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REVIEW

From diabetes to diverse domains: the multifaceted roles of GLP-1 receptor agonists

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Abstract
Glucagon-like Peptide-1 (GLP-1) receptor agonists (GLP-1RAs) emerged as a primary treatment for type-2 diabetes mellitus (T2DM), however, their multifaceted effects on various target organs beyond glycemic control opened a new era of treatment. We conducted a comprehensive literature search using databases including Scopus, Google Scholar, PubMed, and the Cochrane Library to identify clinical, in-vivo, and in-vitro studies focusing on the diverse effects of GLP-1 receptor agonists. Eligible studies were selected based on their relevance to the varied roles of GLP-1RAs in T2DM management and their impact on other physiological functions. Numerous studies have reported the efficacy of GLP-1RAs in improving outcomes in T2DM, with demonstrated benefits including glucose-dependent insulinotropic actions, modulation of insulin signaling pathways, and reductions in glycemic excursions. Additionally, GLP-1 receptors are expressed in various tissues and organs, suggesting their widespread physiological functions beyond glycemic control potentially include neuroprotective, anti-inflammatory, cardioprotective, and metabolic benefits. However, further scientific studies are still underway to maximize the benefits of GLP-1RAs and to discover additional roles in improving health benefits. This article sought to review not only the actions of GLP1RAs in the treatment of T2DM but also explore its effects on potential targets in other disorders.

Keywords GLP-1 receptor agonists · Diabetes · Stroke · Neuroprotective · Cardioprotective · Hepatoprotective · Renoprotective

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Abbreviations

(Camp-GEF2)	(CAMP)-regulated guanine nucleotide exchange factor 2
(MPTP)	1-Methyl-4-phenyl-1,2,3,6-tetrahydropyidine
(ATP)	Adenosine triphosphate
(AGE)	Advances glycation end-product
(ALT)	Alanine aminotransferase
(ALD)	Alcoholic liver disease
(AGI)	Alpha-glucosidase inhibitors
(a-SMA)	Alpha-smooth muscle actin
(AD)	Alzheimer's disease
(ADA)	American diabetes association
(AMPK)	AMP-activated protein kinase
(APP/PS1)	Amyloid polypeptide/Presenilin 1
(ApoE)	Apolipoprotein E
(AST)	Aspartate aminotransferase levels
(ANP)	Atrial natriuretic peptide
(BP)	Blood pressure
(BMI)	Body mass index
(BAT)	Brown adipose tissue

(CICR)	Calcium-induced calcium release
(C-terminus)	Carboxyl terminal
(CV)	Cardiovascular
(CVDs)	Cardiovascular diseases
(CVOT)	Cardiovascular outcome trials
(CNS)	Central nervous system
(CKD)	Chronic kidney disease
(JNK)	C-Jun-N-terminal kinase
(CD14)	Cluster of differentiation 14
(CRP)	C-reactive protein
(cAMP)	Cyclic adenosine monophosphate
(DCCT)	Diabetes control and complications trial
(DM)	Diabetes mellitus
(DN)	Diabetic nephropathy
(DBP)	Diastolic blood pressure
(DPP-4)	Dipeptidyl peptidase-4
(eGFR)	Electronic glomerular filtration rate
(ER)	Endoplasmic reticulum
(EC)	Endothelial cells
(ESRD)	End-stage renal disease
(EGFR)	Epidermal growth factor receptor
(EU)	European union
(ELIXA)	Evaluation of lixisenatide in acute coronary syndrome
(EXSCEL)	Exenatide study of cardiovascular event lowering
(EX-4)	Exendin-4
(ER)	Extended-release
(Erk)	Extracellular signal-related kinase
(FN)	Fibronectin
(FDA)	Food and drugs administration
(FFA)	Free fatty acid
(GIP)	Gastro-inhibitory intestinal peptide
(GI)	Gastrointestinal
(GLP-1RA's)	GLP-1 receptor agonists
(GLP-1)	Glucagon-like peptide-1
(HbA1c)	Glycosylated haemoglobin
(GPCR)	G-protein-coupled receptor
(HR)	Hazard ratio
(IGT)	Impaired glucose tolerance
(IP3)	Inositol 1,4,5-triphosphate
(IR)	Insulin receptors
(ICAM-1)	Intercellular cell adhesion molecule
(IL-1)	Interleukin 1
(ICAM-1)	Intracellular cell adhesion molecule
(ICH)	Intracerebral haemorrhage
(LV)	Left ventricular
(LPS)	Lipopolysaccharide
(LEAD)	Liraglutide effect and action on diabetes
(LDL)	Low-density lipoprotein
(MACE)	Major adverse cardiovascular events
(MAP)	Mean arterial blood pressure
(MCAO)	Middle cerebral artery occlusion
(MCP-1)	Monocyte chemoattractant protein-1
(MS)	Multiple Sclerosis
(NEP 24.11)	Neutral endopeptidase 24.11
(NPH)	Neutral protamine hagedorn
(NO)	Nitric oxide
(NAFLD)	Non-alcoholic fatty liver disease
(NASH)	Non-alcoholic steatohepatitis
(NF-κB)	Nuclear factor-kappa beta
(NTS)	Nucleus tractus solitarii
(OD)	Once in a day
(ox-LDL)	Oxidized low-density lipoprotein
(PD)	Parkinson's disease
(PPBG)	Postprandial blood glucose
(Lbs)	Pounds
(PC)	Propeptide convertase
(PKA)	Protein kinase A
(PKC)	Protein kinase C
(RCTs)	Randomized control trials
(ROS)	Reactive oxygen species
(RhGLP-1 RA's)	Recombinant human GLP-1RAs
(RYR)	Ryanodine receptors
(SUSTAIN-6)	Semaglutide in subjects with type 2 diabetes
(Sr.Cr)	Serum creatinine
(SGLT2)	Sodium-glucose cotransporter 2
(STZ)	Streptozotocin
(SBP)	Systolic blood pressure
(HOMA-beta)	The homeostasis model for β-cell function
TGF-1	Transforming growth factor-1
(TGF-β1)	Transforming growth factor-beta 1
(TBI)	Traumatic brain injury
(TNF-α)	Tumor necrosis factor-alpha
(T2DM)	Type-2 diabetes mellitus
(UACR)	Urine albumin to creatinine ratio
(VCAM-1)	Vascular cell adhesion molecule
(VSMCs)	Vascular smooth muscle cells
(VDCC)	Voltage-dependent calcium channel
(WAT)	White adipose tissue

Introduction

Type-2 diabetes mellitus (T2DM) is primarily recognized by the inability of the human body to control the quantity of glucose (sugar) present in the blood with the help of insulin hormone [1]. Shockingly, the incidences of diabetes are expected to rise from 415 million (2015) to 640 million (2040) worldwide [2]. The incretin hormonal axis is created by the combination of gastrointestinal and endocrine pathways, and any abnormalities in this axis can potentially initiate the onset of T2DM [3]. A majority of the incretin function is constituted by GLP-1 and gastro-inhibitory intestinal peptide (GIP) [3]. GLP-1 exerts its mechanism of action through GLP-1 receptor (GLP-1R), a G-protein coupled receptor (GPCR), generally found extensively in organs including the brain, lung, pancreatic islets, lung, heart, vascular smooth cells, pancreas, macrophages, endothelial cells, central nervous system, kidney, peripheral chemoreceptors such as carotid body, and GI tract [4–6].

Glucagon-like peptide-1 (GLP-1) is a peptide hormone, typically composed of 30 amino acids, released from lower intestinal enteroendocrine L-cells and specific neurons located within the solitary tract in the brainstem, primarily in response to food intake [7]. The active structure of the GLP-1 protein includes two α-helices spanning amino acid positions 13–20 and 24–35, separated by a linker region [3, 8, 9]. Naturally occurring GLP-1 is rapidly cleaved at position 2 (alanine) by dipeptidyl peptidase-4 (DPP-4) along with neutral endopeptidase 24.11 (NEP 24.11) and renal clearance. Hence, this degradation of GLP-1 leads to a short half-life of about 2 min, resulting in only a small fraction (10–15%) of intact GLP-1 reaching circulation, resulting in fasting plasma levels typically within the range of 0–15 pmol/l [7, 9]. To preserve the concentrations of GLP-1, DPP-4 inhibitors are periodically used in patients with Type-2 diabetes mellitus (T2DM) [10]. To address this limitation and maximize the utilization, GLP-1 receptor agonists (GLP-1RAs) and DPP-4 inhibitors were developed to enhance GLP-1 efficacy.

In contrast to conventional treatments like insulin and sulfonylureas, GLP-1-based therapies have been linked to weight loss and a reduced risk of hypoglycemia, making them particularly advantageous for diabetic patients [11]. Currently, the efficacy of GLP-1RAs is most commonly associated with their pivotal role in managing T2DM [12]. The ability of GLP-1RAs to enhance insulin secretion, suppress glucagon release, slow gastric emptying, and promote satiety fundamentally transformed the landscape of diabetes care [13] and is currently, considered a potential ally in the ongoing battle against the global epidemic of diabetes [14]. From the clinical point of view, the narrative of GLP-1RAs has taken an unexpected twist; GLP-1RAs are now captivating the attention of clinicians, researchers, and patients by revealing an astonishing array of their multifaceted roles extending far beyond diabetes [11]. This review embarks on an exciting and transformative journey of GLP-1RAs and their gradual increase in diverse applications in a spectrum of treatments. We delve into the expanding body of knowledge that uncovers the potential of these agents in metabolic health, cardiovascular wellness, hepatic and renal functions, and even the enigmatic scope of neuroprotection. Hence, we aim to explore the latest research findings, clinical insights, and emerging trends that underscore the multifaceted roles of GLP-1RAs in reshaping the future of medicine, offering new hope and possibilities to individuals facing a spectrum of health challenges. GLP-1RA can exhibit various roles beyond just treating T2DM and some of these functions are elucidated in Fig. 1 and discussed in this review.

Current clinical guidelines for diabetes management

The current treatment guidelines are based on a large number of evidence-based information and expert opinions on achieving end glucose level goals [Normal range: fasting plasma glucose < 5.5 mmol/l; Glycosylated hemoglobin (HbA1c: < 5.6%); Prediabetic range: fasting plasma

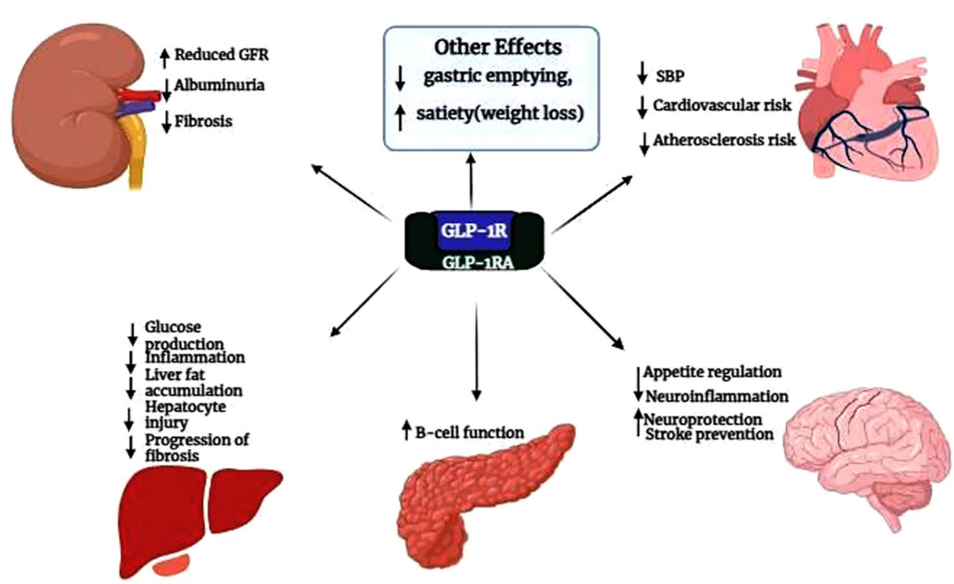

Fig. 1 A diagrammatic representation of the diverse functions of GLP-1RAs across multiple organs. GLP-1RAs characterize the improvement of several conditions, such as fibrosis, neuroinflammation, non-alcoholic steatohepatitis, and weight loss via independent mechanisms in different organs

glucose—5.5 to 7 mmol/l (HbA1c: 5.7 to 6.4%); Diabetic range: fasting plasma glucose > 7 mmol/l (HbA1c: > 6.5%)]. To minimize complications, the treatment goal is to achieve glycated hemoglobin (HbA1c) of 6.5% or less, recognizing the need to reduce the chances of hypoglycemia. Current types of anti-diabetic therapies include monotherapy, dual therapy, and triple therapy, which incorporates eight major classes of medications (biguanides, DPP-4 inhibitors, thiazolidinediones, sulfonylureas, incretin mimetics, bile acid sequestrants, α-glucosidase inhibitors, meglitinides), and insulin-based therapy [15]. Management of hyperglycemia in T2DM recommends a patient-centered approach for selecting appropriate pharmacologic treatment recommended by clinicians. Traditionally, metformin is a safe, effective, and inexpensive start at diagnosis and is considered the first-line treatment. However, if hyperglycemia is severe or any catabolic features (weight loss, hypertriglyceridemia, ketosis) are present, insulin can be used as part of any combination regimen. When blood glucose levels are above 300 mg/dL or HbA1C > 10% or any of the above two characteristics are present, then insulin therapy should be generally initiated [16]. Similarly, sulfonylurea, considered second-line agents, reduces HbA1c by 1–2%. Non-sulfonyl urea secretagogues (repaglinide and nateglinide) can be used in patients with renal insufficiency. The other class, α-glucosidase inhibitors, reduces postprandial blood glucose (PPBG); however, its long-term compliance and higher cost are significant issues. Thiazolidinediones (rosiglitazone and pioglitazone) reduce insulin resistance and HbA1c by 0.5–1.4% when used as monotherapy. DPP-4 inhibitors are the newer class of medicines in which sitagliptin is the only Food and Drugs Administration (FDA)-approved drug showing a reduction in HbA1c by 0.5–0.8%. Patients treated with sodium-glucose cotransporter-2 (SGLT2) inhibitors (empagliflozin, canagliflozin, dapagliflozin) or GLP-1RAs (liraglutide, semaglutide, dulaglutide) have shown a reduction in cardiovascular events along with improvements in glucose levels [17, 18]. As T2DM is a progressive disease, monotherapy with metformin is not sufficient in many patients, and other drugs are optimized stepwise to achieve the ideal HbA1c target [19].

How GLP-1RAs reduce high blood sugar?

GLP-1RAs are available as injectables and in oral form to achieve glycemic targets in diabetic patients [20]. GLP-1RAs are designed to mimic the actions of the naturally occurring GLP-1 hormone, which plays a crucial role in blood glucose homeostasis and satiety [3]. Upon GLP-1RA administration, they stimulate the GLP-1 receptor on pancreatic beta cells, prompting the secretion of insulin in a glucose-dependent manner without risking hypoglycemia [21–25]. Furthermore, GLP-1RAs slow down gastric emptying and suppress glucagon secretion, which eventually controls post-meal glucose spikes [26–29]. Beyond their immediate impact on glycemic control, these analogs have demonstrated benefits for weight management due to their appetite-suppressing effects and promotion of satiety via modifying eating behavior, which leads to reducing energy intake by approximately 12% interacting with the peripheral nervous system [13]. With these dual actions on both glucose regulation and weight management, GLP-1RAs can be a versatile and attractive option for individuals with T2DM, particularly those who struggle with obesity [30]. These benefits of GLP-1 analogs set the stage for a deeper exploration of their clinical applications and the evolving landscape of diabetes care [3].

GLP-1 directly suppresses glucagon secretion in the pancreas and indirectly enhances meal-induced insulin secretion in synergy with the glycemic stimulus, which modulates glucose levels [7]. The presence of histidine at position 7 in the GLP-1 amino acid structure is essential for the hormone's ability to stimulate insulin production and inhibit the secretion of glucagon [3, 11]. As shown in Fig. 2, the insulinotropic effect mainly comes from increased intracellular cAMP levels and then followed by serine/threonine kinase protein kinase A (PKA), cyclic adenosine monophosphate (cAMP)-regulated guanine nucleotide exchange factor 2 (cAMP-GEF2) also called EPAC2 and activated protein kinase A. PKA leads to the closure of Adenosine triphosphate (ATP)-sensitive K^+ channels, causing membrane depolarization, and activation of L-type voltage-dependent calcium channel (VDCC) leads to an increase in intracellular Ca^{2+} causing insulin release [23]. EPAC2 activates Rap1 leading to calcium-induced calcium release, all of which increases Ca^{2+} thereby inducing mitochondrial ATP synthesis and exocytotic insulin release from insulin granules [31, 32]. The insulinotropic effect of GLP-1, mediated by increased intracellular cAMP levels and subsequent activation of PKA and EPAC2 pathways, is depicted in Fig. 2. multiple intracellular pathways, including protein kinase B and extracellular signal-related kinase (Erk), and epidermal growth factor receptor (EGFR) transactivation through the c-src kinase are responsible for the proliferative effects of GLP-1 [33, 34].

GLP-1RAs—An emerging superclass of drugs for diabetes management

Exenatide was the first GLP-1RA approved for clinical use in 2005 by the USFDA and in 2006 by the European Union (EU) for the treatment of T2DM. It is a synthetic form of exendin-4, a naturally occurring peptide in Gila monster [35]. A triple-blind, placebo-controlled study, AMIGO, showed that exenatide maintained the long-term HbA1c

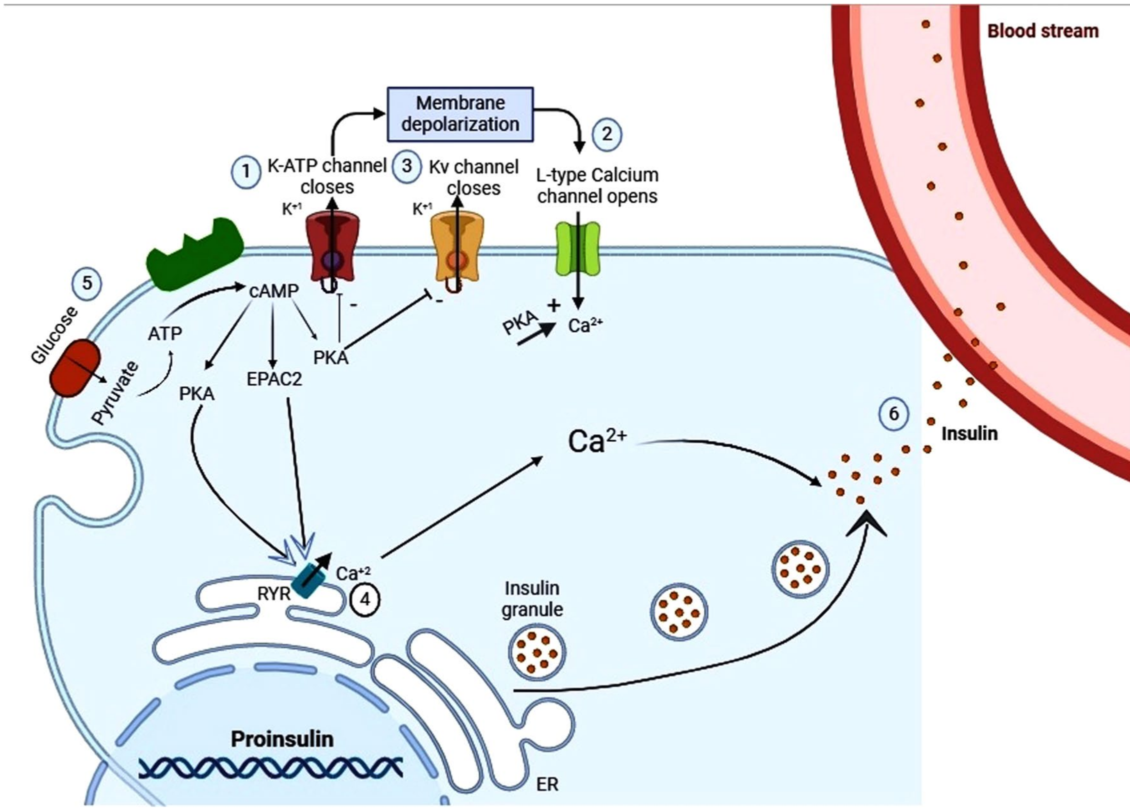

Fig. 2 A figure depicting the intracellular mechanism of GLP-1RAs on insulin secretion Insulin release takes place after several processes: (1) Closure of K_{ATP} channels; (2) Opening of L-type VDC channels; (3) Inhibition of voltage-gated K+channels; (4) PKA- and EAPC2-dependent mechanisms increases the intracellular Ca^{2+} concentrations; (5) Ca^{2+}-induced Ca^{2+} mobilization stimulates ATP synthesis intracellularly which further enhances K_{ATP} channel closure; (6) accumulation of insulin-containing granules near the plasma membrane, ultimate insulin secretion into the circulation. *ATP* adenosine triphosphate, *cAMP* cyclic adenosine monophosphate, *EPAC2* exchange protein activated by cAMP, *ER* endoplasmic reticulum, *Kv* voltage-gated K+channels, *PKA* protein kinase A, *RYR* ryanodine receptors

below ≤ 7 and optimum body weight reduction [36]. Lixisenatide showed a greater reduction in body weight and 2-h post-prandial glucose when compared with sitagliptin. However, more frequent gastrointestinal (GI) side effects, such as nausea, were seen with lixisenatide than with sitagliptin [37]. Liraglutide, another GLP-1RA, is an acylated analog of GLP-1, with a plasma half-life of 10–18 h, [55] showed HbA1c reduction of up to 1.6% and weight loss of up to 2.5 kg over 30 weeks [38]. Liraglutide has been approved for reducing T2DM and has shown promising evidence in the reduction of risk of major cardiovascular (CV) events, obesity, liver disease, and other metabolic dysfunctions [39, 40]. American Diabetes Association (ADA) recommended liraglutide as a second-line drug after metformin for patients suffering from atherosclerotic cardiovascular disease [41]. Semaglutide is structurally similar to liraglutide but has less susceptibility to DPP-4 degradation. These structural modifications improved its binding with albumin and extended its half-life up to 7 days, allowing for once-weekly administration given subcutaneously [42]. SUSTAIN-1, a 30-week clinical study comparing semaglutide with placebo, showed a significant reduction in HbA1c and 0.2% weight reduction than the placebo group [43]. Albiglutide, a long-acting GLP-1 mimetic, is currently in phase 3 trials and is expected to provide a more patient-friendly dosing profile compared to available GLP-1 analogs [44]. Albiglutide has the characteristic to fuse with human albumin with DPP-4 resistant properties which increases its half-life up to 5–8 days and makes it suitable for once-weekly dosing as well [45]. Dulaglutide, a long-acting and large-size GLP-1RA, has a slower renal clearance which results from its prolonged half-life for 5–6 days allowing its once-a-week administration [46, 47]. The AWARD trial, using dulaglutide, showed an HbA1c reduction of 0.7% to 1.6% from its baseline. In the AWARD-1 study, dulaglutide was compared with twice-daily exenatide over 52 weeks which showed superior HbA1c reductions at 26 weeks with no significant difference in weight loss [48]. Overall, these promising evidence and characteristics suggest that

GLP-1RAs have the efficiency to play a major role in diabetic management. Next, we explore the emerging role of GLP-1RAs and their potential benefits in other disorders.

GLP-1RAs in obesity management

In the ever-evolving landscape of obesity management, GLP-1 analogs have emerged as a revolutionary therapeutic option. While initially developed to address the complexities of diabetes care, these drugs have shown remarkable potential in the battle against obesity [49]. Unlike traditional weight loss medications that often come with a range of side effects and limited efficacy, GLP-1RAs offer a multifaceted approach to weight management [50]. GLP-1RAs have been documented to induce weight loss in a dose-dependent and progressive manner. An average weight reduction of 5.8 pounds (lbs.) is seen with long-acting exenatide [3]. The Liraglutide Effect and Action in Diabetes (LEAD) program observed weight reductions in more than 4000 participants, suggesting its potency in obesity management [51, 52]. Along with weight loss, GLP-1RAs have been demonstrated to reduce body mass index (BMI) and waist circumference in overweight or obese people with or without diabetes [53, 54]. Other GLP-1RA potentially works similarly in weight reduction; however, more systematic clinical studies need to be conducted to determine their extended role in weight reduction [55]. A novel dual GIP and GLP-1 receptor agonist Tirzepatide (15 mg) demonstrated dose-dependent reductions in body weight, with a significant difference of − 10.7 kg (SE 0.4; -13.9% reduction) outperforming dulaglutide in glycemic control and body weight reduction in Japanese patients with T2DM [56]. Conclusively, the majority of patients were able to get higher benefits with less adverse responses caused by GLP-1RAs, making them the preferred medication for the treatment of obesity.

Appetite regulation and weight loss effects in obesity management

The central nervous system, which regulates satiety, receives information from the digestive tract via afferent impulses to control eating behavior [57]. GLP-1 has been shown to reduce gut motility and stomach emptying, through which its association has been proposed in appetite regulation. Intravenous infusion of GLP-1 in male Sprague–Dawley rats effectively inhibits food intake in a dose-dependent manner. Neuroimaging studies demonstrated that peripherally injected GLP-1 alters brain activity in regions implicated in the control of food. Several studies in animals have revealed that administration of GLP-1RAs (Dulaglutide, Exenatide, Liraglutide, Exendin-4) resulted in the suppression of food intake mediated by direct GLP-1R activation in the brain and vagal afferents through several signaling pathways [58]. For instance, they stimulate adipocyte development by activating the Wnt signaling pathway and rely on SIRT1 to mediate lipolysis and fatty acid oxidation in adipose tissues [14]. GLP-1RAs encourage the transformation of visceral white adipose tissue (WAT) into brown adipose tissue (BAT), enhancing the thermogenesis of BAT and hence increasing energy expenditure under the control of AMP-activated protein kinase (AMPK) in the ventral medial hypothalamus [14]. These mechanisms are to be investigated further to accurately determine the precise role of GLP-1RAs and food intake in weight reduction.

Clinical trials and real-world evidence

Three notable clinical trials shed light on the interplay between pharmaceutical interventions and patient well-being. The first study (Phase-4; NCT03361098), a randomized and placebo-controlled trial on 65 participants, was conducted to investigate the effect of a dual approach involving exenatide and dapagliflozin (SGLT2 inhibitor) on appetite regulation. This study found that responsiveness to palatable food consumption underscores the synergistic effects of combining these agents, offering great insight into novel approaches for managing T2DM [59]. The combination therapy of GLP-1RAs with SGLT-2 inhibitors has progressively shown improvement in patients suffering from T2DM. Another trial (NCT00375492), a randomized, placebo-controlled trial involving 196 participants, focused on weight loss in diabetic patients. By administering exenatide alongside lifestyle modifications, this study examined the improvement in weight management in individuals with T2DM, measuring the impact on calorie intake and participant weight [60]. Lastly, the third trial (NCT05136287) presents a multicentric, randomized clinical trial assessing the weight loss outcomes with 140 participants investigating the efficacy of various GLP-1RAs (dulaglutide, exenatide, liraglutide, and lixisenatide) found significant reduction in body weight with minimizing adverse events [61]. Additionally, the combination therapy of liraglutide with sulfonylurea analog (glimepiride) was found to be effective in weight reduction compared to that of a placebo when given over 26 weeks [62]. If GLP-1RAs monotherapy or combination therapy with other anti-diabetic agents fails to provide satisfactory glycemic control and weight modulation, the addition of basal insulin to GLP-1RAs had been recommended and evaluated in late randomized control trials (RCTs). It was observed that the insulin titration used in conjunction

Table 1 Clinical trial findings evaluating the role of GLP-1RAs in the modulation of weight and appetite

NCT number	Study design	No. of participants	Eligibility criteria	Arms of the study	Study findings	References
NCT03361098	A Phase IV, randomized, placebo-controlled trial evaluating the impact of combined dapagliflozin (SGLT2 inhibitor) and exenatide therapy on appetite regulation in T2DM patients	65	Patients aged 18–75 years, with a BMI of 27–40 kg/m^2, diagnosed with T2DM for over 3 months, and on a stable dose of metformin and/or sulphonylurea for at least 3 months	Intervention 1: Dapagliflozin (10 mg) and exenatide (0.005 mg) b.i.d. week 5–16 Intervention 2: Dapagliflozin (10 mg) and placebo Intervention 3: Exenatide b.i.d. week 5–16 (0.005 mg) and placebo	Exenatide influences the central regulation of feeding by affecting the brain's responsiveness to palatable food consumption. Additionally, it produced synergistic effects on appetite regulation when combined with dapagliflozin	[65]
NCT00375492	A randomized, placebo-controlled clinical trial to compare the effects of twice-daily exenatide versus placebo on weight loss in diabetic patients	194	Patients suffering from T2DM for at least 6 months are willing to take part in the study	Intervention 1: 0.005 mg or 0.010 mg injected subcutaneously Intervention 2: Placebo injected subcutaneously	Exenatide in combination with lifestyle modifications resulted in a reduced caloric intake and also led to reductions in the weight of participants	[66]
NCT05136287	A multicentric, randomized clinical trial to evaluate weight loss in T2DM patients administered GLP-1RA (semaglutide) compared to dulaglutide, exenatide, liraglutide, and lixisenatide	94	Patients should have an age greater than 18 years, possess a body weight of BMI > 30 kg/m2, be willing to be enrolled in the study, treated with another oral anti-diabetic	Intervention Patients treated on GLP-1RAs (dulaglutide; exenatide, liraglutide, lixisenatide)	All GLP-1RAs led to a significant reduction in body weight with little to no adverse events	[67]
NCT04657016	A randomized clinical trial to evaluate the safety and efficacy of Tirzepatide once weekly in comparison with placebo after a lifestyle intervention program (SURMOUNT-3)	806	Patients that are overweight (BMI ≥ 30 kg/m2 or ≥ 27 kg/m2)	Intervention: Tirzepatide once weekly administered SC Control: Placebo administered SC	Tirzepatide was shown to modulate both glucose levels and weight in patients	[68]
NCT04660643	A clinical study to evaluate the safety and efficacy and safety of Tirzepatide in patients without T2DM who are overweight	783	Patients that are overweight (BMI ≥ 30 kg/m2 or ≥ 27 kg/m2), previous diagnosis of CV comorbidities, hypertension, etc	Intervention: Tirzepatide once weekly administered SC. Control: Placebo administered SC	Participants showed greater weight loss and improved glycemic control	[69]

with the GLP-1RAs had a beneficial impact on glycemic and appetite control and weight reduction [63, 64].

Table 1 shows the result of several clinical investigations performed to evaluate the role of GLP-1RAs to modulate weight and appetite. Such insights provide reasonable evidence to healthcare practitioners with valuable options to tailor treatments for individuals living with T2DM, ultimately improving their quality of life.

Evolution of GLP-1 analogs beyond diabetes and obesity

GLP-1 analogs, such as exenatide and liraglutide, were primarily designed to aid in glycemic control with the vision of a growing global diabetes epidemic. Patients taking these medications started experiencing unexpected weight loss, prompting further investigation [11, 70]. Additionally, studies began to highlight their cardiovascular benefits, particularly in reducing the risk of major adverse cardiovascular events (MACE). These serendipitous discoveries led to investigations into the therapeutic potential of GLP-1RAs in conditions beyond diabetes [71]. Subsequent regulatory approvals and label expansions reflected the shift in the medical paradigm, recognizing these agents as versatile tools in the arsenal of modern medicine. This historical context justifies the need for the review and highlights the urgency of synthesizing the latest research and clinical insights into the evolving landscape of GLP-1RA applications beyond diabetes.

Cardiovascular benefits of GLP-1RAs

The cardiovascular benefits associated with GLP-1RAs have emerged as a groundbreaking revelation in recent years. Beyond their primary function of glycemic control, GLP-1RAs have demonstrated a remarkable capacity to mitigate cardiovascular risk factors and reduce the incidence of MACE in individuals with T2DM [64]. In this discussion, we will delve into the multifaceted cardiovascular advantages offered by GLP-1RAs, exploring the mechanisms behind these benefits, the clinical evidence supporting their use, and the broader implications for the management of T2DM and cardiovascular disease.

Reduction *of major* adverse cardiovascular events (MACE)

Patients suffering from T2DM are at an increased susceptibility to developing cardiovascular complications that can also prove to be fatal. Hence, the prevention of these complications should be considered while choosing a course of treatment [72]. Most GLP-1RAs have shown benefits in lowering cardiovascular disease (CVD) complications such as dyslipidemia and high blood pressure (BP) [73]. GLP-1RAs were found to cause a decrease in the systolic blood pressure (SBP) by 2 to 6 mmHg and eventually a considerable reduction in MACE [74, 75]. Liraglutide and Semaglutide were observed to benefit CV outcomes in clinical studies; however, the precise mechanisms behind this benefit are yet to be discovered [76–79]. Clinical trials such as LEADER, SUSTAIN-6, and EXSCEL demonstrated that GLP-1RAs reduced cardiovascular events in CV patients with acute coronary syndrome and T2DM [80]. In the LEADER trial, liraglutide exhibited a 13% reduction in MACE with a hazard ratio (HR) of 0.87 (95% CI: 0.78; 0.97) compared to placebo, involving 8,121 patients with T2DM. Similarly, in the SUSTAIN-6 trial, semaglutide demonstrated a 26% reduction in MACE with an HR of 0.74 (95% CI: 0.58; 0.95) among 3,297 patients with T2DM, showcasing significant cardiovascular risk reduction [78, 81] Other trial using Lixisenatide, Liraglutide, and Semaglutide lowers the MACE symptoms and promotes positive CV outcomes in patients with T2DM [82].

Impact on atherosclerosis and vascular health

The majority of the population of patients suffering from diabetes may develop myocardial ischemia and heart failure in the future [74]. The SOUL trial revealed improvements using GLP-1Ras in heart failure outcomes, including reduced hospitalization rates and enhanced cardiac function [83]. In clinical practice, the implications of these findings are profound and encouraging. GLP-1RAs are now considered a critical component in individuals who have T2DM with established cardiovascular disease or those at high risk of cardiovascular events [11, 84]. Findings from animal studies revealed that GLP-1RAs had been shown to reduce atherosclerotic plaque development by exerting their anti-inflammatory effects in the endothelial cells and vascular smooth muscle cells and causing a more stabilized and less vulnerable plaque [85]. Based on the data received from clinical trials to evaluate the impact of GLP-1RAs in CV events, a consistent decrease in atherothrombotic events was observed which suggests the beneficial outcomes using GLP-1RAs in patients suffering from T2DM and atherosclerosis [75, 85].

Potential mechanisms of GLP-1RAs to reduce cardiovascular risks

GLP-1RAs have emerged as a pivotal component in managing T2DM due to their multifaceted implications for cardiovascular risk reduction via key mechanisms contributing to the regulation of BP (Fig. 3) [11]. GLP-1RAs

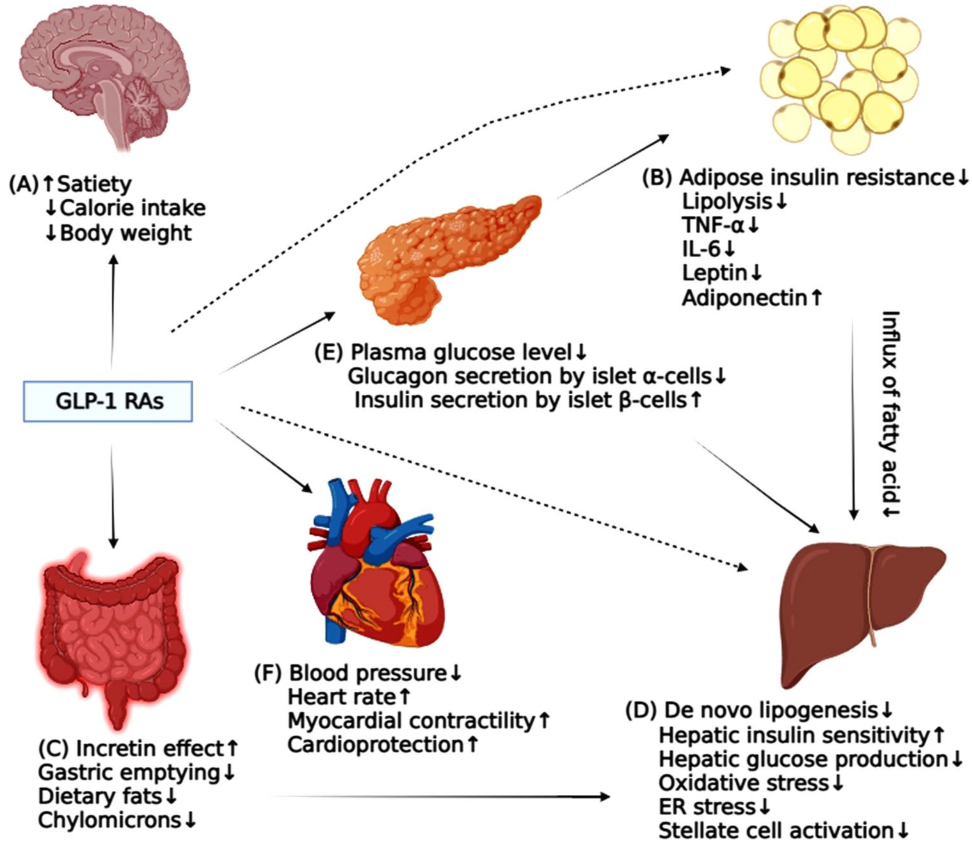

Fig. 3 Schematic illustration of the effects of GLP-1RAs on satiety, cardiovascular outcomes, and non-alcoholic fatty liver disease (NAFLD). GLP-1RAs enhance satiety by reducing body weight and caloric intake along with causing improvements in cardiovascular parameters including blood pressure, heart rate, and myocardial contractility. These effects thereby facilitate improved blood flow to the heart and mitigate the risk of atherosclerosis, stroke, and major adverse cardiovascular events (MACE). Furthermore, they yield favorable outcomes in non-alcoholic fatty liver disease (NAFLD) by optimizing liver fat utilization and diminishing inflammatory markers within the liver

have been associated with a consistent reduction in SBP and diastolic blood pressure (DBP), primarily by influencing the central nervous system possibly by reducing sympathetic nervous system activity [5, 6, 86]. These BP-lowering effects alleviate the strain on the heart and further reduce the risk of adverse cardiovascular events [86]. Furthermore, GLP-1RAs contribute to favorable changes in lipid profiles, characterized by lowered triglyceride levels and increased high-density lipoprotein cholesterol. These alterations promote a more cardioprotective lipid profile, reducing the risk of atherosclerosis and related cardiovascular complications [87, 88]. As discussed earlier, weight loss, often observed as a secondary effect of GLP-1RAs, plays a pivotal role in mitigating associated cardiovascular risk. Weight reduction improves insulin sensitivity, reduces inflammation, and contributes to overall cardiovascular well-being [89]. In essence, the cardiovascular benefits of GLP-1RAs have ushered in a new era of diabetes management, focusing on glucose regulation and the holistic health of individuals with associated disorders [90].

Pre-clinical and clinical findings

Here, we discuss the pre-clinical evidence (Table 2) that serves as the foundational knowledge upon which clinical trials are built, providing a strong rationale for testing these compounds in humans [86].

Table 3 depicts clinical findings that support the implementation of GLP-1RAs in cardiovascular disorders.

GLP-1RAs in non-alcoholic fatty liver disease (NAFLD)

In recent years, GLP-1RA has emerged as a promising avenue of research and treatment in the context of NAFLD [102]. NAFLD encompasses a spectrum of liver conditions, ranging from simple steatosis to non-alcoholic steatohepatitis (NASH), characterized by inflammation and liver cell damage, which can progress to fibrosis, cirrhosis, and even hepatocellular carcinoma [103]. With the global prevalence of NAFLD on the rise, investigations into the potential therapeutic role of GLP-1RAs have gained momentum for their potential to mitigate liver fat accumulation, inflammation, and fibrosis. We assess the intricate interplay between GLP-1RAs and NAFLD by exploring the mechanisms,

Table 2 Pre-clinical findings of GLP-1RAs in atherosclerosis and other CVD disorders

Sr No	Study design	No of animals	The procedure of the study	Study findings	References
1	A study to evaluate the impact of GLP-1RAs (liraglutide, exendin-4) on oxidized low-density lipoprotein (oxLDL) foam cell and atherosclerotic plaque formation in Apolipoprotein E (ApoE) deficient mice	29 Mice (12 control and 17 intervention groups)	ApoE-deficient Mice that were 17 years of age were administered long-acting GLP-1 RA with the help of osmotic mini-pumps for 4 weeks. The development of atherosclerosis, foam cell formation, immunoblotting assay, and gene expressions were determined in vivo and ex vivo	Liraglutide was administered to ApoE-deficient mice, resulting in a significant reduction in atherosclerotic lesion formation and monocyte infiltration in the aortic wall	[91, 92]
2	A study on animals to evaluate the effect of GLP-1 agonist (exendin-4) administration in the monocyte/macrophage recruitment and accumulation in atherosclerosis	25 Mice	Exendin-4 was administered in low (300 pmol/kg/day), and high (24 nmol/kg/day) doses in mice that were ApoE deficient, and monocyte adherence was evaluated in the aortic valve, thoracic aorta, etc., in mouse macrophage and human monocytes	The treatment significantly suppressed the adherence of monocytes and also inhibited nuclear factor-kappa beta (NF-κβ), p65, and monocyte chemoattractant protein-1 (MCP-1)	[93]
3	An animal study to assess the safety and efficacy of liraglutide and semaglutide in a mouse model of atherosclerosis	126 low-density lipoprotein (LDL)-receptor-deficient mice and 180 ApoE-deficient mice	Semaglutide and liraglutide were administered for 12–14 weeks to ApoE-deficient and LDL-receptor-deficient mice. Outcomes such as cholesterol levels, body weight, monocyte aggregation, inflammation, and plaque size were evaluated. The animals were divided into three groups: a) Semaglutide SC at doses of 4, 12, and 60 mg/kg, b) Liraglutide SC at a dose of 1 mg/kg, c) Vehicle control	Liraglutide and semaglutide resulted in the significant attenuation of atherosclerotic plaque in ApoE and LDL-receptor-deficient mice. Semaglutide was also observed to reduce the concentration of the inflammatory markers	[94]
4	A pre-clinical study to determine the acute effect of GLP-1 agonists on Heart rate (HR) and Blood pressure (BP) in rats	Adult male pathogen-free Sprague–Dawley rats (250–350 g, n = 8–12)	The rats were administered with EXN-4 (30, 300, or 3000 ng per rat i.v. (n = 4–6 for each group) or pyrogen-free saline (PFS) (0.25 ml i.v. or 5 µl i.c.v., (n = 4–6 for each group). The mean arterial blood pressure (MAP) and HR were recorded and evaluated	Both peripheral and central administration of GLP-1R agonists elevated MAP acutely in unrestrained, conscious rats via modulating sympathetic outflow	[95]
5	A study to determine the effect of chronic treatment with GLP-1 or the exenatide analog AC3174 in cardio-protection in a rat model of MI-induced CHF	Male Sprague–Dawley rats n = 37–40 (200–225 g)	Two weeks after inducing myocardial infarction (MI) in Sprague–Dawley rats, treatment with GLP-1 agonists (2.5 or 25 pmol/kg/min, n = 11), Exenatide analog (AC3174) (1.7 or 5 pmol/kg/min, n = 13), or vehicle (n = 13) was administered via SC infusion for 11 weeks. Echocardiography was performed before and after treatment to determine cardiac function and morphology	Compared to the vehicle, GLP-1 and AC3174 improved cardiac function, left ventricular (LV) ejection fraction, and end-diastolic pressure, suggesting cardiovascular benefits. Additionally, they decreased body fat and fluid mass and improved respiratory function	[96]

pre-clinical and clinical evidence, and the evolving treatment landscape for complex liver disorders.

Effects on liver fat accumulation

Currently, lifestyle modifications, including weight loss, remain the existing alternatives to cure NAFLD; however, these alternatives are difficult to maintain in patients who cannot adhere to them [104]. The prevalence of NAFLD significantly increased in patients pre-existing with T2DM, with up to 65% in patients suffering from Non-alcoholic steatohepatitis (NASH) [105]. It has been observed that liraglutide also improves the hepatic enzyme lipase activity, thereby modulating liver fat to improve the outcome of liver fatty disease [106]. Recent research has shown that GLP-1RAs influence liver fat processing either directly (impacting hepatocyte fat metabolism) or indirectly (incretin action) due to the ultimate effect of reversing insulin resistance [107, 108]. Another study utilizing exendin-4 revealed that the liver fat content was decreased when this drug was administered to NAFLD-induced mice, along with improved insulin signaling [109]. A recent meta-analysis of 25 trials concluded that GLP-1RAs caused at least 2.8 kg weight reduction in people with or without diabetes, contributing to reducing NAFLD symptoms. Therefore, GLP-1RAs may play a crucial role in regulating liver fat accumulation and, contribute to the treatment of NAFLD.

Improvement in liver function

GLP-1RAs may lead to improvements in liver function for a variety of reasons. They decrease the de novo lipogenesis, which further reduces the lipolysis-induced free fatty acid formation and toxic substances due to triglycerides (Fig. 3) [110]. Several animal studies using GLP-1RAs showed the repair of the dysfunctional adipose tissue, regulate the destructive effects of hepatic fatty acids by maintaining their oxidative processes via controlling the effects of acetyl-CoA carboxylase and fatty acid synthase, and ultimately, alleviating the hepatic toxicity [111, 112]. GLP-1RAs also modulate the liver inflammation in NAFLD by decreasing the levels of inflammatory mediators, including c-Jun-N-terminal kinase (JNK), Interleukin-1 (IL-1), Intracellular cell adhesion molecule (ICAM-1) in the liver and preventing processes such as liver fibrosis, necrosis [91, 113]. However, clinical studies into this context are currently lacking, and further insights may help to adequately prove the role of GLP-1RAs in liver function restoration [104]. Gu and colleagues carried out a meta-analysis combining the results of nine RCTs comparing the effects of GLP-1RAs in contrast to other antidiabetic drugs (pioglitazone) considered as placebo in the improvement of liver histology from steatosis, inflammation, fibrosis, or necrosis [114]. Further clinical investigation may be required to understand more benefits to support the clinical significance of GLP-1RAs in liver disease with or without T2DM [115, 116].

Reno-protective effects of GLP-1RAs

GLP-1RAs have also unveiled a remarkable facet of their pharmacological prowess in renoprotection [3]. Chronic kidney disease (CKD) is a prevalent and debilitating complication of T2DM, with a substantial impact on patient morbidity and mortality [117]. In this discussion, we delve into the link between GLP-1RAs and renal protection with evolving underlying mechanisms in published articles and the promising implications for individuals at risk of diabetic nephropathy and other renal disorders.

Impact on kidney function using GLP-1RAs

Diabetic nephropathy is most commonly associated with patients with T2DM whose kidney functions are negatively affected [118]. In models of diabetic nephropathy, exendin-4 treatment prevented glomerular macrophage infiltration in glomeruli, significantly decreased oxidative stress, inflammation in tubular cells, and gene expression of cluster of differentiation 14 (CD14), ICAM-1, and transforming growth factor-1 (TGF-1) in the renal cortex in streptozotocin (STZ)-induced diabetic rats [119]. Therefore, by lowering renal leukocyte infiltration and proinflammatory mediators, GLP-1RAs may benefit in improving nephropathy [120]. GLP-1R is expressed in the proximal tubules [121], and this expression possibly leads to the inhibition of renal inflammation and oxidative stress using GLP-1 therapy on diabetic nephropathy and acute kidney damage [122]. The direct and indirect effects of GLP-1RAs are illustrated in Fig. 44.

Studies suggest that the reno-protective effects of GLP-1 may be mediated by two signaling pathways: (1) Increasing natriuresis and diuresis in a dose-dependent manner by functioning on the gut-renal (natriuretic) axis, and (2) Reducing the activity of the Na+/H+ exchanger isoform NHE3 to reduce proximal sodium reabsorption, and possibly by boosting glomerular filtration rate. A study also showed that glomerular mesangial proliferation, a characteristic feature of diabetic patients, was remarkably reduced by GLP-1RAs [123]. Recombinant human GLP-1 reduces oxidative stress in the glomeruli and glomerular microvascular endothelial cells in diabetic rats by inhibiting protein kinase C and activating PKA [124]. Another study reported that liraglutide significantly decreased albuminuria and oxidative stress in Type-1 DM rats produced by STZ [125].

Table 3 Clinical trial findings of GLP-1RA in modulation of atherosclerosis and other CVD disorders

NCT number	Study design	No of participants	Eligibility criteria	Arms of the study	Study findings	References
NCT04032197	A clinical trial assessing the efficacy of Semaglutide in diminishing atheroma plaque formation in diabetic patients with cardiovascular comorbidities	101	Patients of either gender, aged between 18 to 50 years, having body mass index (BMI) equal to or less than 39.9 kg/m^2, HbA1c 6.0%—9.0%, willing to provide informed consent for the study	Intervention: Semaglutide SC once a week (1 mg) maximum over 4 weeks Control: Placebo-injected SC	Semaglutide was associated with a reduction in CV events and the size of the plaque by lowering inflammatory processes	[97]
NCT03985384	A study to determine the effect of Semaglutide on coronary progression of atherosclerosis in T2DM patients	140	Patients of either gender suffering from T2DM, having HbA1c 7.0% or more, willing to participate in the study, age > 40 years at the time of visit	Intervention: Semaglutide 2 mg/1.5 ml SC solution Control: Placebo 1.5 ml, pen-injector	Semaglutide was noted to reduce the progression of non-calcified coronary atherosclerotic plaque volume compared to placebo in diabetic patients	[98]
NCT05467514	A study was carried out to evaluate the role of Liraglutide in patients suffering from type 1 diabetes	35	Patients aged 15 to 60 years old diagnosed with type 1 diabetes and willing to take part in the study, C—peptide less than 0.3 nmol/L	Intervention: Liraglutide 1.8 mg SC daily for 6 months	Liraglutide was safely tolerated by the patients and was shown to retard the development of atherosclerosis by regulating inflammatory processes	[99]
REWIND	A clinical trial to assess the effect of dulaglutide on MACE when added to the existing anti-hyperglycaemic regimens of T2DM patients	9901	Patients aged 50 years or older, diagnosed with T2DM, who had experienced a prior cardiovascular event or exhibited cardiovascular risk factors, were allocated randomly in a 1:1 ratio	Intervention: Dulaglutide 1.5 mg SC weekly Control: Placebo	Dulaglutide led to a reduction in cardiovascular events for both males and females, irrespective of their cardiovascular history	[100]
NCT02692716 PIONEER 6	A clinical trial to assess cardiovascular outcomes of once-daily oral Semaglutide in patients with T2DM	3183	Patients aged 50 years or older with documented cardiovascular or chronic kidney disease, or those aged 60 years or older with cardiovascular risk factors in the absence of established disease, along with a confirmed diagnosis of T2DM	Intervention: Oral Semaglutide 14 mg daily for 12 months Control: Placebo	Oral semaglutide exhibited non-inferior cardiovascular risk profiles when compared to placebo, which is consistent with results observed in other GLP-1RAs cardiovascular outcome trials	[101]

Clinical studies of GLP-1RAs impacting renal outcomes

A journey through the clinical investigations using GLP-1RAs on renal outcomes has been categorized in Yin W et al. studied recombinant human GLP-1RAs' effect on kidney function and revealed that these agents improved renal tubules and tubulointerstitial lesions in diabetic nephropathy rats [127]. GLP-1 also inhibits the activity of multiple proteins that have been associated with diabetic nephropathy, notably collagen I, alpha-smooth muscle actin (a-SMA), fibronectin (FN), and tubulointerstitial TNF-α [127, 128]. It also effectively inhibits the level of C-peptide, which is majorly responsible for the inflammation of tubulointerstitial fibrosis [129, 130]. In patients with diabetic kidney disease, GLP-1RAs, namely liraglutide, and lixisenatide, were observed to prolong the decline of renal function towards end-stage renal disease along with a reduction in albuminuria [40, 131]. This response was due to increased cAMP levels and PKA activity while decreasing NADPH oxidase activity, interfering with the expression of advanced glycation end product (AGE) receptors, and suppressing the NF-κβ mediated signaling pathway. This mechanism prevents oxidative damage and the production of reactive oxygen species (ROS). This mechanistic view indicates that GLP-1RAs play a sensible role in renal protection.

Table 4 In the majority of trials, GLP-1 analogs demonstrated enhanced effectiveness in improving serum creatinine (Sr.Cr) levels and glomerular filtration rate (GFR) in patients with T2DM who were at risk of developing CKD or already diagnosed with CKD. Yin W et al. studied recombinant human GLP-1RAs' effect on kidney function and revealed that these agents improved renal tubules and tubulointerstitial lesions in diabetic nephropathy rats [127]. GLP-1 also inhibits the activity of multiple proteins that have been associated with diabetic nephropathy, notably collagen I, alpha-smooth muscle actin (a-SMA), fibronectin (FN), and tubulointerstitial TNF-α [127, 128]. It also effectively inhibits the level of C-peptide, which is majorly responsible for the inflammation of tubulointerstitial fibrosis [129, 130]. In patients with diabetic kidney disease, GLP-1RAs, namely liraglutide, and lixisenatide, were observed to prolong the decline of renal function towards end-stage renal disease along with a reduction in albuminuria [40, 131]. This response was due to increased cAMP levels and PKA activity while decreasing NADPH oxidase activity, interfering with the expression of advanced glycation end product (AGE) receptors, and suppressing the NF-κβ mediated signaling pathway. This mechanism prevents oxidative damage and the production of reactive oxygen species (ROS). This mechanistic view indicates that GLP-1RAs play a sensible role in renal protection.

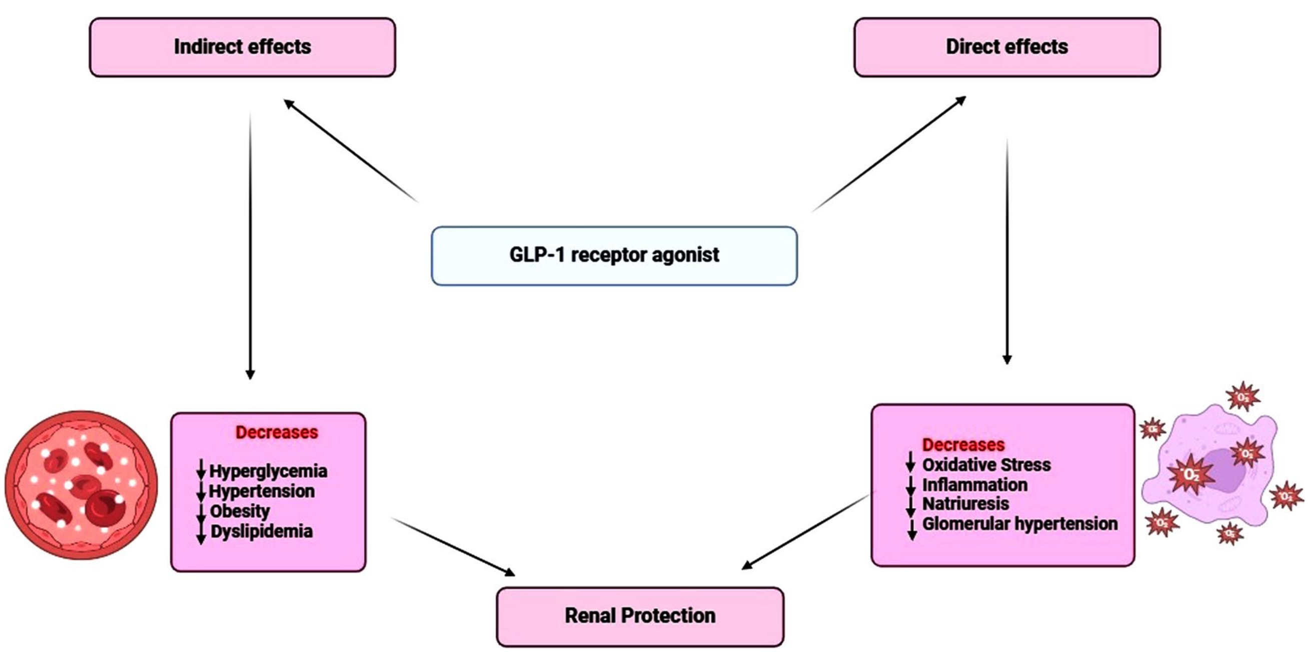

Fig. 4 A figure displaying the mechanisms through which GLP-1RAs can cause renoprotection. Stimulating GLP-1 receptors by GLP-1RAs potentially be directly or indirectly involved in the restoration of kidney functions leading to reno-protective effects. The direct effects include maintenance or reduction of oxidative stress, inflammation, natriuresis, and glomerular hypertension, whereas the indirect effects include regulation of hypertension, dyslipidemia, and other CV risk factors [126]

Exploring the neuroprotective potential of GLP-1RAs

GLP-1RAs have emerged as a beacon of hope, offering a potential advantage for neuroprotection in neurodegenerative diseases. Neurodegenerative disorders, such as Alzheimer's disease (AD), and Parkinson's disease (PD) represent some of the most challenging and devastating health conditions in the modern era [138, 139]. As the global population ages, the burden of these diseases continues to grow, underscoring the urgent need for innovative therapies. GLP-1RAs have expanded their therapeutic role from T2DM and obesity to preserving and restoring neuronal health [11].

Pre-clinical and clinical findings in neurodegenerative disorders

GLP-1R is known to be expressed in the brain, primarily affecting the brain function regarding satiety and appetite via the autonomic nervous system [140]. GLP-1 plays an important role in a variety of neural functions, including hippocampus circuit activity, neurite outgrowth stimulation, cell survival enhancement, and up-regulation of enzyme and neurotransmitter production (Fig. 5) [7, 141]. GLP-1R expressions have been identified on neurons, specifically pyramidal neurons in the hippocampus and neocortex, where they are found on dendrites and cell bodies. This indicates that these receptors are crucial for the movement of synaptic signals among neurons [142, 143]. Novel GLP-1RAs have a significantly greater biological half-life (Val8GLP-1, liraglutide, exendin-4) and have been demonstrated to impact memory formation and synaptic plasticity in the brain significantly. Also, along with such effects, GLP-1RAs can cross the blood–brain barrier, imparting CNS effects unlike most neuroprotective growth factors [138, 144, 145]. Additionally, mice that overexpressed GLP-1R in the hippocampus displayed enhanced learning and increased neurite development [146]. Recent findings show that co-activation of GIP and GLP-1 receptors is neuroprotective in a model of PD and enhances cognitive performance in a rat model of AD [147]. GLP-1R has been found in astrocytes and microglia, suggesting that the glia may be crucial in the inflammatory reactions of the central nervous system [148]. The pathogenesis of both the 1-methyl-4-phenyl-1,2,3,6-tetrahydropyidine (MPTP)-induced PD model and human PD is strongly influenced by microglial activation [149, 150]. In this study, exendin-4 (50mcg/kg) showed significant effectiveness in mitigating the activation of microglial cells induced by MPTP. Moreover, it effectively curbed the production of inflammatory cytokines such as TNF-α and IL-1 triggered by MPTP. A study was conducted with results that showed that the usage of GLP-1RA for more than 3–6 months helped individuals with PD and AD with their motor and cognitive symptoms, respectively. GLP-1 injections daily for eight weeks showed a substantial improvement in the recognition index in mice measuring with an object recognition test, indicating improved learning and memory, while mice feeding on a high-fat diet led to a decline in cognitive performance [151]. These findings suggest that the inhibitory impact of exendin-4 on microglial activation holds promise as a therapeutic approach for the management of PD. In summary, GLP-1RAs exhibit protection in synaptogenesis, neurogenesis, cell repair, and reduced inflammation in the brain [152].

Therapeutic potential of GLP-1RAs in stroke

As the global population ages, the prevalence of stroke continues to rise, necessitating novel and effective interventions. GLP-1RAs recently emerged as promising candidates for stroke therapy due to their multifaceted neuroprotective properties [153].

GLP-1RAs reduce neuroinflammation and improve cognition in stroke

GLP-1R expression within the brain increases the level of intracellular cAMP via its signaling pathways, which also serve as the target for neuroprotection in ischemic stroke [154]. It has been hypothesized that the effect of GLP-1RAs via cAMP/PKA signaling stimulation may contribute to the anti-neuroinflammatory activity, given that brain inflammation is an immunological response mediated by microglia and astrocytes [155].

GLP-1R expression was found when embryonic primary cerebral cortical and ventral mesencephalic (dopaminergic) neurons were experimentally studied. Hypoxia and formation of 6-hydroxydopamine cause cell death, and GLP-1 and exendin-4 protected hypoxia-induced cell death, and this effect disappeared in the cells from GLP-1R knockout (−/−) mice [156]. These findings show that exendin-4 can defend neurons from oxidative and metabolic stresses and provide therapeutic potential in the management of stroke. Exendin-4 had a strong dilatory effect on cortical arterioles in acute brain slices of the rat cerebral cortex and effectively reversed arteriolar constrictions brought on by metabolite lactate and glucose deprivation in an ex-vivo model of ischemic stroke. Exendin-4 caused significant increases in brain tissue pO_2, a sign of elevated cerebral blood flow via strong dilation of cortical arterioles, in rats under anesthesia. These findings show that a pathway involving GLP-1R signaling mediates the neuroprotection against ischemic stroke created by distant

Table 4 Clinical trial findings of GLP-1RA in renal protection

NCT number	Study design	No of participants	Eligibility criteria	Arms of the study	Study findings	References
NCT number not given	A multicentric, retrospective, observational clinical trial to study the effects of Semaglutide in patients with T2DM and Chronic kidney disease (CKD)	122	Patients with (> 18 years, eGFR rate > 15 mL/min/1.73 m^2) diagnosed with T2DM and CKD, willing to comply with study requirements	Intervention: Semaglutide (0.25 mg/kg, 0.5 mg/kg, 1 mg/kg) Control: Other anti-diabetic agents (Basal insulin, SGLT-2 inhibitors)	Patients with increased macroalbuminuria levels were studied to show their risk for developing end-stage renal disease (ESRD) in which Semaglutide reduced albumin levels and also lowered BP compared to placebos	[132]
NCT01847313	A randomized clinical trial to assess the safety and efficacy of liraglutide in patients with diabetic renal disease	24	Patients with T2DM or having HbA1C 6–9%, age above 30 years, BMI 25 kg/m2 or greater	Intervention: Liraglutide 0.6 mg daily for 6 months Control: Patients receiving standard drugs to maintain renal function, such as renin–angiotensin–aldosterone receptor antagonists	Patients exhibited significant reductions in mean body mass index, mean arterial pressure, and urinary and serum inflammatory markers, thus improving renal function	[133]
NCT01394341	A clinical study to evaluate the effects of Liraglutide in patients with T2DM suffering from renal insufficiency	40	Participants aged 18–85 years, suffering from ESRD, on chronic dialysis treatment for 3 months, having a confirmed diagnosis of T2DM	Intervention: Liraglutide with chronic dialysis treatment Control: Daily placebo dialysis treatment	Liraglutide improved the creatinine level and renal function and prevented the development of CV-related comorbidities	[134]
NCT01621178	A Randomized, Open-Label, Parallel-Arm Study to compare Dulaglutide with Insulin Glargine on glycaemic control in patients with T2DM with Moderate to Severe CKD	577	Age > 18 years, on oral insulin or anti-diabetic medication, HbA1c $\geq$ 7.5% and $\leq$ 10.5%	Intervention 1: Insulin Glargine was administered SC at bedtime Intervention 2: 0.75 mg Dulaglutide administered SC once per week Intervention 3: 1.5 mg Dulaglutide administered SC once per week	Dulaglutide performed similarly to insulin glargine in terms of glycaemic control in patients of T2DM suffering from CKD	[135]
(NCT00630825, NCT00791479, NCT01001104, NCT01149421, NCT01064687, NCT00734474, NCT01075282, NCT01191268, NCT01126580)	A meta-analysis was carried out to determine the effects of dulaglutide on kidney function in patients with T2D	6005	Patients who were pre-diagnosed with T2D and were susceptible to developing kidney disease, receiving dulaglutide, were willing to comply with the study requirements	Intervention `1: Patients receiving dulaglutide 0.75 and 1.5 mg, up to 26 weeks Intervention 2: Placebo	No significant difference in serum creatinine and e-GFR values was noted between the placebo and dulaglutide groups. However, there was a slightly higher level of UACR in the dulaglutide group, indicating its increased efficacy. Furthermore, dulaglutide showed no increase in adverse events in T2D patients prone to impaired renal function	[136]

Table 4 (continued)

NCT number	Study design	No of participants	Eligibility criteria	Arms of the study	Study findings	References
NCT01179048	A randomized controlled clinical trial to evaluate the safety of liraglutide in patients of CKD	9340	Patients who were willing to sign the ICF, patients diagnosed with CKD except dialysis-dependent ESRD	Intervention 1: Liraglutide 1.8 mg (or the maximum tolerated dose) OD SC Intervention 2: Placebo OD SC	The study revealed no significant difference in serious adverse events (SAEs) between patients on liraglutide and placebo	[137]

ischemia training [157]. Another study utilizing liraglutide prevented brain edema, and neurologic deficits and reduced the inflammatory response produced by intracerebral hemorrhage (ICH) in mice. This protection was mechanistically medicated via activation of AMPK, which can reduce the expression of proinflammatory mediators like ICAM-1 and E-selectin [158–160]. In a rat model of middle cerebral artery occlusion (MCAO) stroke, liraglutide exhibited comparable protective qualities by reducing apoptosis and oxidative stress in the affected brain region [161]. In another study, animals treated with semaglutide had lower neurological impairment scores on a variety of motor and grip strength measures along with reduced extent of cerebral infarction [159, 162]. GLP-1RAs exhibit neuroprotection, but the definite mechanism that mediates this response is yet to be known, which invites further studies [163]. The effect of GLP-1RAs in improving cognitive behavior, motor skills, and neuroprotection in neurodegenerative diseases and stroke opened up new ways to repurpose drugs as therapeutic interventions for neurological diseases [164].

Safety profile and adverse effects of GLP-1RAs

During clinical trials using GLP-1RAs, gastrointestinal issues were the most reported side effects among all participants. Vomiting, constipation, abdominal discomfort, and dyspepsia were all reasonably prevalent (1/10 to 1/100), but nausea and diarrhea were highly common (1/10) [165]. At the onset of the therapy, these side effects appeared more frequent, but as the therapy proceeded, gastrointestinal issues gradually subsided. The peak of the GLP-1 effects, which is visible in conjunction with the injection, is thought to be the cause of the activation of the brain regions responsible for controlling appetite, satiety, and nausea [166, 167]. Transient nausea may be clinically insignificant but attributed to about 15% of the cases upon administration of GLP-1RAs, which can be due to delayed emptying of gastric contents. When compared exenatide with liraglutide, exenatide shows 15% more cases of nausea and gastric discomfort [168]. Diarrhea may also result using GLP-1RAs in 10% to 20% of patients [169]. It is also postulated that continuous usage of these agents can cause a significant decrease in gastric acid and lipase secretion. Along with gastric disturbances, usage of GLP-1RAs in animals and humans has reported several long-term safety concerns although there are few reliable epidemiological data available on the prevalence of acute pancreatitis in people with T2DM. Exenatide patients suffered pancreatitis at the incidence of 27 occurrences per 100,000 patients [170]. A numerically higher incidence of benign adenomas

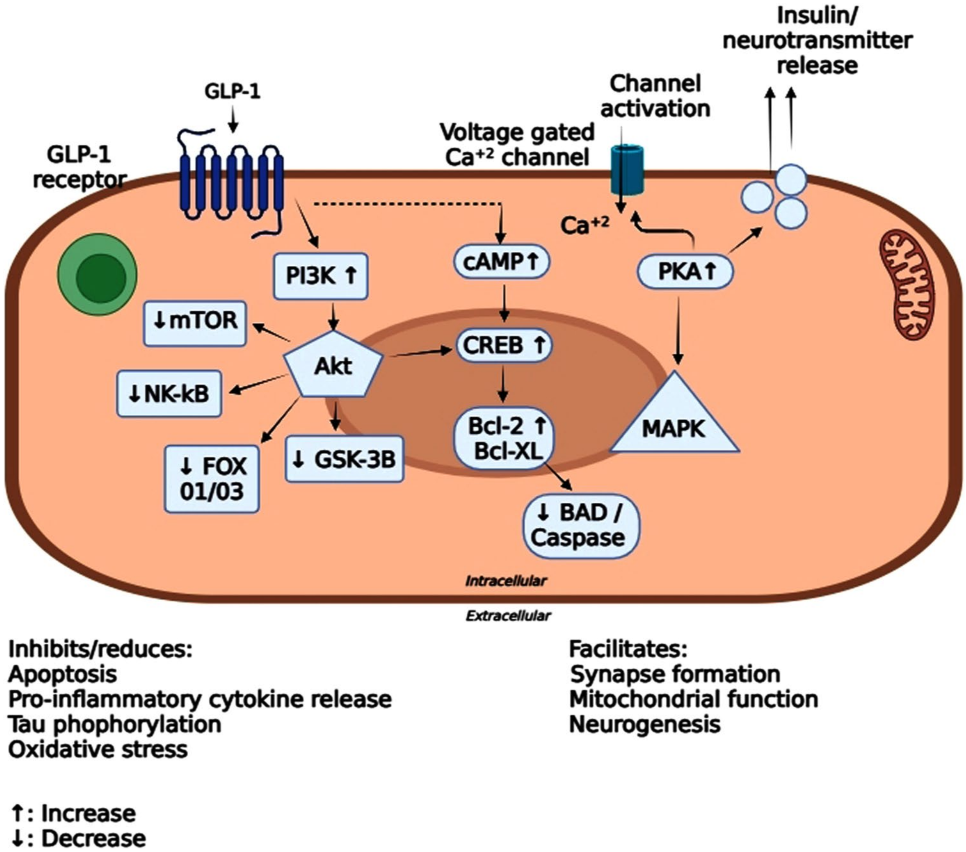

Fig. 5 Visual representation of the beneficial roles of GLP-1RA in neuroprotection. GLP-1RAs facilitate neuronal repair by regulating hippocampal circuit activity, stimulating neurite outgrowth, enhancing cell survival, and increasing the production of enzymes and neurotransmitters. They inhibit neuronal apoptosis, the release of proinflammatory cytokines, and oxidative stress. Conversely, they promote the synaptic formation and improve mitochondrial function, thereby supporting neurogenesis

was seen in preclinical experiments on female rats exposed to exenatide. It was not statistically different when this increase in adenoma incidence was corrected for the rat life span. In humans, only five thyroid neoplasm cases in the clinical studies were reported [171]. Regarding GLP-1 effects on the colon, GLP-1 may decrease intestinal motility via reduced circular contractions in full-thickness muscular colon strips. Hence, gastrointestinal symptoms are common but short-lived, and they do not pose a significant barrier or risks to using these drugs comparing their benefits [172].

Conclusion and future perspectives

GLP-1RAs emerged as a great hope for individuals grappling with the intricate relation of chronic glucose regulation. GLP-1RAs have recently gained global attention for their role in blood glucose control in diabetes, as well as their impact on other diseases. It is well-known that diabetes and other comorbidities may increase the likelihood of other complications, including cardiovascular, hepatic, renal, and cerebrovascular diseases in the patients, and the multifaceted roles of GLP-1RAs in these pathologies have been highlighted in the present review. However, the amount of evidence that supports the comprehensive roles of GLP-1RAs and their mechanisms has not yet been fully explored. Further investigations are warranted considering the expansion of GLP-1RAs in potential benefits from diabetes and associated disorders.

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Code availability We confirm that EndNote Version 9, a freely available software application, was utilized for reference management, and Biorender, another freely available tool, was employed for the creation of figures in this manuscript.

Declarations

Conflict of interest The authors declare no conflict of interest that could have influenced the submitted work.

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