RABENDA, Michal, SŁOMCZYŃSKI, Adam, ZATYKA, Piotr, PAWŁOWSKA, Agata, OPALA, Dominika, OSUCH, Dobromiła and JANIK, Piotr. Glucagon-like peptide-1 receptor agonists and derivatives in the treatment of obesity - review. Quality in Sport. 2024;20:53995. eISSN 2450-3118.
https://dx.doi.org/10.12775/QS.2024.20.53995
https://apcz.umk.pl/QS/article/view/53995

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

The authors declare that there is no conflict of interests regarding the publication of this paper.
Received: 01.08.2024. Revised: 21.08.2024. Accepted: 22.08.2024. Published: 23.08.2024.

Glucagon-like peptide-1 receptor agonists and derivatives in the treatment of obesity - review

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Abstract:
Obesity is a chronic and insidious disease that represents a significant global. The World Health Organization has announced that almost 60% of European adults are overweight or obese. Complex hormonal and metabolic adaptations in obesity can prevent weight loss, despite changes in dietary and activity habits. Over the years, the number of anti-obesity drugs has been small and their efficacy has been inadequate, but powerful new drugs from the GLP-1 receptor agonists group have emerged. Studies indicate that drugs in the GLP-1 RA group can be effective in reducing weight in obese people both with and without diabetes. Several preparations are available on the market with varying efficacy and risk of side effects and new drugs are still being registered.

Materials and Methods:
Analysis of information on the treatment of obesity with GLP-1 receptor agonists using PubMed sources, including the epidemiology of obesity, types of GLP-1 RA drugs, their efficacy and safety.

Aim:
The aim of this publication was to gather the latest information on the treatment of obesity with GLP-1 receptor agonists. We wanted to present the epidemiology of obesity, the types of drugs, their efficacy and safety.

Conclusions:
Obesity is a significant problem in today's world and affects more than half of European adults. Drugs that are GLP-1 receptor agonists can effectively bridge the gap between behavioural strategies and bariatric surgery. Studies indicate that treatment with GLP-1 RAs can lead to significant weight loss in overweight and obese individuals compared to placebo, and tirzepatide appears to have the greatest efficacy.

Keywords: obesity, weight loss, GLP-1 receptor agonist, dual GLP-1/GIP receptor agonist, semaglutide, tirzepatide.

Obesity

Obesity is a chronic and progressive disease with a complex etiology.(1) It is considered a major public health problem.(2) The World Health Organization (WHO) defines obesity as an abnormal or excessive accumulation of fat that can adversely affect health, and the underlying cause of obesity and overweight is an abnormal energy balance.(2) A state of positive energy balance occurs when energy supply exceeds energy consumption, resulting in the storage of excess calories in the form of adipose tissue.(3, 4) The most commonly used index to assess the prevalence of obesity is the Body Mass Index (BMI), which is measured by calculating (weight in kg)/(height inm2). It does not apply to children or athletes. The BMI classifies adults into the following categories: underweight, normal weight, overweight (BMI 25.0 to 29.9 kg/m2), obese (BMI ≥30 kg/m2).(5, 6) In May 2022. The World Health Organization announced that almost 60% of European adults are overweight or obese. According to a WHO report (6), obesity is likely to overtake smoking as a major preventable cancer risk factor in some countries in the coming decades. Overweight and obesity are responsible for more than 1.3 million deaths per year worldwide, and in the European region they have reached epidemic proportions, 63% among men and 54% among women.(6) Obesity ranks fifth among the leading causes of death worldwide.(2) In Europe, the prevalence of obesity is five times higher than it was after World War II, and the number of obese people doubles every year.(3, 7) Obesity is an important risk factor for other diseases, but also a disease that has its own pathophysiology, comorbidities and its own potential for disability.(3) Overweight and obesity lead to many chronic diseases including cardiovascular disease, cancer, diabetes and metabolic syndrome.(2) Excess body fat causes biomechanical complications such as osteoarthritis and obstructive sleep apnoea. In contrast, adipose tissue dysfunction contributes to cardiometabolic complications, starting with insulin resistance.(6) Treatment of obesity in patients without diabetes is important to prevent or delay the onset of diabetes.(8) Complex and long-lasting hormonal, metabolic and neurochemical adaptations in obesity can prevent weight loss and promote weight regain, despite attempts to change lifestyle, diet and sport.(3, 9) Therefore, to date, obesity prevention and treatment strategies have not always been very effective.(9) Complex behavioural, pharmacological or surgical approaches are required to treat obesity. There is therefore a need to develop new drugs that are both effective and safe.(1)

Incretin hormones

Incretins are gut hormones responsible for stimulating insulin secretion by pancreatic islet β-cells. They have a role in the pathophysiology of type 2 diabetes mellitus and obesity.(1, 8, 10) Incretins are secreted in response to food and their action occurs before the postprandial rise in blood glucose has even occurred. Incretins are responsible for the phenomenon of greater insulin secretion after oral glucose administration than after parenteral glucose administration, a phenomenon known as the incretin effect.(8, 11, 12) Incretin hormones also influence the slowing down of gastric emptying and the feeling of satiety, which has the effect of reducing food supply and slowing down the absorption of nutrients.(11, 13) They are secreted into the blood by cells of the gastrointestinal tract. The intestinal peptides belonging to this group of hormones are glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP). Glucose-dependent insulinotropic polypeptide (GIP) is a 42-amino-acid peptide. It is mainly produced by duodenal K cells in the upper small intestine.(13)

The GIP receptor exists as two isoforms, 466 and 493 amino acids. It is expressed in pancreatic β-cells, heart cells, brain and adipose tissue.(13) GIP has incretin and adipogenic effects, causing fat deposition.(14) GLP-1 and GIP have protective effects on pancreatic cells, as they stimulate pancreatic β-cell proliferation and inhibit their apoptosis.(12, 13) Glucagon-like peptide-1 (GLP-1) is a 30-amino acid peptide hormone that is produced by gastrointestinal enteroendocrine L cells in the distal small intestine and colon. The receptor for GLP-1 or Glucagon-like peptide-1 receptor (GLP-1R) is expressed on pancreatic islet cells, cells of the heart, intestine, kidney, blood vessels, lung and nervous system. Within the pancreas, the receptor is predominantly located in β cells, although it is also found in smaller amounts in α and δ cells. GLP-1R is a G protein-coupled receptor.(13, 15, 16) Wang et al.(3) writes that the anorectic effect of GLP-1 is associated with the presence of GLP-1R in hypothalamic feeding centres, hindbrain matrix, the lateral parabrachial nucleus of the posterior nucleus, and mesolimbic substrates.(3, 17-21) Blood levels of the hormone GLP-1 increase within minutes after food ingestion, before the food reaches the small intestine, so it is likely that GLP-1 secretion is stimulated by neural and endocrine pathways.(12, 13, 15) In addition to its incretin effect, GLP-1 inhibits glucagon release by pancreatic islet α cells.(11-13) The broad effects of GLP-1 on various organ systems may play a role in weight loss. According to Nauck M.(16), GLP-1 secretion from the gut is likely to be impaired in obese individuals, suggesting a role for GLP-1 in the pathophysiology of obesity and new therapeutic opportunities. Both hormones are rapidly degraded by the enzyme dipeptidyl peptidase-4 (DPP-4) and lose their activity, making them unsuitable as an interval drug, and this knowledge has contributed to the development of GLP-1 receptor agonists that resist degradation by DPP-4.(6, 12, 13)

Incretin drugs

Incretin drugs include GLP-1 receptor agonists (GLP-1 RA) and dual GLP-1/GIP receptor agonists. This is a group of drugs under intensive development to improve the treatment of type 2 diabetes and to combat obesity. Michalowska et al.(11) writes that the results of recent scientific studies suggest that GLP-1 RAs may find use in the treatment of non-alcoholic steatohepatitis and the prevention of cardiovascular disease. GLP-1 RA mimic the natural hormone GLP-1.(22) The combined central (receptors in the brain) and peripheral (other receptors) actions of GLP-1 RA increase glucose-dependent insulin secretion and reduce inappropriate glucagon secretion, stimulate pancreatic β-cell proliferation, promote satiety, reduce hunger and ultimately reduce food intake. (6,23,24) In addition, GLP-1 RAs slow gastric emptying (by inhibiting the vagus nerve and increasing pyloric contraction) (3) and cause occasional nausea, which may contribute to weight loss, but Popoviciu et al. 2023 (6) writes that this most likely plays a minor and temporary role. For years, the number of anti-obesity drugs was inadequate and their efficacy was poor.(1) Subsequently, new and potent GLP-1 RA drugs emerged. GLP-1 receptor agonists include Exenatide, Lixisenatide, liraglutide, dulaglutide, semaglutide, tirzepatide. All drugs are administered by subcutaneous injection, and semaglutide is also available as an oral version. There are differences between the substances in pharmacokinetics, route and frequency of administration, efficacy and side effects.(24) Exenatide was the first (2005) GLP-1 receptor agonists approved for the treatment of type 2 diabetes. Due to its short half-life, other drugs were sought. Exenatide is in a twice-daily injectable form (exenatide bid) and once weekly.

Lixisenatide and liraglutide are given once daily. Dulaglutide and semaglutide are injected once a week. Subsequently, oral semaglutide was approved, which is administered daily and has comparable efficacy to a subcutaneous formulation administered once a week.(6, 25, 26) More recently, tirzepatide was approved, which is administered subcutaneously once a week. The short-acting drugs (exenatide bid and lixisenatide) show less efficacy in lowering 24-hour glycaemia, but still have an effect on inhibiting gastric emptying.(6, 27) Liraglutide was the first once-daily GLP-1 RA approved for the treatment of T2DM.(6) Long-acting GLP-1 RAs (liraglutide, once-weekly exenatide, dulaglutide and semaglutide) have a greater effect on lowering night-time and fasting glycaemia and the effect on HbA1c.(27) The effect on inhibition of gastric emptying by GLP-1 RA has been observed to diminish over time.(27) Tirzepatide is the first dual agonist of GLP-1 and GIP receptors. It was developed in 2022.(6) Activation of both receptors results in more potent effects on glycaemic control and weight loss.(28)

Efficacy of GLP-1 RA, dual GLP-1/GIP RA

GLP-1 RAs play a significant role in the treatment of type 2 diabetes, and can lower blood glucose levels with HbA1c reductions ranging from -0.8 to -1.9%.(8, 27) In patients with diabetes and obesity, GLP-1RAs can achieve weight loss of -3 kg.(29) Studies indicate that incretin drugs are effective in reducing body weight in obese patients both with and without diabetes.(8, 29) Guo et al.(8) writes that treatment with GLP-1RAs, including liraglutide, exenatide and semaglutide, significantly increased weight loss in overweight/obese patients without diabetes compared with placebo [WMD=-5.39, 95% CI (-6.82, -3.96)] and metformin [WMD=-5.46, 95% CI (-5.87, -5.05)].(8) The aforementioned drugs differ in efficacy. Liraglutide and exenatide in overweight/obese patients without diabetes can result in a weight loss of -2.85 kg.(30) Semaglutide, which has a longer half-life than liraglutide and exenatide, can result in a weight loss of -11.3% in the semaglutide group and -2.3% in the placebo group.(8, 31) Other studies have shown that subcutaneous semaglutide at a dose of 2.4 mg reduces body weight by about 15%, and the newest drug, tirzepatide, can cause weight reduction by as much as more than 20% in obese patients.(1) A metanalysis by Guo et al. 2018 (8) showed that GLP-1 RAs contributed to weight loss in overweight/obese patients, with an overall weight reduction of -5.39 kg [95% CI (-6, 82, -3.96), I2=99.2%, p<0.001] compared with placebo, including -8.12 kg [95% CI (-12.44, -3.80)] in patients treated with semaglutide, -5.45 kg [95% CI (-5. 88, -5.02)], with exenatide by -3.23 kg [95% CI (-3.71, -2.75)]. According to Guo et al. 2018(8), GLP-1 RAs showed a significantly greater effect on weight reduction, BMI and WC (waist circumference) than placebo/metformin in overweight/obese patients. Thus, according to this meta-analysis, semaglutide may be more effective than liraglutide and in the treatment of obesity.(8) GLP-1 RAs also improved the lipid profile by lowering LDL-C levels by 0.04 mg / dl.(8) According to an analysis by Rodriguez et al.(32), tirzepatide had greater efficacy than semaglutide in the treatment of overweight and obesity. Mean weight loss during treatment was -15.3% (95% CI, -16.0% to -14.5%) for tirzepatide vs -8.3% (95% CI, -9% to -7.6%) for semaglutide at 12 months. Those treated with tirzepatide were more likely to achieve 5% or greater, 10% or greater and 15% or greater weight loss than those treated with semaglutide.(32)

Safety of GLP-1 RA, dual GLP-1/GIP RA

The rates of adverse effects associated with GLP-1 RA vary between drugs. However, the most common are gastrointestinal complaints such as nausea, vomiting, diarrhoea, constipation, injection site reactions and hypoglycaemia.(8, 24) This is related to the presence of GLP-1 receptors in the gastrointestinal tract and the effect of the drugs on inhibiting peristalsis. According to a meta-analysis by Guo et al. 2018 (8), GLP-1RA drugs caused more gastrointestinal complaints compared with placebo/metformin, and liraglutide may show a lower risk of complaints than exenatide, which may be related to the different half-life of the drug. Additionally, semaglutide showed fewer gastrointestinal events than liraglutide and exenatide.(8) Patients treated with GLP-1 RA were more likely to report nausea, vomiting, diarrhoea and constipation than placebo [OR=1.46, 95% CI (1.20, 1.77), $p<0.001$, $I2=82.8\%$]. Few serious adverse events were described, such as liver and biliary tract disorders, infections and infestations.(8) Shetty et al. 2022 (33) describes that liraglutide and exenatide caused more adverse drug reactions than dulaglutide, semaglutide, albiglutide and lixisenatide. The main reported adverse drug reactions were gastrointestinal disorders (33%), followed by renal (19%), dermatologic (12%), hepatic (8%) and immunologic problems(11%).(33)

Summary:

Obesity is a very important problem in the modern world and the fight against obesity is not sufficient, as shown by the fact that it affects more than half of European adults. GLP-1 receptor agonists drugs can effectively fill the therapeutic space between behavioural approaches and bariatric surgery. Ongoing studies have shown that treatment with GLP-1 RA can significantly affect weight loss in overweight and obese individuals compared to placebo. Formulations with increasing efficacy and lower risk of side effects are being developed, and currently the formulation with the greatest efficacy in the treatment of obesity appears to be tirzepatide.

Disclosures:
No disclosures.

Financial support:
No financial support was received.

Conflict of interest:
The authors declare no conflict of interest.

Authors contribution statement:
Conceptualization, M.R. and P.Z.; Methodology, D.O. and M.R.; Software A.P.; Check A.S., P.J. and P.Z.; Formal analysis P.J. and A.P.; Investigation P.J; Resources A.S. and D.O.; Data storage, D.O.; Writing - rough preparation M.R., P.Z. and A.S.; Writing - review and editing, M.R., D.O., D.O. and A.P.; Visualization, P.J.; Supervision, P.Z.; Project administration, D.O. and P.J.; Receiving funding, self financed;

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

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