**Medical Science**

**To Cite:**
Grzebyk M, Tokarska A, Arnista A, Świątko M, Sosnowski P, Rybak J, Waszczuk A, Kołodziejczyk A, Gawrońska K. The review of modern prospects for the pharmacological treatment of obesity and its complications – The role of GLP-1, GLP1 / GIP, GLP1 / GIP / GCG receptor agonists. *Medical Science* 2025; 29: e50ms3543
doi: https://doi.org/10.54905/dissi.v29i157.e50ms3543

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**Peer-Review History**
Received: 03 November 2024
Reviewed & Revised: 07/November/2024 to 01/March/2025
Accepted: 04 March 2025
Published: 09 March 2025

**Peer-review Method**
External peer-review was done through double-blind method.

Medical Science
pISSN 2321–7359; eISSN 2321–7367



DISCOVERY
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# The review of modern prospects for the pharmacological treatment of obesity and its complications – The role of GLP-1, GLP1 / GIP, GLP1 / GIP / GCG receptor agonists

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## ABSTRACT

Obesity has emerged as a global epidemic and a chronic neuroendocrine condition, significantly contributing to the prevalence of type 2 diabetes and other metabolic disorders. It is a key predictor of numerous health complications, including diabetic nephropathy, hepatic steatosis and fibrosis, obstructive sleep apnea (OSA), heart failure, degenerative diseases. Furthermore, a higher prevalence of Parkinson's disease has been observed in obese people, which indicates a possible link between the obesity and neurodegenerative diseases. Obese patients are more likely to develop complications such as sleep apnea, hypertension, and hyperlipidemia, thus increasing the risk of cardiovascular events. Lifestyle changes and diet are currently the only accepted treatment of obesity, but researchers have been looking for a good pharmacological therapy to supplement them. The objective of this review is to examine the therapeutic potential of GLP-1 receptor agonists in obesity treatment and its complications, summarizing key clinical trials and outlining future directions for the development of more potent weight-reducing agents, such as Retaglutide. A total of 40 studies retrieved from the New England Medical Journal (nejm.com) were analyzed, focusing on the clinical efficacy of liraglutide, semaglutide, tirzepatide, other less commonly discussed GLP-1 receptor agonists in weight management and metabolic health. This review highlights the expanding role of these agents beyond their primary metabolic applications, offering insights into their evolving therapeutic potential in broader clinical contexts.

**Keywords:** Obesity, GLP-1 receptor agonists, weight management, obesity pharmacotherapy

## 1. INTRODUCTION

As defined by the WHO, obesity is a chronic disease that is a result of excess body fat that is life threatening (Nutter et al., 2024). Changes in the human living environment, including the widespread availability of high-calorie foods, reduced physical activity, shorter sleep duration, significantly contribute to the rising prevalence of obesity. The genetic research suggests that predisposition to obesity may result from mutations in genes responsible for appetite regulation, such as the melanocortin-4 receptor (MC4R) gene or the FTO gene influences fat storage and energy metabolism (Heymsfield and Wadden, 2017).

Furthermore, increasing consideration is being given to how epigenetics and gut microbiomes influence regulating weight. This suggests that the factors contributing to obesity are more intricate than consuming an excess of calories (Heymsfield and Wadden, 2017). Energy balance dysregulation in obesity stems from neurohormonal mechanisms that affect satiety and hunger perception. The hypothalamus is central in this process, integrating peripheral hormonal signals such as leptin, ghrelin, insulin, peptide YY. Under conditions of chronic energy surplus, leptin resistance develops, disrupting satiety signaling and leading to continued excessive food intake.

At the same time, a body's adaptive mechanisms make weight decrease challenging—caloric restriction induces compensatory metabolic slowdown and increased hunger, making long-term weight maintenance difficult (Heymsfield and Wadden, 2017). Beyond its metabolic effects obesity leads to numerous cardiovascular complications, including hypertension, atherosclerosis, heart failure. Excess body mass increases vascular resistance and activates the sympathetic nervous system and the renin-angiotensin-aldosterone system, contributing to hypertension development. Excess visceral fat is also associated with chronic inflammation, insulin resistance, increasing the risk of type 2 diabetes and neurodegenerative diseases.

In addition, fat accumulation in the liver contributes to non-alcoholic fatty liver disease (NAFLD) can lead to: cirrhosis, liver failure (Heymsfield and Wadden, 2017). Treating obesity should involve a comprehensive approach, integrating behavioral, pharmacological, surgical interventions. The most fundamental treatment method is lifestyle modification, including dietary habit changes and increased physical activity. Studies show that even moderate weight loss (5-10%) can yield significant health benefits, including improved glycemic control, reduced blood pressure and blood lipid levels. However, lifestyle changes alone are frequently insufficient, necessitating additional treatment methods (Heymsfield and Wadden, 2017).

Pharmacotherapy for obesity includes medications that influence appetite regulation and metabolism. Fat absorption inhibitors GLP-1 receptor agonists combinations of centrally acting agents provide practical tools for weight loss support (Heymsfield and Wadden, 2017). While pharmacotherapy can enhance behavioral interventions' effectiveness, its use is frequently limited by side effects the need for long-term medication to sustain therapeutic implications. The purpose of this study is to discuss the implications of modern GLP-1 and GIP agonists therapy on the seminal diseases caused by chronic disease known as obesity (Heymsfield and Wadden, 2017).

## 2. METHODOLOGY

A comprehensive analysis was performed using data from the New England Journal of Medicine (nejm.com) database. Researchers performed a systematic search applying primary search terms such as *"Liraglutide"*, *"Semaglutide"*, and *"Tirzepatide"*, along with targeted phrases including *"diabetes treatment"*, *"GLP-1 receptor agonists"*, *"diabetes management"*, *"GIP-1 receptor agonists"*, and *"obesity treatment strategies"*. For purpose of this review 40 articles were selected for publication between January 2015 and September 2024. The analysis identified emerging research directions, which have been categorized into thematic subsections.

The review is based on the findings of extensive scale clinical trials that assessed the efficacy of GLP 1 receptor agonists in weight reduction therapy and their role in preventing obesity-related complications such as diabetes, cardiovascular complications associated with microvascular damage, diabetic nephropathy, osteoarthritis, liver steatosis, obstructive sleep apnea (OSA). Furthermore, the possibility of using GLP-1 receptor agonists in Parkinson's disease treatment is explored, the further development of this drug class is outlined.

The main therapeutic goal will be to improve the weight loss efficacy by manipulating other hormonal pathways and activating new receptor systems which may open new and better possibilities for metabolic therapies. In the analysis of the review studies, certain

research directions can be outlined which are the key areas of the scientific focus. The main goal of researchers was to evaluate the effectiveness of weight loss strategies with emphasis on the prevention and treatment of comorbidities associated with obesity.

**Study Design**

In line with the PRISMA 2020 guidelines, this systematic review was conducted. The primary aim was to evaluate the efficacy and safety of GLP-1 receptor agonists for the management of obesity and its complications, including type 2 diabetes, cardiovascular diseases, metabolic dysfunctions.

**Eligibility Criteria**

***Inclusion Criteria***

Studies published between January 2015 and September 2024
Clinical trials evaluating liraglutide, semaglutide, tirzepatide, other GLP-1 receptor agonists
Studies with at least 50 participants per arm
Randomized controlled trials (RCTs), meta-analyses, extensive observational studies
Primary outcomes assessing weight loss, glycemic control, cardiovascular risk reduction, metabolic health improvements

***Exclusion Criteria***

Case reports, commentaries, non-peer-reviewed articles
Studies with inadequate statistical power or high risk of bias
Animal and in vitro studies
Articles without full-text availability

***Information Sources and the search of strategy***

A comprehensive search was performed in the following databases:
New England Journal of Medicine (nejm.com)
The search strategy included primary search terms such as *"GLP-1 receptor agonists"*, *"obesity treatment"*, *"liraglutide"*, *"semaglutide"*, *"tirzepatide"*, and *"GIP receptor agonists"*.
Reference lists of selected studies were manually screened to identify additional relevant publications.

***Study Selection and Data Extraction***

Two independent reviewers screened the titles and abstracts of identified studies.
Full-text articles were retrieved for eligibility assessment.
Any discrepancies were resolved through discussion or consultation with a third reviewer.

***Data extracted included***

Study characteristics (design, sample size, interventions)
Primary and secondary outcomes
Statistical measures (risk ratios, confidence intervals, p-values)
Adverse events and treatment discontinuation rates

***Risk of Bias and Certainty of Evidence***

The Cochrane Risk of Bias 2.0 tool assessed the quality of randomized controlled trials. The following domains were evaluated:
Selection bias (randomization process)
Performance bias (blinding of participants and personnel)
Detection bias (blinding of outcome assessment)
Attrition bias (incomplete outcome data)
Reporting bias (selective outcome reporting)

The GRADE framework was applied to assess the overall certainty of evidence.

*Data Synthesis and Statistical Analysis*

Meta-analysis was performed using a random-effects model to pool results from RCTs.
Heterogeneity was assessed using $I^2$ statistics and sensitivity analyses.
Publication bias was evaluated using funnel plots and Egger's test.

**PRISMA 2020 Flow Diagram**

A PRISMA 2020 flow diagram was constructed to illustrate the selection process of included studies based on data, derived from multiple trials (SURMOUNT-1, SCALE, STEP, GRAD, SUSTAIN-6 and others).

**PRISMA 2020 Flow Diagram – data set**

Below is the PRISMA 2020 flow diagram (Figure 1) illustrating the selection process of included studies.

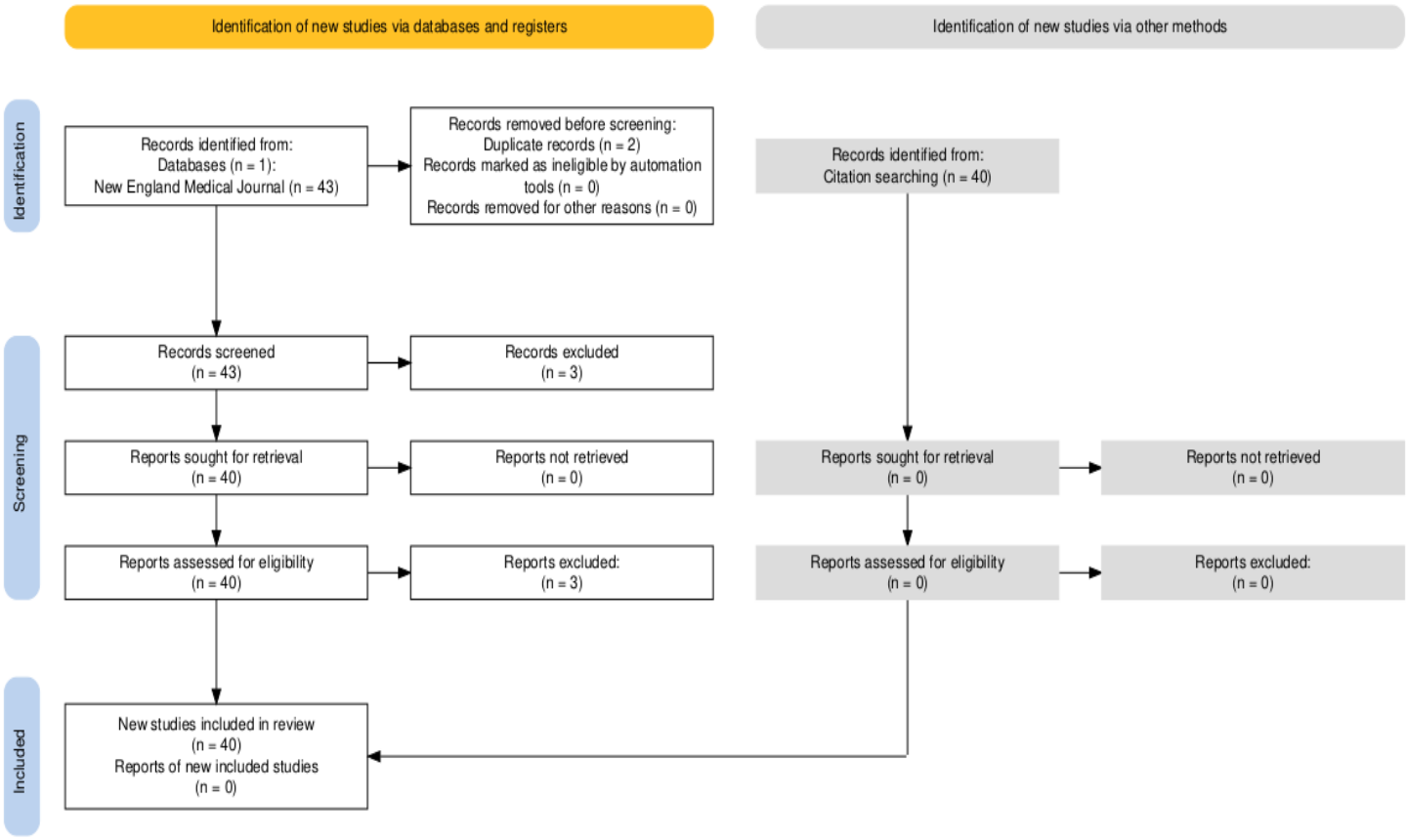


**Figure 1** PRISMA Flow Diagram (Graphical Representation)

*Identification*

Records identified from databases: 40
Duplicate records removed: 2
Records screened: 40
Records excluded: 3

*Screening*
Full-text articles assessed for eligibility: 42
Full-text articles excluded (reasons: sample size, bias, study type): 40

*Inclusion*
Studies included in final systematic review: 6
The diagram was created using the software tool recommended by 'prisma statement'
(source: https://estech.shinyapps.io/prisma_flowdiagram/).

## 3. RESULTS AND DISCUSSION

Observations began with the FDA registration of liraglutide in 2010. In a 2015 article published in nejm.com, researchers observed that liraglutide, - an analog of glucagon-like peptide-1 (GLP-1), used as a pharmacological support in treating obesity, particularly in patients with associated metabolic disorders. The SCALE study showed that its use at a dose of 3 mg daily results in a substantial weight decrease of up to 15% (Gardner and Murphy, 2015). The purpose of this work is to study the effect of GLP-1, GLP1/GIP agonists on treating obesity complications such as diabetes, cardiovascular diseases and chronic kidney disease, non-alcoholic steatosis, obstructive sleep apnea.

These drugs mimic the implications of incretins - the gut hormones GLP-1 and GIP - which are naturally secreted in the body in response to meal intake. This mechanism leads to an increase in insulin secretion and an inhibition of glucagon secretion - is particularly beneficial in treating type 2 diabetes. In addition, these drugs reduce the feeling of hunger and slow gastric emptying, helping control body weight and blood glucose levels. Consumption of unhealthy, processed foods, especially simple sugars, disrupts the taste perception pathway, deregulating the endocrine system, contributing to compulsive-obsessive overeating, to achieve momentary satisfaction with the release of excess dopamine and serotonin.

These mechanisms disrupt the body's hormonal feedback loop, leading to dysregulation of the release of insulin, ghrelin, leptin, in turn contributing to insulin resistance, metabolic syndrome, obesity (Solomon et al., 2010). The mechanism of taste perception begins with the activation of taste receptors, which transmit signals to the brain via a complex neuronal system. There are five basic tastes - sweet, umami, salty, sour and bitter - but research indicates that there are also receptors that respond to fat. Type II taste receptors (known as TAS1R receptors and TAS2R receptors) play a role, in detecting bitter and umami flavors whereas type III receptors are involved in sensing sour taste through the OTOP protons channel.

Different taste receptors respond to specific stimuli and activate signaling pathways that affect the functioning of the digestive system and the body's response to the foods consumed (Egan, 2024). Taste receptors in the system play a role in controlling the release of hormones linked to feelings of fullness and metabolism regulation like GLP-1, ghrelin and insulin. GLP is the hormone that affects, the two factors: Appetite and taste perception, helps to slow down digestion and enhances glucose balance, potentially playing the crucial role in managing conditions, like obesity and type 2 diabetes.

In addition, an interaction between taste receptors and the reward system suggests that sweet taste may induce strong dopaminergic responses in the brain, contributing to sugar addiction and promoting excessive caloric intake (Egan, 2024). GLP - l is a hormone called an incretin that is released by enteroendocrine cells, in the intestine, during eating food. Its primary functions include stimulating insulin secretion, suppressing glucagon release, slowing gastric emptying, exerting neuroprotective implications (Drucker, 2025). Additionally, GLP-1 influences the central nervous system by reducing hunger through receptor activation in the hypothalamus.

These diverse implications have made GLP-1 a critical target in developing modern metabolic therapies (Drucker, 2025). Early research showed that the effectiveness of GLP-1 agonist was limited by its rapid enzymatic degradation via dipeptidyl peptidase-4 (DPP-4), significantly shortening its half-life in circulation. A substantial breakthrough occurred with the discovery of exendin-4, a peptide found in the saliva of the Heloderma suspectum lizard, which exhibited similar properties to GLP-1 but was more resistant to DPP-4 degradation. This discovery led to the development of exenatide, the first synthetic GLP-1 receptor agonists approved for type 2 diabetes treatment (Drucker, 2025).

In the following stage, in the development process for drugs was centered on developing extended-release versions, like the restructured version known as liraglutide that binds with albumin to extend its duration in the body and allow for dosages. Continued

investigations resulted in semaglutide that could be given weekly to boost compliance and treatment effectiveness significantly (Drucker, 2025). Clinical trials have shown that GLP-1 agonists are not helpful for managing diabetes but practical in helping with weight loss and have therefore been used in treating obesity. They work by making individuals feel fuller longer after eating, speeding up the process of digestion and influence the brain's pleasure center to reduce the desire for calorie foods.

Studies on liraglutide and semaglutide reported weight decrease of 15–20% (Drucker, 2025). The impact of GLP-1-based drugs extends beyond metabolic regulation. These medications have been proven beneficial for the heart by lowering the chances of stroke and heart problems in individuals with kidney disease while also to enhance metabolic functions in these patients. Furthermore, new studies indicate that these drugs could be helpful, in addressing conditions associated with brain degeneration and addictive behaviors (Drucker, 2025). To sum up the advancement of GLP-1 derived remedies has transformed the management of metabolic disorders by offering regulation of body weight and metabolic factors.

Nevertheless, more research is necessary to evaluate their long-term safety and investigate their applicability in addressing health issues (Drucker, 2025). Sugar substitutes impact, on metabolism has garnered interest in times. Although researchers initially assumed that low-calorie sweeteners could help with weight loss, new research suggests that they may interfere with natural mechanisms of appetite regulation and glucose homeostasis. Indications are that sugar substitutes may trick the body, leading to compensatory increases in caloric intake and metabolic disturbances. Some studies also suggest their implications on the gut microbiome and possible links to insulin resistance (Egan, 2024).

Having a lot of body weight poses a risk for OBS but it reversed with the right approach. Obstructive sleep apnea (OBS) is characterized by repeated episodes of throat collapse during sleep, leading to apnea and hypopnea, resulting in hypoxemia, hypercapnia and frequent awakenings. The condition accompanied by substantial clinical symptoms, such as excessive daytime sleepiness - this is an independent risk factor for the development of cardiovascular disease (Malhotra et al., 2024). It's a condition globally that implications over 900 million individuals; around 40% experience a to severe variant of the disorder.

The advantages of losing weight in individuals with the issue of obesity in adults is widespread. Clinical guidelines suggest addressing this concern within this demographic (Malhotra et al., 2024). Therefore, pharmacological intervention targeting obesity and its secondary implications on OBS, blood pressure and low-grade inflammation, may provide a holistic approach that traditional mechanical therapies do not (Malhotra et al., 2024). Traditional treatments for OBS have relied mainly on mechanical support during sleep. Positive airway pressure (PAP) therapy improves apnea-hypopnea index (AHI) and relieves symptoms of the condition.

However, the effectiveness of this therapy limited by varying degrees of patient compliance, randomized trials have not confirmed its impact on reducing cardiovascular events or mortality. Other techniques like mandibular advancement or upper airway surgery, including sublingual nerve stimulation, are employed when PAP fails, they are not always successful and are treatment plans that are invasive in nature (Malhotra et al., 2024). Currently, there is no approved pharmacotherapy aimed directly at treating OBS (Malhotra et al., 2024). After analyzing a group of patients, with moderate to sleep apnea and obesity in a research studies outcomes indicated that tirzepatide effectively lowered a apnea-hypopnea index (AHI) body weight measurements, hypoxia burden as well, as levels of high sensitivity C reactive protein (hs - CRP) (Malhotra et al., 2024).

There was decrease in systolic blood pressure and improved sleep parameters as assessed by patient reports. These results indicate a potential multifaceted impact of tirzepatide on the health of obstructive sleep apnea by patients, especially in the context of co-occurring obesity (Malhotra et al., 2024). Most prolonged observations on extensive groups involve Liraglutide, so this GLP agonist-1 received the most attention during this meta-analysis. Observations have confirmed the positive impact of liraglutide treatment on obesity complications such as insulin resistance, type 2 diabetes, diabetic neuropathy, treatment of cardiovascular complications such as heart failure, arteriosclerosis, non-alcoholic fatty liver disease and treatment of Parkinson's disease symptoms.

Using semaglutide and tirzeapide in the above aspects is currently being investigated, but the results are promising, more research is needed on more extensive cohorts. Liraglutide was registered with the FDA in 2010. The introduction of glucagon-like peptide-1 (GLP-1) analogs has come a new hope for the treatment. The multidirectional implications is include by the stimulation of insulin secretion, inhibition of glucagon, slowing of gastric emptying and decrease of appetite. In 2015, FDA approved liraglutide 3.0 mg as the first GLP-1 receptor agonist for treating obesity in adults with BMI ≥ 30 kg/m² or overweight in adults BMI 27-29.9 kg/m² with associated metabolic diseases (Siraj and Williams, 2015). The randomized, controlled clinical trial conducted by Pi-Sunyer and colleagues included more than 3,700 patients without diabetes from six continents.

Participants received liraglutide (3.0 mg/day) or placebo in combination with a lifestyle intervention (Siraj and Williams, 2015) (Table 1). After undergoing 56 weeks on the treatment plan, the liraglutide medication group experienced a weight loss of 8.4 kg, at the same time those in the placebo group saw decreased weight of 2.8 kg, which was much lower (Siraj and Williams, 2015). In comparison (Siraj and Williams, 2015). Additionally, it was found that 63 percent individuals who took liraglutide managed to shed 5 percent of their body weight and a third achieved a decrease more substantial than or equal to 10%. This is significantly higher, than the percentages observed in the placebo group 27 % and 11%, respectively (Table 1) (Siraj and Williams, 2015).

Liraglutide also showed benefits regarding improving glucose metabolism: it reduced the level of insulin resistance - the incidence of type 2 diabetes was significantly lower in the liraglutide-treated group, indicating a potential impact in preventing the development of diabetes in patients with a high metabolic risk (Siraj and Williams, 2015). However, liraglutide therapy was associated with adverse implications, mainly on the gastrointestinal side. Nausea is a symptom experienced by 40 percent of patients. Vomiting and diarrhea were also frequently reported (Siraj and Williams, 2015). There was no substantial increase in calcitonin levels or cases of medullary thyroid cancer, but further observation is needed to fully assess the safety of long-term therapy (Siraj and Williams, 2015).

**Table 1** PI – SUNVEY STUDY, liraglutide – double-anonymized trial (3700 obese patients without diabetes)

| The type of research group | Study group (number of people included in the study) | Dosage | Duration of observation (weeks) | Weight decrease (kg) | Weight decrease (%) |
|---|---|---|---|---|---|
| With drug | n=1850 | 3 mg | 56 weeks | 8,4 kg | 5% wagi u 63% 10% ≥ u 27% |
| Placebo | n=1850 | - | 56 weeks | 2,8 kg | - |

**Treating obesity in children**

Childhood obesity is a gradually developing issue that raises concerns about health risks such as type 2 diabetes and conditions like: nonalcoholic fatty liver disease, cardiovascular problems (Fox et al., 2025). Although, lifestyle intervention strategies are including altering diet and increasing physical activity are the current mainstay of treatment, they are not always sufficient. As a result, there is growing interest in pharmacological options to support therapy (Fox et al., 2025). The multicenter, randomized phase 3a clinical trial (SCALE Kids Trial) evaluated the efficacy and safety of liraglutide, a GLP-1 receptor agonists, in treating childhood obesity. The research showed that liraglutide is practical in lowering BMI in children aged 6 to 12 years with obesity and performs better in comparison to methods (Fox et al., 2025).

**Obesity - treating adolescence**

Obesity in teenagers poses a health risk by raising the chances of developing type 2 diabetes well, as hypertension and heart diseases. The study findings indicated that treatment with Lirgulutide decreased body mass index in cases where combined with behavioral therapy (Hannon and Arslanian, 2023).

**Treating obesity in adults**

The STEP 1 trial adults with overweight and obesity experienced lasting weight loss well as improved metabolic factors in cases where following a lifestyle intervention along with taking 1 dose weekly (2,4 mg equivalent to 3 standard doses). These findings suggest that GLP-1 receptor modulation represents a practical pharmacological option for obesity treatment, outperforming previously available therapies. However, further research is needed to assess its long-term safety (Table 2) (Wilding et al., 2021).

A major challenge is preventing weight gain again after losing weight, a key challenge, which is seen frequently in obese patients. The study, conducted by researchers at the University of Copenhagen, aimed to evaluate the effectiveness of different strategies for maintaining a healthy weight after a low-calorie diet. The study involved 195 adult participants with obesity (BMI 32-43 kg/m$^2$) who were put on an 8-weeks low-calorie diet, leading to an average weight loss of 13.1 kg (Lundgren et al., 2021).

The study demonstrated that combining exercise with liraglutide was the most practical strategy for maintaining weight loss and improving metabolic parameters. Liraglutide alone also contributed to further weight decrease but was associated with more frequent side implications, particularly nausea. These findings suggest that optimal obesity treatment should integrate the two factors of these

pharmacological interventions and physical activity to maximize metabolic benefits while minimizing adverse implications (Lundgren et al., 2021).

**Table 2** STEP - 1 (semaglutide - double-anonymized trial)

| The type of research group | Study group (number of people included in the study) | Duration of observation (weeks) | Dosage | Weight decrease (kg) | Weight decrease (M – mean %) |
|---|---|---|---|---|---|
| Patients with obesity BMI = 30 or greater (≥27 in persons with ≥1 weight-related coexisting condition without diabetes mellitus | n = 1961 | 68 weeks | 2,4 mg once-weekly subcutaneous | -15,3 kg | -14,9 % |
| Placebo | n=1961 | 69 weeks | - | -2,6 kg | -2,4 % |

**Indications for treating obesity during type 2 diabetes mellitus (T2DM)**

The GRADE multicenter clinical trial of 5047 patients with a recent diagnosis of T2DM compared the efficacy of four drugs used in combination therapy with metformin: Insulin glargine, glimepiride (a sulfonylurea derivative), a GLP-1 receptor agonists (liraglutide) and a DPP-4 inhibitor (sitagliptin). The study showed that liraglutide used with metformin or insulin glargine with metformin were the most practical drugs for lowering HbA1c levels (Nathan et al., 2022). In combination with metformin, liraglutide, a GLP-1 receptor agonists, also caused weight loss (Nathan et al., 2022). Sitagliptin was considered least suitable for long-term glycemic control (Nathan et al., 2022).

These results have essential clinical implications, pointing to the need to individualize type 2 diabetes therapy according to the patient's needs (Nathan et al., 2022). Table GRADE – trials (insulina glargine U-100, glimepiride, liraglutide, sitagliptin) Semaglutide was detected in weight decrease in the range of 8-9%,which was associated with improved patients' overall health, increased exercise tolerance and a likely decrease in the risk of heart failure progression (Packer et al., 2025). Based on the STEP-HFpEF DM trial, semaglutide (2.4 mg once a week) among heart failure patients with preserved ejection fraction, obesity and type 2 diabetes provided substantial benefits over placebo - the mean weight decrease was -9.8% for semaglutide and -3.4% for placebo a difference of -6.4 points (95% CI, -7.6 to -5.2; P<0.001).

Tirzepatide was observed during the 3-year SURMOUNT-1 clinical trial, evaluating the efficacy and safety of Tirzepatide's treatment (Jastreboff et al., 2024). Has shown substantial potential for weight decrease having achieved a 12% to 21% decrease in obese patients (Packer et al., 2025). Tirzepatyde in treating obesity and prevention of type 2 diabetes. Weight decrease was identified in 50.7% of patients; the mean weight loss was detected in 12.3% for the 5 mg dose, 18.7% for the 10 mg dose, 19.7% for the 15 mg dose, compared to 1.3% in the placebo group (Table 3) (Jastreboff et al., 2024). After the drug was ceased diabetes was diagnosed in 2.4% of those taking tirzepatide, compared to 13.7% in the placebo group (Jastreboff et al., 2024).

Tirzeptaide demonstrated lasting weight loss results. Notably lowered the chances of transitioning to type 2 diabetes in individuals who are overweight or have pre-diabetic subjects (Jastreboff et al., 2024). The findings indicate that using tirzepetide as a treatment option could be feasible for managing obesity and preventing diabetes; however, it is essential to use it in the run to sustain its benefits. The other study demonstrated that once-weekly administration of dulaglutide. GLP-1 receptor agonist significantly improves glycemic control in youth with type 2 diabetes (Arslanian and Cox, 2022).

During a 26-weeks study done haphazardly. It included participants aged between 10 to 18 years who were either, on metformin medication or basal insulin treatment (some also managed their diabetes through diet and exercise: double-masked) (Arslanian and Cox, 2022). Results showed a significant decrease of glycated hemoglobin levels and fasting glucose concentrations in groups. It was receiving dulaglutide (doses of 0.75 mg and 1.5 mg) compared to placebo. Adverse implications, primarily gastrointestinal symptoms, were mild and transient (Arslanian and Cox, 2022).

Although dulaglutide did not affect BMI, it is operational simplicity and efficacy could make it a valuable tool for managing diabetes in this vulnerable population (Arslanian and Cox, 2022). Metformin remains the first-line therapy at the same time, additional

agents are specifically developed to patient needs GLP-1 receptor agonists (liraglutide, semaglutide) – improves glycemic control, promotes weight loss, reduces cardiovascular risk (Ismail-Beigi, 2012).

**Table 3** SURMOUNT – 1 tial (tirzepatide - double-anonymized trial)

| The type of research group | Study group (number of people included in the study) | Duration of observation (weeks) | Dosage | Weight decrease (kg) | Weight decrease (%) | Weight decrease (M – mean %) |
|---|---|---|---|---|---|---|
| Patients with obesity | =2539 | 176 weeks | 5 mg<br>10 mg<br>15 mg<br>placebo | 8,4 kg | -12,3 %<br>-18,7 %<br>-19,7 %<br>-1,3% | -12,3% |

**Tirzepatide versus Semaglutide – A Comparison of Efficacy and Safety in Type 2 Diabetes Treatment**

The 40-weeks, open-label, phase 3 SURPASS-2 trial evaluated the efficacy and safety of tirzepatide vs. semaglutide in 1879 patients with T2DM (Table 4) (Frías et al., 2021). After 40 weeks of observation, in the study focus was noticed the lowering of HbA1c level. Additionally, the study also looked into weight changes (Frías et al., 2021).

**Table 4** The reduction values for Hba1c (glycated hemoglobin) and body weight depend on the dose used.

| Glycemic Control – decrease of HbA1c | Weight Loss |
|---|---|
| -2.01% (tirzepatide 5 mg) | -7.6 kg (tirzepatide 5 mg) |
| -2.24% (tirzepatide 10 mg) | -9.3 kg (tirzepatide 10 mg) |
| -2.30% (tirzepatide 15 mg) | -11.2 kg (tirzepatide 15 mg) |
| -1.86% (semaglutide 1 mg | -5.7 kg (semaglutide 1 mg) |

Tirzepatide demonstrated more significant efficacy than semaglutide (in the two factors HbA1c), decreased weight. Currently, tirzepatide represents a promising therapeutic option for patients with T2DM, especially those with obesity (Frías et al., 2021).

**Indications for treating obesity in during type 1 diabetes mellitus (T1DM)**

Type 1 diabetes mellitus (also known as T1DM) is a lasting condition that causes the destruction of pancreatic beta cells and results in a complete lack of insulin production. Contrary to previous beliefs, more than half of new T1DM diagnoses occur in adults, significantly influencing treatment strategies and long-term cardiovascular risk assessment (Manrique-Acevedo et al., 2024). The average age of individuals patients with T1DM is 40 years (Manrique-Acevedo et al., 2024). Despite the progress made in treating diabetes patients, with Type 1 Diabetes Mellitus (T1DM) their life expectancy still falls short by an average of about 13 years compared to the population due to disease (CDV) which stands as the primary factor contributing to mortality rates among them.

Studies such as DCCT/EDIC have demonstrated a direct correlation between glycemic control and cardiovascular risk with an HbA1c target below 7% reducing CVD risk by 42% over 17 years (Manrique-Acevedo et al., 2024). T1DM significantly increases cardiovascular risk requiring a comprehensive prevention and treatment strategy. Intensive glycemic control, lipid and blood pressure management, emerging metabolic therapies may improve the two factors quality and longevity in T1DM patients (Manrique-Acevedo et al., 2024).

**Heart Failure with Preserved Ejection Fraction (HFpEF) - the method of diagnosis and treatment.**

Heart failure is when the heart fails to supply sufficient blood flow to meet the body's metabolic needs even though filling pressures are normal. The latest classification categorizes heart failure by the level of ejection fraction (LVEF) dividing it into three groups:

The first group patients - researches have observed heart failure and they have reduced ejection fraction (HFrEF. LVEF ≤40%) (Cannata and McDonagh, 2025).

The second group patients - researchers have observed heart failure and they have reduced mildly ejection fraction (HFmrEF. LVEF 41–49%) (Cannata and McDonagh, 2025).

The third group patients – researchers have observed heart failure with preserved ejection fraction (HFpEF. LVEF ≥50%) (Cannata and McDonagh, 2025).

Over recent decades, the incidence of HFpEF has significantly increased, primarily due to population aging and the rising prevalence of obesity, type 2 diabetes, hypertension (Cannata and McDonagh, 2025). One of the treatment strategies is the use of GLP-1 receptor agonist (semaglutide, tirzepatide) – beneficial for patients with obesity in all groups (Cannata and McDonagh, 2025). Obesity plays a role in increasing the likelihood of heart failure, with preserved ejection fraction (HFPEF), where inflammation caused by fat tissue is one of the contributing factors (Packer et al., 2025). In the STEP-HFpEF DM trial, semaglutide (2.4 mg once a week) provided significant benefits over placebo: Improved distance in the 6-minute walk test: The difference was 14.3 meters in favor of semaglutide (Kosiborod et al., 2024).

Semaglutide reduced C-reactive protein levels by 42% (28,8%) (Kosiborod et al., 2024). Study findings suggest that semaglutide, a GLP-1 receptor agonists initially used for treating diabetes and obesity, shows promising implications in improving outcomes for patients with HFpEF. Throughout, for a year-long study involving participants with a high BMI (>30), semaglutide significantly reduced body weight (by 13.3%) and improved performance in the 6-minute walk test and quality-of-life scores. Improved NT-proBNP levels also suggest reduced intracardiac pressures, though further research is necessary (Kosiborod et al., 2024). The findings support the hypothesis that HFpEF is driven by metabolic and inflammatory disturbances, paving the way for new treatment options, particularly for obese patients (Pinto, 2023).

Obesity significantly increases the chances of developing heart failure with preserved ejection fraction (HFPEF), when inflammation triggered by fat plays a rolein its pathophysiology. Two separate research projects examining how semaglutide is employed in individuals with heart failure who have preserved ejection fraction (HFPEF) along with obesity issues have shown that GLT receptor stimulation might not just ease symptoms but lowers the likelihoods of heart failure complications (Packer et al., 2025). However, the impact of semaglutide on inhibiting the deterioration of HFpEF was studied in exploratory analyses with a limited follow-up period of 52 weeks, requiring further studies to confirm these conclusions.

Tirzepatyd - an agonist of GLP-1 and GIP receptors, has shown efficacy not only in weight decrease, but a positive implications on cardiovascular outcomes in patients with HFpEF and obesity, but observations require further research studies (Packer et al., 2025). Tirzepatide has shown promise in reducing body weight, lowering blood pressure, reducing inflammatory markers and vascular endothelial dysfunction. It may be a viable therapeutic option for individuals with obstructive sleep apnea (Malhotra et al., 2024). Therapeutic goals focus on reducing inflammation caused by visceral fat. Weight decrease lowers blood pressure (Malhotra et al., 2024).

Although the results are promising, there is still a deficiency of complete data from extensive-scale trials on its efficacy and safety in obese patients with heart failure with preserved ejection fraction (HFpEF). Therapy with thirzepatide caused a significant decrease in the risk of cardiovascular death or clinical worsening versus placebo and additionally improved patients with comorbid obesity and heart failure with preserved ejection fraction (HFpEF). The findings highlight the promise of tirzapetide, as a treatment choice for patients, in this category. Most patients with HFpEF also suffer from obesity, which is frequently with the pathogenesis and worsening of the condition.

Visceral obesity induces a state of systemic inflammation, which can negatively affect myocardial function through pro-inflammatory changes in epicardial adipose tissue (Packer et al., 2025). The risk of developing HFpEF increases significantly with increasing body mass index (BMI). Evidence suggests that weight-loss interventions like a bariatric surgery and using GLP-1 receptor agonists, are practical in mitigating inflammation, reducing epicardial fat volume, lowering the risk of heart failure and improving the quality of life of patients with established HFpEF (Packer et al., 2025). In the SUMMIT study, a randomized, placebo-controlled trial, 731 patients with HFpEF, a body mass index (BMI) ≥30 an ejection fraction ≥50% were allocated to receive either tirzepatide (up to 15 mg per week) or placebo (Packer et al., 2025).

In the treatment group, there was a 38% decrease in the risk of death from heart-related causes or worsening heart failure compared to the placebo group (Packer et al., 2025). Tirzepatide led to a significant improved quality of life (mean difference in KCCQ-CSS: 6.9 points) and enhanced exercise tolerance, as measured by the 6-minute walking distance (Packer et al., 2025). Weight loss in the tirzepatide group averaged 13.9%, whereas in the placebo group, it was only 2.2%. This decreased high-sensitivity CRP levels,

indicating decreased inflammation (Packer et al., 2025). Tirzepatide, through its multifaceted action, has the potential to deliver substantial health benefits to individuals with obesity and HFpEF by modulating critical disease-related mechanisms (Packer et al., 2025).

The GRADE study assessed the effectiveness of different classes of glucose-lowering drugs, used in combination with metformin in individuals with type 2 diabetes (Nathan et al., 2022). The medications studied included insulin glargine, glimepiride, liraglutide, sitagliptin. The results demonstrated no significant differences in the development of microvascular complications like peripheral neuropathy or albuminuria between the groups. However, liraglutide demonstrated a potential benefit in reducing cardiovascular event risk compared to the other therapies. These findings may suggest the advantages of GLP-1 receptor agonists in preventing cardiovascular diseases in type 2 diabetes patients (Nathan et al., 2022).

**The treatment of cardiovascular results of diabetes type 2**

Type 2 diabetes is a health issue worldwide, affecting over 450 million people worldwide. It leads to the two factors microvascular (retinopathy, nephropathy, neuropathy) and macrovascular complications (cardiovascular disease, strokes, peripheral vascular disease). Patients with T2DM are more than twice as likely to develop cardiovascular diseases (CVDs) compared to non-diabetic individuals with women facing, a higher risk of coronary artery disease than men (Kalyani, 2021). Type 2 diabetes (T2DM) is contributor, to cardiovascular diseases (CVD), which remain the reason for fatalities in individuals with diabetes. Therefore, every new glucose-lowering therapy must undergo rigorous cardiovascular safety evaluation (Marso et al., 2016). Pathophysiology of Cardiovascular Risk in T2DM (Kalyani, 2021).

- Insulin resistance and chronic hyperglycemia drive oxidative stress, inflammation, endothelial dysfunction, accelerating atherosclerosis.
- Atherogenic dyslipidemia – increased triglycerides and LDL alongside low HDL contribute to cardiovascular risk (Kalyani, 2021).
- Chronic low-grade inflammation and immune activation, which promotes atherosclerosis and plaque destabilization (Kalyani, 2021).
- Microvascular dysfunction and prothrombotic state are leading to an increased risk of thrombosis and ischemia (Kalyani, 2021).

GLP-1 receptor agonist (liraglutide, semaglutide, dulaglutide) – lowers stroke and myocardial infarction risks in patients with T2DM and CVD. The STEP TEENS study demonstrated that weekly administration of semaglutide at a 2.4 mg dose, combined with lifestyle interventions, resulted in significantly more substantial decrease in body mass index (BMI) among adolescents with obesity compared to lifestyle interventions alone. These findings highlight the potential of pharmacological support as an adjunct to behavioral modifications in managing obesity in younger populations (Weghuber et al., 2022). Liraglutide, a glucagon-like peptide-1 (GLP-1) analog, demonstrated significant cardiovascular benefits in the LEADER trial.

This multicenter, randomized study involving patients with type 2 diabetes and high cardiovascular risk found that liraglutide therapy reduced the risks of cardiovascular deaths, myocardial infarctions, strokes compared to placebo. The results showed substantial differences in overall mortality and microvascular complications. The study highlights liraglutide's potential as a practical drug to improve cardiometabolic outcomes in patients with type 2 diabetes (Marso et al., 2016). Type 2 diabetes (T2DM) is a significant risk factor for cardiovascular diseases (CVD), which remain the leading cause of death among diabetic patients. Every new glucose-lowering therapy must undergo rigorous evaluation regarding its cardiovascular impact.

Semaglutide, a glucagon-like peptide-1 (GLP-1) receptor agonist, was previously available only in subcutaneous form. The introduction of oral semaglutide (Rybelsus) represents a breakthrough in diabetes treatment, offering an alternative to injections and improving adherence (Husain et al., 2019). The PIONEER 6 study assessed the cardiovascular safety of oral semaglutide in 3183 high-risk patients. It was a randomized, double-anonymized, placebo-controlled trial. The incidence of major adverse cardiovascular events (MACE) was evaluated: Cardiovascular death, nonfatal myocardial infarction, nonfatal stroke (Husain et al., 2019). Cardiovascular deaths occurred in 0.9% of semaglutide-treated patients vs. 1.9% in the placebo group, indicating a 51% decrease in cardiovascular mortality (Husain et al., 2019).

All-cause mortality was also halved in the group receiving semaglutide, compared to the placebo (Husain et al., 2019). There was no substantial difference in the incidence of nonfatal myocardial infarction or stroke between the groups (Husain et al., 2019). The average weight loss was 4.2 kg, demonstrating significant metabolic (Husain et al., 2019). Oral semaglutide has been found a treatment choice for patients with type 2 diabetes as it does not raise the risk to health in this group. Moreover, its decrease in overall and cardiovascular

mortality suggests potential cardioprotective implications (Husain et al., 2019). The availability of an oral formulation may improve treatment adherence and long-term outcomes, particularly for patients reluctant to use injections (Husain et al., 2019).

The SUSTAIN-6 trial included 3297 patients with T2DM who were at high cardiovascular risk. This randomized, double-masked, placebo-controlled study compared semaglutide (0.5 mg or 1.0 mg once weekly) with placebo over 104 weeks. The main focus was, on tracking the occurrence of cardiovascular events (MACE) which encompassed cardiovascular mortality as well, as instances of nonfatal myocardial infarction and strokes (Marso et al., 2016). Patients receiving semaglutide had fewer substantial cardiovascular events compared to placebo (Marso et al., 2016). The risk of stroke was reduced by 39% in the semaglutide group compared to placebo (Marso et al., 2016). There was no variance in cardiovascular mortality noted among the groups (Marso et al., 2016).

Semaglutide reduced the risk of diabetic nephropathy progression by 36% but increased the risk of retinopathy complications (Marso et al., 2016), decreased HbA1c by 1.1% (dose 0.5 mg) and 1.4% (dose 1.0 mg) compared to 0.4% in the placebo group (Marso et al. 2016). Weight loss of 3.6 kg (0.5 mg) and 4.9 kg (1.0 mg) compared to -0.7 kg and -0.5 kg in the placebo group (Marso et al., 2016). The SUSTAIN-6 trial also confirmed that semaglutide does not increase cardiovascular risk and may have protective benefits, especially in reducing stroke incidence. A valuable therapeutic option for high cardiovascular risk T2DM patients is therefore represented by this GLP-1 analog, with its glucose lowering efficacy, weight loss benefits, nephroprotective effects.

**Treating diabetic nephropathy**

Liraglutide, an analog of glucagon-like peptide-1 (GLP-1), is used in treating type 2 diabetes and is known for its beneficial effects on the cardiovascular system. As part of the LEADER trial, this study was a randomized, controlled trial of the long-term impact of liraglutide on kidney function in patients with type 2 diabetes and high cardiovascular risk (Mann et al., 2017). Altogether of 9,340 patients were included in this randomized, placebo-controlled trial and followed for a median of 3.84 years (Mann et al., 2017). The group treated with liraglutide showed a significantly lower risk of renal complications, such as newly diagnosed persistent macroalbuminuria, a doubling of serum creatinine levels, or end-stage renal disease.

The results suggest that liraglutide use may slow the progression of diabetic nephropathy Mann et al., (2017) chronic kidney disease is a substantial concern for individuals with type 2 diabetes, as it not only affects overall health but also increases the risk of severe complications and mortality. This study assessed the impact of liraglutide on renal health and demonstrated its protective effects. Patients, who received liraglutide, experienced fewer instances of kidney function deterioration than those in the placebo group, however. The decrease in macroalbuminuria incidence suggests that liraglutide may provide renal protection through pathways that extend beyond glucose control.

When this therapy is integrated into standard diabetes treatment, not only can metabolic outcomes be improved, but the progression of chronic kidney disease can be slowed, thus lessening the need for dialysis and improving mortality risk from kidney-related causes (Mann et al., 2017). The study results indicate that liraglutide may contribute to renal function protection in patients with type 2 diabetes and high cardiovascular risk. Patients receiving liraglutide were less likely to develop macroalbuminuria and other severe renal complications compared to those in the placebo group. This suggests that, beyond standard glycemic control, liraglutide may exert an additional, independent nephroprotective impact.

A decrease in the incidence of serious renal complications could lead to an improved quality of life for patients and a lower risk of requiring dialysis therapy in the future (Mann et al., 2017). The article explores the possibility of using small-molecule GLP-1 receptor agonists like orforglipron for obesity management. The current approved GLP-1 drugs, such as liraglutide and semaglutide, are injected which limits their use and acceptance by patients because of the invasive character of the administration method (Wharton et al., 2023). Orforglipron as an oral GLP-1 agonist opens up new possibilities for the treatment of obesity especially for those who are looking for non-invasive solutions (Wharton et al., 2023).

A phase 2 trial demonstrated that orforglipron leads to substantial weight decreas, reaching up to 14.7% in the highest dose group (Wharton et al., 2023). The study also noted cardiometabolic benefits, such as decrease VLDL cholesterol levels and systolic blood pressure The most commonly reported side effects, were gastrointestinal disturbances, may be mitigated through slower dose escalation (Wharton et al., 2023). These discoveries underscore the promise of efficient methods for treating obesity; however additional phase 3 trials are crucial to assess the lasting effectiveness and safety of orforglipron (Wharton et al., 2023).

The results of another study (phase 2) indicates that daily use of the oral GLP-1 receptor agonist, orforglipron, can significantly contribute to weight decrease in individuals with obesity or overweight combined with comorbid conditions (Wharton et al., 2023).

Compared to placebo, orforglipron showed dose-dependent weight loss, achieving an average decrease of 9.4%–14.7% over 36 weeks. The study also confirmed cardiometabolic benefits, such as reduced blood pressure and improved lipid profiles (Wharton et al., 2023). Orforglipron has an efficacy and a safety profile similar to that of the injectable GLP-1 receptor agonists and may represent a new and more convenient therapeutic option for patients with obesity (Wharton et al., 2023).

**Hopes for OBS treatment of obstructive sleep apnea (OBS)**

A substantial risk factor for OBS reversed, but excess body weight is one of them. Obstructive sleep apnea (OBS) is a chronic disease that is defined by repeated episodes of throat collapse during sleep, leading to apnea and hypopnea, resulting in hypoxemia, hypercapnia and frequent awakenings. The condition is also characterized by the presence of severe clinical symptoms, including excessive daytime sleepiness, is itself an independent risk factor for the development of cardiovascular disease (Malhotra et al., 2024). It is a common disorder worldwide, affecting more than 900 million people, about 40% of whom have a moderate or severe form.

The benefits of weight loss in patients with OBS are well established and clinical practice guidelines advise managing obesity (Malhotra et al., 2024). Therefore, pharmacological intervention targeting obesity and its secondary effects on OBS, blood pressure and low-grade inflammation may provide a holistic approach that traditional mechanical therapies do not (Malhotra et al., 2024). Traditional treatments for OBS have relied mainly on mechanical support during sleep. Positive airway pressure (PAP) therapy improves apnea-hypopnea index (AHI) and relieves symptoms of the condition.

However, the effectiveness of this therapy is limited by varying degrees of patient compliance, randomized trials have not confirmed its impact on reducing cardiovascular events or mortality. Other approaches, such as mandibular advancement or upper airway surgery (e.g., sublingual nerve stimulation) are used in cases of PAP intolerance but are not always practical and involve the invasive nature of treatment (Malhotra et al., 2024). Obstructive sleep apnoea (OSA) is a disorder for which there is currently no approved pharmacotherapy, although it exists for other comorbid conditions associated with OSA (Malhotra et al., 2024).

To sum up the findings of the research conducted on individuals with moderate to sleep apnea and obesity; tirzeptide was discovered to have a notable impact on reducing the apnea-hypopnea index (AHI) body weight as well as hypoxia burden. Additionally, it showed a decrease, in levels of high sensitivity C reactive protein (hsCRS), (Malhotra et al., 2024). Additionally, there decreased systolic blood pressure and an enhancement of sleep parameters as documented by patient reports. These results indicate a potential multifaceted impact of tirzepatide on the health of obstructive sleep apnea patients, especially in the context of co-occurring obesity (Malhotra et al., 2024).

**The impact of drugs on treating non-alcoholic fatty liver disease**

Semaglutide was explored for treating nonalcoholic steatohepatitis (NASH). The study included 320 patients with biopsy-confirmed NASH and various stages of liver fibrosis (F1–F3). Participants were randomly assigned to receive semaglutide at doses of 0.1 mg, 0.2 mg, or 0.4 mg daily or a placebo for 72 weeks (Newsome et al., 2021). The results indicate that semaglutide at 0.4 mg dose significantly improved histological resolution of NASH without worsening liver fibrosis compared to placebo (59% vs. 17%). However, there were no significant changes in fibrosis progression between the groups. Semaglutide caused important weight loss, which may have led to better liver status. Semaglutide at a 0.4 mg dose increased the rate of NASH resolution without worsening liver fibrosis than placebo.

The treatment was also associated with substantial weight loss, highlighting its potential to reduce the metabolic and inflammatory burden on the liver. Although fibrosis improvement was not considerably semaglutide therapy may play a critical role in managing NASH, especially in patients with obesity (Newsome et al., 2021). NASH is a chronic disease characterized by the accumulation of fat in the liver, inflammation, fibrosis. NASH is associated with obesity and insulin resistance. This study evaluated the potential impact of semaglutide on NASH resolution. The findings demonstrate that semaglutide can significantly support NASH remission while promoting substantial weight loss, which is critical for treating this condition.

Although the improved fibrosis stages was not statistically considerably, metabolic benefits and decrease in inflammation suggest a positive impact on patient health (Newsome et al., 2021). The study results demonstrated that semaglutide at a daily dose of 0.4 mg significantly increased the percentage of patients achieving NASH resolution without worsening liver fibrosis compared to placebo. The treatment was also associated with substantial weight loss, highlighting its potential to reduce the metabolic and inflammatory burden on the liver. Although fibrosis improvement was not substantial, semaglutide therapy may play a critical role in managing NASH, especially in patients with obesity (Newsome et al., 2021).

Metabolic dysfunction–associated steatohepatitis (MASH) is a progressive liver disease associated with serious complications, including cirrhosis and increased liver-related mortality (Loomba et al., 2024). Current treatment options remain limited, pharmacological therapies have yet to demonstrate consistent efficacy. In this context, tirzepatide, a dual glucose dependent insulinotropic polypeptide (GIP) and glucagon-like peptide-1 (GLP-1) receptor agonist, has been found to have potential in the management of MASH with moderate to severe fibrosis as a therapeutic option (Loomba et al., 2024).

The phase 2, multicenter, randomized SYNERGY-NASH trial, conducted on 190 patients with biopsy-confirmed MASH and stage F2 or F3 liver fibrosis, evaluated the efficacy of once-weekly subcutaneous tirzepatide injections (5 mg, 10 mg, or 15 mg) compared to placebo over 52 weeks. The primary endpoint was MASH resolution without fibrosis progression at the same time the key secondary endpoint was improved fibrosis stage without worsening MASH (Loomba et al., 2024). Tirzepatide demonstrated superior efficacy compared to placebo: MASH resolution without fibrosis progression was achieved in 44% of patients on 5 mg, 56% on 10 mg, 62% on 15 mg, compared to only 10% in the placebo group Loomba et al., (2024), at least one-stage fibrosis improvement without worsening MASH was detected in 55% (5 mg group), 51% (10 mg group), 51% (15 mg group), compared to 30% in the placebo group (Loomba et al., 2024).

In addition, the treatment significantly reduced liver enzyme levels, improved fibrosis biomarkers and decreasesed the level of fat accumulation in the liver (Loomba et al., 2024). Tirzepatide demonstrated remarkable efficacy in MASH patients with moderate to severe fibrosis, significantly surpassing placebo in disease resolution and liver health improvement. These findings suggest that GIP and GLP-1 receptor modulation might be a novel therapeutic strategy for MASH treatment, but long-term studies are required to confirm its efficacy and safety (Loomba et al., 2024).

**The impact of type 2 diabetes mellitus (T2DM) on the increased risk of Parkinson's disease (PD)**

A growing number of epidemiological studies indicate a substantial link between type 2 diabetes mellitus (T2DM) and Parkinson's disease (PD), suggesting common pathophysiological mechanisms responsible for their development and progression (Yu et al., 2022). The diseases described above are age related and have similar metabolic symptoms of insulin resistance, oxidative stress, and chronic inflammation (Yu et al., 2022). The role of abnormal protein aggregation of proteins – amyloid IAPP in diabetes and $\alpha$-synuclein in Parkinson's disease – in the pathogenesis of T2DM and PD, leading to progressive neurodegeneration, has been established (Yu et al., 2022).

Moreover, insulin resistance in the brain leads to impaired neuronal signaling, increasing the vulnerability of dopaminergic neurons to oxidative stress and mitochondrial dysfunction. The involvement of the gut microbiome in influencing the connection between the gut and brain implies that type 2 diabetes mellitus (T2DM) might indirectly impact responses, in the brain that worsen nerve cell deterioration (Yu et al., 2022). In the context of PD therapy, there is growing interest in the potential use of GLP-1 receptor agonists, such as exenatide or liraglutide, which exhibit neuroprotective effects and may slow the progression of motor and cognitive symptoms (Yu et al., 2022).

Therefore, future research should focus on further defining the mechanisms linking these conditions and the potential benefits of antidiabetic drugs in treating Parkinson's disease (Yu et al., 2022). A phase 2 clinical trial of the GLP-1 receptor agonist lyxisenatide provides new evidence of its potential neuroprotective effects in Parkinson’s disease (PD). Studies was conducted on animals have indicated that activating the GLP-1 receptor might help safeguard dopaminergic neurons against degeneration. This has led to trials investigating using these drugs, in Parkinsons disease treatment (Meissner et al., 2024). In a randomized, double-masked, placebo-controlled trial observed 156 patients with early-stage Parkinson's disease. They were randomly assigned to receive either lixisenatide or placebo for 12 months, followed by a 2-month “washout” period of the drug.

Patients were on a stable dose of standard anti-Parkinson's therapy, which made it possible to assess the impact of lyxisenatide independently of the effects of other drugs (Meissner et al., 2024). The results showed that patients receiving lixisenatide showed minimal improvement (Meissner et al., 2024). Despite the promising results, the study had some limitations. There were no substantial differences in other parameters assessed, such as cognitive function or changes in total levodopa dose. In addition, the relatively short study period does not allow for a full assessment of the long-term effects of the therapy. Therefore, the authors emphasize the need for more extensive and longer studies to confirm the neuroprotective effect of GLP-1 agonist in Parkinson's disease (Meissner et al., 2024).

**Using GLP-1 agonists for treating obesity complications of osteoarthritis**

Knee osteoarthritis (OA) is one of the most prevalent forms of arthritis. This disease is caused by chronic pain, reduced mobility, impaired quality of life. Obesity is a substantial risk factor for the two factors the development and progression of knee OA due to increased mechanical stress on joints, metabolic dysfunction, obesity-related inflammation. Current treatment guidelines emphasize weight decrease and physical activity, but long-term symptom management in obese individuals remains challenging (Bliddal et al., 2024). In the STEP 9 research project conducted a randomized phase II trial, at centers to test the effectiveness and safety profile for a weekly injection dosage (2,4 mg) compared with a placebo among obese individuals with moderate knee osteoarthritis (with a BMI equal to 30 kg/m²).

Participants were randomly assigned (2:1) to receive either semaglutide or placebo, in addition to dietary counseling and physical activity recommendations. Primary endpoints included percentage change in body weight and decrease in knee pain (WOMAC pain score) over 68 weeks (Bliddal et al., 2024). Study results after 68 weeks: Semaglutide showed substantial superiority over placebo in weight decrease and knee pain relief: mean body weight decrease: -13.7% with semaglutide vs. -3.2% with placebo (Bliddal et al., 2024). Decrease in WOMAC pain score: patients receiving semaglutide reported a mean decrease of 41.7 points, compared to 27.5 points with placebo (Bliddal et al., 2024).

Improved physical function (SF-36 questionnaire): more substantial improvement was detected in the semaglutide group (mean increase of 12 points) vs. 6.5 points in the placebo group (Bliddal et al., 2024). Once weekly semaglutide (2.4 mg) in obese individuals with knee OA resulted in substantial weight decrease and improved pain and physical function, outperforming placebo. These findings suggest that GLP-1 receptor modulation could represent a novel therapeutic strategy for obesity-related OA, though further research is needed to assess long-term efficacy and safety (Bliddal et al., 2024).

**Prospects for the development of new substances**

***Retatrutide - a novel receptor agonist three hormones: glucagon like peptide - 1 (GLP), glucose - dependent insulinotropic peptide (GIP), glucagon (GCG)***

Strategies to date have mainly involved drugs that act on single hormonal pathways, but in recent years there has been increasing interest in multi-hormonal therapies. Retatrutide was evaluated in a randomized phase II clinical trial to determine its efficacy and safety in treating obesity (Jastreboff et al., 2023). The study enrolled 338 adult patients with BMI ≥ 30 kg/m² or BMI 27-29.9 kg/m² with weight-related comorbidities. Participants were randomly assigned to 1 of 7 groups that received varying doses of retatrutide (1 mg to 12 mg) or placebo (control group). The therapy lasted 48 weeks. Two research objectives were set: to assess long-term effectiveness after 48 weeks of observation and to measure changes in body weight after 24 weeks of observation (Jastreboff et al., 2023).

Moreover, 100% of patients taking 8 mg and 12 mg of retatrutide achieved a weight decrease of at least 5%, compared to only 27% in the placebo group. A decrease of 15% or more was achieved by 83% of patients taking the highest dose, compared to 2% in the placebo group (Jastreboff et al., 2023). Retatrutide showed substantial efficacy in reducing body weight, surpassing the i effects achieved with GLP-1 agonist monotherapy. With its multidirectional action on GLP-1, GIP and GCG receptors, it may represent a breakthrough in the pharmacotherapy of obesity. Although the drug's efficacy is high, further studies are needed to evaluate its long-term safety and impact on cardiometabolic risk (Jastreboff et al., 2023).

Integrating those drugs into clinical practice should prioritize patient selection, balancing efficacy with tolerability and cost considerations. Future investigations should include optimizing treatment regimens, identifying long-term safety outcomes and exploring combination approaches with other metabolic interventions as the understanding of incretin-based therapies is growing through ongoing research. By tackling these challenges, GLP-1 and GIP receptor agonists have the potential to redefine the standard of care for obesity and its complications.

However, the long-term safety and tolerability of GLP 1 and GIP receptor agonists need further study as well. Moreover, a limitation is the cost and availability of these therapies. However, these agents offer significant clinical benefit; their use is likely to be limited to clinical practice by healthcare system budgets and patient ability to pay. Future studies should include cost effectiveness models to help optimize the use of resources in the management of obesity. However, concerns regarding pancreatitis and potential thyroid neoplasms necessitate continued pharmacovigilance.

**Summary**

GLP-1 and GIP receptor agonists have revolutionized obesity pharmacotherapy by providing practical, sustainable, metabolically favorable weight management solutions. Their impact extends beyond weight loss, encompassing cardiovascular protection, glycemic control in T2DM and T1DM, potential benefits in conditions such as non-alcoholic fatty liver disease and obstructive sleep apnea. Liraglutide - the substance meets the expectations for pharmacological obesity treatment. In monotherapy, it regulates insulin secretion and glycemic levels, when combined with metformin, it lowers glycated hemoglobin levels.

It fulfills hopes in treating patients with heart failure and at herosclerosis (diabetic arthropathy), diabetic nephropathy, causes reversal of non-alcoholic steatosis of the liver and fibrosis in the early stages of F1 and F2, finds a place in treating symptoms of Parkinson's disease improving motor aspects in these patients. Tirzepatide significantly improves quality of life and reduces the risk of adverse cardiovascular events in patients with HFpEF and obesity, suggesting it could be a beneficial drug in this population. Tirzepatide has demonstrated multifaceted benefits in a population with HFpEF and obesity, reducing the rate of heart failure events, improving patient function, lowering body weight and inflammatory parameters.

Mechanisms of action include modulation of adipose tissue and a decrease of inflammation. Retatruotide and tirzapatide are most effective as they act through a triple hormonal pathway. All of the trials considered in this review have uniformity in showing that these agents lead to long-term weight loss and a significant decrease in BMI and enhanced metabolic parameters. These benefits are known to be related to increased satiety, delayed gastric emptying and improved insulin sensitivity, all of which are targeted at obesity's multifactorial cause. The key finding of this study was the markedly enhanced cardiovascular effect of GLP-1 and GIP receptor agonists.

The ability of these agents to reduce systemic inflammation, improve lipid profiles, lower blood pressure presents a compelling argument for their broader use in metabolic and cardiovascular risk management. The observed 38% reduction in cardiovascular mortality and morbidity in the tirzepatide group highlights the potential of these agents beyond weight control. The results of ongoing studies of semaglutide and thirzepatide are promising and seem to confirm hopes of an even more substantial weight - decrease impact with less frequent side implications. There appears are some inconvenience for the patient in injecting the semaglutide preparation daily, but the newly developed oral form of the drug alleviates this issue.

Tirzepatide shows the most potent weight - decrease impact, which is why it is favored by doctors. The impact is exacerbated by lifestyle changes and diet associated with the use of GLP-1 agonists It seems that the evolution of this group of drugs focuses on inhibiting additional neurohormonal pathways, as exemplified by the growing research interest in Retatrutide, addressing both market demands and patient expectations for a faster, more effective treatment of chronic disease known as obesity, without the risk of relapse in the form of the yo-yo effect. Oforglipron is recommended for patients with diabetic nephropathy, and for obesity with unregulated type 2 diabetes. More research is required on lixisenatide for the prevention and treatment of Parkinson’s disease and possibly Alzheimer’s disease.

## 4. CONCLUSION

The stigmatizing impact of obesity, the culture of healthy lifestyles, seems to be a more influential enticement for patients than a narrative based on the yo-yo effect or health arguments. A review of the use of this family of drugs is meant to focus on the highest pharmacological efficacy of tirzepatide for the treatment of obesity and its comorbidities. The GLP-1 receptor agonists have a multidirectional effect. We are looking for substances that are more effective in reducing body weight and comorbidities. This group of drugs is likely to be included in algorithms for the prevention and treatment of neurodegenerative diseases:

Parkinson's disease and Alzheimer's disease: Research is becoming more confident, although initial observations are not satisfactory and require replication in larger research trials. Concerning to treating diabetes, it seems that the drugs described in the article prolong patients' survival time and improve their comfort, joining the trend of longevity, aspiring to “longevity molecules” perhaps entering the annals of prevention and treatment of diseases of civilization for good. The emergence of GLP-1 and GIP receptor agonists marks a paradigm shift in obesity management, bridging the gap between metabolic regulation and weight control.

**Authors’ Contribution**

Marcin Grzebyk: Conceptualization, investigation, methodology, writing- rough preparation,

Anna Tokarska: Formal analysis, data curation, methodology, supervision
Aleksandra Arnista: Writing-rough preparation, investigation,
Mateusz Świątko: Visualization, data curation, writing-rough
Paweł Sosnowski: Formal analysis, supervision, writing-review
Joanna Rybak: Formal analysis, writing-review and editing, methodology
Agnieszka Waszczuk: Formal analysis, writing-review and editing,
Aleksandra Kołodziejczyk: Methodology, conceptualization, data curation, supervision
Katarzyna Gawrońska: Data curation, writing-rough preparation, investigation, visualization

**Ethical approval**
Not applicable.

**Informed consent**
Not applicable.

**Funding**
This study has not received any external funding.

**Conflict of interest**
The authors declare that there is no conflict of interests.

**Data and materials availability**
All data sets collected during this study are available upon reasonable request from the corresponding author.

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