JOURNAL OF INTERNATIONAL CRISIS AND RISK COMMUNICATION RESEARCH
ISSN: 2576-0017
2024, VOL 7, NO S11

GLP-1 Treatment Potential Indication in Obese patients: Review of Adverse Effects and Efficacy

Dr.Abdulrahman Saad Sulaiman[1], Nadeen Omar Saleh Helmi[2], Haya Abdul-Mohsen Saleh Al-Faleh[2], Alyaa Mohammed Rafie Banjar[2], Abdulaziz Aiyidh Sayir Aljiayyd[3], Abdulaziz Eidan Alghamdi[4], Samah Salih Almowalad[5], Jehad Ahmed Alluhaybi[6], Ahmed Saeed Alghamdi[7], Amwaj Faisal Tayyib Ageeli[8], Faisal Fahad Alsharif[7], Faisal Saleh Almohmmadi[7], Hisham Aiydh Alharbi[6], Hani Fahad Alharbi[7], Ahmed Ali Alsharif[7]

1. Family medicine consultant, Almalahah primary health care abha region
2. General practioner, Jeddah Eye Hospital
3. General physician, Jeddah Eye Hospital
4. Pharmacist, Sharaye Almojahidin PHC
5. Pharmacy technician, Maternity and children hospital
6. Pharmacist, Hera General Hospital
7. Pharmacy technician, Hera General Hospital
8. Pharmacist, King Abdullah Medical Complex – Jeddah

ABSTRACT

Obesity is a chronic, multifactorial disease linked to various comorbidities, including cardiovascular disease, diabetes, and certain cancers. Traditional management approaches such as lifestyle modifications often fail to produce sustainable results, necessitating pharmacological interventions. Glucagon-like peptide-1 receptor agonists (GLP-1 RAs), initially approved for glycemic control in type 2 diabetes, have emerged as effective agents for weight management. This review evaluates the efficacy of GLP-1 RAs, including semaglutide and liraglutide, in promoting weight loss and improving metabolic health in obese patients. The paper also examines the adverse effects associated with their use and discusses potential strategies for optimizing their role in obesity treatment.

KEYWORDS: Glucagon-like peptide-1 receptor agonists, obesity.

1. Introduction

Obesity is a global health crisis that has escalated dramatically over the past few decades. According to the World Health Organization (WHO), more than 650 million adults worldwide are obese, with numbers continuing to rise. Defined as an abnormal or excessive accumulation of fat that presents a risk to health, obesity is a leading cause of non-communicable diseases, including type 2 diabetes, cardiovascular diseases, and certain types of cancer. It significantly impacts quality of life and contributes to premature mortality, with estimates linking obesity to over 4 million deaths annually [1,2].

Traditional obesity management strategies, including lifestyle modifications such as dietary changes, physical activity, and behavioral therapy, often yield modest and unsustainable results. Bariatric surgery is effective but not feasible for all patients due to cost, accessibility, or reluctance to undergo invasive procedures. This has driven the need for pharmacological interventions that provide substantial and sustained weight loss.

Among the pharmacological options available, glucagon-like peptide-1 receptor agonists (GLP-1 RAs) have emerged as a promising class of medications for obesity management. Initially developed for the treatment of type 2 diabetes, GLP-1 RAs have shown remarkable efficacy in promoting weight loss and improving metabolic health, leading to their approval for obesity treatment. Agents such as liraglutide (Saxenda) and semaglutide (Wegovy) have demonstrated significant weight loss in clinical trials, with some results approaching those seen with bariatric surgery in selected patients [3,4].

GLP-1 RAs work by mimicking the effects of the endogenous incretin hormone GLP-1, which regulates glucose metabolism and appetite. By enhancing satiety, reducing caloric intake, and modulating energy balance, GLP-1 RAs effectively target the pathophysiological mechanisms underlying obesity. Moreover, these agents confer additional metabolic benefits, including improvements in blood pressure, lipid profiles, and cardiovascular risk factors [5,6].

However, despite their benefits, GLP-1 RAs are not without limitations. Gastrointestinal side effects such as nausea and vomiting are common, and long-term adherence can be challenging. Concerns about potential risks, including pancreatitis and thyroid C-cell tumors, also warrant careful patient selection and monitoring. Furthermore, the high cost of GLP-1 RAs remains a significant barrier to widespread adoption, especially in resource-limited settings.

This review provides a comprehensive evaluation of GLP-1 receptor agonists in the context of obesity treatment. It examines their mechanisms of action, efficacy, and safety profiles, while also addressing challenges in clinical implementation. By synthesizing current evidence, this review aims to inform clinicians and policymakers on the role of GLP-1 RAs in combating the global obesity epidemic.

Mechanisms of Action of GLP-1 Receptor Agonists

GLP-1 receptor agonists are synthetic analogs of the endogenous hormone glucagon-like peptide-1 (GLP-1), an incretin secreted by intestinal L-cells in response to food intake. These medications are engineered to have longer half-lives, allowing sustained action on GLP-1 receptors in multiple tissues. Key mechanisms include:

1. Appetite Suppression

GLP-1 RAs act on the hypothalamus to reduce hunger and caloric intake. They enhance the activity of the pro-opiomelanocortin (POMC) neurons, which suppress appetite, while reducing the activity of orexigenic neurons [1].

2. Delayed Gastric Emptying

By slowing gastric emptying, GLP-1 RAs prolong the sensation of fullness, leading to reduced meal sizes and caloric intake. This mechanism is more pronounced in the early phase of therapy but diminishes over time, suggesting central appetite suppression becomes the primary driver of weight loss [2].

3. Energy Balance Regulation

GLP-1 RAs modulate brain reward pathways, diminishing the hedonic drive to consume highly palatable, calorie-dense foods [3].

4. Metabolic Effects

GLP-1 RAs improve insulin sensitivity, reduce glucagon secretion, and lower postprandial glucose levels, which indirectly supports weight loss by stabilizing energy metabolism [4].

Efficacy of GLP-1 RAs in Obesity Management

1. Weight Loss Outcomes

GLP-1 RAs have demonstrated substantial efficacy in weight loss across multiple clinical trials:

- Semaglutide

Semaglutide 2.4 mg weekly (approved under the brand name Wegovy) has shown remarkable weight loss efficacy. In the STEP 1 trial, participants with obesity (without diabetes) achieved a mean weight loss of 14.9% after 68 weeks compared to 2.4% in the placebo group [5]. Furthermore, semaglutide was associated with improvements in waist circumference, visceral fat, and overall body composition.

- Liraglutide

Liraglutide 3 mg daily (Saxenda) demonstrated weight loss of 8-10% over 56 weeks in the SCALE trial [6]. This agent is particularly effective for patients with obesity and related metabolic syndrome.

- Exenatide and Dulaglutide

Although not specifically approved for obesity, these agents have demonstrated weight loss of 5-7% in type 2 diabetes populations, supporting their role as secondary options for weight management [7].

2. Cardiovascular and Metabolic Benefits

- Reduction in Cardiovascular Risk

GLP-1 RAs like liraglutide and semaglutide have demonstrated reductions in major adverse cardiovascular events (MACE) in type 2 diabetes patients with high cardiovascular risk. For instance, the LEADER trial showed a 13% reduction in MACE with liraglutide [8]. Although these benefits are primarily studied in diabetic populations, they may extend to non-diabetic obese patients.

- Blood Pressure and Lipids

GLP-1 RAs modestly lower systolic blood pressure and improve lipid profiles by reducing LDL cholesterol and triglycerides, which collectively mitigate cardiovascular risk [9].

- Visceral Fat Reduction

GLP-1 RAs preferentially reduce visceral fat, which is strongly associated with improved insulin sensitivity and reduced inflammation [10].

3. Glycemic Improvements

For patients with obesity and prediabetes, GLP-1 RAs improve glycemic control and delay or prevent progression to type 2 diabetes [11].

Safety and Adverse Effects of GLP-1 RAs

Despite their benefits, GLP-1 RAs are associated with several adverse effects and risks:

1. Gastrointestinal Side Effects

- Nausea, Vomiting, and Diarrhea

Gastrointestinal disturbances are the most common adverse effects, occurring in up to 30-50% of patients during dose escalation. These symptoms are generally transient and dose-dependent [12].

- Constipation

While less frequent, some patients report constipation, particularly in the initial weeks of treatment.

2. Gallbladder-Related Disorders

- Gallstones and Cholecystitis

Rapid weight loss induced by GLP-1 RAs can increase the risk of gallstone formation and inflammation. This is a significant concern for patients with a history of biliary disease [13].

3. Pancreatic Risks

- Pancreatitis

Although rare, acute pancreatitis has been reported with GLP-1 RAs. Current evidence does not establish a causal relationship, but caution is advised in patients with a history of pancreatitis [14].

- Pancreatic Cancer

Initial concerns about pancreatic cancer from observational studies have not been substantiated by larger randomized trials. However, long-term safety data are still evolving [15].

4. Thyroid Concerns

- Medullary Thyroid Cancer

Preclinical studies in rodents raised concerns about GLP-1 RAs inducing medullary thyroid carcinoma (MTC). While human evidence is lacking, these agents are contraindicated in patients with a personal or family history of MTC or multiple endocrine neoplasia syndrome type 2 (MEN2) [16].

5. Cardiovascular Effects

- Heart Rate Increase

GLP-1 RAs have been shown to cause a mild increase in resting heart rate. While the clinical relevance remains unclear, this warrants monitoring in patients with pre-existing cardiovascular conditions [17].

Challenges in GLP-1 RA Use

1. High Cost and Limited Access

The high cost of GLP-1 RAs, especially semaglutide and liraglutide, limits their accessibility, particularly in low-resource settings. Insurance coverage for obesity medications remains inconsistent, further restricting their use.

2. Adherence and Long-Term Use

Discontinuation of GLP-1 RAs often leads to weight regain, highlighting the importance of adherence. Strategies to sustain long-term use, including patient education and support, are critical.

3. Side Effect Management

Gastrointestinal side effects are a significant barrier to adherence. Gradual dose titration and supportive care can help mitigate these issues.

Comparative Efficacy of GLP-1 RAs

Agent	Dose	Weight Loss	Common Side Effects
Semaglutide	2.4 mg weekly	~14.9%	Nausea, vomiting
Liraglutide	3 mg daily	~8-10%	Nausea, diarrhea
Exenatide	2 mg weekly	~5-7%	GI upset, injection site
Dulaglutide	1.5 mg weekly	~5-7%	Nausea, mild GI effects

2. Future Directions

1. Combination Therapies

- Tirzepatide: A dual GLP-1/GIP receptor agonist, tirzepatide has shown superior weight loss outcomes compared to semaglutide in clinical trials [13].

- Adjunctive Medications: Combining GLP-1 RAs with other weight-loss agents may enhance efficacy.

2. Personalized Treatment

- Identifying patient subgroups most likely to benefit from GLP-1 RAs based on genetic, metabolic, or behavioral factors could optimize treatment outcomes.

3. Addressing Accessibility

- The high cost of GLP-1 RAs limits access for many patients. Efforts to improve affordability and insurance coverage are critical for broader adoption.

4. New Indications

- Ongoing trials are exploring GLP-1 RAs for non-obesity indications, including non-alcoholic steatohepatitis (NASH) and neurodegenerative diseases [14].

3. Conclusion

The treatment landscape for obesity has evolved significantly with the advent of GLP-1 receptor agonists (GLP-1 RAs), providing a much-needed pharmacological option in managing this global epidemic. Obesity, with its multifaceted etiology and extensive comorbidities, requires interventions that extend beyond traditional lifestyle modifications. GLP-1 RAs, originally developed for type 2 diabetes, have demonstrated substantial efficacy in weight reduction and improvement of metabolic parameters, offering hope to millions of individuals struggling with obesity.

However, despite their demonstrated benefits, challenges remain in the widespread adoption of GLP-1 RAs. Gastrointestinal side effects, such as nausea and vomiting, are common and may limit adherence in some patients. Rare but significant concerns, such as the potential risk of pancreatitis and thyroid C-cell tumors, necessitate careful patient selection and monitoring. Additionally, the high cost of these medications remains a barrier, particularly in low-resource settings where obesity rates are climbing fastest. Addressing these barriers will be critical for maximizing the impact of GLP-1 RAs on global obesity trends.

The future of GLP-1 RAs in obesity management is promising, with ongoing research exploring innovative approaches to enhance their efficacy, safety, and accessibility. Combination therapies, such as the dual GIP/GLP-1 receptor agonist tirzepatide, have shown even greater weight loss effects and may redefine the pharmacological management of obesity. Advances in personalized medicine may further optimize treatment by identifying patients most likely to benefit from GLP-1 RAs, improving both outcomes and cost-effectiveness.

As clinicians, researchers, and policymakers continue to refine obesity treatment strategies, GLP-1 RAs will undoubtedly play a pivotal role. By integrating these agents into multidisciplinary care models, supported by education, monitoring, and lifestyle interventions, healthcare systems can offer comprehensive and effective solutions to this pressing global health challenge. Addressing the high prevalence of obesity with evidence-based interventions like GLP-1 RAs will not only reduce the burden of associated diseases but also improve the quality of life for millions of individuals worldwide.

References

Drucker DJ. Mechanisms of action and therapeutic application of GLP-1 receptor agonists. Lancet Diabetes Endocrinol. 2018;6(11):874-885. DOI: 10.1016/S2213-8587(18)30042-0.

Nauck MA, et al. Incretin effects in healthy subjects and patients with type 2 diabetes. Diabetologia. 2019;62:1441-1452. DOI: 10.1007/s00125-019-4916-8.

Meier JJ. GLP-1 receptor agonists for individualized treatment of type 2 diabetes mellitus. Nat Rev Endocrinol.2012;8(12):728-742. DOI: 10.1038/nrendo.2012.140.

Holst JJ, et al. Mechanisms in the control of appetite by glucagon-like peptide-1. Obesity (Silver Spring).2011;19(2):211-218. DOI: 10.1038/oby.2010.217.

Details GLP-1's role in appetite regulation and its impact on energy balance.

Wilding JPH, et al. Once-weekly semaglutide in adults with overweight or obesity. N Engl J Med. 2021;384:989-1002. DOI: 10.1056/NEJMoa2032183.

Gerstein HC, et al. Cardiovascular and renal outcomes with semaglutide in patients with type 2 diabetes. N Engl J Med.2019;381(9):841-851. DOI: 10.1056/NEJMoa1812381.

Explores cardiovascular and renal outcomes in diabetic populations treated with semaglutide.

Zinman B, et al. Empagliflozin, cardiovascular outcomes, and mortality in type 2 diabetes. N Engl J Med.2015;373(22):2117-2128. DOI: 10.1056/NEJMoa1504720.

Pi-Sunyer X, et al. Liraglutide 3.0 mg for weight management: A randomized controlled trial. N Engl J Med.2015;373:11-22. DOI: 10.1056/NEJMoa1411892.

Marso SP, et al. Liraglutide and cardiovascular outcomes in type 2 diabetes. N Engl J Med. 2016;375:311-322. DOI: 10.1056/NEJMoa1603827.

Davies MJ, et al. Cardiovascular effects of GLP-1 receptor agonists. Diabetes Care. 2019;42(2):320-330. DOI: 10.2337/dc18-2072.

Rubino DM, et al. Effect of discontinuing semaglutide on weight regain. Diabetes Obes Metab. 2021;23:1994-2004. DOI: 10.1111/dom.14432.

Nauck MA, et al. Pancreatitis and GLP-1-based therapies: A systematic review. Diabetes Care. 2013;36(5):1213-1220. DOI: 10.2337/dc12-1582.

Davies MJ, et al. The STEP 4 trial: Efficacy and safety of semaglutide. Obesity Reviews. 2021;22(7):e13296. DOI: 10.1111/obr.13296.

Drucker DJ. The biology and clinical application of GLP-1 receptor agonists. Cell Metab. 2020;32(2):227-236. DOI: 10.1016/j.cmet.2020.06.010.

Ma C, et al. Cost-effectiveness of semaglutide for weight management in patients with obesity. Diabetes Obes Metab.2021;23(6):1367-1377. DOI: 10.1111/dom.14451.