REVIEW ARTICLE

Sarcopenia as a Risk of Modern Obesity Treatments: A Review of Molecular Mechanisms and Prevention Strategies

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Abstract

While lifestyle interventions and metabolic surgery for obesity have limitations, incretin-based therapies have emerged as highly effective treatments. However, their success is shadowed by a significant risk, which is the loss of lean skeletal muscle, which can induce sarcopenia or sarcopenic obesity. Given the vital role of skeletal muscle in overall health, it is crucial to accurately assess this condition using standard clinical measures. Exercise stands as the most potent countermeasure, acting as medicine to preserve muscle and improve metabolic health. Its benefits are driven by a complex interplay of mechanisms. Different exercise types trigger the release of myokines and exerkines, while a regulated inflammatory response is essential for muscle adaptation and regeneration. This regenerative process, involving muscle stem cells, is further governed by epigenetic factors and critical molecular pathways like Akt and insulin that maintain muscle mass. To optimize these effects, adequate protein intake and targeted nutritional strategies are essential, supporting muscle protein synthesis and recovery. Supplementation, particularly with leucine-rich amino acids or vitamin D, may further enhance anabolic responses, especially in older adults. Clinical monitoring of muscle mass, strength, and nutritional biomarkers should be integrated into obesity care to detect early signs of sarcopenia and guide individualized interventions. Therefore, it is imperative that obesity therapy evolves to prevent muscle loss. This review highlights the risk of therapy-induced sarcopenia from modern obesity treatments, emphasizing the need for integrated prevention strategies, centered on exercise, and reinforced by nutrition, supplementation, and clinical monitoring to ensure healthy, sustainable weight loss.
KEYWORDS: sarcopenia, skeletal muscle, inflammation, obesity, incretin

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Introduction

The global prevalence of obesity and type 2 diabetes mellitus (T2DM) continues to rise, contributing substantially to morbidity and mortality through cardiovascular disease (CVD), renal dysfunction, and other complications. As of 2024, approximately 1 in 7 individuals worldwide are living with obesity (1), and nearly 11% of adults are affected by diabetes (2). T2DM is a multifactorial condition driven by impaired insulin secretion and increased tissue resistance to insulin.(3,4)

Comprehensive lifestyle interventions remain the cornerstone of initial treatment, offering meaningful weight loss and glycemic control for up to two years. However, their long-term effectiveness wanes, with sustained benefits seen in only a minority of patients.(5) Metabolic surgery provides the most durable outcomes for both obesity and

T2DM, yet its scalability is limited by the availability of specialized surgeons and facilities. Moreover, it carries risks such as nutritional deficiencies, post-bariatric hypoglycemia, and eventual relapse.(6) Pharmacological therapies, including glucagon-like peptide-1 (GLP-1) receptor agonists and dual incretin agonists, have emerged as potent alternatives, though they too present challenges. (7) Across all modalities, a growing concern is therapy-induced sarcopenia, highlighting the need for integrated strategies that preserve lean muscle mass. Incretins, like GLP-1 and gastric inhibitory polypeptide (GIP), are gut-derived hormones that regulate appetite and metabolism by stimulating pancreatic hormone release. Incretin-based therapies may bridge the gap between lifestyle interventions and surgery, or serve as standalone alternatives. Innovations such as 'GLP-1 plus' drugs and oral formulations aim to enhance efficacy and accessibility.(8)

Skeletal muscle, comprising ~40% of body weight, plays a central role in physical function and metabolic health. Rapid weight loss, whether through surgery or pharmacotherapy, often results in muscle depletion, increasing the risk of sarcopenia.(9) Sarcopenic obesity, characterized by inflammatory and lipotoxic interactions between fat and muscle, further exacerbates functional decline.(10)

Multi-agonist weight-loss drugs may intensify this risk, particularly in individuals predisposed to sarcopenia due to aging, chronic illness, inactivity, or poor nutrition. Understanding how these therapies affect muscle mass and strength is critical. While protein supplementation and exercise are logical countermeasures, consensus on optimal intake and training protocols remains elusive. Moreover, many patients may already have sarcopenia or physical limitations that restrict vigorous activity.(10)

This review explores the molecular underpinnings of therapy-induced sarcopenia and reinforces exercise as the primary intervention. Our goal is to raise clinical awareness of this emerging challenge and offer strategies to prevent muscle loss in the context of modern obesity treatments.

Modern Obesity Treatments and Lean Mass Loss

Comprehensive lifestyle interventions, centered on diet, exercise, and behavioral change, are rightly the first line of defense against obesity. In the initial one to two years, structured programs yield significant success, with patients often achieving meaningful weight loss and improved glycemic control. However, this initial progress is notoriously difficult to maintain. The body's powerful biological responses, including a slowing metabolism and hormonal shifts that increase hunger, create a constant physiological drive to regain lost weight. When combined with the psychological fatigue of sustained vigilance and an environment filled with readily available, high-calorie foods, long-term adherence becomes an immense challenge, and only a small minority of individuals can sustain the benefits for years on end.(5)

In stark contrast, metabolic surgery offers the most effective and durable long-term solution for both conditions. Its success lies in fundamentally altering the body's physiology, leading to outcomes that lifestyle changes alone cannot replicate. Despite its proven effectiveness, metabolic surgery remains vastly underutilized, a reality that highlights a critical gap in care.(6) Recent article highlighted that bariatric surgery poses a significant long-term risk of metabolic and bariatric surgery is the development of post-metabolic and bariatric surgery hypoglycemia (MBSH), or low blood sugar, malabsorption which lead to malnutrition, and some cases of gastrointestinal complications.(9)

In the last twenty years, treatments utilizing incretin hormones, particularly GLP-1 receptor agonists, have emerged as the preferred treatment for obesity and T2DM, with clinical data indicating their advantages for CVD. Recent advancements in incretin-based medications include 'GLP-1 plus' drugs, which combine the benefits of GLP-1 receptor agonists with additional hormones like glucose-dependent insulinotropic peptide, glucagon, and amylin to achieve specific therapeutic goals. Second-generation non-peptidic oral GLP-1 receptor agonists are anticipated to enhance the advantages of GLP-1 treatment.(8) Many studies currently focus on the physiological effects resulting from the secretion of GLP-1, GIP, and peptide YY (PYY) from the gastrointestinal tract, as well as glucagon and amylin.

GIP, a 42-amino acid peptide, and GLP-1, a peptide of 30 or 31 amino acids, are released by specialized enteroendocrine cells in the proximal intestine (K cells) and distal intestine (L cells), respectively, in response to food. These hormones, through their specific receptors on pancreatic islet β-cells, enhance the incretin effect, boosting insulin secretion in response to orally ingested glucose compared to intravenous glucose. Among healthy individuals, GIP appears to play a more significant role in the incretin effect than GLP-1.

The incretin impact is diminished in individuals with T2DM, characterized by a reduction in pancreatic β-cell

response to GIP, and incretin secretion is compromised in obesity. The pancreatic β-cell's unresponsiveness to GIP remains unaltered after high-dose GIP infusion (11), but supraphysiological GLP-1 levels can enhance glucose-stimulated insulin (12). In individuals with T2DM, the co-infusion of therapeutic quantities of GLP1 and GIP results in glycaemic benefits solely attributed to GLP-1, that leads to an enhancement of insulin secretion and reduction of glucagon secretion.(13)

Glucagon, a 29-amino acid peptide from pancreatic α-cells, opposes insulin by converting liver glycogen to glucose, raising blood glucose levels. Its effect on hepatic glucose production is brief. The glucagon receptor (GCGR) is mainly in the liver but also on pancreatic β-cells, enhancing insulin production and hepatic insulin sensitivity. In healthy overweight individuals, co-infusion of glucagon and GLP-1 boosts insulin secretion.(14)

Exogenous GLP-1 decreases food consumption, enhances satiety, and alleviates hunger between meals. (15,16) GLP-1 receptor (GLP-1R)-expressing neurons in the hindbrain and hypothalamus are key for reducing food intake. Removing these neurons in mice negates the appetite-suppressing effects of GLP-1R agonists (GLP-1RAs). Functional MRI studies show that GLP-1 and its agonists reduce activity in brain areas that process food rewards, aligning with decreased food consumption.(17) In contrast, endogenous intestinal GLP-1 likely has a limited effect on food consumption. Exendin NH_2, a GLP-1RA, lessens the reduction in food intake and appetite usually caused by endogenous GLP-1 after oral glucose. Although intestinal GLP-1 interacts with local GLP-1R-expressing sensory nerves to send anorexigenic signals to the hypothalamus, the role of these circuits in long-term weight control is still unclear.(18) Overall, postprandial satiety is likely regulated by the combined effects of endogenous GLP-1 and other satiety hormones, including PYY3–36, oxyntomodulin, and cholecystokinin.

Short-term infusion exogenous GIP does not seem to reduce food intake or boost the appetite-suppressing effects of GLP-1 in healthy individuals, those with overweight or obesity, or individuals with T2DM. Animal studies indicate that long-acting GIP receptor agonists can decrease body weight by diminishing food consumption, and that the stimulation of GIP-expressing neurons in the hypothalamus can also lead to reduced food intake.(19) In a phase I study, long-acting GIP receptor agonists (GIPRAs) resulted in a moderate reduction in body weight, decreasing by 1.1–2.2 kg in healthy volunteers and by 1.9–3.1 kg in individuals with T2DM over a period of 57 days with repeated doses administered.(20) The problem is then further complicated by the observation that GIPRAs also diminish food consumption and body weight in animal models, and also showing potential when taken in conjunction with GLP-1RAs.(21,22)

At physiological levels, glucagon suppresses appetite, but during fasting, its effects may be limited by appetite-stimulating neuropeptides like ghrelin.(23) High glucagon levels in healthy and overweight individuals can significantly increase satiety and reduce food intake, likely through the liver–vagus–hypothalamus axis, distinct from GLP-1's mechanism. Low doses of glucagon and GLP-1 together greatly reduce food consumption.(14) The summary of glucagon hormone receptor agonist metabolic effect were described in Figure 1.(8)

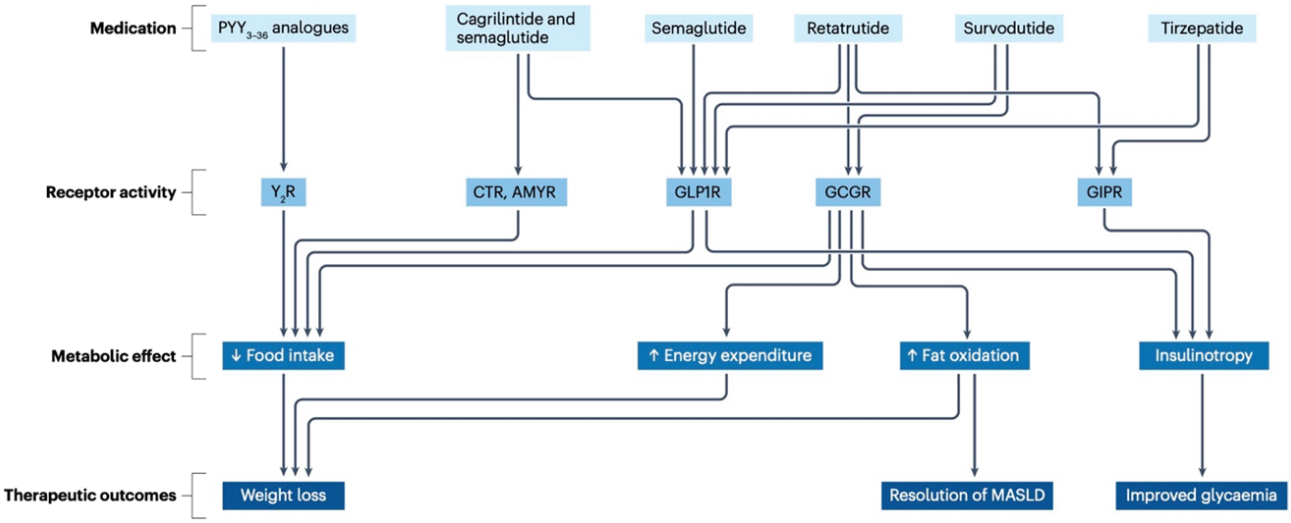

Figure 1. Therapies based on incretin hormones.(8) (Adapted with permission from Springer Nature Limited, 2024).

Tissue Homeostasis and Inflammation in Obesity

Homeostasis and inflammation are often seen as contrasting conditions, linked to health and disease, respectively. Historically, Rudolf Virchow viewed inflammation as pathogenic, a perspective still prevalent today. In contrast, Elie Metchnikoff argued that vascular changes in inflammation were purposeful, aiding phagocyte delivery to infection sites. Metchnikoff also proposed a continuum from homeostasis to physiological inflammation, with pathological inflammation and immunity at the extreme end.(24) Metchnikoff described homeostasis as a balance between harmony and disharmony.(25)

Homeostasis involves actively maintaining specific quantitative properties of a system, known as regulated variables, within a desired range. The homeostatic circuit is designed to sustain them at a steady level, near a preset value referred to as the set point. In the context of homeostasis, sensors and effectors play crucial roles. The values of controlled variables must be monitored by specialized sensors and adjusted by effectors to ensure maintenance. The sensors are specialized cells or receptors that detect changes in the internal environment, while the effectors are the mechanisms or organs that respond to the signals from the sensors to restore balance. Sensors must interact with effectors via specific signals that indicate alterations in the regulated variable. Regulated variables, sensors, signals, and effectors all constitute a homeostatic circuit. In systemic homeostasis, the elements of homeostatic circuits are often clearly delineated. For example, to regulate blood glucose (regulated variable), pancreatic alpha and beta cells function as sensors; glucagon and insulin act as signals indicating glucose concentration; and the liver, skeletal muscle, and adipose tissue serve as effectors that rectify any deviations in blood glucose levels from a set point value.(26)

Inflammation is typically characterized as a reaction to illness or damage. This perspective is accurate; yet, it fails to encapsulate the fundamental nature of the inflammatory response or elucidate its significance in many physiological and pathological contexts. It is now widely recognized that inflammation can arise in the absence of infection or apparent tissue injury, for example in obesity, when there is a disturbance of cellular and tissue homeostasis.(27-29) Cells experiencing homeostasis disruption may undergo senescence and secrete pro-inflammatory factors through the senescence-associated secretory phenotype (SASP).(30) When the cell experiences excessive stress, such as from the endoplasmic reticulum (ER), mitochondria, or osmotic imbalances, and the usual homeostatic mechanisms are overwhelmed, the NLRP3 inflammasome is activated.(31) This results in the expression of interleukin (IL)-1 family cytokines and ligand-independent activation of tumor necrosis factor (TNF)-related apoptosis-inducing ligand (TRAIL) receptors.(32) The excessive buildup of lipids in fat cells and liver cells in obesity triggers ER stress and the production of inflammatory signals. This type of inflammation, known as meta-flammation, arises from a disruption in metabolic homeostasis.(33)

Inflammatory response aims to restore homeostasis, but it temporarily disrupts it in the process. In case of infection, this disruption occurs partly due to unavoidable collateral tissue damage from antimicrobial immune responses and partly because inflammation intentionally modifies various aspects of tissue homeostasis. The recruitment of monocytes and granulocytes changes the cell quantities and composition within tissue compartments, while the inflammatory exudate alters the interstitial fluid volume and protein levels and affect systemic homeostasis including body metabolism and endocrine regulation.(34,35)

While intermittent inflammation is essential for survival during physical trauma and infection, recent studies indicate that specific social, environmental, lifestyle factors and obesity can induce systemic chronic inflammation, which may subsequently result in various diseases that are among the primary causes of disability and mortality globally, including metabolic syndrome and its components, CVD, cancer, autoimmune, neurodegenerative disorders, depression, sarcopenia and osteoporosis (Figure 2).

This suggests that inflammation, including low-grade chronic inflammation, plays a more critical role in physiology than previously understood, with many important functions yet to be discovered. These functions include monitoring, protecting, and maintaining the homeostatic, functional, and structural integrity of tissues and organs. Thorough investigations into various aspects of inflammatory biology are expected to deepen our understanding of the biology and pathophysiology of diseases.(36)

Molecular Mechanisms Linking Obesity Therapy to Sarcopenia

Regulation of Muscle Growth and Regeneration by The Immune System

Over the past forty years, exercise immunology has developed into a unique field, recognizing that the immune

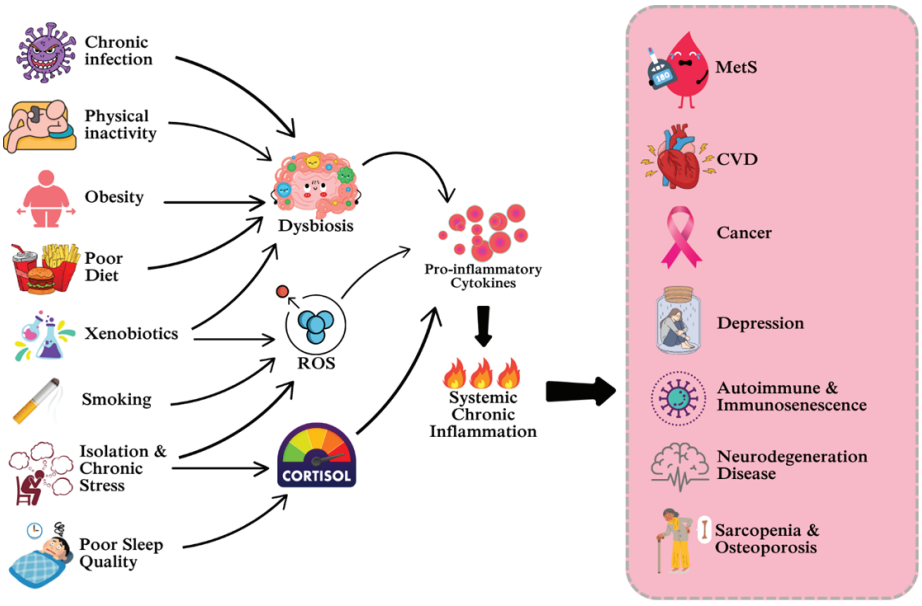

Figure 2. Causes and consequences of low-grade systemic chronic inflammation to chronic diseases.

system significantly impacts the effects of exercise. Additionally, stress responses controlled by the nervous and endocrine systems play a vital role in modulating exercise-induced changes in immunity. A traditional model in exercise immunology posits that immunodepression occurred on post-intense exercise period, referred to as a 'open window', where certain immunological variables (*e.g.*, lymphocyte and natural killer (NK) cell counts, and antibody production) temporarily decline below pre-exercise values. This immunodepression allows microbial pathogens, particularly viruses, to infiltrate the host or reactivate from a dormant state, resulting in infection and disease. Repetitive exercise while the immune system remains compromised may exacerbate immunodepression and extend the susceptibility to infection.(37) Somehow, recent research has provided a more nuanced understanding of how exercise impacts the immune system.

Exercise is a complex stressor. It has been recognized for its significant disease-preventing and health-enhancing benefits. Studies have shown that exercise mobilizes immune cells, such as T cells, to counteract inflammation and enhance muscle endurance. The positive outcomes of an exercise routine will depend on the various exercise stimuli trigger stress responses that are appropriate in type, intensity, and duration. A correlation existed between exercise-induced stress reactions and physical performance. An acute exercise performed by an untrained organism will induce measurable system features that diverge from their homeostatic set points in proportion to the intensity of the activity. These system attributes are termed as regulated substances. The system in this instance may operate at the organism level, including numerous tissues, or at the tissue level, incorporating many cell types within a single tissue. (38,39)

Inflammation is part of the body's stress response to exercise.(40) It is not only a byproduct of exertion; instead, inflammation serves as a crucial regulator of exercise adaptations, especially in skeletal muscle. There is a complex relationship between skeletal muscle and the immune system that governs muscle regeneration. Myeloid cells respond to muscle damage by aiding repair and growth. Acute muscle disruptions trigger interactions between muscle and inflammatory cells, starting with a Th1 response marked by neutrophils and cluster of differentiation (CD)68^+ M1 macrophages. M1 macrophages enhance the Th1 response by releasing proinflammatory cytokines and causing tissue damage via nitric oxide. They support the proliferative phase of myogenesis through TNF-α and IL-6. Studies have noted a delayed transition to early myogenesis differentiation. $CD163^+/CD206^+$ M2 macrophages then reduce M1 populations by secreting anti-inflammatory cytokines like IL-10, crucial for muscle development and regeneration. Their absence hinders muscle growth and differentiation.(41)

Muscle regeneration involves three main phases, regulated by muscle-specific transcription factors from the basic helix-loop-helix (bHLH) family, including MyoD, myogenin, Myf4, and Myf5. These factors form heterodimers with enhancer proteins to bind muscle-specific genes and initiate transcription. The first phase, the proliferative stage, activates dormant satellite cells, leading to proliferation and production of MyoD and Myf5.(42,43)

These proteins remain inactive until satellite cells exit the cell cycle and enter early differentiation, where myogenin and Myf4 are expressed, aided by myocyte enhancer binding factor-2 (MEF2) family transcription factors.(44) MyoD and Myf5 then promote muscle-specific gene expression necessary for muscle cell fusion and progression to terminal differentiation. During terminal differentiation, muscle-specific genes are highly expressed as multinucleated muscle cells mature into fibers. This process mirrors embryonic muscle development, showing similar gene expression patterns during the differentiation of embryonic myoblasts and satellite cells in muscle regeneration.(45)

Skeletal muscle injury are common, mostly due to the substantial amount of total body mass they represent, their superficial location which makes them susceptible to trauma, and their mechanical functions that subject them to harmful stresses.(46) Chronic muscle injuries involve different macrophage invasion mechanisms and profiles compared to acute injuries. In Mdx muscular dystrophy, M1 macrophage infiltration is accompanied by M2a macrophages, which reduce M1 cytotoxicity. M2c macrophages infiltrate dystrophic muscle, aiding the regeneration phase. These findings suggest that changes in macrophage phenotype are crucial for muscle regeneration after acute or chronic injury.(45)

Leukocytes, or white blood cells, are essential for maintaining skeletal muscle health by regulating inflammation and repair processes. After muscle injury, leukocytes like neutrophils and macrophages clear debris and dead cells, setting the stage for repair. M1 macrophages promote inflammation to fight infections, while M2 macrophages reduce inflammation and support tissue repair and regeneration. Additionally, leukocytes release cytokines and growth factors that stimulate satellite cells (muscle stem cells or MuSC) to proliferate and differentiate, aiding in muscle growth and regeneration.(47) Like satellite cells, resident macrophages exist in a quiescent condition inside healthy muscle; nonetheless, heightened muscular activity or injury triggers their rapid activation, essential for proper muscle regeneration.(45)

The regulatory T cells (Tregs) help control the inflammatory response following muscle injury. They secrete anti-inflammatory cytokines, such as IL-10, which reduce inflammation and promote a conducive environment for muscle repair. Tregs release amphiregulin, an epidermal growth factor receptor (EGFR) ligand, which directly acts on muscle satellite cells. This interaction enhances the activation, proliferation, and differentiation of satellite cells, crucial for muscle regeneration. By regulating the balance between pro-inflammatory and anti-inflammatory responses, Tregs ensure that the muscle repair process proceeds efficiently without excessive fibrosis (scar tissue formation).(48)

The regeneration of muscle depends mostly on the reactivation of gene expression programs essential for embryonic muscle development. Muscle regeneration begins with the activation of myogenic precursor cells (MPCs), also known as satellite cells, which are situated on the surface of muscle fibers. Following muscle injury, satellite cells leave their quiescent state and begin to proliferate. Some of the resulting daughter cells continue to develop, while others return to quiescence to replenish the satellite cell reserve. Postmitotic muscle precursor cells, derived from activated satellite cells, form multinucleated myotubes and enter a regenerative phase characterized by terminal differentiation and growth. Throughout this process, each stage involves changes in the expression of myogenic transcription factors regulated by master genes. Quiescent satellite cells contain the paired-box transcription factor (Pax)7 but lack the bHLH transcription factor MyoD ($Pax7^{+}MyoD^{-}$). Activated satellite cells are $Pax7^{+}MyoD^{+}$, and daughter MPCs committed to development express the bHLH protein myogenin. Muscle regeneration is divided into an initial phase of MPC activation and proliferation, followed by a phase of terminal differentiation and growth, based on the sequence of developmental events and changes in transcription factor expression (Figure 3).(45)

Although still in its early stages, the field of muscle immunobiology is poised to reveal new regulatory mechanisms in the coming years that could enhance healing from muscle damage or disease. The increasing collaboration among developmental biologists, immunologists, physiologists, systems biologists, clinicians, and material scientists focused on muscle regeneration will help translate these discoveries into clinically beneficial technologies.

The Role of Skeletal Muscle Akt in The Regulation of Muscle Mass and Glucose Homeostasis

Skeletal muscle serves as the principal locus for insulin-mediated glucose uptake in humans. The risk of muscle loss is heightened in individuals with obesity and those undergoing diabetes therapy. Obesity is associated with poor muscle quality and increased risk of sarcopenia, which exacerbates muscle loss. Diabetes therapy, particularly with GLP-1 receptor agonists, can lead to muscle loss during rapid weight reduction. This muscle loss can further impair glucose metabolism and insulin sensitivity, creating a vicious cycle that worsens both obesity and diabetes outcomes.(49)

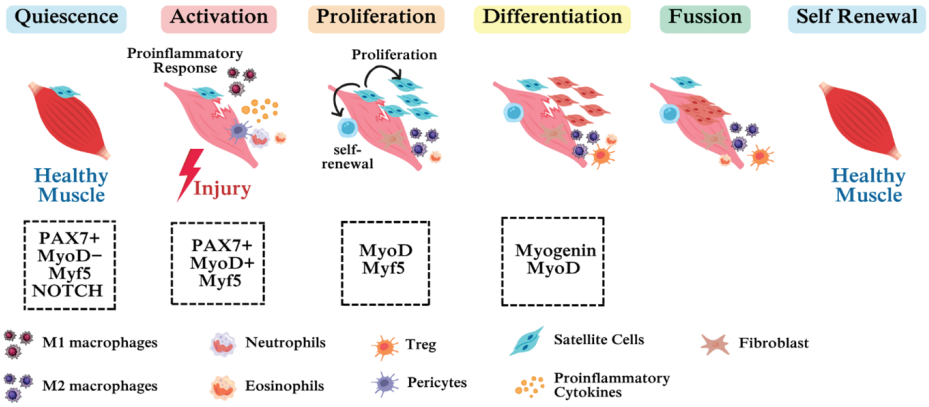

Figure 3. Muscle regeneration phases. Muscle regeneration is divided into some phases including quiescence, MPC activation, proliferation, differentiation, fusion before the self renewal.

In recent decades, the serine/threonine kinase Akt (protein kinase B) has been identified as a key regulator of insulin activity.(50) Insulin binds to its receptor, activating insulin receptor substrate (IRS) proteins, which then attract phosphoinositide 3-kinases (PI3K). PI3K phosphorylates PIP2 to PIP3, leading to Akt activation.(51) There are three Akt isoforms in mammals: Akt1 (expressed in all tissues), Akt2 (in metabolic tissues like muscle, adipose tissue, and liver), and Akt3 (mainly in the brain and testis). Simultaneous deletion of Akt isoforms causes early mortality, indicating compensation among them.(52)

Several investigations have documented impairments in insulin signaling through Akt in skeletal muscle during the advancement of metabolic illness, correlating these impairments with an inability of insulin to promote glucose uptake and glycogen synthesis.(49) Contrary to this prevalent notion, in another study, it was reported that impaired Akt phosphorylation in IR human muscle associated with IR and may contribute to multiple features of the metabolic syndrome.(53)

The significant activation of all recognized Akt targets, despite the substantial decrease in pAkt protein in these animals, clearly demonstrates the ability of residual Akt1 to adjust under these circumstances. This finding is consistent with data from L6 myotubes, showing that insulin reaches maximum glucose transporter (GLUT)4 translocation at doses resulting in about 10% Akt phosphorylation. This supports the notion that minimal Akt phosphorylation is sufficient for the maximal activation of its substrates.(54,55) M-AktDKO animals show reduced body and muscle mass similar to MIGIRKO mice, which lack insulin receptor (IR) and insulin like growth factor 1 receptor (IGF-1R) in skeletal muscle. They also exhibit modest glucose intolerance and decreased whole-body glucose turnover, despite normal insulin-stimulated glucose uptake and glucose transporter expression in skeletal muscle.(56)

Adenosine monophosphate-activated protein kinase (AMPK) is a heterotrimeric serine/threonine kinase that gets activated when cellular energy levels drop and during physical activity. Increased AMPK activity is believed to regulate glucose uptake during exercise independently of insulin.(57) M-AktDKO animals show reduced body and muscle mass similar to MIGIRKO mice, which lack IR and IGF-1R in skeletal muscle. They also exhibit modest glucose intolerance and decreased whole-body glucose turnover, despite normal insulin-stimulated glucose uptake and glucose transporter expression in skeletal muscle. (58-60) The current work together demonstrates that Akt signaling is essential for the anabolic effects of insulin on muscle development *in vivo*. Therefore, understanding the role of Akt in insulin activity and muscle metabolism is crucial for developing strategies to mitigate muscle loss in these populations.

Perspective on Skeletal Muscle Stem Cells

The preservation of muscular health is a crucial factor influencing lifelong quality of life. A distinctive characteristic of healthy adult muscle is its capacity to completely restore its structure and contractile capabilities after routine 'wear-and-tear' and severe injury. This capability stems from the presence of MuSCs, commonly referred to as 'satellite cells,' which are uniquely positioned at the periphery of myofibers within specialized niche microenvironments beneath the basal lamina and adjacent to the plasma membrane of myofibers.(61,62) MuSCs, or satellite cells, typically remain quiescent but can re-enter the cell cycle after damage to rebuild muscle tissue and replenish the stem cell reservoir. Key transcription factors like Pax3, Pax7, and myogenic regulatory factors (MRFs) such as Myf5, MyoD, Myogenin, and MRF4 regulate their quiescent state, activation, and progression to the myogenic lineage. Pax7 is a common marker for MuSCs, with some

cells also expressing Pax3. MRFs guide MuSCs towards myogenic determination, differentiation, and fusion into multinucleated myofibers.(63)

Renewing the MuSC cellular compartment requires a balanced regulation of quiescence and activation, involving significant transcriptional changes and metabolic reprogramming. Recent studies show that MuSCs are a heterogeneous population with varying regenerative capacities. Their behavior is dynamically influenced by the microenvironment and tissue-resident cells, which provide molecular signals to regulate MuSC fate.

Metabolic flexibility is the ability to efficiently adjust metabolism based on substrate availability and needs. In stem cells, this flexibility is evidenced by the gradual transition from glycolysis to oxidative phosphorylation during differentiation. Substrates like glucose, fatty acids, and amino acids, once seen as passive energy sources, can trigger genomic reprogramming through secondary metabolite synthesis. Similar metabolic patterns in MuSCs suggest new possibilities for regulating their states by targeting metabolic pathways.(64) Figure 4 illustrates these metabolic states during myogenesis: In the Quiescence Phase, glucose uptake leading to pyruvate production, which enters the mitochondria for ATP production via the Krebs cycle, with fatty acids also utilized in mitochondria, highlighting anabolism and low levels of reactive oxygen speciec (ROS). In the Proliferation/Self-renewal Phase, glucose uptake leading to higher glycolysis rates, producing lactate and ATP, with genetic reprogramming occurring in this phase, and pyruvate being converted to lactate or entering mitochondria for further energy production. In the Differentiation phase, increased oxidative stress indicated by higher ROS levels. Cellular metabolism shifts during different functional states, highlighting key metabolic pathways and their relevance to cellular functions like energy production and biosynthesis.

During homeostasis, satellite cells infrequently multiply via asymmetric division to replenish injured myofibers and maintain the stem cell reservoir. Following tissue injury, they are vigorously activated, undergoing symmetric divisions to produce new stem cells and proliferating myoblasts, which differentiate into myocytes to reconstruct muscle fibers. Recent findings show significant heterogeneity in satellite cell populations, with their fate decisions influenced by internal and external factors. Extrinsic cues mainly come from interactions with stromal cells within their niche, creating a dynamic microenvironment.(65)

Stem cell functionality in undifferentiated myogenic cells is governed by the transcription factors Pax3 and Pax7. Pax3, produced in the presomitic mesoderm during development.(66) Pax7 is essential for postnatal muscle development and the maintenance of the satellite cell population.(38) The ablation of both Pax3 and Pax7 enabled satellite cells to assume different cell fates, therefore affirming their essential function in preserving myogenic

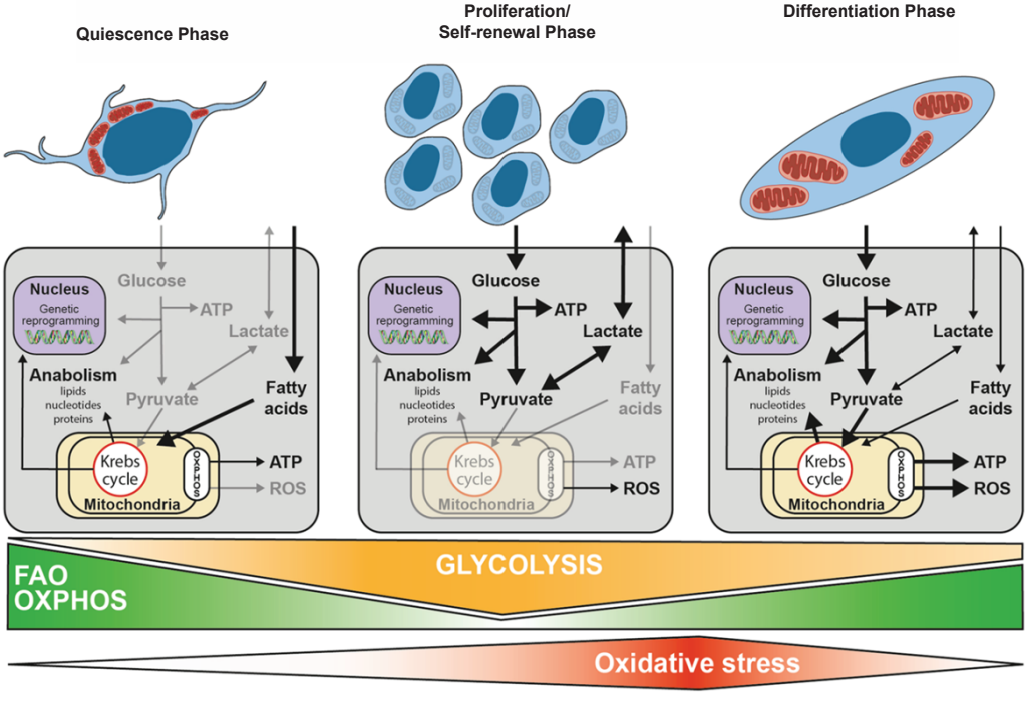

Figure 4. The Proposed metabolic pathways regulating quiescence, self-renewal, and differentiation during myogenesis.(5) (Adapted with permission from Springer Nature)

identity.(67,68) The bHLH proteins Myod1, Myf5, Myf6 (sometimes referred to as MRF4), and myogenin, together termed MRFs, successively facilitate the progression of satellite cells toward myogenic differentiation and fusion, resulting in the formation of multinucleated myofibers. (69) The overexpression of Myf5, followed by Myod1, is essential for myogenic determination.(70,71) Myogenin initiates progression to the myocyte stage and terminal differentiation. Pax7 and the myogenic regulatory factors Myod1 and Myog inhibit each other, but Pax3 and Pax7 do not affect Myf5 expression. These findings categorize satellite cell differentiation into three states: (i) $Pax7^+$ cells that maintain the stem cell reservoir, (ii) $Myod1^+$ myogenic progenitors that have started the myogenic program, and (iii) $Myogenin^+$ myocytes ready to fuse with existing or new myofibers.(72)

To form myofibers, MuSCs transition through several cell fates before reaching full differentiation. Although these intermediate cell fates share the same genome, their identities are shaped by different interpretations of this genomic blueprint. Epigenetic mechanisms determine which genes are expressed by controlling the accessibility of transcriptional machinery to specific loci. Given that the human diploid genome contains six billion base pairs, not all genes can be accessible for expression, as the genetic information must be highly compacted within the nuclear membrane.(73)

Understanding how epigenetic influenced by our daily physical activity and nutrition to maintain muscle mass and function at molecular level can help develop a better muscle rejuvenation therapies. Effective muscle regeneration will likely involve combination treatments targeting both satellite cell limitations and niche deregulations. Gaining insights into how aging, disease and pharmacotherapies affect satellite cells is essential for creating therapies to prevent, delay, or reverse cell dysfunction, improving health and longevity.

Exercise is Medicine

Physical inactivity is a recognized, although alterable, risk factor that leads to lifestyle-related illnesses, including several causes of preventable death.(74) Globally, almost one in three adults and four in five teenagers fail to meet the recommended levels of daily exercise in terms of both quantity and quality. Existing public health recommendations emphasize regular exercise and physical activity as essential strategies for preventing, managing, and treating various chronic conditions such as hypertension, coronary heart disease, obesity, T2DM, and sarcopenia (age-related muscle loss).(75,76) This recognition establishes the fundamental principle that exercise is medicine. For example, short-term exercise training somewhat mitigates the advancement of metabolic illness (77), whereas lifestyle modifications that include enhanced physical activity are the principal preventative strategy for metabolic disease (78). Indeed, consistent physical activity coupled with dietary modifications is more effective than pharmaceutical therapy in the management and prevention of both T2DM and sarcopenia. Although the benefits of and adaptations to regular exercise are well-established, many studies continue to investigate the molecular pathways through which exercise orchestrates adaptive responses to enhance skeletal muscle function and metabolism.

Based on European Working Group on Sarcopenia in Older People 2 (EWGSOP2), sarcopenia is defined as a muscle disease characterized by low muscle strength.(79,80) The diagnosis is confirmed by detecting low muscle quantity and quality, and poor physical performance indicates severe sarcopenia.(81) Sarcopenia is officially acknowledged as a muscular disorder, with an International Classification of Diseases, Tenth Revision, Clinical Modification (ICD-10-CM) Diagnosis Code applicable for billing purposes in some countries.(82) Sarcopenia heightens the risk of falls, fractures, and fear of falling (FoF), while reducing functional capacity.(83) It is further associated with cardiovascular disease (CVD), respiratory dysfunction, and cognitive decline, frequently resulting in mobility deficits, poorer quality of life (QoL), loss of autonomy, and long-term care admission, ultimately driving increased mortality. (84) Exercise is the sole efficacious intervention to postpone the onset of sarcopenia and enhance muscular health in the elderly. Despite the multitude of recommended therapies aimed at mitigating sarcopenia, none have achieved success in clinical studies.(85,86)

Skeletal muscle plays a vital role in glycemic regulation and metabolic equilibrium, serving as the primary site (about 80%) for glucose uptake under insulin-stimulated circumstances. Moreover, skeletal muscle serves as the greatest organ for glycogen storage, with approximately four times the capacity of the liver. Acute exercise improves whole-body insulin sensitivity for up to 48 hours. Additionally, it stimulates insulin-independent glucose uptake in skeletal muscle, demonstrating contraction-mediated regulation of glucose homeostasis.(87)

Mammalian skeletal muscles consist of several fiber types, with their primary classifications and biochemical

features discussed in further depth in other sources.(88) Skeletal muscle fibers are categorized as slow-twitch (type I) or fast-twitch (type II) based on their contractile kinetics, particularly their time-to-peak tension. This functional classification aligns with myofibrillar ATPase histochemistry, where type I fibers exhibit low ATPase activity and type II fibers display high activity. In humans, fast-twitch fibers are further subdivided into type IIa and IIx, whereas rodents primarily express type IIb.

Fiber color reflects metabolic specialization: Type I fibers appear red due to high myoglobin content and mitochondrial density, supporting oxidative metabolism. In contrast, type IIx/IIb fibers are white, indicating glycolytic dominance, while type IIa fibers exhibit an intermediate phenotype. Definitive fiber typing relies on immunohistochemical or electrophoretic analysis of myosin heavy chain (MHC) isoforms, the gold standard for classification. Each isoform exhibits unique contractile qualities that correspond to ATPase activity and twitch characteristics. Uniform fibers including MHC1, 2A, and 2X are present, but hybrid fibers with 1-2A and 2A-2X isoforms have also been documented. The type of muscle fiber is genetically predetermined throughout development, although the adaptive transition of muscle fibers from one type to another remains a contentious issue.(89) With suitable training stimuli, muscle plasticity allows alterations in metabolic capacity and structure, regardless of whether a shift in muscle fiber type, as indicated by changes in MHC expression, is detected.(90) The human body has around 600 skeletal muscles, mostly consisting of elongated contractile cells known as muscle fibers. The intricate structure of these fibers offers insights into the complexities of muscle action and homeostatic regulation, facilitated by the interplay of sarcomeres and mitochondria.(91)

Subsarcolemmal mitochondria predominantly localize in the peripheral sarcoplasm between myofibrils and the sarcolemma. These mitochondria exhibit a globular morphology with extensive cristae development and matrix volume. They penetrate deeply into the myofibrillar space and establish connections with neighboring intermyofibrillar mitochondria via electron-dense intermitochondrial junctions, collectively forming an interconnected mitochondrial reticulum. Intermyofibrillar mitochondria are more morphologically complex than subsarcolemmal mitochondria and interact physically with the myofibrillar matrix, sarcoplasmic reticulum, and intermyofibrillar lipid droplets.(92,93)

Muscle volume consists of approximately 2–10% of various subpopulations of subsarcolemmal (peripheral) and intermyofibrillar mitochondria, which differ in form, function, and location based on fiber type. Persistent contractile activity in skeletal muscle demands unbroken ATP resynthesis, principally supported by mitochondrial oxidative metabolism during both steady-state and sustained near-maximal exercise intensities.(94-97)

Distinct exercise modalities differentially influence muscle fiber types through specialized mechanisms. Traditional resistance training employs repeated dynamic contractions, including concentric (shortening) and eccentric (lengthening) movements against resistance, representing an evidence-based intervention for augmenting both muscle hypertrophy and strength. The total volume, frequency, and intensity of exercise are interrelated training factors that influence adaptation and performance. In resistance training, volume is often quantified by the frequency of sets targeting a specific muscle region each week, serving as the primary stimulus for muscular hypertrophy.(98) Endurance exercise, sometimes referred to as aerobic exercise, is generally defined as a sustained session of structured activity conducted at low (<50%), moderate (~50-79%), or high levels (≥80%) of VO_2max. High-intensity cardiorespiratory exercise (HIIT) is a time-efficient exercise strategy alternating short bursts of near-maximal effort (≥80% VO_2max) with active recovery or rest periods. Typically lasting 10–30 minutes, HIIT elicits superior cardiovascular and metabolic adaptations compared to steady-state training through repeated oxygen debt (EPOC) and enhanced mitochondrial biogenesis. Its potency stems from brief but potent disruption of homeostasis, making it effective for improving VO_2max, insulin sensitivity, and fat oxidation while preserving muscle mass.(99) The extent of adaptation to resistance and endurance exercise varies significantly across individuals. This likely arises partly from the previously mentioned challenges related to exercise standardization (100), as well as from genetic (101), and environmental interactions that culminate in the heterogeneous molecular responses observed both systemically and in muscle following a common exercise session (102).

Physical activity involving skeletal muscle will impact the body systemically, particularly via myokines or exerkines. Exerkines are signaling molecules released in response to exercise that help mediate systemic adaptations to physical activity.(103) Recent studies now also includes exercise-induced humoral factors from the heart (cardiokines), liver (hepatokines), white adipose tissue (adipokines), brown adipose tissue (batokines), and the nervous system (neurokines). These factors have local

autocrine effects (on the originating cell) and paracrine effects (on nearby cells). Exerkines encompass a variety of signaling molecules, such as cytokines, nucleic acids (microRNA, mRNA, mitochondrial DNA), lipids, and metabolites, often released via cell-specific extracellular vesicles.(104,105)

Figure 5 illustrates the metabolic effects of resistance training, endurance training, and HIIT on various physiological systems, particularly in relation to T2DM, CVD risk, and sarcopenia. Resistance training increases muscle mass and strength, lowers blood pressure, improves lipid profile, and reduces visceral fat, impacting the heart, adipose tissue, muscle, endocrine system, and liver. Endurance training enhances cardiovascular fitness, improves lipid profile, reduces resting heart rate, and increases insulin sensitivity, affecting the same systems. HIIT boosts aerobic and anaerobic capacity, improves mitochondrial density, and enhances glucose metabolism, also impacting these systemss, signaling molecules released during exercise, mediate many of these beneficial effects, including improved insulin sensitivity, enhanced fat oxidation, and reduced inflammation.(106)

Aerobic and strength exercises, representing the extremes of the exercise spectrum, elicit distinct training responses.(107) However, not everyone responds to exercise in the same way. The differences in how individuals respond to exercise have led to the classification of 'responders' and 'non-responders.' Increasing the amount of fixed-intensity exercise or the intensity of fixed-volume exercise may help reduce exercise non-response, with higher quantities of more intense exercise likely being the most effective. However, those who are less responsive require a more significant training stimulus and greater time investment to achieve results similar to their more responsive peers. (108,109)

The molecular processes regulating adaptation to exercise training involve gradual changes in protein composition and enzymatic activity. These changes result from the activation or inhibition of specific signaling pathways that control transcription, translation, and exercise-responsive gene expression. Post-exercise, temporary changes in gene transcription include immediate early genes, myogenic regulators, and genes involved in carbohydrate metabolism, lipid mobilization, transport and oxidation,

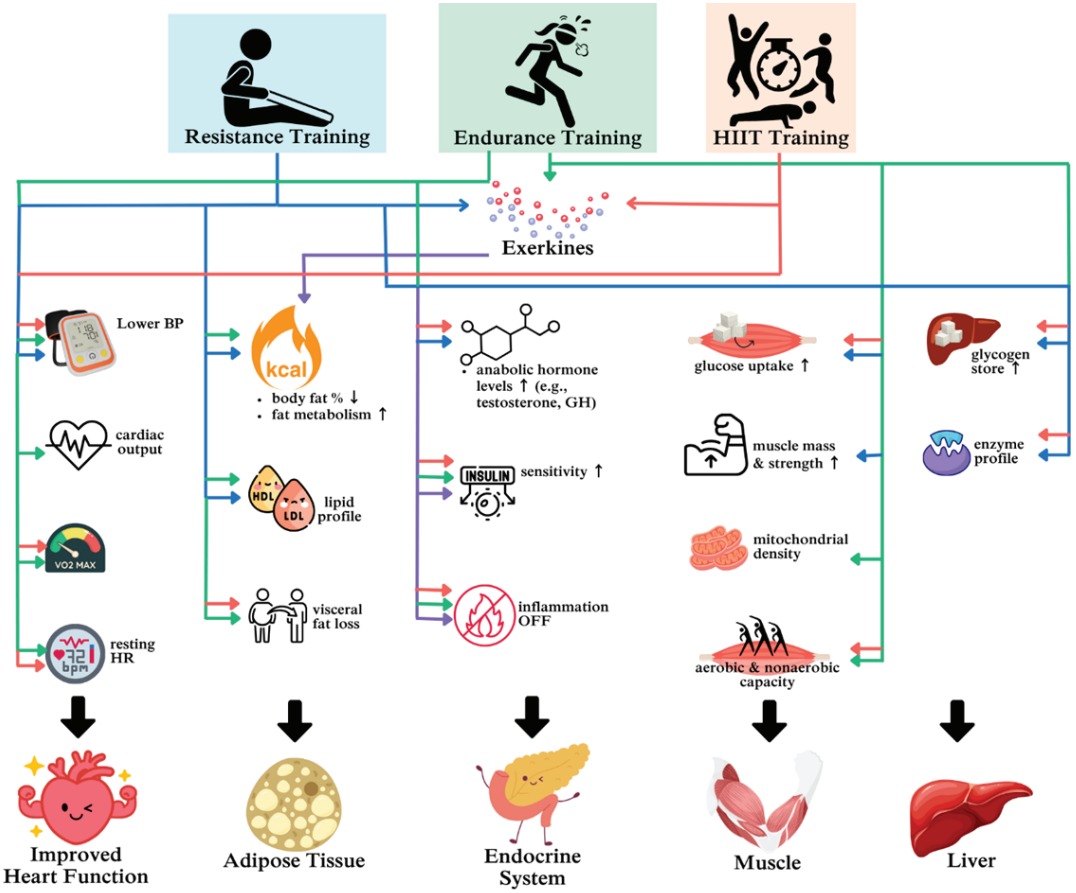

Figure 5. The systemic and adaptive effects of different kind of exercises. Blue Arrows: effects from resistance training. Green Arrows: effects from endurance training. Pink Arrows: Effects from High-Intensity Interval Training. Purple Arrows: Effects mediated by exerkines.

mitochondrial metabolism, oxidative phosphorylation, and transcriptional regulation of gene expression biogenesis. (110) At a regulatory level, a single session of exercise modifies the DNA binding activity of many transcription factors, including MEF2, histone deacetylases (HDACs), and nuclear factor erythroid 2-like (NRFs). The stability of proteins and the subcellular location of transcription factor complexes in the nucleus and mitochondrion are also affected.(111,112) Understanding the varied responses to exercise and the underlying molecular mechanisms can help tailor training programs to maximize benefits and improve individual's overall health outcomes.

Beyond the foundational role of resistance exercise, nutritional approaches are paramount for preserving lean body mass during active weight loss. The cornerstone of this strategy is ensuring adequate protein intake, which often needs to be significantly higher than the standard recommendation, typically in the range of 1.2 to 1.6 g/kg of body weight per day, to offset catabolic losses.(18-20) The timing and quality of this protein are also crucial; distributing protein consumption across multiple meals (*e.g.*, 20-40g per meal) may more effectively stimulate muscle protein synthesis (MPS) than consuming the majority in a single meal. Supplementation with specific amino acids, particularly leucine, has been shown to be a potent trigger for MPS, making it a valuable adjuvant. Furthermore, correcting common micronutrient deficiencies seen in obesity is critical. Vitamin D supplementation 1,500 to 2,000 IU per day for adults over 65 years old, for instance, is vital for muscle function, while omega-3 fatty acids may provide anti-inflammatory and anabolic-sensitizing effects that help preserve muscle quality during calorie restriction. (19,20)

To effectively deploy these interventions, a proactive clinical monitoring strategy is essential to identify patients at high risk of sarcopenia. This requires moving beyond BMI and employing more precise tools like Dual-energy X-ray Absorptiometry (DXA) to accurately quantify lean mass and track its changes relative to fat loss. However, muscle function is often more clinically relevant than mass alone. Therefore, functional assessments, such as handgrip strength, the chair-stand test, or the Short Physical Performance Battery (SPPB), are critical for detecting early declines in strength and mobility.(21) This regular monitoring allows for patient stratification, identifying high-risk individuals (*e.g.*, older adults, those with high inflammation, or rapid functional decline) who may benefit from the most intensive nutritional and exercise support. This stratification also opens the door for future, targeted pharmacological agents, such as myostatin inhibitors or selective androgen receptor modulators (SARMs), which are currently being investigated as potential adjuvant therapies for those who fail to respond to standard interventions.(21)

Clinical Implication and Future Direction

The primary clinical implication is that modern obesity treatments, from lifestyle interventions to incretin-based therapies and metabolic surgery, must promote healthy weight loss by preserving muscle mass, strength, and quality. This mandates a new standard of care where clinicians move beyond tracking total weight to proactively monitoring the quality of that loss. Using tools like DXA scans, functional assessments (*e.g.*, handgrip strength, chair stands), and biomarkers is essential to identify high-risk individuals early. This monitoring allows for the immediate personalization of multimodal interventions, integrating high-protein nutritional plans (1.2-1.6 g/kg/day) with targeted resistance exercise as a non-negotiable component of therapy.

While current incretin-based medications show promising results for obesity and T2DM, the future direction lies in fully understanding their impact on skeletal muscle. More research is urgently needed on new multi-agonists to ensure they uncouple fat loss from muscle catabolism, especially in at risk sarcopenic populations. This research must also delve into underlying mechanisms, such as the complex role of inflammation in restoring muscle homeostasis and the cellular processes of muscle regeneration. Effective, personalized treatments may require combined approaches, such as pairing diet, lifestyle, and incretins with adjuvant pharmacological agents (like myostatin inhibitors), to address satellite cell limitations and ensure truly healthy, functional weight loss.

Conclusion

Weight-loss medications should promote healthy weight loss while preserving muscle mass, strength, and quality. Various exercises support muscle and metabolic health depend on type and duration. Inflammation helps restore homeostasis after stress from injuries, aging, or metabolic issues, involving immune cells for development and regeneration. Effective muscle regeneration may require combined treatments addressing satellite cell limitations and niche deregulations, influenced by diet and lifestyle.

Incretin-based medications for obesity and T2DM show promising results. More research on multi-agonists' effects on skeletal muscle, especially in sarcopenia, could lead to personalized weight-loss treatments.

Authors Contribution

AM drafted the original manuscript and critically revised the manuscript manuscript. NMD edited and revised the manuscript. AW proposed and concepted the manuscript topic, and gave critical suggestions to the final draft. All authors have agreed with the final revisions of the manuscript.

Conflict of Interest

The authors declare no conflicts of interest or competing interests related to the content of this manuscript.

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