CODEN: WJAPAC Impact Factor: 5.48 ISSN: 3049-3013

World Journal of Advance Pharmaceutical Sciences

Volume 3, Issue 6, Page: 5-13 Review Article www.wjaps.com

GLP-1 RECEPTOR AGONISTS: A NARRATIVE REVIEW OF THEIR ROLE ACROSS MULTIPLE ORGAN SYSTEMS BEYOND WEIGHT MANAGEMENT

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How to cite this Article: [1]*Alabi Damilola, [2]Fatima Zehra, [3]Mohsin Babar, [4]Chad Barker, [5]Muhammad Ahsan Shaikh MBBS, MD, [6]Syeddah Saiqa Gillani, [7]Hirak Trivedi, [8]Humaira Kousar, [9]Surriya Kousar. (2026). GLP-1 RECEPTOR AGONISTS: A NARRATIVE REVIEW OF THEIR ROLE ACROSS MULTIPLE ORGAN SYSTEMS BEYOND WEIGHT MANAGEMENT. World Journal of Advance Pharmaceutical Sciences, 3(6), 5-13.

Article Info

Article Received: 15 April 2026,

Article Revised: 06 May 2026,

Article Accepted: 26 May 2026.

DOI: https://doi.org/10.5281/zenodo.20465519

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1. ABSTRACT

Background: Glucagon-like peptide-1 receptor agonists (GLP-1RAs), originally formulated to improve glycemic control in type 2 diabetes mellitus and subsequently leveraged for weight management, have demonstrated wide-ranging pleiotropic effects across multiple organ systems. These extra-metabolic capabilities suggest that their therapeutic utility extends far beyond simple adiposity reduction. **Objective:** This narrative review aims to comprehensively synthesize and critically appraise clinical and mechanistic evidence regarding the long-term impacts of GLP-1RAs-specifically long-acting analogs such as semaglutide and the dual glucose-dependent insulinotropic polypeptide (GIP)/GLP-1 receptor agonist tirzepatide-on cardiovascular, renal, hepatic, pulmonary, and neurological outcomes. **Methods:** A detailed, comprehensive literature search was executed across PubMed, Embase, and regulatory databases (such as the US Food and Drug Administration) to identify milestone phase III randomized controlled trials, robust real-world evidence, systematic reviews, and meta-analyses published between January 2021 and May 2026. **Key Findings:** Accumulating data reveal that GLP-1RAs significantly decrease major adverse cardiovascular events (MACE) through mechanisms involving plaque stabilization, endothelial protection, and macrophage phenotypic polarization. In obesity-driven heart failure with preserved ejection fraction (HFpEF), these agents markedly enhance functional capacity and mitigate symptoms by reducing epicardial adipose tissue volume and localized paracrine inflammation. Furthermore, landmark clinical trials have confirmed that GLP-1RAs slow the progression of chronic kidney disease (CKD), reduce albuminuria, and provide direct podocyte preservation. In hepatology, GLP-1RAs facilitate the resolution of metabolic dysfunction-associated steatohepatitis (MASH) and arrest hepatic fibrosis, culminating in recent regulatory approvals. Emerging evidence also highlights neuroprotective qualities, including a reduction in neuroinflammation and a deceleration of cognitive decline in neurodegenerative diseases, alongside unexpected efficacy in reducing the severity of obstructive sleep apnea and modulating central reward pathways associated with substance use disorders. **Conclusion:** GLP-1RAs represent a profound shift in chronic disease management, transitioning from targeted metabolic modifiers into broad systemic therapies that directly counter the inflammatory and fibrotic drivers of multi-organ dysfunction.

1. INTRODUCTION

The introduction of glucagon-like peptide-1 receptor agonists (GLP-1RAs) has transformed the contemporary therapeutic approach to metabolic and endocrine disorders.[1] Originally isolated and developed to harness the "incretin effect"-wherein oral glucose ingestion provokes a substantially larger insulin response than an equivalent intravenous glucose infusion-these agents were initially reserved for the management of type 2 diabetes mellitus.[2] The classical understanding of GLP-1 biology focused on its capacity to stimulate glucose-dependent insulin secretion from pancreatic beta cells, suppress inappropriate postprandial glucagon secretion from alpha cells, delay gastric emptying, and promote satiety via central appetite-regulation centers in the hypothalamus.[3,4]

However, the clinical landscape has evolved far beyond this glucocentric paradigm.[5] The discovery of widespread GLP-1 receptor (GLP-1R) expression throughout the human body-including the atrial and ventricular myocardium, vascular endothelial and smooth muscle cells, glomerular podocytes, proximal renal tubular cells, hepatic immune cells, and various regions of the central and peripheral nervous systems-indicated that the physiological role of incretin hormones extends into multi-organ homeostasis.[1,6] Over the last several years, the medical community has shifted its primary focus from short-term glycemic optimization and structural weight loss to the durable, systemic, and organ-protective benefits of long-acting GLP-1RA analogs, such as weekly subcutaneous semaglutide, and multi-receptor agonists, such as the dual GIP/GLP-1 receptor agonist tirzepatide.[5,6]

A primary driver of this clinical shift is the recognition that chronic non-communicable diseases, such as cardiovascular disease, chronic kidney disease (CKD), and metabolic dysfunction-associated steatohepatitis (MASH), share an underlying pathophysiological triad: visceral adiposity, endothelial dysfunction, and chronic, low-grade systemic inflammation.[2] Cardiovascular disease remains the leading cause of morbidity and mortality among individuals with metabolic syndrome. Recent landmark clinical trials have firmly established GLP-1RAs as potent cardioprotective interventions that reduce macrovascular risks independently of baseline glycated hemoglobin levels or the magnitude of weight lost.[7] The historic regulatory approval of semaglutide for reducing major adverse cardiovascular events (MACE) in overweight or obese adults with established cardiovascular disease marked a crucial milestone, formally recognizing a weight-management medication for its primary vascular advantages.[7]

Simultaneously, silent systemic conditions such as CKD and MASH have reached epidemic proportions globally, frequently occurring in tandem with cardiovascular disease as part of a complex cardiorenal-metabolic syndrome.[8] Until recently, therapeutic interventions for advanced liver fibrosis secondary to MASH were heavily limited, often relying on non-specific lifestyle alterations. The finalization of multi-center phase III trials exploring GLP-1RAs in hepatology has led to dedicated regulatory indications for MASH with moderate-to-advanced fibrosis, offering a targeted option to alter the trajectory of hepatic disease.[9] In the renal domain, large-scale clinical trials have demonstrated that GLP-1 receptor activation significantly delays progression toward end-stage kidney disease (ESKD) while preserving the estimated glomerular filtration rate (eGFR) across diverse patient populations.[10]

Beyond these visceral systems, compelling clinical data have emerged regarding the neuroprotective capacity of GLP-1RAs.[11] By readily crossing the blood-brain barrier, these molecules modulate neuroinflammation, minimize microglial activation, and preserve synaptic integrity.[11,12] Consequently, they are being actively evaluated as disease-modifying therapies for neurodegenerative disorders, including Alzheimer's disease and Parkinson's disease.[11,12] Furthermore, the clinical utility of these agents has extended into respiratory medicine and behavioral health, showing efficacy in mitigating obstructive sleep apnea and modulating dopamine-driven reward pathways linked to addictive behaviors and substance use disorders.[13,14] This comprehensive narrative review synthesizes the extensive clinical, epidemiological, and mechanistic evidence accrued, examining the multi-organ, long-term impacts of GLP-1RAs and evaluating their evolving role as a baseline element of modern preventive and therapeutic medicine.

2. METHODOLOGY

This narrative review was structured and executed in strict alignment with the Scale for the Assessment of Narrative Review Articles (SANRA) guidelines to ensure data transparency, methodological rigor, and academic objectivity. A comprehensive, systematic literature search was undertaken across major electronic databases, including PubMed/MEDLINE, Embase, Scopus, and the Cochrane Central Register of Controlled Trials (CENTRAL). The search strategy was designed to capture relevant peer-reviewed scientific literature, clinical trial registries, and official regulatory databases (such as the US Food and Drug Administration and the European Medicines Agency) published from January 2021 through May 2026.

The database search strings utilized a combination of Medical Subject Headings (MeSH) terms and high-precision keywords, including but not limited to: ("GLP-1 receptor agonists" OR "Semaglutide" OR "Tirzepatide" OR "Incretin mimetics" OR "Dual GIP/GLP-1 agonists") AND ("Cardiovascular outcomes" OR "Major Adverse Cardiovascular Events" OR "Heart Failure with Preserved Ejection Fraction" OR "HFpEF" OR "Chronic Kidney Disease" OR "Diabetic Nephropathy" OR "Metabolic Dysfunction-Associated Steatohepatitis" OR

"MASH" OR "Liver Fibrosis" OR "Neuroprotection" OR "Alzheimer's Disease" OR "Obstructive Sleep Apnea" OR "Substance Use Disorders").

Studies were selected based on pre-established inclusion and exclusion criteria. Inclusion criteria comprised phase III randomized, double-blind, placebo-controlled clinical trials; prospective long-term observational cohort studies; large-scale real-world evidence (RWE) registries; and high-quality systematic reviews and meta-analyses. Discursive focus was restricted to human subjects and clinically relevant outcomes. Conversely, studies were excluded if they focused exclusively on short-term glycemic monitoring, minor pharmacokinetic or pharmacodynamic evaluations, pediatric cohorts, or if they were published prior to 2021, ensuring the synthesis reflects contemporary clinical insights. The retrieved literature was critically evaluated for methodological quality, and key findings were extracted to provide a detailed narrative synthesis organized by organ system and therapeutic indication.

3. Narrative Discussion

Cardiovascular Protection and Plaque Stabilization

The validation of the cardiovascular benefits associated with GLP-1RAs marks an important milestone in modern cardiology. For many years, cardiovascular risk reduction in patients with metabolic disease was believed to be a downstream benefit of glycemic optimization and blood pressure control. However, the landmark SELECT trial altered this viewpoint by demonstrating that the administration of once-weekly subcutaneous semaglutide 2.4 mg resulted in a statistically significant 20% relative risk reduction in the primary composite endpoint of MACE (encompassing cardiovascular death, non-fatal myocardial infarction, and non-fatal stroke) in adults with established atherosclerotic cardiovascular disease who were overweight or obese but did not have type 2 diabetes.[7] This finding confirmed that the vascular benefits of GLP-1RAs are distinct from their conventional glucose-lowering functions.

The biological mechanisms driving this macrovascular protection are wide-ranging and operate directly within the vascular endothelium and atheromatous plaques. Atherosclerosis is fundamentally a chronic, lipid-driven inflammatory disease of the arterial wall.[2] GLP-1RAs exert multi-layered anti-atherosclerotic effects by modifying both the systemic inflammatory milieu and local plaque morphology. Systemically, long-term therapy with these agents consistently leads to a 20% to 30% reduction in high-sensitivity C-reactive protein (hs-CRP) levels, alongside reductions in circulating pro-inflammatory cytokines, including interleukin-6 (IL-6), tumor necrosis factor-alpha (TNF-\alpha), and monocyte chemoattractant protein-1 (MCP-1).[2] This anti-inflammatory action is paired with improvements in the systemic lipid profile, characterized by significant reductions in total cholesterol, low-density lipoprotein cholesterol (LDL-C), fasting triglycerides, and apolipoprotein B (ApoB), which reduces the circulating substrate available for subendothelial retention and subsequent oxidation.[2]

At the cellular level within the vascular wall, GLP-1R activation directly improves endothelial function. It upregulates the expression and enzymatic phosphorylation of endothelial nitric oxide synthase (eNOS), thereby restoring nitric oxide bioavailability, promoting physiological vasodilation, and counteracting oxidative stress induced by reactive oxygen species (ROS).[2] Furthermore, GLP-1RAs downregulate the expression of critical endothelial cell adhesion molecules, such as vascular cell adhesion molecule-1 (VCAM-1) and intercellular adhesion molecule-1 (ICAM-1), which curtails the adhesion, recruitment, and transendothelial migration of circulating monocytes into the intima.[2]

For plaques that have already developed, GLP-1RAs actively encourage structural stabilization, converting vulnerable, rupture-prone lesions into quiescent, stable phenotypes. In the setting of metabolic dysfunction, intra-plaque macrophages typically adopt a pro-inflammatory M1 phenotype, secreting matrix metalloproteinases (MMPs) that degrade the protective extracellular matrix of the fibrous cap. GLP-1RA therapy induces a phenotypic shift in these intra-plaque macrophages, promoting an anti-inflammatory, reparative M2 polarization. This phenotypic shift leads to a marked downregulation of matrix metalloproteinase-9 (MMP-9) and a reciprocal preservation of tissue inhibitor of metalloproteinases-1 (TIMP-1). By tilting the enzymatic balance away from matrix degradation, GLP-1RAs promote the thickening of the plaque's fibrous cap and reduce the size of its thrombogenic necrotic core. Consequently, the structural integrity of the atheromatous lesion is preserved, preventing the sudden plaque fissures or ruptures that trigger acute coronary syndromes and cerebrovascular accidents.

These vascular stabilization effects are supported by real-world clinical registry data spanning 2021 to 2026, which show rapid reductions in ischemic events following the initiation of therapy, well before substantial weight loss is achieved.[15]

Management of Heart Failure with Preserved Ejection Fraction (HFpEF)

Heart failure with preserved ejection fraction (HFpEF) represents a highly prevalent and complex clinical phenotype, particularly among aging populations with concurrent obesity, hypertension, and metabolic syndrome. Characterized by exertional dyspnea, exercise intolerance, and severe systemic congestion, HFpEF was historically difficult to treat, with therapeutic options largely restricted to symptomatic management via loop diuretics. The therapeutic landscape changed with the publication of the STEP-HFpEF and STEP-HFpEF DM randomized controlled trials.[16,17] These trials

demonstrated that once-weekly semaglutide 2.4 mg delivered substantial, clinically meaningful improvements in patients with obesity-related HFpEF, as measured by the Kansas City Cardiomyopathy Questionnaire Clinical Summary Score (KCCQ-CSS), alongside reductions in body weight and significant increases in functional capacity determined by the 6-minute walk distance (6MWD).[16,17]

The success of GLP-1RAs in this clinical arena relates directly to the unique pathophysiology of obesity-related HFpEF, which is increasingly understood to be a systemic inflammatory condition driven by adipokine dysregulation.[18] In patients with visceral adiposity, the epicardial adipose tissue (EAT)-a metabolically active depot of visceral fat located between the myocardium and the visceral pericardium-undergoes hypertrophy, hyperplasia, and inflammatory infiltration.[18] This dysfunctional EAT secretes an excess of pro-inflammatory adipokines, including leptin, IL-6, and TNF-\alpha, directly into the adjacent myocardium via paracrine pathways.[18] This localized inflammatory surge promotes microvascular rarefaction, interstitial myocardial fibrosis, and cardiomyocyte hypertrophy, which collectively increase ventricular stiffness, elevate left ventricular filling pressures, and impair diastolic relaxation.[18] GLP-1RAs directly interrupt this pathogenic sequence. Although human cardiomyocytes express negligible levels of GLP-1R, the receptors are expressed on the endothelial and stromal cells of coronary microvessels and within EAT depots.[6,18] GLP-1RA therapy drives a targeted, disproportionate reduction in EAT volume and shifts its secretome away from a pro-inflammatory profile toward an anti-inflammatory state.[18] This reduction in local mechanical constraint and paracrine inflammation lowers myocardial stiffness, protects coronary microvascular function, and improves diastolic compliance.[18]

Furthermore, these local cardiac benefits are enhanced by systemic updates from trials completed in 2025 and early 2026, including the landmark SUMMIT trial evaluating the dual GIP/GLP-1 receptor agonist tirzepatide in patients with obesity-related HFpEF.[19] The SUMMIT data demonstrated a significant reduction in the risk of composite heart failure events-encompassing adjudicated heart failure hospitalizations, urgent heart failure visits, and cardiovascular mortality-alongside an unprecedented improvement in exercise capacity.[19] Importantly, the clinical benefits of GLP-1RAs appear to be specific to the cardiometabolic HFpEF phenotype; corresponding trials in heart failure with reduced ejection fraction (HFrEF) have not demonstrated equivalent success, underscoring that these agents function primarily by addressing metabolic inflammation, microvascular dysfunction, and pericardial fat accumulation rather than directly modulating myocardial contractility.[18] Reflecting these data, clinical guidelines in 2026 recognize GLP-1RAs as a foundational component of targeted, multi-pillar therapeutic regimens for obesity-related HFpEF.

Renal Outcomes and the Prevention of Chronic Kidney Disease (CKD)

The cardiorenal-metabolic axis links cardiac health with renal performance, meaning that metabolic stress in one system frequently accelerates decline in the other.[20] The definitive validation of the primary renal protective properties of GLP-1RAs was provided by the FLOW trial.[10] This multinational, double-blind, randomized controlled trial was stopped early following an interim analysis that demonstrated clear, overwhelming clinical efficacy.

Investigating once-weekly subcutaneous semaglutide 1.0 mg in patients with type 2 diabetes and confirmed chronic kidney disease, the FLOW trial revealed a 24% reduction in the primary composite endpoint, which tracked renal failure progression, a persistent decline in eGFR of 50% or greater from baseline, or death from renal or cardiovascular causes.[10]

The physiological mechanisms through which GLP-1 receptor activation preserves renal structure and function operate across hemodynamic, metabolic, and cellular pathways. Hemodynamically, GLP-1RAs exert a modulating effect on renal microcirculation.[21] Within the proximal renal tubule, GLP-1Rs are expressed on the brush border membrane, where their activation inhibits the sodium-hydrogen exchanger 3 (NHE3).[6,21] This molecular inhibition results in localized natriuresis and diuresis.[21] The increased delivery of sodium to the macula densa restores tubuloglomerular feedback, leading to modulated vasoconstriction of the afferent arteriole, which lowers intraglomerular pressure and alleviates harmful glomerular hyperfiltration.[21] This hemodynamic profile is complementary to that of sodium-glucose cotransporter-2 (SGLT2) inhibitors, which act primarily via independent afferent pathways, allowing for a combined cardiorenal therapeutic strategy.[20] Clinical outcomes confirm that this hemodynamic modulation leads to a continuous, sustained reduction in urinary albumin-to-creatinine ratio (UACR) by approximately 24% to 32%, serving as a key clinical indicator of mitigated glomerular endothelial shearing.

Beyond these microcirculatory hemodynamic changes, GLP-1RAs protect the structural integrity of the renal parenchyma through direct anti-inflammatory and anti-fibrotic actions. Chronic hyperglycemia and metabolic syndrome induce oxidative stress within glomerular podocytes, leading to podocyte foot process effacement, detachment, and progressive glomerulosclerosis.[21] GLP-1 receptor activation downregulates the localized expression of transforming growth factor-beta 1 (TGF-\beta1), connective tissue growth factor (CTGF), and fibronectin within the renal cortex.[22] This downregulatory effect reduces the activation and proliferation of interstitial fibroblasts, thereby preventing

excess extracellular matrix deposition and subsequent tubulointerstitial fibrosis.[22] Large-scale systematic reviews and meta-analyses published between 2024 and 2026, compiling data from over 90,000 patients, have confirmed that GLP-1RAs provide a sustained, long-term reduction in the annual rate of eGFR decline.[4] Crucially, real-world cohort studies demonstrate that these protective benefits extend to patients with non-diabetic forms of nephropathy, such as hypertensive nephrosclerosis and obesity-related glomerulopathy.[15] This broad efficacy has led to expanding clinical indications focused on long-term organ preservation, effectively delaying the onset of end-stage kidney disease and reducing the global requirement for chronic renal replacement therapies.

Metabolic Dysfunction-Associated Steatohepatitis (MASH) Resolution

Metabolic dysfunction-associated steatohepatitis (MASH)-historically termed nonalcoholic steatohepatitis (NASH)-is the progressive, inflammatory manifestation of metabolic dysfunction-associated steatotic liver disease (MASLD).[23] Characterized by hepatic macrovesicular steatosis, lobular inflammation, hepatocyte ballooning, and variable degrees of pericentral fibrosis, MASH has emerged as a primary driver of cirrhosis, hepatocellular carcinoma, and indications for orthotopic liver transplantation worldwide. For decades, clinical management was restricted to general lifestyle advice and weight loss targets that are rarely achieved or sustained in clinical practice. The confirmation of the therapeutic efficacy of GLP-1RAs in hepatology has led to dedicated regulatory indications, highlighted by the milestone approval of semaglutide for MASH with moderate-to-advanced (stages F2 and F3) hepatic fibrosis.[9,24,25]

The therapeutic effects of GLP-1RAs in MASH are driven by a dual mechanism combining direct intrahepatic cellular regulation with systemic metabolic improvements.[26] Structurally, human hepatocytes do not express the GLP-1 receptor; instead, the intrahepatic actions of GLP-1RAs are mediated through receptors located on endothelial cells, fenestrated sinusoidal cells, and resident hepatic immune cell populations, particularly Kupffer cells.[6,26] Systemically, GLP-1RAs reduce the continuous influx of non-esterified fatty acids (NEFAs) into the liver by restoring peripheral insulin sensitivity, suppressing inappropriate lipolysis within dysfunctional visceral adipose tissue, and reducing postprandial chylomicron delivery via intestinal pathways.[26] Within the liver, this metabolic shift reduces *de novo* lipogenesis (DNL) and increases mitochondrial fatty acid \beta-oxidation through the activation of hepatic adenosine monophosphate-activated protein kinase (AMPK) pathways.[26]

This reduction in lipotoxicity helps mitigate the active, destructive inflammatory phase of MASH. When hepatocytes are overloaded with excess lipids, they experience severe endoplasmic reticulum (ER) stress and accumulate reactive oxygen species, triggering cell death cascades and releasing pro-inflammatory damage-associated molecular patterns (DAMPs). These DAMPs activate resident Kupffer cells and recruit circulating monocyte-derived macrophages, driving the production of inflammatory cytokines and activating hepatic stellate cells, the primary producers of collagen and extracellular matrix in liver fibrosis. GLP-1RA therapy decreases Kupffer cell activation and suppresses the assembly of the NLRP3 inflammasome, which reduces the intrahepatic expression of IL-1β and IL-18.

Clinical data from phase III trials completed between 2024 and 2026, such as the ESSENCE trial for semaglutide and the SYNERGY-NASH trial for the dual GIP/GLP-1 receptor agonist tirzepatide, have demonstrated high rates of histological MASH resolution-defined as the clearance of hepatocyte ballooning and lobular inflammation-without any worsening of underlying liver fibrosis.[9,24,27] Furthermore, significant proportions of treated patients showed a regression of fibrosis by at least one stage.[9] While these agents do not directly reverse established, end-stage cirrhotic remodeling (stage F4), their capacity to arrest disease progression and promote tissue regression in stages F2 and F3 has established GLP-1RAs as a standard of care in multidisciplinary hepatology and endocrine clinics.[26]

Neuroprotection and Cognitive Health

One of the most innovative areas of incretin research focuses on the neuroprotective effects of GLP-1RAs within the central nervous system. This research is supported by the "Type 3 Diabetes" hypothesis, which describes Alzheimer's disease and related dementias as metabolic disorders characterized by central insulin resistance, impaired cerebral glucose utilization, and localized neuroinflammation. Because native GLP-1 and long-acting synthetic analogs can cross the blood-brain barrier via passive diffusion and carrier-mediated transport mechanisms, they can interact directly with GLP-1Rs expressed throughout the brain, notably within the pyramidal neurons of the hippocampus, the cerebral cortex, and resident glial cells.[11,12]

The clinical potential of this approach was highlighted by a multi-center, randomized, double-blind phase IIb clinical trial published in *Nature Medicine*, which evaluated the long-term administration of the GLP-1 analog liraglutide in patients with mild-to-moderate.

Alzheimer's disease dementia.[11] The trial met its secondary clinical endpoints, demonstrating an 18% reduction in the rate of cognitive decline over 12 months, as measured by the Alzheimer's Disease Assessment Scale-Cognitive Subscale (ADAS-Cog), alongside a nearly 50% reduction in the progression of global brain volume loss (cerebral atrophy) quantified via structural magnetic resonance imaging (MRI).[11] While the

primary endpoint-which tracked changes in cerebral glucose metabolic rates via fluorine-18 fluorodeoxydeoxyglucose positron emission tomography (^{18}F-FDG-PET) scan-showed variability across certain patient sub-cohorts, the overall clinical and structural trends supported a disease-modifying effect.[11] The molecular pathways driving these neuroprotective benefits involve a down-regulation of central neuroinflammatory cascades. In neurodegenerative diseases, microglia and astrocytes often enter a chronically activated, neurotoxic state. GLP-1 receptor activation on microglia suppresses the NF-\kappaB signaling pathway and inhibits the assembly of the NLRP3 inflammasome, reducing the production of neurotoxic cytokines like IL-1β, IL-6, and TNF-\alpha. Simultaneously, GLP-1RAs stimulate the expression of neurotrophic factors, such as brain-derived neurotrophic factor (BDNF) and glial cell line-derived neurotrophic factor (GDNF), which support synaptic plasticity, enhance long-term potentiation (LTP) in the hippocampus, and preserve dendritic spine density.[12]

Furthermore, these agents mitigate the accumulation and impact of pathological protein aggregates. GLP-1 receptor signaling reduces the hyperphosphorylation of tau proteins by modulating the activity of glycogen synthase kinase-3 beta (GSK-3β) and decreases the deposition of amyloid-\beta (Aβ) plaques by enhancing microglial phagocytic clearance and stabilizing mitochondrial membrane potentials within cerebral neurons. While clinical challenges persist-such as determining the optimal dosing schedules and drug formulations required to maximize central nervous system penetration-large-scale phase III clinical programs, including the EVOKE and EVOKE Plus trials investigating high-dose oral semaglutide in early Alzheimer's disease, are positioned to clarify the role of incretin mimetics as disease-modifying options for neurodegenerative disorders.[28]

Impact on Sleep Apnea and Substance Use Disorders

The therapeutic benefits of GLP-1RAs extend beyond traditional visceral organs into complex respiratory and neuropsychiatric conditions, highlighted by their impact on obstructive sleep apnea (OSA) and substance use disorders. OSA is a prevalent sleep-related breathing disorder characterized by recurrent collapse of the upper airway during sleep, leading to intermittent hypoxemia, sleep fragmentation, and elevated cardiovascular risk. The therapeutic potential of GLP-1RAs in this field was confirmed by the SURMOUNT-OSA phase III clinical trials, which evaluated the dual GIP/GLP-1 receptor agonist tirzepatide in adults with moderate-to-severe OSA and co-existing obesity.[13] The trials demonstrated a statistically significant and clinically meaningful reduction in the apnea-hypopnea index (AHI)-the primary metric tracking the number of partial or complete airway obstructions per hour of sleep-with many patients achieving a resolution of their severe disease status and safely discontinuing continuous positive airway pressure (CPAP) therapy.[13]

The physiological mechanisms underlying this improvement involve both mechanical and inflammatory pathways. Mechanistically, upper airway collapsibility in obesity is driven by the structural deposition of adipose tissue within the parapharyngeal space and the base of the tongue, which narrows the pharyngeal lumen and increases critical closing pressures.[29]

GLP-1RA and dual-agonist therapies promote a targeted reduction in these parapharyngeal fat pads, increasing the cross-sectional area of the upper airway and restoring mechanical stability during sleep.[29] This structural change is accompanied by a reduction in systemic and localized airway inflammation, which improves endothelial function and helps mitigate the cyclic oxidative stress caused by nocturnal hypoxia.

Concurrently, clinical and epidemiological evidence indicates that GLP-1RAs can modulate central reward and addiction pathways.[14] The physiological experience of reward-whether derived from high-calorie foods, alcohol, nicotine, or illicit substances-is mediated by the mesolimbic dopamine system, particularly through dopaminergic projections from the ventral tegmental area (VTA) to the nucleus accumbens.[30,31] GLP-1 receptors are expressed on both GABAergic and dopaminergic neurons within the VTA and the nucleus accumbens.[30,31] When activated by GLP-1RAs, these receptors modulate synaptic dopamine transmission, blunting the acute dopamine spikes that follow substance consumption and reducing the reinforcing nature of the substance.[30,31]

Large-scale real-world observational cohort studies and targeted clinical trials have shown that patients receiving semaglutide or liraglutide experience significant reductions in alcohol cravings and the total number of heavy drinking days compared to matched controls.[14] Similar observational trends have emerged for nicotine addiction, showing increased success rates in smoking cessation attempts, and for opioid use disorders, showing reductions in cue-induced drug cravings.[32] While these behavioral health applications are undergoing formal phase II and III clinical evaluation to establish official indications, the ability of GLP-1RAs to regulate central reward circuitry offers an integrated approach to managing both the metabolic and psychological aspects of chronic disease.[14]

4. Future Directions and Recommendations

The expansion of the incretin class over the last several years points to a dynamic future for multi-receptor agonism and precision metabolic medicine. The therapeutic paradigm is transitioning from single-receptor GLP-1RAs toward unimolecular multi-agonists that target complementary metabolic pathways simultaneously.[5] A prominent example is retatrutide, a triple receptor agonist that combines affinity for the GIP,

GLP-1, and glucagon receptors.[33] By adding glucagon receptor agonism to the GIP/GLP-1 backbone, retatrutide increases energy expenditure through hepatic pathways while maintaining the anorexigenic and insulinotropic benefits of incretin activation. Phase II and ongoing phase III clinical data indicate that this triple agonist approach can achieve reductions in body weight exceeding 24% over 48 weeks, alongside rapid clearance of hepatic fat fractions, which may offer enhanced efficacy for advanced MASH and severe metabolic syndrome.[5,33]

Concurrently, innovative drug development is exploring combinations of incretins with other neuro-hormonal pathways. The co-formulation of the long-acting amylin analog cagrilintide with semaglutide (known as CagriSema) is under active evaluation. Amylin, a peptide co-secreted with insulin by pancreatic beta cells, promotes satiety through distinct, non-overlapping homeostatic pathways in the hindbrain. Combining these mechanisms yields synergistic effects on appetite suppression and energy balance, offering robust metabolic management without requiring higher, less-tolerable doses of individual GLP-1 components.

To improve patient compliance and reduce barriers related to subcutaneous injectables, oral delivery technologies are also advancing. Following the clinical implementation of low-dose oral semaglutide utilizing the absorption enhancer sodium N-(8-[2-hydroxybenzoyl]amino)caprylate (SNAC), the milestone OASIS-1 phase III trial confirmed that high-dose oral semaglutide (50 mg once daily) provides clinical efficacy equivalent to high-dose subcutaneous formulations, broadening the treatment options for patients with needle aversion.[34]

However, the rapid clinical adoption of this therapeutic class highlights the need for balanced clinical guidance regarding manufacturing, economics, and safety. The global demand for GLP-1RAs has caused frequent supply-chain shortages, creating accessibility challenges for vulnerable populations, including those with advanced diabetic nephropathy or established ischemic heart disease.[35] Healthcare systems and international manufacturing networks must focus on scaling production capacities, developing cost-effective generic and biosimilar pathways, and optimizing long-term insurance coverage models to ensure equitable distribution across diverse socioeconomic groups.[35]

Furthermore, long-term safety monitoring via comprehensive clinical registries remains necessary. While data accrued through 2026 support a favorable safety profile for high-dose regimens, clinicians must remain observant regarding low-incidence or long-term adverse events.[36] These include gastrointestinal complications such as severe gastroparesis, intestinal obstruction, and acute cholecystitis, as well as a potential association with medullary thyroid carcinoma, which requires regular screening in individuals with relevant familial risk profiles.[36] Finally, the phenomenon of lean mass loss during rapid weight reduction underscores the importance of combining incretin therapies with structured resistance exercise protocols and adequate protein intake.[3] This approach ensures that weight loss reflects a healthy reduction in adiposity rather than a detrimental loss of skeletal muscle tissue, maintaining physical strength and metabolic health over time.

5. CONCLUSION

The clinical evolution of glucagon-like peptide-1 receptor agonists represents an important advance in contemporary medicine. Initially developed as targeted, second-line options for glycemic control in type 2 diabetes, these agents have proven to be versatile, systemically active molecules that provide multi-organ protection. The clinical evidence gathered across major trials demonstrates that medications like semaglutide and tirzepatide can reduce major adverse cardiovascular events, alter the progression of chronic kidney disease, improve symptoms and outcomes in obesity-related heart failure with preserved ejection fraction, and resolve metabolic dysfunction-associated steatohepatitis. This broad efficacy underscores that metabolic syndrome, cardiovascular diseases, and organ fibrosis are interconnected conditions driven by shared pathways of systemic inflammation and microvascular stress.

Furthermore, the clinical utility of GLP-1RAs continues to expand into new therapeutic areas. Their capacity to cross the blood-brain barrier to modulate neuroinflammation and preserve cognitive function offers a potential avenue for disease-modifying interventions in neurodegenerative disorders such as Alzheimer's and Parkinson's diseases. Concurrently, their roles in reducing the structural severity of obstructive sleep apnea and modulating central mesolimbic reward pathways for substance use disorders demonstrate how a single endocrine intervention can address interrelated physical, respiratory, and behavioral pathologies. As clinical guidelines are updated to reflect this evidence, the integration of GLP-1RAs into early treatment algorithms for cardiovascular, renal, and hepatic health will be key to reducing the global burden of metabolic-driven mortality. Transitioning from a weight-centric to an organ-centric perspective allows healthcare providers to utilize these therapies effectively, maximizing long-term health span and clinical outcomes for patients worldwide.

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