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Tirzepatide - A Revolution in Obesity Treatment?

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ABSTRACT

Introduction and aim of study: Obesity is a chronic disease associated with numerous health complications, and the number of patients is steadily increasing. Pharmacological methods for treating obesity are becoming increasingly popular. This paper aims to review publications concerning the efficacy and safety profile of tirzepatide, the only dual agonist of two human incretin receptors: GLP-1 and GIP, and the latest drug used for this indication.

Materials and Methods: Two databases, Pubmed and Medline, were searched using the terms "tirzepatide" and "obesity".

Results: Studies indicate significant and sustained weight reduction in obese patients during tirzepatide use as a complement to lifestyle changes. The greatest average weight reduction (20.9%) was observed in patients without concomitant type II diabetes using a 15 mg dose of tirzepatide. Following an initial intensive lifestyle change, obese patients can expect further clinically significant weight loss with the addition of tirzepatide to their treatment. However, discontinuing tirzepatide after initial weight reduction is associated with significant weight regain. Furthermore, studies show that tirzepatide use results in the greatest weight reduction among available market preparations. The drug also has other health benefits, but its use is associated with numerous adverse effects, including severe ones.

Conclusions: Pharmacotherapy can facilitate the process of lifestyle modification but remains a supportive treatment. During obesity treatment with tirzepatide, it is important to consider the actual health benefits and its effectiveness in weight reduction, keeping in mind its safety profile and potential risks.

KEY WORDS: tirzepatide, obesity, glucagon-like peptide 1, type 2 diabetes, weight loss

INTRODUCTION

According to the definition by the World Health Organization (WHO), overweight and obesity are abnormal or excessive fat accumulation in the human body that presents a risk to health [1]. Obesity is recognized as a disease on the International Classification of Diseases and Related Health Problems list, which needs to be diagnosed and treated. According to data published by WHO in 2022, 1 in 8 people worldwide suffered from obesity. Since 1990, adult obesity has more than doubled globally, and obesity among adolescents has quadrupled. In 2022, 2.5 billion adults (aged 18 and older) were overweight, with 890 million of them suffering from obesity [1]. For many years, WHO has emphasized the urgent need to address the global obesity crisis. Risk factors for obesity include excessive consumption of high-energy foods, especially highly processed ones, insufficient physical activity or lack thereof due to societal advancements reducing the need for movement, and biological, psychogenic,

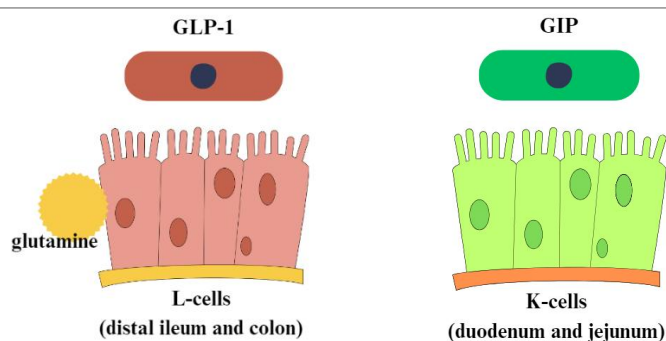
and genetic factors [2]. Obesity has significant health consequences. Primarily, it increases the risk of developing type 2 diabetes, hypertension, hyperlipidemia, and elevated metabolic and cardiovascular risk. Additionally, obesity is associated with obstructive sleep apnea, hormonal disorders, infertility, osteoarthritis, and gallstone disease [3]. Obese patients also have an increased risk of cancer [4]. Studies have shown that both overweight and obesity are linked to an increased risk of death [5,6]. Therefore, obesity should be recognized by doctors as a chronic disease caused by an unhealthy accumulation of body fat, increasing the risk of premature complications and mortality, and should be properly diagnosed and treated.

When choosing a method for treating obesity, one should consider the severity of the disease, existing complications, the patient's overall health, treatment goals, the patient's commitment to the treatment process, and the therapeutic methods they accept. Non-pharmacological methods of treating obesity include comprehensive lifestyle modification, primarily proper nutrition and physical activity, as well as therapeutic education and psychological interventions. Pharmacological treatment aims to enhance the effectiveness of non-pharmacological methods, allowing for greater weight reduction and thereby reducing the risk of obesity-related complications. Pharmacological treatment does not exempt patients from lifestyle modifications. When selecting pharmacological treatment for a patient, the safety profile of the substance should be considered, with particular attention to side effects that may cause patients to discontinue treatment, as well as contraindications to using the substance. Surgical methods for treating obesity are also available, which are among the most effective but also the most burdensome for the patient.

Among the drugs approved by the U.S. Food and Drug Administration (FDA) for the treatment of obesity are pharmacological preparations such as the naltrexone/bupropion combination, orlistat, the phentermine/topiramate combination, and GLP-1 receptor agonists (liraglutide, semaglutide). Additionally, in May 2022, the FDA approved the newest drug, Mounjaro® (tirzepatide), produced by Eli Lilly. This paper aims to review publications on the use of tirzepatide in obese patients. Two databases, Pubmed and Medline, were searched using the terms "tirzepatide" and "obesity," yielding 275 results. Publications on the mechanism of action, efficacy in treating obesity, safety profile, benefits, and risks of tirzepatide were analyzed, as well as comparisons of tirzepatide's effectiveness with other market-available preparations.

MECHANISM OF ACTION OF TIRZEPATIDE

Tirzepatide is a synthetically produced linear peptide molecule containing 39 amino acids. It is the only dual agonist of the receptors for two main human incretins: glucagon-like peptide-1 (GLP-1) and glucose-dependent insulintropic peptide (GIP) [7]. Incretin hormones are produced in specialized enteroendocrine cells and enhance meal-stimulated insulin release after food intake [8]. GLP-1 receptors are expressed throughout the central nervous system, from the olfactory bulb to the spinal cord, in pancreatic islets, the heart, blood vessels, and kidneys [9]. The highest levels of GIP receptors are found in pancreatic islets and the intestines, with confirmed presence also in adipose tissue, the heart, the pituitary gland, the adrenal cortex, and the endothelium of blood vessels [10]. GLP-1 and GIP are peptide hormones secreted in response to nutrient intake and play a crucial role in postprandial metabolism by enhancing glucose-stimulated insulin release from the pancreas [11]. Additionally, dipeptidyl peptidase-4 (DPP-4) inhibitors work by preventing the rapid degradation of endogenous GLP-1 and GIP via DPP-4, enhancing their effectiveness. GLP-1 receptor agonists resist DPP-4 degradation [12]. GLP-1 receptor agonists also help reduce glucagon secretion from pancreatic alpha cells, shorten gastric emptying time, and reduce appetite and nutrient intake, leading to weight loss [11]. The dual action of tirzepatide is associated with promising treatment effects for both type 2 diabetes and obesity. This substance significantly lowers blood glucose levels and improves insulin sensitivity [13]. Tirzepatide's half-life is about 5 days, making it suitable for once-weekly administration [14]. The mechanism of action of tirzepatide is illustrated in Figure 1.










Brain 	↓ Appetite ↓ Food intake ↑ Nausea	↓ Appetite ↓ Food intake ↓ Nausea
Pancreas 	↑ Insulin secretion ↓ Glucagon	↑ Insulin secretion ↑ Glucagon
Stomach 	↓ Gastric emptying	↓ Gastric and secretion
Adipose tissue 	↑ Lipolysis	↑ Lipogenesis ↑ Lipid buffering capacity
Bone 		↓ Bone resorption
Heart 	↑ Cardioprotection	
Kidney 	↑ Natriuresis ↑ Diuresis	

Figure 1. Actions of glucose-dependent insulinotropic polypeptide (GIP) and glucagon-like peptide-1 (GLP-1). [15]

EFFICACY OF TIRZEPATIDE

The efficacy of tirzepatide has been evaluated in studies. The SURMOUNT clinical trial aims to assess whether tirzepatide, administered subcutaneously once a week, is effective in patients with or without diabetes as an adjunct to lifestyle changes for chronic weight management. The SURMOUNT program includes the following studies: efficacy and safety studies of fixed-dose regimens (SURMOUNT-1 and -2) and clinically significant studies on

the maximum tolerated dose (SURMOUNT-3 and -4). The efficacy of tirzepatide was assessed at doses of 5, 10, and 15 mg once a week [16].

In the SURMOUNT-1 study, 2,539 participants with obesity and obesity-related comorbidities but without diabetes were enrolled. Participants were randomly assigned to groups receiving either a specific dose of tirzepatide or a placebo. All participants underwent a 72-week treatment period, which included a dose escalation phase lasting up to 20 weeks and allowed for a 52-week observation period of the highest dose (15 mg). At the start of the study, the average body weight was 104.8 kg, the average BMI was 38.0, and 94.5% of participants had a BMI of 30 or more [14].

Weight reduction was dose-dependent. The greatest average percentage weight loss (20.9%) was achieved in the group of patients receiving 15 mg of tirzepatide once a week. The average percentage changes in body weight at week 72, depending on the dose of tirzepatide or placebo, are shown in Figure 2.

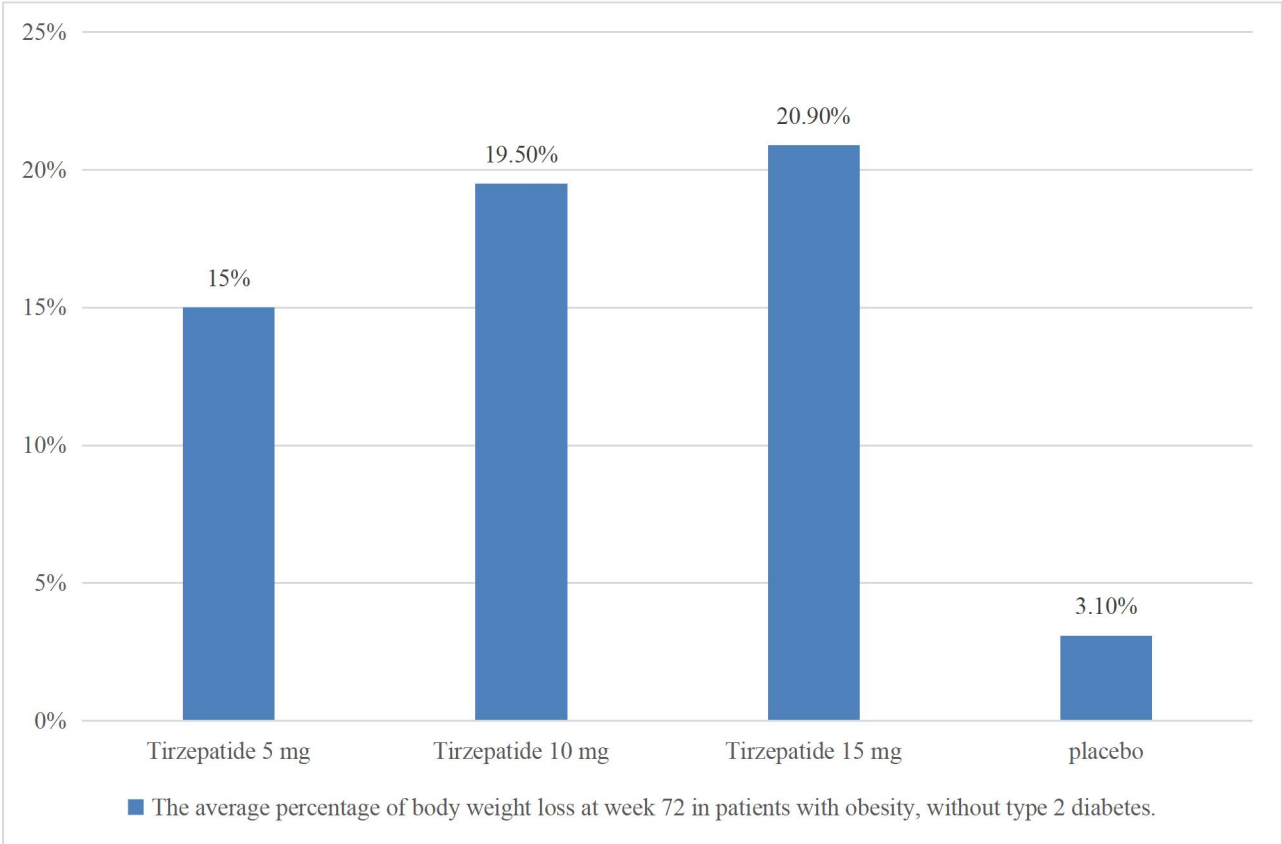


Figure 2. The average percentage of body weight loss at week 72 in patients with obesity, without type 2 diabetes.

In 50% and 57% of participants in the 10 mg and 15 mg groups, respectively, a reduction in body weight of 20% or more was observed, compared to 3% in the placebo group. The study demonstrates that tirzepatide at doses of 5 mg, 10 mg, or 15 mg once a week provided significant and sustained weight reduction in patients with obesity and without type 2 diabetes [14].

The SURMOUNT-2 study enrolled 938 patients with overweight or obesity, additionally suffering from type 2 diabetes with a BMI over 27 kg/m² and HbA1c levels from 7% to 10%, who had been treated at a stable level for over 3 months, excluding those on any injectable therapy. The baseline average body weight was 100.7 kg, BMI 36.1 kg/m², and HbA1c 8.02%. Participants were randomly assigned to groups receiving a specific dose of tirzepatide or a placebo [17]. The greatest average percentage weight loss (14.7%) was achieved in the group of patients with type 2 diabetes taking 15 mg of tirzepatide once a week. The average percentage changes in body weight at week 72, depending on the dose of tirzepatide or placebo, are shown in Figure 3.

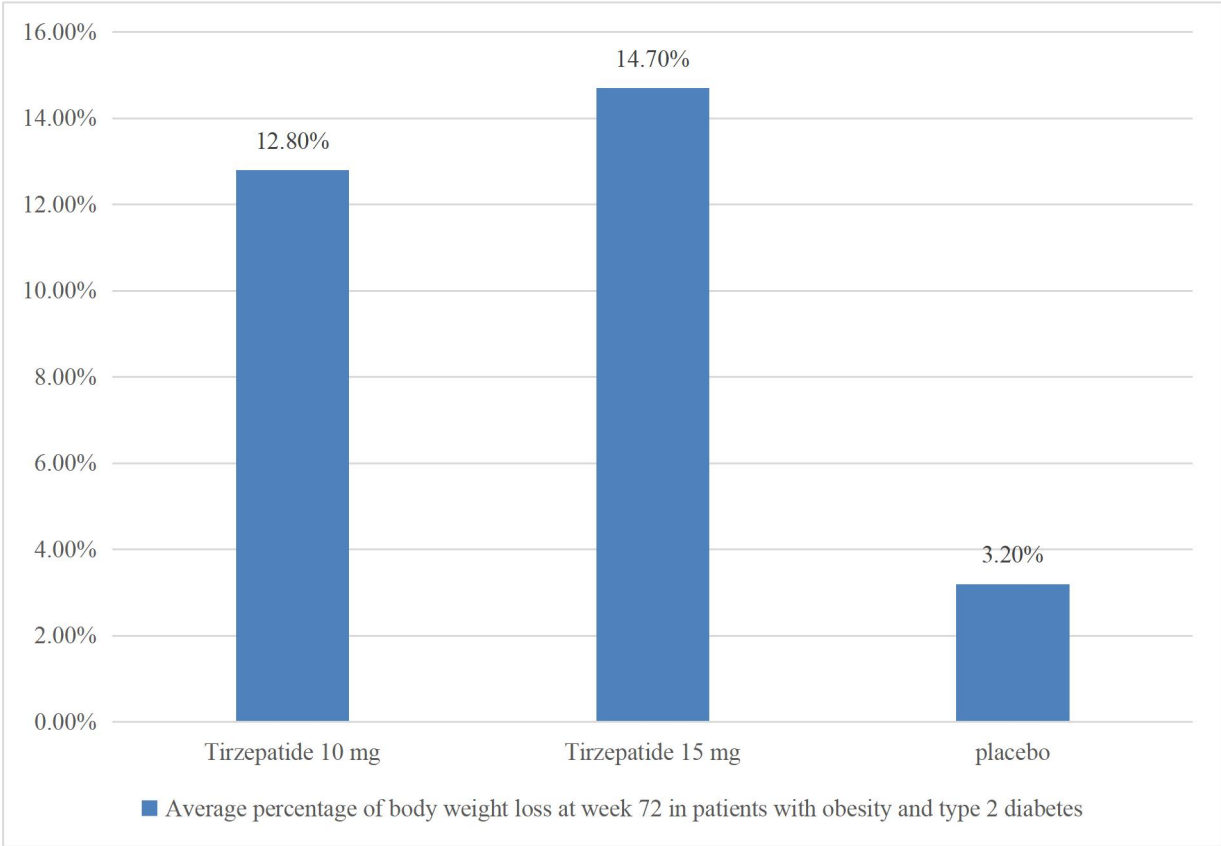


Figure 3. Average percentage of body weight loss at week 72 in patients with obesity and type 2 diabetes

Research shows that tirzepatide at doses of 10 mg or 15 mg once a week provided significant and sustained weight reduction. However, it can be observed that, compared to individuals without type 2 diabetes, those with type 2 diabetes (T2D) and obesity respond less effectively to treatments aimed at supporting weight reduction.

The effectiveness of tirzepatide in reducing body weight in patients with obesity and type 2 diabetes is also demonstrated by the SURPASS program. This study, conducted in six countries, included over 300 patients. Patients were randomly assigned to groups receiving specified doses of tirzepatide (5 mg, 10 mg, 15 mg) or a placebo. In a 52-week observation of patients, 65% to 89% of individuals with T2D receiving 10 or 15 mg of tirzepatide achieved a $\geq 5\%$ weight loss, 40% to 69% achieved a $\geq 10\%$ weight loss, and 17% to 45% achieved a $\geq 15\%$ weight loss [18].

MAINTAINING THE EFFECT THROUGH CONTINUED THERAPY

A key goal in treating obesity seems to be achieving significant weight loss and maintaining it long-term. The SURMOUNT-3 study evaluates whether treatment with tirzepatide administered once a week results in clinically significant additional weight loss in adults with overweight or obesity following an initial effective weight loss of at least 5% of body weight with a 12-week intensive lifestyle intervention. By week 72, participants receiving 10 or 15 mg of tirzepatide lost an additional 18.4% of body weight compared to 2.5% with placebo. A total of 87.5% of participants treated with tirzepatide lost an additional 5% or more of their body weight compared to 16.5% of participants receiving placebo. This proves that overweight or obese individuals who lost about 5–10% of body weight through intensive lifestyle changes can expect further clinically significant weight loss with the addition of tirzepatide to their treatment [16,19].

The goal of the SURMOUNT-4 study was to examine the impact of continuing treatment with the maximum tolerated dose (i.e., 10 or 15 mg) of tirzepatide administered once a week, compared to placebo, on maintaining weight reduction. After 36 weeks of using the maximum tolerated dose of tirzepatide (10 or 15 mg) in adults (n = 670) with obesity or overweight (without diabetes), an average weight reduction of 20.9% was observed. From randomization

(at week 36), individuals who switched to placebo gained 14% of body weight, while those continuing tirzepatide experienced an additional 5.5% weight loss during the 52-week double-blind period. In participants with obesity/overweight, discontinuation of tirzepatide led to significant regain of lost weight, while continuation of treatment maintained and increased the initial weight reduction. Additionally, initiating insulin degludec in the SURPASS-3 study resulted in a weight gain of 2.3 kg after 52 weeks of treatment, whereas tirzepatide at doses of 5–15 mg led to a weight reduction of 7.5–12.9 kg [16,20,21]. In individuals with advanced T2D, starting insulin glargine in combination with other hypoglycemic agents (SURPASS-4) led to a weight gain of 1.9 kg after 52 weeks compared to a weight loss (7.1–11.7 kg) with tirzepatide [20,23].

COMPARISON WITH OTHER MEDICATIONS

The introduction of tirzepatide is associated with comparisons of its effectiveness with other available medications on the market. Cumulative data on weight reduction during the use of various substances are presented in Figure 3. [24,25,26]

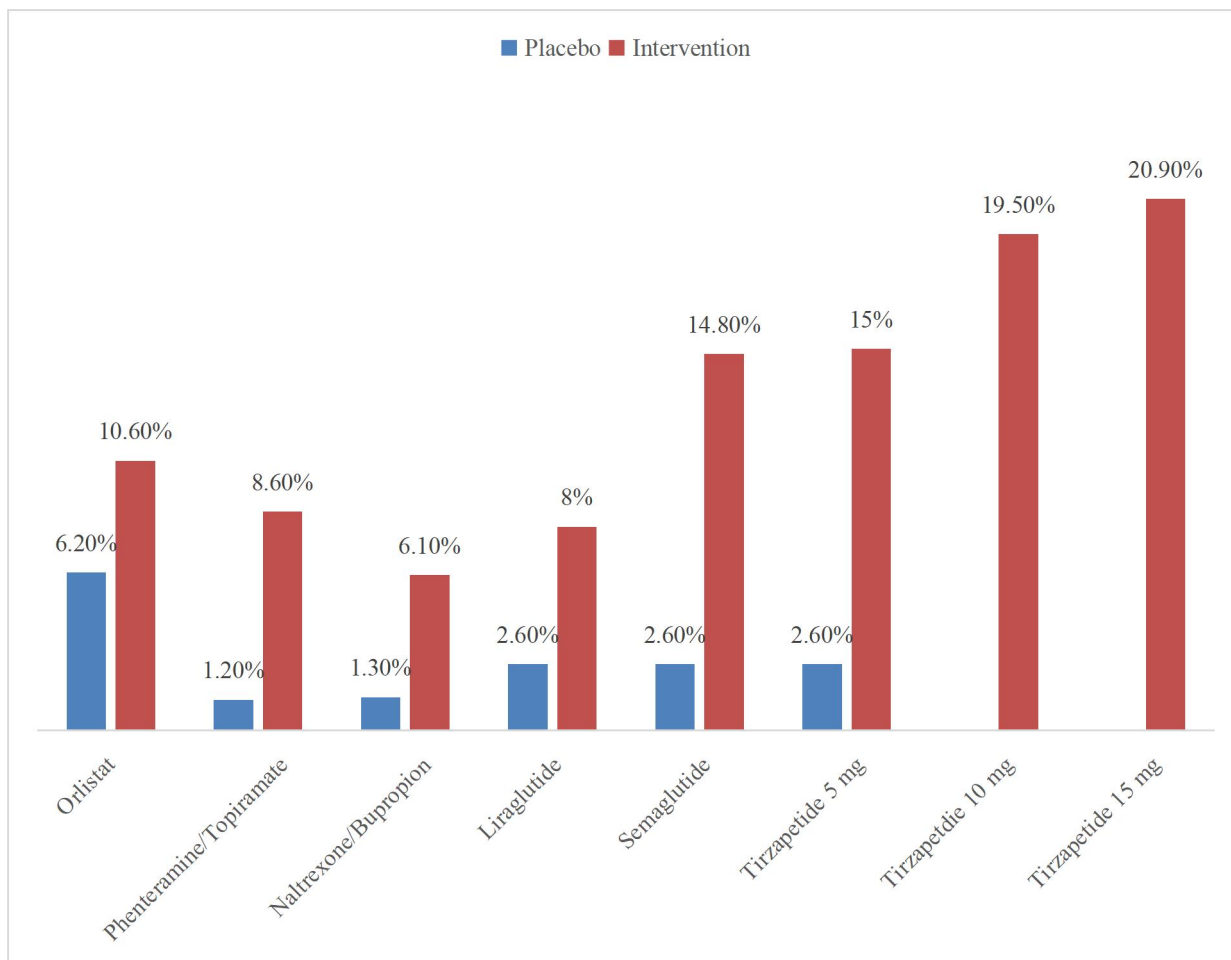


Figure 4. Comparison of percentage weight loss with available preparations in obesity treatment.

The presented data demonstrate that tirzapatide at doses of 5 mg, 10 mg, and 15 mg significantly reduces body weight in patients with obesity. It is more effective in weight reduction than other available market preparations used in the treatment of obesity. It is primarily compared with semaglutide, whose use also yields satisfactory weight loss results in patients with obesity. In direct comparison of the effectiveness of semaglutide and tirzapatide, a greater reduction in percentage weight change was observed with tirzapatide at doses of 10 and 15 mg compared to semaglutide at 2.4 mg (mean difference for tirzapatide at 10 mg: -4.67%, mean difference for tirzapatide at 15 mg: -5.92%). Similarly, more participants achieved a 5% or greater weight loss with tirzapatide than with semaglutide [27].

The effectiveness of tirzapatide can also be compared with available surgical methods for treating obesity. Endoscopic procedures (i.e., intragastric ballooning and endoscopic sleeve

gastroplasty) enable a weight loss of 10–13% after 6 months. Weight loss resulting from metabolic and bariatric surgeries (i.e., laparoscopic sleeve gastrectomy and Roux-en-Y gastric bypass) ranges from 25% to 30% after 12 months. Thus, tirzepatide's effects are comparable to bariatric surgeries, which, despite their effectiveness, are very burdensome for the patient and associated with numerous complications [28].

OTHER HEALTH BENEFITS

Effects on the cardiovascular system.

Several positive effects of GLP-1 have been described in pathways involved in vascular atherogenesis, endothelial function [29, 30] and ventricular contractility [31]. Tirzepatide exerts its beneficial effects on the cardiovascular system by exerting multidirectional effects - including taking excessive body weight, lipid profile, elevated blood pressure, or inflammation as its points of capture. The SURMOUNT-1 trial showed improvements in cardiometabolic risk factors such as waist circumference, lipidogram and blood pressure, as well as inflammatory markers and physical fitness with the use of tirzepatide compared with placebo. [15]

Obesity is one of the major risk factors for the development of cardiovascular disease and one of the primary points of action of tirzepatide. Thus, the weight reduction observed in clinical trials with tirzepatide may also mitigate cardiovascular risk factors and cardiovascular incidents.

The SURPASS-4 and SURPASS-5 clinical trials showed a beneficial effect of tirzepatide on the lipid profile expressed by reducing total cholesterol (TC), low-density lipoprotein (LDL-C) and triglycerides (TG), and significantly increased concentrations high-density lipoprotein cholesterol (HDL-C).[32] In the SURPASS-4 trial, 15 mg of tirzepatide reduced TC, LDL-C, and TG concentrations by 5.6%, 7.9%, and 22.5%, respectively, and increased HDL-C concentrations by 10.8%. [22] The SURPASS-5 trial, in which tirzepatide was added to basal insulin treatment in patients with T2DM, also showed a favorable effect of thromboplatide on lipid profile parameters compared to placebo. TC levels decreased by 12.9%, LDL-C levels decreased by 15.5% , TG levels decreased by 24.9%, and HDL-C levels decreased by 0.9% in patients who took tirzepatide.[33] In both studies, a dose-dependent effect of tirzepatide on the lipid profile was observed - higher doses resulted in greater improvement, which was maintained throughout the whole study.

Tirzepatide has been shown in clinical trials to significantly lower both systolic and diastolic blood pressure. [32] A Bayesian network meta-analysis showed reductions in systolic and diastolic blood pressure of 4.8 and 1.7 mmHg, respectively, regardless of whether tirzepatide was used as monotherapy or as adjunctive therapy. [34]

Tirzepatide treatment further reduces the levels of inflammatory markers such as intercellular adhesion molecule 1 (ICAM-1) and YKL-40, which are important risk factors for cardiovascular disease. [32] The mechanism of this phenomenon is not yet fully understood, but nevertheless the phenomenon itself is not in doubt.

Effects on the pancreas.

In randomized clinical trials, the effects of tirzepatide have been shown to improve biomarkers of pancreatic β -cell function, reduce fasting glucagon levels, and promote a reduction in insulin resistance, as reflected by dose-dependent increases in HOMA2-B indices and reductions in proinsulin levels, proinsulin/peptide C ratio, and proinsulin/insulin ratio. [35] Excess proinsulin in the β -cell is indicative of abnormal folding of the insulin chain, so, by analogy, decreases in proinsulin levels, proinsulin/peptide C ratio and proinsulin/insulin in response to tirzepatide treatment together suggest improvement of insulin protein processing and may reflect reduced pancreatic β -cell stress. In addition, the levels of IGF-binding proteins - IGFBP-1 and IGFBP-2, members of the insulin and IGF signaling pathways and markers associated with insulin sensitivity, have been shown to increase as a result of tirzepatide.[35] The improvement in insulin sensitivity is largely supported by tirzepatide - induced weight loss. By reducing insulin resistance, tirzepatide presumably reduced the metabolic demand for insulin secretion from pancreatic β -cells, and as a result, also reduced ongoing β -cell stress. The improvement in the area of insulin resistance after the 10-mg and 15-mg doses of tirzepatide was only partially attributable to weight loss. This suggests additional mechanisms contributing to the improvement in insulin sensitivity, evident in, among other things, a significant reduction in HbA1c levels. By both improving pancreatic beta-cell function and reducing insulin resistance through dual activation of GLP-1 and GIP receptors, tirzepatide may not only provide glucose control and weight loss, but also reduce disease severity to improve metabolic health.

Effects on the liver.

Obesity is associated not only with atherogenic dyslipidemia, hypertension and cardiovascular disease, but also with metabolic complications related to insulin resistance, such as non-alcoholic fatty liver disease (NAFLD) and non-alcoholic steatohepatitis (NASH).

The term NAFLD describes a whole spectrum of conditions with a common yet defining feature of about 5% fat accumulation in the liver, and which progresses over time to NASH. The inflammation can progress with or without coexisting fibrosis, cirrhosis and/or hepatocellular carcinoma. There is growing evidence that NAFLD is a multiorgan disease that is a strong independent predictor of cardiovascular events, chronic kidney disease and certain types of cancer, including extrahepatic cancers. The magnitude of this risk is proportional to the severity of NAFLD (primarily the stage of liver fibrosis). [39]

The results of a study by Hartmann et al. [36, 37] suggest a beneficial effect of tirzepatide therapy on NASH. In this study, T2DM patients receiving tirzepatide at doses of 10 mg and 15 mg showed a significant decrease in NASH-associated biomarkers and an increase in adiponectin (a polypeptide hormone that stimulates, among other things, beneficial adipose tissue metabolism, increases insulin sensitivity of liver cells, in addition to exhibiting anti-inflammatory and anti-atherosclerotic effects). Analyses showed a significant decrease in the activity of aspartate aminotransferase (AST), serum alanine aminotransferase (ALT) and M30 fragment compared to baseline values. In addition, there was a decrease in fragments of keratin-18 (K-18), a marker of hepatocyte apoptosis, and procollagen III (pro-C3), a marker of fibrosis in T2DM patients. The results of the cited study require further evaluation for confirmation, but nevertheless raise considerable hopes and show potential future indications for the use of tirzepatide in non-alcoholic steatohepatitis.

Effects on the kidneys.

To date, no specific study has yet been conducted that examines the effects of tirzepatide in patients with chronic kidney disease (CKD). Renal-specific endpoints have tended to be secondary outcomes - some pre-specified chronic kidney disease outcomes have been determined in studies of overweight, obesity and type 2 diabetes. These studies included patients with chronic kidney disease, defined as eGFR <60 ml/min/1.73 m² or urine albumin/creatinine ratio (UACR) ≥ 30 mg/g, as well as patients who did not meet the above criteria for a diagnosis of chronic kidney disease.[36,38] An analysis of the SURPASS-4 randomized clinical trial showed that tirzepatide may have a nephroprotective effect compared to insulin glargine, as demonstrated by a reduction in albuminuria and total estimated glomerular filtration rate (eGFR) and the risk of a pre-specified composite renal endpoint (eGFR decline $\geq 40\%$, death, renal failure or newly diagnosed macroalbuminuria) in patients with T2DM and high cardiovascular risk compared with insulin glargine. [38] Although the potential protective effect of tirzepatide for the prevention and treatment of

CKD needs to be confirmed with many clinical trials, the results obtained so far seem promising .

SAFETY PROFILE AND SIDE EFFECTS

The most common side effects associated with tirzepatide are related to gastrointestinal symptoms, i.e. diarrhea, nausea and vomiting [15,39]. Nausea was the most common of these, gradually decreasing over the first 6 months of treatment. Comparisons of the profile of adverse effects occurring during the use of tirzepatide, which is a dual agonist of GLP-1 and GIP receptors, with the profile of adverse effects induced by semaglutide and dulaglutide, GLP-1 analogs, showed that they were similar. [15]

In addition, there are other, albeit rarer, side effects associated with taking tirzepatide. In some cases, patients may experience changes in appetite, bloating, or abdominal pain. There are also reports of possible allergic reactions, such as skin rash, itching, or facial swelling. In addition, some patients have reported fatigue, headache or dizziness as a side effect during therapy with this drug

In the SURPASS program, tirzepatide at a dose of 5 to 15 mg was largely well tolerated. Serious adverse events were reported in 1% to 8% of participants with early or established diabetes (SURPASS 1-3, SURPASS J-mono and SURPASS J-combo) and in 6% to 17% of those with advanced diabetes (SURPASS 4-5). Similar values were reported in groups of patients taking both the active substance and placebo. Most side effects were mild to moderate in severity, dose-dependent. They were occurring during dose escalation and decreasing thereafter. In addition, very rare cases of pancreatitis, cholelithiasis and injection site reactions were reported. [15]

Overall, adverse effects were more common in patients with G3+ chronic kidney disease, in both the tirzepatide and insulin glargine groups. Treatment was discontinued due to adverse effects in 4.3%, 7.1%, 6.2% and 2.6% of patients receiving 5 mg, 10 mg and 15 mg/week of tirzepatide or placebo, respectively. [14]

On the basis of preclinical observations in rats, the FDA issued a warning against the use of tirzepatide in patients with a personal or family history of medullary thyroid cancer and in patients at particularly high risk for medullary thyroid cancer, such as those with multiple endocrine neoplasia type 2 (MEN2) syndrome.[40]

It should also be emphasized that it is important to monitor patients during treatment with tirzepatide due to potential side effects. Regular medical check-ups can help detect possible health problems early and adjust the dose of the drug accordingly. It is also worth remembering the need to inform the doctor of any observed side effects to ensure safe and effective therapy.

CONCLUSIONS

The prevalence of obesity worldwide is significantly increasing, necessitating improved prevention and proper treatment of obesity. It should be emphasized that obesity is a chronic disease that constitutes a significant risk factor for the development of chronic diseases. Each patient requires an individualized treatment plan, considering the disease's severity, existing complications, overall health status, treatment goals, patient engagement in the treatment process, and the therapeutic methods accepted by the patient. The decision to undertake pharmacological treatment should be based on the presence of specific indications in the patient and after excluding contraindications. Pharmacological treatment should start with small doses, gradually increasing according to the scheme. During pharmacological treatment of obesity with tirzepatide, attention should be paid to the actual health benefits and its effectiveness in reducing body weight, considering its safety profile and potential risks. It is crucial to monitor the patient for adverse effects, paying special attention to the necessity of discontinuing the drug in case of ineffectiveness or severe intolerance symptoms.

The primary barrier to long-term use of pharmacotherapy consists of numerous adverse effects, high treatment costs, and limited availability of the latest medications. Additionally, it should be remembered that pharmacological treatment should be used as an adjunct to lifestyle changes and cannot be treated as the basis of treatment, especially considering that significant weight gain occurs after discontinuation of tirzepatide following initial weight loss. Pharmacotherapy can facilitate the process of lifestyle modification but remains supportive treatment, with patient engagement in the treatment process being the most crucial element for the effective treatment of obesity.

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