2 mg, 1 mg, and 0.5 mg, respectively. The weight loss in the case of 15 mg of tirzepatide reached 9.57 kg and 5 mg to 5.27 kg. Meanwhile, patients using semaglutide lost from 4.97 kg in the dose of 2 mg to 2.52 kg in the dose of 0.5 mg [34]. In addition to the reduced efficacy of semaglutide compared to tirzepatide, the former is associated with increased treatment costs per 1% of body weight loss (32).

Systemic action of tirzepatide

Tirzepatide has been used in the treatment of type II diabetes for many years. It is an analog of incretin hormones released in the intestine in response to the consumption of nutrients. By binding to GLP-1 and GIP receptors on the β cells of the pancreas, it leads to increased insulin secretion, which translates into a decrease in postprandial blood glucose levels and effective control of carbohydrate metabolism (24). The SURPASS studies have shown that using tirzepatide leads to a decrease in HbA1c and fasting glycemia in patients with type II diabetes, with an initial increase in this parameter, more effectively than in the case of semaglutide. The HbA1c value decreased from the baseline by 1.8%, 1.89%, and 2.07%, respectively, at doses of 5 mg, 10 mg, and 15 mg of tirzepatide, compared to placebo, where the HbA1c level increased by 0.04%. In the majority of the study participants (87-92%) treated with tirzepatide, the HbA1c parameter decreased below 7%, and in some of them, it was even possible to achieve the level of normoglycemia, 31-50% and 27-46%, respectively, for the SURPASS-1 and SURPASS-2 studies, depending on the dose of the drug (33,34). In addition to the β cells of the pancreas, the expression of GIP receptors was also detected in adipose tissue, the central nervous system, the heart, the adrenal cortex, and the vascular endothelium. GLP-1 receptors are located in the α and β cells of the pancreas, the central nervous system, the heart, the lungs,

the gastrointestinal tract and the kidneys. For this reason, tirzepatide, an analog of both GLP-1 and GIP, may have a systemic effect (35).

The expression of GIP and GLP1 receptors in the brain in areas responsible for regulating appetite, satiety, desire to eat, and energy expenditure causes the use of this drug to reduce caloric intake and decrease energy expenditure (26). Tirzepatide, due to its beneficial effect on carbohydrate metabolism, also leads to a decrease in glucose concentration, thereby mitigating the neurodegenerative process and overcoming insulin resistance of neurons, which results from too high a level of glycemia (36).

Tirzepatide also has a beneficial effect on reducing cardiovascular risk in patients with obesity or overweight without diabetes (37). During its use, there is a significant reduction in biomarkers YKL-40, hsCRP, and ICAM associated with cardiovascular risk, thanks to which tirzepatide leads to a reduction in inflammation and stabilization of the endothelium, favorably affecting the reduction of the risk of major adverse cardiovascular events (38). The SURPASS studies demonstrated a significant effect of the drug on the reduction of both systolic blood pressure (SBP) and diastolic blood pressure (DBP). The dose of the drug influenced the level of blood pressure reduction: at a dose of 5 mg, SBP was reduced by 4.8 mmHg and DBP by 1.9 mmHg; at a dose of 10 mg, SBP by 5.3 mmHg and DBP by 2.5 mmHg, and at 15 mg, SBP by 6.5 mmHg and DBP by 2.8 mmHg. In the SURPASS-5 study, mean changes in SBP and DBP were -6.1 to -12.6 mmHg and -2.0 to -4.5 mmHg, respectively (34,39–41). Tirzepatide, being a dual analog for GLP-1 and GIP receptors, may influence the modification of insulin and glucagon concentrations secreted by the pancreas, delayed gastric emptying, which promotes a faster and longer feeling of satiety, as well as increased glucose and triglyceride uptake by adipose tissue.

Conversely, highly metabolically active tissues and organs such as the liver or skeletal muscles do not have receptors for incretin hormones. However, this drug may affect them indirectly by modifying insulin and glucagon concentrations. This leads to increased glucose uptake by the liver, increased glycogenesis, and decreased gluconeogenesis (26).

Tirzepatide side effects

Tirzepatide has a favorable safety profile. At least one side effect associated with the use of the drug is indicated in studies by approximately 70-90% of participants. However, these results are slightly higher than those of the placebo.

Juan Pablo Frias, in his study, draws attention to the increase in the number and intensity of side effects depending on the dose of the drug used, which the SURMOUNT studies, which

include a larger number of participants, deny. Adverse events appear mainly at the time of dose escalation and are mostly mild and transient.

The most common side effects were gastrointestinal disorders: nausea, diarrhea, and constipation. Other disorders included, among others, decreased appetite, headache, abdominal pain, alopecia, dizziness, belching, or inflammation at the site of drug administration. Serious side effects were reported by 5-7% of participants.

There was no significantly increased risk of acute pancreatitis, acute cholecystitis, cholelithiasis, or pancreatic cancer with tirzepatide compared with a placebo. Its safety profile was consistent with that of GLP-1 receptor agonists without significant episodes of hypoglycemia (7,21,22,27).

Conclusions

Tirzepatide is a breakthrough drug in the treatment of obesity, mainly due to its bidirectional agonist activity towards GIP and GLP-1 receptors. Numerous clinical studies, including the SURMOUNT and SURPASS series, have confirmed its efficacy in both weight loss and improvement of metabolic parameters in people with obesity, with and without type II diabetes. Tirzepatide stands out for its ability to achieve clinically significant weight loss while reducing the risk of cardiovascular events, improving the lipid profile, and regulating carbohydrate homeostasis.

The results of the studies indicate that therapy with tirzepatide shows greater efficacy compared to other GLP-1 receptor agonists, such as semaglutide, in terms of weight loss and maintenance. At the same time, these benefits go hand in hand with a favorable safety profile of the drug despite frequent but primarily mild and transient side effects.

It is worth emphasizing that the effectiveness of tirzepatide in the treatment of obesity can be further increased by integrating intensive interventions into the lifestyle of patients before starting pharmacotherapy. This indicates the need for a holistic approach to the treatment of obesity, in which pharmacotherapy is a key element, but at the same time complements other treatment methods.

In summary, tirzepatide as a modern drug is a valuable contribution to the management of obesity treatment, providing promising tools for achieving long-term results. At the same time, its use emphasizes the importance of a long-term approach to the treatment of a chronic disease such as obesity.

Disclosure

Author's Contribution

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References

1. Obesity and overweight [Internet]. [cited 2025 Apr 13]. Available from: <https://www.who.int/news-room/fact-sheets/detail/obesity-and-overweight>
2. Conway B, Rene A. Obesity as a disease: no lightweight matter. *Obes Rev.* 2004;5(3):145–51. doi:10.1111/j.1467-789X.2004.00144.x
3. The top 10 causes of death [Internet]. [cited 2025 Apr 14]. Available from: <https://www.who.int/news-room/fact-sheets/detail/the-top-10-causes-of-death>
4. de Leeuw AJM, Oude Luttikhuis MAM, Wellen AC, Müller C, Calkhoven CF. Obesity and its impact on COVID-19. *J Mol Med Berl Ger.* 2021;99(7):899–915. doi:10.1007/s00109-021-02072-4
5. Higuera-Hernández MF, Reyes-Cuapio E, Gutiérrez-Mendoza M, Rocha NB, Veras AB, Budde H, et al. Fighting obesity: Non-pharmacological interventions. *Clin Nutr ESPEN.* 2018 Jun 1;25:50–5. doi:10.1016/j.clnesp.2018.04.005
6. Ostrowska L., Bogdański P., Mamcarz A. *Otyłość i jej powikłania.* 1st ed. Warszawa: PZWL; 2021. 1054 p.

7. Wadden TA, Chao AM, Machineni S, Kushner R, Ard J, Srivastava G, et al. Tirzepatide after intensive lifestyle intervention in adults with overweight or obesity: the SURMOUNT-3 phase 3 trial. *Nat Med*. 2023 Nov;29(11):2909–18. doi:10.1038/s41591-023-02597-w
8. Obesity Canada [Internet]. [cited 2025 Apr 14]. Adult clinical practice guideline. Available from: <https://obesitycanada.ca/healthcare-professionals/adult-clinical-practice-guideline/>
9. PTLO - Polskie Towarzystwo Leczenia Otyłości [Internet]. [cited 2025 Apr 14]. Available from: https://ptlo.org.pl/aktualnosci/258-zalecenia_kliniczne_dotyczace_postepowania_u_chorych_na_otylosc_2024_stanowisko_polskiego_towarzystwa_leczenia_otylosci
10. Žižka O, Haluzík M, Jude EB. Pharmacological Treatment of Obesity in Older Adults. *Drugs Aging*. 2024;41(11):881–96. doi:10.1007/s40266-024-01150-9
11. Heck AM, Yanovski JA, Calis KA. Orlistat, a New Lipase Inhibitor for the Management of Obesity. *Pharmacotherapy*. 2000 Mar;20(3):270–9. doi:10.1592/phco.20.4.270.34882.
12. Sherman MM, Ungureanu S, Rey JA. Naltrexone/Bupropion ER (Contrave). *Pharm Ther*. 2016 Mar;41(3):164–72.
13. Billes SK, Greenway FL. Combination therapy with naltrexone and bupropion for obesity. *Expert Opin Pharmacother*. 2011 Aug;12(11):1813–26. doi:10.1517/14656566.2011.591382
14. Monami M, Dicembrini I, Marchionni N, Rotella CM, Mannucci E. Effects of Glucagon-Like Peptide-1 Receptor Agonists on Body Weight: A Meta-Analysis. *Exp Diabetes Res*. 2012;2012:672658. doi:10.1155/2012/672658
15. van Can J, Sloth B, Jensen CB, Flint A, Blaak EE, Saris WHM. Effects of the once-daily GLP-1 analog liraglutide on gastric emptying, glycemic parameters, appetite and energy metabolism in obese, non-diabetic adults. *Int J Obes* 2005. 2014 Jun;38(6):784–93. doi:10.1038/ijo.2013.162
16. Blundell J, Finlayson G, Axelsen M, Flint A, Gibbons C, Kvist T, et al. Effects of once-weekly semaglutide on appetite, energy intake, control of eating, food preference and body weight in subjects with obesity. *Diabetes Obes Metab*. 2017 Sep;19(9):1242–51. doi:10.1111/dom.12932

17. Wilding JPH, Batterham RL, Calanna S, Davies M, Gaal LFV, Lingvay I, et al. Once-Weekly Semaglutide in Adults with Overweight or Obesity. *N Engl J Med*. 2021 Mar 17;384(11):989–1002. doi:10.1056/NEJMoa2032183
18. Žižka O, Haluzík M, Jude EB. Pharmacological Treatment of Obesity in Older Adults. *Drugs Aging*. 2024;41(11):881–96. doi:10.1007/s40266-024-01150-9
19. Zhao F, Zhou Q, Cong Z, Hang K, Zou X, Zhang C, et al. Structural insights into multiplexed pharmacological actions of tirzepatide and peptide 20 at the GIP, GLP-1 or glucagon receptors. *Nat Commun*. 2022 Feb 25;13(1):1057. doi:10.1038/s41467-022-28683-0
20. Wang L. Designing a Dual GLP-1R/GIPR Agonist from Tirzepatide: Comparing Residues Between Tirzepatide, GLP-1, and GIP. *Drug Des Devel Ther*. 2022 May 25;16:1547–59. doi:10.2147/DDDT.S358989
21. Jastreboff AM, Aronne LJ, Ahmad NN, Wharton S, Connery L, Alves B, et al. Tirzepatide Once Weekly for the Treatment of Obesity. *N Engl J Med*. 2022 Jul 21;387(3):205–16. doi:10.1056/NEJMoa2206038
22. Frias JP, Nauck MA, Van J, Kutner ME, Cui X, Benson C, et al. Efficacy and safety of LY3298176, a novel dual GIP and GLP-1 receptor agonist, in patients with type 2 diabetes: a randomised, placebo-controlled and active comparator-controlled phase 2 trial. *The Lancet*. 2018 Nov;392(10160):2180–93. doi:10.1016/S0140-6736(18)32260-8
23. Pelle MC, Provenzano M, Zaffina I, Pujia R, Giofrè F, Lucà S, et al. Role of a Dual Glucose-Dependent Insulinotropic Peptide (GIP)/Glucagon-like Peptide-1 Receptor Agonist (Twincretin) in Glycemic Control: From Pathophysiology to Treatment. *Life*. 2021 Dec 25;12(1):29. doi:10.3390/life12010029
24. Forzano I, Varzideh F, Avvisato R, Jankauskas SS, Mone P, Santulli G. Tirzepatide: A Systematic Update. *Int J Mol Sci*. 2022 Nov 23;23(23):14631. doi:10.3390/ijms232314631
25. Coskun T, Sloop KW, Loghin C, Alsina-Fernandez J, Urva S, Bokvist KB, et al. LY3298176, a novel dual GIP and GLP-1 receptor agonist for the treatment of type 2 diabetes mellitus: From discovery to clinical proof of concept. *Mol Metab*. 2018 Dec;18:3–14. doi:10.1016/j.molmet.2018.09.009
26. Nauck MA, Quast DR, Wefers J, Pfeiffer AFH. The evolving story of incretins (GIP and GLP -1) in metabolic and cardiovascular disease: A pathophysiological update. *Diabetes Obes Metab*. 2021 Sep;23(S3):5–29. doi:10.1111/dom.14496

27. Garvey WT, Frias JP, Jastreboff AM, Le Roux CW, Sattar N, Aizenberg D, et al. Tirzepatide once weekly for the treatment of obesity in people with type 2 diabetes (SURMOUNT-2): a double-blind, randomised, multicentre, placebo-controlled, phase 3 trial. *The Lancet*. 2023 Aug;402(10402):613–26. doi:10.1016/S0140-6736(23)01200-X
28. Wadden TA, Chao AM, Machineni S, Kushner R, Ard J, Srivastava G, et al. Tirzepatide after intensive lifestyle intervention in adults with overweight or obesity: the SURMOUNT-3 phase 3 trial. *Nat Med*. 2023 Nov;29(11):2909–18. doi:10.1038/s41591-023-02597-w
29. Rubino D, Abrahamsson N, Davies M, Hesse D, Greenway FL, Jensen C, et al. Effect of Continued Weekly Subcutaneous Semaglutide vs Placebo on Weight Loss Maintenance in Adults With Overweight or Obesity: The STEP 4 Randomized Clinical Trial. *JAMA*. 2021 Apr 13;325(14):1414. doi:10.1001/jama.2021.3224
30. James WPT, Astrup A, Finer N, Hilsted J, Kopelman P, Rössner S, et al. Effect of sibutramine on weight maintenance after weight loss: a randomised trial. *The Lancet*. 2000 Dec;356(9248):2119–25. doi:10.1016/S0140-6736(00)03491-7
31. Aronne LJ, Sattar N, Horn DB, Bays HE, Wharton S, Lin WY, et al. Continued Treatment With Tirzepatide for Maintenance of Weight Reduction in Adults With Obesity: The SURMOUNT-4 Randomized Clinical Trial. *JAMA*. 2024 Jan 2;331(1):38. doi:10.1001/jama.2023.24945
32. Azuri J, Hammerman A, Aboalhasan E, Sluckis B, Arbel R. Tirzepatide versus semaglutide for weight loss in patients with type 2 diabetes mellitus: A value for money analysis. *Diabetes Obes Metab*. 2023 Apr;25(4):961–4. doi:10.1111/dom.14940
33. Rosenstock J, Wysham C, Frías JP, Kaneko S, Lee CJ, Fernández Landó L, et al. Efficacy and safety of a novel dual GIP and GLP-1 receptor agonist tirzepatide in patients with type 2 diabetes (SURPASS-1): a double-blind, randomised, phase 3 trial. *The Lancet*. 2021 Jul;398(10295):143–55. doi:10.1016/S0140-6736(21)01324-6
34. Frías JP, Davies MJ, Rosenstock J, Pérez Manghi FC, Fernández Landó L, Bergman BK, et al. Tirzepatide versus Semaglutide Once Weekly in Patients with Type 2 Diabetes. *N Engl J Med*. 2021 Aug 5;385(6):503–15. doi:10.1056/NEJMoa2107519
35. Michałowska J, Bogdański P. Rola hormonów i leków inkretynowych w terapii otyłości i wybranych zaburzeń metabolicznych. *Forum Zaburzeń Metab*. 2021;12(2):61–9.
36. Fontanella RA, Ghosh P, Pesapane A, Taktaz F, Puocci A, Franzese M, et al. Tirzepatide prevents neurodegeneration through multiple molecular pathways. *J Transl Med*. 2024 Jan 29;22(1):114. doi:10.1186/s12967-024-04927-z

37. Hankosky ER, Wang H, Neff LM, Kan H, Wang F, Ahmad NN, et al. Tirzepatide reduces the predicted risk of atherosclerotic cardiovascular disease and improves cardiometabolic risk factors in adults with obesity or overweight: SURMOUNT-1 post hoc analysis. *Diabetes Obes Metab*. 2024 Jan;26(1):319–28. doi:10.1111/dom.15318
38. Wilson JM, Lin Y, Luo MJ, Considine G, Cox AL, Bowsman LM, et al. The dual glucose-dependent insulintropic polypeptide and glucagon-like peptide-1 receptor agonist tirzepatide improves cardiovascular risk biomarkers in patients with type 2 diabetes: A post hoc analysis. *Diabetes Obes Metab*. 2022 Jan;24(1):148–53. doi:10.1111/dom.14553
39. Ludvik B, Giorgino F, Jódar E, Frias JP, Fernández Landó L, Brown K, et al. Once-weekly tirzepatide versus once-daily insulin degludec as add-on to metformin with or without SGLT2 inhibitors in patients with type 2 diabetes (SURPASS-3): a randomised, open-label, parallel-group, phase 3 trial. *The Lancet*. 2021 Aug;398(10300):583–98. doi:10.1016/S0140-6736(21)01443-4
40. Del Prato S, Kahn SE, Pavo I, Weerakkody GJ, Yang Z, Doupis J, et al. Tirzepatide versus insulin glargine in type 2 diabetes and increased cardiovascular risk (SURPASS-4): a randomised, open-label, parallel-group, multicentre, phase 3 trial. *The Lancet*. 2021 Nov;398(10313):1811–24. doi:10.1016/S0140-6736(21)02188-7
41. Dahl D, Onishi Y, Norwood P, Huh R, Bray R, Patel H, et al. Effect of Subcutaneous Tirzepatide vs Placebo Added to Titrated Insulin Glargine on Glycemic Control in Patients With Type 2 Diabetes. *JAMA*. 2022 Feb 8;327(6):534–45. doi:10.1001/jama.2022.0078