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Comprehensive obesity management: A Review of GLP-1 receptor agonists and dual incretin therapies

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Abstract
Obesity is a chronic, relapsing metabolic disease associated with cardiovascular disease, type 2 diabetes mellitus, non-alcoholic fatty liver disease, chronic kidney disease, obstructive sleep apnea, osteoarthritis, infertility, and several cancers. Traditional management strategies involving calorie restriction, physical activity, behavioural therapy, and bariatric surgery have demonstrated variable long-term success, emphasizing the need for more effective pharmacological interventions. Over the past decade, glucagon-like peptide-1 receptor agonists (GLP-1RAs) have revolutionized obesity treatment by producing unprecedented weight reduction while simultaneously improving metabolic health. More recently, dual incretin agonists, particularly glucose-dependent insulinotropic polypeptide (GIP)/GLP-1 receptor agonists such as tirzepatide, have demonstrated even greater efficacy. Emerging multi-receptor agonists targeting GLP-1, GIP, and glucagon receptors promise additional metabolic benefits. Beyond weight reduction, these agents improve insulin sensitivity, reduce cardiovascular risk, attenuate hepatic steatosis, preserve renal function, decrease systemic inflammation, improve reproductive health, and potentially influence neurodegenerative diseases. This review summarizes current evidence regarding the mechanisms of action, clinical efficacy, cardiometabolic benefits, safety profile, limitations, and future directions of GLP-1 receptor agonists and dual agonists in comprehensive obesity management. Current evidence supports a paradigm shift from weight-centered treatment toward holistic metabolic disease management.

Keywords: Obesity, GLP-1 receptor agonists, tirzepatide, semaglutide, dual agonists, incretins, metabolic syndrome, cardiovascular disease

Introduction

Obesity has emerged as one of the most significant global public health challenges of the twenty-first century (Abad-Jiménez & Vezza, 2025) [1]. According to the World Health Organization (WHO), over one billion individuals worldwide are currently living with obesity (Boutari & Mantzoros, 2022) [9]. The condition substantially increases morbidity and mortality by predisposing individuals to cardiovascular disease, type 2 diabetes mellitus (T2DM), hypertension, dyslipidemia, chronic kidney disease, metabolic dysfunction-associated steatotic liver disease (MASLD), certain cancers, reproductive disorders, and psychological illnesses (Boutari & Mantzoros, 2022) [9]. Historically, obesity management focused primarily on lifestyle modifications including dietary intervention and physical activity (Wang *et al*., 2023) [74]. Although effective initially, long-term weight maintenance remains difficult due to complex neuroendocrine adaptations that favour weight regain (Wang *et al*., 2023) [74].

Recent advances in obesity pharmacotherapy have transformed clinical practice (Wang *et al*., 2023) [36]. Glucagon-like peptide-1 (GLP-1) receptor agonists were initially developed for T2DM but later demonstrated remarkable effects on appetite regulation and sustained weight reduction (Liu, 2023; Rabbani, 2025) [30, 57]. Subsequently, dual incretin agonists targeting both GLP-1 and glucose-dependent insulinotropic polypeptide (GIP) receptors have achieved unprecedented clinical outcomes (Liu, 2023) [36]. This review discusses the expanding role of GLP-1 receptor agonists and dual agonists beyond simple weight reduction, highlighting their pleiotropic effects on metabolic, cardiovascular, hepatic, renal, neurological, and reproductive health (Rabbani, 2025; Zafer, 2025) [57, 77].

Pathophysiology of Obesity

1. Neuroendocrine Regulation

The neuroendocrine regulation of obesity is governed by a complex interaction between the central nervous system, peripheral hormones, and the gastrointestinal tract that collectively regulate appetite, satiety, and energy homeostasis (Morton *et al*., 2014) [46]. The hypothalamus, particularly the arcuate nucleus, serves as the primary control center by integrating signals from adipose tissue, the gastrointestinal tract, and the pancreas to modulate food intake and energy expenditure (Schwartz *et al*., 2000). Two key neuronal populations within the hypothalamus include orexigenic neurons expressing neuropeptide Y (NPY) and agouti-related peptide (AgRP), which stimulate appetite, and anorexigenic neurons expressing proopiomelanocortin (POMC) and cocaine- and amphetamine-regulated transcript (CART), which promote satiety (Sainsbury *et al*., 2002; Schwartz *et al*., 2000).

In obesity, chronic positive energy balance often leads to leptin resistance, whereby elevated circulating leptin levels fail to suppress appetite or increase energy expenditure, resulting in persistent hyperphagia (Myers *et al*., 2010) [52]. Conversely, ghrelin, an orexigenic hormone predominantly secreted by the stomach during fasting, stimulates hunger

through activation of NPY/AgRP neurons, although its postprandial suppression may be impaired in obesity (Tschöp *et al*., 2000). Satiety hormones such as peptide YY (PYY), released from intestinal L-cells after food intake, reduce appetite by inhibiting hypothalamic orexigenic pathways and slowing gastrointestinal motility (Batterham *et al*., 2002) [6].

Similarly, glucagon-like peptide-1 (GLP-1) enhances glucose-dependent insulin secretion, delays gastric emptying, suppresses glucagon release, and activates central satiety centers, making it a key therapeutic target in obesity management (Holst, 2007; Müller *et al*., 2019) [22, 71]. Glucose-dependent insulinotropic polypeptide (GIP), secreted by intestinal K-cells, primarily potentiates insulin secretion but also influences lipid metabolism and adipose tissue function; when combined with GLP-1 receptor activation, it exerts synergistic effects on appetite suppression and metabolic regulation (Campbell & Drucker, 2013; Müller *et al*., 2019) [10, 47].

Beyond homeostatic mechanisms, the brain reward system, particularly the mesolimbic dopaminergic pathway involving the ventral tegmental area and nucleus accumbens, regulates hedonic eating by enhancing the motivational and pleasurable aspects of food consumption (Volkow *et al*., 2011). Dysregulation of these reward pathways, coupled with impaired hormonal signaling, contributes to overeating, food cravings, and the chronic progression of obesity (Kenny, 2011; Volkow *et al*., 2011) [31]. Consequently, targeting both homeostatic and hedonic pathways has emerged as a promising strategy for comprehensive obesity treatment (Müller *et al*., 2019) [71].

2. Chronic Low-grade Inflammation

Obesity is increasingly recognized as a state of chronic low-grade systemic inflammation, often referred to as "metaflammation," which plays a central role in the development of insulin resistance, metabolic syndrome, cardiovascular disease, and other obesity-related complications (Zatterale *et al*., 2020) [17]. Excess adipose tissue, particularly visceral fat, functions as an active endocrine organ that secretes numerous pro-inflammatory cytokines and adipokines, creating a persistent inflammatory environment (Stojanović & Najman, 2016) [69]. Among these, tumor necrosis factor-alpha (TNF-α) is one of the earliest cytokines implicated in obesity-induced inflammation, impairing insulin signaling by promoting serine phosphorylation of insulin receptor substrate proteins, thereby contributing to insulin resistance (Corrao, 2026; Zatterale *et al*., 2020) [12, 17]. Similarly, interleukin-6 (IL-6) is produced by hypertrophic adipocytes and infiltrating immune cells, stimulating hepatic production of acute-phase proteins such as C-reactive protein (CRP), a widely recognized biomarker of systemic inflammation and an independent predictor of cardiovascular disease (Wang, 2014) [75]. Elevated circulating CRP levels are consistently associated with increased adiposity and metabolic dysfunction (Wang, 2014) [75].

Another important chemokine, monocyte chemoattractant protein-1 (MCP-1), recruits circulating monocytes into expanding adipose tissue, where they differentiate into pro-inflammatory macrophages (Faria *et al*., 2020; Zhang *et al*., 2022) [17, 79]. These infiltrating macrophages, particularly the classically activated M1 phenotype, accumulate around necrotic adipocytes forming characteristic crown-like structures and release additional inflammatory mediators including TNF-α, IL-1β, IL-6, and reactive oxygen species, thereby amplifying local and systemic inflammation (Faria *et al*., 2020; Stojanović & Najman, 2016) [17, 69]. This inflammatory cascade disrupts adipocyte function, promotes ectopic lipid accumulation, exacerbates insulin resistance, and contributes to endothelial dysfunction and atherosclerosis (Faria *et al*., 2020; Zatterale *et al*., 2020) [17].

Furthermore, chronic inflammation adversely affects multiple organs, including the liver, skeletal muscle, pancreas, and cardiovascular system, accelerating the progression of metabolic dysfunction-associated steatotic liver disease (MASLD), type 2 diabetes mellitus, and cardiovascular complications (Corrao, 2026; Ros-Madrid, 2025) [12, 60]. Notably, emerging evidence suggests that incretin-based therapies, particularly GLP-1 receptor agonists and dual GIP/GLP-1 agonists, not only induce substantial weight loss but also attenuate chronic inflammation by reducing adipose tissue macrophage infiltration, lowering circulating concentrations of TNF-α, IL-6, MCP-1, and CRP, and improving overall metabolic homeostasis (Ros-Madrid, 2025; Wang, 2014) [60, 75]. Thus, targeting obesity-associated inflammation has become a key therapeutic strategy in the comprehensive management of obesity and its related metabolic disorders (Ros-Madrid, 2025) [60].

3. Insulin Resistance

Insulin resistance is a hallmark of obesity and represents a key pathophysiological mechanism linking excess adiposity to type 2 diabetes mellitus (T2DM), metabolic dysfunction-associated steatotic liver disease (MASLD), cardiovascular disease, and other obesity-related complications (Choi, 2024; Suresh, 2024) [11]. It is characterized by a diminished biological response of insulin-sensitive tissues, including skeletal muscle, adipose tissue, and the liver, resulting in impaired glucose uptake, increased hepatic glucose production, and compensatory hyperinsulinemia (Mega *et al*., 2024; Rabiee, 2025) [42, 58]. Multiple interconnected mechanisms contribute to the development of insulin resistance in obesity. Lipotoxicity, caused by excessive accumulation of free fatty acids (FFAs) and toxic lipid intermediates such as diacylglycerols and ceramides in non-adipose tissues, disrupts insulin signaling by activating protein kinase C and inhibiting insulin receptor substrate (IRS)-mediated pathways (Bednarz *et al*., 2022; Mega *et al*., 2024; Risi *et al*., 2024) [7, 42, 59].

Mitochondrial dysfunction further exacerbates metabolic impairment by reducing mitochondrial oxidative capacity, decreasing ATP production, and impairing fatty acid β-oxidation, leading to intracellular lipid accumulation and enhanced generation of reactive oxygen species (ROS) (Choi, 2024; Mega *et al*., 2024) [11, 42]. Another major contributor is adipokine imbalance, whereby obesity alters the secretion profile of adipose tissue-derived hormones (Rabiee, 2025) [58]. Increased production of pro-inflammatory adipokines such as leptin, resistin, and visfatin, together with reduced levels of the insulin-sensitizing adipokine adiponectin, promotes chronic inflammation, endothelial dysfunction, and impaired glucose metabolism (Choi, 2024; Rabiee, 2025; Risi *et al*., 2024) [11, 58]. Additionally, oxidative stress, resulting from excessive ROS production and inadequate antioxidant

defenses, damages cellular proteins, lipids, and DNA while activating stress-sensitive signaling pathways such as nuclear factor-kappa B (NF-κB) and c-Jun N-terminal kinase (JNK) (Choi, 2024; Mega *et al*., 2024) [11, 42]. These pathways inhibit insulin receptor signaling and amplify inflammatory responses, creating a vicious cycle that perpetuates insulin resistance (Choi, 2024) [11]. The combined effects of lipotoxicity, mitochondrial dysfunction, adipokine dysregulation, and oxidative stress contribute to progressive β-cell dysfunction, hyperglycemia, and metabolic deterioration (Choi, 2024; Rabiee, 2025) [11, 58]. Importantly, recent evidence indicates that GLP-1 receptor agonists and dual GIP/GLP-1 receptor agonists improve insulin sensitivity through multiple mechanisms beyond weight loss, including enhanced glucose-dependent insulin secretion, suppression of glucagon release, reduction of ectopic fat deposition, attenuation of oxidative stress and inflammation, preservation of β-cell function, and restoration of normal metabolic homeostasis (Bednarz *et al*., 2022; Khalifa, 2025; Lonardo, 2024) [7, 32, 37]. These pleiotropic effects have established incretin-based therapies as cornerstone interventions in the modern management of obesity and insulin resistance (Khalifa, 2025; Lonardo, 2024) [11, 32].

Incretin Biology

1. Glucagon-Like Peptide-1 (GLP-1)

Glucagon-like peptide-1 (GLP-1) is an endogenous incretin hormone primarily synthesized and secreted by the intestinal L cells located predominantly in the distal ileum and colon in response to nutrient ingestion, particularly carbohydrates, fats, and proteins (Baggio & Drucker, 2007; Drucker, 2006) [5, 14]. It is derived from the post-translational processing of the proglucagon gene and plays a pivotal role in maintaining glucose homeostasis and energy balance (Holst, 2007) [22]. Following food intake, GLP-1 is rapidly released into the circulation and exerts its biological effects through activation of GLP-1 receptors expressed in the pancreas, gastrointestinal tract, central nervous system, heart, kidneys, and other peripheral tissues (Müller *et al*., 2019) [26]. One of its principal actions is the enhancement of glucose-dependent insulin secretion from pancreatic β-cells, thereby improving postprandial glucose control while minimizing the risk of hypoglycemia. Simultaneously, GLP-1 suppresses glucagon secretion from pancreatic α-cells, reducing hepatic glucose production and further contributing to glycemic regulation (Nauck & Meier, 2018) [53]. In the gastrointestinal tract, GLP-1 delays gastric emptying, slowing nutrient absorption and prolonging the feeling of fullness after meals (Meier, 2012) [43]. Within the central nervous system, particularly the hypothalamus and brainstem, GLP-1 activates satiety pathways while inhibiting orexigenic neuropeptide Y (NPY)/agouti-related peptide (AgRP) neurons and stimulating anorexigenic proopiomelanocortin (POMC)/cocaine- and amphetamine-regulated transcript (CART) neurons (Secher *et al*., 2014; Sisley *et al*., 2014) [64, 67]. These neuroendocrine actions reduce appetite, decrease food cravings, and improve satiety, leading to a sustained reduction in caloric intake and body weight (Secher *et al*., 2014) [64]. Beyond its metabolic effects, GLP-1 exhibits cardioprotective, renoprotective, anti-inflammatory, and neuroprotective properties by improving endothelial function, reducing oxidative stress, attenuating chronic inflammation, and preserving pancreatic β-cell function (Drucker, 2018; Müller *et al*., 2019) [15, 47]. However, native GLP-1 has a very short plasma half-life of approximately 1–2 minutes due to rapid degradation by the enzyme dipeptidyl peptidase-4 (DPP-4), which has prompted the development of long-acting GLP-1 receptor agonists such as liraglutide and semaglutide (Holst, 2007; Knudsen & Lau, 2019) [22, 33]. These pharmacological agents mimic the physiological actions of endogenous GLP-1 while providing prolonged receptor activation, thereby offering substantial benefits in the treatment of obesity, type 2 diabetes mellitus, and multiple obesity-related cardiometabolic disorders (Nauck *et al*., 2021; Wilding *et al*., 2021) [54, 76].

2. Glucose-Dependent Insulinotropic Polypeptide (GIP)

GLP-1 receptor agonists (GLP-1RAs) exert their anti-obesity and antidiabetic effects through coordinated actions on the central nervous system, gastrointestinal tract, pancreas, and peripheral metabolic tissues, resulting in sustained weight reduction and improved metabolic health (Holst, 2007 [22]; Müller *et al*., 2019). Following administration, these agents bind to GLP-1 receptors expressed in the hypothalamus, particularly within the arcuate nucleus, where they activate anorexigenic proopiomelanocortin (POMC) and cocaine- and amphetamine-regulated transcript (CART) neurons while inhibiting orexigenic neuropeptide Y (NPY) and agouti-related peptide (AgRP) neurons (Secher *et al*., 2014; Sisley *et al*., 2014) [64, 67]. This central modulation suppresses hunger signals, reduces food cravings, and enhances satiety, leading to a significant decrease in energy intake (Müller *et al*., 2019). Concurrently, GLP-1 receptor agonists delay gastric emptying, slowing the delivery of nutrients from the stomach to the small intestine and prolonging postprandial fullness, thereby reducing meal size and frequency (Meier, 2012; Drucker, 2018) [15, 43]. In the pancreas, they stimulate glucose-dependent insulin secretion from β-cells while suppressing inappropriate glucagon secretion from α-cells, improving postprandial glucose control without substantially increasing the risk of hypoglycemia (Nauck & Meier, 2018) [53]. The reduction in caloric intake, together with improved glycemic regulation and enhanced insulin sensitivity, promotes progressive loss of adipose tissue, particularly visceral fat, while preserving lean body mass (Wilding *et al*., 2021) [76]. Beyond weight reduction, GLP-1 receptor agonists improve lipid metabolism, decrease hepatic fat accumulation, reduce systemic inflammation and oxidative stress, enhance endothelial function, lower blood pressure, and confer significant cardiovascular and renal protection (Drucker, 2018; Nauck *et al*., 2021) [15, 54]. Collectively, these pleiotropic effects transform obesity management from a weight-centric approach to comprehensive metabolic disease treatment, making GLP-1 receptor agonists a cornerstone of modern obesity pharmacotherapy (Knudsen & Lau, 2019; Wilding *et al*., 2021) [33, 76].

GLP-1 agonists
↓
Hypothalamus
↓
Reduced hunger
↓
Delayed gastric emptying
↓
Lower calorie intake
↓
Weight loss
↓
Improved metabolism

Dual Agonists

Tirzepatide is the first clinically approved dual incretin receptor agonist that simultaneously activates both the glucagon-like peptide-1 (GLP-1) receptor and the glucose-dependent insulinotropic polypeptide (GIP) receptor, representing a major advancement in the pharmacological management of obesity and type 2 diabetes mellitus (Coskun *et al*., 2018 [53]; Müller *et al*., 2022). By combining the complementary physiological actions of GLP-1 and GIP, tirzepatide produces superior metabolic effects compared with GLP-1 receptor agonists alone (Frias *et al*., 2018; Jastreboff *et al*., 2022) [19, 27]. Activation of the GLP-1 receptor suppresses appetite through central hypothalamic pathways, delays gastric emptying, enhances glucose-dependent insulin secretion, and inhibits glucagon release, whereas activation of the GIP receptor potentiates insulin secretion, improves β-cell function, enhances adipose tissue metabolism, and contributes to improved energy homeostasis (Holst & Rosenkilde, 2020; Samms *et al*., 2021) [25, 61]. The synergistic interaction between these two incretin pathways results in greater appetite suppression, more effective regulation of hunger and satiety, and a substantial reduction in caloric intake (Müller *et al*., 2022). Tirzepatide also markedly improves insulin sensitivity by reducing ectopic fat accumulation, enhancing glucose utilization in peripheral tissues, lowering hepatic glucose production, and decreasing chronic inflammation and oxidative stress (Sattar *et al*., 2023) [62]. Furthermore, it promotes greater fat mass reduction, particularly in visceral adipose tissue, while largely preserving lean body mass, thereby improving overall body composition and metabolic health (Jastreboff *et al*., 2022) [27]. Clinical studies have demonstrated significant reductions in glycated hemoglobin (HbA1c), blood pressure, triglycerides, inflammatory biomarkers, and liver fat content, alongside improvements in cardiovascular and renal risk factors (Ludvik *et al*., 2021; Sattar *et al*., 2023) [38, 62]. Notably, the SURMOUNT clinical trial program reported that participants receiving the highest dose of tirzepatide achieved average weight reductions exceeding 20% of baseline body weight, with many individuals experiencing weight loss approaching that typically observed after metabolic or bariatric surgery (Jastreboff *et al*., 2022) [27]. These remarkable outcomes have established tirzepatide as one of the most effective anti-obesity medications currently available and have shifted the treatment paradigm toward comprehensive metabolic disease management rather than simple weight reduction (Aronne *et al*., 2024; Jastreboff *et al*., 2022) [3, 27]. Ongoing research is evaluating its long-term efficacy, cardiovascular benefits, and potential applications in metabolic dysfunction-associated steatotic liver disease (MASLD), heart failure with preserved ejection fraction, chronic kidney disease, and other obesity-related disorders, highlighting its expanding role in modern precision obesity therapy (Sattar *et al*., 2023; Müller *et al*., 2022) [7, 36].

Triple Agonists

Triple agonists represent the next frontier in obesity pharmacotherapy by simultaneously targeting the glucagon-like peptide-1 (GLP-1) receptor, glucose-dependent insulinotropic polypeptide (GIP) receptor, and glucagon receptor (GCGR) to achieve superior metabolic outcomes compared with single or dual incretin therapies (Müller *et al*., 2022; Finan *et al*., 2021) [7, 18]. Several investigational agents, including retatrutide, survodutide, and mazdutide, have shown promising results in early- and late-phase clinical trials (Jastreboff *et al*., 2023; Tillner *et al*., 2019) [28, 71]. These novel molecules are designed to exploit the complementary physiological actions of the three hormone pathways: GLP-1 receptor activation suppresses appetite, delays gastric emptying, and enhances glucose-dependent insulin secretion; GIP receptor activation further improves insulin secretion, β-cell function, and adipose tissue metabolism; while glucagon receptor activation increases energy expenditure, stimulates lipolysis, enhances fatty acid oxidation, and reduces hepatic fat accumulation (Müller *et al*., 2022; Finan *et al*., 2021) [18]. The integration of these mechanisms results in higher energy expenditure, allowing the body to burn more calories even at rest, alongside greater fat oxidation, which preferentially reduces visceral and ectopic fat stores while preserving lean body mass (Tschöp *et al*., 2023) [72]. Consequently, triple agonists produce profound improvements in body composition, insulin sensitivity, glycemic control, lipid metabolism, and systemic inflammation (Müller *et al*., 2022) [50].

Among these agents, retatrutide has demonstrated particularly impressive results, with Phase II clinical trials reporting mean weight reductions approaching 24% of baseline body weight after 48 weeks of treatment, making it one of the most potent anti-obesity therapies currently under investigation (Jastreboff *et al*., 2023) [36]. Survodutide has shown encouraging benefits in obesity and metabolic dysfunction-associated steatotic liver disease (MASLD), while mazdutide has demonstrated significant efficacy in reducing body weight and improving metabolic parameters, particularly in Asian populations (Tillner *et al*., 2019 [71]; Ji *et al*., 2023). Beyond weight reduction, triple agonists exhibit the potential to improve cardiovascular health, reduce hepatic steatosis and fibrosis, preserve renal function, lower inflammatory biomarkers, and enhance overall metabolic flexibility (Finan *et al*., 2021; Müller *et al*., 2022) [18, 50]. Although these agents remain under clinical evaluation, their remarkable efficacy suggests they may redefine future obesity management by offering therapeutic outcomes approaching or, in some cases, rivaling those achieved through bariatric surgery (Jastreboff *et al*., 2023) [28]. As long-term safety and cardiovascular outcome studies continue, triple agonists are expected to play an increasingly important role in precision medicine and comprehensive treatment strategies for obesity and its associated cardiometabolic disorders (Tschöp *et al*., 2023; Müller *et al*., 2022) [50, 72].

Beyond Weight Loss

The therapeutic benefits of GLP-1 receptor agonists and dual incretin agonists extend far beyond weight reduction, offering comprehensive improvements across multiple organ systems and redefining obesity treatment as a strategy for overall metabolic disease management (Drucker, 2018; Müller *et al*., 2022) [15, 16]. In individuals with type 2 diabetes mellitus (T2DM), these agents significantly reduce glycated hemoglobin (HbA1c) through enhanced glucose-dependent insulin secretion, suppression of glucagon release, preservation of pancreatic β-cell function, improved insulin sensitivity, and a consequent reduction in the need for exogenous insulin or other glucose-lowering medications (Nauck & Meier, 2018; Nauck *et al*., 2021) [53, 54]. Cardiovascular protection is another major advantage, as

GLP-1-based therapies reduce major adverse cardiovascular events (MACE) by lowering systolic blood pressure, improving endothelial function, attenuating systemic inflammation and oxidative stress, decreasing low-density lipoprotein (LDL) cholesterol and triglyceride concentrations, and enhancing overall vascular health (Marso *et al*., 2016; Sattar *et al*., 2023) [40, 62]. Renal benefits have also been consistently demonstrated, including reduced albuminuria, slower progression of chronic kidney disease (CKD), decreased renal inflammation, improved renal perfusion, and preservation of kidney function (Mann *et al*., 2017; Muskiet *et al*., 2019) [39, 51].

In patients with metabolic dysfunction-associated steatotic liver disease (MASLD), these therapies substantially reduce hepatic steatosis, improve liver fibrosis, lower liver enzymes such as alanine aminotransferase (ALT) and aspartate aminotransferase (AST), and decrease overall liver fat content through improved insulin sensitivity and reduced ectopic lipid accumulation (Newsome *et al*., 2021; Armstrong *et al*., 2016) [2, 56]. Weight loss achieved with incretin-based therapies also contributes to significant improvements in obstructive sleep apnea (OSA) by reducing cervical and visceral fat deposition, decreasing upper airway obstruction, improving sleep architecture, and reducing apnea severity (Blackman *et al*., 2016 [8]; Malhotra *et al*., 2024). In women with polycystic ovary syndrome (PCOS), GLP-1 receptor agonists improve reproductive and metabolic health by promoting weight loss, reducing insulin resistance and hyperinsulinemia, lowering circulating androgen levels, restoring ovulatory function, and enhancing fertility outcomes (Jensterle *et al*., 2015; Elkind-Hirsch *et al*., 2022) [16, 29].

Furthermore, reductions in body weight alleviate mechanical stress on weight-bearing joints, thereby decreasing joint loading, pain, stiffness, and functional disability in individuals with osteoarthritis, ultimately improving mobility and quality of life (Messier *et al*., 2013; Hunter & Bierma-Zeinstra, 2019) [26, 45]. Emerging evidence also indicates potential benefits for brain health, with GLP-1 receptor agonists exhibiting neuroprotective effects through the reduction of neuroinflammation, oxidative stress, and neuronal apoptosis (Hölscher, 2020; Grieco *et al*., 2019) [17, 20]. Preclinical and early clinical studies suggest these agents may slow cognitive decline and offer therapeutic potential in neurodegenerative disorders such as Alzheimer's disease and Parkinson's disease (Hölscher, 2020; Athauda & Foltynie, 2018) [4]. Collectively, these pleiotropic effects demonstrate that incretin-based therapies are not merely anti-obesity medications but multifunctional metabolic agents capable of improving cardiovascular, renal, hepatic, endocrine, musculoskeletal, and neurological health, thereby establishing a new paradigm in the comprehensive management of obesity and its associated chronic diseases (Müller *et al*., 2022; Sattar *et al*., 2023) [7, 62].

Mechanisms Beyond Weight Reduction

The therapeutic efficacy of GLP-1 receptor agonists and dual incretin agonists extends well beyond their ability to induce weight loss, encompassing multiple biological mechanisms that improve overall metabolic and cardiovascular health (Drucker, 2018; Müller *et al*., 2022) [15, 16]. One of the most important effects is their potent anti-inflammatory action, whereby treatment reduces circulating inflammatory biomarkers including C-reactive protein (CRP), interleukin-6 (IL-6), and tumor necrosis factor-alpha (TNF-α) (Nauck *et al*., 2021; Sattar *et al*., 2023) [54, 62]. This attenuation of chronic low-grade inflammation improves endothelial function by enhancing nitric oxide bioavailability, reducing vascular oxidative stress, and preventing endothelial dysfunction, ultimately lowering the risk of atherosclerosis and major adverse cardiovascular events (Drucker, 2018; Marso *et al*., 2016) [15, 40]. In addition to their anti-inflammatory properties, GLP-1-based therapies improve mitochondrial function by enhancing mitochondrial biogenesis and oxidative phosphorylation, reducing excessive production of reactive oxygen species (ROS), and restoring cellular energy homeostasis (Lee *et al*., 2018; Müller *et al*., 2022) [35, 50]. These effects increase adenosine triphosphate (ATP) production, improve fatty acid β-oxidation, and enhance insulin signaling, thereby contributing to greater insulin sensitivity and improved glucose utilization in skeletal muscle, liver, and adipose tissue (Lee *et al*., 2018; Nauck & Meier, 2018) [35, 53].

Furthermore, the gut–brain axis plays a central role in the metabolic actions of GLP-1. Following nutrient ingestion or pharmacological activation, GLP-1 signals are transmitted through the vagus nerve to the brainstem, where they are integrated and relayed to the hypothalamus, the principal center for appetite regulation (Holst, 2007; Sisley *et al*., 2014) [22, 67]. Simultaneously, GLP-1 influences the mesolimbic reward system, including dopaminergic pathways involved in food reward and motivation (Müller *et al*., 2019; Van Bloemendaal *et al*., 2014) [73]. Through these central mechanisms, GLP-1 receptor agonists suppress appetite, reduce food cravings, diminish emotional eating, and attenuate hedonic hunger, which refers to eating driven by pleasure rather than physiological energy needs (Secher *et al*., 2014; Van Bloemendaal *et al*., 2014) [64, 73]. By simultaneously modulating inflammatory pathways, mitochondrial function, endothelial health, and neuroendocrine regulation of appetite and reward, incretin-based therapies provide comprehensive metabolic benefits that extend far beyond simple reductions in body weight (Müller *et al*., 2022; Sattar *et al*., 2023) [16, 62]. These pleiotropic actions explain the significant improvements observed in glycemic control, cardiovascular outcomes, renal function, hepatic steatosis, and overall metabolic homeostasis, positioning GLP-1 and dual agonists as disease-modifying therapies in modern obesity management (Jastreboff *et al*., 2022; Wilding *et al*., 2021) [27, 76].

Major Clinical Trials

Trial	Drug	Main Findings
STEP	Semaglutide	~15% weight loss
SUSTAIN	Semaglutide	Diabetes control
SURPASS	Tirzepatide	Superior HbA1c reduction
SURMOUNT	Tirzepatide	>20% weight loss
SELECT	Semaglutide	Reduced cardiovascular events

Conclusion

GLP-1 receptor agonists and dual incretin agonists have fundamentally transformed obesity treatment by addressing the underlying neuroendocrine and metabolic mechanisms rather than focusing solely on caloric restriction. Beyond producing substantial and sustained weight loss, these agents offer broad cardiometabolic benefits, including improved glycemic control, reduced cardiovascular and

renal risk, attenuation of hepatic steatosis, decreased systemic inflammation, enhanced reproductive health, and potential neuroprotective effects. Dual agonists such as tirzepatide and emerging triple agonists represent the next generation of obesity therapeutics, with efficacy approaching that of bariatric surgery in selected populations. Future research should focus on long-term safety, precision medicine approaches, combination therapies, and expanding indications to optimize individualized obesity care. Collectively, these advances signal a paradigm shift from weight-centric management to comprehensive treatment of obesity as a chronic, multisystem metabolic disease.

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