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# Antidiabetic drugs as the future of obesity treatment
# Leki przeciwcukrzycowe jako przyszłość leczenia otyłości

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## Abstrakt

Otyłość jest to wieloczynnikowa choroba przewlekła o złożonej patogenezie. U podstaw jej przyczyn doszukuje się czynników genetycznych, biologicznych, epigenetycznych, środowiskowych, rozwojowych i behawioralnych, prowadzących do nadmiernego spożycia kalorii i w konsekwencji przyrostu masy ciała. Wraz ze wzrostem masy ciała rośnie ryzyko

wystąpienia wielu chorób przewlekłych a co za tym idzie skrócenia przewidywanej długości życia. Podstawą leczenia otyłości jest wprowadzenie zmian w zachowaniu i modyfikacja stylu życia, opierających się przede wszystkim na przyjęciu zdrowej, zbilansowanej diety z deficytem kalorycznym, regularnej aktywności fizycznej i ograniczeniu czasu siedzącego. Jeżeli są one nieskuteczne, rozważa się metody farmakologiczne oraz w razie potrzeby przeprowadza się zabiegi chirurgiczne. W obecnych czasach coraz więcej uwagi się zwraca na otyłość jako wieloczynnikową chorobę, którą należy skutecznie leczyć. Nie jest to tylko problem natury estetycznej ale także poważne schorzenie które może prowadzić do przedwczesnego zgonu. Nasza praca skupia się na przeglądzie obecnych metod w leczeniu otyłości ze szczególnym zwróceniem uwagi na najnowsze metody farmakologiczne.

**Keywords:** otyłość, dieta, aktywność fizyczna, chirurgia bariatryczna, metody farmakologiczne, semaglutyd, tirzepatyd

**Abstract**

Obesity is a multifactorial chronic disease with complex pathogenesis. Its causes are considered to be genetic, biological, epigenetic, environmental, developmental and behavioral factors leading to excessive caloric intake and, consequently, weight gain. As body weight increases, the risk of developing many chronic diseases increases and, as a result, life expectancy decreases. The basis of obesity treatment is the introduction of changes in behavior and lifestyle modification, based primarily on the adoption of a healthy, balanced diet with a caloric deficit, regular physical activity and limiting sedentary time. If they are ineffective, pharmacological methods are considered and, if necessary, surgical procedures are performed. Nowadays, more and more attention is paid to obesity as a multifactorial disease that must be effectively treated. It is not only an aesthetic problem but also a serious disease that can lead to premature death. Our work focuses on a review of current methods in the treatment of obesity, with particular attention to the latest pharmacological methods.

**Keywords:** obesity, diet, physical activity, bariatric surgery, pharmacological methods, semaglutide, tirzepatide

## Introduction

Obesity is a chronic, complex disease characterized by abnormal or excessive fat accumulation, leading to negative health consequences. It poses a significant public health challenge [1] and the associated complications and high mortality [2] necessitate continuous improvement of treatment methods. It is estimated that up to 13% of the world's population suffers from this condition [1] and its prevalence worldwide has tripled since the mid-1970s [3]. The occurrence of obesity depends on many factors, with age, gender, race and socioeconomic status being among the most common [4]. Obesity is defined using the body mass index (BMI), calculated by dividing body weight in kilograms by the square of height in meters [1]. Although widely used in clinical practice, this index has limitations, including the lack of consideration for differences in the distribution of fat tissue among individuals. According to guidelines, the disease is defined at values equal to or greater than 30 kg/m2 in adults [3]. At a BMI above 40 kg/m2, the mortality rate associated with obesity increases by up to 100% compared to individuals with a normal body weight [5]. Alternative methods for assessing fat tissue include waist circumference measurements, skinfold thickness or evaluation of the percentage of body fat using dual-energy X-ray absorptiometry [6]. The pathogenesis of obesity involves the interaction of genetic, biological, epigenetic, environmental, developmental and behavioral factors, leading to excessive calorie intake and consequently weight gain [3]. It is estimated that polygenic inheritance may account for up to 50% of cases. Considering these complex interactions, it is worth emphasizing that the disease is not solely caused by a lack of self-control but by multiple mechanisms that should be considered in the selection of treatment methods [5]. Obesity is associated with numerous complications, including type 2 diabetes, hypertension, dyslipidemia, obstructive sleep apnea, cardiovascular diseases, asthma, non-alcoholic fatty liver disease, infertility, joint inflammation, increased risk of cancer and increased mortality [1,2,4,7]. The health and financial burdens off obesity associated with its treatment contribute to a deepening global health crisis. Therefore, there is a need for introducing new drugs to improve both the quality of life of patients and the condition of healthcare systems [4,7]. The basis of obesity treatment is the implementation of behavioral changes and lifestyle modification, primarily based on adopting a healthy, balanced diet with a calorie deficit, regular physical activity and reducing sedentary time [1]. These interventions are the first step in therapeutic management. If they

are ineffective, pharmacological methods are considered and, if necessary, surgical procedures are performed [5].

The aim of this article was to review the literature on drugs used in the treatment of obesity, with particular emphasis on antidiabetic drugs - their mechanism of action and therapeutic benefits. Electronic search engine PubMed/MEDLINE was used to identify relevant studies. The search focused on publications presenting the latest knowledge in this field.

## Treatment of obesity

### *Non-pharmacological methods*

Treating obesity remains a significant challenge for modern medicine. When selecting therapeutic methods, an individualized approach considering the patient's gender, age, chronic diseases, organ function and economic status should be taken into account [8]. The first component of treatment is non-pharmacological therapy, which includes a reduced-calorie diet (e.g.,1200-1500 kcal per day – the caloric requirement depends on factors such as the patient’s body weight and gender), regular physical activity (at least 150 minutes per week) and frequent behavioral therapy (at least 14 sessions over six months). These interventions are conducted over a period of six months. If satisfactory results are not achieved within this timeframe, pharmacotherapy can be introduced as a supportive element of treatment. The short-term goal is to reduce body weight by 5-10% of the initial weight and the long-term goal is to maintain this weight loss [4, 9].

Various diets are available to support obesity treatment, including vegan diets, low-carbohydrate or low-fat diets, low glycemic index diets and high-protein diets. However, the low-calorie and Mediterranean diets particularly stand out due to their proven efficacy in controlled studies [5, 8]. The very low-calorie diet relies on formula products (containing balanced portions of carbohydrates, proteins and fats) to achieve a caloric deficit (around 810 kcal per day) for the first eight weeks, after which normal food intake resumes [1, 8]. This approach can lead to a weight loss of 7 to 10 kg over a year [10]. On the other hand, the Mediterranean diet, rich in monounsaturated fatty acids, fiber, antioxidants and glutathione,

reduces the risk of obesity, type 2 diabetes, coronary artery disease, other cardiovascular diseases and related complications [5].

Regular physical activity combined with dietary intervention typically leads to a weight loss of 0 to 4 kg. Exercise not only improves body composition by reducing fat mass and preserving muscle mass but also has a beneficial impact on various physical functions and enhances cardiorespiratory fitness [1, 10].

Implementing numerous lifestyle changes is a long-term and challenging process, often requiring patients to change their existing habits, demonstrate commitment, perseverance and patience in striving to reduce and subsequently maintain weight. All therapeutic interventions should be supported by frequent behavioral therapies to help patients effectively and sustainably manage their weight in the long term [5, 8].

*Bariatric surgery*

Currently, bariatric surgery is recommended for severely obese patients with a body mass index (BMI) >40 kg/m2, who failed to benefit from previous dietary modifications and non-surgical treatment options. Alternatively, bariatric surgery may be suggested for individuals presenting with a BMI ≥35 kg/m2 but with obesity-related comorbid conditions [11]. Moreover, the International Diabetes Federation proposed to recommend bariatric surgery to patients with type 2 diabetes mellitus (T2DM) having suboptimal blood glucose control on a background of adequate medical therapy even though their BMI might be 30 kg/m2 [12]. Four operative procedures are commonly used in clinical practice and are listed with increasing body weight reducing potential: adjustable gastric banding (AGB), sleeve gastrectomy (SG), Roux-en-Y gastric bypass (RYGB) and biliopancreatic diversion (BPD), with RYGB and SG being most frequently performed. While all bariatric interventions aim to reduce the capacity of the food-intake-reservoir (stomach or pouch), the RYGB and the BPD also result in malabsorption due to a shorter (partly bypassed) small intestine. Procedures that result in greater lengths of the built intestinal bypass (e.g. bilio-pancreatic diversion, omega bypass) seem to have greater weight-loss effects and induce greater metabolic improvements, but have more side effects [13]. Despite the undoubtedly positive aspects of bariatric surgery, possible side effects must be considered. As mentioned before, malnutrition is a consequence of most bariatric surgical procedures, with reduced uptake of vitamins and trace elements,

making a life-long supplementation of vitamins and trace elements as well as a frequent monitoring of their respective blood levels necessary. Furthermore, anastomotic leak potentially resulting in peritonitis occurs in 1–6% after RYGB and 3–7% after SG at ten days post intervention [14]. One reason for weight regain appears to be the fact that bariatric surgery patients typically remain in the obesogenic environment that is conducive for weight gain in the first place. Given that this environment is the main cause of obesity in a majority of humans, bariatric surgery is only a symptomatic treatment but does not attack the root cause of obesity, which would require removal or neutralization of the obesogenic environment. However, the sustained effects on body weight after bariatric surgery are nothing but remarkable, considering that similar weight loss induced by dieting provokes very strong adaptive and counter-regulatory responses such as increased hunger and reduced metabolism [15,16].

Bariatric surgery can be a treatment option for sickly obese patients who have not succeeded with the medical treatment of obesity [17]. Such patients are at increased risk for premature death, type 2 diabetes, high blood pressure, gallstones, coronary heart disease, dyslipidemia, some cancers, anxiety, depression and degenerative joint disorders [18]. However, patients with additional diseases, such as severe respiratory failure, heart failure or kidney failure, may not be approved for surgical treatment if the risk for complications is considered high. Also, patients with severe mental illness, intoxication or mental retardation may be unsuitable candidates for obesity surgery [19,20].

*Pharmacological Methods*

In the past decade, several medications have been approved for the treatment of obesity, achieving therapeutic effects by suppressing hunger and promoting satiety. Historically, many pharmacological agents have been tested, but numerous were withdrawn due to dangerous side effects and safety concerns for patients. These medications include sibutramine which increased the risk of cardiovascular events and complications, rimonabant which raised the risk of mood disorders and suicides and lorcaserin which was associated with a potential risk of cancer [1].

Currently approved therapeutic options for obesity by regulatory authorities include orlistat, phentermine and topiramate (only in the USA), naltrexone and bupropion, liraglutide,

semaglutide and tirzepatide. Orlistat, a gastrointestinal lipase inhibitor, is a safe medication but leads to only moderate weight loss (3-5%) by reducing fat absorption in the body. It is also the only approved medication for obesity that does not affect the brain [1,6,21]. Phentermine acts as a sympathomimetic agent by stimulating the release of norepinephrine and blocking its reuptake, while topiramate is a gamma-aminobutyric acid (GABA) agonist. These two agents are used in combination. Another combination therapy involves naltrexone, a non-selective opioid receptor antagonist with bupropion, a dopamine and norepinephrine reuptake inhibitor. Liraglutide and semaglutide are GLP-1 receptor agonists that reach the brain through the blood-brain barrier, leading to reduced glucose levels, increased glucose-dependent insulin secretion, decreased glucagon release, delayed gastric emptying and reduced food intake [1]. Tirzepatide is a GIP/GLP-1 agonist, exhibiting similar effects to GLP-1 agonists, but with a much stronger effect and greater impact on weight loss efficacy due to the synergistic action of both hormones [6,22].

*Semaglutide*

Semaglutide is a long-acting GLP-1 receptor agonist administered subcutaneously once a week. It can be used as monotherapy or in combination with other hormonal medications. The drug was originally approved by the Food and Drug Administration (FDA) for the treatment of type 2 diabetes in 1997 and in 2021 it was the first to be approved for the treatment of obesity. Semaglutide leads to a weight loss of about 15% in patients without diabetes when combined with moderate lifestyle changes. This is a remarkable efficacy, twice as effective as previously used pharmacological methods. However, it should be noted that rapid weight loss with this agent may be temporary. There are indications in the literature that weight gain may occur after discontinuation of the drug. The secret of semaglutide's action lies in its incretin effect [1,6,11]. Incretins include GLP-1 and GIP, hormones produced in the intestines and brain, which are responsible for maintaining normal blood glucose levels. Semaglutide, by binding to GLP-1 receptors, leads to increased insulin secretion, inhibition of glucagon release, decreased appetite and delayed gastric emptying [6,23,24]. Additionally, in patients with type 2 diabetes, the drug has a beneficial effect on the course of the metabolic disease by reducing HbA1c levels. The SELECT and SUSTAIN studies are ongoing to confirm the positive impact of the drug on cardiovascular outcomes and to determine the safety profile in patients with established cardiovascular diseases. Initial reports are very promising [1]. Studies are also underway on oral semaglutide, which was approved by the FDA in 2019 for

the treatment of type 2 diabetes. This drug, in a higher dose, is currently undergoing phase 3 trials in patients with obesity and without type 2 diabetes in the OASIS study. The main adverse effects of semaglutide include nausea, vomiting, diarrhea and constipation. Gastrointestinal symptoms usually occur at the beginning of treatment during dose escalation and are likely related to interactions with GLP-1 receptors in the central nervous system. Other side effects include dizziness and allergic reactions of varying severity. The use of this drug can also lead to acute kidney injury or acute pancreatitis. These effects are dose dependent. Therefore, caution and vigilance should be exercised when administering this medication [1,6,11].

*Tirzepatyde*

Tirzepatide is a once-weekly subcutaneous injectable peptide (approved by the FDA for type 2 diabetes) engineered from the native GIP sequence, with agonist activity at both the GIP and GLP-1 receptors. Tirzepatide is a 39-amino acid synthetic peptide with agonist activity at the glucose-dependent insulinotropic polypeptide (GIP) and GLP-1 receptors. As a GIP and GLP-1 receptor agonist, tirzepatide could result in weight reduction beyond that achieved with selective GLP-1 receptor agonists by affecting tissues not targeted by these mono-agonist agents and integrating the activation signals of both GIP and GLP-1 receptor pathways in the brain [25,26]. In 2022, tirzepatide was approved by the US FDA for the treatment of obesity [27]. In a recent clinical trial, it was shown that tirzepatide can safely reduce BMI, waist circumference and body weight by 20% and its weight loss effect is far superior to the older generation of weight loss drugs [28]. The latest research results released by SURMOUNT-2 [29] also support this conclusion. Tirzepatide is bound to become a strong competitor in the field of weight loss and it can also effectively prevent cardiovascular disease. As typically observed with this medication, transient, mostly mild-to-moderate gastrointestinal events were the most frequently reported adverse events, occurring primarily during the dose-escalation period [30,31]. The incidence of hypoglycemia is low, based on phase 2 trials [30]. Although there was no difference observed in reported cholelithiasis between recipients of tirzepatide and placebo, cholecystitis was observed more frequently with tirzepatide. Gallbladder-related events have been reported to increase in individuals with considerable weight reduction and are also observed with other obesity therapies, such as bariatric surgery and treatment with GLP-1 receptor agonists.

## Conclusion

Obesity is a civilization disease associated with a number of life-threatening consequences. Therefore, new therapeutic solutions, involving not only better effectiveness but also additional pleiotropic activities are continually being sought. Due to the growing number of drugs that reduce body weight, the therapeutic choice is becoming more and more difficult. Therefore, when deciding on a specific medication, we must consider not only its effectiveness, but also the patient's preferences and concomitant diseases. These improvements of weight loss may translate to reduced risk of cardiovascular disease, chronic kidney disease, non-alcoholic fatty liver disease and type 2 diabetes, among other outcomes especially while usage of pharmaceuticals methods. But still future trials are needed to test this hypothesis. In addition, it is worth carefully analyzing the needs of patients and the severity of side effects, in order to obtain the best therapy compliance. New drugs seem thus have a much higher potency and are expected to change the medical weight management landscape in the not-sodistant future.

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