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## **Will Tirzepatide become a game-changer in the pharmacological treatment of obesity? - literature review**

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## **Abstract**

**Introduction and objective:** Obesity has become an important public health issue in Poland. Furthermore, it is one of the most common preventable causes of diseases and mortality. Pharmacological methods of treating obesity have been developing significantly in recent years. Tirzepatide is a new dual incretin receptor agonist that activates both GIP (glucose-dependent insulinotropic polypeptide) and GLP-1 (glucagon-like peptide-1) receptors. The aim of this review is to assess the effectiveness of this medication in reducing body weight.

**Current state of knowledge:** According to data from the Central Statistical Office (GUS) in Poland, 65% of men and 49% of women are struggling with the issue of excessive body weight [1]. Obesity in Polish society is steadily increasing in every age group. However, it affects most significantly children aged 7-13 years and adolescents. In 2022, the novel dual GLP and GIP-1 agonist has been registered for the treatment of type 2 diabetes which is not satisfactorily controlled. It can be also used together with diet and physical activity in patients diagnosed with obesity (BMI of 30 kg/m<sup>2</sup> or more) or who are overweight (BMI 27-30 kg/m<sup>2</sup>) and have weight-related health problems such as hypertension, metabolic syndrome, dislipidaemia and diabetes mellitus [2].

**Summary:** The increasing prevalence of obesity leads to a dynamic search for the most effective pharmacological methods of treating obesity. The combined activation of GLP-1 and GIP receptors by Tirzepatide has been shown to have additional benefits beyond satisfying glucose control. The biological mechanism of action of this medication additionally causes decreased food intake, slowed gastric emptying and enhanced insulin secretion, all of which can contribute to weight reduction. Overall, Tirzepatide represents a promising option for individuals struggling with obesity, offering the potential for significant weight loss in conjunction with lifestyle modifications such as diet and physical activity.

**Keywords:** tirzepatide, anti-obesity drug, obesity, excessive body weight, GLP agonist, GIP-1 agonist,

## **Introduction**

The prevalence of obesity in Poland has been steadily increasing over the past few decades, mirroring global trends. According to data from the Central Statistical Office (GUS), a substantial proportion of the Polish population is affected by obesity. For instance, recent statistics indicate that approximately one in five Poles is obese, with even higher rates among certain demographic groups. Furthermore, research from the past decade suggests that the prevalence of obesity in Poland is particularly high among adults, with significant proportions of both men and women classified as overweight or obese. According to data, 65% of men and 49% of women are struggling with the issue of excessive body weight. Moreover, there has been a concerning rise in childhood obesity with an increasing number of children and adolescents being affected by excess weight. Several factors contribute to the rising prevalence of obesity in Poland. These include changes in dietary habits, such as elevated intake of energy-dense and processed foods. Mass production has led to a significant decrease in the quality of food products [3]. According to the analysis of energy consumption in 167 countries conducted in 2018, Poles were ranked 10<sup>th</sup> [4]. It is also concerning that Polish studies proved low fiber intake in the middle-aged population (16 g per day, referring to the lowest recommended 25 g per day) [5]. Additionally, socioeconomic factors, urbanization, environmental influence and a shift towards sedentary lifestyles, characterized by reduced physical activity levels, play a role in shaping patterns of obesity in the Polish population.

## **Methods of treating obesity**

There are several methods for treating obesity, including lifestyle modifications, pharmacotherapy or bariatric surgery. It's important for patients with this health issue to work closely with healthcare providers to determine the most appropriate treatment plan based on their individual needs and circumstances. Additionally, a multidisciplinary approach that addresses both physical and psychological aspects of obesity is often most effective in achieving long-term success. Pharmacological treatment for obesity is gaining popularity due to its high effectiveness in reducing body weight in a relatively short period of time with relatively few adverse effects. Before the registration of Tirzepatide in the European Union, there were four medications available for the treatment of obesity: Orlistat, Naltrexon-Bupropion, Liraglutide and Semiglutide.

Short-term (3-6 months) use of pharmacotherapy does not provide long-term health benefits and it is not recommended. The duration of obesity treatment should be  $\geq 12$  months and adjusted to the individual needs of the patient, including the treatment goals. Pharmacotherapy can be used for as long as it is effective and well tolerated. Obesity is a chronic disease without a tendency to resolve spontaneously. Premature discontinuation of treatment may lead to difficulties in maintaining achieved effects. During treatment, proper monitoring of weight loss and metabolic parameters should be ensured and treated as an additional indicator of both the appropriateness and effectiveness of treatment and a significant argument in determining the duration of therapy [6].

### **Incretin receptor agonists**

Incretin receptor agonists is a class of medications that mimic the action of incretin hormones, such as GLP-1 (glucagon-like peptide-1) and GIP (glucose-dependent insulinotropic peptide). These medications stimulate the incretin receptors found on pancreatic beta cells, leading to increased insulin secretion in response to elevated blood sugar levels. By enhancing insulin release and suppressing glucagon secretion, incretin receptor agonists help regulate blood glucose levels, particularly after meals. They are commonly used in the treatment of type 2 diabetes to improve glycemic control. Additionally, GLP-1 can inhibit gastric emptying and reduce gastric acid secretion, suppress gastric and duodenal peristalsis by inhibiting the vagus nerve and increase pyloric pressure, which reduces appetite and enhances the feeling of satiety. All these mechanisms lead to a reduction in body weight [7,8].

### **Tirzepatide**

Tirzepatide is the first “twincretin”, a synthetic peptide composed of 39 amino acids based on the GIP native sequence [9]. This polypeptide has an affinity for the GIP receptor equal to that of native GIP and an affinity for the GLP-1 receptor, which is five times weaker than that of native GLP-1 [10]. GIP and GLP-1 are classified as incretin hormones. They are released in small intestine after food intake. Clinical trials have shown their additional beneficial impact on metabolic processes. GLP1, in particular, reduces food intake and delays gastric emptying. Moreover, Tirzepatide has been shown to have a positive impact on blood pressure and to reduce low-density lipoprotein (LDL) cholesterol and triglycerides [11].

The efficacy and safety of this medical substance were assessed in a phase III SURPASS 1-5 clinical trial program. Patients with type 2 diabetes were randomly assigned and received at least one dose of tirzepatide 10 mg, tirzepatide 15 mg or placebo. The results indicated a clinically significant

reduction in HbA1c values and body weight, with a low frequency of hypoglycemia episodes [12].

In another clinical trial, named SURMOUNT-1, 2539 adults without diabetes were involved. The study group consisted of a population of patients with a BMI equal to or greater than 30 or a BMI equal to or greater than 27 with at least one complication related to being overweight. The trial included administering the medication along with lifestyle modifications such as healthy diet and physical activity. After 72 weeks, there was an average weight loss correlated with the Tirzepatide dose (5mg, 10mg, 15mg), resulting in 15%, 19.5%, and 20.9%, respectively. Meanwhile, the placebo group showed a weight loss of 3.1% [13].

### **The adverse effects of therapy**

Based on available data, the majority of Tirzepatide users do not experience significant adverse drug reactions. The primary adverse effects reported are gastrointestinal, mainly nausea and diarrhea, which may occur in up to 10% [14]. Infrequent cases of acute kidney injury have been reported, likely secondary to dehydration from gastrointestinal losses. Less commonly reported adverse effects include: hypersensitivity reactions at the injection site, asymptomatic elevation of lipase and amylase, acute pancreatitis, cholelithiasis and cholecystitis. Regarding the endocrine adverse effects of Tirzepatide, there is a small risk of hypoglycemia, which is dose-dependent. This risk is more significant for those on insulin therapy and/or those treated with sulfonylureas [15].

### **Conclusions**

In conclusion, the increasing prevalence of obesity leads to a dynamic search for the most effective pharmacological methods of treating obesity.

The combined activation of GLP-1 and GIP receptors by Tirzepatide has been shown to have additional benefits beyond satisfying glucose control.

The biological mechanism of action of this medication additionally causes decreased food intake, slowed gastric emptying and enhanced insulin secretion, all of which can contribute to weight reduction. Clinical trial results indicate a significant reduction in body weight, high efficacy and safety of the therapy, with few adverse effects.

Overall, Tirzepatide represents a promising option for individuals struggling with obesity, offering the potential for significant weight loss in conjunction with lifestyle modifications such as diet and physical activity.

## **Author's contribution**

Conceptualization, AD, KW; methodology, MaxJ, MagJ; software, PH, WU; check, AD, KW and M G-B; formal analysis, KK, KM, KW; investigation, AS; resources, AD; data curation, KW, WU; writing-rough preparation, KWa, PH, KK; writing-review and editing, MagJ, AS, M G-B; visualization, AD, MaxJ; supervision, KWa; project administration, AD; receiving funding, (-).

All authors have read and agreed with the published version of the manuscript.

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## **Conflicts of Interest**

The authors declare no conflict of interest.

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