

GLP-1 Receptor Agonists as Multisystem Therapeutics: Mechanistic Basis, Translational Evidence, and Emerging Clinical Applications Beyond Metabolic Disease

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Abstract:

Glucagon-like peptide-1 receptor agonists (GLP-1 RAs) have gained popularity as important therapeutic agents extending beyond glycaemic control and weight management. Growing evidence suggests their potential benefits across multiple organ systems through metabolic regulation, intracellular signalling, anti-inflammatory activity, and effects on cellular energy homeostasis. This review examines the molecular basis of GLP-1 receptor signalling, including cAMP–PKA–EPAC, PI3K–AKT, AMPK, and MAPK pathways, and their possible contributions to multisystem protection. Particular emphasis is placed on cardiovascular and renal outcomes, including atherosclerotic cardiovascular disease, obesity-related heart failure with preserved ejection fraction, and chronic kidney disease. Hepatic applications are explored through the effects of GLP-1 RAs on metabolic dysfunction-associated steatosis liver disease and steatohepatitis, with consideration of histological outcomes and emerging multi-incretin therapies. The review further evaluates potential applications in neurological and neuropsychiatric disorders, musculoskeletal and inflammatory conditions, respiratory diseases, sleep-related disorders, and oncology. Evidence from clinical trials is considered alongside preclinical findings to distinguish established therapeutic benefits from emerging hypotheses. Safety considerations, including gastrointestinal and hepatobiliary adverse effects, long-term treatment, discontinuation, affordability, and equitable access, are also discussed. Finally, developments in oral and long-acting formulations, combination therapies, biomarker-guided treatment selection, and artificial intelligence-assisted drug discovery are examined as potential directions for precision incretin pharmacotherapy. Overall, GLP-1-based therapies represent a promising platform for addressing interconnected metabolic and non-metabolic diseases. However, the strength of evidence varies substantially across indications, highlighting the need for well-designed clinical trials, long-term safety evaluation, and clearer identification of patients most likely to benefit from these therapies.

Keywords: GLP-1 receptor agonists, Multisystem effects, Cardiovascular protection, Renal outcomes, Precision incretin pharmacotherapy.

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1. Introduction

GLP-1 (glucagon-like peptide-1) is a peptide derived from the cleavage of proglucagon and is primarily synthesized in intestinal mucosal L-cells, pancreatic islet α -cells, and neurons in the nucleus of the solitary tract. By activating GLP-1 Receptors (glucagon-like peptide-1 receptor agonists), GLP-1RAs reproduce major actions of endogenous GLP-1, including stimulation of insulin secretion, suppression of glucagon release, delayed gastric emptying, and reduced food intake through appetite regulation ¹. The primary uses of GLP-1 receptor agonists (glucagon-like peptide-1 receptor agonists) are the management of type 2 diabetes mellitus (T2DM; a chronic metabolic disorder characterized by insulin resistance and inadequate insulin secretion, resulting in elevated blood glucose levels) and chronic weight management/obesity ^{2,3}. Therefore, GLP-1 signalling contributes to glucose homeostasis and appetite control, thereby influencing whole-body energy balance and substrate availability ⁴.

The therapeutic development of GLP-1-based therapies has progressed from the earliest observations of glucose lowering and modest weight loss with native GLP-1 and short-acting compounds to the development of highly active formulations and new molecules ⁵. However, endogenous GLP-1 has an extremely short systemic duration of action, with circulating activity persisting for only about 1-2 min under physiological conditions. Its biological activity is rapidly terminated following cleavage by the enzyme dipeptidyl peptidase-4 (DPP-4) ⁶. Structural modifications of the GLP-1 molecule subsequently enabled the development of GLP-1RAs with preserved GLP-1 activity, greater resistance to DPP-4 degradation and prolonged pharmacological action. Exenatide was approved by the U.S. Food and Drug Administration (FDA) in 2005 for the treatment of T2DM, followed by liraglutide in 2010 and semaglutide in 2017 ⁷. The introduction of highly potent incretin receptor agonists such as semaglutide and tirzepatide has marked a new era in the treatment of type 2 diabetes and obesity ⁸. **Figure 1** illustrates the key milestones in this progression, highlighting advances in drug design, clinical applications, and the emerging potential of GLP-1-based therapies in multisystem disease management.

The evidence supporting the use of GLP-1-based medicines beyond glucose control and weight loss was substantially strengthened in 2024, as clinical trial data reported benefits across a range of disorders ⁹. Semaglutide has been shown to reduce cardiovascular morbidity and all-cause mortality in people with obesity and improve cardiovascular and renal outcomes in people with type 2 diabetes mellitus and chronic kidney disease ¹⁰. Beyond their established metabolic indications, GLP-1-based medicines are now being investigated across a broader range of conditions, including neurodegenerative and substance use disorders, metabolic liver disease, arthritis, type 1 diabetes and inflammatory bowel disease. These expanding applications highlight the need to further examine the safety, efficacy, and potential utility of new and emerging GLP-1-based therapies ¹¹. Despite their increasing therapeutic potential, important knowledge gaps also remain regarding the optimal duration of treatment, rare adverse effects and identification of patient subgroups most likely to benefit ¹².

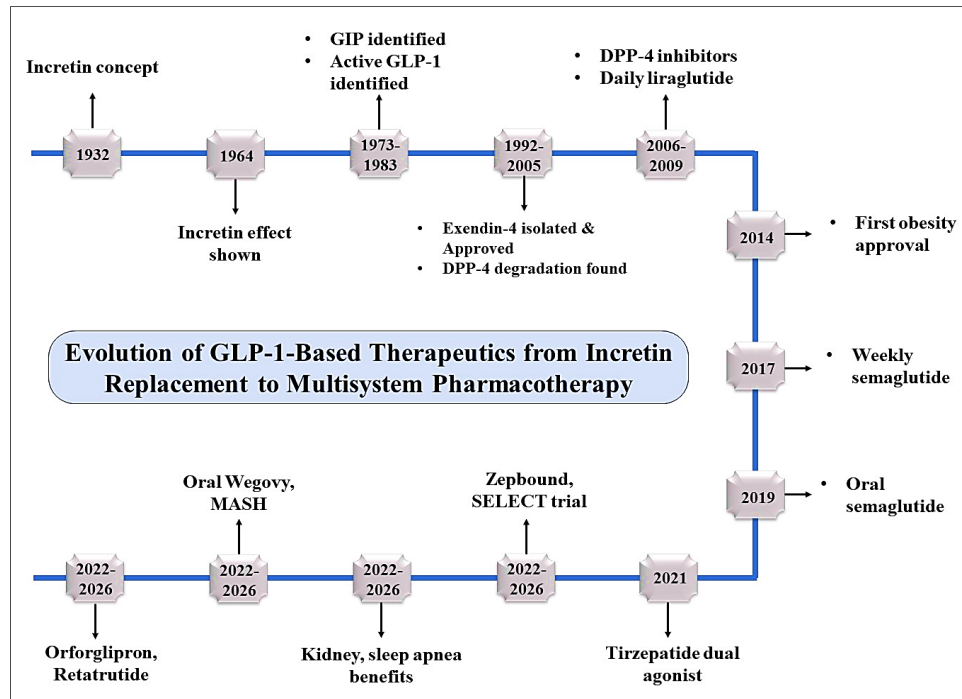


Figure 1: Evolution of GLP-1-Based Therapeutics from Incretin Replacement to

Therefore, this review explores the emerging therapeutic potential of glucagon-like peptide-1 (GLP-1)-based therapies beyond their established use in diabetes and obesity. It focuses on their beneficial effects across multiple organ systems, particularly the cardiovascular, renal, hepatic, and neurological systems, along with other promising therapeutic applications. The review examines current preclinical and clinical evidence, discusses the mechanisms underlying these effects, and identifies key limitations in existing research. It also highlights key knowledge gaps and future research directions to understand better their long-term safety, therapeutic effectiveness, and potential role in expanding treatment options for a broader range of diseases.

2. GLP-1 Receptor Biology and Molecular Basis of Multisystem Effects

Glucagon-like peptide-1 receptor (GLP-1R) biology provides the molecular basis for the multisystem effects of GLP-1 receptor agonists. GLP-1 receptor activation initiates interconnected molecular pathways that influence glucose homeostasis, inflammation, oxidative stress, vascular function, and cellular metabolism across multiple organ systems. **Figure 2** demonstrates the key signalling networks linking GLP-1 receptor activation to its diverse physiological effects and emerging therapeutic potential beyond diabetes and obesity. GLP-1R activation initiates intracellular signalling through the cAMP–PKA and EPAC pathways and interacts with PI3K–AKT, AMPK, and MAPK signalling networks. These pathways regulate glucose homeostasis, cellular survival, energy metabolism, and inflammatory responses¹³. Emerging evidence also suggests potential antioxidant, mitochondrial, and endothelial effects that may contribute to tissue protection. However, the relative importance of these mechanisms varies across tissues and disease contexts. Understanding these molecular pathways helps explain the broader metabolic, cardiovascular, renal, and neuroprotective effects investigated in subsequent sections^{14,15}.

2.1 GLP-1 physiology and tissue-specific GLP-1R distribution

Glucagon-like peptide-1 (GLP-1) is an incretin hormone released primarily by intestinal enteroendocrine L cells in response to nutrient intake. It enhances glucose-dependent insulin secretion, suppresses glucagon release, delays gastric emptying, and promotes satiety. These effects are mediated by the GLP-1 receptor (GLP-1R), a G-protein-coupled receptor expressed prominently in pancreatic islets and specific neuronal populations¹⁶. GLP-1R expression has also been identified in selected gastrointestinal and cardiovascular cell populations; however, its distribution and functional significance vary across tissues. Importantly, evidence for direct receptor-mediated effects in several peripheral organs remains limited or debated, and some systemic benefits may occur indirectly through weight loss and improved metabolic control¹⁷.

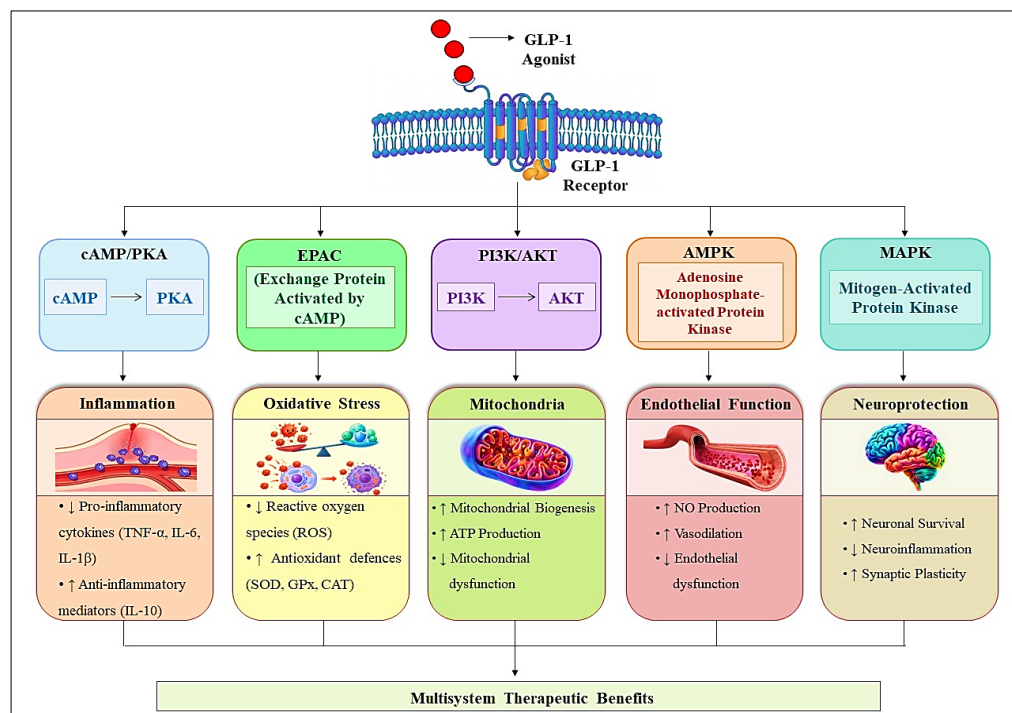


Figure 2: Molecular Network Underlying the Multisystem Effects of GLP-1 Receptor Activation

2.2 Canonical cAMP/PKA–EPAC signalling

GLP-1 receptor (GLP-1R) activation primarily stimulates G α s protein, activating adenylyl cyclase and increasing intracellular cyclic adenosine monophosphate (cAMP). This second messenger activates protein kinase A (PKA) and exchange proteins directly activated by cAMP (EPAC), particularly EPAC2 in pancreatic β -cells. These pathways regulate ion-channel activity, intracellular calcium mobilisation, insulin-granule exocytosis, and glucose-dependent insulin secretion. PKA also modulates cAMP-response element-binding protein (CREB), linking receptor activation with gene regulation. The specificity of these responses depends on cellular context and the spatial and temporal organisation of intracellular signalling^{18,19}.

2.3 PI3K/Akt, AMPK and MAPK pathways

GLP-1 receptor activation may influence several intracellular pathways beyond canonical cAMP signalling. The phosphoinositide 3-kinase (PI3K)–protein kinase B (AKT) pathway is associated with cellular survival and metabolic regulation, while AMP-activated

protein kinase (AMPK) acts as an energy sensor involved in glucose and lipid metabolism. Mitogen-activated protein kinase (MAPK), particularly ERK1/2, regulates cellular responses to growth and stress. Experimental and mechanistic studies suggest that modulation of these pathways may contribute to the metabolic and cardioprotective effects of GLP-1 receptor agonists; however, their activation is tissue-dependent, and their direct contribution to clinical organ protection requires further investigation^{20,21}.

2.4 Anti-inflammatory and antioxidant mechanisms

Chronic inflammation and oxidative stress contribute to insulin resistance, endothelial dysfunction, and metabolic tissue injury. GLP-1 receptor agonists may modulate inflammatory pathways, including nuclear factor-kappa B (NF-κB) signalling, and influence the production of pro-inflammatory cytokines such as TNF-α, IL-1β, and IL-6²². Their potential antioxidant effects include reductions in oxidative stress markers and modulation of cellular antioxidant defence systems. A 2025 systematic review and meta-analysis of randomized trials in adults with type 2 diabetes reported reduced malondialdehyde levels and increased superoxide dismutase and glutathione peroxidase levels following GLP-1 receptor agonist treatment. However, the extent to which these effects independently mediate clinical organ protection remains under investigation²³.

2.5 Mitochondrial and endothelial effects

Mitochondrial dysfunction and endothelial injury contribute to cardiometabolic disease by increasing oxidative stress and impairing vascular homeostasis. Experimental and clinical evidence suggests that GLP-1 receptor agonists may improve mitochondrial respiration, reduce reactive oxygen species (ROS) production, and modulate leukocyte–endothelial interactions²⁴. In vascular endothelial cells, these agents may also enhance endothelial nitric oxide synthase (eNOS) activity and nitric oxide (NO) bioavailability, supporting vasodilation and vascular function²⁵. However, these effects vary across experimental models and clinical settings, and their direct contribution to cardiovascular protection remains incompletely established. The major GLP-1 receptor signalling pathways and their associated multisystem therapeutic consequences are summarized in **Table 1**. GLP-1 signalling also contributes to coordinated physiological responses across multiple organs through interconnected metabolic, neural, hormonal, and inflammatory pathways. The **Figure 3** shows the emerging role of GLP-1-mediated inter-organ communication in maintaining systemic homeostasis and its potential therapeutic implications beyond glycaemic control and weight management.

Table 1: GLP-1 Receptor Signalling Pathways and Their Multisystem Therapeutic Consequences

GLP-1-R signalling pathway	Major cellular effects	Target organs/tissues	Therapeutic relevance	Ref.
cAMP/PKA	Increase cAMP, PKA activation, enhance insulin secretion, reduce B-cell apoptosis	Pancreatic B-cells	Glucose-responsive insulin secretion with reduced hypoglycaemia risk	26

cAMP/EPAC	cAMP signalling activates PKA and EPAC, both of which support production and release of insulin	Pancreatic B-cells	Increases insulin synthesis and release	27
PI3K/Akt	Akt activation improves survival, increases proliferation, reduces apoptosis	Pancreatic B-cells, heart, neurons	Maintains cell viability and reduces injury in metabolic states	28
AMPK/MAPK	AMPK/ERK signalling reduces oxidative stress and apoptosis, enhancing metabolic adaptation	Heart, liver, kidney, brain	Supports cardiometabolic protection and stress resistance	29
Inflammatory pathways	Reduce NF-KB/NLRP3, lower TNF- α /IL-1B, /IL-6, improve immune balance	Immune cells, kidney, brain, systemic tissues	Decreases chronic inflammation linked to metabolic and organ injury	30,31
Mitochondrial pathways	Enhance mitochondrial remodelling or function, decrease ROS, increase stress survival	Pancreatic B-cells, heart, neurons	Guards against oxidative and metabolic stress	32
Integrated GLP-1R signalling	Multiple pathway integration, Regulated secretion-survival-inflammation control	Pancreas, heart, kidney, multi-organ systems	Describes the transition from glucose control to multi-organ treatment	33,34

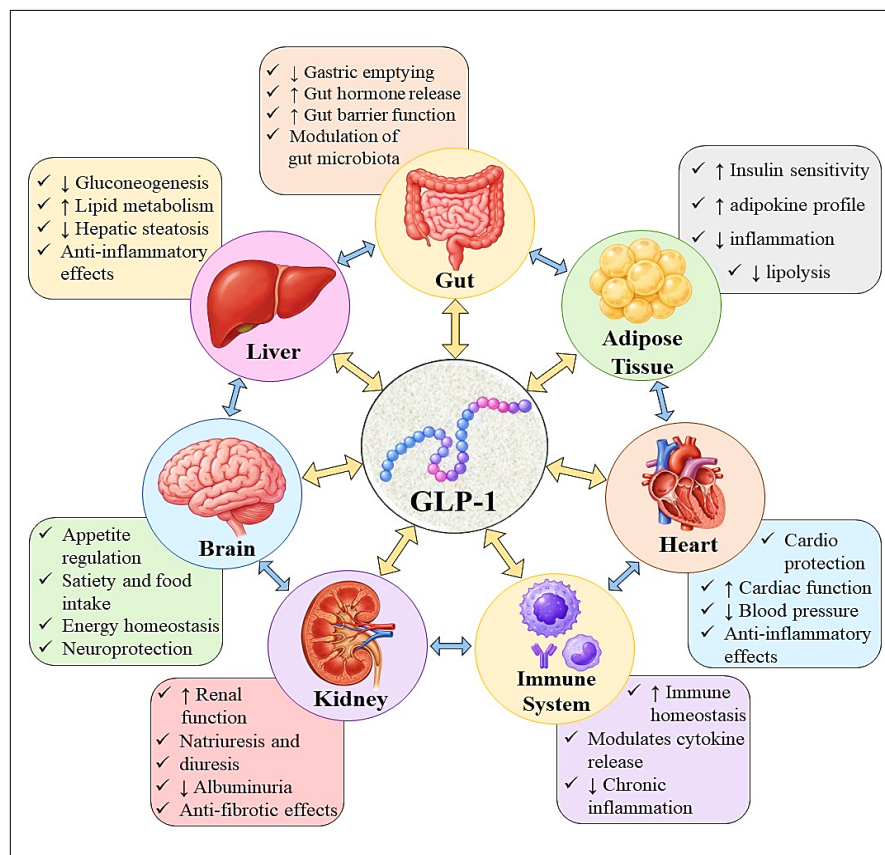


Figure 3: Organ–Organ Communication Mediated by GLP-1 Signalling

3. Cardiovascular and Renal Applications: From Metabolic Effects to Organ Protection

Glucagon-like peptide-1 receptor agonists (GLP-1 RAs) have demonstrated cardiovascular and renal benefits beyond glycaemic control and weight reduction. Clinical evidence supports their role in reducing major adverse cardiovascular events and kidney-related outcomes in selected populations³⁵. Potential mechanisms include improvements in metabolic risk factors, modulation of vascular inflammation, and enhanced endothelial function, although their individual contributions remain incompletely understood. These findings provide a basis for examining atherosclerotic cardiovascular disease, obesity-related heart failure, vascular dysfunction, and evidence from major cardiovascular and renal outcome trials³⁶.

3.1 Atherosclerotic cardiovascular disease

Atherosclerotic cardiovascular disease (ASCVD) is characterized by lipid accumulation, chronic vascular inflammation, endothelial dysfunction, and plaque formation. GLP-1 receptor agonists (GLP-1 RAs) may provide cardiovascular protection through improvements in metabolic parameters, modulation of inflammatory pathways, and potential effects on endothelial function and plaque stability³⁷. In the SELECT trial, semaglutide 2.4 mg reduced major adverse cardiovascular events (MACE) by 20% in patients with overweight or obesity and established cardiovascular disease without diabetes³⁸. A 2025 meta-analysis of 21 randomized trials involving 99,599 participants further reported a 13% reduction in MACE with GLP-1 RAs, supporting their role in cardiovascular risk reduction³⁹.

3.2 HFpEF and obesity-related cardiovascular dysfunction

Obesity-related heart failure with preserved ejection fraction (HFpEF) involves systemic inflammation, volume overload, and impaired functional capacity. In the 2025 SUMMIT trial, tirzepatide reduced the risk of cardiovascular death or worsening heart failure and improved health status in patients with obesity-related HFpEF. A 2025 mechanistic analysis further demonstrated reductions in systolic blood pressure, estimated blood volume, and C-reactive protein levels with tirzepatide. These findings highlight the potential of incretin-based therapies to address obesity-associated cardiovascular dysfunction beyond weight reduction^{40,41}.

3.3 Chronic kidney disease and diabetic kidney disease

GLP-1RAs reduce urinary albumin excretion rate and delay renal function impairment. Anti-inflammatory, hemodynamic, and metabolic actions underlie these beneficial effects. Several studies now show that GLP-1 receptor agonists offer renoprotective action that goes beyond lowering glucose levels. The mechanism by which GLP-1 signalling is activated offers protection from inflammation, oxidative stress, and fibrosis in the kidneys, in addition to improved function of the endothelium and tubules⁴². Albuminuria and decreased eGFR loss have been noted in patients taking GLP-1RAs in several clinical studies⁴³. In addition, any improvement in BP, body weight, and glucose levels can offer an indirect effect on kidney protection. Despite sodium-glucose cotransporter-2 inhibitors being the backbone of nephroprotection, GLP-1RAs are emerging as another treatment for diabetic kidney disease patients with high cardiovascular risk^{44,45}.

3.4 Vascular inflammation and endothelial dysfunction

GLP-1 receptor agonists may improve endothelial function by reducing oxidative stress, inflammatory signalling, and vascular inflammation. They may enhance endothelial nitric oxide (NO) availability, promoting vasodilation and vascular health. Experimental evidence suggests that GLP-1 receptor activation influences AMPK/Akt/eNOS-related pathways, potentially contributing to cardiovascular protection. However, the clinical significance of these mechanisms requires further investigation, as effects may vary among individual agents and patient populations ^{46,47}.

3.5 Clinical evidence from major cardiovascular and renal outcome trials

Major cardiovascular outcome trials have demonstrated the cardiorenal benefits of selected GLP-1 receptor agonists. In the LEADER trial, liraglutide reduced major adverse cardiovascular events (MACE) by 13% compared with placebo (HR 0.87; 95% CI 0.78–0.97) ^{48,49}. The SELECT trial demonstrated a 20% reduction in MACE with semaglutide in patients with overweight or obesity and established cardiovascular disease without diabetes (HR 0.80; 95% CI 0.72–0.90) ⁵⁰. In the FLOW trial, semaglutide reduced the primary kidney and cardiovascular-death composite outcome by 24% in patients with type 2 diabetes and chronic kidney disease (HR 0.76; 95% CI 0.66–0.88) ⁵¹.

4. Hepatic Applications: GLP-1 Signalling in MASLD and MASH

Novel therapies are urgently required for the management of metabolic dysfunction-associated steatotic liver disease (MASLD) and metabolic dysfunction-associated steatohepatitis (MASH). Recent evidence has suggested that GLP-1RAs contribute to improvements in hepatic fat accumulation and liver histology in MASLD/MASH models ⁵². Incretin mimetics and other gastrointestinal hormones targeting the multifaceted pathophysiological pathways underlying MASLD have emerged as promising disease-modifying therapies. Recent evidence from phase 2 clinical trials in MASH has demonstrated that pharmacological agents based on GLP-1 receptor agonism can effectively improve disease activity ⁵³.

4.1 Pathophysiological Rationale

It is well established that obesity, insulin resistance, and T2DM are closely associated with MASLD / MASH. Preclinical studies demonstrated that GLP-1RAs decreased hepatic fatty acid accumulation, alleviated endoplasmic reticulum stress, promoted autophagy, and modulated the activity of enzymes involved in fatty acid metabolism ⁵⁴. Semaglutide acts by reducing appetite and enhancing satiety, thereby decreasing dietary intake and subsequent free fatty acid export to the liver; decreasing insulin resistance and improving insulin sensitivity and adipose dysfunction. It also reduces de novo lipogenesis by downregulating ChREBP and SREBP-1c signalling, as well as the expression of lipid-synthesizing genes ⁵⁵. Although GLP-1R expression is limited or absent in major hepatic cell types such as hepatocytes, emerging evidence suggests that GLP-1R may be expressed in specific non-parenchymal hepatic cells, indicating that both indirect and cell-specific mechanisms may contribute to the hepatic effects of semaglutide ⁵⁶.

4.2 Effects on steatosis, inflammation and fibrosis

Overall, GLP-1 RAs treatment for a median of 24 weeks resulted in a significant reduction in LFC by 5.21%. GLP-1 RAs treatment produced significant histological improvements in steatosis, hepatocellular ballooning, and lobular inflammation, but did not significantly improve fibrosis⁵⁷. GLP-1RAs treatment significantly reduced serum alanine aminotransferase, aspartate aminotransferase, and γ -glutamyl transferase compared with the control group. GLP-1RAs improved hepatic stiffness, with semaglutide showing the most pronounced treatment effect. Furthermore, GLP-1RAs reduced liver fat content measured by magnetic resonance imaging⁵⁸.

4.3 Histological and clinical evidence

Resolution of steatohepatitis without worsening of fibrosis occurred in 62.9% of the 534 patients in the semaglutide group and in 34.3% of the 266 patients in the placebo group. A reduction in liver fibrosis without worsening of steatohepatitis was reported in 36.8% of patients in the semaglutide group and in 22.4% of those in the placebo group. The combined resolution of steatohepatitis and reduction in liver fibrosis was reported in 32.7% of patients in the semaglutide group and in 16.1% of those in the placebo group. The mean change in body weight was -10.5% with semaglutide and -2.0% with placebo⁵⁹.

A meta-analysis identified 13 phase 2 or phase 3 RCTs involving 1,811 participants. GLP-1RAs, particularly semaglutide 2.4 mg/week, were superior to placebo in achieving MASH resolution and improving liver fibrosis for up to 72 weeks. However, among individuals with MASH-related compensated cirrhosis, for whom only one RCT was available, semaglutide did not result in MASH resolution or improved fibrosis compared to placebo⁵⁸.

4.4 GLP-1 RA versus multi-incretin approaches

The percentage of participants who achieved the MASH resolution without worsening of fibrosis was 10% in the placebo group, 44% in the 5-mg tirzepatide group, 56% in the 10-mg tirzepatide group and 62% in the 15-mg tirzepatide group. The percentage of participants who experienced an improvement of at least one stage of fibrosis without worsening of MASH was 30% in the placebo group, 55% in the 5-mg tirzepatide group, 51% in the 10-mg tirzepatide group, and 51% in the 15-mg tirzepatide group⁶⁰.

Additionally, tirzepatide and survodutide have shown potential clinical benefits in reducing liver fibrosis. GLP-1 receptor agonists, either alone or in combination with GIP and/or glucagon receptor agonists, represent promising pharmacotherapeutic approaches for MASLD / MASH. However, larger and longer-duration clinical trials are needed to further evaluate the efficacy and safety of GIP receptor and glucagon receptor agonism⁵³.

5. Neurological, Neuropsychiatric and Behavioural Applications

Glucagon-like peptide-1 receptor agonist (GLP-1 RAs) are increasingly being investigated for their potential effects on neurological function, mental health, and reward-related behaviours beyond their established metabolic applications. GLP-1 receptor signalling may influence neuroinflammation, neuronal survival, synaptic plasticity, and brain energy metabolism, providing a biological rationale for research into neurodegenerative disorders⁶¹. Emerging evidence also suggests possible effects on food-reward processing and compulsive behaviours through central reward pathways⁶². However, findings from experimental models and observational studies do not establish clinical efficacy. Further well-designed randomized

controlled trials are required to clarify the therapeutic potential, safety, and long-term effects of GLP-1 RAs across neurological and psychiatric conditions ⁶³.

5.1 Alzheimer's disease and neurodegeneration

Alzheimer's disease (AD) involves progressive cognitive decline, amyloid- β accumulation, tau pathology, neuroinflammation, and impaired neuronal insulin signalling. Preclinical studies suggest that GLP-1 receptor agonists may support neuronal function by modulating inflammation and cellular energy metabolism ⁶⁴. However, clinical evidence remains inconclusive. In the 2025 EVOKE and EVOKE+ phase 3 trials, oral semaglutide did not significantly slow Alzheimer's disease progression, despite effects on certain disease-related biomarkers. These findings highlight the need for further research to establish whether GLP-1-based therapies offer meaningful neuroprotection in humans ⁶⁵.

5.2 Parkinson's disease and neuronal protection

Parkinson's disease (PD) is a progressive neurodegenerative disorder characterized by the loss of dopaminergic neurons in the substantia nigra, leading to motor dysfunction. GLP-1 receptor agonists may exert neuroprotective effects by reducing neuroinflammation, modulating microglial activity, and improving neuronal metabolic signalling ⁶⁶. However, clinical findings remain inconsistent. A 2026 systematic review and network meta-analysis of five randomized controlled trials involving 708 participants found no significant overall improvement in motor scores in the conventional pooled analysis. However, selected agents showed benefits in network comparisons. Larger, long-term trials are therefore required to establish their efficacy and disease-modifying potential in PD ⁶⁷.

5.3 Neuroinflammation, mitochondrial dysfunction and insulin signalling

Neuroinflammation, mitochondrial dysfunction, and impaired insulin signalling are interconnected processes implicated in neurodegenerative diseases. GLP-1 receptor agonists (GLP-1 RAs) may attenuate microglial activation and inflammatory mediator release while improving mitochondrial function and cellular energy regulation ⁶⁸. Activation of PI3K–AKT and cAMP–PKA signalling may also support neuronal survival and synaptic function. Furthermore, these agents may improve brain insulin signalling, which is associated with neuronal metabolism and plasticity. However, much of this mechanistic evidence comes from experimental models, and further clinical studies are needed to determine whether these effects translate into meaningful neurological benefits in humans ⁶⁹.

5.4 Reward circuitry, appetite and compulsive behaviour

GLP-1 receptor agonists (GLP-1 RAs) influence appetite regulation and reward-related behaviours through interactions between metabolic signals and central neural circuits. Receptors in brain regions associated with reward processing, including the ventral tegmental area and nucleus accumbens, may contribute to changes in food motivation and responses to rewarding stimuli ⁷⁰. Human studies suggest that GLP-1 RAs can reduce hunger, energy intake, and responsiveness to high-calorie food cues. Their potential role in substance-related cravings is also under investigation; however, clinical evidence remains preliminary, and further randomized controlled trials are required before these agents can be recommended for compulsive behaviours or addiction ⁷¹.

5.5 Depression, cognition and emerging psychiatric applications

Depression and cognitive impairment frequently coexist with obesity and diabetes, prompting interest in the potential neuropsychiatric effects of GLP-1 receptor agonists (GLP-1 RAs). A systematic review and meta-analysis of randomized controlled trials found no significant improvement in depressive symptoms or global cognition compared with placebo; however, improvements in emotional eating and overall quality of life were observed⁷². Emerging research also investigates their possible roles in anxiety and other psychiatric conditions, but the evidence remains limited. Further trials are needed to distinguish direct effects on brain function from indirect benefits associated with weight loss and improved metabolic health⁷³.

5.6 Translational barriers and quality of clinical evidence

Despite promising preclinical findings, several barriers limit the clinical translation of GLP-1 receptor agonists (GLP-1 RAs) for neurological and psychiatric disorders. Small sample sizes, heterogeneous patient populations, short follow-up periods, and differences in drug selection and outcome measures constrain the evidence. Furthermore, blood–brain barrier penetration, optimal dosing, treatment duration, and reliable biomarkers for identifying responders remain insufficiently established⁷⁴.

Recent clinical evidence also indicates that statistically significant changes in cognitive scores may not translate into clinically meaningful benefits. Therefore, larger, well-designed randomized controlled trials with standardized neurological endpoints and long-term safety assessment are essential before GLP-1 RAs can be recommended for these indications⁷⁵.

6. Musculoskeletal, Inflammatory and Other Emerging Applications

GLP-1 receptor agonists (GLP-1RAs) are increasingly utilized for metabolic disease, while their potential effects on musculoskeletal and inflammatory disorders are being investigated. Preclinical and clinical evidence suggests that GLP-1 RAs may have anti-inflammatory and chondroprotective effects, including regulating inflammatory pathways, beyond their established metabolic actions⁷⁶.

6.1 Osteoarthritis and pain/function outcomes

Weight reduction can reduce symptoms of knee osteoarthritis (OA), including pain. Clinical evidence indicates that semaglutide improves OA-related knee pain and physical function, whereas similar benefits have not been consistently observed with liraglutide. In the 68-week STEP 9 randomized, placebo-controlled trial involving 407 participants with obesity and moderate knee OA, semaglutide produced greater decreases in body weight and WOMAC pain than placebo. Body weight decreased by 13.7% versus 3.2%, while WOMAC pain decreased by 41.7 versus 27.5 points, respectively. Physical-function scores also showed significant improvement with semaglutide⁷⁷. Observational evidence additionally suggests a reduced risk of knee OA surgery among GLP-1 RAs users⁷⁸.

6.2 Rheumatologic and inflammatory disorders

Evidence in rheumatoid arthritis (RA) remains scarce. A 2025 retrospective study of patients with RA and overweight or obesity found that GLP-1RA treatment was associated with greater decreases in RA disease activity, pain, body weight, total cholesterol and HbA1c than controls. Pain and inflammatory marker reductions were not significantly correlated with

weight loss, suggesting some effects may involve mechanisms independent of weight reduction. GLP-1 RAs may also suppress proinflammatory cytokine secretion. However, these findings need to be validated through prospective and randomized studies ⁷⁹.

6.3 Perioperative and musculoskeletal implications

Perioperative use of GLP-1 RAs has generated safety concerns because delayed gastric emptying may result in residual gastric contents despite conventional fasting and may elevate aspiration risk during sedation or general anaesthesia. Current multi-society guidance emphasizes individualized assessment of risk and shared decision-making among the patient, anaesthesia team and prescribing clinicians. GLP-1RA therapy may be continued in patients without elevated aspiration risk, whereas management should be tailored when risk factors for delayed gastric emptying are present ^{80,81}.

6.4 Current evidence limitations

A 2026 systematic review and meta-analysis including 60 studies and more than 1.25 million individuals found no significant overall effects on bone or joint outcomes, whereas lean body mass/fat-free mass was consistently decreased with GLP-1 RAs. The clinical significance of these changes for muscle function and physical performance remains unclear. Perioperative recommendations are also supported mainly by case reports and retrospective data, representing low-quality evidence. Overall, larger prospective studies and randomized trials are needed to clarify disease-specific efficacy, muscle function, long-term safety and optimal clinical translation ^{76,80}.

7. Respiratory and Sleep-Related Applications

Visceral obesity and systemic low-grade inflammation cause great mechanical as well as other strain on respiratory function. Besides imposing a direct mechanical stress on the chest wall and upper airway, obesity causes dysfunction of the vascular endothelium, chronic bronchitis, and blunting of the central ventilatory response. GLP-1 receptor agonists and dual incretins have been shown to produce the substantial clinical benefits in sleep-disordered breathing and chronic lung disease ⁸².

7.1 Obstructive sleep apnea (OSA)

OSA involves repeated blockages of the upper respiratory tract during sleep, causing intermittent episodes of hypoxia, sympathetic activation, and fragmented sleep. The increase in adiposity due to adipose fat accumulation in the parapharyngeal region and the tongue is the primary mechanism involved in OSA. The use of incretin-based therapy addresses this obstruction through the mobilization of ectopic fat in the parapharyngeal region and enlarging the cross-section of the upper airway ⁸³. Also, the positive mechanical effect of reducing adipose fat, activation of the GLP-1 receptor in the nucleus tractus solitarius and autonomic central nervous system control mechanisms may provide neuromodulation effects that can modulate ventilation drive and enhance the tone of the upper airway dilator muscles during sleep ¹.

7.2 Obesity-related respiratory dysfunction

Besides obstructive sleep apnea, obesity is associated with restrictive breathing problems like obesity hypoventilation syndrome (OHS), which occurs due to an elevated

arterial CO₂ pressure during wakefulness (Pa ["CO"] ≥ 45 " mmHg") with severe nocturnal hypoventilation. Obesity decreases lung compliance and reduces central chemosensitivity to both hypercapnia and hypoxia. GLP-1 receptors have been identified in the brainstem areas of autonomic functions, such as the nucleus tractus solitarius (NTS) ⁸⁴. Furthermore, the secretion of proinflammatory adipokines from adipose tissue also plays a role in causing chronic non-atopic airway hyperresponsiveness and corticosteroid-resistant asthma. GLP-1 receptor stimulation has been shown in animal studies to reduce pulmonary macrophage influx, prevent inflammatory cascades, and reduce airway hyperresponsiveness ⁸⁵.

7.3 Clinical evidence and positioning alongside established therapies

Continuous Positive Airway Pressure (CPAP) therapy still represents the cornerstone treatment for rapid mechanical splinting of the airways at night, but it does not affect the cardiometabolic pathophysiology or the visceral fat tissue, and its drawback is poor compliance with the treatment. The incretin therapies target the basic cause of respiratory disorders and affect heart disease and adiposity ⁸⁶. GLP-1 drugs act as disease-modifying medications in the clinical setting, as they reduce the need for therapeutic stress needed for efficient CPAP treatment and help in de-escalating the disease. These drugs also work as a pharmacological option for patients who are not able to tolerate positive airway pressure treatment ⁸⁷.

8. Oncological Applications: Promise, Mechanisms and Controversies

Obesity and type 2 diabetes are associated with elevated cancer burden, while weight reduction has a protective role in cancer risk reduction. GLP-1 receptor agonists have significantly improved the management of obesity and type 2 diabetes and may affect associated disorders. Current clinical evidence overall indicates that GLP-1 receptor therapies do not elevate overall cancer incidence and may reduce the risk of certain malignancies, although translational evidence remains incomplete ⁸⁸.

8.1 GLP-1 signalling and obesity-associated cancer risk

Obesity and type 2 diabetes are well-recognized risk determinants for malignancy, underscoring the potential significance of GLP-1-targeted therapies in the prevention of obesity-associated cancers. Emerging evidence indicates that GLP-1 receptor agonist (GLP-1RA) use is linked to a reduced overall risk of obesity-related malignancies, with decreases observed across multiple cancer types. Nevertheless, these findings primarily reflect associations, and prospective investigations are warranted to substantiate the potential protective effects and elucidate the underlying biological mechanisms ⁸⁹.

8.2 Potential direct anti-neoplastic mechanisms

GLP-1 signalling stimulates the PI3K/Akt pathway, which modulates cellular proliferation, metabolic activity, and survival. In vitro and in vivo studies have demonstrated that GLP-1 RAs can reduce cancer-cell proliferation in several preclinical cancer models. These actions may include regulation of signalling pathways such as MAPK/ERK, AMPK, and p53, which regulate cell-cycle progression and cell survival. GLP-1 RAs may also affect apoptosis in a tissue- and context-dependent manner. However, direct anticancer effects remain

mainly supported by preclinical evidence, and their significance to human cancer biology requires further research ⁹⁰.

8.3 Preclinical versus human evidence

Preclinical studies indicate that GLP-1 receptor agonists may exhibit anticancer activity by modulation of tumour-related signalling, cellular growth, apoptosis and inflammation. However, the relevance of these findings to humans remains unclear. A systematic review of 48 randomized clinical trials involving 94,245 participants found that GLP-1RAs may have little or no effect on multiple obesity-related cancers, although cancer-related outcomes were not the primary endpoints and follow-up duration was comparatively brief ⁹¹. Real-world data have also indicated a decreased overall cancer risk among GLP-1RA users, but some cancer-specific findings remain uncertain, highlighting the need for prolonged prospective studies ⁹².

9. Clinical Evidence, Safety and Translational Challenges

Though incretin-based treatments offer transformative advances in metabolism, heart health, and renal function, application of such treatments for lifelong and non-metabolic uses calls for an assessment of safety and feasibility of clinical use. Expanding the reach of clinical trials presents its own difficulties regarding side-effect profile, organ tolerance, physiological adaptability, and cessation effects ⁹³.

9.1 Evidence hierarchy across emerging indications

The evidence in favour of incretin-based therapies varies significantly based on different clinical indications. It has been demonstrated unequivocally that the effectiveness of incretin therapy for such disorders as type 2 diabetes mellitus, obesity, MACE, and chronic kidney disease has been proven by means of randomized, double-blind, large-scale trials. At the same time, the use of incretin for other purposes, for example, MASH and HFpEF, is yet to be proven based on intermediate endpoints or surrogate endpoint trials. Among the novel indications, there are uses for neurodegenerative diseases (Parkinson's disease and Alzheimer's disease), substance use disorders, and chronic pulmonary inflammation ⁹⁴. The strength and maturity of evidence for GLP-1 receptor agonists vary across emerging indications, ranging from established clinical findings to preliminary translational observations. The available clinical and translational evidence beyond metabolic disease is summarized in **Table 2**.

Table 2: Clinical and Translational Evidence for GLP-1 Receptor Agonists Beyond Metabolic Disease

Indication	Representative agent	Study type	Major endpoint	Principal finding	Current status	Ref.
Cardiovascular disease	Semaglutide	CV Outcomes RCT	3-point MACE	Lower major adverse cardiovascular events in obesity and CVD populations	Demonstrated clinical benefit beyond glucose control	³⁷

Heart failure with preserved ejection fraction	Semaglutide	Pooled phase 3 RCT analysis	KCCQ-CSS, 6MWD, body weight	Better symptoms, physical limitation, exercise ability, and fewer HF events	Supportive clinical evidence	95
Chronic kidney disease	Semaglutide	Systematic review and meta-analysis of RCTs	Composite kidney outcomes	Extended -acting GLP-1 RAs lowered combined kidney events and overall mortality	Robust supportive kidney evidence	96
Metabolic liver disease	Semaglutide	Phase 3 RCT	MASH resolution, fibrosis	Enhanced steatohepatitis resolution and fibrosis-related tissue outcomes	Advanced clinical development	59
Obstructive sleep apnea	Tirzepatide	Meta-analysis/clinical trial synthesis	Apnea-hypopnea index	Markedly lowered AHI and reduced hypoxic burden in obesity-associated OSA	Clinical evidence with regulatory progress	97
Neurodegenerative disorders	Liraglutide	Review including preclinical and early clinical data	Cognitive and neuroinflammatory outcomes	Neuroprotective and anti-inflammatory activity are encouraging but confirmed efficacy is unproven	Early translational stage	31
Substance use disorders	Semaglutide	Analysis of preclinical, epidemiologic, and early clinical research	Substance use outcomes	Findings suggest reduced addictive behaviours, but direct clinical evidence is limited	Emerging indication	30
Cancer	Semaglutide /Liraglutide	Comprehensive review/meta-analysis	Cancer incidence	Overall cancer risk appears generally unchanged, with cancer-specific signals remaining inconsistent	Oncologic safety generally reassuring; efficacy remains unconfirmed	98

Arthritis/inflammatory disorders	Semaglutide / Liraglutide	Scoping review	Disease activity, inflammatory markers	Anti-inflammatory and possible disease-modifying effects observed, but clinical trials remain limited	Promising but investigational	99
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9.2 Gastrointestinal and hepatobiliary adverse effects

The most common form of adverse reactions associated with GLP-1 receptor stimulation involves gastrointestinal complications due to central signalling through the area postrema and decreased motility in the periphery. Dose-dependent symptoms of nausea, vomiting, diarrhoea, and constipation are experienced especially during the initiation phase and the period of increasing dosing. Also, there is delayed gastric emptying that causes problems like retained stomach content, which leads to an increased risk of pulmonary aspiration when one undergoes general anaesthesia and upper endoscopy procedures. Weight loss along with motility issues makes one susceptible to biliary sludge and gallstones, among others ¹⁰⁰.

9.3 Pancreatic and other safety considerations

Most concerns regarding possible problems concerning the use of GLP-1 agonists and acute pancreatitis or cancer of the pancreas have been addressed with the help of studies related to cardiovascular outcomes over time, and even with the help of meta-analysis, which proves that there is no risk of developing pancreatic carcinoma. However, according to studies conducted on animals like rodents, continuous agonist stimulation results in C-cell hyperplasia and Medullary thyroid carcinoma (MTC); though the importance of the problem in case of humans is debatable due to the low presence of receptors in C-cells, it is contraindicated for patients who have a personal or familial history of MTC or MEN 2 ¹⁰¹.

9.4 Long-term safety in non-diabetic populations

When it comes to the use of incretins in treating any other chronic disorder apart from diabetes and severe obesity, there are various physiological considerations. Reduction in body mass leads to a loss in lean body mass, and if this is not offset by sufficient exercise and good nutrition, it may accelerate the development of sarcopenia among older or non-obese individuals. Appetite suppression is yet another concern that needs consideration when thinking about the issue of malnutrition, eating disorders, and bone mineral density ¹⁰².

9.5 Treatment discontinuation and adherence

Observational real-world registries demonstrate that a significant number of patients have to stop their treatment during the first 12 to 24 months because of their intolerance to gastrointestinal issues, financial burden, or lack of medication. The end of GLP-1 receptor agonist therapy results in an immediate loss of satiety signals, which causes body weight restoration and resumption of existing cardiometabolic, inflammatory, and breathing disorders. It is crucial to develop persistence models and analyze stepped step-down or intermittent maintenance therapies ¹⁰³.

9.6 Cost, accessibility and health-equity challenges

The clinical application of the next generation incretin pharmacotherapies is greatly hindered by both economic and structural constraints. The high cost per month, along with strict reimbursement policies, makes access restricted to only affluent areas, thereby creating extensive inequalities in healthcare access for vulnerable communities that are largely affected by cardiometabolic conditions. Continuous care is further hampered by frequent drug shortages. Tackling these issues requires an increased manufacturing capacity along with incorporation into national essential medicines lists ¹⁰⁴. Taken together, uncertainties in the evidence base, safety considerations, treatment adherence, and disparities in cost and accessibility highlight the challenges of translating the multisystem potential of GLP-1-based therapies into routine clinical practice. The major evidence gaps, current limitations, and potential strategies to address these challenges are summarized in *Table 3*.

Table 3: Translational Challenges and Future Strategies for Multisystem GLP-1-Based Therapy

Challenges	Evidence gaps	Safety & tolerability	Current limitation	Potential solution	Translational priority	Re f.
Long-term evidence	Limited long-term follow-up beyond study durations across organ systems	Gastrointestinal events and AE-related discontinuation remain ongoing long-term barriers	Sustainability of cardiorenal and multisystem benefits is poorly defined	Long-term practical follow-up and real-world follow-up studies	Define long-term net benefit across multisystem indications	¹⁰⁵
Tissue targeting	Organ-specific GLP-1R expression, occupancy, and delivery efficiency poorly characterized in patients	Continuous stimulation may cause receptor desensitization; nanocarriers add immune and retention issues	Current therapies do not provide targeted tissue delivery	GLP-1R-directed nanocarriers with complementary imaging diagnostics	Achieve organ-selective efficacy with lower off-target effects	¹⁰⁶
Biomarkers & patient selection	Responses exist, but most lack forward validation and standardization	Inadequate selection can expose nonresponders to cost and side effects without clear benefit	Individual response variability stays high	Combine clinical, genetic, and multi-omics biomarkers for personalized treatment	Build personalized-medicine algorithms for treatment and monitoring	¹⁰⁷
Safety& tolerability	Long-term systemic safety remains less established	GI adverse events are frequent; gallbladder disorders and	Tolerability affects adherence and treatment persistence	Low-dose starting, gradual dose increase, counselling,	Enhance persistence while preserving	¹⁰⁸

	than short-term efficacy	discontinuation are increased		and active AE management	risk-benefit balance	
Trial design	Combined endpoints can obscure which components explain benefits across systems	Safety findings may be diluted when endpoints emphasize efficacy outcomes	Diverse populations, endpoints, and subgroup data reduce interpretability	Use hierarchical or component-specific endpoints with predefined subgroup analyses	Standardize multisystem outcome frameworks for regulators and clinicians	109
Cost & access	Economic value across healthcare systems remains understudied for expanding indications	Frequent discontinuation can increase economic inefficiency	Reimbursement policy and fair access evidence remains limited	Relative cost-effectiveness and responder-focused prescribing strategies	Balance affordability with long-term public benefit	110
Translation from preclinical to clinical research	Mechanistic and preclinical findings frequently exceed available clinical validation	Species variation and limited causal validation limit confidence in mechanistic translation	Several suggested markers and mechanisms remain preliminary in humans	Clinical translational pathways incorporating imaging, omics, and prospective validation groups	Connects mechanisms-to-clinical evidence across tissues	107

10. Next-Generation GLP-1-Based Therapeutics and Precision Incretin Pharmacotherapy

The rapid success of mono- and dual agonists has spurred a revolution in novel incretin engineering strategies. Contemporary translational research is centred around dealing with the pharmacokinetic and bio-manufacturing challenges associated with peptide-based subcutaneous administration therapies, and utilizing multi-receptor unimolecular agonists in tandem with precision medicine and artificial intelligence¹¹¹. Also, the translation of emerging GLP-1 receptor agonist indications into clinical practice requires a systematic assessment of mechanistic evidence, preclinical findings, and clinical trial outcomes. **Figure 4** presents an evidence-to-translation framework highlighting key validation steps, translational challenges, and priorities for establishing the safety and therapeutic efficacy of GLP-1 RAs in emerging indications.

10.1 Long-acting and oral GLP-1 RAs

While peptide-based compounds like semaglutide and tirzepatide show promising efficacy on a weekly basis, the need for cold chain and subcutaneous delivery remains a significant barrier to success. In next-generation treatments, orally active non-peptide small-

molecule agonists that are primarily orforglipron are being considered. While the peptide-based compounds are co-administered with absorption promoters like oral semaglutide with SNAC, the non-peptide small molecule acts directly on the GLP-1 transmembrane site without undergoing enzymatic degradation in the absence of fasting or water ¹¹².

10.2 Combination therapies

Concurrent co-stimulation of two separate pathways of nutrient-sensing hormones leads to a synergistic effect on metabolism better than the maximum of each therapy. Combination of GIP/GLP-1 receptor stimulation (tirzepatide) results in improved insulin secretion and increased suppression of central appetite. Going beyond dual therapy, unimolecular triple agents (retatrutide; acting on GLP-1, GIP, and glucagon receptors) make use of the glucagon pathway for higher lipolysis and metabolic rate, balancing out the diabetic risks from insulin secretion by GIP/GLP-1 receptor action ¹¹³.

10.3 Biomarker-guided patient stratification

It is important to note that there is a great amount of heterogeneity between patients regarding their response to incretin-based drugs. This includes different effects on the level of glycemia, weight loss, and tolerance of the gastrointestinal system. The move from empirical to precise pharmacotherapy can be achieved through discovering predictive circulating biomarkers (fasting insulin, C-peptide, and CGM values), as well as non-invasive markers for the diagnosis of steatosis and fibrosis of the liver (such as MRI-PDFF and FIB4) ⁹⁴.

10.4 AI-assisted drug discovery and therapeutic optimization

Artificial intelligence systems and computational biology methods are revolutionizing the discovery, design, and pharmacokinetic characterization of new incretin-based drugs. Machine learning techniques and de novo protein design algorithms (graph neural networks and deep sequence learning models) are used to characterize the conformational behaviour of receptor-ligand interactions for the design of selective agonists that activate cAMP signalling but not beta-arrestin binding, which leads to desensitization and gastrointestinal side effects. Moreover, artificial intelligence systems model actual multi-omics data to predict drug adherence and side effect risk ¹¹⁴.

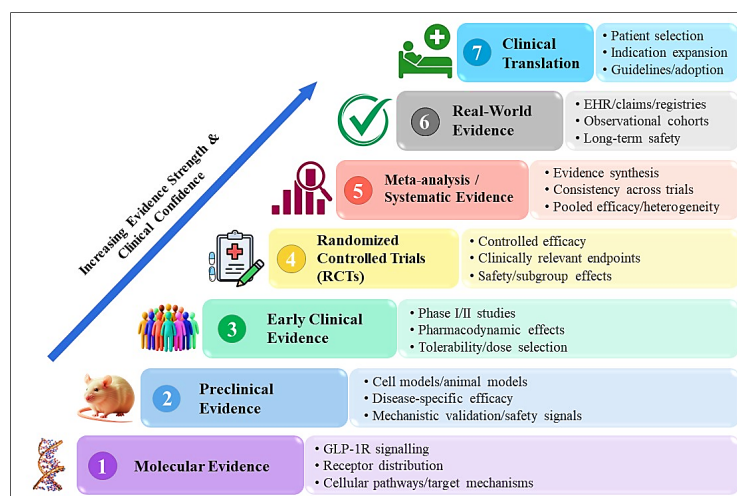


Figure 4: Evidence-to-Translation Framework for Emerging GLP-1 RA Indications

11. Future Perspectives

Development of GLP-1 receptor agonists from gut insulin secretagogues to the group of multisystem drugs definitely stands out as one of the greatest achievements of pharmacological translation. The presence of glucose-regulating activity along with systemic effects, including anti-inflammatory, cytoprotective, and vasoprotective effects, still revolutionizes the treatment of cardiovascular, renal, and metabolic diseases ¹¹⁵. However, translating this approach into non-metabolic indications throughout life presents certain challenges. The translational problem that needs to be solved is the separation of direct autonomous tissue receptor effects from effects associated with weight and dietary changes, especially for new indications in the nervous system and lungs, including obstructive sleep apnea and neurodegeneration ⁸².

In addition, new techniques in drug discovery have enabled the bypassing of the limitations in conventional pharmacokinetics and bioprocessing techniques. Oral, non-peptide small molecule agonists of GLP-1, GIP, and glucagon, as well as co-agonists for multiple receptors, have improved metabolic efficiency without using peptide cold chains. Additionally, computational biology and artificial intelligence have made this scenario even better by developing receptor-biased agonists that enhance the efficiency of signal transduction and prevent beta-arrestin desensitisation and gastrointestinal complications ¹¹⁶.

Long-lasting success in providing these benefits will be made possible by the development of approaches to safety monitoring, medication adherence and health care disparity at the same time. To deliver the individualized intensity of the treatment based on the specific pathophysiological characteristics, monitoring of muscle mass preservation, bile duct problems and patient stratification according to the biomarkers will be crucial when treating older individuals and the non-diabetic population with the incretin-based therapies ¹¹⁷. In addition, since the withdrawal of the drug usually causes a metabolic reversal, it is crucial to create sustainable step-down and maintenance programs. Lastly, to fully exploit the potential of these drugs internationally, a lot of work should be done in the field of disparities in costs and accessibility ¹¹⁸.

12. Conclusions

GLP-1 agonists have undergone a development from endogenous insulin-producing hormones to a new type of multi-targeted drugs. The numerous studies and data obtained from clinical trials have unambiguously shown that stimulation of GLP-1 receptors influences not only metabolism and glucose levels, but also has significant anti-inflammatory, cytoprotective, and vasculoprotective properties in multiple organs, and in particular the cardiovascular system, kidneys, liver, and lungs. The opportunity to preserve organs from the development of endothelial dysfunction, fat accumulation in inappropriate places, and effects from the central nervous system autonomic pathways is one of the strongest means of organ protection.

The future development of incretin-based drugs is going to require overcoming some translational barriers. First of all, in the clinic, they are going to be a need to distinguish the effects caused by intrinsic autonomic activity and compensatory responses due to body weight reduction, protect muscle mass in patients without diabetes mellitus, and create effective long-term therapy to avoid consequences of post-treatment withdrawal syndrome. Together with the

development of multifunctional unimolecular agonists targeting different incretins and oral small-molecule agonists, individual therapy based on appropriate biomarkers will be available.

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