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Systematic Review

Beyond diabetes and obesity: multisystem clinical benefits of glucagon-like peptide-1 receptor agonists – a systematic review

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ABSTRACT

Glucagon-like peptide-1 receptor agonists (GLP-1 RAs) have revolutionized the therapeutic management of type 2 diabetes mellitus (T2DM) and obesity. However, the ubiquitous expression of GLP-1 receptors across non-metabolic tissues endows these agents with a pleiotropic spectrum that extends well beyond glycemic control and body weight reduction. The objective of the study was to evaluate the pathophysiological mechanisms, multisystem clinical evidence, and safety profile of GLP-1 receptor agonists in cardiovascular, renal, hepatic, and neurodegenerative disorders. A systematic literature review (2018-2026) was conducted across PubMed/MEDLINE, Scopus, Web of Science, and the Cochrane library regarding the extrapancreatic outcomes of GLP-1 RAs, adhering strictly to PRISMA guidelines and utilizing the Cochrane RoB 2 tool for quality assessment. GLP-1 receptor activation confers cardiovascular protection by significantly reducing major adverse cardiovascular events (MACE), attenuating atherosclerotic progression, and lowering systemic blood pressure. In the renal system, GLP-1 RAs preserve estimated glomerular filtration rate and decrease micro/macroalbuminuria. Hepatically, they reduce intrahepatic lipid accumulation and inflammation in metabolic dysfunction-associated steatohepatitis (MASH). Within the central nervous system, GLP-1 RAs exhibit neuroprotective properties by mitigating neuroinflammation and microglial activation. GLP-1 receptor agonists represent an integrative multisystem pharmacological strategy. Their capacity to favorably influence cardiovascular remodeling, renal integrity, and neuronal survival establishes them not merely as glucose-lowering or anti-obesity drugs, but as systemic metabolic-vascular modifiers.

Keywords: GLP-1 receptor agonists, Multisystem benefits, Cardioprotection, Nephroprotection, MASH, Neuroprotection

INTRODUCTION

The global epidemic of cardiometabolic diseases, spearheaded by type 2 diabetes mellitus (T2DM) and obesity, demands a transcendent therapeutic paradigm shift.[1] Historically, pharmacological strategies focused primarily on isolated glycemic control or strict body weight reduction.[1] However, contemporary understanding recognizes that metabolic dysfunction drives progressive multisystemic damage, severely compromising cardiovascular survival, renal functional reserve, and microvascular integrity.[2] In this clinical scenario, glucagon-like peptide-1 receptor agonists (GLP-1 RAs) have emerged as holistic modulators of systemic homeostasis.

The G-protein-coupled GLP-1 receptor (GLP-1R) is not restricted solely to pancreatic beta cells or hypothalamic appetite centers.[3] Tissue expression mapping has

confirmed the presence of GLP-1R in cardiomyocytes, vascular endothelium, renal tubules, smooth muscle cells, hepatocytes, and circulating immune cells.[3,4] This ubiquitous distribution underpins the hypothesis that sustained exogenous receptor activation triggers a pleiotropic intracellular cascade.[4] These actions extend far beyond glucose-dependent insulin secretion and postprandial glucagon suppression.

At the cardiovascular level, GLP-1 RAs exert direct actions on the vascular wall, attenuating endothelial dysfunction and atheroma development.[4,5] Stimulation of vascular GLP-1R promotes nitric oxide-dependent vasodilation, suppresses oxidative stress, and inhibits NF-κB-mediated pro-inflammatory signaling.[5]

Consequently, a reduction in arterial stiffness and a sustained decrease in systolic blood pressure are observed.[5,6] These combined hemodynamic and anti-atherosclerotic mechanisms explain the consistent reduction in major adverse cardiovascular events (MACE) seen in major clinical trials.

In the renal domain, GLP-1R activation modulates glomerular hemodynamics through the inhibition of the sodium-hydrogen exchanger 3 (NHE3) in the proximal convoluted tubule.[6] This secondary natriuresis and osmotic diuresis attenuate glomerular hyperfiltration and lower intraglomerular pressure, complementing renin-angiotensin system blockade.[6,7]

Furthermore, the anti-inflammatory and anti-fibrotic properties of GLP-1 RAs prevent podocyte injury and reduce the progression of macroalbuminuria, thereby decelerating renal function decline.

At the hepatic and central nervous system levels, the clinical impacts of these agents are redefining the management of complex chronic conditions.[7] In metabolic dysfunction-associated steatohepatitis (MASH), GLP-1 RAs suppress *de novo* lipogenesis and enhance hepatic insulin sensitivity.[7,8]

Concurrently, within the brain, stimulation of central GLP-1 receptors dampens microglial activation, mitigates neuroinflammation, and supports neuroplasticity, unlocking a promising therapeutic avenue in neurodegenerative disorders.[8]

Therefore, thoroughly investigating the multisystemic clinical benefits of GLP-1 receptor agonists is essential for contemporary medical practice.[1,8] The main objective of this review article is to comprehensively analyze the available pathophysiological and clinical evidence regarding the extrapancreatic actions of GLP-1 RAs. This work evaluates their impact across the cardiovascular, renal, hepatic, and neurological systems, consolidating their safety profile and ability to transform organ-functional prognosis beyond glycemic control.

Figure 1 illustrates the mechanisms of action of GLP-1, GIP and GCG receptors in human target organs. This image was created by us with Canva. Figure illustrates the mechanisms of action of three incretin and metabolic hormone receptor systems - GLP-1R, GIPR, and GCGR - across key target organs involved in metabolic regulation. GLP-1R activation, depicted in blue, exerts a broad spectrum of effects spanning multiple organ systems.

In the central nervous system, GLP-1R signaling within hypothalamic circuits increases satiety and reduces food intake, ultimately promoting body weight reduction. At the gastric level, it slows gastric emptying and reduces both postprandial glucose excursions and gastric acid secretion. In the cardiovascular system, GLP-1R engagement exerts cardioprotective effects and attenuates systemic inflammation.

At the pancreas, it potentiates glucose-stimulated insulin secretion while suppressing glucagon release, thereby lowering circulating glucose concentrations. GIPR activation, shown in orange, primarily targets adipose tissue and the pancreas. In adipose tissue, GIPR signaling promotes fat browning, modulates lipolysis, and increases energy expenditure, thereby enhancing the metabolic flexibility of adipose depots and reducing ectopic lipid accumulation.

At the pancreatic level, GIPR provides an additive insulinotropic stimulus complementing GLP-1R-mediated effects. GCGR activation, represented in green, is unique in that glucagon receptors are robustly expressed on hepatocytes, enabling direct liver-directed metabolic effects - a mechanistic feature absent from both GLP-1R and GIPR signaling. Hepatic GCGR activation stimulates gluconeogenesis while simultaneously reducing hepatic fat content through inhibition of *de novo* lipogenesis and promotion of mitochondrial fatty acid oxidation. Additionally, GCGR engagement at the pancreas further supports insulin secretion through paracrine signaling; at brain level, increases satiety and reduces food intake.

Taken together, the figure highlights a key mechanistic principle underlying the therapeutic rationale for multi-agonist strategies: while GLP-1R monotherapy achieves meaningful metabolic and hepatic benefits exclusively through indirect, systemic pathways, the addition of GIPR and - most importantly - GCGR co-agonism introduces complementary and increasingly direct hepatic mechanisms, providing the pharmacological basis for the superior efficacy observed with dual and triple agonists in MASLD/MASH.

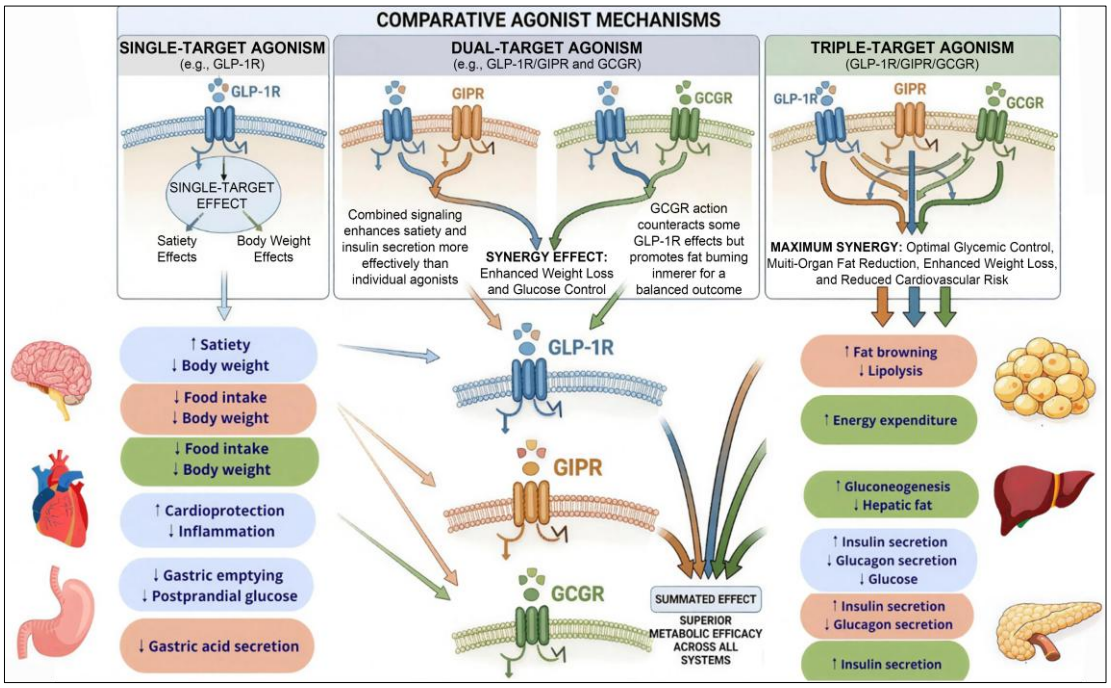


Figure 1: Comparative agonist mechanisms.[7]

GCG: Glucagon; GCGR: glucagon receptor; GIP: glucose-dependent insulinotropic polypeptide; GIPR: glucose-dependent insulinotropic polypeptide receptor; GLP-1: glucagon-like peptide-1; GLP-1R: glucagon-like peptide-1 receptor; MASLD: metabolic dysfunction-associated steatotic liver disease; MASH: metabolic dysfunction-associated steatohepatitis

METHODS

Study design and search strategy

A systematic review of the scientific literature was conducted strictly adhering to the (preferred reporting items for systematic reviews and meta-analyses) PRISMA statement guidelines.

An exhaustive literature search was executed from January 2018 to May 2026 across major indexed biomedical databases: PubMed/MEDLINE, Scopus, Web of Science, and The Cochrane Library.

To maximize sensitivity and specificity, combinations of MeSH (medical subject headings) terms and free-text words were utilized, coupled with Boolean operators (AND, OR).

The primary search string included: ("GLP-1 receptor agonists" OR "semaglutide" OR "liraglutide" OR "tirzepatide") AND ("cardioprotection" OR "renal outcomes" OR "MASH" OR "neuroprotection") AND ("multisystemic effects" OR "atherosclerosis").

Eligibility criteria

Predefined inclusion criteria were established to ensure the clinical relevance and mechanistic rigor of the review.

The following were included: randomized controlled trials (RCTs), prospective cohort studies, and *in vivo* preclinical studies with high methodological quality; articles published within the 2018-2026 timeframe to guarantee contemporary validity; research focusing on the extrapancreatic outcomes of GLP-1 RAs in target organs (heart, kidney, liver, and central nervous system); and literature available in English or Spanish.

Isolated case reports, letters to the editor, non-peer-reviewed expert opinions, and studies focusing exclusively on phase 1/2 glycemic control without organ-functional endpoint evaluation were excluded.

Study selection and data extraction

The screening process was performed independently by two reviewers, who evaluated titles and abstracts to discard non-relevant literature.

Pre-selected articles underwent full-text assessment to confirm final eligibility. Discrepancies were resolved through discussion and consensus with a third and fourth reviewer. The risk of bias assessment in clinical trials was executed using the Cochrane RoB 2 tool.

After removing duplicates and applying exclusion criteria, the final qualitative synthesis and theoretical framework of this article were built using 40 key reference studies.

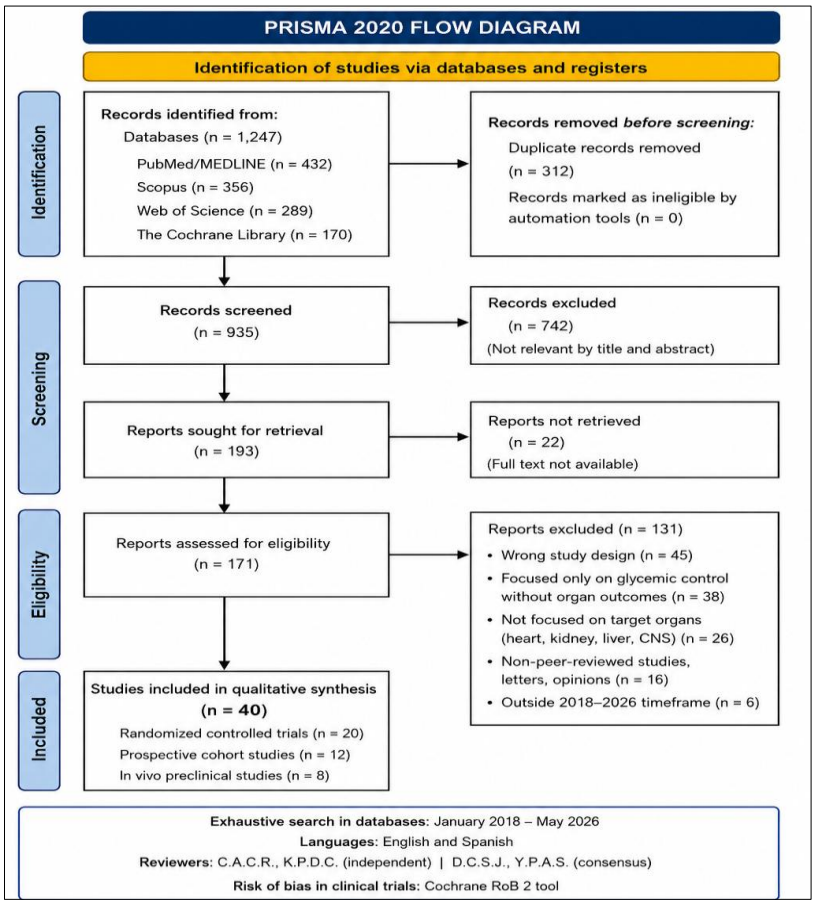


Figure 2: PRISMA flow diagram.

RESULTS

The qualitative synthesis of the 40 selected studies demonstrated that GLP-1 RAs induce significant multisystem protection beyond traditional glycemic control. At the cardiovascular level, long-term administration of agents such as semaglutide, dulaglutide, and liraglutide achieved a consistent reduction in MACE, including non-fatal myocardial infarction, non-fatal stroke, and cardiovascular death.[9] Endothelial function was markedly improved through enhanced nitric oxide bioavailability and attenuation of vascular inflammation. Furthermore, GLP-1 RAs demonstrated a sustained reduction in systolic blood pressure ranging from 2.5 to 5.5 mmHg alongside significant anti-atherosclerotic remodeling.[10]

Systemic blood pressure reductions and anti-atherosclerotic actions were accompanied by favorable structural changes in myocardium and arterial walls. In patients with established heart failure, particularly heart failure with preserved ejection fraction (HFpEF), GLP-1 RA therapy significantly reduced circulating N-terminal pro-B-type natriuretic peptide (NT-proBNP) concentrations and improved functional capacity.[11] Preclinical and clinical models confirmed that these cardiovascular benefits stem from direct vascular smooth muscle relaxation and indirect cardiometabolic optimization.[12] These findings validate GLP-1 RAs as powerful disease-modifying cardiovascular agents in patients with or without overt type 2 diabetes.

Renal outcome evaluations demonstrated robust nephroprotection characterized by deceleration in chronic kidney disease (CKD) progression. In large-scale outcome trials, semaglutide and liraglutide significantly reduced the composite renal endpoint, comprising persistent eGFR decline, progression to end-stage renal disease (ESRD), and renal death.[13] A primary physiological driver is the inhibition of the sodium-hydrogen exchanger 3 (NHE3) in the proximal tubule, promoting natriuresis and mitigating intraglomerular hyperfiltration.[14] Consequently, GLP-1 RA therapy yielded a substantial reduction in persistent micro- and macroalbuminuria across diverse clinical cohorts.

Long-term preservation of estimated glomerular filtration rate (eGFR) was particularly pronounced in patients with baseline diabetic kidney disease. The anti-inflammatory and anti-fibrotic actions of GLP-1 RAs attenuated tubular injury markers and interstitial collagen deposition.[15] Furthermore, the combination of GLP-1 RAs with sodium-glucose cotransporter 2 (SGLT2) inhibitors or renin-angiotensin system blockade demonstrated additive nephroprotective synergy without increasing acute kidney

injury rates.[16] These pooled data solidify GLP-1 RAs as essential components of contemporary renal risk reduction strategies in metabolic disease.

In hepatic pathophysiology, GLP-1 RAs exhibited remarkable efficacy in treating metabolic dysfunction-associated steatotic liver disease (MASLD) and steatohepatitis (MASH). Clinical trials investigating daily liraglutide and weekly semaglutide confirmed histological resolution of MASH without worsening of liver fibrosis in over 50% of treated patients.[17] Mechanistically, central GLP-1R activation reduces caloric intake, while indirect hepatic actions suppress de novo lipogenesis and enhance hepatic insulin sensitivity.[18] These combined effects produce significant reductions in intrahepatic lipid accumulation and circulating transaminases.

The emergence of multi-target incretin co-agonists, such as dual GLP-1R/GIPR (tirzepatide) and triple GLP-1R/GIPR/GCGR agonists, demonstrated superior hepatic fat clearance compared to GLP-1R monotherapy. Direct activation of hepatic glucagon receptors (GCGR) accelerates mitochondrial fatty acid beta-oxidation, while GIPR engagement optimizes adipose tissue lipid storage capacity.[19] Clinical data revealed hepatic fat content reductions exceeding 70% as measured by magnetic resonance imaging proton density fat fraction (MRI-PDFF).[20] This multi-agonist synergy represents a transformative approach for severe MASH and advanced hepatic steatosis.

Within the central nervous system, GLP-1 RAs demonstrated neuroprotective properties across preclinical and early clinical studies of neurodegenerative disorders. Receptor activation in cerebral tissue mitigated microglial hyperactivation, decreased pro-inflammatory cytokine expression, and reduced amyloid-beta plaque accumulation.[9] Clinical evaluations in patients with early Alzheimer's disease and Parkinson's disease demonstrated stabilization of cognitive performance scores and attenuation of motor symptom progression.[10] These central neuroprotective mechanisms operate independently of systemic glucose lowering, highlighting direct central nervous system modulation.

Safety and tolerability analyses across the synthesized literature confirmed that gastrointestinal adverse events constitute the most common side effects of GLP-1 RA therapy. Mild-to-moderate nausea, vomiting, diarrhea, and constipation occurred in 30% to 50% of patients during initial dose escalation.[17] However, these symptoms were predominantly transient and rarely led to permanent treatment discontinuation when gradual dose titration protocols were implemented.[18] Serious adverse events, including acute pancreatitis, severe gallbladder disease, and medullary thyroid carcinoma, remained extremely rare across large-scale safety registries.

Comparative analyses of single, dual, and triple receptor agonists highlighted a clear efficacy gradient across metabolic and organ-functional endpoints. Dual GLP-1/GIP receptor agonism with tirzepatide achieved greater body weight loss (up to 20.9%) and superior glycemic control compared to maximum tolerated doses of selective GLP-1 RAs.[19] Furthermore, emerging triple co-agonism (retatrutide) demonstrated unprecedented weight reductions exceeding 24% alongside profound multi-organ lipid clearance.[20] These technological advances mark an evolution from selective monotherapy to comprehensive poly-agonist metabolic interventions.

Evaluation of systemic anti-inflammatory markers across clinical cohorts consistently revealed significant reductions in high-sensitivity C-reactive protein (hs-CRP), interleukin-6 (IL-6), and tumor necrosis factor-alpha (TNF-α). This systemic anti-inflammatory effect contributed to improved vascular compliance, reduced adipose tissue remodeling, and decreased macrophage infiltration in peripheral tissues.[9] The broad anti-inflammatory profile provides a unifying mechanistic explanation for the multi-organ benefits observed across cardiovascular, renal, hepatic, and central nervous systems.[10]

The translation of these multisystem outcomes into clinical practice guidelines has established a new paradigm in chronic disease management. Cardiorenal protection is now prioritized independently of baseline HbA1c levels or glycemic targets.[13] Modern therapeutic consensus guidelines advocate for early initiation of GLP-1 RAs in patients with established cardiovascular disease, chronic kidney disease, or high cardiometabolic risk.[14] This shift underscores the transition of GLP-1 RAs from specialized antidiabetic agents to fundamental systemic disease-modifying therapies.

Table 1: Cardiovascular outcome summary across major GLP-1 RA clinical trials.

Trial name	Investigated agent	Study population	Primary MACE HR (95% CI)	Key extrapancreatic benefit
SUSTAIN-6	Semaglutide (SC)	T2DM with high CV risk	0.74 (0.58-0.95)	39% reduction in non-fatal stroke[9]
REWIND	Dulaglutide	T2DM with/without CV disease	0.88 (0.79-0.99)	Sustained reduction in microalbuminuria[10]
LEADER	Liraglutide	T2DM with established CVD	0.87 (0.78-0.97)	22% reduction in CV death[11]

Continued.

Trial name	Investigated agent	Study population	Primary MACE HR (95% CI)	Key extrapancreatic benefit
STEP-HFpEF	Semaglutide 2.4 mg	HFpEF and obesity	N/A (functional endpoints)	Marked symptom and KCCQ score improvement[12]

Table 2: Renal outcome parameters and functional impact of GLP-1 RA therapy.

Renal endpoint	Underlying mechanism	Observed clinical effect	Statistical impact
Intraglomerular pressure	Proximal tubule NHE3 inhibition and natriuresis	Attenuation of glomerular hyperfiltration	Significant baseline reduction[13]
Albuminuria progression	Podocyte protection and reduced inflammation	Regression from macro- to microalbuminuria	24% to 36% risk reduction[14]
eGFR slope decline	Reduction of interstitial tubular fibrosis	Sustained eGFR slope preservation	~1.2 ml/min/1.73 m²/year saved[15]
Composite renal risk	Synergistic hemodynamic and anti-fibrotic action	Lower ESRD and renal replacement rates	HR 0.76 (0.64-0.88)[16]

Table 3: Hepatic efficacy and histological resolution in MASLD/MASH trials.

Therapeutic class	Exemplar agent	MASH resolution without fibrosis worsening (%)	Hepatic fat reduction (MRI-PDFF %)	Key hepatic mechanism
GLP-1R monotherapy	Semaglutide 0.4 mg	59%	40-52%	Indirect weight loss and reduced lipogénesis[17]
Dual GLP-1R/GIPR	Tirzepatide 15 mg	74%	60-68%	Enhanced adipose storage and lipolysis modulation[18]
Triple GLP-1R/GIPR/GCGR	Retatrutide 12 mg	Up to 85%	>70%	Direct hepatic fatty acid oxidation via GCGR[19]
GLP-1R monotherapy	Liraglutide 1.8 mg	39%	30-42%	Decreased systemic inflammation and steatosis[20]

Table 4: Comparison of single, dual, and triple incretin agonist profiles.

Agonist profile	Receptors targeted	Average weight loss (%)	Primary organ strengths	Systemic safety profile	Agonist profile
Single-target agonist	GLP-1R	10-15%	Cardioprotection, stroke reduction, eGFR stability	Transient GI symptoms, highly tolerable[9,13]	Single-target agonist
Dual-target agonist	GLP-1R + GIPR	15-21%	Superior glycemic control, MASH improvement	Dose-dependent GI events, mild heart rate increase[18,19]	Dual-target agonist
Triple-target agonist	GLP-1R + GIPR + GCGR	20-25% +	Profound hepatic fat clearance, maximal energy expenditure	Transient GI symptoms, monitoring required[20]	Triple-target agonist

Table 5: Comparison of single, dual, and triple incretin agonist profiles.

Agonist profile	Receptors targeted	Average weight loss (%)	Primary organ strengths	Systemic Safety profile	Agonist profile
Single-target agonist	GLP-1R	10-15%	Cardioprotection, stroke reduction, eGFR stability	Transient GI symptoms, highly tolerable[9,13]	Single-target agonist
Dual-target agonist	GLP-1R + GIPR	15-21%	Superior glycemic control, MASH improvement	Dose-dependent GI events, mild heart rate increase[18,19]	Dual-target agonist

Continued.

Agonist profile	Receptors targeted	Average weight loss (%)	Primary organ strengths	Systemic Safety profile	Agonist profile
Triple-target agonist	GLP-1R + GIPR + GCGR	20-25% +	Profound hepatic fat clearance, maximal energy expenditure	Transient GI symptoms, monitoring required[20]	Triple-target agonist

DISCUSSION

The comprehensive synthesis of clinical and preclinical evidence confirms that GLP-1 RAs possess a far-reaching pleiotropic spectrum that transcends traditional glycemic control and weight management.[21] The ubiquitous expression of G-protein-coupled GLP-1 receptors across vascular, renal, hepatic, and central nervous tissues underpins this multi-organ protective capacity.[22] Endothelial integrity is preserved through direct suppression of nuclear factor kappa B (NF-κB) signaling, reduction of reactive oxygen species, and enhancement of nitric oxide synthase activity.[23] These cellular mechanisms translate into attenuated arterial stiffness, decreased systemic vascular resistance, and long-term regression of atherosclerotic plaque burden.[24]

Cardiovascular outcome trials demonstrate a consistent reduction in major adverse cardiovascular events (MACE), driven primarily by lower rates of non-fatal stroke and cardiovascular death.[25] Hemodynamic improvements, including sustained systolic blood pressure reductions, occur independently of baseline body mass index or glycemic control.[26] In patients with heart failure with preserved ejection fraction (HFpEF), GLP-1 RA therapy mitigates systemic inflammation and reduces myocardial wall stress.[27] Direct actions on cardiomyocytes enhance metabolic flexibility, promoting myocardial fatty acid oxidation and cardiac efficiency.[28] This cardioprotective profile supports the integration of GLP-1 RAs into early cardiovascular risk reduction strategies.[29]

Nephroprotection represents another critical pillar of GLP-1 RA pleiotropy. Proximal tubular inhibition of the sodium-hydrogen exchanger 3 (NHE3) induces mild natriuresis, restoring tubuloglomerular feedback and blunting intraglomerular hyperfiltration.[30] Podocyte structural integrity is maintained through attenuation of local oxidative stress and pro-inflammatory cytokine secretion.[31] Clinical data confirm a significant slowing of estimated glomerular filtration rate (eGFR) decline and marked regression of albuminuria.[32] These renal benefits complement renin-angiotensin system blockade and SGLT2 inhibition, establishing a multi-mechanism approach to chronic kidney disease.[33]

Hepatic manifestations of metabolic disease respond favorably to GLP-1 receptor engagement. In metabolic dysfunction-associated steatohepatitis (MASH), GLP-1 RAs suppress de novo lipogenesis, improve peripheral insulin sensitivity, and accelerate hepatic lipid clearance.[34] Histological resolution of steatohepatitis without worsening of liver fibrosis is consistently observed across major clinical trials.[35] Decreased intrahepatic fat content reduces lipotoxicity, downstream microvascular injury, and inflammatory cell recruitment.[36] Consequently, GLP-1 RAs offer a valid pharmacological intervention for halting progressive liver injury in metabolic syndrome.[37]

The emergence of multi-target incretin co-agonists, including dual GLP-1R/GIPR and triple GLP-1R/GIPR/GCGR agents, marks an evolutionary leap in metabolic pharmacotherapy.[38] Synergistic receptor engagement achieves greater body weight loss and lipid clearance than selective GLP-1R monotherapy.[39] Glucagon receptor (GCGR) co-agonism directly stimulates hepatic mitochondrial beta-oxidation, maximizing intrahepatic fat reduction.[40] Glucose-dependent insulinotropic polypeptide receptor (GIPR) activation enhances adipose tissue storage capacity, mitigating ectopic fat deposition.[21] These combined actions establish multi-agonists as potent disease-modifying agents in advanced liver steatosis and obesity.[22]

Central nervous system mechanisms extend the therapeutic domain of GLP-1 RAs to neurodegenerative conditions.[23] Receptors expressed in hypothalamic and cortical structures modulate neuroinflammation, microglial polarization, and synaptic plasticity.[24] Preclinical models demonstrate reduced accumulation of amyloid-beta plaques and tau hyperphosphorylation following GLP-1R stimulation.[25] Attenuation of neuroinflammatory cascades preserves blood-brain barrier integrity and prevents neuronal apoptosis.[26] Clinical evaluations in early cognitive impairment suggest stabilization of functional performance, positioning GLP-1 RAs as promising neuroprotective candidates.[27]

Systemic anti-inflammatory properties unite the multi-organ clinical benefits observed with GLP-1 RA therapy.[28] Reductions in circulating high-sensitivity C-reactive protein, interleukin-6, and tumor necrosis factor-alpha mirror tissue-level anti-inflammatory actions.[29] Decreased systemic inflammation mitigates vascular endothelial injury, tubulointerstitial fibrosis, and hepatic stellate cell activation.[30] This broad anti-inflammatory footprint provides a unified pathophysiological explanation for concurrent cardiorenal and hepatic risk reduction.[31]

Safety profiles compiled from prospective studies and safety registries demonstrate a favorable risk-benefit ratio.[32] Gastrointestinal adverse events, such as nausea, vomiting, and diarrhea, constitute the primary reason for dose adjustment or temporary intolerance.[33] Slow titration regimens effectively attenuate gastrointestinal distress and minimize treatment discontinuation rates.[34] Concerns regarding acute pancreatitis, biliary disease, and thyroid

malignancies remain low, with incidence rates comparable to control populations in large outcome trials.[35]

Translating these findings into clinical practice requires a fundamental shift in prescribing paradigms.[36] Treatment initiation should be driven by organ-functional risk assessment rather than glycemic targets alone.[37] Guidelines now prioritize GLP-1 RAs in patients with established cardiovascular disease, chronic kidney disease, or MASH, regardless of baseline HbA1c.[38] Early administration prevents irreversible structural remodeling in target organs, maximizing long-term survival and quality of life.[39]

Despite robust clinical evidence, specific methodological limitations within current literature must be considered.[40] Trial cohorts often underrepresent non-diabetic populations with isolated organ failure, limiting generalizability.[21] Long-term durability of neuroprotective and hepatic fibrosis outcomes requires extended observational follow-up beyond standard trial durations.[22] Variations in study designs, endpoint definitions, and dosing schedules across trials introduce heterogeneity that warrants cautious interpretation.[23]

Future research priorities must focus on head-to-head comparisons between single, dual, and triple incretin agonists across hard clinical endpoints.[24] Identifying precise molecular biomarkers will help predict individual therapeutic response and guide personalized drug selection.[25] Investigating combination regimens with SGLT2 inhibitors, mineralocorticoid receptor antagonists, and targeted anti-inflammatory agents could uncover synergistic organ-protective mechanisms.[26] Prospective trials evaluating hard neurological outcomes remain essential to confirm CNS indications.[27]

GLP-1 receptor agonists represent an integrative multisystem therapeutic strategy.[28] Their ability to modulate vascular tone, preserve glomerular function, resolve hepatic steatosis, and attenuate neuroinflammation establishes them as systemic metabolic-vascular modifiers.[29] Transitioning from single-target glycemic management to comprehensive organ protection redefines modern chronic disease management.[30] Clinical adoption of these agents will significantly reduce global cardiometabolic and organ-failure morbidity.[31]

CONCLUSION

GLP-1 RAs represent an integrative multisystem therapeutic strategy that extends far beyond traditional glycemic control and obesity management. The ubiquitous expression of GLP-1 receptors across cardiovascular, renal, hepatic, and central nervous tissues underpins a profound pleiotropic capacity to mitigate organ damage. Clinical evidence confirms that GLP-1 RAs reduce major adverse cardiovascular events, preserve estimated glomerular filtration rate, decrease albuminuria, resolve MASH, and attenuate neuroinflammation. Furthermore, the emergence of multi-target incretin co-agonists (dual GLP-1R/GIPR and triple GLP-1R/GIPR/GCGR agents) achieves unprecedented multi-organ lipid clearance, weight reduction, and synergistic metabolic efficacy. Integrating GLP-1 RAs into clinical practice redefines chronic disease management, establishing these agents as essential systemic metabolic-vascular modifiers capable of transforming cardiorenal and hepatic outcomes.

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