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REVIEW ARTICLE

Systemic Effects of GLP-1 and Dual GIP/GLP-1 Receptor Agonism in Obesity, Cardiovascular Health, and Neurodegeneration

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Abstract: Glucagon-like peptide-1 receptor agonists (GLP-1 RAs) and the novel dual GIP/GLP-1 receptor agonists have transcended their initial designation as merely anti-hyperglycemic agents to become pivotal tools in the management of systemic metabolic pathology. The transition from Liraglutide to Semaglutide, and subsequently to the dual agonist Tirzepatide, marks a paradigm shift in pharmacotherapy, moving from glucocentric control to substantial adiposity reduction and end-organ protection. Clinical data indicates that these agents facilitate weight loss magnitudes previously attainable only through bariatric intervention, primarily via central mechanisms involving the hypothalamus and hindbrain to regulate satiety and energy expenditure. Beyond anthropometrics, recent landmark outcomes, particularly from the SELECT trial, demonstrate that Semaglutide confers significant cardiovascular protection in non-diabetic individuals with obesity, reducing major adverse cardiovascular events through mechanisms distinct from weight loss alone, including anti-inflammatory pathways and endothelial stabilization. Moreover, emerging research suggests these peptides cross the blood-brain barrier to mitigate neuroinflammation and enhance neuronal insulin signaling, offering potential disease-modifying effects in Alzheimer's and Parkinson's disease. These findings point towards a unified therapeutic strategy addressing the intersection of metabolic, cardiovascular, and neurological health.

Keywords: GLP-1 Receptor Agonists; Tirzepatide; Semaglutide; Cardiovascular Outcomes; Neuroprotection.

1. Introduction

The clinical management of Type 2 Diabetes Mellitus (T2DM) is based on glucocentric paradigm, prioritizing HbA1c reduction often through the use of sulfonylureas, thiazolidinediones, or insulin—agents frequently associated with the paradox of iatrogenic weight gain and significant hypoglycemic risk. The isolation and subsequent therapeutic application of incretin hormones, specifically Glucagon-like peptide-1 (GLP-1), initiated a new era in metabolic medicine, shifting the focus towards physiological restoration. GLP-1 is a gut-derived peptide secreted by intestinal L-cells in the distal ileum and colon in response to nutrient ingestion; it potentiates glucose-dependent insulin secretion, suppresses inappropriate glucagon release, and centrally mediates satiety while delaying gastric emptying to blunt postprandial excursions [1]. However, the therapeutic utility of native GLP-1 is severely limited by its pharmacokinetic instability; it is rapidly degraded by the ubiquitous enzyme dipeptidyl peptidase-4 (DPP-4), which cleaves the N-terminal dipeptide, rendering the hormone inactive within minutes and necessitating the development of structurally resistant analogues to achieve viable duration of action [2].

Early therapeutic agents such as Liraglutide demonstrated that sustained GLP-1 receptor activation extended far beyond the pancreatic beta-cell, influencing diverse organ systems that express the GLP-1 receptor, including the cardiovascular system and the central nervous system. The subsequent development of Semaglutide, a long-acting analogue modified with a C18 fatty diacid to enhance albumin binding, and Tirzepatide, a first-in-class dual glucose-dependent insulinotropic polypeptide (GIP) and GLP-1 receptor agonist, has amplified these systemic effects to unprecedented levels [3].

Tirzepatide, in particular, leverages the synergistic potential of GIP—historically considered inert or counterproductive in T2DM—to enhance insulin secretion and modulate lipid metabolism in adipose tissue, resulting in superior efficacy profiles compared to selective GLP-1 agonism alone [4]. Current evidence points to a therapeutic expansion where these drugs address the root pathologies of obesity, atherosclerotic cardiovascular disease (ASCVD), and potentially neurodegenerative disorders.

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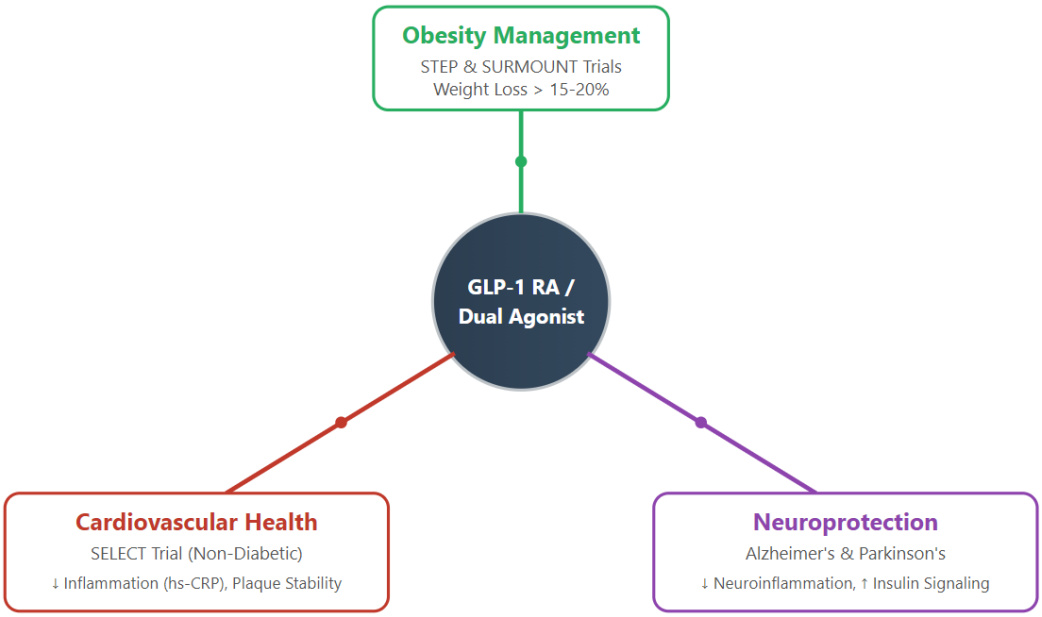

Figure 1. Therapeutic expansion of GLP-1 receptor agonists

2. Management of Obesity

The pharmacologic management of obesity has historically been characterized by modest efficacy and significant safety concerns, with previous generations of sympathomimetic agents often failing to provide sustainable long-term weight reduction. The introduction of high-dose GLP-1 RAs has fundamentally altered this landscape, establishing a new efficacy threshold that bridges the substantial gap between behavioral modifications and invasive bariatric surgery.

2.1. The STEP Program

Liraglutide 3.0 mg was the first GLP-1 RA to receive regulatory approval specifically for chronic weight management, marking a critical milestone in obesity pharmacotherapy. The SCALE obesity and prediabetes trial demonstrated that Liraglutide could achieve a mean weight loss of approximately 8.0% over 56 weeks, a result significantly higher than placebo and sufficient to improve metabolic parameters [5]. However, the clinical utility of Liraglutide was often limited by a "therapeutic ceiling"; weight loss frequently plateaued due to compensatory metabolic adaptations that drive hunger and reduce energy expenditure, necessitating agents with greater potency to overcome these biological defenses.

Table 1. Comparison of Pharmacological Profiles of Incretin-Based Therapies

Feature	Liraglutide	Semaglutide	Tirzepatide
Drug Class	GLP-1 Receptor Agonist	GLP-1 Receptor Agonist	Dual GIP/GLP-1 Receptor Agonist
Structural Modification	Acylated with C16 fatty acid (palmitic acid)	Acylated with C18 fatty acid (stearic diacid)	Linear peptide with C20 fatty diacid moiety
Half-life	~13 hours	~165 hours (approx. 1 week)	~116 hours (approx. 5 days)
Dosing Frequency	Once Daily (Subcutaneous)	Once Weekly (Subcutaneous)	Once Weekly (Subcutaneous)
Primary Mechanism	Selective GLP-1R activation	Selective GLP-1R activation	Synergistic GIPR and GLP-1R activation
Max Approved Weight Loss Dose	3.0 mg	2.4 mg	15 mg

Semaglutide, utilized at a once-weekly dose of 2.4 mg, represented the next evolutionary step in potency and convenience. The Semaglutide Treatment Effect in People with Obesity (STEP) clinical trial program provided robust evidence of its superiority over daily Liraglutide. In STEP 1, participants without diabetes achieved a mean weight reduction of 14.9% from baseline compared to 2.4% with placebo, with a substantial proportion of patients (over 30%) achieving profound weight loss exceeding 20% [6]. This

magnitude of weight loss—approaching 15%—is clinically critical as it represents the threshold required for the remission of complex obesity-related complications such as obstructive sleep apnea, amelioration of mobility issues, and histological improvement in non-alcoholic fatty liver disease (NAFLD) [7]. The mechanism driving this superior efficacy involves prolonged receptor occupancy and deeper penetration into appetite-regulating centers of the brain. Specifically, Semaglutide accesses the arcuate nucleus of the hypothalamus via the fenestrated capillaries of the circumventricular organs, where it directly stimulates anorexigenic pro-opiomelanocortin (POMC) neurons and simultaneously inhibits orexigenic neuropeptide Y/agouti-related peptide (NPY/AgRP) neurons, thereby fundamentally altering the homeostatic set-point for body weight [8].

2.2. Dual Agonism

Tirzepatide introduces a novel mechanism by targeting both GIP and GLP-1 receptors, creating a single molecule with dual incretin activity. Historically, GIP was thought to be obesogenic due to its anabolic effects on adipose tissue, which promote fat storage in physiological states. However, emerging data suggests that in the presence of GLP-1 co-agonism, GIP signaling is redirected to potentiate weight loss through distinct central mechanisms and the improvement of white adipose tissue function and insulin sensitivity [9]. This "biased agonism" or synergistic effect allows for aggressive weight reduction without a proportional increase in adverse events.

Table 2. Efficacy Milestones in Chronic Weight Management (Non-Diabetic Cohorts)

Trial Name	SCALE Obesity & Prediabetes	STEP 1	SURMOUNT-1
Agent	Liraglutide 3.0 mg	Semaglutide 2.4 mg	Tirzepatide 15 mg
Mechanism	Mono-agonist (GLP-1)	Mono-agonist (GLP-1)	Dual Agonist (GIP/GLP-1)
Treatment Duration	56 Weeks	68 Weeks	72 Weeks
Mean Body Weight Change	-8.0%	-14.9%	-20.9%
Participants achieving ≥15% Loss	14.4%	50.5%	56.7% (with 36.2% losing ≥25%)
Adverse Effects	Nausea, Diarrhea	Nausea, Diarrhea	Nausea, Diarrhea, Dyspepsia
Reference	Pi-Sunyer et al. [5]	Wilding et al. [6]	Jastreboff et al. [10]

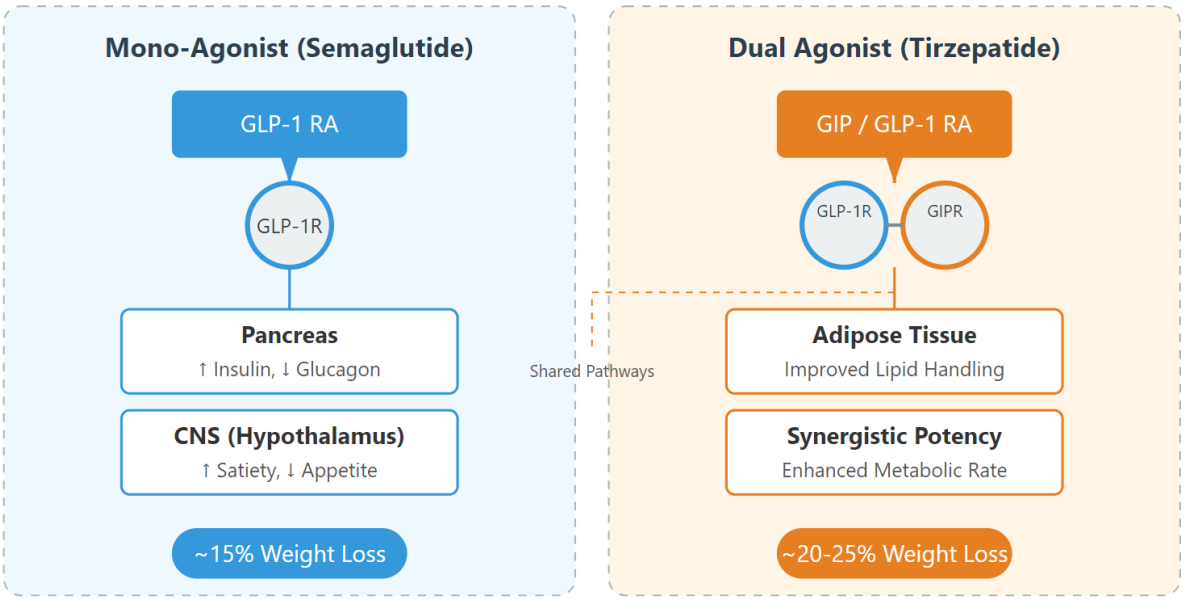

Figure 1. Schematic comparison of mono-agonist (Semaglutide) and dual-agonist (Tirzepatide) pathways

The SURMOUNT-1 trial evaluated Tirzepatide in individuals with obesity but without diabetes, testing the hypothesis that dual agonism could surpass the ceiling of mono-agonist therapy. The results were unprecedented for pharmacotherapy, with the highest dose (15 mg) yielding a mean weight reduction of 20.9% at 72 weeks, demonstrating a clear dose-dependent efficacy [10]. Notably, over one-third of participants in the 15 mg cohort achieved a weight reduction of at least 25%, a figure that rivals outcomes seen with sleeve gastrectomy and represents a transformative potential for medical weight management. This data suggests that dual

agonism may overcome the resistance mechanisms often seen with mono-agonists, likely through complementary effects on central satiety signaling and peripheral lipid handling, effectively resetting the metabolic set-point [11]. By engaging receptors in the hindbrain (area postrema) and the hypothalamus simultaneously, Tirzepatide appears to uncouple the body's defensive response to weight loss, allowing for sustained reduction in adiposity.

3. Cardiovascular Risk Reduction

For decades, glucose-lowering drugs were evaluated primarily on their ability to lower HbA1c, with cardiovascular safety being a secondary regulatory requirement essentially checking for "non-inferiority." The GLP-1 RA class has pivoted this paradigm, demonstrating that these agents can actively modify the natural history of atherosclerotic cardiovascular disease (ASCVD) through mechanisms that appear independent of their glucose-lowering effects.

3.1. Establishing Safety and Benefit in Diabetes

The initial confirmation of cardiovascular benefit came from cardiovascular outcomes trials (CVOTs) in patients with T2DM. The LEADER trial investigated Liraglutide and reported a 13% relative risk reduction in major adverse cardiovascular events (MACE), driven primarily by a reduction in cardiovascular death [12]. Similarly, the SUSTAIN-6 trial showed that Semaglutide significantly reduced the risk of MACE, largely through a profound decrease in non-fatal strokes [13].

Table 3. Cardiovascular Outcomes Trials (CVOT) Summary

Trial	LEADER	SUSTAIN-6	SELECT
Agent	Liraglutide	Semaglutide (OW)	Semaglutide (OW)
Population	T2DM + High CV Risk	T2DM + High CV Risk	Overweight/Obesity + CVD (No Diabetes)
Sample Size (n)	9,340	3,297	17,604
Primary Endpoint (MACE)	3-point MACE	3-point MACE	3-point MACE
Hazard Ratio (95% CI)	0.87 (0.78–0.97)	0.74 (0.58–0.95)	0.80 (0.72–0.90)
Risk Reduction	13%	26%	20%
Findings	Reduced CV Death	Reduced Non-fatal Stroke	Benefit independent of glycemic control
Reference	Marso et al. [12]	Marso et al. [13]	Lincoff et al. [16]

OW: Once Weekly; CVD: Cardiovascular Disease; MACE: Major Adverse Cardiovascular Events.

These benefits are likely mediated through pleiotropic mechanisms independent of glucose lowering. GLP-1 receptors are abundant in the endothelium and vascular smooth muscle, not just the pancreas. Activation of these receptors leads to increased nitric oxide production, improved endothelial function, and a reduction of oxidative stress, which collectively contribute to plaque stabilization [14]. Moreover, these agents exhibit natriuretic effects, contributing to consistent reductions in systolic blood pressure, and beneficial alterations in postprandial lipid profiles, particularly the reduction of postprandial triglyceride excursions which are increasingly recognized as atherogenic.

3.2. The SELECT Trial

The most transformative data regarding cardiovascular protection comes from the SELECT trial (Semaglutide Effects on Heart Disease and Stroke in Patients with Overweight or Obesity). Unlike previous CVOTs, SELECT enrolled nearly 17,600 participants with established cardiovascular disease and overweight or obesity, but without diabetes [15]. This trial design was pivotal as it aimed to isolate the cardiovascular benefit from glycemic control. The trial met its primary endpoint, demonstrating that Semaglutide 2.4 mg reduced the risk of MACE by 20% compared to placebo [16]. This finding is critical because it decouples the cardiovascular benefit from diabetes management, positioning obesity itself as the modifiable risk factor. Notably, the separation of survival curves occurred early in the trial, suggesting that the benefits are not solely attributable to the timeline of weight loss, but rather to direct anti-atherosclerotic and anti-inflammatory actions of the molecule [17]. Reductions in high-sensitivity C-reactive protein (hs-CRP) observed in SELECT and prior trials corroborate the hypothesis that GLP-1 RAs function as potent vascular anti-inflammatory agents. These agents likely stabilize atherosclerotic plaques and reduce rupture risk by dampening the chronic low-grade inflammation associated with visceral adiposity, offering a mechanistic explanation for the reduction in sudden cardiac death and myocardial infarction.

4. Neuroprotective Potential in Neurodegenerative Disease

The expansion of GLP-1 RA therapeutics into neurology represents the frontier of incretin biology. It is increasingly recognized that insulin resistance is not confined to the periphery; the brain is an insulin-sensitive organ, and dysregulation of neuronal insulin signaling is a pathological feature of both Alzheimer's disease (AD) and Parkinson's disease (PD). This concept has led to the framing of AD by some researchers as "Type 3 Diabetes.".

4.1. Mechanisms of Central Action

GLP-1 RAs such as Liraglutide and Semaglutide, as well as Tirzepatide, have been shown to cross the blood-brain barrier (BBB) via transport mechanisms or direct diffusion at circumventricular organs [18]. Once in the central nervous system (CNS), they activate receptors on microglia and astrocytes as well as neurons. Preclinical models indicate that GLP-1 receptor activation exerts a potent anti-inflammatory effect, reducing neuroinflammation by inhibiting cytokine release from activated microglia and promoting mitochondrial biogenesis [19]. This is crucial, as chronic neuroinflammation and mitochondrial failure are key drivers of neuronal apoptosis in neurodegeneration. Moreover, these agents appear to normalize insulin signaling pathways in the brain (IRS-1/PI3K/Akt pathway), restoring glucose metabolism in neurons and potentially enhancing synaptic plasticity and survival.

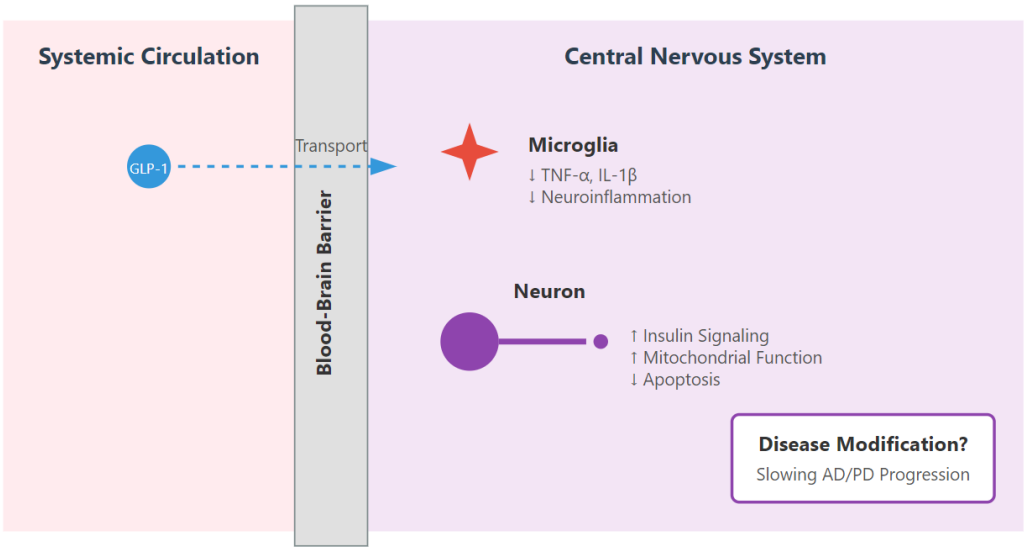

Figure 4. Neuroprotective pathways of GLP-1 receptor agonists

Table 4. Putative Mechanisms of GLP-1 RA Neuroprotection

Target Pathology	Mechanism of Action	Potential Clinical Outcome
Neuroinflammation	Inhibition of microglial activation and reduction of pro-inflammatory cytokines (TNF-α, IL-1β).	Slowed disease progression; reduced neuronal damage.
Insulin Signaling	Resensitization of neuronal insulin receptors (IRS-1/PI3K/Akt pathway).	Improved cerebral glucose metabolism; enhanced synaptic plasticity.
Protein Aggregation	Reduction in oxidative stress and modulation of autophagy.	Potential reduction in Amyloid-β plaque load and Tau hyperphosphorylation.
Mitochondrial Function	Promotion of mitochondrial biogenesis and reduction of reactive oxygen species (ROS).	Increased neuronal survival and energy stability.
Neurogenesis	Stimulation of stem cell proliferation in the dentate gyrus (observed in rodent models).	Preservation of cognitive function and memory.

4.2. Emerging Evidence in Parkinson's Disease

In Parkinson's disease, the loss of dopaminergic neurons in the substantia nigra is exacerbated by chronic neuroinflammation and mitochondrial dysfunction. Earlier phase II trials utilizing Exenatide, a short-acting GLP-1 RA, provided the first clinical signal of efficacy. The trial suggested a halting of motor symptom progression even after drug washout, implying a disease-modifying effect

rather than mere symptomatic relief, which distinguishes it from current dopamine replacement therapies [20]. Liraglutide has also been investigated in this context. While results have been mixed regarding definitive motor score improvements in smaller cohorts, secondary endpoints such as the preservation of cerebral glucose metabolism on PET imaging suggest underlying neuroprotection and preservation of metabolic integrity in key brain regions [21]. Ongoing phase III trials are currently aiming to validate these findings with longer-acting agents like Semaglutide, which may offer more consistent CNS receptor occupancy and improved patient compliance.

4.3. Alzheimer's Disease and Cognitive Decline

The correlation between T2DM and an increased risk of dementia is well-established, with shared pathology including amyloid accumulation and tau hyperphosphorylation. Post-hoc analyses of large cardiovascular outcome trials (specifically REWIND and LEADER) hinted at reduced rates of dementia diagnoses in patients treated with GLP-1 RAs compared to placebo [22]. These observations have spurred dedicated clinical trials to test the cognitive preservation hypothesis. The EVOKE and EVOKE-Plus phase III trials are currently evaluating oral Semaglutide in patients with early Alzheimer's disease [23]. The hypothesis is that by reducing systemic and central inflammation, and by improving vascular health and cerebral perfusion, Semaglutide may slow the accumulation of amyloid-beta and tau pathology, or at minimum, preserve cognitive function through metabolic support of neurons. If successful, this would represent the first instance of a metabolic therapy crossing over to become a standard of care in neurodegeneration, treating the metabolic underpinning of cognitive decline rather than just clearing protein aggregates

Table 5. Clinical Trials Investigating Incretins in Neurodegeneration

Disease Area	Trial Name / ID	Agent	Phase	Status/Notes
Parkinson's	Exenatide-PD	Exenatide (QW)	Phase 2	**Positive:** Improvement in MDS-UPDRS motor scores persisted after washout (off-medication state) [20].
Parkinson's	Exenatide-PD3 (NCT04232969)	Exenatide (QW)	Phase 3	Ongoing. Testing disease-modifying potential in a larger cohort.
Parkinson's	LIRA-PD	Liraglutide	Phase 2	Mixed clinical results; improved cerebral glucose metabolism on PET [21].
Alzheimer's	EVOKE / EVOKE-Plus	Oral Semaglutide	Phase 3	Ongoing. Investigating efficacy in early Alzheimer's disease (MCI/Mild Dementia) [23].
Alzheimer's	ELAD	Liraglutide	Phase 2b	Evaluating effect on cerebral glucose metabolic rate and cognitive measures.

5. Conclusion

The therapeutic profile of GLP-1 and dual GIP/GLP-1 receptor agonists has evolved rapidly from glucose-lowering agents to systemic metabolic modifiers. The evidence from the STEP and SURMOUNT programs confirms their status as the most potent non-surgical interventions for obesity available to date. Concurrently, the SELECT trial has validated the hypothesis that treating adiposity with these agents confers substantial cardiovascular protection independent of glycemic status. As research probes deeper into the central nervous system, the potential for these drugs to mitigate the progression of Alzheimer's and Parkinson's diseases offers a glimpse into a future where metabolic, cardiovascular, and neurological health are managed via unified pathways. This expansion of therapeutic scope necessitates a re-evaluation of clinical guidelines, prioritizing agents with proven pleiotropic benefits to address the multimorbidity characteristic of modern chronic disease.

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