Unlocking the potential of glucagon-like peptide-1 receptor agonists in revolutionizing type 2 diabetes management: a comprehensive review

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Abstract

Diabetes mellitus (DM) is a long-term metabolic disorder caused by inadequate production and resistance to insulin. The prevalence of DM is rapidly increasing, with type 2 diabetes (T2D) accounting for more than 90% of cases. Despite new treatments, many patients with T2D do not meet their glycemic targets due to clinical inertia. This review provides an overview of glucagon-like peptide 1 receptor agonists (GLP-1 RAs) in the management of T2D. The review synthesizes data from clinical trials and meta-analyses on the efficacy, safety, and cost-effectiveness of GLP-1 RAs. It also discusses the mechanisms of action, classification, and barriers to adherence and persistence in therapy. GLP-1 RAs improve glycemic control by lowering A1C levels and promoting weight loss. They have cardioprotective effects and may reduce endothelial inflammation, oxidative stress, and blood pressure. Adherence to GLP-1 RAs is better with once-weekly injections, though gastrointestinal side effects and cost can affect persistence. Semaglutide and liraglutide have shown significant weight reduction, with semaglutide being particularly effective. GLP-1 RAs are cost-effective due to reduced healthcare costs associated with fewer hospitalizations and lower mortality rates. Safety concerns include gastrointestinal issues, pancreatitis, and rare cases of diabetic retinopathy and thyroid C-cell tumors. For clinical practice, GLP-1 RAs represent a valuable option not only for glycemic control but also for weight management and cardiovascular protection. Incorporating GLP-1 RAs into treatment plans can improve patient outcomes, and optimizing dosing regimens and addressing barriers such as cost and side effects are crucial to enhancing patient adherence and long-term treatment success.

Keywords: glucagon-like peptide-1 receptor agonists, glycemic control, injectable glucagon-like peptide-1 receptor agonists, type 2 diabetes, weight loss

Introduction

Diabetes mellitus (DM) is a long-term metabolic disorder caused by inadequate production and resistance to insulin. This condition results from both environmental and genetic factors. It is considered one of the fastest-growing diseases globally, posing severe health risks to the public. The burden of DM has risen from 151 million in the year 2000 to 537 million in 2021, with a forecasted prevalence of 643 million by 2030 and 783 million by 2045. More than 90% of these cases were type 2 diabetes (T2D). In 2021, global health expenditure attributed to diabetes was close to one trillion USD, and it is projected to overshoot this by 2030[1]. Despite new treatments introduced in the last decade, many people with T2D do not meet their glycemic targets[2,3] due to clinical inertia, which is the failure to start or intensify treatment even when goals are not met[3]. This issue is complex and

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involves factors related to patients, doctors, and the healthcare system. Common barriers to reaching treatment goals include fears about hypoglycemia, weight gain, and the complexity of treatment options[4].

Primary care remains the mainstay for the management of T2D, with more than 90% of patients being treated in this setting in the USA[5,6]. The complexity of T2D management in primary care keeps growing, not only because of various classes of therapeutics but also because of other comorbidities needing attention. Although diet and exercise form cornerstones of disease management, most patients eventually require pharmacological intervention. A treatment plan has to be individualized, considering treatment goals, patient preferences, and comorbidities[7]. Currently, the target level of HbA1c below 7.0%, according to the recommendation of the ADA, is estimated to be reached by less than 50% of patients with T2D in the U.S., needing an improvement in the quality of care and availability of multiple therapeutic options[2,8]. A significant part of the problem is delays in intensifying therapy to reach glycemic goals, especially initiating injectable treatments[9,10].

Early, intensive T2D management has been shown to have a positive impact on the course of the disease, the likelihood of complications, and the amount of time before treatment failure[11–15]. Metformin is the first-line pharmaceutical medication for hyperglycemia at diagnosis, in addition to dietary and lifestyle changes[16]. However, within 3 years of diagnosis, more than half of the patients require adding a second glucose-lowering medication[17,18]. In fact, patients frequently require further intensification involving multiple medications and insulin as T2D naturally progresses[19–21]. Because they lower blood sugar, reduce weight, and have a low inherent risk of hypoglycemia, glucagon-like peptide 1 receptor agonists (GLP-1RAs) have been the focus of much research over the past 10 years, making them appropriate for the management of T2D in primary and secondary care and also having positive cardiovascular effects[22,23]. An overview of the clinical data pertaining to the safety and effectiveness of GLP-1RAs is given in this review.

## Mechanisms of action and classification of GLP-1 receptor agonists

GLP-1 RAs are injectable peptides that mimic endogenous GLP-1 in terms of structure and function[24]. Therapeutic effects of GLP-1 RAs agonists are exhibited at therapeutic dosages through the GLP-1 receptor, a seven-transmembrane G protein-coupled receptor that is extensively expressed in several important cells and human organs, including alpha, beta, and gamma cells, with expression also noted in the kidney, heart, central and peripheral nervous system, GI tract, and liver. Research suggests that GLP-1 RAs enhance β-cell proliferation while decreasing apoptosis, ultimately safeguarding β-cells[25,26]. Moreover, they also bind to δ-cell receptors, subsequently increasing somatostatin secretion, which in turn lowers blood glucose levels[27]. Additionally, researchers put forward the result that GLP-1 RAs, when interacting with the β-cell receptor in the pancreas, cause glucose-dependent insulin production and secretion[28]. As mentioned above, GLP-1 RAs function similarly to endogenous GLP-1. The gut-derived incretin hormone GLP-1 has a significant role in maintaining glucose homeostasis as it is released following an oral meal containing fats or carbohydrates. In T2DM, this

HIGHLIGHTS

- GLP-1 RAs significantly reduce A1C levels and promote weight loss, making them effective in managing type 2 diabetes (T2D).
- These medications improve endothelial function, reduce inflammation and oxidative stress, lower blood pressure, and potentially reduce cardiovascular risks in patients with T2D.
- Despite their benefits, adherence to GLP-1 RAs remains suboptimal due to gastrointestinal side effects, injection-related concerns, and high costs.
- GLP-1RAs are an effective class of therapeutic agents for people with T2D and have well-established safety and tolerability profiles.
- Despite higher initial costs, GLP-1 RAs can be cost-effective due to reduced hospitalizations and improved long-term health outcomes, highlighting their economic impact.

response of GLP-1 to an oral glucose load is blunted. GLP-1 stimulates insulin production; however, in the presence of increased glucose, it increases both the in vivo release of insulin from pancreatic beta cells and glucose-dependent insulin synthesis. Hence, based on clinical evidence, GLP-1 RAs have been shown to assist in the restoration of insulin secretory capabilities, which in turn help patients with T2D manage their blood sugar levels and weight[29]. Figure 1 *depicts the mechanism of action of GLP-1 receptor agonists*. In brief, GLP-1 RAs have a positive impact directly on five pathways of the ominous octet in humans: (i) increasing β-cells' secretion of insulin; (ii) decreasing α-cells' secretion of glucagon; (iii) reducing the production of glucose in the liver; (iv) reversing incretin failure; and (v) reducing appetite and promoting weight loss[30].

Two categories may be established among GLP-1 RAs based on their ability to activate the GLP-1 receptor. Short-acting agonists, lasting less than a day, includes exenatide twice daily and lixisenatide once daily, and long-acting agonists, lasting more than a day, include extended-release formulations of exenatide, albiglutide, semaglutide, dulaglutide, and liraglutide once daily. Notably, exenatide and lixisenatide, the formulations derived from the exendin-4 molecule, exhibit merely 53% and around 50% similarity to the native human GLP-1, respectively. On the other hand, natural human GLP-1 is 94% identical to semaglutide, 95% to albiglutide, 90% to dulaglutide, and 97% to liraglutide[30]. While short-acting agonists reduced postprandial hyperglycemia, likely through the reduction of gastric emptying, long-acting agonists lowered HbA1c and also reduced fasting hyperglycemia with inhibition of glucagon production, a mechanism shared by all GLP-1 RAs[31]. Basal hyperglycemia can be reduced when long-acting analogs are used since they can sustain high GLP-1 levels and promote insulin production for 24 h, even during the state of fasting. The main mechanisms by which these GLP-1 RAs affect postprandial hyperglycemia are by suppressing glucagon secretion, decreasing hunger, and delaying gastric emptying. Compared to long-acting agonists, short-acting GLP-1 RAs have a less noticeable influence on insulin secretion during the fasting phase but a more noticeable effect on gastric emptying, which can be explained by tachyphylaxis, which occurs because of the continuous receptor stimulation, as in the case with long-acting agonists, but not with the activation that is

Mechanism of action of GLP-1RAs

Figure 1. Mechanism of action of GLP-1 receptor agonists.
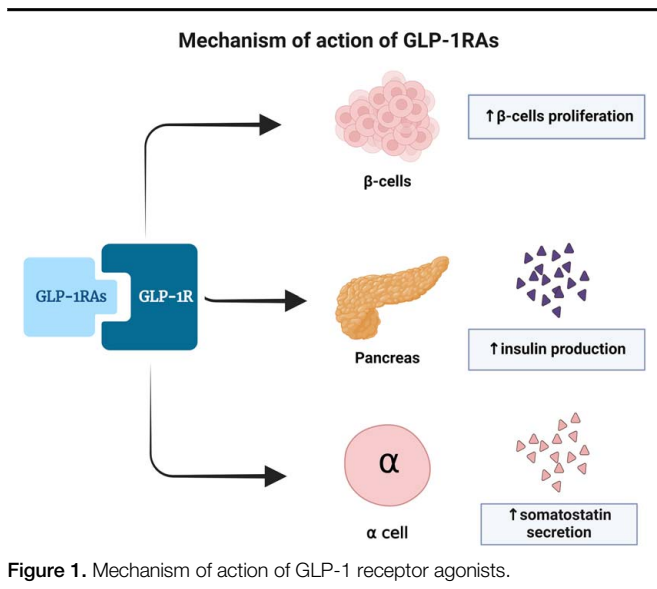
intermittent. Moreover, postprandial hyperglycemia for the meal directly after administration was more significantly reduced under short-acting agonists, which was primarily due to their more remarkable influence on gastric emptying[31]. For dosage, all drugs should be administered subcutaneously, administering 5 μg of exenatide, 10–20 μg of lixisenatide, 0.6–1.2 mg of liraglutide, 2 mg of exenatide extended-release, 30–50 mg of albiglutide, 0.25 mg of semaglutide, and 0.75–1.5 mg of dulaglutide to get desired outcomes[32]. *Classification and overview of GLP-1 receptor agonists are summarized in* Table 1.

GLP-1 receptor agonists in type 2 diabetes management

Treatment for T2D is individualized for each patient based on their needs, considering weight loss, glycemic control, and complications from illnesses such as chronic kidney disease (CKD), atherosclerotic cardiovascular disease (ASCVD), and hypoglycemia. According to the American Diabetes Association (ADA), GLP-1RAs should be used as the second line of treatment after metformin and lifestyle modifications in patients who have heart failure, CKD, or ASCVD or who do not have any of these conditions but have a compelling need to minimize weight gain, reduce the risk of hypoglycemia, or promote weight loss[7]. Based on a wealth of information gathered over more than 10 years of clinical usage, including findings from real-world research and clinical trials, subcutaneous GLP-1 RAs have established themselves as a mainstay of T2D treatment[23,33–36]. The possible direct and indirect effects of GLP-1RAs on glycemic control, weight loss, and cardioprotective benefits are outlined below.

Glycemic control

The GLP-1 RAs (exenatide, liraglutide, albiglutide, taspoglutide, lixisenatide, and dulaglutide) were shown to lower A1C levels (range –0.55 to –1.38 percentage points) when compared to placebo or another GLP-1 RA in a meta-analysis of 34 randomized trials that included patients with T2D with inadequate control on oral medications (mostly metformin)[37,38]. While

significant drug-specific differences were evident in head-to-head comparisons, longer-acting GLP-1 receptor agonists exhibited greater reductions in A1C compared to their shorter-acting agents. In another meta-analysis of primarily short-term studies lasting 26 weeks, often funded by pharmaceutical companies, it was demonstrated that GLP-1 RA treatment, in comparison to active comparators such as basal insulin glargine, sitagliptin, pioglitazone, or daily exenatide, resulted in greater reductions in A1C levels (ranging from 0.2 to 0.8 percentage points) among patients with initial A1C values falling between 8 and 8.5%[38,39]. Another meta-analysis of trials found no significant differences in the glycemic efficacy of basal insulin with liraglutide or exenatide twice daily in terms of decreasing A1C levels[40]. Injectable semaglutide led to a notably higher reduction in A1C, exceeding that of glargine by 0.8 percentage points, whereas exenatide injected once weekly and dulaglutide achieved a modest reduction in A1C (about 0.3 percentage points) compared to basal insulin[41]. In the GRADE comparative effectiveness trial, which followed 5047 patients diagnosed with T2D over an average of 5 years receiving metformin monotherapy, it was found that patients receiving additional treatment with liraglutide or glargine had a lower cumulative occurrence of A1C levels ≥7% (68% and 67%, respectively) compared to those given glimepiride or sitagliptin (72% and 77%, respectively)[42].

Weight loss

GLP-1 RA-based treatments frequently result in weight loss[38,39,43–45]. The impact of GLP-1 on delayed gastric emptying, along with its commonly known side effects of nausea and vomiting, could potentially contribute to weight loss. Nevertheless, delayed gastric emptying tends to diminish gradually over time, particularly with longer-acting GLP-1 RA, as they enhance the sensation of fullness by affecting the brain's appetite-regulating areas[46–48]. In patients with T2D inadequately controlled on oral medications, typically metformin, a meta-analysis of 34 trials compared the effects of GLP-1 RAs (albiglutide, dulaglutide, exenatide, liraglutide, lixisenatide, and taspoglutide) versus placebo or another GLP-1 RA. All approved GLP-1 RAs were found to cause weight loss compared to placebo, with very little heterogeneity seen with the individual agents[37]. In the GRADE comparative effectiveness trial involving patients with T2D on metformin monotherapy, the incidence of body weight increase ≥10% was lower in the patients when assigned to liraglutide as an additional medication and exhibited a lower incidence (6.1%) compared to individuals receiving glargine (13.1%), sitagliptin (9.1%), or glimepiride (12.1%)[42]. When compared to the glimepiride (0.73 kg), sitagliptin (2.0 kg), and glargine (0.61 kg) groups, which all saw very small weight reductions, the liraglutide cohort saw a substantially larger mean reduction in body weight (3.5 kg).

Compared to placebo, liraglutide and semaglutide caused weight reduction in studies intended specially to assess weight loss in people with T2D[44,45,49]. In a 56-week trial involving 846 individuals with T2D and obesity (with a mean A1C of 7.9% and a mean weight of 106 kg), once-daily subcutaneous liraglutide (at dosages of 3 or 1.8 mg) was compared to a placebo. The results showed considerable weight loss in the liraglutide treatment groups, with decreases of –6.4 kg (–6%) and –5 kg (–4.7%) compared to the placebo group, which showed –2.2 kg (–2%) of weight loss. The mean difference between 3 mg of liraglutide and

Table 1

Classification and overview of GLP-1 receptor agonists.

Classification	Duration of action	Dosage
Short acting		
Exenatide	Twice daily	Administer 5 μg subcutaneously twice a day before having a meal; depending on clinical response, increase to 10 μg subcutaneously twice a day after 1 month
Lixisenatide	Once daily	Administer 10 μg subcutaneously once daily, 1 h prior to the first meal of the day; on the 15th day, increase the dosage up to 20 μg
Long acting		
Liraglutide	Once daily	Administer 0.6 mg daily for 1 week, later can be increased to 1.2 mg
Exenatide extended-release	Once weekly	Once a week, or every 7 days, 2 mg subcutaneously
Albiglutide	Once weekly	30 mg once a week via subcutaneous injection; if glycemic control is ineffective, this dosage can be increased to 50 mg once a week
Semaglutide	Once weekly	Administer 0.25 mg subcutaneously once a week
Dulaglutide	Once weekly	Administer 0.75 mg subcutaneously once a week; if glucose control is not sufficient, increase the dose to 1.5 mg subcutaneously

placebo was –4% (95% CI –5.1 to –2.9)[44]. In a 68-week trial, 1210 individuals diagnosed with T2D and obesity (with a mean A1C of 8.1% and a mean weight of 99.8 kg) were randomly assigned to receive once-weekly subcutaneous semaglutide [at doses of 2.4 mg (investigational dosage) or 1 mg (standard dose)] with placebo. The semaglutide treatment groups experienced significant weight loss [–9.7 kg (–9.6%) and –6.9 kg (–7%)] compared to the placebo group [–3.5 kg (–3.4%)]. Oral semaglutide became the first oral formulation of a GLP-1 RA approved by the FDA in 2019[50]. The approval came after a thorough series of phase 3a clinical trials performed within the Peptide Innovation for Early Diabetes Treatment (PIONEER) study program. Within this program, eight multinational trials (PIONEER 1–8) were carried out[51–58], and two more trials were conducted in Japan (PIONEER 9 and 10)[59,60]. These trials enrolled more than 9500 adults with T2D and evaluated oral semaglutide as monotherapy and as an adjunct to the following background treatments: metformin, sulfonylureas, SGLT2 inhibitors, thiazolidinediones, and insulin. Comparators in these studies included a placebo, injectable GLP-1 RAs, a DPP-4 inhibitor, and an SGLT2 inhibitor. Out of all these medications, only semaglutide 2.4 mg has been demonstrated to result in a mean reduction in weight of at least 10% when compared to a placebo. The FDA has authorized a weekly subcutaneous dose of semaglutide of 2.4 mg for the treatment of chronic obesity management in people without diabetes, which is greater than the existing weekly permitted dose of 1 mg for diabetes, based on the results.

Tirzepatide is a dual GIP and GLP-1 RA that was first approved in May 2022 for improvement of glycemic control in adults with T2D and later approved in November 2023 for chronic weight management in adults. It exerts its action by stimulating the receptors of the incretin hormones GIP and GLP-1, which reduces food intake and delays gastric emptying. Also, this is targeted at people with obesity or excess weight with related health conditions. FDA approval for using tirzepatide was based on two major phase 3 trials, namely SURMOUNT-1 in adults without T2D and SURMOUNT-2 in adults with T2D. Both studies showed significant reductions in body weight at 72 weeks of treatment compared with placebo. In the SURMOUNT-1 trial, participants who received the highest dose of tirzepatide (15 mg) had an average weight loss of 48 pounds, while those on the low dose (5 mg) lost an average of 34 pounds, compared with 7 pounds on placebo. In SURMOUNT-2, the 15 mg dose had a mean weight loss of 15.7% (34.4 pounds), and the 10 mg was an average of 13.4% (29.8 pounds), which were both statistically significant compared to the placebo group, reflecting a 3.3% reduction (7.0 pounds). Administer via once-weekly subcutaneous injection into the abdomen, thigh, or upper arm[61].

Cardioprotective effects of GLP-1 receptor agonists

GLP-1 RAs offer multifaceted cardioprotective effects. They decrease endothelial inflammation and oxidative stress, reduce systolic blood pressure (BP) by roughly 2–3 mmHg, and enhance the production of endothelial nitric oxide synthase, which will raise nitric oxide's availability[62,63]. Moreover, GLP-1 RAs induce natriuresis and diuresis by inhibiting the sodium-hydrogen exchanger 3 in renal proximal tubular cells, potentially contributing to their ability to lower BP[64]. Additionally, when GLP-1 RAs are administered, the concentration of certain proinflammatory cytokines, such as IL-1β, tumor necrosis factor (TNF)-α, interleukin (IL)-6, and C-reactive protein, is reduced[65,66]. They also suppress vascular cellular adhesion molecule-1, intercellular adhesion molecule-1, and P-selectin on the endothelial cell surfaces, subsequently reducing the way by which inflammatory cells, such as neutrophils and monocytes, adhere to and migrate through the arterial wall, lessening the way an atherosclerotic plaque is formed[67]. Moreover, an abundant number of preclinical studies have shown that GLP-1 RAs reduce aggregation of both human and murine platelets[68].

The financial burden of GLP-1 receptor agonists

Cost considerations greatly influence the selection and transition of medications. A cost-effectiveness study conducted in Saudi Arabia revealed semaglutide to be the most affordable GLP-1 RA when compared to liraglutide, dulaglutide, exenatide, and lixisenatide. It offered the most economical method for attaining target HbA1C levels and glycemic control[69]. According to a study conducted in Taiwan, from the payer's point of view, GLP-1 RA treatment was more expensive per patient than insulin. However, because there were fewer ER visits and hospital stays, the GLP-1 RA group's expenses in the healthcare sector were lower. Real-world use of GLP-1 RAs demonstrated cost-effectiveness despite the higher medication costs, with decreased

healthcare costs linked to lower death rates and fewer hospitalizations for hypoglycemia[70]. In a research study conducted in the United States, once-weekly dulaglutide was linked to greater expenditures when compared to once-weekly exenatide, but its diabetes-related total costs were comparable to daily liraglutide[71]. An additional study in the United States indicates that an objective treatment regimen for both individuals and combinations discovered that semaglutide dosages of 0.5 mg and 1.0 mg given once per week were more economical than alternatives with exenatide ER and dulaglutide, including maintaining a lower body weight, avoiding hypoglycemia, and improving glycemic control. Therefore, the study proposed that once-weekly semaglutide at these prescribed dosages is cost-effective in the United States, particularly for patients with T2D who want to meet their overall treatment objectives[72].

Several strategies may be instituted to make GLP-1 RAs more affordable for patients, thus making the financial burden lighter. The coverage of insurance on GLP-1s is rather variable and, in many cases, considerably covers medication for diabetes but perhaps not altogether for others, including weight loss. Physicians can further help by reviewing patients' insurance benefits and investigating options in ways that maximize the benefits, including making sure diagnostic criteria have been met that could widen access to these medications. Patient assistance programs through GLP-1 RA manufacturers can further help with the financial burden of those who may qualify, and manufacturer savings cards can help decrease monthly costs for patients who face high copays or deductibles. Educating the patient about how to locate these resources, medication coupons, and cost-saving programs might be of particular importance to help patients with the financial issues associated with their treatment. Health policy interventions may also afford considerable relief from these costs. Policies supportive of the inclusion of GLP-1 RAs in standard coverage plans would go a long way in improving access. Moreover, legislation that would encourage and motivate pharmaceutical companies toward more patient assistance programs and affordable pricing structures of GLP-1 RAs would help alleviate the financial burden on the patients. Since it is envisioned that, with time, generic forms of GLP-1s will be readily available, these strategies serve to bridge the gap until then, ensuring that patients have access to these effective therapies without undue financial strain[73].

Adherence and persistence in therapy with injectable GLP-1 receptor agonists

Although GLP-1 RAs have been proven effective in glycemic control, removing the risk of hypoglycemia and even causing weight loss[7,33], adherence and persistence have not been quite optimal[74–76]. In fact, adherence and persistence have improved with once-weekly injectable GLP-1RAs compared to daily or twice-a-day injections[75,77–79]. However, after 6 months, about 40% of patients were not fully adherent to once-weekly GLP-1RA dulaglutide, according to a research study that was conducted based on claims from the United States[75]. Poor adherence and persistence are frequent problems in not just GLP-1RA therapy but also the treatment of many chronic illnesses, including those treated with different antihyperglycemic, antihypertensive, antidepressant, and lipid-lowering medications[80]. Adherence and persistence to medication are essential, as patients

who take GLP-1RA consistently see higher HbA1c level reductions[75,81]. Diabetes, if effectively managed in the first year following diagnosis, will lead to reduced chances of developing long-term diabetes consequences such as retinopathy, cardiovascular events, and, in rare circumstances, death[15,82,83].

Below optimal adherence and persistence with GLP-1RAs can be caused by a variety of issues that impact both prescribers and patients. These variables include the number of injections administered, the administration device, the size of the needle, its effectiveness, any gastrointestinal side effects, safety, and cost-effectiveness[84,85]. While the diversity of the GLP-1RA class gives patients with T2D more individualized treatment options, it also poses a challenge for prescribers who need to become familiar with the various dosage schedules and delivery systems, and patients cannot receive enough time or resources to learn about correct administration and titration[4,86]. The introduction of an oral version of GLP-1RA may increase its utilization and encourage early treatment implementation since some patients may prefer oral drugs, which may be perceived as less stressful by patients and healthcare professionals[87].

Various studies have said that interactive voice response (IVR) and SMS text messaging support medication adherence through telephone-delivered diabetes education, and interactive reminders have enhanced medication adherence in patients with diabetes[88–90]. Mobile communication also includes one-way and two-way text messages, and weekly IVR calls to improve medication adherence for low-income, racially and ethnically diverse adults with type 2 diabetes[91,92]. In addition, telemonitoring, telehealth, and virtual classrooms have been shown to enable people with diabetes to adopt adherence strategies[93,94].

Adverse effects of GLP-1 receptor agonists

The most common gastrointestinal problems associated with GLP-1 RAs are diarrhea, early satiety, vomiting, abdominal discomfort, and bloating. When starting therapy with GLP-1 RA or following a dosage, they are usually most noticeable[47]. A meta-analysis of 35 trials involving exenatide and liraglutide revealed that the risk of nausea was considerably higher when exenatide 10 µg was administered twice daily as opposed to exenatide 5 µg was administered twice daily and exenatide once weekly. Likewise, in comparison with liraglutide at 1.2 and 1.8 mg/d, exenatide at 10 µg twice daily had a noticeably increased chance of producing nausea[95]. GLP-1RAs appropriately highlight the danger of acute pancreatitis, which has raised concerns from the FDA over the intake of these medications. Investigation in mice reveals that GLP-1 RA administration causes the pancreatic acinar cell mass to grow, stimulating the synthesis of lipase and amylase, which could lead to pancreatitis[96]. Upper respiratory and urinary tract infections are reported in GLP-1 RA studies. Infections with viruses, influenza, nasopharyngitis, and cystitis are also frequently associated with these medications[97]. Since GLP-1 has a glucose-dependent influence on insulin secretion, GLP-1RAs have a naturally low risk of hypoglycemia[98]. One frequent microvascular result that arises from vascular damage in the eye is diabetic retinopathy (DR). In the context of GLP1-RA use, DR is a safety risk that needs more explanation. It was more common in patients at high risk for cardiovascular disease who took semaglutide as opposed to a placebo. In comparison to placebo, dulaglutide caused an insignificant rise in DR. This

Table 2

Adverse effects and clinical considerations for GLP1-1 receptor agonists[101].

Adverse effect	Clinical consideration
Nausea and vomit	(a) Inform patients that there may be an effect but that it will subside in a few weeks.
	(b) Provide solutions, such as eating in moderation, lowering portion sizes, halting consumption before feeling full, and staying away from fatty foods.
	(c) If required, postpone the twice-daily exenatide or semaglutide dose-up titration
Gastroparesis	(a) Take careful if one has a history of severe GERD or gastroparesis.
	(b) Compared to twice-daily exenatide, weekly GLP1-RA may have less gastrointestinal adverse effects
Hypoglycemia	(a) Minimal danger, although it should be taken into account while using GLP1-RAs in conjunction with sulphonylureas or insulin.
	(b) Depending on baseline HbA1c and glucose levels, think about reducing the dosage of sulphonylurea or insulin (in clinical investigations, a 10–20% insulin dose decrease has been conducted on initiation of GLP1-RA therapy)
	(c) Patients who are at risk should be informed about managing hypoglycemia and initially advised to have more frequent blood glucose assessments
Diabetic retinopathy	(a) While administering GLP1-RA to individuals with a HbA1c substantially higher than target or a history of retinopathy, make sure they have had their retinal screenings completed.
	(b) Before beginning GLP1-RA treatment, schedule an ophthalmology consultation to determine if the patient has proliferative diabetic retinopathy
Pancreatitis	(a) If a patient has a history of pancreatitis, take into account alternate medications and start them only after discussing the potential dangers.
	(b) Stop using GLP1-RA if you have acute pancreatitis. Make sure that the root cause is thoroughly investigated without discounting the possibility of future GLP1-RA medication resumption.
	(c) Regular pancreatic enzyme monitoring is not necessary unless pancreatitis is identified
Pancreatic cancer	(a) Although there is no clinical proof of an elevated risk, it is advised to stay away from GPL1-RA if pancreatic cancer or precancerous pancreatic lesions already exist
Medullary thyroid carcinoma	(a) If there is a family or personal record of multiple endocrine neoplasia syndrome type 2 or medullary thyroid cancer, stay away from using GLP1-RA

could be partially explained by the phenomenon of pre-existing DR deteriorating due to quick glycemic recovery[99]. In patients with a personal or familial history of thyroid C-cell malignancies, as well as those with multiple endocrine neoplasia syndrome type 2 (MEN 2), these drugs have been proven to induce malignant thyroid C-cell tumors in rats in a dose-dependent and treatment-dependent manner[29].

Safety and tolerance of GLP-1 receptor agonists

With well-established safety and tolerability profiles, GLP-1RAs are an effective class of therapeutic agents for people with T2D. They can be considered in a variety of clinical situations, from patients whose metformin-induced glycemic target is not being met to those who have comorbidities or whose glycemic control is not being achieved despite treatment with multiple oral anti-hyperglycemic agents[98]. Recent studies and real-world data continue to confirm the safety profile of GLP-1 RAs, particularly in terms of gastrointestinal side effects such as nausea, vomiting, and diarrhea, which remain the most commonly reported adverse events. These side effects, while more frequent compared to control groups, are generally transient and manageable with dose titration[100]. Furthermore, GLP-1RAs have been successfully linked to significant reductions in weight and have a positive safety profile[79]. Table 2 *gives an overview of adverse effects and clinical considerations for GLP1-1 receptor agonists.*

Future research directions

Reversing fatty liver disease

Based on the evidence available, GLP-1 RAs have a potential role in the course deceleration and even the reversal of NAFLD[102]. For example, patients treated with 1.2 mg of liraglutide daily for 6 months in the Lira-NAFLD trial had been observed to have a reduction in liver fat content by 31% ($P < 0.0001$). A multivariate analysis demonstrated that this reduction correlated with baseline liver fat content, age, body weight, triglycerides, and

hemoglobin A1c reductions. Liver fat content decreased significantly only in patients who lost weight, and no significance was observed in those without weight loss[103,104]. Similarly, Newsome *et al.*, in phase 2 clinical trial, reported that at the end of up to 72 weeks of treatment with semaglutide at a dose of 0.4 mg, 59% of patients had significant resolution of NASH compared with 17% of the placebo-treated patients ($P < 0.001$). However, there was no difference in the semaglutide group with respect to fibrosis progression when compared with the placebo group. The currently accepted management includes lifestyle modifications, supplementation with vitamin E, and the use of pioglitazone in carefully selected patients[105]. If further clinical trial results are encouraging, GLP-1 RAs' place in therapeutic regimens may well be cemented in the near future for both NAFLD and NASH.

Use in polycystic ovary syndrome

The antagonistic effects of GLP-1 RAs, such as liraglutide and exenatide, have been illustrated by several studies reporting significant reductions in testosterone levels and body mass index in PCOS patients versus placebo or metformin-treated patients[106,107]. However, menstrual frequency, circulating sex hormone-binding globulin, fasting glucose, and fasting insulin levels did not appear to be affected by these medications. Further studies will be necessary to fully assess the potential benefits of GLP-1 RAs for patients with PCOS.

Use in type 1 diabetes safety and tolerance of GLP-1 receptor agonists

GLP-1 RAs, together with insulin, lower hemoglobin A1c, body weight, and total insulin dose in type 1 diabetes patients. This is evidenced by clinical studies such as the ADJUNCT ONE (Efficacy and Safety of Liraglutide as Adjunct Therapy to Insulin in the Treatment of Type 1 Diabetes)[108], the ADJUNCT TWO trial[109], and a large meta-analysis[110]. These trials also demonstrated an increased incidence of hyperglycemia with ketosis, likely related in part to reductions in insulin dosages when GLP-1 RA therapy was

initiated. No significant changes in C-peptide levels were reported in the above trials[108–110]. Although GLP-1 RAs are neither FDA-approved nor officially recommended in the management of type 1 diabetes[111,112], off-label use added to insulin might contribute to weight reduction and better glycemic control in a subset.

Conclusion

Given the increasing prevalence of DM, effective therapeutic strategies are crucial. GLP-1 RAs improve glycemic control, promote weight loss, and offer cardiovascular benefits. These medications enhance endothelial function, reduce inflammation, oxidative stress, and lower blood pressure, addressing the multifaceted nature of T2D. Adherence to GLP-1 RA therapy is challenging due to gastrointestinal side effects, such as nausea and vomiting, and the high cost of these medications. The safety profile, while favorable, requires monitoring for pancreatitis, diabetic retinopathy, and thyroid C-cell tumors. The cost-effectiveness of GLP-1 RA therapy is demonstrated by reduced hospitalization rates and healthcare expenditures. High upfront costs necessitate strategies to improve patient adherence and persistence, including enhanced patient education and support systems. In conclusion, while GLP-1 RAs offer substantial benefits in managing T2D, addressing barriers to their effective use is essential. A multidisciplinary approach involving healthcare providers, patients, and policymakers is necessary to overcome challenges related to side effects, treatment costs, and patient adherence. By working collaboratively, we can maximize the therapeutic potential of GLP-1 RAs and improve outcomes for individuals with T2D.

Ethical approval

As this is a review article without the involvement of patients, no ethical approval was necessary.

Consent

As this is a review article without patient involvement, ethical considerations regarding patient consent and privacy do not apply.

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Author contribution

N.J.: conceptualization, writing – original draft, and writing – review and editing; K.M.B., S.R., A.M.K., F.M., H.K., M.Z., G.A., S.K., I.F.A., and S.M.N.: writing – original draft; V.K.: conceptualization, supervision, writing – original draft, and writing – review and editing; I.B.A.: visualization and writing – original draft; F.G.: writing – review and editing.

Conflicts of interest disclosure

The authors declare no conflicts of interest.

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Data availability statement

The datasets generated and/or analyzed during the current study are not applicable. No data were generated or analyzed in this research project.

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