WIŚNIEWSKA, Katarzyna, GMITRZUK, Julita, MALINKA, Zuzanna, JACHYMEK, Anna, OPATOWSKA, Martyna, JAKUBIEC, Joanna, KUCHARSKI, Tomasz and PIOTROWSKA, Marta. Thirzepatide. A novelty in the treatment of obesity - literature review. Quality in Sport. 2024;15:52005. eISSN 2450-3118.
https://dx.doi.org/10.12775/QS.2024.15.52005
https://apcz.umk.pl/QS/article/view/52005

The journal has had 20 points in Ministry of Higher Education and Science of Poland parametric evaluation. Annex to the announcement of the Minister of Higher Education and Science of 05.01.2024. No. 32553.
Has a Journal's Unique Identifier: 201398. Scientific disciplines assigned: Economics and finance (Field of social sciences); Management and Quality Sciences (Field of social sciences).
Punkty Ministerialne z 2019 - aktualny rok 20 punktów. Załącznik do komunikatu Ministra Szkolnictwa Wyższego i Nauki z dnia 05.01.2024 r. Lp. 32553. Posiada Unikatowy Identyfikator Czasopisma: 201398.
Przypisane dyscypliny naukowe: Ekonomia i finanse (Dziedzina nauk społecznych); Nauki o zarządzaniu i jakości (Dziedzina nauk społecznych).

The authors declare that there is no conflict of interests regarding the publication of this paper.
Received: 01.06.2024. Revised: 20.06.2024. Accepted: 01.07.2024. Published: 05.07.2024.

Thirzepatide. A novelty in the treatment of obesity - literature review

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Abstract

Introduction

Obesity results from a complex interplay of environmental, genetic, and behavioral factors, making it challenging to treat. Globally, the prevalence of obesity has tripled over the past fifty years. The WHO reports that 60% of Europeans are overweight or obese mainly due to

sedentary lifestyles and poor dietary habits. Effective treatment of obesity requires a combination of lifestyle modifications, including diet and physical activity, and pharmacological interventions. In 2023 a new drug - tirzepatide was registered. The purpose of this study is to discuss the mechanisms of action of tirzepatide, its safety and its effectiveness in body mass reduction, as well as its comparison with other available drug.

Aim of the Study

The purpose of this study is to provide a comprehensive review of current treatments for obesity, with particular emphasis on the role of recent development in pharmacotherapy - the introduction of tirzeptide. The study aims to discuss the mechanisms of action of tirzepatide, its safety and its effectiveness in body mass reduction, as well as its comparison with semaglutide.

Materials and methods

A review of the literature collected in the PubMed database was performed to gather information found under the keywords: tirzepatide, obesity, obesity treatment

Conclusions

Studies have shown that tirzepatide is more effective in weight loss than placebo and semaglutide, and reduces cardiovascular and metabolic risks. Furthermore, it does not increase the risk of serious adverse events or mortality compared to placebo, and its main side effects manifested by gastrointestinal symptoms are described as mild to moderate.

Keywords

Tirzepatide, obesity, obesity treatment

Introduction

Obesity is a condition with environmental, genetic and behavioral origins. Its global nature and complexity result in difficulties in treatment [1]. The population of people struggling with obesity is successively increasing; a threefold increase in the number of cases has been observed over the past fifty years [2], [3]. The main reasons of this change are seen in the

dominance of a sedentary lifestyle over increasingly reduced physical activity, combined with inappropriate eating habits [3]. According to the data, the treatment of obesity in Europe consumes an average of 2.16% of GDP, and it is expected that by 2060 this number will increase to 3.07% [4].

Obesity shortens life expectancy by 5-20 years, increasing the risk of developing diseases such as metabolic diseases, hypertension, stroke, myocardial infarction, osteoarthritis, Alzheimer's disease, depression, and various cancers, including colorectal, kidney and endometrial cancer [5], [6]. In addition, overweight and obesity as early as childhood and adolescence correlate with an increased risk of premature morbidity and mortality [7].

In the adult population, obesity is defined by body mass index (BMI), which is calculated by dividing body weight in kilograms by the square of height in meters. A BMI value equal to or greater than 30 kg/m² is a criterion for the diagnosis of obesity, while a value in the range of 25-29.9 kg/m² indicates overweight [8]. A 2022 WHO report shows that 60% of Europe's population is at least overweight. In the patient population, there is a higher prevalence of obesity in women than in men, and an upward trend with age, reaching its highest intensity in the 50-65 age range [3].

Strategies of treatment

Due to the complexity of obesity, effective treatment requires a holistic approach [9]. The key to the weight reduction is a high-quality diet and physical activity, defined as a minimum of 150 minutes of moderate or 75 minutes of intense exercise per week [10], [11].

There are also standpoints indicating that, for weight loss to be significant, that is, greater than 5%, the number of minutes dedicated to physical activity should increase to 225-400 per week. 150 minutes of moderate-intensity exercise such as fast, moderate walking, dancing, housework, or cycling can contribute to weight control, but this is not enough to make an effective weight reduction [12].

Nevertheless, studies indicate that adding physical activity to the diet results in an additional loss of about 1-1.5 kg over 12 months [10]. The type of undertaken physical activity can be varied and it depends on the patient's preference and ability. Although endurance exercise is the most common, resistance exercise does not appear to be inferior in providing

higher energy expenditure. That is because of increased basal metabolism, the result of a higher proportion of fat-free body mass, and increased muscle strength, which results in a greater amount of free activity [12].

With the change in diet and the amount of physical activity, it is necessary to introduce behavioral interventions, understood as strategies developed in cooperation with a psychologist, in order to consolidate the achieved weight reduction [13]. The goal of these interventions is to eliminate the brain's compensatory defense mechanisms that promote hunger feelings and increased caloric supply in response to a negative calorie balance [14].

The body weight at which the body stops the process of weight loss achieved through lifestyle modifications does not always equate to meeting the target BMI. In such situations, appropriate pharmacological or surgical treatment should be considered in addition to diet, behavioral interventions and physical activity [14].

Until the registration of tirzepatide, obesity pharmacotherapy in the European Union was based on four drugs: a compound formulation of naltrexone hydrochloride and bupropion hydrochloride, orlistat, liraglutide and semaglutide [15]. In November 2023, tirzepatide, which was previously approved by the US Food and Drug Administration (FDA) and the European Medicines Agency (EMA) as a drug to improve glycemia in patients with type 2 diabetes, joined this group [16], [17].

The combination of bupropion and naltrexone leads to weight loss by an average of 6.1% or 5.0% (depending on the dose) by acting on proopiomelanocortin neurons in the hypothalamus. Bupropion stimulates these neurons, while naltrexone prevents their opioid-mediated autoinhibition, leading to an appetite suppression, a reduction in food intake and an increase in the activity of regions responsible for self-control [18][19]. In addition, the combination affects the mesolimbic pathway, part of the reward system, reducing the rewarding effects of the food intake stimulus [20].

Orlistat effects by inhibiting gastric and pancreatic lipases, which reduces the hydrolysis of lipids found in admitted food and increases their excretion in the feces [21]. Treatment with orlistat for 1-2 years leads to weight loss of approximately 3% compared to placebo [22].

Liraglutide and semaglutide approved by the Food and Drug Administration's (FDA) in 2021 to obesity treatment , GLP-1 receptor agonists, mimic the action of natural GLP-1 by

activating its receptors. In hyperglycemic states, they increase insulin secretion and reduce glucagon secretion, slow gastric emptying and reduce food intake by suppressing appetite. In addition to lowering blood glucose levels, they also contribute to weight reduction [23][24].

Continuation of pharmacotherapy is appropriate if, after 3 months of initiation, patients with type 2 diabetes achieve weight loss greater than 3%, and patients without diabetes achieve weight loss greater than 5% [15].
For patients with BMI ≥ 40 kg/m² or BMI ≥ 35 kg/m² and at least one obesity-related disease, bariatric surgery may be considered [14].

Mechanism of action

Tirzepatide is a dual agonist of glucose-dependent insulinotropic polypeptide (GIP) and glucagon-like peptide-1 (GLP-1) receptors [25]. GIP and GLP-1 are incretin hormones, whose action is based on the incretin effect - a severalfold increase in insulin secretion after oral glucose administration compared to intravenous administration [26]. Incretins are hormones produced in the intestines, released after meal ingestion, which regulate after-meal metabolism by stimulating glucose-dependent insulin secretion [27].

GLP-1 binds to GLP-1 receptors, the expression of which can be seen in the pancreas, gastrointestinal tract, kidneys and heart. GLP-1 exhibits insulinotropic properties in response to nutrients in the intestine, slows gastric emptying, induces satiety and reduces food intake. GIP, like GLP-1, stimulates glucose-dependent insulin secretion, but is in charge of a greater proportion of the incretin effect than GLP-1 [28]. GIP receptors are present throughout adipose tissue, while GLP-1 receptors are not. Some studies suggest that GIP receptor activity plays a role in lipid uptake and lipolysis [29].

The ability of GIP to improve lipid and glucose metabolism is clearly demonstrated in combination with the weight-reducing mechanism of GLP-1 [30]. The action of tirzepatie is based on the complementary activation of GLP-1 and GIP receptors, allowing greater weight loss than with single GLP-1 receptor agonism [25].

Efficacy studies

A randomized, multicenter, double-blind study, SURPASS-1, was conducted to investigate the safety and efficacy of tirzepatide in patients with type 2 diabetes who had inadequate glycemic control despite diet and physical activity. The characteristics of the study participants included a mean body mass index (BMI) of 31.9 kg/m² and a mean glycated hemoglobin (HbA1c) of 7.94%. Patients agreed to take no other weight-reduction activities besides lifestyle changes.

The patients were randomly assigned to groups receiving 5 mg, 10 mg or 15 mg of tirzepatide subcutaneously once a week and to a group receiving placebo at the same intervals. The results of the study showed that 87-92% of participants treated with tirzeptide achieved an HbA1c < 7.0%. In addition, 67-78% of participants in this group experienced weight loss of 5% or more, 31-47% of 10% or more, and 13-27% of 15% or more, compared to 14%, 1% and 0%, respectively, in the placebo group (Table 1). The weight-reduction effect was dose-dependent, with a difference in body weight of -6.3 kg for the 5 mg dose ($p<0.001$), -7.1 kg for the 10 mg dose ($p<0.0001$) and -8.8 kg for the 15 mg dose ($p<0.0001$).

Moreover, the use of tirzepatide was associated with beneficial changes in levels of total cholesterol, triglycerides, VLDL cholesterol and HDL cholesterol, improved insulin sensitivity and lowered systolic blood pressure [31].

Percentage of participants presenting weight reduction by:	**Tirzepatide 5 mg N=121**	**Tirzepatide 10 mg N=121**	**Tirzepatide 15 mg N=121**	**Placebo N=115**
5% or more	67%	78%	89%	14%
10% or more	31%	40%	47%	1%
15% or more	13%	17%	27%	0%

Table 1. Comparison of the efficacy of tirzepatide doses versus placebo expressed as the percentage of participants with type 2 diabetes who achieved weight reductions of at least 5%, 10%, and 15% [31].

In parallel with the SURPASS-1 study, the SURPASS-2 study was conducted to compare the efficacy of tirzeptide and semaglutide in hypoglycemic and weight-reducing

treatment. The study group consisted of 1,879 patients with type 2 diabetes inadequately controlled with metformin at a dose of at least 1,500 mg. The mean glycated hemoglobin in this group was 8.28%, and mean body weight was 93.7 kg, with a BMI of at least 25 as one of the inclusion criteria.

Patients were randomly assigned to four groups, in which they received 5 mg, 10 mg, 15 mg of tirzepatide or 1 mg of semaglutide, respectively. After 40 weeks of the study, it was observed that the efficacy of tirzepatide was greater at all three doses compared to semaglutide, with 65-80% of tirzepatide-treated patients experiencing a weight reduction of at least 5% compared to 54% receiving semaglutide, 34-57% and 24% by at least 10% and 15-36% and 8% by at least 15%, respectively (Table 2). Estimated differences in body weight at the end of the study were -1.9 kg for tirzepatide at 5 mg, -3.6 kg at 10 mg and -5.5 kg at 15 mg ($p<0.001$).

In addition, the superiority of tirzepatide over semaglutide in reducing glycated hemoglobin levels was also observed, with the drug proving equivalent and superior at all doses tested. The estimated mean change in HbA1c levels after 40 weeks was -2.01 percentage points for the 5 mg dose, -2.24 percentage points for 10 mg, -2.30 percentage points for 15 mg and -1.86 percentage points for 1 mg of semaglutide, relative to the baseline level. [32].

Percentage of participants presenting weight reduction by:	**Tirzepatide 5 mg N=470**	**Tirzepatide 10 mg N=469**	**Tirzepatide 15 mg N=470**	**Semaglutide 1mg N=469**
5% or more	65%	76%	80%	54%
10% or more	34%	47%	57%	24%
15% or more	15%	24%	36%	8%

Table 2. Comparison of the efficacy of tirzepatide versus semaglutide doses expressed as the percentage of participants who achieved weight reductions of at least 5%, 10%, and 15% [32].
Another randomized, double-blind study, SURMOUNT-1, conducted on 2,539 adult patients, evaluated the efficacy of tirzepatide in obese or overweight, non-diabetic patients. The study lasted 72 weeks and was conducted in nine countries. The inclusion criterion was a BMI greater than or equal to 30, or greater than 27 with at least one obesity-related complication other than diabetes mellitus. Patients were randomly assigned to groups receiving one of three doses of tirzepatide (5 mg, 10 mg, 15 mg) or placebo. The drug was administered once a week by

subcutaneous injection as an addition to a lifestyle change aimed specifically at weight reduction.

After 72 weeks of the study, it was observed that 85% of patients taking tirzepatide at the 5 mg dose, 89% at the 10 mg dose and 91% at the 15 mg dose achieved a weight reduction of 5% or more, compared to 35% in the placebo group ($p<0.001$). Weight reduction of 20% or more occurred in 50% of patients taking tirzepatide at the 10 mg dose and in 57% at the 15 mg dose, compared to 3% in the placebo group (Table 3).

In addition, total body fat mass was reduced by an average of 33.9% in the tirzeptide group, compared to 8.2% in the placebo group. Reductions in systolic and diastolic blood pressure, improvements in fasting insulin and lipid levels were also observed, resulting in reduced cardiovascular and metabolic risk factors [33].

Percentage of participants presenting weight reduction by:	**Tirzepatide 5 mg N=630**	**Tirzepatide 10 mg N=636**	**Tirzepatide 15 mg N=630**	**Placebo N=643**
5% or more	85,1%	88,9%	90,9%	34,5%
10% or more	68,5%	78,1%	83,5%	18,8%
15% or more	48,0%	66,6%	70,6%	8,8%
20% or more	30,0%	50,1%	56,7%	3,1%

Table 3. Comparison of the effectiveness of tirzepatide doses versus placebo expressed as the percentage of participants who achieved body weight reductions of at least 5%, 10%, 15% and 20%. [33].

Safety and side effects

A study on the efficacy and safety of tirzepatide showed that the most commonly reported side effects involved the gastrointestinal tract in both healthy patients and those with type 2 diabetes. Symptoms indicating poor tolerance of the substance by participants included decreased appetite, nausea, vomiting, diarrhea and flatulence. Their intensity was described as moderate or mild [25]. Another study proved that the incidence of adverse symptoms was dose-dependent - in the case of nausea, vomiting and diarrhea, the incidence of these symptoms was higher at a dose of 15 mg of tirzepatide (60.4%) than at a dose of 5 mg (25.5%) [34].

It was also proven that the use of higher doses was better tolerated if the therapy was started with a lower dose, and the final dosage was achieved gradually [25].

It was also observed that the incidence of reported gallbladder inflammation incidents was higher in patients using tirzepatide compared to the placebo group, despite no difference in the incidence of gallstones between the groups [33].

It is noteworthy that the use of tirzepatide was not associated with serious adverse events or increased mortality from any cause compared to placebo and other comparator drugs such as basal insulin and semaglutide. In addition, there was no increased risk of hypoglycemic incidents compared with placebo [35].

Summary

Obesity is the result of a combination of environmental, genetic and behavioral factors, and its global spread makes treatment a challenge [1]. The number of obesity cases has tripled over the past five decades, mainly due to sedentary lifestyles and poor eating habits [2], [3]. According to the WHO, 60% of Europeans are overweight or obese [3]. Obesity shortens life and increases the risk of many diseases, including metabolic, cardiovascular, cancer and depression [5], [6]. Treatment of obesity requires a holistic approach, including diet, physical activity and psychological interventions [9]. Pharmacotherapy and surgery can be used as an adjunct when lifestyle modifications are insufficient [13]. The aim of this study was to summarize the current knowledge on the efficacy and safety of tirzepatide in the treatment of obesity.

By 2023, four drugs were in use in the EU: a combination of naltrexone and bupropion, orlistat, liraglutide, and semaglutide. Thirzepatide was approved in 2023 as a new treatment option [15], [16]. Thirzepatide is a dual agonist of GIP and GLP-1 receptors, incretin hormones that increase insulin secretion after a meal [25], [26]. GLP-1 slows gastric emptying, induces satiety and reduces food intake, while GIP improves lipid and glucose metabolism [28], [30]. The synergistic action of these receptors leads to greater weight loss [25].

Studies on the efficacy of tirzepatide clearly show that the drug is superior to placebo and semaglutide in reducing body weight [31], [32]. In addition, tirzepatide has been shown to reduce cardiovascular and metabolic risks [33].

Despite some side effects, tirzepatide did not increase the risk of serious adverse events or mortality compared to placebo [35].

However, its most common side effects such as decreased appetite, nausea, vomiting and diarrhea, through their inconvenient nature, may more often lead to discontinuation of therapy [34].

Nevertheless, tirzepatide appears to be a drug worth considering for the treatment of obesity, as a drug with high efficacy and satisfactory safety.

Author's contribution

Conceptualization, Katarzyna Wiśniewska; methodology, Katarzyna Wiśniewska and Marta Piotrowska; software, Tomasz Kucharski and Julita Gmitrzuk; check, Joanna Jakubiec and Anna Jachymek; formal analysis, Katarzyna Wisniewska and Marta Piotrowska; investigation, Katarzyna Wiśniewska and Martyna Opatowska; resources, Zuzanna Malinka and Tomasz Kucharski; data curation, Joanna Jakubiec, Julita Gmitrzuk; writing – rough preparation, Katarzyna Wiśniewska; writing - review and editing, Katarzyna Wiśniewska and Marta Piotrowska; visualization, Katarzyna Wiśniewska, Zuzanna Malinka and Anna Jachymek; supervision, Tomasz Kucharski and Martyna Opatowska; project administration, Katarzyna Wiśniewska, Julita Gmitrzuk. All authors have read and agreed with the published version of the manuscript.

Funding Statement

Study did not receive special funding.

Institutional Review Board Statement

Not applicable.

Informed Consent Statement

Not applicable.

Data Availability Statement

Not applicable.

Acknowledgments

Not applicable.

Conflict of Interest Statement

The authors of the paper report no conflicts of interest.

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