JENTKIEWICZ, Aleksander, HAJ OBEID, Esmail, ULRYCH, Jakub, KRUPA, Jan, MALINOWSKI, Maciej, KRASOWSKI, Michał, KALINOWSKA, Alicja, PIETRAS, Wiktoria, KOZIEŁ, Adrian and KUREK, Zofia. Glucagon-like peptide 1 receptor agonists in obesity treatment - a literature review. Journal of Education, Health and Sport. 2025;78:57712. eISSN 2391-8306.
https://doi.org/10.12775/JEHS.2025.78.57712
https://apcz.umk.pl/JEHS/article/view/57712

The journal has had 40 points in Minister of Science and Higher Education of Poland parametric evaluation. Annex to the announcement of the Minister of Education and Science of 05.01.2024 No. 32318. Has a Journal's Unique Identifier: 201159. Scientific disciplines assigned: Physical culture sciences (Field of medical and health sciences); Health Sciences (Field of medical and health sciences).
Punkty Ministerialne 40 punktów. Załącznik do komunikatu Ministra Nauki i Szkolnictwa Wyższego z dnia 05.01.2024 Lp. 32318. Posiada Unikatowy Identyfikator Czasopisma: 201159. Przypisane dyscypliny naukowe: Nauki o kulturze fizycznej (Dziedzina nauk medycznych i nauk o zdrowiu); Nauki o zdrowiu (Dziedzina nauk medycznych i nauk o zdrowiu).
The authors declare that there is no conflict of interests regarding the publication of this paper.
Received: 11.01.2025. Revised: 05.02.2025. Accepted: 06.02.2025. Published: 06.02.2025.

GLUCAGON-LIKE PEPTIDE 1 RECEPTOR AGONISTS IN OBESITY TREATMENT- A LITERATURE REVIEW

Author names and affiliations:
Aleksander Jentkiewicz[1] 0009-0008-4224-4069, Esmail Haj Obeid[1] 0009-0008-5165-1221, Jakub Ulrych[1] 0009-0004-7460-965X, Jan Krupa[1] 0009-0001-2175-806X, Maciej Malinowski[1] 0009-0003-7637-6290, Michał Krasowski[2] 0009-0006-6243-1246, Alicja Kalinowska[1] 0009-0000-9011-843X, Wiktoria Pietras[1] 0009-0003-2887-8755 Adrian Koziel[1] 0009-0006-6096-5850, Zofia Kurek[1] 0009-0002-4156-8666,
[1]Medical University of Warsaw
[2]Poznan University of Medical Sciences

ABSTRACT:

Introduction and Purpose: Obesity is an escalating global health challenge, affecting over 2 billion individuals worldwide, contributing to many challenges for healthcare providers such as cardiovascular disorders, cancers, and type 2 diabetes mellitus. There is a need for effective treatments targeting T2DM, and obesity. Glucagon-like peptide-1 (GLP-1) receptor agonists developed originally for T2DM treatment, have emerged as key agents for

weight loss. This review examines current evidence regarding efficacy, safety, and mechanisms of action of GLP-1 RAs, particularly semaglutide and tirzepatide in obesity and weight loss treatment.

Description of the State of Knowledge: GLP-1 receptor agonists modulate appetite, resulting in lower calory intake. Gastric emptying and insulin secretion are also affected by GLP-1 RAs. Clinical trials consistently demonstrate significant weight loss, positive action on cardiovascular risk and better glycemic control. All GLP-1 RAs have common side effects which are gastrointestinal disorders, and gallbladder-related issues, but their safety profiles are acceptable.

Summary: Available evidence recommends GLP-1 receptor agonists in type 2 diabetes mellitus and obesity treatment. Tirzepatide and semaglutide are two pharmacological agents which show best results in terms of weight loss.

Materials and Evidence: A literature review was conducted using the PubMed database for articles published from January 2016 to January 2024, supplemented by earlier foundational papers. After screening 121 abstracts, 51 full-text articles were assessed, and 30 were ultimately included.

Keywords: tirzepatide; semaglutide; weight loss; GLP-1 receptor agonists; obesity treatment; liraglutide; type 2 diabetes mellitus

INTRODUCTION

Obesity is a growing challenge for healthcare providers worldwide. Research indicates that a total of 2.1 billion individuals are overweight or obese. For adults body mass index (BMI) count of 25-29.9 kg/m2 is defined as overweight, while BMI of 30 kg/m2 or higher is defined as obese [1]. Obesity is classified into three severity levels: class I- BMI of 30-34.9 kg/m2, class II- BMI of 35-39.9 kg/m2 and class III- BMI of 40 kg/m2 or higher [2]. Increase in body mass index is associated with higher diabetes-related mortality, cardiovascular mortality and overall mortality. Raised BMI is also a risk factor for ischemic heart disease, stroke and cancer. Every 5 kg/m2 of BMI is associated with 5 mmHg higher systolic blood

pressure (SBP), and 4 mmHg higher diastolic blood pressure (DBP) [3]. One of the most significant health consequences of obesity is the development of type 2 diabetes mellitus (T2DM). Diabetes mellitus is a condition in which blood glucose levels are high due to defects in insulin secretion or action or both. T2DM is more common than type 1, and it accounts for over 90% of cases. In type 2 DM adipose tissue promotes insensitivity to insulin by releasing free fatty acids. T2DM is diagnosed when the patient meets several criteria which are: glycated hemoglobin of 6.5% or more, fasting blood glucose of 126 mg/dL or more, or 2-hour post-prandial glucose of 200 mg/dL or more. Obesity plays a major role in the increased prevalence of T2DM [4]. Therefore, it is necessary to find safe and effective treatments which affect both body weight and higher blood glucose levels.

Glucagon-like peptide-1 (GLP-1) receptor agonists are pharmaceutical agents that were initially developed for the treatment of type 2 DM, but they were later found to be effective for weight loss. Current research indicates that daily injections of 3 mg of liraglutide is a good treatment for obesity [5]. Semaglutide, another GLP-1 receptor agonist was also approved by the US Food and Drug Administration (FDA), for chronic weight management. The dose of semaglutide that is recommended is 2.4 mg per week [6]. GLP-1 is an incretin hormone that is secreted from intestinal endocrine L-cells in response to nutrient ingestion [7], playing a critical role in glucose homeostasis and appetite regulation [8]. Given GLP-1's role in appetite regulation and glucose homeostasis, these agents provide dual benefit in both obesity and T2DM management.

The aim of this review is to provide an overview of GLP-1 receptor agonists in the treatment of obesity, focusing on their mechanisms of action, clinical efficacy, safety profiles, and their potential role in future obesity management strategies.

METHODS

We conducted a comprehensive literature review using the PubMed database. The search included articles published from January 2016 to January 2024, although in introduction as a source of basic knowledge we used papers published earlier. Keywords that we used were: "obesity", "semaglutide", "weight loss", "GLP-1 receptor agonists", "liraglutide" and "type 2 diabetes mellitus". We used Medical Subject Headings (MeSH) terms when looking for appropriate articles. The search was limited to studies published in English, which were also

available in full text for free. Titles and abstracts found because of the search were screened for relevance. Full-text articles were then assessed for eligibility. We aimed to include the newest, most interesting and impactful papers. Our main goal was to select articles that provide the broadest view on GLP-1 receptor agonists in terms of their mechanisms of action, safety and role in obesity treatment.

RESULTS

Our initial PubMed search, limited to articles in English from January 2016 to January 2024, retrieved 606 publications. 121 abstracts were screened for relevance. Of these, 51 were assessed for eligibility in full text, and 30 fulfilled our inclusion criteria. The final 30 articles included 3 meta-analyses, 11 randomized controlled trials (RCTs) and 16 observational or review papers examining GLP-1 receptor agonists for obesity or T2DM. One review study [7] was used in introduction section to provide key physiological background to the review.

REVIEW

Physiology of GLP-1

In humans, location of proglucagon gene is within the long arm of 2 chromosome. Within that gene there is also located coding sequence for GLP-1. In pancreatic a-cells, intestinal L-cells, and in neurons in hypothalamus and caudal brainstem, there is expression of proglucagon gene. Glucose-dependent insulin secretion is enhanced by GLP-1 due to its incretin-like activity, however gastric passage, food intake and glucagon secretion are inhibited by GLP-1. In pancreas GLP-1 stimulates proliferation of beta-cells, and Glucagon-like peptide receptor (GLP-1R) signaling path stimulates hypertrophy. Available literature suggests that it is not yet completely understood in what ways GLP-1R signaling pathway restores glucose sensitivity to diabetic human beta-cells in pancreas. GLP-1R pathway however inhibits pancreatic alpha-cells secretion activity, in consequence inhibiting glucagon secretion [8].

Pharmacological treatments for obesity and diabetes focus on mimicking or enhancing GLP-1 activity. Action of GLP-1 on neurons in the brain affects hunger and reward behavioral patterns. In hypothalamus GLP-1 acts on several nuclei, including hypothalamic paraventricular nucleus which contains GLP-1R expressing neurons that are being affected by GLP-1 agonists, in result their activity is one of mechanisms in Central nervous system (CNS) that modifies food intake. Inactivation of those neurons increase food intake. The

mesolimbic system, part of brain's reward pathway, also contains GLP-1R expressing neurons, which alter the dopamine regulatory system after being activated. [9].

Human studies indicate that brown adipose tissue (BAT) was not activated by GLP-1, suggesting that GLP-1 does not increase energy expenditure in humans [10]. Evidence shows that peripheral tissues glucose uptake and insulin signaling were not directly modified by GLP-1 agonists [8].

GLP-1 receptor agonists overview

Currently approved by the FDA or EMA GLP-1 RA are: exenatide, lixisenatide; liraglutide; dulaglutide, albiglutide, semaglutide and tirzepatide [12][13]. Clinical trials show that best results in terms of body weight loss are result of treatments which include semaglutide or tirzepatide. Liraglutide, lixisenatide and semaglutide(oral) are administered once daily, exenatide twice per day (or once a week), dulaglutide, albiglutide, semaglutide(subcutaneous) and tirzepatide once a week. Albiglutide however has been withdrawn from many markets. Tirzepatide while being a GLP-1 RA is also acting on glucose-dependent insulinotropic polypeptide (GIP) receptors [14]. GLP-1 RAs can lower blood glucose and glycosylated hemoglobin levels; therefore, they are recommended in T2DM treatments. GLP-1 RAs are also proven to be effective in prevention and treatment of T2DM complications, they reduce cardiovascular events, and mortality, while also reducing decline of eGFR in T2DM-associated renal damage [15].

Semaglutide is widely used and has quickly become one of the most prominent GLP-1 RAs, initially indicated for T2DM treatment. Its positive effects on cardiovascular outcomes are well documented. In patients with T2DM with high cardiovascular risk, those receiving semaglutide were at lower risk of cardiovascular death, nonfatal myocardial infarction and nonfatal stroke [11]. In STEP 3 randomized clinical trial 611 adults with overweight or obesity were included to assess semaglutide effectiveness in weight loss. This study compared once-weekly subcutaneous administration of either placebo or semaglutide combined with behavioral therapy and low-calorie diet. Individuals with T2DM, glycated hemoglobin levels of 6.5% or more were excluded. At week 68 of the trial 86.6% of participants in semaglutide group and 47.6% in placebo group achieved at least 5% loss of baseline body weight. Gastrointestinal disorders such as nausea, constipation, diarrhea and vomiting were more frequent in semaglutide group compared to placebo (82.8% vs 63.2%). Adverse effects were also gallbladder related problems such as cholelithiasis. This study has

shown that once-weekly subcutaneous semaglutide injection increased mean weight loss more than placebo [16]. Dosage of semaglutide in obesity treatment (2.4 mg subcutaneous per week) is higher than in T2DM treatment. The STEP 4 randomized clinical trial compared efficacy of semaglutide vs placebo after an initial semaglutide assisted weight loss. 803 participants completed run-in and then were randomized into intervention groups, semaglutide was at 2.4 mg dose per week. First 20 weeks of the study was an initial intervention, because of this treatment mean body weight declined by 10.6%. Body weight change from week 0 to week 68 was -17.4% in continued semaglutide group compared to -5.0% in group where semaglutide at week 20 was changed to placebo. Systolic blood pressure decreased in both groups in the initial 20-week treatment, however in placebo group it rose while continuous treatment with semaglutide SBP remained stable. Adverse effects in this study were like the STEP 3 results. Gastrointestinal tract disorders were reported by 71.4% of participants during the run-in period, while in randomized period 41.9% of patients receiving semaglutide reported GI tract disorders, and 26.1% of placebo patients did the same [17]. STEP 5 trial was conducted to assess long-term treatments of adults with obesity using semaglutide in 2.4 mg weekly dose vs placebo. 304 participants were randomly assigned to intervention groups. This study also enrolled only participants without T2DM. Patients were analyzed for a period of 104 weeks. Mean change in body weight from week 0 to week 104 was -15.2% in semaglutide group and -2.6% in placebo group. Also, lipid profile was improved in semaglutide group compared to placebo, LDL cholesterol was lowered more effectively in semaglutide group (-6.1% to -2.7% in placebo group), triglycerides were found to be lowered in semaglutide group, while in placebo group their levels in blood rose
(-19.0% to 3.7%). Patients receiving semaglutide were more likely to reduce body weight by 10%, 15% or 20% of baseline bogy weight. Adverse effects such as gastrointestinal tract disorders were reported more frequently in semaglutide intervention group than in placebo group (82.2% to 53.9%). Weight loss of at least 5% is a clinically meaningful response, in this study this threshold was achieved by more than 75% of participants in the semaglutide group at week 104, moreover 61.8% of participants in this group achieved at least 10% loss of baseline body weight [18]. The STEP 8 randomized clinical trial compared effectiveness of treatments including either semaglutide or liraglutide. Study included 338 participants; intervention lasted for 68 weeks. Patients were randomized into 4 groups: once-weekly subcutaneous semaglutide in 2.4 mg dose, corresponding placebo group, once-daily subcutaneous liraglutide in 3.0 mg dose, and matching placebo group. Mean body weight

change in semaglutide group was -15.8% compared to -6.4% in liraglutide receiving group. Patients receiving semaglutide were also more likely to reduce body weight by at least 10%, 15%, and 20% compared to liraglutide group (70.9% vs 25.6%, 55.6% vs 12%, 38.5% vs 6.0%). Systolic and diastolic blood pressure reduction was also higher by average in semaglutide group than in liraglutide receiving group (systolic -5.7 vs -2.9, diastolic -5.0 vs -0.5). LDL cholesterol was lowered on average in semaglutide group (-6.5), while in liraglutide group it rose (0.9). Adverse effects were reported by 95.2% of patients receiving semaglutide and 96.1% of patients receiving liraglutide. GI disorders were reported more frequently in semaglutide group compared to liraglutide group (84.1% vs 82.7%). Gallbladder-related disorders were reported by 0.8% of patients receiving semaglutide, while 3.1% of patients treated with liraglutide reported such disorders [19]. Study STEP TEENS was a randomized clinical trial that compared 2.4 mg weekly dose of subcutaneous semaglutide with placebo. Researchers assessed percentage change in BMI from baseline to week 68. Similarly to other studies weight loss of at least 5% was also assessed. 201 patients aged 12 to <18 years were randomized into two groups. All of patients were obese but one participant was overweight. Mean percentage change in BMI at week 68 was -16.1% in semaglutide receiving group and 0.6% in placebo group. 73% of participants treated with semaglutide achieved at least 5% of baseline body weight compared to 18% in placebo group. Semaglutide proved to have greater effect than placebo at reducing LDL cholesterol lipid levels (-10.2 vs -3.4). Adverse effects were reported by 79% of patients in semaglutide group and 82% in placebo group. Gastrointestinal disorders were reported by 62% of semaglutide receiving patients and 42% in placebo receiving patients. Five participants had cholelithiasis in semaglutide group, while in placebo group none [25].

Tirzepatide is a medical agent approved by FDA in T2DM treatment. It is administered subcutaneous in monotherapy or combination therapy with diet and physical exercise. Series of clinical trials have been conducted to assess molecules effectiveness. SURPASS-1, a randomized clinical trial has shown that tirzepatide is more effective than placebo in terms of body weight reduction and reducing HbA1c. In this study tirzepatide doses were 5, 10 or 15 mg, once a week injected subcutaneously. Body weight reduction from baseline ranged from 7 to 9.5 kg. SUPRASS-2 was an open-label study, which compared tirzepatide with semaglutide. Tirzepatide was superior to semaglutide at all doses in terms reduction of HbA1c levels. Tirzepatide doses were 5, 10 or 15 mg and semaglutide 1 mg. SURPASS-3 compared tirzepatide administered once a week, with once-daily insulin degludec together

with metformin and/or inhibitors of Sodium/Glucose transporter 2 (SGLT2) in patients with T2DM. In this study tirzepatide was proven to be more effective in control of HbA1c levels and body weight reduction compared to insulin. Weight reduction was higher the higher dose of tirzepatide was administered, at 5 mg/week it was -7.5 kg, at 10 mg/week -10.7 kg, and at 15 mg/week -12.9, while group treated with insulin body weight rose on average by 2.3 kg. SURPASS-4 trial compared tirzepatide with insulin glargine in patients with inadequate control of T2DM. Results of this study concluded that all three doses of tirzepatide were more effective at lowering cardiovascular risk, reducing body weight and improved glucose control compared to insulin glargine [12]. SURPASS-5 also compared tirzepatide with insulin glargine, however in this study to insulin glargine treatment was added a placebo. This randomized clinical trial had population of 475 adults. Researchers included patients with inadequately controlled T2DM, and BMI of at least 23. Patients were randomized to receive once-weekly subcutaneous injections of tirzepatide or placebo for 40 weeks. In terms of HbA1c change from baseline 10 mg of tirzepatide had best result (-2.4) followed by 15 mg (-2.34), and 5 mg (-2.11) compared to placebo (-0.86). This study shows similar results to other SURPASS studies in terms of body weight reduction where higher doses proved to be more effective (-5.4, -7.5, -8.8). Of patients receiving tirzepatide in dose of 15 mg/week 71.6% met at least 5% of body weight loss from baseline, for group receiving 10 mg/week 57.9% and 5 mg/week 47.9%. Adverse effects were reported by 68.1% to 78.3% of patients receiving tirzepatide, compared to 67.5% of placebo-treated patients. Most frequent adverse effects were gastrointestinal disorders [20]. The SURPASS-6 randomized clinical trial aimed to compare tirzepatide with insulin lispro added to basal insulin. 1428 patients were randomized and treated for 52 weeks. Adult patients with inadequately controlled T2DM were enrolled. Tirzepatide was initiated at 2.5 mg subcutaneous once weekly dose and increased by 2.5 mg every 4 weeks until randomized dose was achieved. Tirzepatide was shown to reduce HbA1c by at least -1.8 at all doses. Baseline mean body weight for each group receiving 5, 10 or 15 mg were 91.7, 89.1, 91.2 reduced by week 52 to 83.8, 81.2, 79.5 accordingly, which corresponded to change of -6.7, -9.3, -11 accordingly [21]. Another study compared tirzepatide in 15 mg/week dose with semaglutide 1 mg once-weekly dose and placebo. 117 patients were randomized, in those patient's body weight was measured every 4 weeks, and body composition was assessed at beginning of the trial and at week 28. Most patients were male (73.5%) and white. At week 28 patients receiving tirzepatide achieved -11 kg of body weight reduction, semaglutide receiving patients -7 kg and placebo receiving patients 0 kg. Researchers observed differences at week 5 which were as follows, tirzepatide

group -2.6 kg, semaglutide group -1.9, placebo group -1 kg of body weight reduction. Percentage of fat mass reduction was greater in tirzepatide (-7.1%) than in semaglutide (-4.0%) group. Energy intake at baseline was similar in all groups, however at week 28 patients receiving tirzepatide in comparison to placebo taking patients achieved reduction of -309.8 kcal, and semaglutide vs tirzepatide -64.3 kcal [22]. SURMOUNT-3 randomized clinical trial assessed effects of tirzepatide vs placebo in body weight reduction. 806 patients were enrolled into first intervention which was a 12-week intensive lifestyle intervention. Patients who achieved at least 5% body weight reduction were then randomized to receive maximum tolerated dose of tirzepatide or placebo. Average body weight in those 579 patients decreased from 109.5 kg to 101.9 kg at randomization. Majority of randomized participants were white (86.0%) and female (62.9%). Patients with T2DM were excluded from trial. In tirzepatide group 86.4% of participants received a dose of 15 mg once a week subcutaneous. At week 72 94.0% of patients treated with tirzepatide maintained at least 80% of body weight reduction achieved by week 12, compared to placebo group in which only 43.8% of patients maintained such body weight reduction. In terms of BMI tirzepatide treated patients on average lost -7.7 kg/m2, while placebo patients gained 1.2 kg/m2. 87.1% of tirzepatide receiving patients reported at least one adverse effect and 76.7% in placebo group [23].

DISCUSSION

This review highlights the growing evidence that GLP-1 receptor agonists, especially semaglutide and tirzepatide, prove to be highly effective and relatively safe agents for obesity management. Beyond promoting weight reduction, those molecules have strong theoretical basis for their efficiency and prove to have other positive effects besides body weight reduction. The STEP (semaglutide) and SURPASS (tirzepatide) clinical trials consistently report improved glycemic control, beneficial effects on cardiovascular risk markers, and significant reduction in body weight.

In all trials semaglutide and tirzepatide were proven to be superior in comparison to placebo in terms of body weight reduction. Of note, large-scale randomized clinical trials directly comparing semaglutide at 2.4 mg/week and tirzepatide at 5, 10 or 15 mg/week are lacking. It remains unclear which agent or dosing regimen may be optimal across various patient populations.

Although liraglutide appears less effective than semaglutide in certain head-to-head trials, meta-analysis confirms liraglutide effectiveness in body weight reduction [24]. Studies also

show that liraglutide provides better glycemic control than placebo and has positive effects on cardiovascular risk factors [26].

Semaglutide has also been shown to affect positively LDL cholesterol levels, in both adults and adolescents, studies also suggest that GLP-1 RAs slow the progression of fibrosis in patients with non-alcoholic steatohepatitis (NASH) [15]. Studies included in this review show that semaglutide is both safe and effective in weight loss treatment.

Tirzepatide is a dual GIP/GLP-1 receptor agonist registered for treatment of T2DM. Its dual-mechanism action proves to be effective in both diabetes treatment, and weight loss assistance. Studies show that tirzepatide has positive impact on cardiovascular risk [27]. Tirzepatide also takes effect in brown adipose tissue, stimulating catabolism of BCAAs [28]. Moreover, tirzepatide and semaglutide potentially result in reduction of alcohol consumption in obese individuals [29].

As observed across these trials the most common adverse effects of GLP-1 RAs are gastrointestinal disorders such as nausea, vomiting, constipation, diarrhea, and gallbladder-related issues such as cholelithiasis. These adverse effects seem to be common for all GLP-1 RAs [30]. Research suggests than definitive conclusions for connection of semaglutide treatment and pancreatic and thyroid cancer, cannot be drawn [31].

Both semaglutide and tirzepatide however are newly developed medical agents and there is a need for further research regarding their long-term effects on organism. There is also a lack of studies comparing both of those agents in weight loss treatment, T2DM treatment, and their effects on cardiovascular risk. It remains unknown whether the 2.4 mg/week dosage of semaglutide is superior, equivalent, or comparable to 5, 10 or 15 mg/week of tirzepatide. There is also a need for clinical trials including more diverse patient populations. Future randomized clinical trials should consider head-to-head comparison of tirzepatide and semaglutide in broad range of patients, and parameters.

Disclosure:

The authors declare that they do not possess financial or non-financial conflicts of interest that could be perceived as influencing the interpretation of the research findings or the

content of this manuscript. This work was conducted independently without any external funding or support.

Author's contribution

Conceptualization: Aleksander Jentkiewicz, Esmail Haj Obeid; methodology: Jakub Ulrych, Jan Krupa; software: Maciej Malinowski; check: Michał Krasowski; formal analysis: Alicja Kalinowska; investigation: Wiktoria Pietras; resources: Jakub Ulrych; data curation: Adrian Kozieł; writing – rough preparation: Zofia Kurek, Maciej Malinowski; writing – review and editing: Jan Krupa, Aleksander Jentkiewicz, Esmail Haj Obeid; visualization: Wiktoria Pietras; supervision: Michał Krasowski; project administration: Aleksander Jentkiewicz;

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

Funding Statement

This paper has not received any founding.

Institutional Review Board Statement

Not applicable

Informed Consent Statement

Not applicable

Data Availability Statement

As a review paper, our work does not present new data or analyses. The information and findings presented in this review are based on previously published studies, which can be accessed through their respective sources as cited in the reference section.

Conflicts of Interest Statement

The authors declare that there are no conflicts of interest associated with this research work.

References:

1. Apovian CM. Obesity: definition, comorbidities, causes, and burden. Am J Manag Care. 2016 Jun;22(7 Suppl):s176-85. PMID: 27356115.
2. Lin X, Li H. Obesity: Epidemiology, Pathophysiology, and Therapeutics. Front Endocrinol (Lausanne). 2021 Sep 6;12:706978. doi: 10.3389/fendo.2021.706978. PMID: 34552557; PMCID: PMC8450866.
3. Prospective Studies Collaboration; Whitlock G, Lewington S, Sherliker P, Clarke R, Emberson J, Halsey J, Qizilbash N, Collins R, Peto R. Body-mass index and cause-specific mortality in 900 000 adults: collaborative analyses of 57 prospective studies. Lancet. 2009 Mar 28;373(9669):1083-96. doi: 10.1016/S0140-6736(09)60318-4. Epub 2009 Mar 18. PMID: 19299006; PMCID: PMC2662372.
4. Chandrasekaran P, Weiskirchen R. The Role of Obesity in Type 2 Diabetes Mellitus-An Overview. Int J Mol Sci. 2024 Feb 4;25(3):1882. doi: 10.3390/ijms25031882. PMID: 38339160; PMCID: PMC10855901.
5. Ard J, Fitch A, Fruh S, Herman L. Weight Loss and Maintenance Related to the Mechanism of Action of Glucagon-Like Peptide 1 Receptor Agonists. Adv Ther. 2021 Jun;38(6):2821-2839. doi: 10.1007/s12325-021-01710-0. Epub 2021 May 11. PMID: 33977495; PMCID: PMC8189979.
6. Chao AM, Tronieri JS, Amaro A, Wadden TA. Semaglutide for the treatment of obesity. Trends Cardiovasc Med. 2023 Apr;33(3):159-166. doi: 10.1016/j.tcm.2021.12.008. Epub 2021 Dec 21. PMID: 34942372; PMCID: PMC9209591.
7. Baggio LL, Drucker DJ. Biology of incretins: GLP-1 and GIP. Gastroenterology. 2007 May;132(6):2131-57. doi: 10.1053/j.gastro.2007.03.054. PMID: 17498508.
8. Drucker DJ. Mechanisms of Action and Therapeutic Application of Glucagon-like Peptide-1. Cell Metab. 2018 Apr 3;27(4):740-756. doi:

10.1016/j.cmet.2018.03.001. PMID: 29617641.

9. Smith NK, Hackett TA, Galli A, Flynn CR. GLP-1: Molecular mechanisms and outcomes of a complex signaling system. Neurochem Int. 2019 Sep;128:94-105. doi: 10.1016/j.neuint.2019.04.010. Epub 2019 Apr 17. PMID: 31002893; PMCID: PMC7081944.
10. Drucker DJ. GLP-1 physiology informs the pharmacotherapy of obesity. Mol Metab. 2022 Mar;57:101351. doi: 10.1016/j.molmet.2021.101351. Epub 2021 Oct 6. PMID: 34626851; PMCID: PMC8859548.
11. Kristensen SL, Rørth R, Jhund PS, Docherty KF, Sattar N, Preiss D, Køber L, Petrie MC, McMurray JJV. Cardiovascular, mortality, and kidney outcomes with GLP-1 receptor agonists in patients with type 2 diabetes: a systematic review and meta-analysis of cardiovascular outcome trials. Lancet Diabetes Endocrinol. 2019 Oct;7(10):776-785. doi: 10.1016/S2213-8587(19)30249-9. Epub 2019 Aug 14. Erratum in: Lancet Diabetes Endocrinol. 2020 Mar;8(3):e2. doi: 10.1016/S2213-8587(20)30037-1. PMID: 31422062.
12. Forzano I, Varzideh F, Avvisato R, Jankauskas SS, Mone P, Santulli G. Tirzepatide: A Systematic Update. Int J Mol Sci. 2022 Nov 23;23(23):14631. doi: 10.3390/ijms232314631. PMID: 36498958; PMCID: PMC9741068.
13. Nauck MA, Quast DR, Wefers J, Meier JJ. GLP-1 receptor agonists in the treatment of type 2 diabetes - state-of-the-art. Mol Metab. 2021 Apr;46:101102. doi: 10.1016/j.molmet.2020.101102. Epub 2020 Oct 14. PMID: 33068776; PMCID: PMC8085572.
14. Popoviciu MS, Păduraru L, Yahya G, Metwally K, Cavalu S. Emerging Role of GLP-1 Agonists in Obesity: A Comprehensive Review of Randomised Controlled Trials. Int J Mol Sci. 2023 Jun 21;24(13):10449. doi: 10.3390/ijms241310449. PMID: 37445623; PMCID: PMC10341852.
15. Nevola R, Epifani R, Imbriani S, Tortorella G, Aprea C, Galiero R, Rinaldi L, Marfella R, Sasso FC. GLP-1 Receptor Agonists in Non-Alcoholic Fatty Liver Disease: Current Evidence and Future Perspectives. Int J Mol Sci. 2023 Jan 15;24(2):1703. doi: 10.3390/ijms24021703. PMID: 36675217; PMCID: PMC9865319.
16. Wadden TA, Bailey TS, Billings LK, Davies M, Frias JP, Koroleva A, Lingvay I, O'Neil PM, Rubino DM, Skovgaard D, Wallenstein SOR, Garvey

WT; STEP 3 Investigators. Effect of Subcutaneous Semaglutide vs Placebo as an Adjunct to Intensive Behavioral Therapy on Body Weight in Adults With Overweight or Obesity: The STEP 3 Randomized Clinical Trial. JAMA. 2021 Apr 13;325(14):1403-1413. doi: 10.1001/jama.2021.1831. PMID: 33625476; PMCID: PMC7905697.

17. Rubino D, Abrahamsson N, Davies M, Hesse D, Greenway FL, Jensen C, Lingvay I, Mosenzon O, Rosenstock J, Rubio MA, Rudofsky G, Tadayon S, Wadden TA, Dicker D; STEP 4 Investigators. Effect of Continued Weekly Subcutaneous Semaglutide vs Placebo on Weight Loss Maintenance in Adults With Overweight or Obesity: The STEP 4 Randomized Clinical Trial. JAMA. 2021 Apr 13;325(14):1414-1425. doi: 10.1001/jama.2021.3224. PMID: 33755728; PMCID: PMC7988425.
18. Garvey WT, Batterham RL, Bhatta M, Buscemi S, Christensen LN, Frias JP, Jódar E, Kandler K, Rigas G, Wadden TA, Wharton S; STEP 5 Study Group. Two-year effects of semaglutide in adults with overweight or obesity: the STEP 5 trial. Nat Med. 2022 Oct;28(10):2083-2091. doi: 10.1038/s41591-022-02026-4. Epub 2022 Oct 10. PMID: 36216945; PMCID: PMC9556320.
19. Rubino DM, Greenway FL, Khalid U, O'Neil PM, Rosenstock J, Sørrig R, Wadden TA, Wizert A, Garvey WT; STEP 8 Investigators. Effect of Weekly Subcutaneous Semaglutide vs Daily Liraglutide on Body Weight in Adults With Overweight or Obesity Without Diabetes: The STEP 8 Randomized Clinical Trial. JAMA. 2022 Jan 11;327(2):138-150. doi: 10.1001/jama.2021.23619. PMID: 35015037; PMCID: PMC8753508.
20. Dahl D, Onishi Y, Norwood P, Huh R, Bray R, Patel H, Rodríguez Á. Effect of Subcutaneous Tirzepatide vs Placebo Added to Titrated Insulin Glargine on Glycemic Control in Patients With Type 2 Diabetes: The SURPASS-5 Randomized Clinical Trial. JAMA. 2022 Feb 8;327(6):534-545. doi: 10.1001/jama.2022.0078. PMID: 35133415; PMCID: PMC8826179.
21. Rosenstock J, Frías JP, Rodbard HW, Tofé S, Sears E, Huh R, Fernández Landó L, Patel H. Tirzepatide vs Insulin Lispro Added to Basal Insulin in Type 2 Diabetes: The SURPASS-6 Randomized Clinical Trial. JAMA. 2023 Nov 7;330(17):1631-1640. doi: 10.1001/jama.2023.20294. Erratum in: JAMA. 2023 Nov 21;330(19):1915. doi: 10.1001/jama.2023.22757. PMID: 37786396; PMCID: PMC10548360.

22. Heise T, DeVries JH, Urva S, Li J, Pratt EJ, Thomas MK, Mather KJ, Karanikas CA, Dunn J, Haupt A, Milicevic Z, Coskun T. Tirzepatide Reduces Appetite, Energy Intake, and Fat Mass in People With Type 2 Diabetes. Diabetes Care. 2023 May 1;46(5):998-1004. doi: 10.2337/dc22-1710. PMID: 36857477; PMCID: PMC10154650.
23. Wadden TA, Chao AM, Machineni S, Kushner R, Ard J, Srivastava G, Halpern B, Zhang S, Chen J, Bunck MC, Ahmad NN, Forrester T. Tirzepatide after intensive lifestyle intervention in adults with overweight or obesity: the SURMOUNT-3 phase 3 trial. Nat Med. 2023 Nov;29(11):2909-2918. doi: 10.1038/s41591-023-02597-w. Epub 2023 Oct 15. Erratum in: Nat Med. 2024 Jun;30(6):1784. doi: 10.1038/s41591-024-02883-1. PMID: 37840095; PMCID: PMC10667099.
24. Khera R, Murad MH, Chandar AK, Dulai PS, Wang Z, Prokop LJ, Loomba R, Camilleri M, Singh S. Association of Pharmacological Treatments for Obesity With Weight Loss and Adverse Events: A Systematic Review and Meta-analysis. JAMA. 2016 Jun 14;315(22):2424-34. doi: 10.1001/jama.2016.7602. Erratum in: JAMA. 2016 Sep 6;316(9):995. doi: 10.1001/jama.2016.11657. PMID: 27299618; PMCID: PMC5617638.
25. Weghuber D, Barrett T, Barrientos-Pérez M, Gies I, Hesse D, Jeppesen OK, Kelly AS, Mastrandrea LD, Sørrig R, Arslanian S; STEP TEENS Investigators. Once-Weekly Semaglutide in Adolescents with Obesity. N Engl J Med. 2022 Dec 15;387(24):2245-2257. doi: 10.1056/NEJMoa2208601. Epub 2022 Nov 2. PMID: 36322838; PMCID: PMC9997064.
26. Marso SP, Daniels GH, Brown-Frandsen K, Kristensen P, Mann JF, Nauck MA, Nissen SE, Pocock S, Poulter NR, Ravn LS, Steinberg WM, Stockner M, Zinman B, Bergenstal RM, Buse JB; LEADER Steering Committee; LEADER Trial Investigators. Liraglutide and Cardiovascular Outcomes in Type 2 Diabetes. N Engl J Med. 2016 Jul 28;375(4):311-22. doi: 10.1056/NEJMoa1603827. Epub 2016 Jun 13. PMID: 27295427; PMCID: PMC4985288.
27. Nicholls SJ, Bhatt DL, Buse JB, Prato SD, Kahn SE, Lincoff AM, McGuire DK, Nauck MA, Nissen SE, Sattar N, Zinman B, Zoungas S, Basile J, Bartee A, Miller D, Nishiyama H, Pavo I, Weerakkody G, Wiese RJ, D'Alessio D;

SURPASS-CVOT investigators. Comparison of tirzepatide and dulaglutide on major adverse cardiovascular events in participants with type 2 diabetes and atherosclerotic cardiovascular disease: SURPASS-CVOT design and baseline characteristics. Am Heart J. 2024 Jan;267:1-11. doi: 10.1016/j.ahj.2023.09.007. Epub 2023 Sep 25. PMID: 37758044.

28. Samms RJ, Zhang G, He W, Ilkayeva O, Droz BA, Bauer SM, Stutsman C, Pirro V, Collins KA, Furber EC, Coskun T, Sloop KW, Brozinick JT, Newgard CB. Tirzepatide induces a thermogenic-like amino acid signature in brown adipose tissue. Mol Metab. 2022 Oct;64:101550. doi: 10.1016/j.molmet.2022.101550. Epub 2022 Jul 31. PMID: 35921984; PMCID: PMC9396640.
29. Quddos F, Hubshman Z, Tegge A, Sane D, Marti E, Kablinger AS, Gatchalian KM, Kelly AL, DiFeliceantonio AG, Bickel WK. Semaglutide and Tirzepatide reduce alcohol consumption in individuals with obesity. Sci Rep. 2023 Nov 28;13(1):20998. doi: 10.1038/s41598-023-48267-2. PMID: 38017205; PMCID: PMC10684505.
30. Liu L, Chen J, Wang L, Chen C, Chen L. Association between different GLP-1 receptor agonists and gastrointestinal adverse reactions: A real-world disproportionality study based on FDA adverse event reporting system database. Front Endocrinol (Lausanne). 2022 Dec 7;13:1043789. doi: 10.3389/fendo.2022.1043789. PMID: 36568085; PMCID: PMC9770009.
31. Smits MM, Van Raalte DH. Safety of Semaglutide. Front Endocrinol (Lausanne). 2021 Jul 7;12:645563. doi: 10.3389/fendo.2021.645563. Erratum in: Front Endocrinol (Lausanne). 2021 Nov 10;12:786732. doi: 10.3389/fendo.2021.786732. PMID: 34305810; PMCID: PMC8294388.