GLP-1R Agonists and Muscle Health: Potential Role in Sarcopenia Prevention and Treatment.

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Abstract: Glucagon-like peptide-1 receptor agonists (GLP-1RAs) have emerged as a cornerstone therapy for weight loss and glycemic control in type 2 diabetes mellitus (T2DM) and obesity. Moreover, robust cardiometabolic benefits and favorable safety profiles have positioned GLP-1RAs at the forefront of modern obesity pharmacotherapy. However, findings from large-scale trials (e.g., SUSTAIN, STEP, SURPASS) have raised concerns that a significant proportion of the weight loss achieved with GLP-1RA treatment may derive from lean body mass—particularly skeletal muscle—which could be detrimental in populations already at risk for sarcopenia.

However, emerging preclinical evidence suggests that GLP-1RAs may directly and indirectly influence skeletal muscle through anti-inflammatory, antioxidant, and mitochondria1-supportive mechanisms. These include modulation of key signaling pathways such as PI3K/Akt/mTOR and AMPK–PGC-1α, suppression of proteolytic activity, and promotion of myogenic differentiation. In experimental models of aging, sarcopenic obesity, and chronic disease, GLP-1RAs have shown muscle-preserving properties. Nevertheless, the balance between adipose tissue reduction and lean mass preservation remains incompletely understood in clinical settings.

This review examines the existing experimental and clinical evidence and identify critical research directions to determine whether GLP-1RAs confer overall benefit or carry unintended risks for skeletal muscle integrity in the context of weight loss.

Keywords: Sarcopenia, muscle homeostasis, GLP-1RAs, diabetes, obesity

Significance: Glucagon-like peptide-1 receptor agonists (GLP-1RAs) are now widely used for obesity and type 2 diabetes because they lower weight and improve cardiometabolic risk. Their rapid uptake has raised concern that they may accelerate skeletal muscle loss and

worsen sarcopenia. This review integrates mechanistic, imaging and clinical evidence linking GLP-1RAs to muscle mass, quality and function. Current data suggest that, although some lean tissue is lost during treatment, GLP-1RAs predominantly reduce fat mass, may improve muscle composition and metabolism, and do not consistently impair physical performance. We outline biological pathways through which GLP-1RAs could protect muscle, identify key gaps, and define research priorities for safely managing weight loss in people at risk of sarcopenia.

1. Introduction

Sarcopenia is defined as a progressive and generalized skeletal muscle disorder involving accelerated loss of muscle mass and function that has become a public health concern linked to disability, hospitalization, and mortality [1-3]. Traditionally associated with older age, sarcopenia is now increasingly recognized in younger cohorts affected by metabolic disorders such as type 2 diabetes mellitus (T2DM) and obesity, particularly in the form of sarcopenic obesity [4-6]. Importantly, sarcopenia is not an inevitable consequence of aging, but a preventable condition that justifies specific diagnostic criteria and therapeutic interventions [7].

Current pharmacological options for sarcopenia are limited, with exercise and nutritional interventions remaining the primary strategies. The multifactorial nature of sarcopenia, involving chronic inflammation, insulin resistance, mitochondrial dysfunction, and hormonal imbalances, continues to present significant challenges to the development of effective therapies [7]. Multiple candidate therapies (e.g., myostatin inhibitors, selective androgen receptor modulators, and mitochondria-targeting compounds such as urolithin A) have been explored with mixed functional results [7–11].

In this therapeutic landscape, glucagon-like peptide-1 receptor agonists (GLP-1RAs) have become central to diabetes and obesity care. These drugs improve glycemia by enhancing insulin secretion and suppressing glucagon while reducing body weight via effects on gastric emptying and appetite [12–16]. Owing to their potent weight-reducing effects, GLP-1RAs such as liraglutide (Saxenda®) and semaglutide (Wegovy®) have been approved for the treatment of obesity. More recently, tirzepatide, a dual glucose-dependent insulinotropic polypeptide (GIP) and GLP-1 receptor agonist—marketed as Mounjaro® and Zepbound®—has been approved for chronic weight management with greater weight-loss efficacy than GLP-1RA monotherapy. However, the success of GLP-1RAs has prompted debate about their effect on muscle.

While weight loss therapies aim to reduce excess adiposity and alleviate obesity-related complications—including cardiovascular disease—they are often accompanied by unfavorable changes in body composition, particularly reductions in lean mass (LM). Notably, losses of LM have been reported to account for up to 40% of total weight reduction with semaglutide and approximately 25% with tirzepatide [17–20], raising concerns in populations already in risk of sarcopenia, such as individuals with obesity and T2DM, who constitute the primary candidates for these treatments [21]. Importantly, LM is a composite encompassing all non-fat tissues, including skeletal muscle, organs, and extracellular fluid (excluding bone), and is commonly used in clinical research as a surrogate for skeletal muscle mass due to the predominance of muscle within lean soft tissue. However, LM does not equate to skeletal muscle and LM loss during weight reduction may reflect non-muscle compartments, so careful interpretation is required to gauge clinical relevance.

Conversely, emerging clinical and especially preclinical data suggests that GLP-1RAs may preserve or even support muscle despite overall weight loss. These potential benefits are attributed to the pleiotropic effects of GLP-1RAs, including anti-inflammatory, metabolic, microvascular, and mitochondrial effects, and any direct effects on skeletal muscle tissue still under investigation [22,23]. Clinical trials such as STEP 1 and SUSTAIN 8 have demonstrated that semaglutide-associated weight loss is primarily driven by fat mass reduction, with relative LM preservation in people with obesity or T2DM [24,25]. Additionally, preclinical studies suggest that GLP-1RAs may exert anabolic or anti-catabolic effects on skeletal muscle [26–28]. In this review, we synthesize evidence to address whether GLP-1RAs harm, spare, or benefit skeletal muscle in the context of weight loss. We first outline how weight loss *per se* affects skeletal muscle, then synthesize clinical observations with GLP-1RAs relevant to sarcopenia, integrate mechanisms by mapping core sarcopenia pathways and their potential modulation by GLP-1RAs, and finally review experimental evidence linking GLP-1RAs to muscle mass.

2. Skeletal Muscle in weight loss interventions

Skeletal muscle is the most abundant tissue, accounting for approximately 25–30% of resting energy expenditure (REE) [29]. Beyond locomotion, it is central to metabolic regulation and glucose homeostasis. People with obesity typically have higher absolute skeletal muscle mass than normal-weight individuals due to increased mechanical loading, yet muscle quality is typically lower, marked by increased intramuscular fat infiltration (myosteatosis), impaired mitochondrial function, altered muscle fiber composition (fiber-type shift from oxidative type I fibers to glycolytic type II fibers), and chronic low-grade inflammation [19,30].

Collectively, these alterations compromise muscle contractility and endurance and promote functional limitation.

Muscle homeostasis is tightly governed by hormonal and metabolic signals. Insulin, a key anabolic hormone, suppresses muscle proteolysis and promotes protein synthesis, thus favoring net muscle accretion [31,32]. In states of insulin resistance this anabolic signaling is blunted, predisposing to sarcopenic obesity, which is characterized by the coexistence of excess adiposity with reduced muscle strength and function despite normal or high body weight.

Weight loss interventions (lifestyle modification, pharmacotherapy, bariatric surgery) typically reduce both fat and LM. Approximately, 20%–25% of total weight lost is LM, with skeletal muscle comprising a significant portion [33]. This reduction in energy expenditure contributes to adaptive thermogenesis, a physiological response in which metabolic rate declines disproportionately to the amount of weight lost. This phenomenon plays a key role in the weight-loss plateau and is a major contributor to long-term weight regain, which occurs in over 80% of individuals within five years [34].

Preserving muscle during weight loss is therefore essential not only to maintain REE and reduce metabolic adaptation, but also to support musculoskeletal integrity, glucose metabolism, and long-term weight maintenance. This is particularly critical in older adults, people with T2DM, and postmenopausal women due to anabolic resistance, hormonal shifts, and lower baseline muscle mass [35,36]. Evidence from the LOOK AHEAD trial, which included individuals with T2DM, participants with ≥6% weight loss experienced a higher incidence of frailty fractures than controls [37]. Similarly, very-low-calorie diets can expedite

short-term weight loss in severe obesity but may accelerate LM decline and reduce bone mineral density [38,39]. Accordingly, guidelines discourage overly restrictive diets in high-risk groups and emphasize LM preserving strategies through the incorporation of resistance training, adequate protein intake, and targeted reduction of metabolically harmful fat depots—such as visceral adipose tissue and hepatic fat [40,41].

3. Clinical Observations and Potential Applications in Sarcopenia Management

Several large-scale randomized controlled trials (RCTs) have evaluated GLP-1RAs across diverse populations, primarily focusing on glycemic control, cardiovascular protection, and renal outcomes, but only a few included accurate measurements of muscle mass usually inferred from dual-energy X-ray absorptiometry (DXA) determinations or imaging sub-studies. Across these primary and ancillary studies, the consistent pattern is preferential fat loss with relative LM preservation, with no signal of impaired physical performance (**Table 1**).

Thus, in people with advanced heart failure or T2DM, liraglutide did not worsen physical endurance determinations, including maximal oxygen uptake (VO_2 max), cycle-ergometry duration, or 6-minute walk distance [42]. Similarly, in obesity cohorts, liraglutide was associated with improvements in self-reported physical function, [43].

Regarding the effects on body composition, the SUSTAIN trials (1–6) semaglutide consistently led to significant body weight reductions in people with T2DM; although most of these studies did not include comprehensive assessments of body composition, available data suggest that weight loss was primarily driven mainly by fat rather than LM. In SUSTAIN 8— which compared semaglutide to the sodium-glucose co-transporter 2 inhibitor (SGLT2i) canagliflozin— semaglutide demonstrated greater total weight loss [44], and a DXA-based

substudy revealed that despite the absolute decline, both groups experienced an increase in the relative proportion of LM to total body weight (semaglutide: +1.2%; canagliflozin: +1.1%), suggesting a favorable effect on body composition and potential mitigation of sarcopenic risk [25].

The SURPASS program, which evaluated the efficacy and safety of tirzepatide, similarly demonstrated large reductions in visceral and subcutaneous adipose tissue with a preservation of a greater proportion of LM based on DCA assessments [45,46]. A recent post-hoc analysis of the SURPASS-3 trial (T2DM cohort) utilized magnetic resonance imaging (MRI)-based assessments to evaluate changes in muscle and fat within the thigh; highlighted findings included thigh muscle volume reductions in proportion to overall weight loss, while intramuscular fat infiltration declined more than expected, indicating improved muscle quality despite weight reduction. [47,48].

Complementary MRI studies with liraglutide reported reductions in ectopic fat (visceral adipose tissue (VAT) by 12.5%, hepatic fat content by 31.5%, and epicardial fat by 13.4%); these reductions were disproportionately greater than expected from weight loss, suggesting direct pharmacologic effects on ectopic fat depots [49]. A subsequent post hoc analysis of this cohort revealed a significant 2.87% absolute reduction in thigh intramuscular fat with size-adjusted muscle volume largely unchanged; moreover, the proportion of participants with adverse muscle composition—defined as high fat infiltration with low muscle mass—declined from 11.0% to 8.2% in the liraglutide group, with no such improvement observed in the placebo arm [50]. Collectively, these studies provide robust, imaging-based evidence that liraglutide preferentially reduces ectopic and visceral fat while concurrently enhances skeletal muscle quality.

Further support comes from the STEP 1 trial, which included adults with obesity or overweight without diabetes treated with semaglutide [24]; a post hoc analysis, which included data from DEXA scans at baseline and week 68, showed that although absolute LM decreased 9.7% along with fat mass, the relative proportion of LM relative to total body mass increased by ~3.0%, highlighting preferential adipose tissue targeting by semaglutide [52]. SUSTAIN FORTE confirmed dose-dependent metabolic benefits, although muscle-specific endpoints were not collected [51].

Although not designed to assess skeletal muscle outcomes, several cardiovascular and renal outcome trials, together with and real-world cohorts, suggest potential indirect benefits to muscle via systemic improvements. In the LEADER trial, liraglutide reduced major adverse cardiovascular events (MACE) in subjects with T2DM [53]; while muscle-specific endpoints were not assessed, improvements in systemic inflammation, metabolic efficiency, and functional capacity—especially in frail subgroups—suggest potential indirect benefits for muscle health [53].The SUSTAIN 6 and LEADER trials both demonstrated significant reductions in MACE after semaglutide or liraglutide treatment, respectively, in people with T2DM and high cardiovascular risk; again, again, muscle parameters were not directly evaluated, but the systemic anti-inflammatory and metabolic improvements observed may contribute to the preservation of muscle mass and function in this population [53,54]. Similarly, in the AWARD-11 trial, higher-dose dulaglutide produced significant weight loss with no excessive loss of LM in subjects with T2DM [55]. Efpeglenatide, a long-acting GLP-1RA, showed improved cardiovascular and renal outcomes in high-risk diabetic populations in the AMPLITUDE-O trial; despite lacking muscle assessments, the potent anti-

inflammatory, anti-catabolic, and endothelial effects could indirectly benefit skeletal muscle, especially in comorbid states predisposing to sarcopenia [56].

Real-world and exploratory analyses in populations with T2DM further support the preferential fat-loss effects of GLP-1RAs by assessing body composition through bioelectrical impedance analysis (BIA). Thus, an observational study in adults initiating oral semaglutide reported a total weight loss of 4.0 kg, including an average reduction of 3.2 kg in fat mass, with no significant change in skeletal muscle mass after 16 weeks [57]. Similarly, in older adults with obesity, semaglutide combined with caloric restriction and exercise interventions for 3 months preserved appendicular LM and improved physical function scores [58]. Likewise, a recent real-world quasi-experimental study reported 9.5% of weight loss primarily driven by fat mass reduction, while skeletal muscle mass and fat-free mass were preserved, after 24 weeks of semaglutide [59]; notably, the phase angle remained unchanged, suggesting that semaglutide-induced weight loss did not compromise muscle quality or cellular health [59]. Finally, some cohorts also show improvements in health-related quality of life (HRQoL) and functional performance tests (such as the six-minute walk test) in populations receiving GLP-1RA therapy, although data remain limited and largely observational [60].

Taken together, while landmark GLP-1RA trials were not specifically designed to assess sarcopenia, their consistent demonstration of fat mass reduction with relative LM preservation, combined with improvements in systemic metabolic and inflammatory profiles, supports the hypothesis that GLP-1RAs may help prevent or slow muscle wasting.

4. Pathophysiological Pathways in Sarcopenia and Their Modulation by GLP-1RAs

Sarcopenia results from a complex interplay of mechanisms, including impaired protein homeostasis, chronic inflammation, mitochondrial dysfunction, and oxidative stress, among other contributing factors (**Figure 1**). These interconnected processes drive progressive losses in muscle mass, strength, and function observed with aging and chronic disease. Notably, many of these same pathways are modulated by GLP-1RAs, which exert pleiotropic actions beyond glycemic control. By attenuating inflammation, improving metabolic regulation, and supporting mitochondrial integrity, GLP-1RAs may counteract key drivers of muscle wasting, positioning them as plausible candidates for the prevention and treatment of sarcopenia.

The GLP-1R, a member of the class B G-protein-coupled receptor family, was first identified in rat insulinoma-derived cells and human pancreatic islets. GLP-1R mRNA has since been detected in several human tissues, including lung, pancreatic islets, stomach, kidney, hypothalamus, and heart—but not in adipose tissue or liver [61]. The presence and functional relevance of GLP-1R in human skeletal muscle remains uncertain: while experimental studies in animal models and cell studies suggest receptor expression in myofibers, evidence in humans is limited and inconsistent [61–63]. Accordingly, putative muscle benefits of GLP-1RAs in people are likely mediated indirectly—via improved glycemia/insulin action, reduced systemic inflammation, enhanced microvascular perfusion, and reduced ectopic lipid—rather than robust, receptor-driven actions within myocytes.

Nevertheless, preclinical studies show that GLP-1RAs engage pathways relevant to muscle anabolism and cytoprotection, including PI3K/Akt/mTOR, AMPK, and MAPK cascades, while limiting catabolic processes such as FoxO-mediated upregulation of E3 ligases

Atrogin-1 and MuRF1 [64], alongside reductions in oxidative stress and improved mitochondrial function in rodent and cell models [26,28]. These findings support biological plausibility form muscle preservation, but wether–and through which tissues- these effects translate to humans remains to be clarified.

In the following subsections, we integrate the pathophysiological drivers of sarcopenia with their potential modulation by GLP-1RAs, providing a framework for their pleiotropic and translational relevance to muscle health.

4.1 Impaired Protein Homeostasis: Insulin Resistance and Proteolysis

A central hallmark of sarcopenia is the dysregulation of muscle protein turnover, characterized by a shift toward net catabolism. In healthy muscle, a dynamic equilibrium between protein synthesis and degradation preserves mass. Aging and disease disrupt this balance, reducing the synthesis of myofibrillar, mitochondrial, and sarcoplasmic proteins and accelerating atrophy and loss of function. Protein synthesis is primarily driven by insulin/insulin-like growth factor-1 (IGF-1) signaling through the PI3K/Akt/mTOR pathway. Activation of insulin or IGF-1 receptors triggers phosphorylation of the insulin receptor substrate 1 (IRS-1) and downstream activation of mTORC1, promoting anabolic processes [60,64,65]. In insulin-resistant states (e.g., T2DM and obesity), this pathway is blunted, contributing to muscle loss and sarcopenic obesity [66]. Interventions that improve insulin sensitivity—such as weight loss or insulinotropic therapies—can help to restore anabolic signaling [32].

Conversely, protein degradation is mediated by two key proteolytic systems: the ubiquitin–proteasome system (UPS) and the autophagy–lysosome pathway [41,67]. The Forkhead box O (FoxO) transcription factors driev both processes by inducing muscle E3 ubiquitin ligases

(*Atrogin-1*, *MuRF-1*) and atrophy genes (e.g., *Bnip3, Beclin1*) under catabolic stress [68-71]. Normally, Akt signaling downstream of IRS-1 restrains FoxO and thereby suppresses both the UPS and autophagy. Myostatin, a TGF-β family member antagonized by follistatin, further promotes catabolism by activating ActRIIB/Smad2/3 signaling, which suppresses Akt/mTOR and facilitates FoxO-dependent atrogene expression [72,73]. Age- and disease-related hormonal changes (declines in insulin, IGF-1, GH, testosterone, and estrogen with higher cortisol) amplify anabolic resistance and proteolysis [74–78].

GLP-1RAs can mitigate this anabolic–catabolic imbalance through both systemic metabolic effects and pathway crosstalk. In pancreatic β-cells, GLP-1R activation raises cAMP and activates PKA/Epac, augmenting insulin secretion and suppressing glucagon release from α-cells [79] (**Figure 2**). Beyond pancreatic islets, GLP-1RA treatment in muscle models is associated with increased Akt phosphorylation—facilitating GLUT4 translocation and glucose uptake—and with inhibition of FoxO, reducing Atrogin-1/MuRF-1 induction while down-modulating myostatin signaling and supporting myogenic regulators (MyoD, MyoG) [83,84]. Conceptually, restoring Akt/mTOR activity would be expected to shift the myostatin–follistatin balance toward anabolism, favoring protein synthesis and myogenesis. Direct evidence that GLP-1RAs modify this axis in humans is limited; we therefore present it as a mechanistic rationale consistent with preclinical data. Akt activation further stimulates mTORC1, reinforcing protein synthesis and cellular growth [64]. Studies with exendin-4, liraglutide, and semaglutide report reduced E3-ligase expression and proteolysis in diabetic/cachectic models—even when glycemia is not fully normalized [26,28].

Adult muscle repair depends on satellite cells (SCs), whose activation, proliferation, and differentiation are blunted by aging, insulin resistance, chronic inflammation, and niche

dysfunction [85,86]. By restoring insulin/IGF-1–Akt–mTOR signaling, reducing inflammatory tone, and improving microvascular perfusion, GLP-1RAs may indirectly favor myogenesis and preserve regenerative capacity. In preclinical models under hyperglycemic/lipotoxic stress, GLP-1RAs increase MyoD/MyoG expression and myotube formation while lowering FoxO-linked atrogenes—implicating AMPK, YAP/TAZ, and PGC-1α pathways [135–137]. Direct, SC-specific effects in humans remain to be established [121].

Importantly, insulin's role in human muscle is permissive: basal insulin is required to maintain synthesis and restrain breakdown, but supraphysiologic elevations do not proportionally increase synthesis in the fed state, where amino acid availability is the dominant driver [85]. Thus, GLP-1RA contributions to protein balance likely reflect restored insulin sensitivity, improved nutrient delivery, and reduced catabolic stress rather than sustained hyperinsulinemia.

In summary, impaired protein homeostasis is a core defect in sarcopenia. By improving insulin action and glycemic control, engaging Akt/FoxO pathways, and potentially tilting the myostatin–follistatin axis toward anabolism, GLP-1RAs may help counter sarcopenic muscle loss.

4.2 Chronic Inflammation and Immune-Mediated Catabolism

Systemic low-grade inflammation is a major driver of sarcopenia, closely linked to insulin resistance, impaired regeneration, and accelerated muscle catabolism. Elevated concentrations of pro-inflammatory cytokines—particularly tumor necrosis factor-α (TNF-α) and interleukin-6 (IL-6)—and higher C-reactive protein (CRP; an inflammatory marker) are common in individuals with sarcopenia and correlate with muscle loss [88,89]. In

experimental models, TNF-α blockade improves muscle function and attenuates atrophy [90]. A central effector of inflammation-induced wasting is the nuclear factor-κB (NF-κB) pathway: cytokine stimulation (e.g., TNF-α) leads to IκB degradation, NF-κB nuclear translocation, and transcription of catabolic programs, including upregulation of the E3 ligase MuRF-1; in parallel, FoxO transcription factors prominently drive Atrogin-1 expression [91,92].

Mitochondrial dysfunction amplifies inflammation-driven catabolism. Impaired biogenesis and respiratory function reduce oxidative capacity and ATP availability while increasing reactive oxygen species (ROS), which further activate pro-apoptotic signaling and myofiber loss. Age-related declines in regulators of mitochondrial homeostasis—including including peroxisome proliferator-activated receptor gamma coactivator-1 alpha PGC-1α and sirtuins—exacerbate these deficits and contribute to fatigue, fiber degeneration, and loss of contractile capacity [93–96].

GLP-1RAs have demonstrated anti-inflammatory and cytoprotective effects that may counteract these processes. Initially characterized in pancreatic islets and adipose tissue, where they reduce pro-inflammatory cytokine output and improve insulin sensitivity [97,98], similar actions have been reported across liver, vasculature, brain, and kidney. Importantly, emerging evidence suggests direct benefits in skeletal muscle, where GLP-1RAs reduce immune cell infiltration and downregulate the secretion of TNF-α and IL-6 [98,99].

Mechanistically, macrophages express functional GLP-1R, enabling GLP-1RAs to modulate inflammatory signaling. Activation of GLP-1R in macrophages stimulates the cAMP/PKA pathway, which in turn inhibits NF-κB activation and nuclear translocation, thereby reducing

the transcription of pro-inflammatory mediators such as TNF-α, IL-1β, and IL-6 [100–106]. GLP-1RAs also suppress the NLRP3 inflammasome, further dampening chronic inflammatory responses and preventing tissue injury [107]. Beyond cytokine suppression, GLP-1RAs promote immunomodulation by shifting macrophage polarization from pro-inflammatory (M1) toward anti-inflammatory (M2) phenotypes and by supporting regulatory T-cells activity, collectively fostering a more favorable immunometabolic milieu [99].

These effects have been functionally validated in preclinical models of muscle wasting. In aged mice, dulaglutide administration reduced Toll-like receptor 9 (TLR9)- and NF-κB-dependent signaling, downregulated Atrogin-1 and MuRF-1, and protected against muscle atrophy [108]. Similarly, PF1801, a long-acting GLP-1RA, improved muscle inflammation, reduced necroptosis, and preserved fiber integrity in a mouse model of chronic inflammatory myopathy [109]. Together, these findings highlight the ability of GLP-1RAs to mitigate inflammation-driven muscle decline in age- and disease-related sarcopenia.

4.3 Oxidative Stress and Mitochondrial Dysfunction

Aging muscle fibers often exhibit profound mitochondrial abnormalities, including reduced organelle density and enzymatic activity, impaired electron transport chain function, and altered fusion-fission dynamics that compromise oxidative phosphorylation [93-96]. The result is diminished ATP production and excess ROS generation. Elevated ROS and reactive nitrogen species inflict cumulative damage on proteins, lipids, and DNA, accelerating muscle fiber degeneration. Beyond structural damage, oxidative stress activates redox-sensitive signaling cascades, such as NF-κB and FoxO, which trigger catabolic programs and

upregulate muscle-specific atrogenes, thereby linking mitochondrial dysfunction directly to muscle proteolysis [93-96].

These deficits are compounded by blunted mitochondrial biogenesis with aging and chronic disease, driven by downregulation of PGC-1α and sirtuins—key governors of mitochondrial renewal and energy homeostasis. The consequence is a vicious cycle: damaged mitochondria generate more ROS, further injuring organelles, amplifying catabolic signaling, and triggering apoptosis via mitochondrial outer-membrane permeabilization and cytochrome c release, culminating in myocyte loss. This oxidized, energy-depleted milieu is a fundamental driver of sarcopenia, promoting fatigue, atrophy, and reduced regenerative capacity [93–96].

GLP-1RAs exert anti-oxidative effects in multiple tissues, with mechanistic implications for skeletal muscle. They attenuate ROS generation by limiting nicotinamide adenine dinucleotide phosphate (NADPH) oxidase activity—a major enzymatic source of superoxide—while enhancing endogenous defenses. Reported adaptations include increased superoxide dismutase (SOD) and glutathione peroxidase (GPx) expression/activity, restoring redox balance and limiting oxidative injury [110,111]. Mechanistically, GLP-1R signaling can inhibit protein kinase C (PKC)–dependent activation of NADPH oxidase, particularly under hyperglycemic conditions [112], and may activate AMP-activated protein kinase (AMPK), which suppresses ROS production and supports mitochondrial quality control [113].

Beyond anti-oxidant actions, GLP-1RAs promote mitochondrial biogenesis and function. Preclinical studies show upregulation of PGC-1α—via AMPK and sirtuin-1 (SIRT1)—with downstream transcriptional programs for oxidative phosphorylation, mitochondrial DNA

replication, and organelle dynamics [114–116]. Coordinated AMPK–SIRT1–PGC-1α activation enhances respiration, ATP generation, and efficiency while reducing ROS output [117]. In diabetic rodent muscle, GLP-1RA treatment increased mitochondrial DNA content, boosted OXPHOS complex expression, and raised citrate synthase and cytochrome c oxidase activities, changes accompanied by improved endurance, reduced fatigue, and better insulin sensitivity [118]. Preservation of mitochondrial function also limits apoptosis by stabilizing mitochondrial membranes and preventing cytochrome c release. Notably, PGC-1α–driven improvements in mitochondrial quality also support the SCs program, linking redox control to regenerative capacity [119–121]. Collectively, by reducing oxidative stress and enhancing mitochondrial health, GLP-1RAs may protect skeletal muscle against two core drivers of sarcopenia: bioenergetic decline and redox imbalance.

4.4 Vascular Perfusion and Muscle Energy Supply

In sarcopenia—particularly when compounded by cardiovascular disease, T2DM, or sedentary behavior—skeletal-muscle perfusion is frequently impaired. Endothelial dysfunction in resistance arterioles and capillaries blunts vasodilatory responses to insulin and exercise, limiting delivery of oxygen, glucose, and amino acids while allowing metabolic by-products to accumulate. Chronic under-perfusion preferentially atrophies oxidative (type I) fibers and diminishes adaptive capacity to physical activity. In T2DM, skeletal-muscle microvascular dysfunction and capillary rarefaction are well described and closely linked to reduced insulin-mediated glucose uptake and anabolic resistance, underscoring vascular health as a critical—often underappreciated—determinant of sarcopenia progression [122].

Evidence from endothelial and in-vivo studies indicates that GLP-1RAs exert vasculoprotective actions. In endothelial models, GLP-1/GLP-1R signaling enhances nitric-oxide (NO) bioavailability and microvascular recruitment via eNOS, PKA, and PI3K/Akt pathways; for example, exendin-4 stimulates endothelial proliferation through eNOS- and PKA/Akt-dependent mechanisms [123]. In humans, GLP-1RA treatment improves skeletal-muscle microvascular perfusion in both healthy and insulin-resistant states—largely through NO-dependent mechanisms—thereby enhancing insulin delivery to muscle and facilitating glucose uptake [124,125].

Clinical data in T2DM and coronary artery disease show improved flow-mediated dilation with GLP-1RA therapy, suggesting partial restoration of endothelial responsiveness even in advanced vascular dysfunction [126]. Mechanistically, GLP-1RAs increase eNOS phosphorylation and NO production, attenuate oxidative stress, and improve vascular insulin sensitivity. Over longer durations, they may also support pro-angiogenic signaling (e.g., VEGF) and capillary remodeling, though definitive reversal of capillary rarefaction in human skeletal muscle remains to be established. Collectively, these actions help preserve perfusion, nutrient supply, and energy homeostasis—counteracting vascular limitations that contribute to sarcopenia.

4.5 Neuromuscular Junction Integrity and Motor Neuron Support

An often-underappreciated contributor to age-related muscle loss is the deterioration of the neuromuscular system. Aging and chronic disease lead to motor-neuron attrition and progressive degeneration of neuromuscular junctions (NMJs)—the synapses connecting motor nerves to muscle fibers [34,35,127]. As motor neurons lose function or undergo

apoptosis, affected fibers become denervated and atrophy rapidly. Surviving neurons may initially sprout and reinnervate orphaned fibers, but this compensatory remodeling is limited; over time, entire motor units are lost. Clinically, the result is reduced strength, impaired fine motor control, and increasing disability in older adults. Denervation also heightens local oxidative stress and inflammation, further accelerating myofiber apoptosis and compounding sarcopenia progression. Preserving NMJ integrity and motor-neuron viability is therefore essential to maintaining muscle mass and function with aging.

Direct evidence linking GLP-1RAs to NMJ preservation in humans is limited, but converging data from neurological models suggest GLP-1R activation can support neuromuscular connectivity [128,129]. GLP-1 and the analog exendin-4 enhance axonal regeneration, improve synaptic transmission, and protect neurons from excitotoxic injury via cAMP/PKA/CREB and PI3K/Akt signaling—core regulators of neuronal survival, plasticity, and neurotransmitter release [130]. In neurodegenerative models, GLP-1RAs also reduce neuroinflammation and strengthen synaptic connections, effects that could plausibly benefit motor neurons innervating skeletal muscle [129].

Moreo compelling evidence come from Li et al. (2012) who showed that exendin-4 improved motor performance and preserved choline acetyltransferase (ChAT) expression—a marker of motor-neuron viability—in a murine amyotrophic lateral sclerosis (ALS) model [131]. GLP-1R activation conferred resistance to oxidative and apoptotic stress in neuronal cells, implying dual protection of motor neurons and their synaptic interfaces with muscle fibers.

Together, these findings raise the possibility that GLP-1RAs may help maintain NMJ integrity by supporting motor-neuron health and synaptic stability. While sarcopenia-specific

and human NMJ data are still lacking, the neuroprotective and anti-inflammatory properties of GLP-1RAs provide a mechanistic rationale for exploring their role in preserving motor-unit connectivity during aging.

4.6 Modulation of Autophagy and Apoptosis

Autophagy and apoptosis are tightly regulated processes that maintain myocyte quality control. Basal autophagic flux is protective—clearing damaged proteins and organelles—whereas chronic suppression or excessive activation contributes to proteolysis and fiber loss in aging and disease. Although direct evidence in human skeletal muscle is limited, growing data from other tissues indicate that GLP-1RAs can favorably modulate these pathways.

In cardiomyocytes exposed to high glucose, exendin-4 attenuates apoptosis by alleviating endoplasmic reticulum (ER) stress and enhancing sarco/endoplasmic reticulum Ca^{2+}-ATPase 2a (SERCA2a) activity. These effects coincide with reduced CHOP and cleaved caspase-3, consistent with suppression of ER stress–mediated apoptotic signaling [132]. Likewise, liraglutide confers neuroprotection in diabetic rat models of ischemic injury by limiting oxidative and ER-stress pathways and preventing neuronal apoptosis [133].

Beyond apoptosis, GLP-1RAs can restore autophagic flux via AMPK–mTOR cross-talk. In cardiac and renal models, GLP-1RA treatment activates AMPK and constrains aberrant mTOR signaling, normalizing autophagy, promoting clearance of dysfunctional mitochondria, and reducing downstream proteolytic stress [112,134,135]. Given the conservation of these signaling nodes in skeletal muscle, similar modulation of AMPK–mTOR–autophagy could support proteostasis and limit activation of catabolic programs that otherwise drive sarcopenic atrophy.

While most evidence derives from non-muscle tissues and preclinical models, the same ER-stress, AMPK–mTOR, and mitochondrial-quality pathways operate in myofibers. Thus, by mitigating ER-stress–induced apoptosis and promoting balanced autophagy, GLP-1RAs may help preserve myocyte viability, reduce proteolytic burden, and maintain structural/functional integrity, particularly in the context of aging, metabolic dysfunction, or chronic inflammatory disease.

5. Experimental Evidence Linking GLP-1RAs to Muscle Mass

Studies spanning *in vitro* and animal model experiments have collectively highlighted the multifaceted actions of GLP-1RAs on skeletal muscle biology. Moreover, experimental research has demonstrated that GLP-1RAs may exert direct beneficial effects on muscle remodeling and function.

Many in-vitro reports use rodent myoblast/myotube lines (e.g., C2C12) or early human myotubes have demonstrated that GLP-1RAs exert cytoprotective, metabolic, and anabolic effects that may help counteract muscle wasting. In these cells, low-level GLP-1R signals can appear under culture/differentiation conditions that do not mirror mature human myofibers [61–63]. In intact human muscle, GLP-1R is more consistently localized to non-myocyte populations (endothelium, perivascular and immune cells), enabling paracrine effects on perfusion and inflammation that secondarily benefit myofibers [61–63,123–126,97–107]. Accordingly, we interpret preclinical signals as biological plausibility, while direct myocytic actions in adult humans remain unproven [61–63].

Under hyperglycemic/lipotoxic stress, liraglutide reduces cellular senescence and promotes myogenic differentiation in C2C12 myoblasts primarily via the modulation of the

mechanosensitive YAP/TAZ signaling pathway [135]. Also in C2C12, exendin-4 improves mitochondrial respiration, promotes oxidative fiber-type gene expression, and enhances glucose uptake via AMPK activation—effects that are abolished upon AMPK knockdown, underscoring the importance of the GLP-1R/AMPK signaling axis [136,137].; these benefits are further supported by the PKA-dependent induction of thermogenic genes (UCP1, PPARα, and β3-adrenergic receptor) [136]. In inflammatory settings, the GLP-1RA PF1801 limits FasL-induced necroptosis in myotubes by AMPK-mediated PGAM5 degradation, boosting antioxidant defenses and lowering ROS [112].Also *in vitro*, GLP-1RAs have shown to attenuate catabolic-atrophy. Thus, exendin-4 activates PI3K/Akt/mTOR and downregulates MuRF-1/Atrogin-1 [26,28,111], restores GLUT4 and protein synthesis under palmitate or dexamethasone [26,28], and enhances insulin-independent glucose uptake via AMPK in L6 and C2C12 cells [138,139]. GLP-1RAs have also been shown to improve autophagic flux through SESN2- and LC3B-mediated mechanisms in L6 cells, contributing to protein homeostasis and stress resilience [140].

Beyond direct effects on muscle cells, GLP-1RAs may confer additional benefits through vascular mechanisms that improve perfusion and metabolic support. Exendin-4 promotes smooth-muscle cells redifferentiation via AMPK/SIRT1/FOXO3a and vasodilatation through cAMP/PKA activation and RhoA/ROCK inhibition [141–143]. These actions may indirectly support skeletal muscle maintenance by enhancing oxygen and nutrient delivery.

However, some findings suggest potential drawbacks of prolonged GLP-1 exposure. A recent study by Huang et al. (2024) reported that sustained treatment with GLP-1 in C2C12 myoblasts led to impaired differentiation capacity, GLUT4 translocation, and diminished mitochondrial ATP production [144]. These results raise concerns about the long-term impact

of chronic GLP-1 signaling on muscle regeneration, particularly in aging populations with sarcopenia.

In vivo models further support and extend some of the findings derived from *in vitro* studies. In aged mice, exendin-4 activates the AMPK–SIRT1–PGC-1α axis, improves mitochondrial biogenesis, reduces oxidative stress, preserves fiber integrity, and enhances grip strehght/endurance [137]. In diet-induced sarcopenic obesity models, semaglutide not only reduces adiposity and systemic inflammation but also enhances relative skeletal muscle mass and fiber structure (including increased fiber area, density, sarcomere length, and mitochondrial content) with favorable shifts in amino acid, lipid, and organic acid pathways, suggesting improved anabolic signaling and metabolic efficiency [145]. Similarly, in a model of liver disease–related sarcopenia (diabetic KK-Ay mice fed a DDC diet), semaglutide prevents muscle atrophy and improves function while downregulating catabolic genes, inflammation and oxidative stress, thereby improving grip strength and function [28]. In *db/db* mice, liraglutide increases fiber cross-sectional area, improves grip strength, and suppresses *Atrogin-1* and *MuRF-1* expression independently of glycemia [146]. Also in *db/db* mice, dulaglutide protects against skeletal muscle injury by inhibiting inflammation and regulating the differentiation of myoblasts [147]. In a related model of spontaneously diabetic torii (SDT) fatty rats, liraglutide preserved mitochondrial function in skeletal muscle by maintaining citrate synthase activity and cytochrome c oxidase levels, emphasizing its beneficial role in sustaining oxidative metabolism [120].

GLP-1 overexpression via adeno-associated viral (AAV) vectors has been shown to improve muscle endurance, enhance type I fiber proportion, and increase glycogen storage and glucose uptake in mice, effects that were phenocopied by exendin-4 and associated with

increased AMPK activity and metabolic remodeling [137]. Exendin-4 also enhances muscle glucose uptake in type 2 diabetic rats and attenuates atrophy in dexamethasone and Duchenne models [148,26]. Additionally, dulaglutide has shown improvements in fiber size, mass, and strength in aged and disuse-induced muscle atrophy models [28,111]. In diabetic sarcopenia, dulaglutide further reduces necroptosis and promotes myoblast differentiation, while its anti-inflammatory effects appear mediated through the OPA-1–TLR9 signaling pathway in tibialis anterior and quadriceps muscles [111].

Furthermore, GLP-1RA administration in a hindlimb unloading model—a surrogate for disuse-related sarcopenia—attenuates muscle mass loss, preserves mitochondrial content, and reduces oxidative stress markers [149]. These effects are especially significant given the shared mechanisms between disuse atrophy and sarcopenia related to aging and chronic disease.

6. Limitations and Future Directions

The dramatic adoption of incretin-based therapies for obesity has generated an urgent need to reassess their broader physiological effects beyond weight reduction. Landmark clinical trials have demonstrated their robust efficacy in weight loss, with semaglutide and tirzepatide showing profound benefits in patients with obesity, even in the absence of T2DM. However, as the use of these agents expands, their impact on skeletal muscle, a key determinant of metabolic health and independence, remains a central concern.

Although most clinical trials of GLP-1RAs were not specifically designed to assess sarcopenia outcomes, post-hoc analyses and body composition substudies suggest a favorable impact on LM preservation. These findings, while exploratory, highlights a

potential for GLP-1RAs to enhance muscle quality—an emerging priority in sarcopenia assessment. However, LM is a composite that includes water, connective tissue, organs, and other non-contractile tissues. As a result, changes in LM do not necessarily equal changes in contractile muscle. Short-term shifts in hydration and glycogen (common during energy restriction, gastrointestinal side effects, diuresis, or sodium/carbohydrate changes) can artifactually lower LM without true myofiber loss. Conversely, LM may remain unchanged even as muscle quality improves with reductions in intramuscular fat, a change that standard DXA cannot capture. Moreover, because most trials were not designed for sarcopenia, they rarely pair LM with validated functional outcomes or diagnostic criteria for sarcopenia, such as those recommended by EWGSOP2 or the Sarcopenia Definition and Outcomes Consortium [1]. Also, the oldest and frailest adults are under-represented, and important confounders (weight-loss magnitude, protein intake, resistance training, and co-medications such as SGLT2 inhibitors) are inconsistently controlled, while fluid shifts may bias LM estimates.

Future research should prioritize large, dedicated trials that assess both quantity and quality of muscle. Endpoints should pair appendicular LM or MRI muscle volume with strength, power, and performance (e.g., gait speed/ Short Physical Performance Battery), plus MRI studies of intramuscular fat. Studies should use harmonized sarcopenia frameworks, prospectively capture falls and fractures, include weight-loss–matched comparators, and pre-specify mechanistic substudies (microvascular perfusion; muscle-biopsy signaling such as Akt/FoxO, atrogenes, autophagy; mitochondrial respiration; inflammatory/immunologic profiles). Given the central role of lifestyle, factorial or add-on designs testing GLP-1RA with progressive resistance training and adequate protein are warranted. Comparative work

across GLP-1RA classes/doses, dual/triple incretin agonists, and rational combinations (e.g., myostatin/activin-pathway modulators) should test whether fat-loss efficacy can be paired with preservation—or improvement—of muscle mass, quality, and function, including in multimorbid and post-bariatric populations. In this sense, activin type II receptor blockade with bimagrumab has reduced fat mass with concurrent lean-mass gain in adults with T2DM and obesity [150], but showed no functional benefit in inclusion body myositis [151] and mixed results in sarcopenia [152]. These data motivate ongoing combination trials with semaglutide or tirzepatide (NCT05616013 and NCT06901349, respectively).

7. Conclusions

GLP-1RAs are transforming obesity and diabetes care, but their role in sarcopenia prevention or management remains uncertain. Preliminary findings derived from ancillary substudies not designed for sarcopenia suggest preferential adiposity reduction, potential improvements in muscle quality, and no consistent detriment in physical performance. The overall pattern is compatible with indirect support of muscle via improved metabolic and inflammatory profiles, yet direct myocytic effects in humans remain unclear. Accordingly, in individuals at risk of sarcopenia, GLP-1RAs should be used with caution and paired with progressive resistance exercise, adequate protein intake, and routine monitoring of strength and function. Robust, sarcopenia-focused randomized trials with standardized quantity-and-quality endpoints are still required to draw firm conclusions. Closing this gap is essential given the substantial contribution to disability resulting from sarcopenia, the health-care burden, and the reduction in quality of life.

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Authors Contributions

J.D.C., A.G.L., and V.L.A. contributed in the conception and design. A.G.L., V.L.A., C.E.M.A., C.H.C., C.M.F. and J.F.N.G. contributed to collection, analysis and interpretation of the data; J.D.C., A.G.L., V.L.A. and C.E.M.A. contributed to the drafting of the paper; J.D.C. supervised the manuscript development and was responsible for final review and editing of the manuscript. All authors approved the final version of the manuscript.

Disclosure Statement

No conflicts of interest.

Ethical approval

This study was conducted according to the Declaration of Helsinki. As this is a review of previously published literature and does not involve human participants, identifiable personal data, or animal subjects, ethical approval was not required in accordance with institutional and international guidelines.

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Figure legends:

Figure 1. Contributing mechanisms of sarcopenia and potential therapeutic effects of GLP-1RAs therapy. Abbreviations: AGE, advanced glycation end-products; AKT, protein kinase B; AMPK, AMP-activated protein kinase, ChAT, choline acetyltransferase; CHOP, C/EBP homologous protein; eNOS, endothelial nitric oxide synthase; ER, endoplasmic reticulum; GLUT4, glucose transporter type 4; GPx, glutathione peroxidase; IR, insulin resistance; mtDNA, mitochondrial DNA; mTOR, mechanistic target of rapamycin; NADPH, nicotinamide adenine dinucleotide phosphate; NF-KB, nuclear factor kappa-light-chain enhancer of activation B cells; NLRP3, NOD-like receptor family pyrin domain containing 3; NMJ, neuromuscular junction; NO, nitric oxide; OXPHOS, oxidative phosphorylation; PGC1-α, peroxisome proliferator-activated receptor gamma coactivator 1 alpha; PI3K, phosphoinositide 3 kinase; RAGE, receptor for advanced glycation end products; ROS, reactive oxygen species; SERCA2a, sarcoplasmic-endoplasmic reticulum calcium ATPase 2A; SIRT1,sirtulina 1; SOD, superoxide dismutase; VEGF, vascular endothelial growth factor.

Figure 2. Major signaling pathways activated by GLP-1RAs and potentially related with muscle homeostasis. Abbreviations: AKT, protein kinase B; AMPK, AMP-activated protein kinase; ATP, adenosine triphosphate; cAMP, cyclic adenosine monophosphate; CREB, cAMP response element-binding protein; eNOS, endothelial nitric oxide synthase; Epac, exchange protein directly activated by cAMP; FoxO, forkhead box O; GLP-1RA, glucagon like peptide 1 receptor agonist; MAPK, mitogen activated protein kinase; mTORC, mechanistic target of rapamycin complex; NF-KB, nuclear factor kappa-light-chain enhancer of activation B cells; PI3K, phosphoinositide 3 kinase; SIRT1, sirtuin 1.

Table 1 Summary of Key GLP-1RA Trials with Secondary Outcomes on Muscle Health

Study	GLP-1RA	Population	Main Outcomes	Impact on Body Composition	Reference
STEP 1	Semaglutide 2.4 mg QW	Obese/ overweight w/o T2DM	Weight loss (14.9%) and metabolic improvements	Preferential fat loss. Relative preservation of LM	24, 52
SUSTAIN 8	Semaglutide 1.0 mg QW *vs* Canagliflozin 300 mg QD	T2DM	Greater weight loss with semaglutide (5.3 kg vs. 4.2 kg)	Modest LM loss; increased LM% (1.2%); favorable fat/lean loss ratio	25, 44
SURPASS-3 & 5	Tirzepatide 5.0–15 mg QW	Obese/ overweight w/ T2DM	Weight loss; improved steatosis and metabolic parameters	Modest relative LM loss; reductions in muscle fat infiltration (MRI study)	45 - 48
AWARD 11	Dulaglutide 1.5-4.5 mg QW	T2DM	Improved glycemic control	FM reduction, LM preservation	55

LEADER / SUSTAIN 6	Liraglutide up to 1.8 mg QD / Semaglutide 0.5 / 1.0 mg QW	T2DM, high CV risk	Reduced risk of MACE and mortality. Improved inflammation/metabolism	Body weight reductions. Indirect muscle benefit via systemic effects	53, 54
SUSTAIN FORTE	Semaglutide 1.0 / 2.0 mg QW	T2DM	Dose-dependent weight and glycemic control	Indirect muscle benefit via improvement of metabolic balance	51
AMPLITUDE-O	Efpeglenatide 4.0 / 6.0 mg QW	T2DM with CVD and CKD	Reduced cardiovascular events and kidney outcomes	Weight loss with potential LM benefit via anti-inflammatory & vascular effects	56

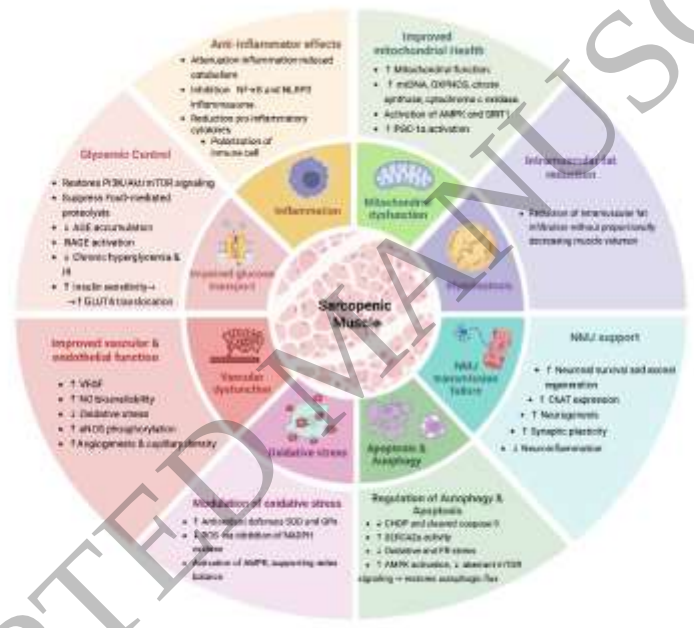

Figure 1
381x229 mm (x DPI)

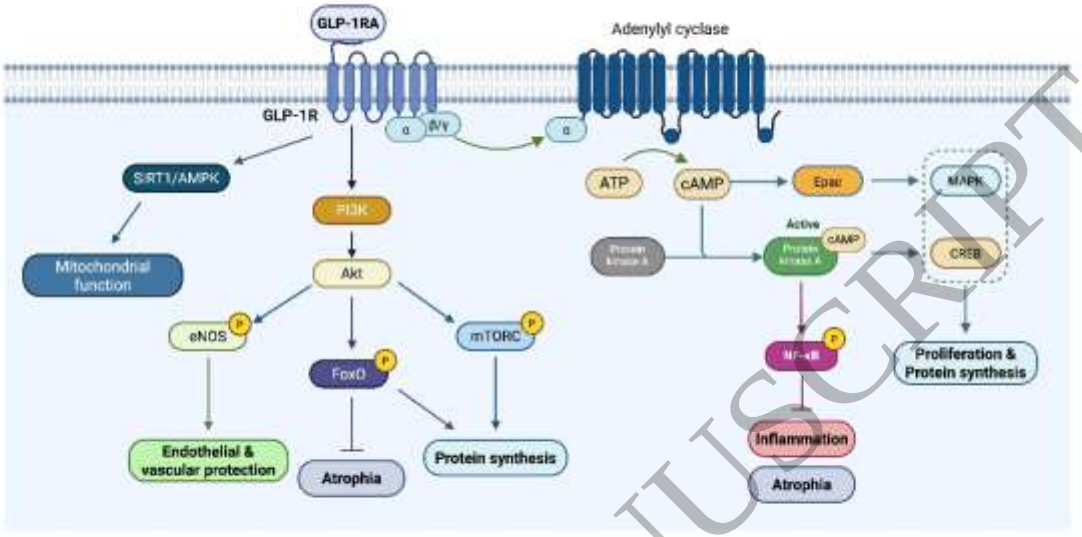

Figure 2
254x178 mm (x DPI)