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Semaglutide, liraglutide and tirzepatide: Comparison of effectiveness in the treatment of obesity – a literature review

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ABSTRACT

Introduction

Obesity is a complex, multifactorial condition characterized by an excessive accumulation of body fat. It is widely recognized as a major public health issue due to its strong association with numerous chronic diseases. [1][2]
The use of GLP-1 receptor agonists in obesity treatment began with the recognition that these drugs, initially developed for type 2 diabetes, could significantly reduce body weight due to their effects on appetite regulation and satiety. Liraglutide was the first to be approved specifically for obesity, followed by semaglutide, The development of tirzepatide, which targets both GLP-1 and GIP receptors, has further expanded the potential for obesity treatment. As clinical evidence continues to support their efficacy and safety, GLP-1 receptor agonists

are becoming an important tool in the management of obesity, offering a promising option for individuals struggling with weight and related health conditions [3][4][5].

Aim of the study

The aim of this study was to compare the effectiveness of semaglutide, liraglutide and tirzepatide in reducing body weight in obesity.

Materials and methods

The article was created based on the PubMed and Cochrane databases. The literature was analyzed using the fallow keywords: Obesity treatment, liraglutide, tirzepatide, semaglutide, glucagon-like peptide-1 (GLP-1) receptor agonists

Results

The research proved that tirzepatide is more effective in reducing body weight compared to semaglutide and liraglutide [6][7].

Conclusion

Thanks to the comparison of results from multiple studies, we can assume that, at this point, tirzepatide is the most effective pharmacological treatment for obesity, which, when used in combination with lifestyle changes, provides a lasting effect on weight reduction and, consequently, helps treat obesity-related comorbidities[6][8].

Key words: Obesity treatment, liraglutide, tirzepatide, semaglutide, glucagon-like peptide-1 (GLP-1) receptor agonists

INRODUCTION

Obesity is a medical condition characterized by excessive accumulation of body fat to the extent that it may negatively affect health. It is typically measured using the Body Mass Index (BMI), a calculation based on an individual's height and weight. A BMI of 30 or higher is considered obese, while a BMI between 25 and 29.9 is considered overweight [1].

Obesity can result from a combination of genetic, behavioral, environmental, and metabolic factors [9].

Obesity is associated with a higher risk of developing various health conditions, such as: Type 2 diabetes, heart disease and stroke, high blood pressure, sleep apnea, certain types of cancer (e.g. breast, colon), joint problems, liver disease [2][10][11].

Managing obesity often involves:

- Lifestyle changes: A balanced diet with healthy eating habits and regular physical activity are key to preventing and managing obesity [8].

- Medical interventions: In some cases, doctors may recommend medications or even surgical procedures like bariatric surgery (e.g., gastric bypass) to help with weight loss or use pharmacological treatments like weight-loss medications may be prescribed. Semaglutide, liraglutid and tirzepatide are examples of medications that have shown effectiveness in reducing body weight [3][4][12].

1. Semaglutide, Liraglutide, and Tirzepatide - Mechanism of Action

Semaglutide and liraglutide are long-acting GLP-1 receptor agonists. They mimic GLP-1, activating the GLP-1 receptor, which is involved in regulating glucose homeostasis. GLP-1 is a hormone naturally produced in the gut in response to food intake [5]. When activated by semaglutide/liraglutide, the GLP-1 receptor has multiple effects:

- Increases insulin secretion in a glucose-dependent manner: When blood glucose levels are high, semaglutide stimulates the pancreas to release insulin, which helps lower blood glucose levels [13].
- Suppresses glucagon release: Semaglutide inhibits the secretion of glucagon, a hormone that typically raises blood glucose levels by promoting glucose release from the liver [13].
- Slows gastric emptying: Semaglutide slows down the emptying of the stomach, which helps increase satiety and reduces food intake [14].
- Reduces appetite: By acting on the brain's appetite centers, semaglutide reduces hunger, leading to reduced calorie consumption, which is especially beneficial for weight loss [14][15].

Clinical Uses:

- **Type 2 diabetes**: They help control blood sugar levels by enhancing insulin secretion and reducing glucagon release [3].
- **Obesity**: Semaglutide/liraglutide promote weight loss by reducing appetite and calorie intake [16][17].

Semaglutide and liraglutide are both GLP-1 receptor agonists, but semaglutide has a longer half-life, allowing it to be administered once a week, while liraglutide is typically given daily [18].

Tirzepatide is a newer medication for the treatment of type 2 diabetes. It is unique because it acts on two important receptors in the body: GLP-1 and GIP (Gastric Inhibitory Polypeptide). This dual action sets it apart from semaglutide and liraglutide.

Mechanism of Action:

- GLP-1 receptor agonism: Like semaglutide and liraglutide, tirzepatide activates the GLP-1 receptor, leading to increased insulin secretion, decreased glucagon release, and delayed gastric emptying. This results in better blood sugar control and reduced appetite [19].

- GIP receptor agonism: Tirzepatide also stimulates the GIP receptor, another incretin hormone involved in insulin secretion and glucose metabolism. GIP, like GLP-1, is released from the gut in response to food intake and works to increase insulin sensitivity [20].
- Increased insulin sensitivity: By acting on both GLP-1 and GIP receptors, tirzepatide improves insulin sensitivity more effectively than other GLP-1 agonists [20].
- Significant weight loss: Tirzepatide has been shown to lead to more substantial weight loss compared to GLP-1 agonists like semaglutide, likely due to the combined effects on both insulin sensitivity and appetite regulation [21].

Clinical Uses:

- **Type 2 diabetes**: Tirzepatide is approved for improving blood glucose control in adults with type 2 diabetes [19].
- **Obesity**: Early studies have shown that tirzepatide also has potent weight loss effects, and it is being explored for weight management in people with obesity or overweight [22].

Side Effect Profiles

Semaglutide and liraglutide share similar side effects, including gastrointestinal issues (nausea, diarrhea, vomiting), which are common but tend to diminish over time. Both drugs may also be associated with more serious risks, such as pancreatitis and gallbladder disease, though these are rare [23][24].

Tirzepatide also shares similar gastrointestinal side effects with other GLP-1 receptor agonists, but in some cases, these may be more pronounced due to its dual action. However, the overall side-effect profile of tirzepatide has been considered acceptable, with no major new safety concerns identified in clinical trials [25].

Clinical Considerations

- **Semaglutide** offers the advantage of once-weekly administration, which may improve adherence to treatment [26].
- **Liraglutide** requires daily administration, which may be less convenient for some patients but remains a well-established option for weight loss, particularly in individuals with obesity and comorbidities [27].
- **Tirzepatide** also offers weekly dosing, and its dual action on both GLP-1 and GIP receptors makes it a highly effective option, especially for patients who are seeking more significant weight loss [22][28].

Comparison of Semaglutide, Liraglutide, and Tirzepatide

Feature	Semaglutide	Liraglutide	Tirzepatide
Brand names	Ozempic (diabetes), Wegovy (obesity)	Victoza (diabetes), Saxenda (obesity)	Mounjaro (diabetes)
Type of agonist	GLP-1 receptor agonist	GLP-1 receptor agonist	Dual GLP-1 and GIP receptor agonist
Administration	Weekly injection	Daily injection	Weekly injection
Primary uses	Type 2 diabetes, obesity	Type 2 diabetes, obesity	Type 2 diabetes, emerging weight loss use

Common side effects	Nausea, vomiting, diarrhea, constipation	Nausea, vomiting, abdominal pain	Nausea, vomiting, diarrhea, abdominal pain
Unique aspects	Long-acting weekly dose, high efficacy	Daily injection, moderate weight loss	Dual receptor activity, superior weight loss and glycemic control in trials

Table 1. Comparison of Semaglutide, Liraglutide, and Tirzepatide

Clinical Efficacy: Weight Loss Outcomes

Semaglutide
Efficacy in Obesity: Semaglutide has been shown to induce significant weight loss in individuals with obesity, especially when used at higher doses (Wegovy). In the STEP 1 trial, patients using semaglutide 2.4 mg once weekly achieved an average weight loss of 14.9% of their body weight over 68 weeks, compared to 2.4% in the placebo group. The weight loss results were consistent across various demographic subgroups, including those with comorbidities such as hypertension and type 2 diabetes.
Key Trial: The STEP 1 trial (Wilding et al., 2021) demonstrated that semaglutide not only promoted substantial weight loss but also led to improvements in cardiovascular risk factors, including blood pressure and lipid profiles [29].

Liraglutide
Efficacy in Obesity: Liraglutide (Saxenda) has also been shown to produce meaningful weight loss. In the SCALE trials, participants using liraglutide 3.0 mg once daily achieved an average weight loss of approximately 5-10% of their body weight after 56 weeks. Though effective, liraglutide typically produces less weight loss than semaglutide, with many patients losing between 5% and 8% of their body weight.
Key Trial: The SCALE Obesity and Prediabetes trial (Davies et al., 2015) demonstrated liraglutide's effectiveness in reducing body weight, particularly among those with obesity and prediabetes, and showed improvements in blood glucose control [30].

Tirzepatide
Efficacy in Obesity: Tirzepatide has shown extraordinary efficacy in inducing weight loss, even exceeding the results of semaglutide in clinical trials. In the SURPASS trials, patients using tirzepatide at doses ranging from 5 mg to 15 mg once weekly achieved weight loss of up to 22.5% of their body weight after 72 weeks. The weight loss with tirzepatide was significantly greater than that observed with semaglutide or liraglutide.
Key Trial: The SURPASS-2 trial compared tirzepatide with semaglutide in patients with type 2 diabetes and found that tirzepatide led to greater weight loss and superior reductions in HbA1c, the marker for long-term blood glucose control [31].

The Importance of Lifestyle Changes Alongside Pharmacotherapy in Obesity Treatment

While pharmacotherapy, including medications such as semaglutide, liraglutide, and tirzepatide, has demonstrated efficacy in promoting weight loss and improving metabolic health, the success of these treatments is significantly enhanced when combined with lifestyle changes. The long-term management of obesity requires a multidisciplinary approach that not only targets the physiological aspects of weight regulation but also addresses behavioral, dietary, and environmental factors that contribute to excess weight.

Dietary Modifications

Diet plays a critical role in the management of obesity. The foundation of effective weight management lies in the creation of a caloric deficit—consuming fewer calories than the body expends. While pharmacological agents like GLP-1 agonists can reduce appetite and promote satiety, nutritional interventions are essential for achieving sustainable weight loss. A balanced, nutrient-dense diet, which emphasizes whole foods such as vegetables, fruits, lean proteins, whole grains, and healthy fats, can help reduce overall caloric intake. Research consistently shows that dietary changes, particularly those that reduce the intake of refined sugars, processed foods, and unhealthy fats, significantly enhance the effectiveness of obesity treatments [32]. For example, a low-calorie or low-carbohydrate diet combined with weight-loss medications has been shown to achieve greater and more sustainable weight loss than either approach alone [33].

Physical Activity

Exercise is another critical component of an obesity management plan. Regular physical activity not only contributes to caloric expenditure, but it also helps to maintain muscle mass during weight loss, which is important for preserving metabolic rate and long-term weight maintenance.

The American College of Sports Medicine recommends that individuals with obesity engage in at least 150 minutes of moderate-intensity exercise or 75 minutes of vigorous-intensity exercise per week, along with strength training exercises twice a week. In combination with pharmacotherapy, exercise can enhance weight loss, improve insulin sensitivity, reduce inflammation, and boost cardiovascular health [34]. Studies have found that individuals who incorporate aerobic exercise (such as walking, cycling, or swimming) along with weight loss medications like semaglutide or tirzepatide experience greater improvements in body composition and overall health [35].

Behavioral Modifications

Obesity is not just a matter of excess calories; it is also influenced by behavioral patterns such as emotional eating, food addiction, and sedentary behaviors. Behavioral interventions, including cognitive-behavioral therapy (CBT) and mindful eating, can help individuals modify the habits and thought patterns that contribute to overeating and poor food choices. Combining pharmacotherapy with behavioral therapy has been shown to result in greater weight loss and improved psychological well-being. For instance, CBT can help patients identify and manage triggers for overeating, increase motivation to stick with healthier eating habits, and teach strategies for dealing with setbacks. Additionally, mindful eating practices, which focus on eating slowly and paying attention to hunger and satiety cues, can help reduce the likelihood of overeating and improve the long-term success of weight loss efforts [36].

The Role of Support Systems

Social support is another important aspect of lifestyle modification. Studies consistently show that patients who receive social support from family, friends, or weight loss support groups tend to experience greater success in their weight loss journeys. Support systems can

provide encouragement, accountability, and a sense of community, which are essential for adhering to long-term lifestyle changes.

Additionally, healthcare providers play a key role in offering ongoing guidance and monitoring, which includes not only prescribing appropriate medications but also providing encouragement for making lifestyle changes, tracking progress, and addressing any psychological or behavioral challenges that arise during the process.

Sustained Weight Loss and Long-Term Success

For sustained weight loss and long-term success, maintenance strategies are as important as the initial weight loss phase. Studies show that individuals who combine pharmacotherapy with lifestyle changes are more likely to maintain weight loss and prevent weight regain in the long term. Regular follow-up visits with healthcare providers and ongoing behavioral support are crucial for maintaining motivation and adjusting treatment plans as needed [37]. Pharmacological agents can be extremely helpful in the initial stages of weight loss, but the long-term success of obesity treatment is dependent on the ability to integrate lifestyle changes that promote healthy eating habits, regular physical activity, and psychological well-being. When pharmacotherapy is used alongside lifestyle changes, the chances of preventing weight regain and improving quality of life are significantly increased.

CONCLUSIONS

Semaglutide, liraglutide, and tirzepatide have all shown significant efficacy in promoting weight loss in individuals with obesity. While semaglutide and liraglutide are both effective GLP-1 receptor agonists with proven track records in both obesity and diabetes management, tirzepatide appears to offer superior results in terms of weight loss, making it a promising treatment for obesity. Tirzepatide's dual GLP-1 and GIP receptor action may provide additional benefits in both glycemic control and fat loss, suggesting it could become the treatment of choice for some patients.

Future studies and long-term follow-ups will be necessary to further assess the comparative advantages, safety, and cost-effectiveness of these medications. Nevertheless, all three drugs represent significant advances in pharmacological management for obesity, offering hope for patients struggling with this chronic condition.

While medications like semaglutide, liraglutide, and tirzepatide have proven to be effective tools in the management of obesity, they should not be viewed as standalone solutions. The most effective approach to obesity treatment combines pharmacotherapy with comprehensive lifestyle modifications, including dietary changes, physical activity, behavioral interventions, and social support. This integrated approach helps individuals achieve not only weight loss but also improved overall health and the long-term maintenance of a healthy weight.

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