

Glucagon-Like Peptide-1 (GLP-1) Receptor Agonists in the Management of Diabetes Mellitus: A Review

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ABSTRACT

In particular, type 2 diabetes mellitus (T2DM) is a fast growing global health concern associated with high rates of morbidity, mortality, and financial burden. Despite the availability of various pharmacological treatments, the long-term management of type 2 diabetes remains challenging due to weight gain, hypoglycemia, increasing β -cell dysfunction, and the limited cardiovascular benefits of standard therapy. The introduction of incretin-based drugs, particularly glucagon-like peptide-1 receptor agonists (GLP-1 RAs), is a significant advancement in the treatment of diabetes. GLP-1, an endogenous incretin hormone secreted by intestinal L-cells, inhibits the release of glucagon, postpones stomach emptying, promotes satiety, and increases glucose-dependent insulin production. Native GLP-1 is rapidly broken down by dipeptidyl peptidase-4 (DPP-4), whereas synthetic GLP-1 RAs are made to resist this breakdown and preserve glycemic control.

A. GLP-1 RAs effectively demonstrate a low risk of hypoglycemia, promote significant weight loss, and reduce glycated hemoglobin (HbA1c) by 0.8–1.5%, according to clinical research. Several important cardiovascular outcome trials, such as LEADER (liraglutide), SUSTAIN-6 (semaglutide), and REWIND (dulaglutide), have shown reductions in major adverse cardiovascular events and renal protection in addition to lowering blood sugar, establishing GLP-1 RAs as disease-modifying medications. Recent developments that have improved patient acceptance and adherence include oral semaglutide and once-weekly formulations. While tirzepatide and other next-generation dual and triple incretin agonists show promise for improved metabolic outcomes, future research focuses on expanding its use beyond diabetes to include obesity, non-alcoholic steatohepatitis, and neurodegenerative diseases. Long-term safety, stomach intolerance, and high cost are still problems and accessibility in resource-constrained settings. Lastly, GLP-1 receptor agonists represent a paradigm shift in the management of type 2 diabetes by providing numerous benefits that go well beyond glucose control. The therapeutic value of multi-agonist therapy is expected to rise over the next 10 years due to greater research in precision medicine and novel delivery technologies.

Keywords- GLP-1 receptor agonists, type 2 diabetes, obesity, cardiovascular consequences, incretin, and future directions.

I. INTRODUCTION

Synopsis Diabetes mellitus (DM) is a chronic, progressive metabolic condition characterized by persistent hyperglycemia caused by reduced insulin secretion, insulin resistance, or both. It is associated with long-term microvascular and macrovascular effects, including retinopathy, nephropathy, neuropathy, cardiovascular disease, and cerebrovascular disease, and is one of the leading causes of morbidity and mortality

worldwide [1]. Type 2 diabetes mellitus (T2DM) accounts for 90–95% of diabetes cases. [2]

Over 537 million adults (20–79 years old) have diabetes in 2021, according to the International Diabetes Federation (IDF) Atlas, 10th edition (2021). This number is expected to increase to 643 million by 2030 and 783 million by 2045 [3]. Sedentary lifestyles, urbanization, dietary changes, and the worldwide obesity pandemic are the main causes of the sharp rise in prevalence. Diabetes not only affects quality of life but also has a significant

financial cost; in 2021, worldwide health expenditures are projected to reach USD 966 billion [3].

1.1 Limitations of Conventional Therapies:

Type 2 diabetes is managed with pharmacological treatments and lifestyle modifications. Conventional drugs include insulin, metformin, sulfonylureas, thiazolidinediones, DPP-4 inhibitors, and sodium-glucose cotransporter-2 (SGLT2) inhibitors [4]. Despite the fact that these therapies effectively lower blood sugar, they often have disadvantages such as: [5]

- Putting on weight, particularly while taking sulfonylureas, thiazolidinediones, and insulin [6].
- The risk of hypoglycemia, especially when taking sulfonylureas with insulin [7].
- Gastrointestinal intolerance associated with metformin [8].
- Long-term glycemic durability is lost as β -cell depletion advances [9].

Additionally, despite the fact that the primary causes of death for individuals with diabetes are atherosclerotic cardiovascular disease (ASCVD) and chronic kidney disease (CKD), most conventional treatments primarily concentrate on reducing blood sugar levels and provide minimal protection for the heart or kidneys [10]. This unmet need highlighted the need to develop treatments with both glycemic and extra-glycemic benefits.

1.2 The Incretin Effect and GLP-1 Physiology

The discovery of the incretin effect led to new medicinal approaches and significant insights into glucose regulation. The incretin effect refers to the fact that oral glucose administration results in a greater insulin response than intravenous glucose, even at same plasma glucose concentrations [11]. hormones produced from the gut, primarily glucose-dependent insulintropic polypeptide (GIP) and glucagon-like peptide-1 (GLP-1), mediate this procedure [12].

GLP-1 is produced by enteroendocrine L-cells in the colon and distal ileum in response to dietary intake. It affects glucose homeostasis in a number of physiochemical ways, including:

- An increase in glucose-dependent insulin secretion.
- Induction of satiety and reduced food intake through central appetite-regulating mechanisms; slowing of stomach emptying, which reduces postprandial glucose excursions;
- Inhibition of inappropriate glucagon release, which reduces the amount of glucose generated by the liver [13,14].

However, native GLP-1 has a plasma half-life of less than two minutes due to its rapid breakdown by the enzyme dipeptidyl peptidase-4 (DPP-4) [15]. This pharmacokinetic limitation led to the development of GLP-1 receptor agonists (GLP-1 Ras), which offer prolonged GLP-1 receptor activation and are resistant to DPP-4 degradation.

1.3 GLP-1 Receptor Agonist Development

Exenatide, the first GLP-1 RA approved in 2005, was derived from exendin-4, a naturally occurring peptide found in the saliva of the Gila monster (*Heloderma suspectum*) [16].

Many GLP-1 RAs with various molecular structures, half-lives, and dosing schedules have been developed since then.

They fall under the following general categories:

- Short-acting GLP-1 RAs that mainly target postprandial glucose excursions by delayed stomach emptying, as lixisenatide and exenatide (twice daily) [17].
- Long-acting GLP-1 RAs, like semaglutide, dulaglutide, and liraglutide, provide higher effects on fasting plasma glucose and HbA1c as well as longer-lasting receptor stimulation [18].
- Once-weekly formulations, including semaglutide and dulaglutide, have greatly improved convenience and adherence [19]. Additionally, a noteworthy advance is the recent approval of oral semaglutide, the first GLP-1 RA that is available orally [20].

1.4 The Clinical Significance of GLP-1

GLP-1 RAs offer a multifaceted therapeutic profile, in contrast to many conventional treatments.

Glycemic control: a drop in HbA1c of 0.8–1.5% [21].

Weight Loss: They are particularly beneficial for obese T2DM patients because patients usually lose 2 to 5 kg [22].

Cardiovascular Benefits: Large cardiovascular outcome trials (CVOTs) such as LEADER (liraglutide), SUSTAIN-6 (semaglutide), and REWIND (dulaglutide) showed a significant reduction in major adverse cardiovascular events (MACE) [23, 24].

Renal Protection: Research indicates a reduction in albuminuria and a postponement of the onset of chronic kidney disease [25, 26].

Low Risk of Hypoglycemia: Because of their glucose-dependent mode of action, GLP-1 RAs have a far lower risk of hypoglycemia than insulin or sulfonylureas [27]. Because of these qualities, GLP-1 RAs are a vital therapy option, particularly for T2DM patients who have considerable cardiovascular risk, obesity, or current ASCVD. Obstacles and Restrictions.

1.5 GLP-1 RAs have a number of disadvantages:

In spite of their talent. The most common side effects are gastrointestinal problems such nausea, vomiting, and diarrhea. Long-term use often eliminates these dose-dependent effects [28]. Pancreatitis, gallbladder disease, and possible links to thyroid C-cell cancers are rare but serious issues, notwithstanding the paucity of human data at this time [29, 30].

Two more important limitations are cost and accessibility. Because GLP-1 RAs are much more expensive than older drugs like metformin and sulfonylureas, they are not commonly used in areas with limited resources [31].

1.6 Rationale for the Evaluation

Given the drawbacks of conventional therapies and the rising incidence of type 2 diabetes, GLP-1 receptor agonists represent a groundbreaking advancement in the management of diabetes. They offer improved quality of life, weight loss, kidney and cardiovascular protection, and effective glucose reduction. As a result, they play a crucial role in the present management of type 2 diabetes.

The goal of this study is to provide a comprehensive examination of GLP-1 receptor agonists, with a focus on their mechanisms of action, clinical efficacy, safety profile, and potential applications in the treatment of diabetes.

II. MECHANISM

Glucagon-like peptide-1 (GLP-1), a 30–31 amino acid incretin hormone, is crucial for preserving glucose homeostasis. It is mostly secreted by enteroendocrine L-cells located in the colon and distal ileum in response to the ingestion of nutrients, especially fats and carbohydrates [32]. GLP-1 has a variety of effects on the pancreatic, gastrointestinal, central nervous system, and cardiovascular tissues once it is generated and binds to the GLP-1 receptor (GLP-1R), a member of the class B G-protein-coupled receptor family [33].

The enzyme dipeptidyl peptidase-4 (DPP-4) quickly breaks down endogenous GLP-1, which has a half-life of less than two minutes despite its strong antihyperglycemic actions [34]. This limitation spurred the development of GLP-1 receptor agonist (GLP-1 RAs) which are structurally modified resistant to DPP-4 degradation, allowing sustained activation of GLP-1 receptor and longer duration of action [35].

2.1 Effects on Pancreatic Islets:

GLP-1 RAs mostly affect both β -cells and α -cells in the pancreas

2.1.1 Insulin Secretion Stimulation

GLP-1 RAs increase pancreatic β -cells' glucose-dependent insulin release. Intracellular signaling cascades, such as the cyclic AMP (cAMP)-protein kinase A (PKA) pathway and exchange protein activated by cAMP (EPAC2), are triggered upon binding to GLP-1R, a G-protein-coupled receptor [36]. These pathways include:

- Increasing intracellular calcium concentrations;
- Improving insulin granule exocytosis;
- Encouraging β -cell proliferation and insulin gene transcription.

Unlike sulfonylureas or exogenous insulin, this glucose-dependent mechanism guarantees that insulin is only produced when blood glucose levels are elevated, reducing the risk of hypoglycemia [37].

2.1.2 Inhibition of Secretion of Glucagon

GLP-1 RAs not only increase the release of insulin but also decrease the secretion of glucagon from α -cells in the pancreas during hyperglycemia. Hepatic

gluconeogenesis and glycogenolysis are reduced when glucagon levels are low, which results in decreased hepatic glucose production [38]. Crucially, proper glucagon counterregulation during hypoglycemia is maintained because glucagon suppression is glucose-dependent [39].

2.2 Effect on Gastric Emptying and Gastrointestinal Tract

GLP-1 RAs slow down the rate at which consumed nutrients enter the small intestine and then the circulation by delaying gastric emptying [40]. This result:

- Attenuates postprandial glucose spikes.
- Aids in decreasing food intake and boosting satiety.

Short-acting GLP-1 RAs (such as lixisenatide and lixisenatide) have a greater impact than long-acting agents (like liraglutide and semaglutide), which have longer-lasting effects on fasting glucose [41].

2.3 Central Nervous System Effects

Several parts of the brain, including the brainstem and hypothalamus, express GLP-1 receptors. Satiety and appetite control depend heavily on the activation of these receptors [42].

GLP-1 RAs decrease appetite by stimulating pro-opiomelanocortin (POMC)/cocaine- and amphetamine-regulated transcript (CART) neurons in the hypothalamic arcuate nucleus.

Neuropeptide Y (NPY)/agouti-related peptide (AgRP) neurons, which stimulate eating, are likewise inhibited by them [43].

This dual effect lowers caloric intake, which greatly aids in weight loss—a crucial advantage for T2DM patients who are overweight or obese. Furthermore, GLP-1 signaling in the brain may affect reward pathways, which could help with long-term weight management by lowering desires for meals high in calories. [44].

2.4. Effects on cardiovascular System

The heart, blood vessels, and kidneys all have GLP-1 receptors, and GLP-1 RAs have pleiotropic cardiovascular effects there:

- Endothelial function is enhanced by vasodilation through nitric oxide-mediated pathways [45].
- Cardioprotection via enhanced myocardial glucose absorption, decreased oxidative stress, and anti-inflammatory actions [46].
- A decrease in blood pressure, partially as a result of natriuresis, weight loss, and direct vascular effects [47].

These processes align with the results of cardiovascular outcome trials (LEADER, SUSTAIN-6, REWIND), which showed that patients treated with GLP-1 RAs had fewer major adverse cardiovascular events (MACE) [48,49].

2.5 Effects on Renal System

GLP-1 RAs enhance renal outcomes through a variety of mechanisms:

- A decrease in albuminuria, potentially as a result of lower intraglomerular pressure and enhanced endothelial function [51].
- Inhibition of sodium-hydrogen exchanger 3 (NHE3) in the proximal tubules causes natriuresis and diuresis [52].
- Anti-fibrotic and anti-inflammatory properties that support renoprotection [53].

In addition to their glucose-lowering effects, these systems offer extra renal advantages that are unrelated to glycemic management.

2.6 Mechanism Synopsis

In conclusion, GLP-1 receptor agonists affect a variety of target organs (Figure 1):

- The pancreas suppresses glucagon and increases insulin release.
- Digestive system → postpone emptying the stomach.
- The central nervous system reduces appetite and increases satiety.
- Cardiovascular system: lower cardiovascular risk and enhance endothelial function.
- The kidneys use anti-inflammatory and natriuretic processes to protect the kidneys. GLP-1 RAs work together to ameliorate glycemic control, weight reduction, and cardiovascular/renal protection, making them a cornerstone in modern diabetes therapy.

III. AVAILABLE GLP -1 RECEPTOR AGONISTS

Exenatide and Lixisenatide are examples of:

- Short-acting medications that are currently licensed.
- Long-acting: Albiglutide (removed from various markets), Liraglutide, Dulaglutide, and Semaglutide. Because they only need to be taken once a week, long-acting formulations offer better adherence and long-term glycemic control.

IV. CLINICAL EFFICACY

The effectiveness of GLP-1 RAs has been shown in numerous clinical trials:

Glycemic control: a 0.8–1.5% drop in HbA1c.

Weight Loss: 2–5 kg on average.

Cardiovascular Benefits: Major adverse cardiovascular events (MACE) were significantly reduced by dulaglutide (REWIND trial), semaglutide (SUSTAIN-6 study), and liraglutide (LEADER trial).

Renal Protection: Research points to decreased albuminuria and a slower rate of diabetic nephropathy progression.

4.1 Glycemic Control

Glycemic parameters are significantly improved with GLP-1 RAs:

- HbA1c reduction: Usually between 0.8 and 1.5%, depending on the drug, dose, and baseline HbA1c.

Control of fasting and postprandial glucose:

Long-acting medications (liraglutide, dulaglutide, and semaglutide) primarily reduce fasting glucose. Because they have a greater impact on stomach emptying, short-acting medications like exenatide and lixisenatide are more effective on postprandial hyperglycemia.

V. SAFETY PROFILE AND ADVERSE EFFECTS

5.1 Overall Safety Profile

GLP-1 receptor agonists (GLP-1 RAs) have a better benefit-risk ratio than a number of conventional antidiabetic medications, including insulin and sulfonylureas, and are typically regarded as safe and well tolerated. When administered alone or in conjunction with medications not linked to hypoglycemia, their glucose-dependent mode of action lowers the risk of hypoglycemia. They also help with weight loss and cardiovascular health, which increases their therapeutic effectiveness in the treatment of type 2 diabetes. However, some gastrointestinal, pancreatic, and uncommon systemic side effects restrict their use.

5.2 Common Adverse Effects

Most GLP-1 RA side effects are gastrointestinal (GI) in origin, usually dose-dependent and temporary:

- Nausea (most prevalent, initially reported in 20–40% of patients; normally goes away over time).
- Diarrhea and vomiting, which can sometimes result in stopping therapy.
- Although they are less common, constipation and stomach pain are frequently noted. GLP-1-mediated central satiety signaling and delayed stomach emptying are responsible for the GI effects.

5.3 Hypoglycemia Risk

Increased risk when taken with insulin or sulfonylureas; low when administered alone because of glucose-dependent insulin secretion. As a result, concurrent therapeutic dose modifications can be necessary.

5.4 Pancreatic Safety Concerns

Pancreatitis: Concerns about acute pancreatitis have been raised by post-marketing reports and certain observational studies. Clinicians are urged to be cautious when treating patients with a history of pancreatitis, even though massive randomized controlled trials (RCTs) and meta analyses have not established a causative association.

Pancreatic cancer: Although early indicators pointed to a potential connection, the information is still conflicting and unconfirmed.

5.5 Gallbladder and Biliary Disease

GLP-1 RAs are linked to a marginally elevated risk of gallbladder illness, such as cholecystitis and cholelithiasis. This is believed to be associated with decreased gallbladder motility and weight loss.

5.6 Cardiovascular Safety

- Several medications showed notable decreases in major adverse cardiovascular events (MACE), while large CV outcome trials (LEADER, SUSTAIN-6, REWIND, etc.) showed no increased cardiovascular risk.
- There have been reports of a slight increase in heart rate (2–4 bpm), but no negative consequences.

5.7 Renal Safety

- Nephroprotective (lower albuminuria, slower kidney disease progression) and generally safe.
- In patients who are vulnerable, nausea, vomiting, and dehydration can occasionally cause acute renal injury.

5.8 Thyroid Safety

Research on rodents indicated that certain GLP-1 RAs may increase the risk of C-cell malignancies (medullary thyroid cancer). These drugs should not be used in patients with a personal or family history of multiple endocrine neoplasia type 2 (MEN2) or medullary thyroid cancer (MTC), however human studies have not verified this risk.

5.9 Injection-Site Reaction and Immunogenicity

- It is possible for anti-drug antibodies to develop, particularly with exenatide.
- Although they are rare, mild injection-site reactions (erythema, pruritus, nodules) can cause cessation.

5.10 Rare Adverse Events

- Co-administration of oral medications may be complicated by delayed gastric emptying (drug-drug interaction potential) and hypersensitivity events, such as urticaria and angioedema.
- Complications from diabetic retinopathy (especially with semaglutide in SUSTAIN-6), which may be brought on by fast glucose reduction.

VI. ROLE IN COMBINATION THERAPY

GLP-1 RAs are frequently used in conjunction with the first-line medication metformin.

- SGLT2 inhibitors, which provide further advantages for renal and cardiovascular outcomes.
- Basal insulin, which minimizes weight gain and lowers the need for insulin.

VII. FUTURE DIRECTIONS OF GLP-1 RECEPTOR AGONISTS

Since GLP-1 receptor agonists (GLP-1 RAs) were first approved as glucose-lowering medications, their therapeutic use has quickly expanded to become a vital component of contemporary diabetic care. They are now recognized as disease-modifying agents rather than just antidiabetic medications due to their proven cardiovascular and renal advantages, which go beyond glucose management. Despite these developments,

research is still being conducted to increase their clinical value, improve formulations, and investigate new therapeutic approaches. The potential of GLP-1 RAs to change the way that diabetes, obesity, metabolic syndrome, and other chronic diseases are managed is being investigated in a number of future avenues.

7.1 Expansion Beyond Diabetes Mellitus

Despite being created for type 2 diabetes mellitus (T2DM), GLP-1 RAs are appealing options for non-diabetic reasons due to their pleiotropic effects:

- **Obesity and Weight Management:** Regardless of diabetes status, high-dose formulations of semaglutide (2.4 mg/week; licensed as Wegovy) and liraglutide (3.0 mg/day; approved as Saxenda) have demonstrated notable weight-loss advantages [54,55]. Studies like STEP-1 showed that semaglutide 2.4 mg reduced body weight by about 15% when compared to a placebo [56]. This implies that GLP-1 RAs are becoming more and more important as anti-obesity medications, potentially taking the place of or postponing bariatric surgery.
- **Non-Alcoholic Steatohepatitis (NASH) and Non-Alcoholic Fatty Liver Disease (NAFLD):** GLP-1 RAs lower hepatic steatosis by improving insulin sensitivity, reducing weight, and directly affecting hepatic inflammation. Liraglutide improved NASH histology and slowed the advancement of fibrosis, according to the LEAN study [57]. With encouraging outcomes in phase 3 trials, semaglutide is presently being studied for NASH [58].
- **Neurodegenerative Disorders:** GLP-1 RAs may have neuroprotective effects, according to preclinical and early clinical research. They lower oxidative stress, amyloid deposition, and neuroinflammation by passing through the blood-brain barrier [59]. Research on liraglutide and semaglutide for Parkinson's and Alzheimer's disease is expanding the field of neurometabolic medicine [60].

7.2 Next-Generation Incretin-Based Therapies

Dual and multi-agonist treatments that target several incretin pathways at once to optimize metabolic advantages are a key area of future research. GLP-1/GIP Dual Agonists (Twincetins):

Tirzepatide, a once-weekly dual GLP-1 and GIP receptor agonist, is the most well-known. Tirzepatide outperformed semaglutide in the SURPASS clinical program in terms of weight loss (up to 12–15 kg) and HbA1c decrease (up to 2.5%) [61,62]. This implies that the effectiveness of existing GLP-1 RAs may be exceeded by dual incretin therapy.

GLP-1/Glucagon Receptor Co-Agonists: In order to improve weight loss, agents that concurrently activate GLP-1 and glucagon receptors seek to combine glucose regulation with increased energy expenditure and fat oxidation [63]. Significant improvements in lipid metabolism and decreases in body weight have been shown in early-phase experiments.

Triple Agonists (GLP-1/GIP/Glucagon): By concurrently addressing several pathways in obesity, diabetes, and NAFLD, novel tri-agonists that are in preclinical and early human trials have the potential to completely transform metabolic therapy [64].

7.3 Advances in Drug Formulations and Delivery Systems

Except for oral semaglutide, most GLP-1 RAs are now given subcutaneously. Future plans seek to enhance patient comfort and adherence:

The approval of oral semaglutide (Rybelsus) constitutes a breakthrough. Alternative oral formulations, transdermal patches, nasal sprays, and implantable devices that guarantee prolonged medication delivery are being researched [65].

Longer-Acting Agents: In order to improve compliance, new long-acting GLP-1 analogues with monthly dose schedules are being researched [66].

Fixed-Dose Combinations: To provide synergistic benefits on glycemia, weight, and cardiovascular outcomes, GLP-1 RAs in combination with SGLT2 inhibitors or basal insulin (such as insulin degludec + liraglutide [IDegLira]) are being investigated [67].

7.4 Precision Medicine and Patient Stratification

Finding patient subgroups that benefit most with GLP-1 RAs is another area of interest. Pharmacogenomic determinants of response are currently being investigated [68]. Creation of biomarkers to determine which patients are most likely to lose weight or benefit from cardiovascular conditions [69].

Customized treatment for older patients, people with chronic kidney disease (CKD), and people at high risk for ASCVD, where cost, tolerability, and efficacy must be balanced.

7.5 Safety and Long-Term Outcomes

Although GLP-1 RAs are usually safe, more investigation is needed to determine: long-term safety with long-term use, especially with reference to thyroid C-cell malignancies, gallbladder illness, and pancreatitis [70]. consequences of lifetime exposure in populations without diabetes (neurodegeneration, NASH, obesity). As its use grows worldwide, post-marketing surveillance will be used to record infrequent adverse events.

7.6 Health Economics and Global Accessibility

GLP-1 RA costs continue to be a significant obstacle, especially in low- and middle-income nations. Future tactics ought to concentrate on:

Creation of biosimilars to cut expenses. Interventions in health policy for insurance coverage and payment. Research on cost-effectiveness in the real world that take long-term cardiovascular and renal consequences into account [71].

VIII. SUMMARY

Overall, the safety profile of GLP-1 receptor agonists is excellent, with gastrointestinal side effects being the most common but typically temporary.

Although there is no conclusive proof of a human cause, concerns about pancreatitis, gallbladder illness, thyroid tumors, and diabetic retinopathy need to be monitored. Renal and cardiovascular safety data are solid and frequently provide protective advantages. Therapeutic advantages can be maximized while hazards are minimized with careful patient selection and monitoring.

IX. CONCLUSION

GLP-1 receptor agonists, which provide better glycemic control, weight loss, and cardiovascular advantages than conventional medicines, are a mainstay in the treatment of type 2 diabetes mellitus. They are a vital part of contemporary diabetic therapy because to their good safety profile and growing therapeutic roles. The therapeutic value of combination medicines and innovative delivery technologies will be further improved by ongoing research.

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