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GLP-1 RECEPTOR AGONISTS BEYOND OBESITY: EXPANDING HORIZONS IN CARDIOMETABOLIC, RENAL, AND NEUROLOGICAL DISEASE

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Abstract

Glucagon-like peptide-1 (GLP-1) receptor agonists were initially created to reduce blood glucose in type 2 diabetes (T2D). In the last ten years, there has been clear evidence of their effectiveness beyond glucose-lowering and weight loss. This review consolidates the emerging evidence on the pleiotropic actions of GLP-1 receptor agonists in cardiovascular, renal, liver, brain, and inflammation. Pioneering cardiovascular outcomes studies (LEADER, SUSTAIN-6, REWIND, and SELECT) have shown marked improvement in major adverse cardiovascular events (MACE), hospitalizations for heart failure, and cardiovascular death. Growing evidence suggests renoprotective effects beyond glucose lowering, and preclinical and early clinical data show promise in non-alcoholic steatohepatitis (NASH), neurodegenerative diseases, and addiction. These results suggest that GLP-1 receptor agonists are a game-changing drug class with a wide range of potential applications beyond metabolic disease.

Keywords: GLP-1 receptor agonists; semaglutide; liraglutide; cardiovascular outcomes; chronic kidney disease; NASH; neurodegeneration; heart failure

1. Introduction

Glucagon-like peptide-1 (GLP-1) is an incretin hormone released from enteroendocrine L-cells in the distal small intestine and colon after a meal. It stimulates glucose-dependent insulin secretion, inhibits glucagon, slows gastric emptying, and increases satiety [1]. In 2005, exenatide, the first GLP-1 receptor agonist (GLP-1 RA), was approved by the US Food and Drug Administration (FDA) for treatment of T2D. There have now been many additions to the class, with once-weekly GLP-1 RAs (semaglutide, dulaglutide, and efpeglenatide) now the mainstay of pharmacotherapy for T2D and obesity [2]. GLP-1 receptors are widely expressed. They are found in the heart, kidney, blood vessels, brain, liver, and immune cells - providing a molecular explanation for the pleiotropic (multifaceted) effects seen in clinical practice [3]. Several pivotal cardiovascular outcome trials (CVOTs) have confirmed its cardiovascular benefits, and recent evidence now suggests GLP-1 RAs are involved in renal protection, reversal of hepatic steatosis, prevention of neurodegeneration, and inflammation [4,5]. Here, we offer a brief synopsis of the evidence supporting these pleiotropic effects and their mechanisms of action.

2. Mechanisms of Pleiotropic Action

The wide range of effects of GLP-1 RAs is due to the presence of the GLP-1 receptor (GLP-1R) throughout the body. On binding to GLP-1Rs, GLP-1 RAs stimulate adenylate cyclase through Gs-protein-mediated coupling, increasing intracellular cAMP. This results in anti-

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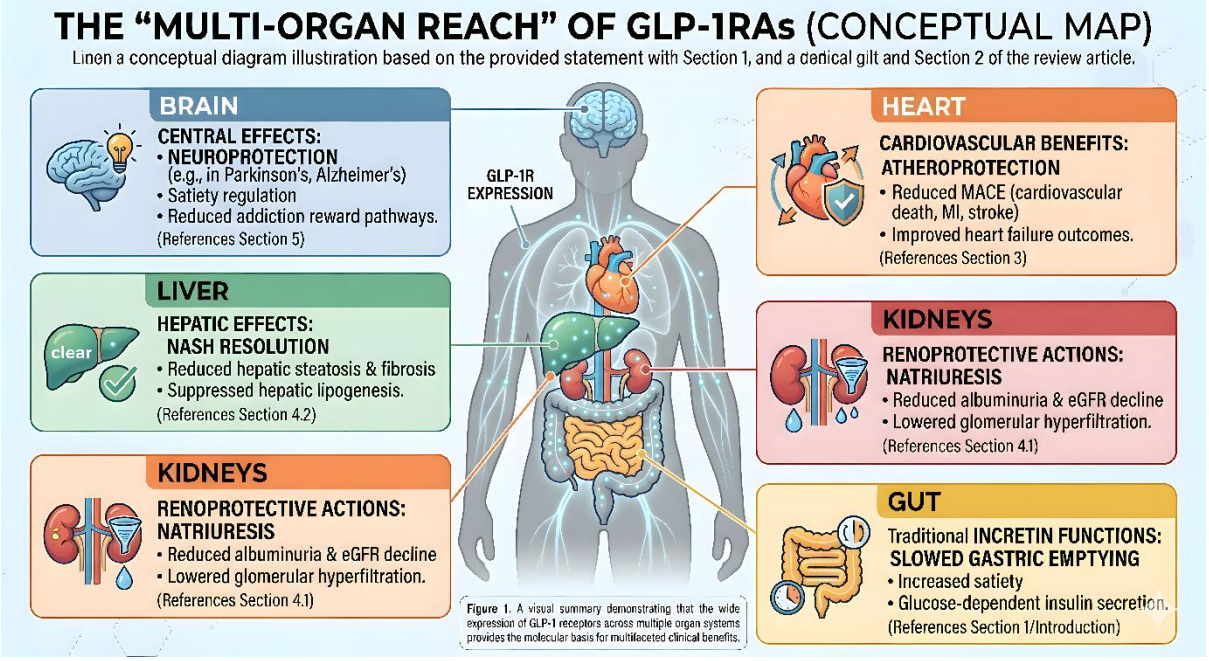
inflammatory, anti-apoptotic, and vasodilatory effects in the heart and blood vessels [3]. Renal effects include regulation of tubular and podocyte sodium-glucose cotransporters and antioxidant effects [6]. In the brain, GLP-1Rs are found in the hypothalamus (hunger), brainstem (nausea/vomiting), hippocampus (learning), and reward centres [7]. Anti-inflammatory effects include inhibition of NF-κB, suppression of macrophage activation and pro-inflammatory cytokines (TNF-α, IL-6) [8]. These effects collectively explain the observations below. It's shown in Figure 1.



3. Cardiovascular Effects

3.1 Cardiovascular Outcome Trials

LEADER (n=9,340) showed liraglutide reduced the primary composite endpoint of MACE (cardiovascular death, non-fatal MI, non-fatal stroke) by 13% compared to placebo (HR 0.87; 95% CI 0.78-0.97) over a median of 3.8 years in patients with T2D and established cardiovascular disease [9]. Cardiovascular death was reduced by 22%. SUSTAIN-6 showed semaglutide reduced MACE by 26% (HR 0.74; 95% CI 0.58–0.95) [10]. The REWIND trial showed that dulaglutide reduced MACE by 12% (HR 0.88; 95% CI 0.79-0.99) over 5.4 years in patients with T2D with established or high-risk cardiovascular disease [11]. Importantly, the SELECT trial (2023) recruited people without diabetes but with obesity and established cardiovascular disease, with a 20% MACE reduction with semaglutide 2.4 mg, proving cardiovascular benefit without an impact on blood glucose levels [12].

3.2 Heart Failure

Results from the STEP-HFpEF and FLOW trials suggest GLP-1 RAs are beneficial in reducing symptoms, exercise capacity, and quality of life in patients with obesity and heart failure with preserved ejection fraction (HFpEF) [13,14]. Epicardial fat, cardiac fibrosis, inflammation, and natriuretic peptides are reduced. The most recent American College of Cardiology (ACC) and American Heart Association (AHA) guidelines now include GLP-1 RAs

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as an option in obese HFpEF [15]. Significantly, there was no harm when used in patients with reduced ejection fraction heart failure (HFrEF), although the benefit has not yet been proven.

3.3 Atherosclerosis and Blood Pressure

Systolic blood pressure is reduced by 2-4 mmHg by GLP-1 RAs via natriuresis and direct vascular action [3]. Liraglutide and semaglutide reduce carotid intima-media thickness, an indicator of atherosclerosis [9]. LDL-C, triglycerides, and CRP are also lowered, adding to the beneficial effects.

4. Renal and Hepatic Effects

4.1 Chronic Kidney Disease

Diabetic kidney disease (DKD) is the most common cause of end-stage renal disease. The FLOW trial (2024) is the first dedicated renal outcome trial for a GLP-1 RA: semaglutide 1.0 mg decreased the composite renal endpoint (≥50% eGFR decline, dialysis, renal transplant, or renal death) 24% (HR 0.76; 95% CI 0.66-0.88) [16]. There was also marked albuminuria reduction, with effects persisting after adjustment for glucose and BP reduction, suggesting a direct renal protective effect. These are mediated by lowering of glomerular hyperfiltration, anti-inflammatory effects on mesangial cells and tubular sodium reabsorption [6]. KDIGO 2024 recommends GLP-1 RAs as a preferred second-line agent in T2D with CKD [17].

4.2 Non-Alcoholic Fatty Liver Disease / NASH

Non-alcoholic steatohepatitis (NASH) is an important area of unmet need with few therapeutic options. Liraglutide induced resolution of NASH in 39% of patients in the LEAN trial versus 9% with placebo [18]. The phase 3 ESSENCE trial of semaglutide 2.4 mg (2024) showed 62% of patients achieved NASH resolution with semaglutide compared to 20% with placebo, and significant improvement in hepatic fibrosis [19]. Semaglutide (Wegovy) was approved for the treatment of NASH in March 2025 by the FDA. GLP-1 RAs exert effects by suppressing hepatic lipogenesis, hepatocyte apoptosis, and stellate cell activation [20].

5. Neurological and Behavioral Effects

5.1 Neurodegenerative Disease

Retrospective analysis of the CPRD database demonstrated that in patients with T2D, use of a GLP-1 RA was associated with a 40-50% reduction in the incidence of Parkinson's disease when compared to other anti-diabetic medications [21]. The first phase 3 trial of lixisenatide for early Parkinson's disease (2023) showed reduced motor decline as measured by MDS-UPDRS Part III after 12 months (between-group difference -3.08 points; $p<0.001$) [22]. GLP-1 RAs have anti-inflammatory, enhance BDNF expression, decrease α-synuclein aggregation, and protect mitochondria in dopaminergic neurons [7]. For Alzheimer's disease, phase 3 trials of semaglutide (EVOKE, EVOKE PLUS) are underway. Animal studies show GLP-1 RAs decrease amyloid-β, tau phosphorylation, and plaque formation in rodents [23]. Epidemiological data show GLP-1 RA use in T2D patients is associated with lower dementia risk than other drugs [24], but awaits confirmation in randomized trials.

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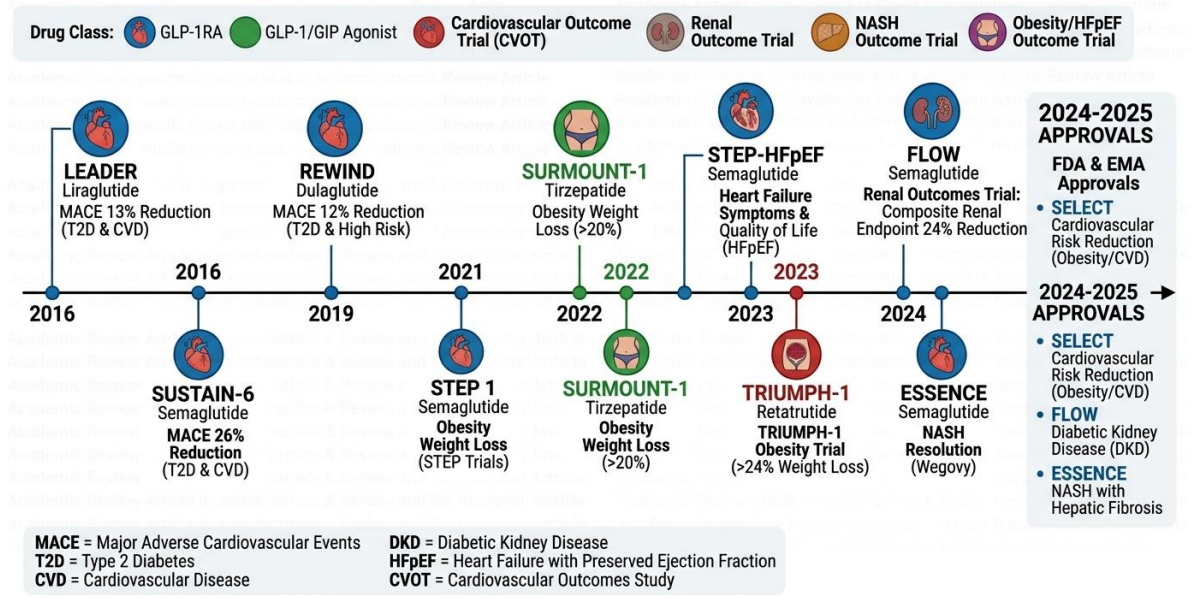
5.2 Addiction and Substance Use

GLP-1Rs are found in the nucleus accumbens and ventral tegmental area - regions important in reward pathways. GLP-1 RA treatment reliably decreases alcohol intake, nicotine self-administration and opioid reward in animals [25]. Registry data from the Nordic countries show lower incidence of alcohol-related hospital admissions, alcohol use disorder, and failed smoking cessation in GLP-1 RA users with T2D [26]. Trials of semaglutide in alcohol use disorder and smoking cessation are in phase 2 (NCT05186376, NCT05632094).

Figure 3: Timeline of Major Clinical Trials (CVOTs & Beyond) for GLP-1 Receptor Agonists



6. Anti-Inflammatory and Immune Effects

Chronic systemic low-grade inflammation is common among people with obesity, T2D and complications. GLP-1 RAs lower high-sensitivity C-reactive protein (hsCRP), interleukins (IL-6), tumor necrosis factor (TNF-α), and monocyte chemoattractant protein (MCP-1) in several studies [8]. At a molecular level, stimulation of the GLP-1R on macrophages drives M2 polarization, blocks the NLRP3 inflammasome and prevents NF-κB nuclear translocation [3]. This may explain improvement in psoriasis (observational), inflammatory bowel disease (animal studies) and polycystic ovary syndrome (PCOS), where small studies demonstrate improvement in androgen levels and ovulation [27]. For COVID-19, retrospective analyses showed GLP-1 RA users with obesity were less likely to require mechanical ventilation or ICU care, but it is unclear whether this was influenced by other factors. Prospective studies of GLP-1 RAs in acute inflammatory diseases are underway [28].

7. Safety Considerations

GLP-1 RAs have a good safety profile. Gastrointestinal symptoms (nausea, vomiting, diarrhoea) are the most frequent adverse events, dose-dependent, usually transient, and can be minimised by dose titration [2]. Longitudinal studies have not supported concerns of pancreatitis and pancreatic cancer [9]. The FDA introduced a warning about potential thyroid C-cell tumors based on animal studies, but this has not been reported in humans, and is unlikely at

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pharmacologic doses [2]. Long-term risk of gastroparesis should be considered, especially in patients with gastroparesis. High-dose semaglutide has been associated with lean muscle mass loss, but this is being investigated [29]. Occasional reports of non-arteritic anterior ischemic optic neuropathy (NAION) have been made with semaglutide, and the FDA released a statement in 2024 confirming review of this risk [30]. Pharmacovigilance and long-term safety monitoring is crucial.

8. Future Directions

Novel multi-receptor agonists are a key focus. The GLP-1/GIP receptor agonist tirzepatide is more effective than semaglutide for both glucose and weight loss in head-to-head studies [31]. Triple agonists for the GLP-1, GIP, and glucagon receptors (retatrutide) are in phase 3 studies, with >24% weight loss, close to bariatric surgery [32]. Oral GLP-1 RA (oral semaglutide, oral orforglipron) could vastly increase accessibility and compliance. Central nervous system (CNS)-targeted GLP-1 RA formulations are being investigated for central nervous system indications. Biomarker-based patient grouping to select the right patient for non-metabolic indications is a key focus [7,32].

9. Conclusion

The GLP-1 receptor agonists have evolved from glucose-lowering medications to a multifunctional drug class with cardio-, renal-, hepatic-, brain-, and anti-inflammatory protective properties. The combination of compelling evidence from large randomized trials (LEADER, SUSTAIN-6, SELECT, and FLOW) with plausible mechanisms based on the high density of GLP-1R in various organ systems has established their place in the treatment of non-metabolic diseases. As the drug class expands to include more potent and pleiotropically active agents, it is logical to extend GLP-1 RA therapy to non-obese and non-diabetic patients with cardiovascular, renal, neurological, and other factors that predict benefit. Healthcare professionals should be vigilant in observing new indications, safety signals, and guidelines across specialties.

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