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GLP-1 Receptor Agonists in Obesity: Mechanisms of Weight Loss, Body Composition, Skeletal Muscle, and Cutaneous Implications

Isabelli Rodrigues Neumann and Rodrigo Cé*

Department of Biomedical Sciences, Centro Universitário Avantis, UNIAVAN - Av. Marginal Leste, 3600, Estados, Balneário Camboriú – SC – Brazil. CEP: 88339125.

***Correspondence:**
Isabelli Rodrigues Neumann and Rodrigo Cé, Department of Biomedical Sciences, Centro Universitário Avantis, UNIAVAN - Av. Marginal Leste, 3600, Estados, Balneário Camboriú, SC, Brazil.

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ABSTRACT

Obesity is a chronic, multifactorial disease associated with metabolic, endocrine, inflammatory, and neuroendocrine alterations. Glucagon-like peptide-1 (GLP-1) receptor agonists have become important therapies for obesity due to their effects on appetite regulation, food intake, glycemic control, and body weight. This qualitative literature review aimed to examine the physiological mechanisms of GLP-1 signaling and the effects of GLP-1 receptor agonists on weight loss, body composition, skeletal muscle, metabolic function, and potential cutaneous and musculoskeletal implications. A bibliographic search was conducted in PubMed/MEDLINE, SciELO, Web of Science, the Virtual Health Library, and Google Scholar. The available evidence indicates that GLP-1 receptor agonists promote weight reduction primarily through reduced appetite and food intake, increased satiety, delayed gastric emptying, and broader metabolic effects. Although substantial weight loss may be accompanied by reductions in lean mass and skeletal muscle, current evidence does not indicate that muscle loss is necessarily disproportionate to overall weight reduction. Preservation of muscle mass and quality appears to be influenced by nutritional status and physical activity, particularly resistance exercise. Emerging dual, triple, and oral small-molecule therapies may further expand the therapeutic potential of GLP-1-based pharmacology, although their long-term effects remain under investigation. Overall, the benefits of GLP-1 receptor agonists should be evaluated not only by the magnitude of weight loss but also by their effects on body composition, metabolic health, physical function, and tissue integrity.

Keywords

GLP-1 receptor agonists, Obesity, Weight loss, Skeletal muscle, Body composition.

Introduction

Obesity is a chronic, multifactorial disease characterized by complex metabolic, inflammatory, and endocrine alterations that substantially affect health and quality of life [1,2]. Its clinical relevance extends beyond excess body weight, as obesity is associated with an increased risk of several chronic conditions, including type 2 diabetes mellitus, cardiovascular disease, and endocrine disorders, as well as significant functional and psychosocial consequences [1]. The pathophysiology of obesity involves a complex interaction between genetic, environmental, metabolic, and neuroendocrine factors that regulate energy intake and expenditure [3,4]. Among these mechanisms, the neuroendocrine control of hunger and satiety has received considerable attention because of its central role in the maintenance of energy homeostasis [3,4].

Glucagon-like peptide-1 (GLP-1) is an important component of this regulatory network. Primarily produced by enteroendocrine L cells in response to nutrient ingestion, GLP-1 participates in the bidirectional communication between the gastrointestinal tract, pancreas, and central nervous system, thereby contributing to glucose regulation, energy homeostasis, and the control of food intake [5,6]. Its physiological actions include stimulation of glucose-dependent insulin secretion, suppression of glucagon

release, delayed gastric emptying, and enhancement of satiety through effects on neural pathways involved in appetite regulation [5,7]. Collectively, these actions contribute to the coordinated regulation of postprandial metabolism and energy balance.

The pharmacological exploitation of these physiological pathways has led to the development of GLP-1 receptor agonists, which have become increasingly important in the treatment of type 2 diabetes mellitus and obesity [3,6]. These agents mimic or prolong key effects of endogenous GLP-1 and can promote clinically meaningful reductions in food intake and body weight, in addition to improving several metabolic parameters [6,8,9]. Liraglutide and semaglutide, among other GLP-1 receptor agonists, have been extensively investigated and incorporated into clinical strategies for the management of overweight and obesity, with demonstrated efficacy in weight reduction and metabolic control [8,9].

Given the expanding use of GLP-1 receptor agonists in obesity management, understanding their physiological and pharmacological effects beyond weight loss is increasingly important. These therapies may influence body composition, skeletal muscle, metabolic and musculoskeletal function, and tissue characteristics, with potential functional and aesthetic implications. Therefore, this review aimed to examine the effects of GLP-1 receptor agonists on weight loss, body composition, skeletal muscle, metabolic and musculoskeletal adaptations, and potential cutaneous implications, as well as emerging therapies and future perspectives.

Methodology

This study consists of a qualitative literature review aimed at analyzing the effects of glucagon-like peptide-1 (GLP-1) receptor agonists on weight loss and their potential implications for skin quality, with particular emphasis on skin laxity associated with significant weight reduction. A bibliographic search was conducted in the following scientific databases: PubMed/MEDLINE, Scientific Electronic Library Online (SciELO), Web of Science, Virtual Health Library (BVS), and Google Scholar. The search strategy included combinations of controlled descriptors and free-text terms in English and Portuguese, using the Boolean operators AND and OR. The following terms and their corresponding combinations were considered: “GLP-1”, “GLP-1 receptor agonists”, “glucagon-like peptide-1”, “obesity”, “semaglutide”, “liraglutide”, “weight loss”, “body weight reduction”, “skin laxity”, “skin quality”, “cutaneous changes”, and “energy metabolism”. Eligible publications included original research articles, clinical and observational studies, literature and systematic reviews, clinical guidelines, and relevant book chapters published in English or Portuguese. Studies were considered eligible when they addressed the physiological mechanisms of GLP-1 signaling, the clinical effects of GLP-1 receptor agonists in the management of obesity, or cutaneous changes potentially associated with substantial weight loss.

Duplicate publications, studies unrelated to the research question, articles with insufficient methodological description, and publications lacking adequate scientific support were excluded. Studies for which the available information was insufficient to establish a relevant relationship with the proposed topic were also excluded. Given the qualitative nature of the review, the findings were synthesized descriptively, without quantitative statistical pooling.

Theoretical Framework

GLP-1 Physiology and Mechanisms of Action

GLP-1

According to Holst [10], GLP-1 is an incretin hormone produced predominantly by intestinal L cells, with higher concentrations in the ileum and colon, and released in response to nutrient ingestion. GLP-1 plays a central role in glucose homeostasis by stimulating insulin secretion in a glucose-dependent manner [11]. It also suppresses glucagon secretion from pancreatic alpha cells, thereby reducing hepatic glucose production [12,13]. Postprandial GLP-1 secretion is regulated not only by the direct presence of nutrients within the gastrointestinal tract but also by integrated neuroendocrine mechanisms [10]. However, the physiological effects of endogenous GLP-1 are limited by its short half-life, primarily as a consequence of rapid degradation by the enzyme dipeptidyl peptidase-4 (DPP-4) [14].

From a structural perspective, GLP-1 is generated through the proteolytic processing of proglucagon, a precursor that also gives rise to other peptides, including glucagon and GLP-2 [3,10]. The predominant biologically active form is GLP-1 [7-36] -amide, which accounts for most of the peptide's metabolic effects [11,15]. Among its major physiological functions is the delay of gastric emptying, which contributes to limiting postprandial increases in blood glucose [6,16]. GLP-1 also reduces gastrointestinal motility and modulates gastric secretion, thereby contributing to metabolic regulation [3,10]. In addition, through the gut-brain axis, GLP-1 promotes satiety and reduces food intake [6,13].

Beyond its classical metabolic effects, GLP-1 exerts relevant extrapancreatic actions, including cardioprotective and anti-inflammatory effects [3,5]. Evidence suggests that GLP-1 may improve endothelial function and reduce oxidative stress, mechanisms that may contribute to cardiovascular protection [5,14]. Within the central nervous system, GLP-1 participates in the regulation of appetite and feeding behavior and has also been associated with potential neuroprotective effects [6,16]. These diverse biological actions extend the physiological and therapeutic relevance of GLP-1 beyond glycemic control alone [3,5].

GLP-1 Receptor (GLP-1R)

The GLP-1R belongs to the class B family of G protein-coupled receptors and is expressed in several tissues, including the pancreas, gastrointestinal tract, central nervous system, and cardiovascular system [10,15]. Receptor activation occurs following GLP-1 binding, which stimulates adenylyl cyclase and increases intracellular cyclic adenosine monophosphate (cAMP) levels, subsequently triggering intracellular signaling pathways involved in insulin secretion [11]. In pancreatic beta cells, GLP-

1R activation promotes glucose-dependent insulin release and contributes to the maintenance of cellular function and viability [6].

GLP-1R expression in extrapancreatic tissues also mediates effects beyond glucose regulation [3]. In the central nervous system, receptor activation is associated with appetite regulation and increased satiety, whereas in the gastrointestinal tract it contributes to delayed gastric emptying [16]. In the cardiovascular system, GLP-1R activation has been associated with improved endothelial function and cardioprotective effects [5]. Collectively, these findings support GLP-1R as an important therapeutic target in the management of metabolic disorders, particularly type 2 diabetes mellitus and obesity [6].

GLP-1 Receptor Agonists (GLP-1RAs)

GLP-1RAs comprise a class of pharmacological agents developed to reproduce the biological effects of endogenous GLP-1 while providing greater molecular stability and resistance to degradation by dipeptidyl peptidase-4 (DPP-4). These properties extend their half-life and duration of action [17,18]. GLP-1RAs bind to the GLP-1 receptor and activate intracellular signaling pathways that stimulate glucose-dependent insulin secretion and suppress glucagon release, thereby contributing substantially to glycemic control [17]. These agents also affect gastrointestinal function, particularly by delaying gastric emptying and increasing satiety, effects that are associated with reduced food intake and body weight [19].

GLP-1RAs have distinct pharmacokinetic profiles and can broadly be classified according to their duration of action as short- or long-acting formulations. This characteristic influences both dosing frequency and clinical outcomes [18]. The main agents in this class include exenatide, liraglutide, dulaglutide, and semaglutide, whose structural modifications were developed to enhance molecular stability and therapeutic efficacy [20]. In addition to their glucose-lowering effects, evidence indicates that GLP-1RAs may provide cardiovascular benefits, reduce mortality, and exert favorable effects across several organ systems [17,21]. Nevertheless, their use may be associated with adverse events, most commonly involving the gastrointestinal tract [19].

Pathophysiological Mechanisms of GLP-1

GLP-1 signaling begins with the binding of the hormone to GLP-1R, a G protein-coupled receptor whose activation stimulates adenylyl cyclase and increases intracellular cyclic adenosine monophosphate (cAMP) concentrations [10,17]. Increased cAMP activates downstream effectors, including protein kinase A (PKA) and exchange protein directly activated by cAMP (Epac), which play important roles in insulin secretion by pancreatic beta cells [16,22]. GLP-1 signaling can also modulate intracellular pathways such as phosphoinositide 3-kinase/protein kinase B (PI3K/Akt) and mitogen-activated protein kinase (MAPK), which are involved in cell survival and energy metabolism and may contribute to the preservation of pancreatic function and glucose homeostasis [3,23].

GLP-1 also interacts with multiple metabolic pathways, exerting integrated effects on energy homeostasis [3]. Its actions include modulation of insulin and glucagon secretion, as well as interactions with other hormones involved in energy balance, such as leptin and ghrelin, thereby influencing appetite regulation and glucose metabolism [10,24]. Recent evidence further suggests that GLP-1 receptor agonists may have beneficial effects on hepatic function in individuals with metabolic liver disease associated with diabetes, supporting a broader role for the GLP-1 system in metabolic regulation [25].

In type 2 diabetes mellitus, GLP-1 has a central role in glycemic regulation by stimulating glucose-dependent insulin secretion and suppressing glucagon release [11]. It may also contribute to the preservation of pancreatic beta-cell function and mass by reducing apoptotic processes and improving insulin secretory responses [5,26]. Evidence further suggests that GLP-1 can improve insulin sensitivity in peripheral tissues, thereby contributing to the control of hyperglycemia [3]. Its multiple physiological actions therefore place the GLP-1 pathway among the relevant mechanisms underlying the pathophysiology and therapeutic management of type 2 diabetes.

In obesity, GLP-1 has an important role in the regulation of appetite and body weight, particularly through its effects on the central nervous system [5,10]. Activation of GLP-1 signaling is associated with increased satiety, reduced food intake, and delayed gastric emptying [6,16]. GLP-1 also acts on neural circuits involved in feeding behavior and reward processing, contributing to the modulation of eating patterns [3].

GLP-1 Receptor Agonists and Weight Loss

Development of GLP-1 Receptor Agonists

The development of GLP-1RAs was driven by the pharmacokinetic limitations of endogenous GLP-1, whose rapid degradation by dipeptidyl peptidase-4 (DPP-4) markedly restricts its therapeutic applicability [27]. To overcome this limitation, synthetic molecules with greater structural stability and increased resistance to enzymatic degradation were developed, resulting in a longer duration of action [28]. Exenatide was the first GLP-1RA approved for clinical use. As an analogue of exendin-4, it represented an important milestone in the pharmacological treatment of type 2 diabetes mellitus and marked the emergence of therapies targeting the incretin system [19,29].

Subsequent advances in this pharmacological class led to the development of new agents designed to improve clinical efficacy and extend therapeutic duration [30]. Liraglutide, for example, was structurally modified to achieve greater similarity to human GLP-1 and a longer half-life [28]. Long-acting agents, including semaglutide and dulaglutide, were subsequently introduced, allowing once-weekly administration and potentially improving treatment adherence [29]. These developments also broadened the therapeutic indications of GLP-1RAs, particularly their application in the management of obesity [21].

Currently Available GLP-1 Receptor Agonists

Several GLP-1 receptor agonists are currently available for clinical use, with differences in their pharmacokinetic profiles, duration of action, and dosing frequency [6]. Short-acting agents include exenatide and lixisenatide, which are administered daily and have a relatively transient pharmacological effect [27]. Liraglutide is a longer-acting agent developed through structural modifications that increase molecular stability, allowing once-daily administration with a more sustained pharmacokinetic profile [28]. Dulaglutide and semaglutide have longer half-lives and can therefore be administered once weekly, providing greater convenience and potentially improving treatment adherence [31]. More recently, the availability of oral semaglutide has expanded therapeutic options within this class by providing an alternative route of administration [32].

Mechanisms of Action and Current Pharmacological Agents

GLP-1 receptor agonists influence body weight through coordinated central and peripheral mechanisms involved in the regulation of energy balance, leading primarily to reductions in hunger and food intake [10,33]. Within the central nervous system, these effects involve hypothalamic nuclei and other neural pathways that integrate neuroendocrine signals responsible for appetite regulation [34]. GLP-1RAs may also modulate neural circuits involved in food reward, thereby reducing the preference for highly energy-dense foods [35].

At the peripheral level, GLP-1RAs delay gastric emptying and prolong postprandial fullness [35]. At the same time, they stimulate glucose-dependent insulin secretion and suppress glucagon release, contributing to improved glycemic control [33]. Additional evidence suggests that these agents may influence adipose tissue inflammation and lipid metabolism, potentially contributing to reductions in adiposity [36]. Weight loss associated with GLP-1RA treatment therefore results from the combined effects of reduced energy intake and broader metabolic changes involving interconnected physiological pathways [3].

Among the currently available GLP-1RAs, liraglutide, semaglutide, and dulaglutide are notable for their prolonged duration of action and established clinical efficacy [36]. Semaglutide, in particular, has demonstrated substantial effects on body weight and has been extensively investigated in recent clinical studies [37]. Importantly, clinically meaningful weight reduction has also been demonstrated in individuals without diabetes mellitus, supporting the use of these agents in the pharmacological management of obesity [38]. Accordingly, GLP-1RAs have become an important contemporary therapeutic strategy, supported by evidence from randomized clinical trials and meta-analyses [39].

Figure 1 summarizes the main physiological and pharmacological pathways through which GLP-1 receptor agonists influence appetite regulation, weight loss, body composition, skeletal muscle, and potential functional and tissue implications.

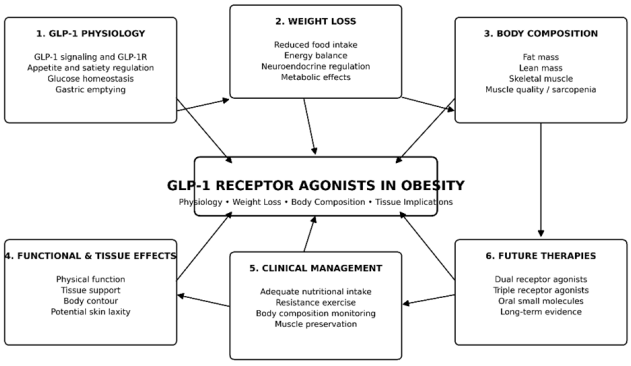

Figure 1: Conceptual framework of the physiological and pharmacological effects of GLP-1 receptor agonists in obesity.

Use of GLP-1 Receptor Agonists for Weight Loss

GLP-1 receptor agonists have become an established pharmacological approach to obesity management and are associated with significant reductions in body weight across different populations [39]. Clinical evidence indicates that these agents can produce clinically meaningful weight loss, frequently exceeding 5% of baseline body weight, particularly with longer treatment durations [40]. In addition to weight reduction, GLP-1RA therapy has been associated with improvements in cardiometabolic parameters, including reductions in waist circumference and favorable changes in lipid profiles [41]. These effects have been observed in both individuals with and without diabetes mellitus, further expanding the clinical applicability of this therapeutic class [42].

Clinical Benefits and Current Applications

Weight loss induced by GLP-1RAs is accompanied by favorable changes in several cardiometabolic parameters, including improvements in lipid metabolism and hemodynamic regulation [41]. The reduction in body weight is also associated with improved insulin sensitivity and glycemic control [40]. In addition, decreases in visceral adipose tissue may occur, which is particularly relevant given the established association between visceral adiposity and cardiovascular risk [43]. Sustained weight reduction may further contribute to lowering the long-term risk of metabolic complications and related chronic diseases [44].

In contemporary clinical practice, GLP-1RAs are increasingly being incorporated into different therapeutic settings [45]. At the same time, continued pharmacological development has led to innovative formulations, including oral preparations and dual-acting agonists, thereby expanding the range of available treatment options [3]. Their use may also be incorporated into individualized treatment strategies based on the clinical characteristics, therapeutic goals, and needs of each patient [45]. Within this context, GLP-1-based therapies have become increasingly integrated into the management of obesity and other metabolic disorders [43].

Safety, Tolerability, and Practical Considerations

GLP-1 receptor agonists generally have a favorable safety profile and are tolerated by most patients [46]. The adverse events reported most frequently are gastrointestinal, particularly nausea, vomiting, and diarrhea, which tend to occur during the initial stages of treatment [47]. The risk of hypoglycemia is relatively low when GLP-1RAs are used as monotherapy because their effects on insulin secretion are glucose-dependent [43]. Recent reviews suggest that the overall safety profile is broadly comparable among agents within this class, although individual molecules may differ in the frequency or severity of specific adverse events [3].

Regarding long-term tolerability, treatment adherence appears to be influenced by the severity of early adverse effects and by appropriate management of these symptoms [41,48]. Less common events, including pancreatitis and gallbladder-related disorders, have been reported and may warrant clinical monitoring, although their incidence remains low [47]. Specific precautions may also apply to certain patient populations, particularly individuals with a history of severe gastrointestinal disease [48]. Individualized clinical assessment is therefore essential to balance treatment efficacy, tolerability, and patient safety.

From a practical standpoint, the selection of a GLP-1RA should take into account factors such as dosing frequency, cost, treatment objectives, and individual clinical characteristics [31,49]. Long-acting formulations may facilitate adherence because they require less frequent administration [31]. Appropriate patient counseling regarding potential adverse effects, dose escalation, and the importance of maintaining treatment is also an important component of successful long-term therapy [28].

Neuroendocrine Regulation of Appetite and Metabolism

Distribution and Regulation of the GLP-1 System

The distribution of the GLP-1 system extends beyond the sites of hormone synthesis and involves GLP-1R expression across multiple target tissues [31]. GLP-1R has been identified in organs such as the pancreas, liver, heart, and adipose tissue, as well as in specific regions of the central nervous system, supporting the systemic and integrated actions of GLP-1 [5,50]. This heterogeneous receptor distribution is thought to underlie the broad physiological effects of GLP-1, including its involvement in metabolic and cardiovascular regulation [5,15]. GLP-1R expression may also vary according to metabolic status and can be influenced by conditions such as obesity and insulin resistance [16].

An important regulatory feature of the GLP-1 system is the rapid degradation of the hormone by dipeptidyl peptidase-4 (DPP-4), which limits the circulating half-life of endogenous GLP-1 to only a few minutes [10,11]. This enzymatic inactivation represents an important physiological mechanism for controlling the duration of GLP-1 activity following secretion [4]. In addition, nutritional status, dietary composition, and hormonal sensitivity can modify the magnitude of the GLP-1 response [52].

The regulation of the GLP-1 system also involves dynamic adaptations over time. Chronic exposure to metabolic stimuli may alter receptor sensitivity and consequently affect the magnitude of the physiological response to GLP-1 [6]. At the same time, interactions with other intestinal hormones, including glucose-dependent insulinotropic polypeptide (GIP) and peptide YY (PYY), contribute to the coordinated regulation of enteroendocrine responses [53]. Recent studies have further suggested that GLP-1 signaling is involved in processes extending beyond energy metabolism, including inflammatory mechanisms and intracellular signaling pathways [4].

GLP-1 Signaling in the Central and Peripheral Nervous Systems

GLP-1 signaling involves coordinated interactions between central and peripheral systems [54]. Within the central nervous system (CNS), GLP-1 is produced predominantly by neurons located in the brainstem and acts on several brain regions, including the hypothalamus [53]. In particular, signaling within hypothalamic circuits involved in energy homeostasis contributes to the regulation of appetite, satiety, and energy balance through GLP-1R-dependent activation of intracellular pathways involving cAMP and protein kinase A (PKA) [54,55]. Central GLP-1 signaling also interacts with neurotransmitter systems, including glutamatergic pathways, thereby influencing feeding behavior as well as cognitive and neuroprotective processes [54,56]. GLP-1R activation within the CNS has additionally been associated with the modulation of stress-related responses and increased satiety, further supporting its role in energy homeostasis [57].

In peripheral tissues, GLP-1 is released primarily by intestinal L cells in response to nutrient ingestion and exerts classical endocrine effects, including stimulation of insulin secretion and suppression of glucagon release [56]. However, communication between central and peripheral systems is bidirectional, allowing signals originating in the CNS to influence peripheral metabolism, including glucose regulation through the brain-pancreas axis [55,56]. This integration occurs through both neural and hormonal pathways, enabling GLP-1 to contribute to the coordination of food intake, energy expenditure, and glycemic control [54]. GLP-1 signaling should therefore be considered as part of an integrated network connecting the gastrointestinal tract, brain, and peripheral organs [54,56].

Arcuate Nucleus (ARC)

The arcuate nucleus (ARC) of the hypothalamus is a key regulator of energy homeostasis and functions as an integrative center for peripheral and central metabolic signals [58]. Two major neuronal populations with opposing effects on energy balance are particularly important in this region: neuropeptide Y/agouti-related peptide (NPY/AgRP) neurons, which stimulate food intake, and proopiomelanocortin/cocaine- and amphetamine-regulated transcript (POMC/CART) neurons, which promote satiety and increase energy expenditure [59,60]. These neuronal populations respond to multiple hormonal signals, including leptin, insulin, and GLP-1, allowing the ARC to adjust feeding behavior according to the body's energetic state [55,61].

The ARC also contributes directly to the central effects of GLP-1, including through signaling involving GLP-1 receptors expressed by POMC-related neuronal circuits, thereby contributing to reduced food intake and improved glucose regulation [55,56]. This hypothalamic region maintains functional connections with other hypothalamic and brainstem nuclei, allowing the integration of short- and long-term signals involved in satiety and energy balance [56,58,61]. The ARC therefore represents a critical component of the neural network governing energy homeostasis and metabolic regulation.

Paraventricular Nucleus of the Hypothalamus (PVN)

The PVN plays a central role in energy homeostasis by integrating neuroendocrine and autonomic responses [62]. The PVN receives projections from the ARC, including inputs from POMC neurons associated with satiety and NPY/AgRP neurons involved in the stimulation of food intake, forming an important circuit for the regulation of energy balance [62,63]. The PVN also integrates peripheral hormonal signals and adjusts physiological responses according to the nutritional and metabolic state of the organism [64].

The PVN is involved in GLP-1 signaling through the expression of GLP-1R and the reception of projections from brainstem neurons, contributing to the regulation of satiety and glucose homeostasis [64,65]. Activation of this region is also associated with modulation of autonomic activity, including effects on sympathetic outflow and cardiovascular function [66,67]. Thus, the PVN represents an important interface between central neural circuits and peripheral signals involved in metabolic regulation.

Mesolimbic Reward System

The mesolimbic reward system plays an important role in the pleasurable and motivational aspects of feeding, influencing food intake not only in response to energy requirements but also in response to the hedonic properties of food [68,69]. This circuitry includes structures such as the ventral tegmental area and nucleus accumbens, where dopaminergic signaling contributes to motivation, reinforcement, and food-related behaviors [68,70]. Consequently, mesolimbic circuits can promote food consumption even in the absence of an immediate metabolic need, particularly in response to highly palatable foods rich in sugars and fats [69,71].

GLP-1 signaling modulates this reward circuitry and may reduce the reinforcing value attributed to food, thereby attenuating hedonic-driven food seeking and consumption [68,69]. Its effects on dopaminergic neurotransmission have also been associated with reduced intake of highly palatable foods and modulation of other behaviors involving reward pathways, supporting a broader role for GLP-1 in the regulation of motivated behavior [69,70]. The mesolimbic reward system therefore represents an important functional interface between metabolic signals and the neural mechanisms governing food intake [69].

Energy Substrate Utilization

Energy substrate utilization primarily involves the oxidation of glucose and fatty acids to generate energy and is regulated by multiple hormonal signals, including GLP-1 [72,73]. GLP-1 contributes to glucose metabolism by stimulating insulin secretion, promoting glucose uptake in peripheral tissues, and favoring glycogen synthesis in the liver and skeletal muscle, thereby supporting glucose and energy homeostasis [72,74]. GLP-1 also influences lipid metabolism and has been associated with reduced lipid accumulation and increased utilization of fatty acids as an energy source [73]. Through these effects, the GLP-1 system participates in metabolic adaptation to different nutritional states and contributes to the coordinated regulation of carbohydrate and lipid metabolism within the broader context of energy balance [72,75].

GLP-1-Induced Weight Loss

Rapid Weight Loss with GLP-1 Receptor Agonists

Weight loss associated with GLP-1 receptor agonist (GLP-1RA) therapy has been consistently demonstrated in clinical studies, with significant reductions in body weight often becoming evident during the early stages of treatment [35]. This early response is primarily attributed to reduced food intake, increased satiety, and delayed gastric emptying, which collectively influence the regulation of energy balance [7,40]. In addition to the initial reduction in body weight, GLP-1RAs can produce sustained weight loss that exceeds the effects observed with placebo, supporting their efficacy in the pharmacological management of obesity [39,40].

More recent evidence indicates that potent GLP-1-based therapies, including semaglutide and tirzepatide, may produce greater reductions in body weight, with weight loss exceeding 10% of baseline body weight in some treatment settings over relatively short periods [35,39]. These effects are largely mediated through the modulation of hypothalamic pathways and neural circuits involved in food reward, resulting in reductions in both hunger and the consumption of highly palatable foods [7,35].

Impact of Weight Loss on Muscle Mass

Weight loss induced by GLP-1 receptor agonists is accompanied by changes in body composition, including reductions in both fat mass and fat-free mass, the latter of which includes skeletal muscle [76]. Although most of the weight lost during GLP-1RA treatment is attributable to reductions in adipose tissue, a variable proportion—generally estimated at approximately 20%-50%—may consist of lean mass [76,78]. This pattern is not unique to GLP-1-based pharmacotherapy and has also been observed with calorie-restricted interventions and following bariatric surgery, suggesting that some degree of lean mass loss is a common component of substantial weight reduction [76,78].

Importantly, the reduction in muscle mass associated with GLP-1RA-induced weight loss does not appear to be disproportionate relative to the reduction in fat mass [78]. Moreover, measures of muscle strength and physical function tend to be preserved and may even improve when considered relative to body weight, suggesting a degree of functional adaptation during treatment. Thus, although an absolute reduction in muscle mass may occur,

measures related to muscle quality and functional capacity can be maintained throughout treatment [78,79].

Muscle Physiology in Obesity and Weight Loss

Skeletal Muscle Physiology in Obesity and Weight Loss

Skeletal muscle physiology is substantially altered in obesity, with metabolic and structural changes that include insulin resistance, intramuscular lipid accumulation, and mitochondrial dysfunction [75]. These abnormalities impair glucose uptake and reduce the efficiency of energy production within skeletal muscle [76,80]. As a consequence, the metabolic capacity of muscle tissue is compromised, contributing to the development and progression of obesity-related conditions such as type 2 diabetes mellitus and metabolic syndrome [6]. Obesity is also characterized by a state of chronic low-grade inflammation, which can adversely affect protein synthesis and muscle function, further contributing to skeletal muscle metabolic dysfunction [2,80].

Muscle Mass versus Lean Mass

The distinction between muscle mass and lean mass is important for the accurate interpretation of body composition, particularly in the context of obesity and weight loss [76]. Lean mass refers to the non-fat component of the body and includes skeletal muscle, bone, organs, body water, and other non-adipose tissues. Muscle mass, in contrast, specifically refers to muscle tissue responsible for force generation, movement, and a substantial proportion of whole-body energy metabolism [81,82]. Although the terms are sometimes used interchangeably, they are not synonymous; muscle represents one component of total lean mass [76,81].

This distinction becomes particularly relevant during weight loss because reductions in body weight may involve not only skeletal muscle but also other components of lean mass, including body water and mineral content [82]. Skeletal muscle has a major role in energy metabolism, contributing to resting energy expenditure and substrate utilization, whereas lean mass encompasses a broader range of tissues required for the maintenance of physiological functions [76,81]. Accordingly, distinguishing these measures is essential when assessing the effects of weight loss and developing strategies aimed at preserving muscle mass and function [81,82].

Sarcopenia, Obesity, and Weight Loss

Sarcopenia is characterized by a progressive decline in skeletal muscle mass, strength, and physical performance and may coexist with obesity, a condition commonly referred to as sarcopenic obesity [83,84]. This combination of excess adiposity and impaired muscle status is associated with systemic inflammation, insulin resistance, and a worsening metabolic profile [83-85]. In addition, intramuscular lipid accumulation and alterations in mitochondrial function may contribute to deterioration in muscle quality, even among individuals with a high body weight [84,85].

During weight loss, particularly with interventions involving GLP-1 receptor agonists, substantial reductions in body weight may be accompanied by decreases in lean mass, raising concerns regarding the development or progression of sarcopenia in susceptible individuals [83,85]. A clinically relevant proportion of weight loss may consist of fat-free mass, including skeletal muscle, underscoring the importance of monitoring body composition throughout treatment [85].

Conversely, recent studies suggest that GLP-1-based therapies may have favorable effects on skeletal muscle, including improvements in mitochondrial function and attenuation of inflammatory processes, which could contribute to the preservation of muscle quality despite reductions in overall muscle mass [86,87]. The relationship between sarcopenia, obesity, and weight loss is multifactorial. Accordingly, complementary strategies, including adequate protein intake and resistance exercise, are important to limit muscle loss and optimize metabolic and functional outcomes [84,86].

Muscle Composition and GLP-1-Based Therapies

Muscle composition encompasses not only the quantity of muscle tissue but also its quality, including factors such as lipid infiltration, metabolic characteristics, and functional capacity [76]. In individuals with obesity, increased intramuscular fat and alterations in skeletal muscle function are frequently observed and may impair insulin sensitivity and the regulation of energy metabolism [76,78]. In this context, GLP-1 receptor agonist therapies have demonstrated favorable effects on body composition, primarily through reductions in adiposity and improvements in metabolic parameters [2,76,78].

Although weight loss associated with these interventions may include a reduction in lean mass, most of the reduction in body weight is attributable to the loss of adipose tissue, resulting in an overall more favorable body composition [76,78]. GLP-1 receptor agonists may also contribute indirectly to the preservation of muscle quality through improvements in metabolic function, mitochondrial activity, and inflammatory signaling, although evidence regarding direct effects on skeletal muscle remains evolving [2,78]. Thus, the effects of these therapies extend beyond reductions in body weight and may influence body composition and metabolic health more broadly [76,78].

Intramuscular Fat Infiltration

Fat infiltration within skeletal muscle, commonly referred to as intramuscular adipose tissue or myosteatosis, is frequently observed in obesity and is associated with impaired muscle quality [88]. Lipid accumulation may occur within and between muscle fibers and can be accompanied by structural alterations that negatively affect force generation and mechanical efficiency [2,79,88]. Increased intramuscular fat is also closely associated with insulin resistance and metabolic dysfunction, as excessive lipid deposition can interfere with glucose uptake and fatty acid oxidation in skeletal muscle. These alterations may contribute to the progression of metabolic disorders, including obesity and type 2 diabetes mellitus [76,79,88].

Implications of GLP-1-Based Therapies for Muscle Health

Although rapid weight loss may initially be accompanied by

reductions in lean mass, available evidence suggests that GLP-1 receptor agonists produce metabolic effects that may support the preservation of skeletal muscle tissue [73,76]. These agents have been associated with improvements in glucose utilization and energy metabolism, potentially contributing to the maintenance of substrate availability and metabolic function during periods of negative energy balance [79,89]. Resistance exercise is also particularly important for preserving muscle mass and function during weight loss, indicating that pharmacological treatment should be considered as part of a broader strategy rather than as an isolated intervention [73,76].

At the cellular level, GLP-1 receptor agonists have also been associated with adaptations in energy metabolism and mitochondrial function that may promote a more favorable metabolic environment for skeletal muscle [73,79]. Nevertheless, reductions in lean mass may occur when nutritional support is inadequate, particularly when protein intake is insufficient [76,89]. Preservation of muscle quality during pharmacologically induced weight loss therefore requires an integrated approach combining appropriate pharmacotherapy, adequate nutritional intake, and regular physical activity, with particular emphasis on resistance exercise [73,76].

Body Composition Changes Following Weight Loss

Reduction in Muscle Mass and Its Impact on Tissue Support

Loss of muscle mass is a common component of weight reduction, particularly when substantial caloric restriction occurs without interventions aimed at preserving lean tissue [76]. During weight loss, reductions in body weight are not limited to adipose tissue but may also involve a decline in fat-free mass, which includes skeletal muscle [90,91]. To some extent, this response reflects physiological adaptation to reduced energy availability, during which increased protein breakdown may occur as the body adjusts to maintain essential functions [76,92].

Loss of skeletal muscle may influence tissue support and body contour, with potential functional and aesthetic consequences, including increased skin laxity and reduced tissue firmness [90]. Skeletal muscle contributes to the structural foundation underlying the skin and soft tissues; therefore, substantial reductions in muscle volume may alter the support provided to superficial tissues and affect body contour [93]. In addition, reductions in lean mass may be accompanied by decreases in muscle strength and physical capacity, potentially affecting quality of life, particularly when weight loss is substantial or occurs rapidly [93,94].

From both clinical and aesthetic perspectives, these findings underscore the importance of strategies designed to minimize muscle loss during weight reduction, particularly adequate protein intake and resistance training [91,94]. Evidence indicates that interventions combining nutritional support with structured physical exercise can help preserve lean mass over time, thereby reducing unfavorable changes in body composition and supporting the functional integrity of musculoskeletal tissues [90,91].

Changes in Body Composition Following Weight Loss

Changes in body composition following weight loss involve alterations in the relative contribution of adipose tissue and fat-free mass, and weight reduction does not occur uniformly across these compartments [82]. Most of the weight lost is generally attributable to reductions in adipose tissue, particularly visceral and ectopic fat depots, which are closely associated with improvements in metabolic health [82,95]. However, fat-free mass is also commonly reduced and may account for approximately 20%-50% of total weight loss, depending on the type, magnitude, and duration of the intervention [76,95].

Weight loss may also alter the distribution of adipose tissue, with a more pronounced reduction in visceral fat relative to some subcutaneous depots, contributing to improvements in cardiometabolic risk [82,96]. Although absolute lean mass may decline, its proportion relative to total body mass can remain stable or increase over time, reflecting a more favorable overall body composition [76,96]. Therefore, assessment of body composition after weight loss should consider not only the magnitude of weight reduction but also the relative changes and redistribution among the different body compartments [82].

Musculoskeletal System and GLP-1-Related Lipid Metabolism

Effects of GLP-1 Receptor Agonists on Skeletal Muscle

GLP-1 receptor agonists exert relevant effects on skeletal muscle, particularly through changes in energy metabolism and cellular function [82,89]. Evidence suggests that GLP-1 receptor activation is associated with increased glucose uptake and utilization, as well as improved insulin sensitivity in skeletal muscle, thereby supporting more efficient metabolic function [82,89]. These agents may also promote fatty acid oxidation and influence mitochondrial activity, contributing to metabolic adaptations within skeletal muscle [73,76].

Effects on Lipid Metabolism

GLP-1 receptor agonists influence lipid metabolism by modulating the balance between lipid storage and utilization. GLP-1R activation has been associated with reduced lipogenesis and increased fatty acid oxidation, favoring greater utilization of endogenous energy stores [82,97]. In addition, GLP-1-based therapies may reduce ectopic fat accumulation, particularly in the liver, thereby decreasing lipotoxic stress and contributing to a more favorable systemic metabolic environment [89,97].

At the cellular level, these effects involve modulation of metabolic pathways such as AMP-activated protein kinase (AMPK), a major regulator of cellular energy homeostasis [97,98]. AMPK activation is associated with inhibition of lipogenic regulators, including sterol regulatory element-binding protein 1c (SREBP-1c), which may reduce lipid synthesis while promoting fatty acid oxidation [97,98]. Although the effects of GLP-1 signaling on these pathways are likely mediated through interconnected and predominantly indirect mechanisms, available evidence indicates that GLP-1 receptor agonists can influence lipid metabolism through modulation of these intracellular signaling networks [82,97].

Impact on Musculoskeletal Health

The effects of GLP-1 receptor agonists on the musculoskeletal system extend beyond metabolic regulation and may involve adaptations across several tissues [76]. The identification of GLP-1 receptors in bone and joint tissues has raised the possibility of direct effects on these compartments, including modulation of osteoblast and osteoclast activity and local inflammatory processes [99,100]. Clinically, these mechanisms may be relevant to obesity-associated musculoskeletal conditions, including inflammatory joint disorders, although some of the observed benefits may also result indirectly from weight reduction and improved metabolic status [76,100].

In skeletal muscle, the available evidence suggests that the effects of GLP-1-based therapies may relate more closely to tissue quality and metabolic function than to preservation of absolute muscle mass [99]. Improvements in muscle perfusion and reductions in intramuscular fat have been reported and may contribute to functional performance despite reductions in lean mass during weight loss [76,100]. Regarding bone health, weight loss itself may influence bone mineral density; however, current evidence does not indicate a consistent increase in fracture risk attributable to GLP-1 receptor agonists, suggesting an overall neutral or potentially modulatory effect in this context [99,100].

Emerging Therapies and Future Perspectives

Next-Generation Agonists: Dual, Triple, and Small-Molecule Agents

The development of next-generation GLP-1-based therapies has progressed beyond selective GLP-1 receptor activation toward pharmacological strategies that simultaneously target multiple metabolic pathways within a single molecule [101]. Among these approaches, dual agonists that activate both the GLP-1 and glucose-dependent insulinotropic polypeptide (GIP) receptors have attracted considerable attention [100]. These agents have demonstrated greater effects on body weight and metabolic control than some conventional incretin-based therapies, although their clinical benefits vary according to the specific molecule, dose, and population studied [102,103]. The combined activation of GLP-1 and GIP signaling may produce complementary effects on insulin secretion, appetite regulation, and energy metabolism, thereby expanding the therapeutic potential of incretin-based pharmacotherapy [6,103].

Further advances include triple agonists designed to simultaneously target GLP-1, GIP, and glucagon receptors. Retatrutide is an example of this approach and has demonstrated substantial potential for weight reduction and metabolic improvement in clinical development programs [104,105]. Activation of the glucagon receptor may additionally increase energy expenditure and promote lipid mobilization, complementing the effects of GLP-1- and GIP-mediated appetite and metabolic regulation [106,107]. This pharmacological strategy therefore combines suppression of energy intake with enhanced energy expenditure and broader metabolic effects, although the long-term clinical relevance and safety of these agents remain under investigation [107].

In parallel, the development of small-molecule GLP-1 receptor agonists, such as orforglipron, represents an important advance because these compounds can provide oral administration without the structural and administration requirements associated with peptide-based therapies [108,109]. Clinical studies have demonstrated meaningful effects on glycemic control and body weight, supporting their potential as an alternative to injectable GLP-1 receptor agonists [108-110]. Oral small-molecule agents may also offer greater flexibility and convenience, which could facilitate treatment acceptance and adherence in some patients [108]. Collectively, these developments are broadening the therapeutic landscape of GLP-1-based pharmacology by combining different mechanisms of action with alternative routes of administration and potentially improved treatment convenience.

Future Perspectives for GLP-1 Receptor Agonists

Future applications of GLP-1 receptor agonists are likely to extend beyond weight management and glycemic control toward a broader approach to obesity and its associated comorbidities [111]. In addition to substantial weight reduction, clinical evidence has linked GLP-1-based therapies with reductions in cardiovascular events, including myocardial infarction, stroke, and cardiovascular mortality, as well as with effects on inflammatory and atherosclerotic pathways [111,112]. These findings support an expanding role for GLP-1 receptor agonists in cardiovascular risk reduction, including in populations without diabetes mellitus. Interest is also increasing in their potential applications in hepatic disorders, including metabolic dysfunction-associated steatotic liver disease, and in kidney disease, given their effects on inflammation, lipid metabolism, and vascular and endothelial function [111].

Emerging therapeutic strategies are increasingly focused not only on the magnitude of weight loss but also on its durability, metabolic quality, and effects on body composition. Preservation of lean mass and prevention of weight regain are therefore becoming important considerations in the long-term management of obesity [78,85]. Future approaches may increasingly incorporate combination therapies and individualized treatment strategies aimed at optimizing clinical outcomes, maintaining weight reduction, and maximizing systemic benefits while limiting adverse effects [6]. The development of these interventions reflects a broader shift in the understanding of obesity as a chronic, multifactorial, and systemic disease requiring long-term, individualized, and integrated therapeutic management.

Conclusion

GLP-1 receptor agonists have become important therapies for obesity by regulating appetite, energy homeostasis, glucose metabolism, and body weight. Although substantial weight loss may involve reductions in lean mass and skeletal muscle, current evidence does not indicate disproportionate muscle loss, with outcomes influenced by the magnitude of weight reduction, nutritional status, and physical activity. Preservation of lean tissue is relevant to physical function, tissue support, body contour, and potential skin laxity, highlighting the importance of adequate

nutrition and resistance exercise alongside pharmacological treatment. Emerging dual and triple agonists and oral small-molecule agents may further expand therapeutic options, although their long-term effects remain uncertain. Overall, GLP-1-based therapies should be integrated into a broader strategy that considers weight loss, body composition, muscle preservation, metabolic health, and tissue quality.

Authors' contributions

Investigation, conceptualization, methodology, writing - original draft, I.R.N; Conceptualization, formal analysis, writing-reviewing and editing, supervision, validation, R.C.

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