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BEYOND WEIGHT LOSS: EMERGING EXTRA-METABOLIC APPLICATIONS OF GLP-1 RECEPTOR AGONISTS IN CARDIOVASCULAR, RENAL, NEUROLOGICAL AND INFLAMMATORY DISORDERS: A NARRATIVE REVIEW

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BEYOND WEIGHT LOSS: EMERGING EXTRA-METABOLIC APPLICATIONS OF GLP-1 RECEPTOR AGONISTS IN CARDIOVASCULAR, RENAL, NEUROLOGICAL AND INFLAMMATORY DISORDERS: A NARRATIVE REVIEW

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ABSTRACT

Introduction. Glucagon-like peptide-1 receptor agonists (GLP-1 RAs) were originally developed as antidiabetic agents exploiting the incretin effect to achieve glucose-dependent insulin secretion. Over the past decade, evidence from large-scale cardiovascular outcome trials (CVOTs), mechanistic studies, and emerging clinical investigations has demonstrated that the therapeutic potential of this drug class extends well beyond glycaemic control. GLP-1 receptors are expressed in the heart, vasculature, kidneys, brain, liver, lungs, and immune cells, providing the biological substrate for diverse extra-metabolic effects observed in both preclinical models and clinical cohorts.

Methodology. This narrative review was conducted through a systematic search of PubMed, MEDLINE, and the Cochrane Library using MeSH terms and free-text keywords related to GLP-1 RAs and their extra-metabolic effects. Publications up to early 2026 were considered, including randomised controlled trials, CVOTs, systematic reviews, meta-analyses, and mechanistic preclinical studies. Eligibility was based on methodological rigour, sample size, and clinical relevance to four main domains: cardiovascular, renal, neurological, and anti-inflammatory effects.

Results. GLP-1 RAs demonstrated a 13–14% reduction in major adverse cardiovascular events (MACE) across CVOTs, with semaglutide reducing MACE by 20% in patients with obesity but without diabetes (SELECT trial). In the renal domain, the FLOW trial showed a 24% reduction in the composite renal endpoint (HR 0.76; 95% CI: 0.66–0.88; $p < 0.001$) with semaglutide in patients with diabetic kidney disease. In the neurological domain, preclinical evidence strongly supports neuroprotection in Alzheimer's and Parkinson's disease, with initial clinical trials showing improvement in motor function in Parkinson's patients treated with exenatide or lixisenatide and prevention of cerebral metabolic decline in Alzheimer's disease with liraglutide. Anti-inflammatory properties — demonstrated across hepatic (NASH resolution in up to 59% with semaglutide), pulmonary, dermatological, and systemic contexts — further broaden the therapeutic scope. Emerging data also suggest potential roles in obstructive sleep apnoea, substance use disorders, and knee osteoarthritis.

Conclusions. GLP-1 RAs constitute a versatile class of pleiotropic, disease-modifying agents with organ-protective properties extending far beyond glycaemic management. The advent of dual GIP/GLP-1 agonists (tirzepatide) and investigational triple agonists further expands this landscape. Significant gaps remain regarding long-term neurological outcomes, optimal patient selection, and the relative contributions of direct receptor-mediated versus weight-loss-dependent effects, necessitating dedicated mechanism-focused trials and biomarker-guided patient stratification.

KEYWORDS

GLP-1 Receptor Agonists, Cardiovascular Outcome Trials, Diabetic Kidney Disease, Neurodegeneration, Alzheimer's Disease, Parkinson's Disease, Anti-inflammatory, MASLD, Semaglutide, Liraglutide, Tirzepatide

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1. Introduction

Glucagon-like peptide-1 (GLP-1) is a 30-amino acid incretin hormone secreted predominantly by enteroendocrine L-cells of the distal small intestine and colon in response to nutrient ingestion. First characterised in the 1980s following the sequencing of the proglucagon gene, GLP-1 was identified as a potent, glucose-dependent insulin secretagogue and a physiological inhibitor of glucagon release, establishing its foundational role in postprandial glucose homeostasis (Holst, 2007; Drucker, 2006). Under physiological conditions, GLP-1 is rapidly degraded by the enzyme dipeptidyl peptidase-4 (DPP-4) at the N-terminal alanine residue, yielding an inactive metabolite with a plasma half-life of approximately one to two minutes — a pharmacokinetic limitation that spurred the development of DPP-4-resistant structural analogues and synthetic receptor agonists (Holst, 2007).

The first GLP-1 receptor agonist (GLP-1 RA) approved for clinical use was exenatide (2005), a synthetic version of the naturally occurring lizard peptide exendin-4, which shares 53% amino acid sequence identity with human GLP-1 but is resistant to DPP-4 cleavage. Subsequent agents — including liraglutide, lixisenatide, albiglutide, dulaglutide, and semaglutide (available in subcutaneous and oral formulations) — were developed

to achieve progressively longer durations of action, ranging from hours to one week, through structural modifications including fatty acid acylation for albumin binding, Fc-fragment fusion, or PEGylation (Drucker, 2018; Gallwitz, 2009). Despite pharmacokinetic heterogeneity, all approved GLP-1 RAs share the capacity to lower glycated haemoglobin (HbA1c) by 0.8–2.0 percentage points, reduce body weight by 2–7 kg at diabetes doses (and up to 15–22% at obesity doses), suppress appetite, and delay gastric emptying (Drucker, 2018).

The transformative moment in GLP-1 RA research arrived with the 2016 publication of the LEADER trial, which demonstrated not merely the cardiovascular safety of liraglutide — as required by regulatory agencies following the 2008 FDA guidance — but its superiority over placebo in reducing major adverse cardiovascular events (MACE) in patients with T2DM and established cardiovascular disease or high risk (Marso et al., 2016). This finding catalysed a wave of cardiovascular outcome trials (CVOTs) and stimulated mechanistic investigations that collectively revealed a far broader therapeutic profile than originally anticipated. Crucially, the realisation that GLP-1 receptors are expressed across a remarkable diversity of tissues — including cardiac myocytes, vascular endothelium, renal tubular epithelium, cerebral neurons, hepatocytes, pulmonary epithelial cells, immune cells, and dermal fibroblasts — provided a compelling biological framework for these pleiotropic effects (Mehdi et al., 2023; Drucker, 2018).

It is now understood that GLP-1 RAs exert organ-protective effects through multiple pathways: direct GLP-1R-mediated signalling (cAMP/PKA, PI3K/Akt, ERK1/2) that reduces apoptosis, oxidative stress, and inflammation; indirect systemic benefits mediated through weight loss, blood pressure reduction, and improved glycaemic control; and modulation of the gut-brain axis including effects on autonomic nervous system tone and neuroinflammation (Mehdi et al., 2023; Lee & Jun, 2016). The relative contributions of these mechanisms vary by organ and agent, and disentangling direct from indirect effects remains an active area of investigation.

This narrative review synthesises current evidence on the extra-metabolic applications of GLP-1 RAs, with particular focus on cardiovascular, renal, neurological, and anti-inflammatory domains. We additionally discuss emerging and investigational applications — including substance use disorders, obstructive sleep apnoea, metabolic-associated steatotic liver disease (MASLD), osteoarthritis, and the evolving landscape of next-generation dual and triple receptor agonists. The goal is to provide a comprehensive and critically appraised framework for understanding GLP-1 RAs as pleiotropic disease-modifying agents whose therapeutic horizon continues to expand.

2. Methodology

This narrative review was conducted through a systematic search of the PubMed, MEDLINE, and Cochrane Library databases, supplemented by manual screening of reference lists from retrieved articles and recent review publications. Literature searches were performed using the following MeSH terms and free-text keywords, applied individually and in Boolean combinations: 'glucagon-like peptide-1 receptor agonists,' 'GLP-1 RA,' 'incretin therapy,' 'semaglutide,' 'liraglutide,' 'exenatide,' 'dulaglutide,' 'lixisenatide,' 'tirzepatide,' combined with 'cardiovascular outcomes,' 'MACE,' 'heart failure,' 'atherosclerosis,' 'myocardial infarction,' 'stroke,' 'diabetic kidney disease,' 'chronic kidney disease,' 'albuminuria,' 'glomerular filtration rate,' 'Alzheimer's disease,' 'Parkinson's disease,' 'neurodegeneration,' 'blood-brain barrier,' 'addiction,' 'alcohol use disorder,' 'anti-inflammatory,' 'NAFLD,' 'NASH,' 'MASLD,' 'hepatic steatosis,' 'liver fibrosis,' 'psoriasis,' and 'obstructive sleep apnoea.' No language restriction was applied, although the analysis was limited to English-language publications. The search covered publications up to early 2026, with particular emphasis on randomised controlled trials, cardiovascular outcome trials, systematic reviews, and meta-analyses published in peer-reviewed journals. Preclinical studies were included where mechanistic insights were directly relevant to interpreting human findings. Study selection was based on methodological rigour, sample size, relevance to the defined objectives, and clinical applicability. This review was conducted in accordance with the principles of narrative review methodology; no formal quality assessment was applied, and no registration or ethical approval was required.

3. GLP-1 Receptor Agonists: Mechanisms of Action and General Overview

GLP-1 exerts its biological effects exclusively via the GLP-1 receptor (GLP-1R), a class B1 G-protein-coupled receptor (GPCR) comprising 463 amino acids arranged in seven transmembrane alpha-helices with an extracellular N-terminal domain and an intracellular C-terminal tail (Drucker, 2006). The receptor is encoded by the *GLP1R* gene and lacks significant alternative splicing in humans, though tissue-specific post-translational modifications may contribute to signalling heterogeneity. Ligand-receptor interaction proceeds in a two-step mechanism: the C-terminus of the GLP-1 peptide first binds the extracellular N-terminal domain, inducing conformational changes that allow the peptide N-terminus to engage the transmembrane core and activate intracellular signalling (Drucker, 2018).

Upon ligand binding, the GLP-1R couples primarily to the stimulatory Gs protein, leading to adenylyl cyclase activation and a rapid rise in intracellular cyclic adenosine monophosphate (cAMP). In pancreatic beta-cells, this cAMP elevation activates protein kinase A (PKA) and exchange protein directly activated by cAMP-2 (Epac-2), which potentiate glucose-stimulated insulin exocytosis through inhibition of ATP-sensitive potassium channels, enhancement of voltage-gated calcium channel currents, and sensitisation of the secretory machinery to calcium (Drucker, 2006). Beyond cAMP, GLP-1R also signals through Gq-mediated phospholipase C activation, PI3K/Akt, ERK1/2, and — in some tissues — β -arrestin-dependent pathways that influence receptor internalisation and biased agonism. The pharmacological significance of biased signalling is an area of active investigation, as different GLP-1 RA molecules may differentially engage these pathways with downstream consequences for efficacy and tolerability (Liu, 2024).

The extra-pancreatic distribution of the GLP-1R is extensive and functionally consequential. High-level expression has been confirmed in the cardiac atria and sinoatrial node (mediating chronotropic effects and cardioprotection), vascular endothelial cells (mediating vasodilation and anti-atherogenic actions), renal proximal tubular cells (mediating natriuresis and glomerular haemodynamic modulation), neurons of the hypothalamic arcuate nucleus, paraventricular nucleus, and NTS (mediating appetite suppression and energy expenditure), dopaminergic neurons of the substantia nigra and ventral tegmental area (mediating neuroprotection and reward modulation), hepatocytes (mediating lipid metabolism), pulmonary type II pneumocytes (mediating surfactant production), macrophages and dendritic cells (mediating immunomodulation), and dermal fibroblasts (mediating wound healing) (Mehdi et al., 2023; Drucker, 2018; Kalinderi et al., 2024).

Pharmacologically, approved GLP-1 RAs are conventionally classified by their molecular origin and duration of action. Short-acting agents — exenatide twice daily and lixisenatide once daily — are derived from exendin-4 and have half-lives of 2–3 and 3–5 hours respectively; they exert preferential effects on postprandial glucose through pronounced gastric emptying inhibition. Long-acting agents — liraglutide (half-life ~13 hours, once daily), semaglutide subcutaneous (half-life ~7 days, once weekly), dulaglutide (half-life ~4–5 days, once weekly), and oral semaglutide (once daily, absorption enhanced by SNAC co-formulation) — achieve more stable receptor occupancy and confer greater reductions in fasting glucose and body weight, and are those most consistently associated with cardiovascular and renal benefits in outcome trials (Drucker, 2018; Gallwitz, 2009).

The most recent pharmacological evolution has produced tirzepatide, a 39-amino acid dual agonist of the GIP and GLP-1 receptors approved for T2DM and obesity. Tirzepatide exhibits balanced GIP/GLP-1R co-agonism with a half-life of approximately 5 days, and has demonstrated superior glycaemic efficacy (HbA1c reductions of up to 2.4%) and weight loss (up to 22.5% in SURMOUNT-1) compared with selective GLP-1 RAs, attributable in part to GIP receptor-mediated enhancement of insulin sensitisation in adipose tissue and potentiation of GLP-1-driven anorectic signalling (Liu, 2024; Nauck et al., 2026). Investigational agents including retatrutide (GIP/GLP-1/glucagon triagonist), CagriSema (cagrilintide plus semaglutide), and non-peptide oral GLP-1 RAs such as orforglipron further expand the pharmacological horizon of this class.

4. Cardiovascular Effects

4.1 Cardiovascular Outcome Trials

The cardiovascular benefits of GLP-1 RAs were established through a series of regulatory-mandated CVOTs that collectively enrolled more than 60,000 patients across diverse clinical populations. The landmark LEADER trial (Liraglutide Effect and Action in Diabetes: Evaluation of Cardiovascular Outcome Results) randomised 9,340 patients with T2DM and established cardiovascular disease or high cardiovascular risk to liraglutide 1.8 mg daily or placebo, with a median follow-up of 3.8 years. The primary three-point MACE endpoint — composite of cardiovascular death, non-fatal myocardial infarction, and non-fatal stroke — occurred in 13.0% of the liraglutide group versus 14.9% of the placebo group (HR 0.87; 95% CI: 0.78–0.97; $p = 0.01$ for superiority). The absolute risk reduction was driven predominantly by a significant reduction in cardiovascular mortality (HR 0.78; 95% CI: 0.66–0.93) and all-cause mortality (HR 0.85; 95% CI: 0.74–0.97), with a non-significant trend toward reduced non-fatal myocardial infarction and stroke (Marso et al., 2016).

SUSTAIN-6 (Trial to Evaluate Cardiovascular and Other Long-term Outcomes with Semaglutide) randomised 3,297 patients with T2DM to subcutaneous semaglutide (0.5 or 1.0 mg weekly) or placebo over 104 weeks. Semaglutide significantly reduced the primary MACE endpoint (HR 0.74; 95% CI: 0.58–0.95; $p < 0.001$ for non-inferiority; $p = 0.02$ for superiority), with a particularly pronounced reduction in non-fatal stroke (HR 0.61; 95% CI: 0.38–0.99; $p = 0.04$). The REWIND trial (Researching Cardiovascular Events with a Weekly Incretin in Diabetes) with dulaglutide 1.5 mg weekly in 9,901 patients — notably including approximately 31% without prior cardiovascular events — demonstrated a 12% MACE reduction (HR 0.88; 95% CI: 0.79–0.99), establishing benefit in a primary prevention population (Helmstädter et al., 2022; Ferhatbegović et al., 2023).

In contrast, ELIXA (lixisenatide) and EXSCEL (exenatide once weekly) demonstrated cardiovascular non-inferiority without superiority. This agent-level heterogeneity is likely attributable to differences in GLP-1R occupancy profiles: short-acting agents with peak-and-trough receptor stimulation may exert less sustained endothelial and plaque-stabilising effects compared with long-acting agents with continuous receptor engagement (Helmstädter et al., 2022). The HARMONY Outcomes trial (albiglutide) and AMPLITUDE-O (efpeglenatide) both demonstrated MACE superiority, further consolidating the class effect among long-acting GLP-1 RAs (Ferhatbegović et al., 2023).

A pooled meta-analysis incorporating all GLP-1 RA CVOTs demonstrated an overall 13–14% relative risk reduction in three-point MACE (HR approximately 0.87; 95% CI: 0.80–0.93), a 13–17% stroke risk reduction, a 13–14% cardiovascular mortality reduction, and a 12% reduction in all-cause mortality — with the benefit being most pronounced in patients with established ASCVD (HR 0.83) compared with those with risk factors only (HR 0.94) (Nauck et al., 2026). The SELECT trial (Semaglutide Effects on Cardiovascular Outcomes in People with Overweight or Obesity) was a pivotal extension of this narrative: enrolling 17,604 adults with BMI ≥ 27 kg/m², established ASCVD, but without diabetes, it demonstrated a 20% MACE reduction with semaglutide 2.4 mg weekly (HR 0.80; 95% CI: 0.72–0.90; $p < 0.001$), establishing the cardiovascular benefit of GLP-1 RAs independently of the diabetic context and suggesting a potential role in primary cardiovascular prevention in high-risk obese individuals (Nauck et al., 2026).

4.2 Mechanisms of Cardiovascular Protection

The cardiovascular benefits of GLP-1 RAs arise from a convergence of direct receptor-mediated and indirect haemodynamic and metabolic mechanisms. At the vascular level, GLP-1R activation in endothelial cells increases nitric oxide (NO) production via cAMP/PKA-dependent phosphorylation of endothelial nitric oxide synthase (eNOS), promoting vasodilation, reducing endothelial oxidative stress, and suppressing the expression of pro-inflammatory adhesion molecules (ICAM-1, VCAM-1, E-selectin) (Ma et al., 2021; Helmstädter et al., 2022). In smooth muscle cells, GLP-1 RAs inhibit proliferation and migration — key processes in neointima formation and atherogenesis. In macrophages, GLP-1R agonism shifts polarisation toward the anti-inflammatory M2 phenotype, reducing foam cell formation and limiting macrophage-driven plaque progression (Ma et al., 2021; Mullur et al., 2024).

At the myocardial level, GLP-1 RAs exert cardioprotective effects through cAMP-mediated improvement of cardiac glucose utilisation, reduction of cardiomyocyte apoptosis via PI3K/Akt signalling, and attenuation of ischaemia-reperfusion injury through preservation of mitochondrial membrane potential. Liraglutide and semaglutide have been shown in animal models to reduce infarct size and improve left ventricular ejection fraction after experimental myocardial infarction (Ma et al., 2021). Platelet aggregation is

also reduced by GLP-1 RAs through cAMP-dependent inhibition of thromboxane A2 signalling, contributing to the observed reduction in non-fatal myocardial infarction across trials (Helmstädter et al., 2022). Indirect contributors include consistent reductions in systolic blood pressure of 2–4 mmHg (independent of weight loss), modest improvements in triglycerides, reduction in heart rate variability-associated vagal tone, and significant reductions in inflammatory markers including hsCRP — reported at 25–43% with semaglutide — TNF- α , and IL-6 (Gallwitz, 2009; Mehdi et al., 2023).

4.3 Heart Failure with Preserved Ejection Fraction

Heart failure with preserved ejection fraction (HFpEF) — characterised by diastolic dysfunction, elevated filling pressures, and preserved LVEF $\geq 50\%$ — represents approximately 50% of all heart failure cases and is strongly associated with obesity, hypertension, and metabolic syndrome. Unlike HFrEF, in which earlier GLP-1 RA trials yielded neutral or unclear results, HFpEF has emerged as a compelling target for GLP-1 RA therapy owing to the central pathophysiological role of adiposity-driven inflammation, epicardial fat deposition, and cardiometabolic dysfunction (Mullur et al., 2024).

The STEP-HFpEF trial enrolled 529 patients with HFpEF, BMI ≥ 30 kg/m², and no T2DM, randomised to semaglutide 2.4 mg weekly or placebo for 52 weeks. Semaglutide significantly improved the dual primary endpoint — Kansas City Cardiomyopathy Questionnaire Clinical Summary Score (KCCQ-CSS) increased by 7.8 points more than placebo ($p < 0.001$), and body weight decreased by 13.3% versus 2.6% ($p < 0.001$). Secondary endpoints including six-minute walk distance, NT-proBNP, hsCRP, and left atrial volume index also improved significantly (Nauck et al., 2026). The SUMMIT trial in HFpEF with T2DM confirmed and extended these findings. Mechanistically, improvements in HFpEF are attributed to reductions in pericardial and epicardial fat, attenuation of systemic and cardiac inflammation, reduction in left ventricular wall stress through blood pressure and weight lowering, and potentially direct GLP-1R-mediated improvement in cardiomyocyte calcium handling (Ma et al., 2021; Mullur et al., 2024).

5. Renal and Urinary System Effects

5.1 Evidence from Cardiovascular Outcome Trials

The recognition of nephroprotective properties of GLP-1 RAs emerged initially from pre-specified renal secondary endpoints embedded within CVOTs designed primarily to assess cardiovascular safety. In LEADER, liraglutide significantly reduced the composite renal outcome — defined as new-onset macroalbuminuria (UACR > 300 mg/g), doubling of serum creatinine with eGFR ≤ 45 mL/min/1.73 m², ESRD, or renal death — with an HR of 0.78 (95% CI: 0.67–0.92; $p = 0.003$), with the dominant contributor being new-onset macroalbuminuria (HR 0.74; 95% CI: 0.60–0.91) (Marso et al., 2016; Mosterd et al., 2020). The REWIND trial demonstrated a 15% composite renal outcome reduction (HR 0.85; 95% CI: 0.77–0.93; $p = 0.003$) with dulaglutide, notably including patients with baseline eGFR as low as 15 mL/min/1.73 m² without dose modification, establishing renal safety and efficacy across the CKD spectrum (Mosterd et al., 2020).

The AWARD-7 trial provided the first direct comparison of a GLP-1 RA with insulin in patients with DKD and moderate-to-severe CKD (eGFR 15–59 mL/min/1.73 m²). Dulaglutide preserved eGFR more effectively than insulin glargine (mean difference -1.6 mL/min/1.73 m² per year favouring dulaglutide; $p = 0.005$), significantly reduced UACR, and was associated with less hypoglycaemia, offering a clinically meaningful alternative to insulin intensification in advanced DKD (Michos et al., 2023). Furthermore, SUSTAIN-6 demonstrated a 46% reduction in new or worsening nephropathy with semaglutide (HR 0.64; 95% CI: 0.46–0.88; $p = 0.005$), adding to the convergent evidence from multiple agents and trial designs (Mosterd et al., 2020).

5.2 The FLOW Trial

The most definitive and clinically pivotal evidence for GLP-1 RA nephroprotection emerged from the FLOW trial (Evaluate Renal Function with Semaglutide Once Weekly) — the first prospective, dedicated renal outcome trial of a GLP-1 RA. FLOW enrolled 3,533 patients with T2DM and established CKD (eGFR 20–75 mL/min/1.73 m² and UACR 300–5,000 mg/g) at high renal and cardiovascular risk, randomised 1:1 to subcutaneous semaglutide 1.0 mg weekly or placebo. The primary composite endpoint — sustained $\geq 50\%$ decline in eGFR, ESRD (eGFR < 15 mL/min/1.73 m² or renal replacement therapy), renal death, or cardiovascular death — was significantly reduced in the semaglutide group (HR 0.76; 95% CI: 0.66–0.88;

$p < 0.001$), representing a 24% relative risk reduction and an absolute risk difference of 4.9 percentage points (Nauck et al., 2026; Granata et al., 2022).

Critically, the renal benefit in FLOW was observed across pre-specified subgroups including those stratified by baseline eGFR, UACR, and concomitant SGLT-2 inhibitor or renin-angiotensin-aldosterone system (RAAS) blocker use — suggesting that GLP-1 RA-mediated nephroprotection is additive to, rather than dependent upon, existing standard-of-care therapies (Nauck et al., 2026). The eGFR slope analysis demonstrated a slower rate of kidney function decline with semaglutide (-1.0 vs -2.5 mL/min/1.73 m² per year), and significant reductions in UACR were sustained throughout the follow-up period. Cardiovascular outcomes were also improved, consistent with the established CVOT findings, confirming the cardiorenal continuum of GLP-1 RA benefit (Granata et al., 2022).

5.3 Albuminuria and Glomerular Effects

Albuminuria reduction is a consistent pharmacodynamic effect of GLP-1 RAs across populations and appears to be partially independent of haemodynamic and glycaemic improvements. A post-hoc analysis of the STEP 1–3 trials — which evaluated semaglutide 2.4 mg weekly in adults with overweight or obesity, with or without T2DM — demonstrated UACR reductions of 28–33% compared with placebo in T2DM subgroups (Heerspink et al., 2023). Importantly, statistical adjustment for changes in HbA1c, body weight, and systolic blood pressure attenuated but did not fully explain these reductions, suggesting direct glomerular and tubular mechanisms (Heerspink et al., 2023). This finding is clinically significant because albuminuria is a well-validated surrogate endpoint for renal progression and an independent cardiovascular risk factor, and its reduction with GLP-1 RAs may therefore carry dual cardiorenal prognostic value.

5.4 Mechanisms of Nephroprotection

GLP-1Rs are expressed in multiple renal cell types — proximal tubular epithelial cells, podocytes, mesangial cells, and glomerular endothelial cells — enabling direct pharmacological action on kidney structure and function (Granata et al., 2022; Mehdi et al., 2023). The nephroprotective mechanisms of GLP-1 RAs are both haemodynamic and non-haemodynamic. In the proximal tubule, GLP-1R activation inhibits the sodium-hydrogen exchanger 3 (NHE3), reducing sodium reabsorption and decreasing tubular fluid delivery to the macula densa, which activates tubuloglomerular feedback to reduce afferent arteriolar vasodilatation and lower intraglomerular pressure — a mechanism analogous to that of SGLT-2 inhibitors (Granata et al., 2022; Michos et al., 2023). This haemodynamic effect may partially explain the reduction in glomerular hyperfiltration — a key early mediator of progressive DKD — observed in clinical trials.

At the molecular level, GLP-1R activation in renal cells increases cAMP and PKA activity, enhancing nitric oxide bioavailability in glomerular endothelial cells and reducing NADPH oxidase-mediated superoxide production (Mehdi et al., 2023). This antioxidant effect counteracts the oxidative stress generated by advanced glycation end products (AGEs) — potent stimuli of ROS production in diabetic kidneys — which activate NF- κ B and drive pro-inflammatory and pro-fibrotic gene expression. GLP-1 RAs suppress this cascade by reducing phosphorylation of NF- κ B and MAPK, lowering levels of MCP-1, TGF- β , TNF- α , ICAM-1, and fibronectin in tubular and glomerular cells, and preventing mesangial expansion — key histological features of progressive DKD (Granata et al., 2022; Mehdi et al., 2023). Additionally, the natriuretic and modest blood pressure-lowering effects of GLP-1 RAs reduce glomerular wall stress and may directly attenuate podocyte injury, which is a critical early event in albuminuric DKD.

6. Neurological Effects and Neuroprotection

6.1 GLP-1 Receptors in the Central Nervous System

Beyond its peripheral incretin role, GLP-1 is produced centrally by a distinct population of neurons in the nucleus tractus solitarius (NTS) of the caudal brainstem, from which NTS-GLP-1 axons project to reward circuits, limbic structures, and hypothalamic nuclei, functioning as a neuropeptide with roles in energy homeostasis, stress responses, and neuroprotection (Holst, 2007; Klausen et al., 2022). GLP-1Rs are expressed across a wide array of CNS regions including the hypothalamic arcuate, paraventricular, and dorsomedial nuclei, the hippocampal CA1–CA3 subfields and dentate gyrus, the cortex, striatum, substantia nigra pars compacta, ventral tegmental area (VTA), lateral septal nucleus, amygdala, and cerebellum — expressed on neurons, activated microglia, and astrocytes (Kalinderi et al., 2024; Klausen et al., 2022).

A pharmacologically important consideration is the degree to which systemically administered GLP-1 RAs achieve CNS penetration. Evidence indicates considerable heterogeneity: exenatide and lixisenatide cross the BBB via receptor-mediated transcytosis at circumventricular organs (area postrema, subfornical organ) and via passive diffusion, resulting in measurable brain concentrations after systemic administration and the detection of exenatide in cerebrospinal fluid of Parkinson's patients treated at clinical doses (West et al., 2025; Kalinderi et al., 2024). Liraglutide crosses the BBB to a more limited extent but achieves functionally relevant concentrations in specific brain regions including the hypothalamus, demonstrating significant neurogenesis and neuroprotection in murine models (West et al., 2025). Semaglutide interacts with circumventricular organs and accesses BBB-protected regions including the lateral septal nucleus, NTS, and hypothalamic arcuate nucleus, consistent with its pronounced central effects on appetite (Du et al., 2022; West et al., 2025). The degree of CNS penetration appears to be an important determinant of neuroprotective efficacy across experimental models.

6.2 Alzheimer's Disease

Alzheimer's disease (AD) — the most common neurodegenerative disorder, affecting approximately 55 million people worldwide — shares profound pathophysiological overlap with T2DM. Both conditions feature insulin resistance, impaired glucose metabolism, oxidative stress, mitochondrial dysfunction, neuroinflammation, and dysregulated autophagy; indeed, the term 'type 3 diabetes' has been applied to AD in recognition of the central role of brain insulin resistance in its pathogenesis (Du et al., 2022). Postmortem analyses of AD brains consistently demonstrate significantly reduced expression of insulin receptors, IRS-1, IRS-2, PI3K, and phosphorylated Akt compared with age-matched controls — findings recapitulated in animal models of T2DM with concomitant AD pathology.

In preclinical models of AD, GLP-1 RAs have demonstrated remarkably comprehensive neuroprotection across multiple pathological domains. With respect to amyloid pathology, exendin-4, liraglutide, lixisenatide, and semaglutide reduce APP processing and A β production, decrease A β plaque load in APP/PS1 transgenic mice, and attenuate A β oligomer-induced impairment of LTP (Du et al., 2022). In relation to tau pathology, GLP-1 RAs reduce hyperphosphorylation of tau through inhibition of GSK-3 β — the primary kinase responsible for pathological tau phosphorylation — via PI3K/Akt-mediated phosphorylation of the GSK-3 β inhibitory site (Ser9), thereby preventing tau aggregation into neurofibrillary tangles (Du et al., 2022). GLP-1 RAs also suppress microglial activation and astrogliosis, reduce pro-inflammatory cytokine levels (TNF- α , IL-1 β , IL-6) in cortex and hippocampus, attenuate oxidative stress by upregulating antioxidant enzymes (SOD1, GPx1), rescue mitochondrial function and biogenesis, promote neurogenesis in the dentate gyrus, enhance synaptic plasticity and LTP, restore calcium homeostasis disrupted by A β , and activate autophagic clearance of protein aggregates (Du et al., 2022; Mehdi et al., 2023).

Despite this compelling preclinical evidence, translation to clinical benefit has been partial. A systematic review and meta-analysis of four RCTs — evaluating liraglutide (two trials) and exenatide (two trials) in patients with mild cognitive impairment or early AD — found no statistically significant changes in amyloid or tau biomarkers in CSF or on PET imaging, and no significant improvements on primary cognitive endpoints including ADAS-cog and MMSE (Liang et al., 2024). Potential explanations include insufficient drug concentrations in the CNS, trial duration too short for disease-modifying effects to manifest, recruitment of patients at stages where neurodegeneration is already advanced, and the possibility that GLP-1 RA effects may be primarily metabolic and preventive rather than curative. Notably, however, a 26-week double-blind placebo-controlled trial of liraglutide in 38 patients with early AD demonstrated statistically significant prevention of the expected decline in cerebral glucose metabolism (measured by FDG-PET) in frontal, parietal,

temporal, occipital, and precuneus cortices — regions characteristically affected in early AD — alongside trends toward improved hippocampal connectivity on fMRI (Liang et al., 2024). The EVOKE trial, evaluating oral semaglutide 14 mg daily in cognitively normal participants at elevated AD risk over two years, is ongoing and represents the most definitive prospective test of GLP-1 RA neurological disease modification (Nauck et al., 2026).

6.3 Parkinson's Disease

The epidemiological relationship between T2DM and Parkinson's disease (PD) — characterised by a 34–40% increased risk of PD in individuals with T2DM, worsening of motor symptoms in diabetic PD patients, and shared alterations in insulin signalling, mitochondrial function, and neuroinflammation — has provided a strong rationale for GLP-1 RA investigation in PD (Kalinderi et al., 2024). GLP-1Rs are expressed in dopaminergic neurons of the substantia nigra pars compacta and in the striatum, where they modulate dopaminergic neurotransmission, neuroinflammatory cascades, and autophagy pathways critical to PD pathogenesis.

Preclinical evidence from MPTP and 6-OHDA rodent models — the most widely used models of dopaminergic neurodegeneration — demonstrates that GLP-1 RAs protect against the selective loss of tyrosine hydroxylase (TH)-positive neurons in the substantia nigra and restore striatal dopamine levels and motor function. The mechanisms involve: suppression of microglial activation and NLRP3 inflammasome-driven neuroinflammation via AMPK/NF- κ B inhibition; enhancement of mitochondrial biogenesis and dynamics through PGC-1 α upregulation; promotion of autophagic clearance of α -synuclein aggregates (the pathological hallmark of PD) via suppression of mTOR/Akt and enhancement of LC3-II expression; reduction of ROS through Nrf-2 activation; and inhibition of apoptotic cascades by increasing Bcl-2/Bax ratios and reducing caspase-3 activity (Kalinderi et al., 2024). Notably, semaglutide demonstrated superior efficacy over liraglutide in restoring TH levels in MPTP models, and dual GLP-1/GIP receptor agonists outperformed monoagonists in several comparative studies (Kalinderi et al., 2024).

Clinical evidence from randomised trials is encouraging and mechanistically plausible. The first open-label, randomised trial (NCT01174810) of exenatide twice daily in 45 patients with moderate PD on stable dopaminergic therapy demonstrated significant improvements in MDS-UPDRS motor score and Mattis Dementia Rating Scale-2 at 14 months, with benefits persisting through a 12-week washout period — a pattern consistent with disease modification rather than symptomatic masking (Kalinderi et al., 2024). A subsequent double-blind, placebo-controlled phase II trial (NCT01971242, $n = 60$) confirmed superior off-medication motor control at 48 weeks with once-weekly exenatide (Kalinderi et al., 2024). The multicentre, randomised, placebo-controlled LIXIPARK trial (NCT03439943) evaluated daily lixisenatide in early PD ($n = 156$) and demonstrated significantly less motor disability on MDS-UPDRS III in both ON and OFF medication states after 12 months, with a mean between-group difference of -3.08 points (95% CI: -5.36 to -0.80 ; $p = 0.007$) — representing a clinically meaningful and statistically significant benefit (Kalinderi et al., 2024). Phase III evaluation of exenatide extended release (Exenatide-PD3, NCT04232969) and phase II trials of semaglutide (NCT03659682) and the modified exenatide formulation NLY01 (NCT04154072) are ongoing.

6.4 Addictive Disorders

The application of GLP-1 RAs to addictive behaviours represents an unexpected but mechanistically coherent extension of their CNS activity. GLP-1Rs are expressed in key nodes of the mesolimbic dopaminergic reward circuit — the VTA, NAc (core and shell), NTS, lateral septum, laterodorsal tegmental nucleus, and prefrontal cortex — regions whose dysregulation underlies the pathological reward processing, craving, and compulsive drug-seeking characteristic of substance use disorders (Klausen et al., 2022). GLP-1 produced in the NTS projects directly to the VTA and NAc, where it modulates dopaminergic tone through both presynaptic (reducing VTA firing rate) and postsynaptic (modulating AMPA receptor trafficking in NAc neurons) mechanisms, effectively 'dampening' the exaggerated dopamine responses that characterise addicted states.

Preclinical evidence for GLP-1 RA efficacy in addiction is extensive and spans multiple substances. Regarding alcohol, systemic exenatide reduces voluntary alcohol intake in two-bottle choice paradigms, operant alcohol self-administration, and alcohol-conditioned place preference in rats and mice; non-human primate studies demonstrated that both exenatide and liraglutide reduced alcohol consumption in alcohol-preferring African vervet monkeys over 5 and 2 weeks respectively without inducing emesis (Klausen et al., 2022). Long-acting dulaglutide reduced alcohol intake for up to 9 weeks without tolerance development. The effects are centrally mediated: ablation of CNS GLP-1Rs eliminates the anti-alcohol effects of systemically

administered exenatide, and direct infusion into the VTA, NTS, NAc shell, and laterodorsal tegmental nucleus replicates systemic effects (Klausen et al., 2022). For cocaine, exenatide suppresses self-administration, conditioned place preference, and reinstatement of cocaine-seeking in rodents, and attenuates cocaine-induced dopamine release in the NAc and lateral septum. For nicotine, exenatide and sitagliptin reduced intravenous nicotine self-administration and attenuated nicotine-induced locomotor sensitisation and conditioned place preference (Klausen et al., 2022).

Clinical translation remains at an early stage. A randomised pilot trial demonstrated that exenatide 2.0 mg weekly combined with transdermal nicotine replacement therapy increased 12-week smoking abstinence and reduced post-cessation weight gain compared with nicotine replacement alone (Klausen et al., 2022). A randomised, double-blinded, placebo-controlled trial of once-weekly exenatide in 127 patients with alcohol use disorder (NCT03232112) completed enrolment, with results awaited; a post-hoc analysis indicated that the anti-alcohol benefit may be preferentially observed in obese patients with insulin resistance — a phenotype particularly relevant to metabolic-psychiatric comorbidity (Klausen et al., 2022). Population-level pharmacoepidemiological data have also reported associations between GLP-1 RA prescriptions and lower rates of alcohol-related hospitalisation and opioid overdose, though confounding by indication limits causal inference (Nauck et al., 2026).

7. Anti-Inflammatory and Immunomodulatory Effects

7.1 Molecular Mechanisms of Immunomodulation

Chronic low-grade inflammation is a central feature shared by obesity, T2DM, cardiovascular disease, neurodegenerative disorders, and non-alcoholic fatty liver disease — all conditions for which GLP-1 RAs have demonstrated clinical benefit. The anti-inflammatory actions of GLP-1 RAs operate through both direct receptor-mediated mechanisms on immune and structural cells and indirect suppression of the inflammatory milieu secondary to weight loss, glycaemic improvement, and reduced lipotoxicity (Lee & Jun, 2016; Mehdi et al., 2023).

At the molecular level, GLP-1R activation increases intracellular cAMP and activates PKA, which phosphorylates and inactivates the inhibitor of κ B kinase (IKK), preventing I κ B degradation and consequent NF- κ B nuclear translocation — the master transcriptional programme driving expression of TNF- α , IL-1 β , IL-6, IL-12, MCP-1, and inducible nitric oxide synthase (iNOS) (Lee & Jun, 2016). Complementarily, GLP-1 RAs activate AMPK — an energy sensor that suppresses the NLRP3 inflammasome complex independently of NF- κ B — reducing caspase-1 activation and the maturation of IL-1 β and IL-18 in macrophages and astrocytes (Mehdi et al., 2023). GLP-1 RAs also attenuate Toll-like receptor 4 (TLR-4) signalling in macrophages stimulated by lipopolysaccharide — the canonical innate immune pathway activated during gram-negative infection and by circulating bacterial products (leaky gut) in metabolic disease — thereby reducing TNF- α , IL-6, and COX-2 expression (Mehdi et al., 2023; Lee & Jun, 2016).

GLP-1Rs are expressed on innate and adaptive immune cells including macrophages (where agonism promotes M2 anti-inflammatory polarisation), dendritic cells, T-regulatory (Treg) cells, natural killer cells, and neutrophils (Mehdi et al., 2023). In T2DM murine models, exenatide increased pancreatic islet Treg cell frequency and reduced insulinitis, suggesting potential relevance in type 1 diabetes and immune-mediated beta-cell destruction. Systemically, GLP-1 RA treatment consistently reduces circulating levels of hsCRP — by 25–43% with semaglutide in a dose-dependent fashion across STEP trials — alongside reductions in TNF- α , IL-6, and oxidised LDL, markers that predict cardiovascular events and organ damage independently of traditional risk factors (Mehdi et al., 2023; Nevola et al., 2023).

7.2 Hepatic Effects: MASLD and NASH

Metabolic dysfunction-associated steatotic liver disease (MASLD) — encompassing the spectrum from simple steatosis through non-alcoholic steatohepatitis (NASH) to cirrhosis and hepatocellular carcinoma — represents the most prevalent liver disorder worldwide, affecting an estimated 32.4% of the global population and up to 70% of patients with T2DM (Nevola et al., 2023). In the absence of pharmacological therapies with regulatory approval specifically for MASLD (as of the time of this review), GLP-1 RAs have emerged as highly promising candidates on the basis of their combined metabolic, anti-inflammatory, and direct hepatic mechanisms.

Weight reduction is an established therapeutic target in MASLD: a weight loss of ≥ 7 –10% significantly improves hepatic steatosis, lobular inflammation, hepatocyte ballooning, and fibrosis stage on biopsy (Nevola

et al., 2023). GLP-1 RAs achieve clinically meaningful weight loss across the therapeutic spectrum (1.5–6 kg at diabetes doses; up to 17.4% with semaglutide 2.4 mg weekly), and this weight reduction is associated with proportional improvements in hepatic fat content as quantified by MRI spectroscopy. Liraglutide reduced liver fat by 44% versus placebo in a controlled MRI study in PCOS patients, and the STEP-8 trial demonstrated that 70.9% of semaglutide-treated patients achieved >10% weight loss — the hepatologically meaningful threshold — compared with only 25.6% in the liraglutide group (Nevola et al., 2023).

The landmark LEAN trial (Liraglutide Efficacy and Action in Non-alcoholic steatohepatitis) enrolled 52 adults with biopsy-confirmed NASH randomised to liraglutide 1.8 mg daily or placebo for 48 weeks. The primary endpoint — histological NASH resolution without worsening of fibrosis — was achieved in 39% of the liraglutide group versus 9% of the placebo group (relative risk 4.5; 95% CI: 1.1–18.9; $p = 0.017$). Furthermore, fibrosis progression occurred in only 9% of liraglutide-treated patients versus 36% of the placebo group ($p = 0.04$), representing the first randomised evidence that a GLP-1 RA could retard hepatic fibrogenesis in NASH (Nevola et al., 2023). A subsequent phase II trial ($n = 320$) evaluated semaglutide at three doses (0.1, 0.2, 0.4 mg daily) versus placebo in biopsy-confirmed NASH over 72 weeks. NASH resolution without fibrosis worsening was achieved in 40%, 36%, and 59% of semaglutide dose groups versus 17% placebo ($p < 0.001$ for 0.4 mg dose), and the NAFLD activity score improved in 83% of the 0.4 mg group versus 44% placebo — although no significant difference in fibrosis stage improvement was observed in this trial, likely due to insufficient duration and power (Nevola et al., 2023).

Direct hepatocyte mechanisms of GLP-1 RAs have been identified independently of weight loss. GLP-1R expression has been confirmed in human hepatocytes, where receptor activation promotes AKT phosphorylation and downstream suppression of de novo lipogenesis through AMPK-mediated inhibition of acetyl-CoA carboxylase and fatty acid synthase (Nevola et al., 2023). Activation of the farnesoid X receptor (FXR) and liver X receptor (LXR) pathways by GLP-1 RA-mediated signalling further suppresses hepatic lipogenesis and reduces inflammation. GLP-1 RAs also enhance autophagy-dependent lipid degradation via the TFEB-regulated autophagy-lysosomal pathway, and reduce endoplasmic reticulum stress-mediated hepatocyte apoptosis — a key driver of NASH progression. Liraglutide reduces hepatic expression of PPAR- γ (an adipogenic transcription factor overexpressed in NASH), restoring physiological lipid homeostasis (Nevola et al., 2023). The suppression of three of five collagen biosynthesis genes by semaglutide in murine NASH models provides a plausible mechanistic explanation for the observed anti-fibrotic trend in clinical trials, and supports the hypothesis that longer treatment durations may demonstrate more robust fibrosis regression.

7.3 Pulmonary, Dermatological, and Systemic Effects

GLP-1Rs are distributed throughout the respiratory system, expressed in airway smooth muscle cells, bronchial epithelial cells, vascular endothelium of pulmonary arteries, and alveolar type II pneumocytes (Mehdi et al., 2023). In asthma and chronic obstructive pulmonary disease (COPD) models, GLP-1 RAs attenuate airway inflammation by suppressing NF- κ B-mediated cytokine release (IL-5, IL-13, IL-33), reducing eosinophil, neutrophil, and basophil infiltration into bronchoalveolar lavage fluid, inhibiting mast cell degranulation, and inducing bronchodilation through cAMP-mediated smooth muscle relaxation. Exenatide increases FOXA2 expression in airway epithelium, restoring mucus homeostasis and reducing goblet cell hyperplasia — a pathological feature of asthma and COPD. In the LIRALUNG randomised crossover trial, liraglutide significantly improved forced vital capacity compared with placebo in adults with T2DM (Mehdi et al., 2023). In acute lung injury models, liraglutide downregulated NLRP3 inflammasome activation, reduced bronchoalveolar concentrations of IL-1 β and IL-18, and increased surfactant protein A (SPA) expression in type II pneumocytes via the TTF-1 signalling pathway (Mehdi et al., 2023).

In dermatology, GLP-1R upregulation has been identified in psoriatic skin lesions compared with uninvolved skin, providing a direct tissue target for GLP-1 RA therapy (Mehdi et al., 2023). In patients with concurrent T2DM and psoriasis, liraglutide treatment reduced the Psoriasis Area and Severity Index (PASI) score, and histopathological analysis of psoriatic plaques after 12 weeks of liraglutide demonstrated reduced epidermal thickness, decreased dermal inflammatory infiltrate, and evidence of lesion resolution — attributed mechanistically to suppression of the IL-23/Th-17 axis, a central driver of psoriatic inflammation (Mehdi et al., 2023). Semaglutide has also been reported to dramatically improve severe psoriasis in a T2DM patient in a case report, with effects potentially exceeding those attributable to weight loss alone. In wound healing, exenatide normalises the elevated MMP-9/TIMP-1 ratio in diabetic foot ulcers — a biomarker of impaired wound closure — and reduces wound fluid CRP, accelerating healing in patients with chronic diabetic wounds (Mehdi et al., 2023).

8. Emerging and Future Therapeutic Applications

8.1 Obstructive Sleep Apnoea

Obstructive sleep apnoea (OSAS) affects an estimated 1 billion adults worldwide and is strongly associated with obesity — with a prevalence exceeding 50% in individuals with severe obesity. OSAS is an independent risk factor for cardiovascular disease, hypertension, and metabolic dysfunction, establishing a compelling rationale for weight-loss-driven intervention. The SURMOUNT-OSA programme enrolled patients with obesity and moderate-to-severe OSAS (apnoea-hypopnoea index [AHI] ≥ 15 events/hour) in two parallel phase III trials stratifying by CPAP use. Tirzepatide 15 mg weekly achieved a 55.0% reduction in AHI in participants not using CPAP and 49.5% in CPAP users, compared with placebo reductions of approximately 5%. Notably, approximately 42% of tirzepatide-treated participants achieved complete OSAS resolution (AHI < 5 events/hour) compared with $< 5\%$ in the placebo group, alongside significant improvements in hypoxic burden, sleep architecture, and patient-reported outcomes (Nauck et al., 2026). While the predominant mechanism is weight-loss-mediated reduction in upper airway adiposity, emerging evidence from animal models also suggests a direct GLP-1R-mediated effect on respiratory neuromuscular control, which may contribute independently to AHI reduction.

8.2 Knee Osteoarthritis

A recent randomised placebo-controlled trial of semaglutide in patients with knee osteoarthritis and overweight or obesity demonstrated a significant reduction in the WOMAC pain score (primary endpoint) compared with placebo, alongside improvements in physical function and global assessment. Post-hoc analyses suggested that the magnitude of pain reduction exceeded that predicted by the degree of weight loss alone, raising the possibility of direct anti-inflammatory or chondroprotective effects mediated via GLP-1R signalling in synoviocytes and chondrocytes (Nauck et al., 2026). GLP-1R expression has been reported in synovial tissue and articular chondrocytes in preclinical studies, where agonism reduces IL-1 β -driven matrix metalloproteinase production and promotes anabolic signalling — mechanistic pathways that merit dedicated investigation in future clinical trials.

8.3 Next-Generation Dual and Triple Agonists

The pharmacological evolution beyond selective GLP-1 RAs is progressing rapidly. Tirzepatide — the first approved dual GIP/GLP-1 receptor agonist — has demonstrated superiority over semaglutide in both T2DM (SURPASS-2: -0.45 percentage point greater HbA1c reduction; -5.5 kg greater weight loss; $p < 0.001$ for both) and obesity (SURMOUNT-1: mean weight loss 20.9% with 15 mg vs 14.9% with lower doses), and is now indicated for T2DM and chronic weight management (Liu, 2024; Nevola et al., 2023). In preclinical models of AD and PD, dual GLP-1/GIP receptor agonists consistently outperform monoagonists — demonstrating greater reductions in neuroinflammation, A β plaque load, and α -synuclein aggregation — suggesting that GIP receptor co-agonism may have additive neuroprotective properties (Du et al., 2022; Kalinderi et al., 2024).

Triple receptor agonists targeting GLP-1, GIP, and glucagon receptors simultaneously — including retatrutide (phase III) and investigational unimolecular triagonists — have demonstrated mean weight losses of up to 24% in phase II trials, superior hepatic fat reduction compared with monoagonists or dual agonists in NASH models, and favourable metabolic profiles combining the weight-loss amplification of glucagon receptor agonism with the glycaemic protection of GLP-1 and GIP co-activation (Nauck et al., 2026). CagriSema (subcutaneous cagrilintide plus semaglutide), combining GLP-1 RA with an amylin analogue, achieved up to 25% weight loss in phase III — approaching the efficacy of bariatric surgery (Nauck et al., 2026). Non-peptide oral GLP-1 RAs represent a further transformative development: orforglipron, a small-molecule oral GLP-1R agonist not requiring food-restricted SNAC-mediated absorption, demonstrated HbA1c reductions of up to 2.1% and weight loss of approximately 14.7% in phase II trials across T2DM and obesity cohorts, with a side-effect profile consistent with the class (Nauck et al., 2026). If validated in ongoing phase III programmes, non-peptide oral GLP-1 RAs could dramatically expand access to GLP-1 RA therapy in populations with injection aversion or limited healthcare access.

8.4 Limitations and Gaps in Current Evidence

Despite the breadth and consistency of evidence reviewed, several important methodological and clinical limitations must be acknowledged. First, separating the direct, weight-independent receptor-mediated effects of GLP-1 RAs from those attributable to weight loss and glycaemic improvement remains methodologically challenging; most CVOTs and renal outcome trials did not include weight-matched control groups, and pharmacodynamic adjustments for confounders are imprecise. Second, neurological applications — while mechanistically compelling and supported by consistent preclinical evidence — have not yet been convincingly established in adequately powered, long-duration RCTs in AD or PD; the EVOKE trial and ongoing PD phase III studies will be definitive. Third, the long-term durability of organ protection after discontinuation of GLP-1 RAs is largely unknown: the STEP-4 trial demonstrated substantial weight regain after semaglutide cessation, raising questions about whether cardiovascular and renal benefits are similarly reversible. Fourth, safety in specific populations — including those with advanced HFrEF, active autoimmune disease, inflammatory bowel disease, and end-stage renal disease — has not been systematically characterised. Fifth, the substantial cost of GLP-1 RAs and their often-restricted reimbursement represent a major access and health equity challenge, with potentially the largest unmet need in precisely those populations — socioeconomically disadvantaged, with high obesity burden and multiple comorbidities — who might benefit most. Finally, pharmacogenomic predictors of GLP-1 RA response, including GLP1R gene variants, remain incompletely characterised and are not yet clinically actionable.

9. Conclusions

GLP-1 receptor agonists have undergone a remarkable transformation from incretin-based antidiabetic agents to a versatile class of pleiotropic, disease-modifying drugs with documented or emerging benefits across cardiovascular, renal, neurological, hepatic, pulmonary, and immunological domains. The convergence of large-scale clinical trial evidence — encompassing CVOTs demonstrating 13–14% MACE reductions, the FLOW trial demonstrating 24% composite renal endpoint reduction, the STEP-HFrEF and SUMMIT trials establishing HFrEF efficacy, the SELECT trial extending cardiovascular benefit beyond diabetes, and the LIXIPARK trial providing the most rigorous PD evidence to date — with a mechanistic understanding rooted in the broad tissue distribution of GLP-1Rs, provides a coherent and compelling framework for this expanded therapeutic potential.

Cardiovascular protection, now established across both secondary and primary prevention contexts in cardiometabolic risk populations, has repositioned GLP-1 RAs as central components of multi-drug cardiometabolic management strategies. Renal protection, additive to SGLT-2 inhibitors and RAAS blockade, positions GLP-1 RAs as a third pillar of DKD pharmacotherapy. The neurological data — while requiring further validation — offer a scientifically grounded rationale for the hypothesis that GLP-1 RAs may represent the first viable pharmacological approach to disease modification in Alzheimer's disease, Parkinson's disease, and potentially substance use disorders. Anti-inflammatory properties spanning hepatic, pulmonary, dermatological, and systemic domains further broaden the clinical indications of this drug class beyond metabolic disease.

The pipeline of next-generation agents — tirzepatide, retatrutide, CagriSema, orforglipron, and investigational triple agonists — promises continued innovation and expansion of the therapeutic scope of incretin pharmacology. However, this optimism must be tempered by the recognition of significant remaining uncertainties: the weight-independence of organ-protective effects, optimal patient selection and treatment duration, long-term safety in vulnerable populations, reversibility of benefits upon discontinuation, and the urgent need for equitable access in clinical practice. The field demands mechanism-focused trials that disentangle direct receptor effects from metabolic confounders, long-term follow-up studies establishing the durability of organ protection, and implementation research that ensures GLP-1 RA therapy reaches the broadest possible spectrum of at-risk individuals. In sum, GLP-1 receptor agonists stand at the frontier of multi-organ medicine, offering a unique and historically unprecedented opportunity to simultaneously address the metabolic, cardiovascular, renal, and neurological burden of the global obesity and diabetes pandemic.

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