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Review

Role of GLP-1 Agonists in Obesity: A Comprehensive Review

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Abstract: Obesity is a major public health concern globally, significantly increasing the risk of numerous metabolic and cardiovascular diseases. While lifestyle interventions remain the primary strategy for weight management, pharmacotherapy is increasingly recognized as an essential component for patients with obesity, especially when lifestyle modifications alone are insufficient. Glucagon-like peptide-1 (GLP-1) receptor agonists, originally developed for the management of type 2 diabetes, have emerged as effective agents in promoting weight loss in both diabetic and non-diabetic populations. This literature review examines the efficacy, safety, and mechanisms of action of GLP-1 receptor agonists, focusing on liraglutide and semaglutide, in obesity treatment. Furthermore, it discusses the impact of GLP-1 receptor agonists on obesity-related comorbidities, their comparison with other pharmacological treatments, and future perspectives.

Keywords: GLP-1 receptor agonists; obesity; weight loss; liraglutide; semaglutide; pharmacotherapy; metabolic health

Introduction

Obesity, a chronic relapsing disease characterized by excessive adiposity, is a global epidemic that significantly contributes to the development of numerous comorbid conditions, including type 2 diabetes, cardiovascular diseases, and certain cancers (World Health Organization, 2016). Current obesity management strategies focus on lifestyle interventions such as diet and exercise, but these approaches often fail to achieve sustained weight loss, especially in individuals with severe obesity. Pharmacotherapy, as an adjunct to lifestyle modification, has become increasingly important for weight management, and among the available options, GLP-1 receptor agonists stand out due to their efficacy in reducing body weight and improving metabolic parameters. Originally developed for glycemic control in type 2 diabetes, GLP-1 receptor agonists have been found to induce clinically significant weight loss in non-diabetic populations as well (Pi-Sunyer et al., 2015). This review provides an analysis of the mechanisms of action, efficacy, safety, and potential future applications of GLP-1 receptor agonists in the management of obesity, with a focus on liraglutide and semaglutide, the two most studied agents in this drug class.

Method

This literature review was conducted to examine the use of GLP-1 receptor agonists in the management of obesity. A comprehensive search was performed using databases such as PubMed, Cochrane Library, and Embase to identify relevant studies published between 2000 and The search terms included "GLP-1 receptor agonists," "obesity," "liraglutide," "semaglutide," "weight loss," and "pharmacotherapy for obesity." Inclusion criteria included studies that involved with obesity, and use of FDA approved drugs and dosages specifically, liraglutide 3mg and semaglutide 2.4mg. Some studies of exanetide were considered if results focused on weight loss. Randomized controlled trials, systematic reviews, meta analysis, that reported weight loss as primary outcomes and published in English and published later than 1997 were used. Exclusion criteria included short term

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studies (<6 months), other forms of publication like letter to editor, opinion pieces etc., studies focused on non obese population and studies that did not have weight loss as important outcome.

Mechanism of Action

GLP-1 is an incretin hormone secreted from the intestinal L-cells in response to nutrient intake. It has multiple physiological effects, including enhancing glucose-dependent insulin secretion, inhibiting glucagon release, and delaying gastric emptying (Holst et al., 2007). In the context of obesity, GLP-1 also plays a crucial role in appetite regulation, acting on the hypothalamus to increase satiety and reduce food intake (Flint et al., 1998). GLP-1 receptor agonists mimic the actions of endogenous GLP-1 by binding to its receptor on pancreatic beta cells and in various regions of the central nervous system. This leads to a decrease in caloric intake and, over time, significant weight reduction. GLP-1 receptor agonists also slow gastric emptying, which prolongs satiety and decreases hunger (Garber, 2011).

Clinical Efficacy of GLP-1 Receptor Agonists in Obesity

Liraglutide:

Liraglutide was the first GLP-1 receptor agonist approved for obesity management at a dose of 3.0 mg, distinct from the 1.8 mg dose used for type 2 diabetes. The pivotal SCALE trial (Satiety and Clinical Adiposity—Liraglutide Evidence) enrolled over 3,700 participants with obesity (BMI ≥30) or overweight (BMI ≥27) with comorbid conditions. The trial demonstrated that participants receiving liraglutide 3.0 mg achieved a mean weight loss of 8.4% after 56 weeks, compared to 2.8% in the placebo group (Pi-Sunyer et al., 2015). Additionally, liraglutide was associated with significant improvements in cardiometabolic parameters, including reductions in blood pressure, fasting glucose levels, and triglycerides (Davies et al., 2015).

Semaglutide:

Semaglutide, a newer GLP-1 receptor agonist, is administered once weekly and has demonstrated superior efficacy in weight loss compared to liraglutide. The STEP (Semaglutide Treatment Effect in People with Obesity) trials evaluated the efficacy of semaglutide 2.4 mg in individuals with obesity. In the STEP 1 trial, participants treated with semaglutide experienced a mean weight reduction of 14.9% over 68 weeks, significantly greater than the 2.4% weight loss observed in the placebo group (Wilding et al., 2021). Semaglutide also improved glycemic control and other metabolic outcomes, making it a highly effective option for obesity management.

Exenatide:

Exenatide, another GLP-1 receptor agonist, has been studied in both its immediate-release (twice daily) and extended-release (once weekly) formulations. While it is primarily used for glycemic control in diabetes, exenatide has demonstrated modest weight loss in clinical trials, with reductions of approximately 2-5% in body weight (Astrup et al., 2009). However, exenatide is generally less effective for weight loss compared to liraglutide and semaglutide.

Safety and Tolerability

The safety profile of GLP-1 receptor agonists is well characterized, with gastrointestinal (GI) side effects being the most common. Nausea, vomiting, and diarrhea are frequently reported, particularly during the initial weeks of treatment (Blonde et al., 2015). These side effects are dose-dependent and tend to resolve over time as patients adapt to the medication. To minimize GI symptoms, GLP-1 receptor agonists are typically initiated at a low dose and gradually titrated to the target dose (Davies et al., 2015).

In terms of serious adverse events, the risk of pancreatitis and thyroid C-cell tumors has been a concern, particularly in animal studies. However, clinical trials in humans have not shown a definitive increase in the risk of these conditions (Marso et al., 2016). Nonetheless, caution is advised when prescribing GLP-1 receptor agonists to individuals with a history of pancreatitis or thyroid

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cancer. Cardiovascular safety studies, including the LEADER trial for liraglutide and the SUSTAIN-6 trial for semaglutide, have demonstrated reductions in major adverse cardiovascular events (MACE) in patients with type 2 diabetes, providing reassurance regarding their use in populations at high cardiovascular risk (Marso et al., 2016; Marso et al., 2017).

Comparative Efficacy with Other Pharmacological Treatments:

GLP-1 receptor agonists have demonstrated superior weight loss efficacy compared to other pharmacological treatments for obesity. Orlistat, an intestinal lipase inhibitor, promotes modest weight loss of approximately 3-4% but is associated with significant GI side effects such as steatorrhea and flatulence, which limit its use (Torgerson et al., 2004). Phentermine-topiramate, a combination medication, offers greater weight loss (up to 9-10%) but carries risks such as increased heart rate and teratogenic effects, restricting its use in women of childbearing potential (Gadde et al., 2011).

In contrast, GLP-1 receptor agonists provide a balance of significant weight loss and cardiometabolic benefits, with a more favorable safety profile, particularly regarding cardiovascular outcomes.

Impact on Obesity-Related Comorbidities

GLP-1 receptor agonists not only promote weight loss but also have beneficial effects on obesity-related comorbidities. Liraglutide and semaglutide have been shown to improve glycemic control, reduce blood pressure, and lower low-density lipoprotein (LDL) cholesterol levels, contributing to an overall reduction in cardiovascular risk (Davies et al., 2015; Wilding et al., 2021). Furthermore, these agents have demonstrated anti-inflammatory properties, which may help mitigate the progression of non-alcoholic fatty liver disease (NAFLD), a common comorbidity in patients with obesity (Armstrong et al., 2016).

Future Directions

The development of newer GLP-1 receptor agonists with enhanced efficacy and tolerability is an area of active research. Tirzepatide, a dual GLP-1 and glucose-dependent insulinotropic polypeptide (GIP) receptor agonist, has shown even greater weight loss than semaglutide in phase III trials, with reductions exceeding 15% of baseline body weight (Jastreboff et al., 2022). In addition, combination therapies involving GLP-1 receptor agonists and other weight-loss agents are being explored to further enhance treatment outcomes.

There is also a rising use of bariatric surgery in the vision of weight loss which have also produced significant results (Courcoulas, Anita P et al, 2014)

Future research should focus on the long-term safety and efficacy of GLP-1 receptor agonists in diverse populations, including adolescents, older adults, and individuals with severe obesity.

Conclusions

GLP-1 receptor agonists, particularly liraglutide and semaglutide, have emerged as highly effective pharmacological treatments for obesity, offering substantial weight loss and improvements in cardiometabolic health. Their safety profile, while generally favorable, requires ongoing monitoring for potential adverse effects, particularly in individuals at risk for pancreatitis or thyroid cancer. As the prevalence of obesity continues to rise globally, GLP-1 receptor agonists are likely to play an increasingly central role in the long-term management of obesity, either as standalone treatments or in combination with other modes of management.

References

1. 1.World Health Organization. “Obesity and overweight.” World Health Organization, 2016.
2. Pi-Sunyer FX, et al. “A randomized, controlled trial of 3.0 mg of liraglutide in weight management.” New England Journal of Medicine, 2015; 373(1): 11-22.
3. Holst JJ. “The physiology of glucagon-like peptide 1.” Physiological Reviews, 2007; 87(4): 1409-1439.
4. Flint A, et al. “Effects of glucagon-like peptide-1 on appetite and food intake in humans: a dose–response study.” American Journal of Clinical Nutrition, 1998; 68(4): 720-726.

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5. Garber AJ. "Long-acting glucagon-like peptide 1 receptor agonists: a review of their efficacy and tolerability." Diabetes Care, 2011; 34(Supplement 2): S279-S284.
6. Davies MJ, et al. "Liraglutide 3.0 mg for weight management: a randomized, controlled study of weight loss and maintenance in overweight or obese adults." Diabetes Care, 2015; 38(4): 734-742.
7. Wilding JPH, et al. "Once-weekly semaglutide in adults with overweight or obesity." New England Journal of Medicine, 2021; 384(11): 989-1002.
8. Astrup A, et al. "Exenatide promotes weight loss in overweight and obese patients with type 2 diabetes." Diabetes Care, 2009; 32(3): 403-409.
9. Blonde L, et al. "Efficacy and safety of liraglutide in combination with oral agents in patients with type 2 diabetes." Endocrine Practice, 2015; 21(12): 1403-1412.
10. Marso SP, et al. "Liraglutide and cardiovascular outcomes in type 2 diabetes." New England Journal of Medicine, 2016; 375(4): 311-322.
11. Marso SP, et al. "Semaglutide and cardiovascular outcomes in patients with type 2 diabetes." New England Journal of Medicine, 2017; 377(9): 891-897.
12. Torgerson JS, et al. "Xenical in the prevention of diabetes in obese subjects (XENDOS) study: a randomized study of orlistat as an adjunct to lifestyle changes for the prevention of type 2 diabetes in obese patients." Diabetes Care, 2004; 27(1): 155-161.
13. Gadde KM, et al. "Effects of low-dose, controlled-release, phentermine combined with topiramate on weight and associated comorbidities in overweight and obese adults (CONQUER): a randomised, placebo-controlled, phase 3 trial." The Lancet, 2011; 377(9774): 1341-1352.
14. Armstrong MJ, et al. "Liraglutide safely reduces liver fat content and improves markers of inflammation and fibrosis in non-alcoholic fatty liver disease: a phase 2, randomised, placebo-controlled trial." The Lancet Gastroenterology & Hepatology, 2016; 1(12): 889-898.
15. Jastreboff AM, et al. "Tirzepatide once weekly for the treatment of obesity." New England Journal of Medicine, 2022; 387(3): 205-216.
16. Courcoulas, Anita P., et al. "A Randomized Trial of Metabolic Surgery for the Treatment of Type 2 Diabetes in Obese Patients." New England Journal of Medicine, vol. 370, no. 20, 2014, pp. 1991-DOI: 10.1056/NEJMoa1402288.

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