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# Physiological and morphological impact of physical activity and nutritional interventions to offset disuse-induced skeletal muscle atrophy

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***Abstract***

Skeletal muscle tissue acts as a functional unit for physical movements, energy metabolism, thermogenesis, and metabolic homeostasis. In this literature review, the underlying mechanisms of skeletal muscle atrophy and the prevention strategies, including vigorous training and nutritional modifications are focused. Furthermore, the comparative analysis of multiple interventions is briefly explained. Ageing is an inevitable process often associated with cognitive impairment and physical decline due to muscular atrophy. Skeletal muscle atrophy is characterized by low muscle mass due to multiple underlying factors, *i.e.,* genetic predisposition, ageing, inflammation, and trauma. The structural alterations include myofiber shrinkage, changes in myosin isoforms, decrease in myofiber diameter, and total protein loss. Furthermore, there is an imbalance in protein anabolic and catabolic reactions. This may be due to changes in multiple signal transduction pathways of protein degradation (*i.e.,* caspase, calpain, ubiquitin protein degradation system, autophagy) and protein anabolism via the mTOR pathway. Consequently, certain pathophysiological factors associated with health disparities may reduce mobility and functional capacity to perform ADLs. To tackle this issue, novel strategies linked to physical movement, and dietary intake must be incorporated in life. Exercise poses multiple health benefits, including improved muscle mass and mobility. Diet diversification [particularly protein-rich meals] and the "whole food" approach (based on non-protein nutrients) may enhance intramuscular anabolic signaling and tissue remodeling. However, there is a pressing need to fund large-scale evidence-based trials based on modern machine learning techniques (AI-driven nutrition). Additionally, entrepreneurial platforms for commercialization of consumer-friendly food products must be initiated in future.

**Key Words:** skeletal muscle atrophy, sarcopenia, leucine, ubiquitin protein degradation system, diet diversification, mTOR pathway, activities of daily life (ADLs), functional body capacity.

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Skeletal muscle, a major protein reservoir involved in functional body capacity, accounts for 40% of total body composition. The skeletal tissue is crucial for physical movements, thermogenesis, and metabolic homeostasis.[1] Ageing leads to cognitive impairment and physical decline, thus reducing the capacity to perform Activities of Daily Life (ADLs). Disuse is a state of reduced physical activity that may affect muscles' morphological and functional characteristics. The diminished capacity to move the limb's skeletal muscles will initiate a sequence of adaptive responses leading toward muscular atrophy. Muscular atrophy is associated with low muscle mass due to an imbalance in protein synthesis or degradation preceding muscle wasting. A vast array of pathophysiological ailments (inherited and acquired comorbidities) can be subcategorized into primary skeletal or secondary skeletal muscle atrophy, respectively. Muscular atrophy is characterized by structural modifications *i.e.,* myofiber shrinkage, alterations in myosin isoforms, decrease in myofiber diameter, and total protein loss.[2]

Sarcopenia may reduce the ability to conduct daily activities, thus diminishing the quality of life. It further burdens the body's immune system by exceeding recovery time in any ailment. This review examines the etiology of skeletal muscle disorders and related interventional therapies to mimic their detrimental impact on the body. Effective prevention strategies must be initiated within time to avoid skeletal muscular atrophy's negative impacts [social or fi-

nancial]. These may include improved daily activity via exercise, appropriate medication, and nutritional interventions such as dietary supplementation. However, there is a massive gap in finding an effective cure for skeletal muscle atrophy through therapeutic drugs. Therefore, scientific research must be focused on understanding the mechanisms of muscle wasting to develop novel drugs to combat atrophy.[3]

## Primary and secondary skeletal muscle atrophy

Primary skeletal muscle atrophy is associated with multiple inherited muscle disorders (congenital and genetic comorbidities). Inherited ailments can be subcategorized into muscular dystrophy, mitochondrial myopathy, metabolic disorders, and congenital myopathy. It affects skeletal muscles by progressive muscular atrophy, muscle spasms, inflammation, and metabolic dysfunction of muscle fiber.[4] Muscular myopathies consist of Becker muscular dystrophy, Duchenne muscular dystrophy, and type-1 and type-2 myotonic muscular dystrophy, while congenital disorders include Nemaline myopathies.[2]

Secondary muscle atrophy may occur in physical conditions and acquire systematic diseases. Acquired causes include age-related cachexia and sarcopenia, chronic renal failure, diabetes mellitus, neurodegenerative diseases, sepsis, and burns. Other factors linked to muscular atrophy are immobilization due to bone fractures or trauma, and a sedentary lifestyle. PEM and severe fasting lead to physiological changes such as muscular atrophy. The muscle contraction and stimulation imbalance results in cell apoptosis and protein loss, which initiate muscular atrophy in the body. In chronic diseases, protein degradation is higher than protein synthesis, resulting in skeletal muscle atrophy.[5]

## Age-related sarcopenia

With ageing, sarcopenia, *i.e.*, reduced muscle strength and muscle mass (5-10% loss), affects a large segment of the geriatric population. Globally, 50 million of the geriatric population suffer from sarcopenia, with a rate of 5-13% in the 70s, which may rise to 11% to 50% above 80 years. The ratio of women affected is twice (12%) than in men. The average muscle capacity is reduced significantly in the elderly, leading to immobilization and a higher ratio of bone fractures due to falls, thus subsequently increasing the need for medical assistance to perform ADLs. Multifaceted extrinsic and intrinsic factors such as slower metabolism, and diminished biosynthesis result in loss and strength of skeletal muscles. Sarcopenia is a detrimental health issue that may shorten the lifespan of an individual and increase drastically after the 50s (Figure 1).[3]

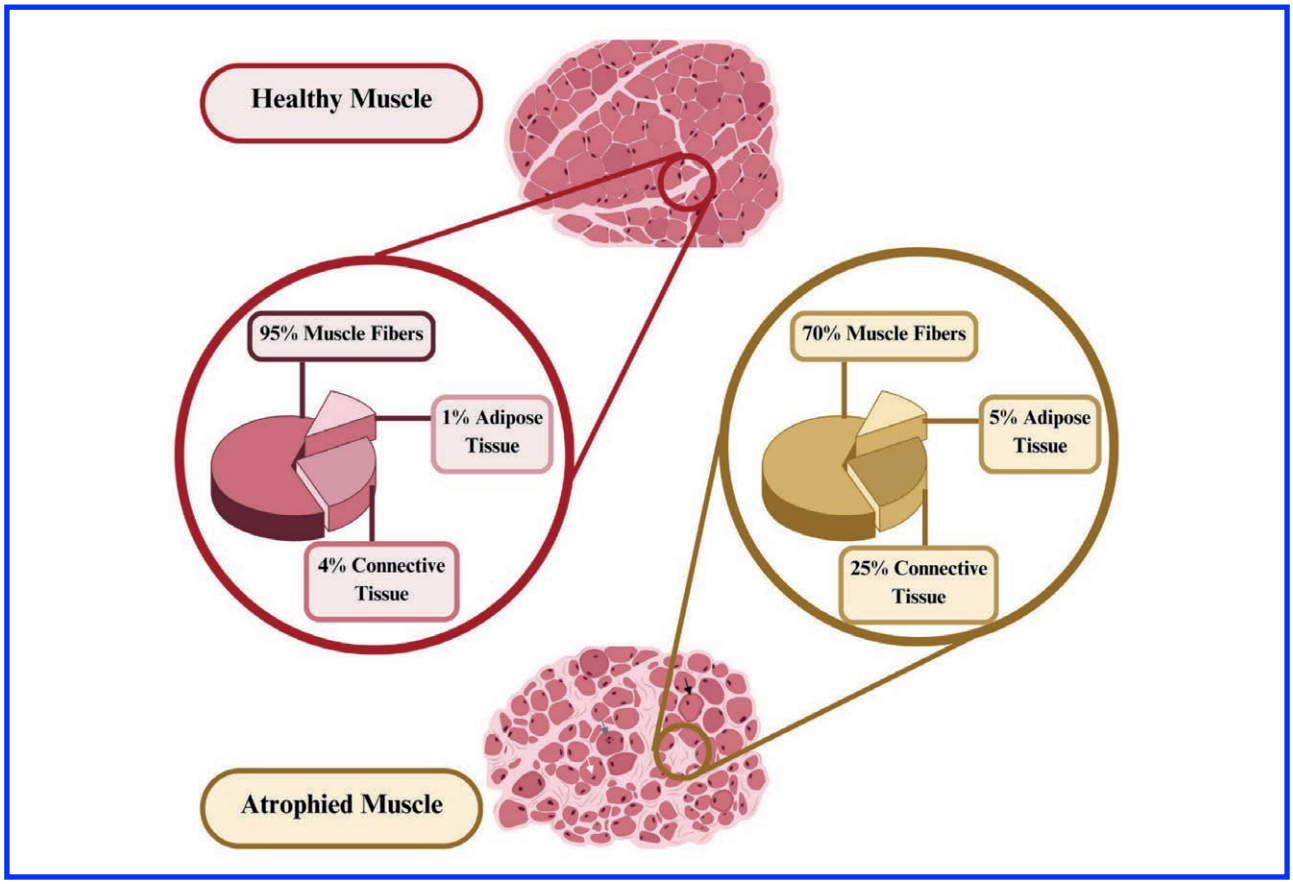


***Figure 1.*** *Differences between healthy muscle and atrophied muscle.*

## Intracellular mechanisms underlying disuse-induced skeletal muscle atrophy

Atrophic processes can accelerate in prolonged periods of immobilization or the absence of chronic comorbidities. The molecular mechanism of muscular atrophy must be understood to improve physical movement and quality of life. The factors involved include protein synthesis, conjugated ubiquitin, autophagy, and protease activation. This may occur by an increased ratio of proteolysis to protein synthesis. The skeletal proteases are caspase-3, ubiquitin-proteasome pathway, lysosomal proteases, and $Ca^{2+}$-activated proteases (calpain). Cytoskeletal remodeling involves calpain regulation of cytoskeletal protein's attachment with plasma membrane. This process is required for cell fusion and cell motility in muscles. Mutations in the calpain3 gene cause limb-girdle muscular atrophy. Furthermore, calpains are crucial for the cell cycle, signal transduction, and apoptosis. Thus, any modulation may result in pathological disorders.[6]

The increase in the rate of calpain activation was observed in the disuse and denervation of muscles. Studies have shown that caplain2 inhibition may result in approximately 30% reduction in protein degradation during skeletal muscle atrophy. The underlying molecular mechanism of atrophy is briefly discussed here. Skeletal muscle is composed of myofibrillar proteins, stroma proteins, and sarcoplasmic proteins. The myofibrillar proteins critical for muscle contraction must extend in structure from one end to another. These myofibrils have smaller diameters during atrophic conditions, resulting in muscle dysfunction. In muscle sarcomere, calpain's proteolytic activity is at the site of Z-disc during atrophy. Evidence suggests that 80% of muscle protein degradation falls under the UPP pathway. The increased phosphorylated Akt (protein kinase B) activity causes hypertrophy leading to muscle wasting. The distinct factors associated are loss of myofibril proteins, sarcomere cleavage by calpains, and UPS-mediated proteolytic myofibril degradation.[6]

## Morphology of disuse-induced skeletal muscle dysfunction

The regulation of skeletal muscle atrophy is a complex process based on numerous mechanisms. Although losing muscle strength and mass during periods of inactivity has apparent adverse effects on mobility, it is a physiologically appropriate response to decreased contractile activity. When muscles are not commonly used, the body adapts by reducing muscle size. This is in response to the downregulation of signals promoting muscle growth, while the processes that break down muscle proteins may accelerate. Muscle building and breakdown balance is disrupted during inactivity, leading to muscle loss.[7]

The intracellular mechanisms of structural modification in inactive muscle protein synthesis have yet to be studied. The regulation of MPS is via the activated rapamycin (mTOR) and phosphorylation of various substrates (p70 ribosomal protein S-6 kinase, 4-E binding protein-1, and ribosomal protein S-6), which further initiates mRNA translation.[8] However, during immobile postabsorptive periods, the activation of this pathway is unaltered, indicating an independent decrease in postabsorptive MPS in short and prolonged disuse. However, the impact of disuse on the elongation process or ribosomal biogenesis in mTOR is still under investigation and warrants further exploration in future studies (Figure 2).[5]

## Specific sites of reactive oxygen species production in inactive muscle fibers

Researchers have been trying to study the exact mechanism behind harmful ROS production in immobile skeletal muscles for the last three decades. It has been a tough challenge because tracking precisely where these molecules appear within muscle cells is hard. Evidence-based studies suggest that when skeletal muscles are inactive for long periods, three main pathways are responsible for the increased production of superoxide (ROS). These sources are xanthine oxidase, NADPH oxidase, and mitochondria.[0] Previously, numerous animal trials assessed how endurance exercise protects against DOX-induced skeletal muscle damage. In inactive muscles, superoxide production primarily depends upon mitochondrial ROS emission. For instance, the ROS emission is higher during «resting» respiration states, where a restricted ADP supply to mitochondria exists (state-4 respiration), compared to conditions of activated ADP (state-3 respiration). This is critical to align processes in inactive skeletal muscle with respiration (state-4), while respiration (state-3) occurs in actively contracting muscle. Additionally, experiments with isolated mitochondria from rodent's diaphragm muscle subjected to prolonged mechanical ventilation (leading to diaphragm inactivity) have shown increased ROS release compared to spontaneous breathing animals (Figure 3).[10]

## Physical activity and disuse-induced skeletal muscle atrophy

Disuse-induced skeletal muscle atrophy results from an imbalance of muscle protein synthesis and degradation processes. The multifactorial causes underlying this condition include trauma, limb fractures, and immobilization for more extended periods. The therapies to tackle muscle wasting must be incorporated into daily life to avoid detrimental effects on health. The two strategies focused on are balanced nutrition and incorporating exercise into daily routine to enhance quality of life. Furthermore, exercise improves physical performance in immobile individuals. A single bout of physical activity alters the molecular expression of different factors involved in movement. The appropriate intensity, frequency, and duration of exercise enhance the contractile pathways in muscle via specific signaling mechanisms. The growth factors, androgenic compounds, and circulating inflammatory markers may increase during exercise. The phenotypic characteristics that alter through physical activity are improved fiber-type transitioning, capillary density, mitochondrial density, and cross-sectional area of muscle cells.[11]

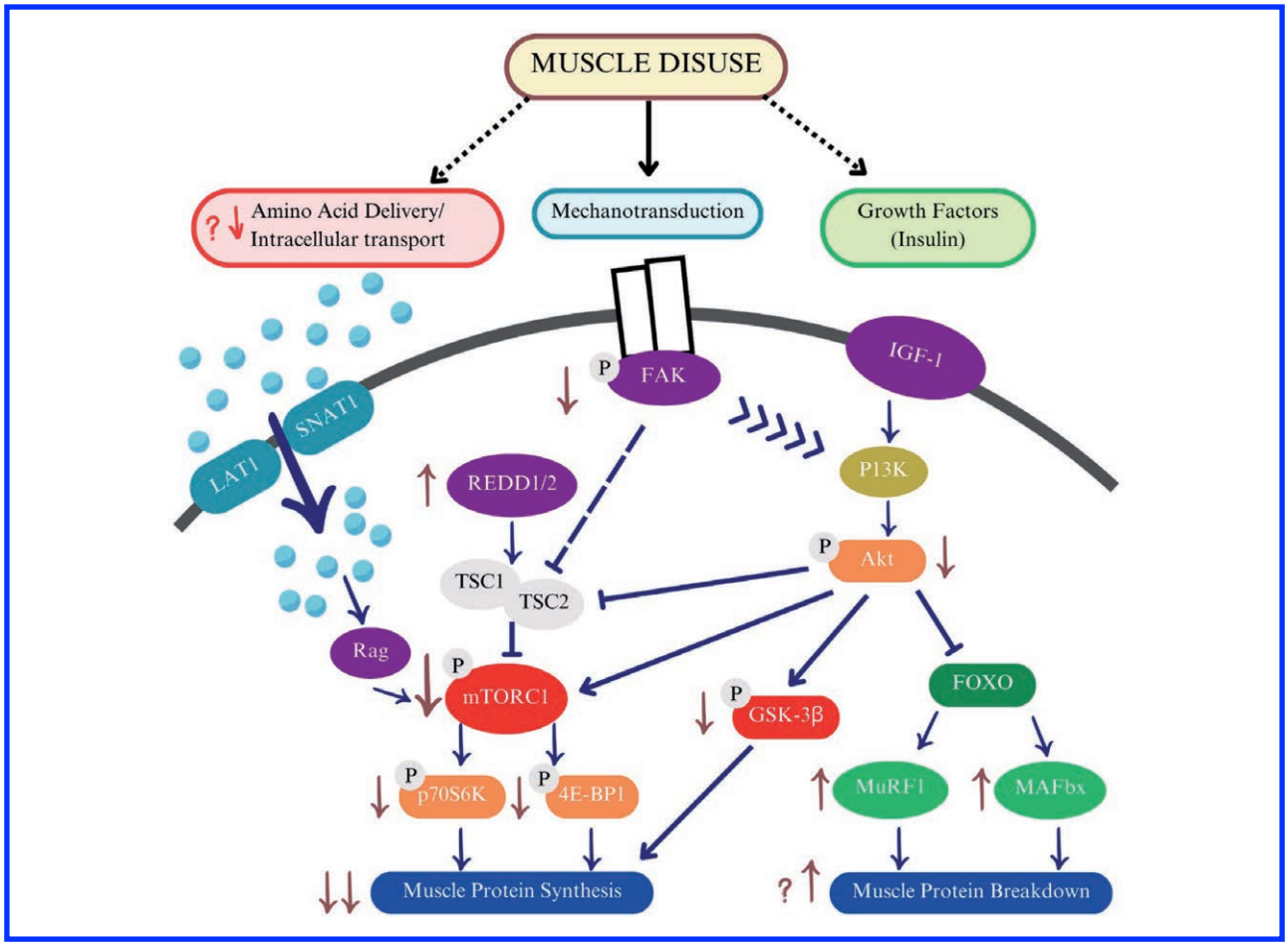


***Figure 2.*** *Intracellular mechanisms triggered in skeletal muscle disuse.*

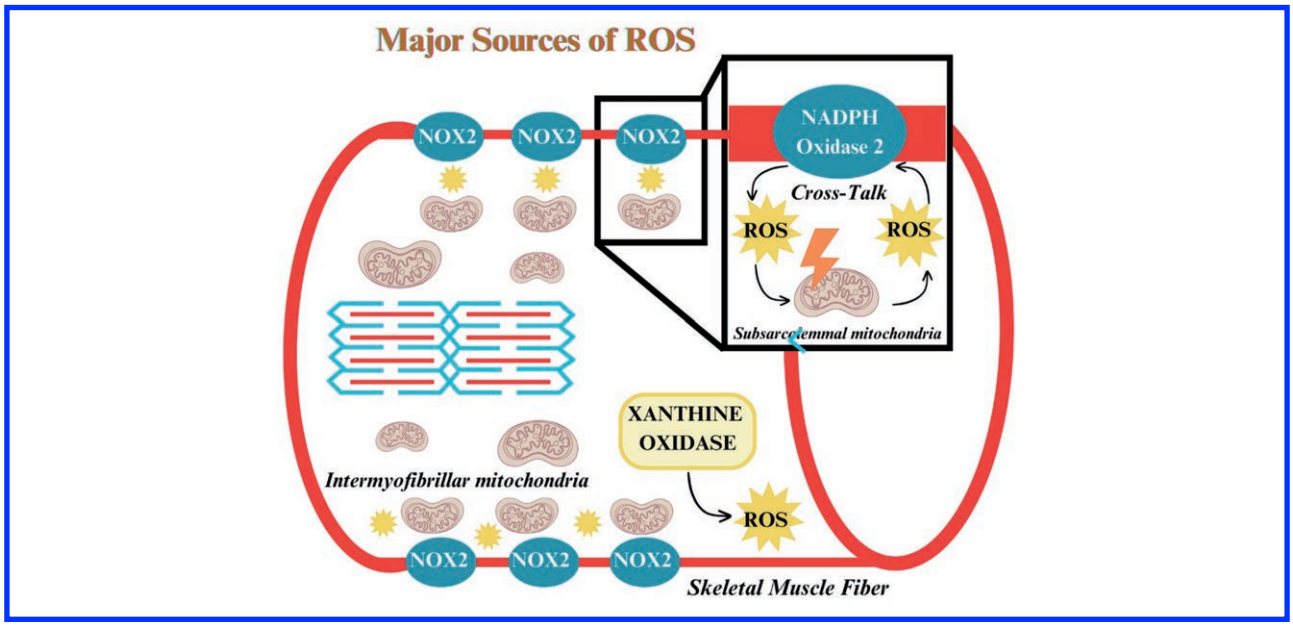


***Figure 3.*** *Major ROS sources in skeletal muscle fiber.*

The surge in mitochondrial density in response to exercise is an adaptive process that increases functional proteins required for muscle contraction. Endurance exercise fosters specific adaptations (biochemical and protective phenotypes) in response to stress, also known as exercise-preconditioning of skeletal muscles. Improved physical activity elevates heat shock proteins and endogenous antioxidants in muscle fibers.[12] Exercise improves the ratio of cardiac and skeletal muscle's bioenergetic enzymes to enhance activity. These changes are beneficial for skeletal muscle, *i.e.*, protective against DOX-induced wasting and muscle atrophy during the prolonged immobilized phase.[13] Exercise-preconditioning protects skeletal muscle fibers against multiple factors such as contraction-induced muscle injury, fiber atrophy, sepsis-induced muscle damage, and doxorubicin-mediated muscle wasting.[14]

## Morphological impact of exercise in disuse-induced skeletal muscle atrophy

Being inactive for extended periods (illness or hospital stays) can quickly cause muscle loss and hinder muscle protein synthesis in the geriatric population. This limited ability to bounce back from inactivity worsens over time, contributing to the development of sarcopenia, a condition marked by muscle loss. Furthermore, over half of hospitalized elderly struggle to regain mobility even a year after discharge.[15] When muscles are not used, the most apparent change is muscle atrophy. Muscular atrophy includes shrinkage in size, with individual fibers getting thinner and, thus, an overall reduction in muscle mass. Additionally, the disease process can alter the muscle fiber types. Fast-twitch fibers (type II) and mixed fibers may increase, while a drop in several slow-twitch type-1 fibers appears. Interestingly, the total number of fibers stays the same. Scientific evidence suggests this switch mainly happens in the slow-twitch fibers of muscles essential for standing upright [like the soleus muscle], but not in other leg muscles.[16]

Chronic exercise induces adaptations in skeletal muscle fibers, *i.e.*, systematic remodeling through a coordinated interplay between catabolic and anabolic processes (protein degradation and synthesis, respectively). Among the four major proteolytic systems present in skeletal muscle—namely, the ubiquitin-proteasome, autophagy, caspase, and calpain systems—calpain stands out due to its activation by $Ca^{2+}$, the primary allosteric regulator released from the Sarcoplasmic Reticulum (SR) to facilitate actin-myosin contractions during exercise. Consequently, it is plausible that calpains become activated during training, characterized by prolonged elevation of free $Ca^{2+}$ in the cytosol. Thus, activated calpains are critical for skeletal muscle adaptation to exercise. The subsequent sections delineate the evidence supporting the activation of calpains during exercise, followed by a discourse on the physiological function of active calpains in remodeling skeletal muscle during exercise training (Figure 4).[12]

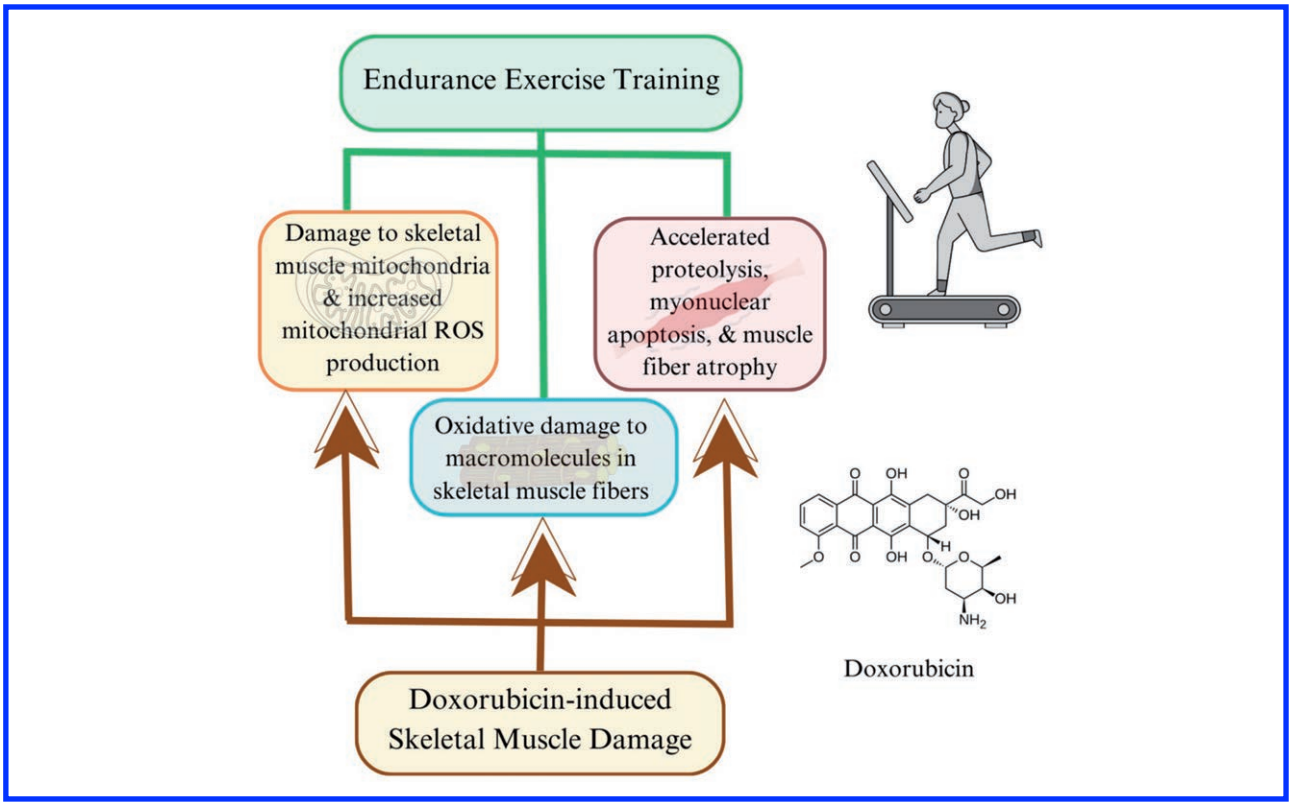


***Figure 4.*** *Endurance exercise preconditioning protects skeletal muscles from the harmful effects of Doxorubicin.*

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## Exercise preconditioning and doxorubicin-induced muscle wasting

Doxorubicin, a quinone-containing anthracycline antibiotic frequently used as an antitumor agent, has deleterious effects on cardiac and skeletal tissues. Doxorubicin-induced muscle wasting may occur because of a rise in mitochondrial ROS in redox cycling events. In mitochondria, ROS-producing enzymes, *i.e.* NADPH oxidase via electron reduction in quinone moiety (ring C), transform DOX into semiquinone. This semiquinone further reacts with oxygen to form superoxide radicals. This sequence of events may lead to protein and cellular membrane damage in muscles.[16] DOX-mediated ROS production further oxidizes mitochondrial macromolecules and proteins in the skeletal muscles. This process activates specific proteolytic systems of skeletal tissue, including the ubiquitin-proteasome system, autophagy, calpain, and caspase-3, thus, accelerating atrophy. Preclinical trials suggest physical activity has a protective mechanism in muscular wasting.[17] A 60-minute moderate-intensity ten-day exercise protects against proteolysis and DOX-induced wasting in rodents. The phenotypic alterations observed are reduced conjunction of 4-hydroxy-2-nonenal to proteins and carbonyl derivatives within skeletal muscle myofibrils. Furthermore, exercise preconditioning downregulates expression of autophagy genes, muscle RING finger-1, pro-apoptotic protein, forkhead-box transcription of E-3 ubiquitin ligase, and BCL2/adenovirus E1B 19 kDa protein-interacting protein-3 in skeletal muscles. Exercise-preconditioning may protect muscle fibers through three distinct mechanisms, including HSP72 levels, cytosolic and mitochondrial antioxidants, and the upregulation of mitochondrial-specific ABC and sarcolemmal transporters.[18]

## Exercise preconditioning against inactivity-induced muscle atrophy

Exercise-preconditioning against inactivity-induced muscle atrophy is well explained by a sequence of atrophic events in skeletal muscle fibers. The size of fibers depends on the ratio of protein catabolism and anabolism in skeletal tissue. In an immobilized state, the muscle fibers undergo increased catabolism and reduced protein biogenesis via specific signaling pathways, resulting in skeletal muscle atrophy. In inactive muscle fibers, ROS production occurs at multiple cellular locations (xanthine oxidase, mitochondria, and NADPH oxidase). In inactive skeletal muscles, the limited DP supply to mitochondria leads to greater ROS emission, *i.e.*, the state-4 "resting" respiration compared to state-3 respiration in active muscles: an ADP-stimulated condition.[19] During immobilization, the increased expression of DNA damage-inducible Gadd45α and growth arrest accelerates muscular atrophy. The rise in Gadd45α may form a complex structure with MEKK4 involved in the phosphorylation of downstream muscle proteolytic proteins. Additionally, exercise may place a protective barrier against class II histone deacetylase-4 and Gadd45α.[20]
Mitochondrial transcription factor-A, a DNA-binding protein, may hinder oxidative stress in muscular atrophy. TFAM forms a histone-like nucleoid complex with mitochondrial DNA to protect DNA from oxidative damage.[21] Furthermore, a five-fold increase in the expression of TFAM may provide resistance against muscle atrophy via an increase in SOD1 and SOD2 during hind limb suspension.[22] These cellular antioxidants [SOD1 and SOD2] may improve the antioxidant capacity of muscles during exercise. In an exercise-mediated increase of diaphragmatic SOD2, muscle fibers may be protected against the deleterious effects of MV-induced diaphragmatic atrophy.[23] During endurance training, a rise in HSP72 levels in skeletal muscle results in diverse protective mechanisms against muscle atrophy, *i.e.*, improved mitochondrial biogenesis, protection against mitochondrial ROS damage, proteolysis, and refolding of damaged proteins. Furthermore, antisense oligonucleotide increase may halt the protective impact of exercise-induced diaphragmatic HSP72, thus leading to MV-mediated muscle atrophy (Figure 5).[24]

## Nutritional interventions in disuse-induced skeletal muscle atrophy

Skeletal muscle atrophy significantly impacts various facets of human health. It is commonly linked to diminished quality of life, general mobility reduction, and decreased personal independence.[25] Sarcopenia primarily affects the elderly, with its occurrence rising steadily after the 60s. With ageing, muscular wasting is anticipated as a pressing issue that will exert a more significant burden on the health system.[26] Lifestyle modifications linked to physical activity and dietary interventions provided protective therapy for skeletal muscle disorders. Diet diversification provides an antioxidant and anti-inflammatory impact through foods rich in peptides, polyphenols, minerals, and other bioactive compounds. Peptides can positively influence multiple body processes through distinct protein-protein interactions. Bioactive peptides are known to affect the endocrine, digestive, immune, cardiovascular, and nervous systems. Exogenous peptides from the hydrolyzed protein sources depict functional effects beyond essential nutrition. These bioactive compounds released by proteome offer significant potential for preventing and treating chronic conditions like skeletal muscle atrophy. Plant-based diets and plant-based proteins provide a potential strategy to combat sarcopenia in the geriatric population. Additionally, whole and raw legumes are particularly remarkable sources of nutrients associated with multiple health benefits.[27]

## Whole food and combined meal approaches

The "whole food" approach in human metabolic research, unlike isolated proteins (whey and casein), is based on a vast array of non-protein nutrients that may enhance intramuscular anabolic signaling and tissue remodeling. Evidence-based trials have shifted focus from isolated proteins to protein-rich whole foods (*i.e.*, eggs, poultry, beef, skimmed milk, and other mixed meals) and their impact on the muscle anabolic response. However, this review has not covered a detailed discussion comparing the food-first ap-

proach to isolated proteins.[28] Polyphenols, the largest class of phytochemicals, play a crucial role in protecting against ailments associated with oxidative stress. Recently, extensive research has shifted on polyphenol's roles in preventing neurodegenerative diseases and skeletal muscle atrophy. These nutrients are among the most abundant and widespread natural products in the plant kingdom. Rich sources of polyphenols may include whole grains, fruits, vegetables, plant-based foods, beverages (tea, wine), and chocolate.[29] Vitamins, especially ascorbic acid, may mitigate overload-induced skeletal muscle hypertrophy by downregulating oxidative stress in rodent models via pathways linked to skeletal muscle metabolism and physiology (Figure 6).[30]

## Essential amino acids disuse-induced skeletal atrophy

With ageing, a decline in functional capacity and muscle wasting are experienced by the geriatric population. Evidence suggests that an isocaloric intake of 15 g essential amino acids (2.79 g leucine) may increase 30 % muscle protein synthesis as compared to 15 g whole protein (1.79 g leucine) in the elderly.[31] Additionally, nutritional interventions based on the consumption of 30 g of whole protein and 15 g of EAA have depicted max—protein synthesis in skeletal muscles. The EAA in meals rather than in isolated form improves protein synthesis without affecting insulinemia or blood glucose levels.[32] Furthermore, a blend of EAA and non-essential AAs (arginine, n-acetylcysteine, and glutamine) may combat skeletal muscle atrophy and raise adolescent intramuscular lipid accumulation. The intracellular mechanism behind this is that glutamine may hinder catabolism, arginine acts to maintain capillary perfusion, and n-acetylcysteine significantly reduces ROS stress in disuse-induced skeletal muscle atrophy.[33] Leucine, a branched-chain amino acid, is crucial for an increase in muscle strength and mass if consumed in high doses, *i.e.*, 0.06 g/kg/body weight/meal or 5 g. Additionally, athletes consume leucine supplementation in their daily diet to improve quadriceps or leg strength. However, scientific evidence suggests that leucine without a complete essential amino acids profile may not provide a healthy impact on multiple skeletal muscle disorders.[28]

## Comparative analysis of physical activity and dietary interventions

Lifestyle modifications have been a core focus of the modern scientific era to add healthy years with ageing. The blend of physical activity interventions and diet diversification has depicted positive impact on quality of life. However, there are multiple limitations that may hinder the beneficial outcome. A few of these are briefly listed in Table 1.

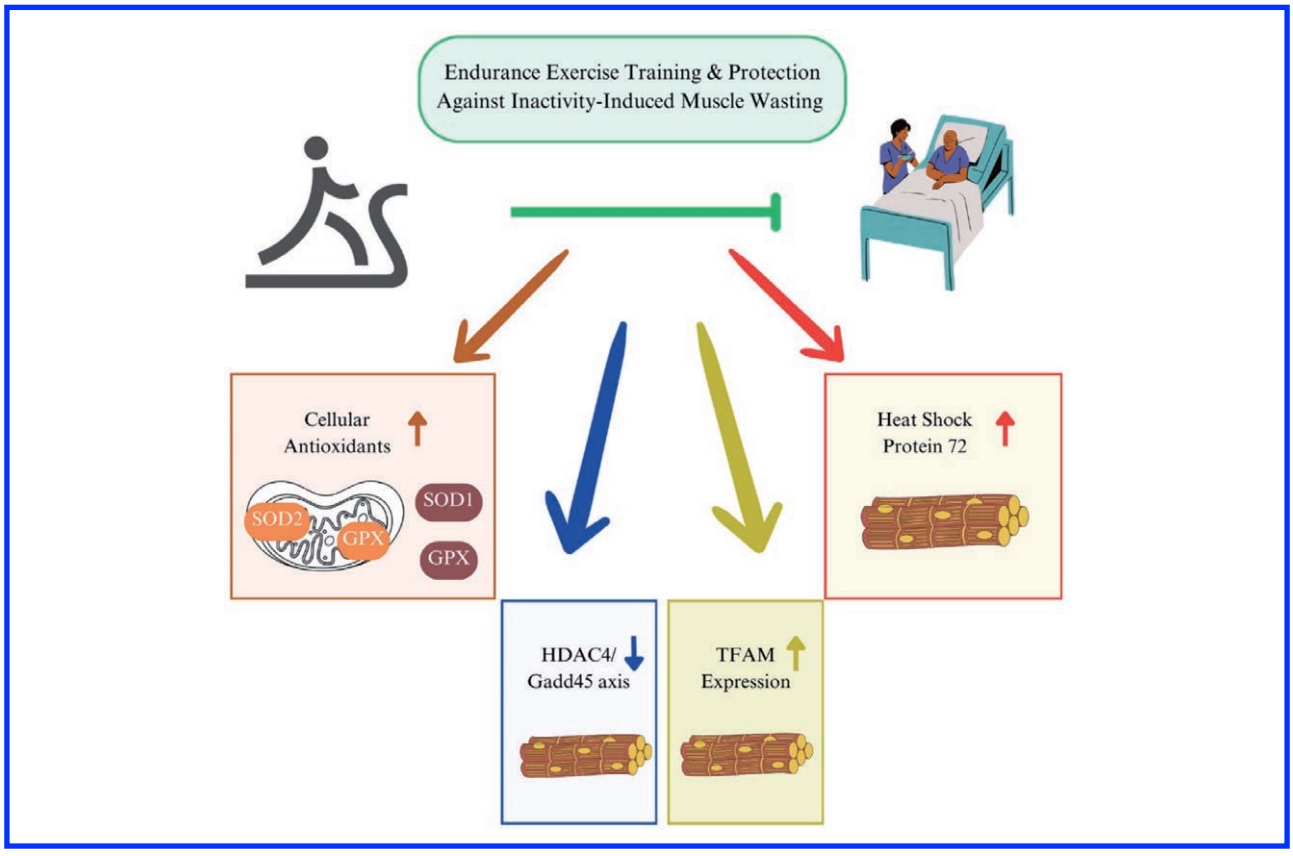


***Figure 5.*** *Vigorous physical training promotes biochemical alterations in the skeletal muscle.*

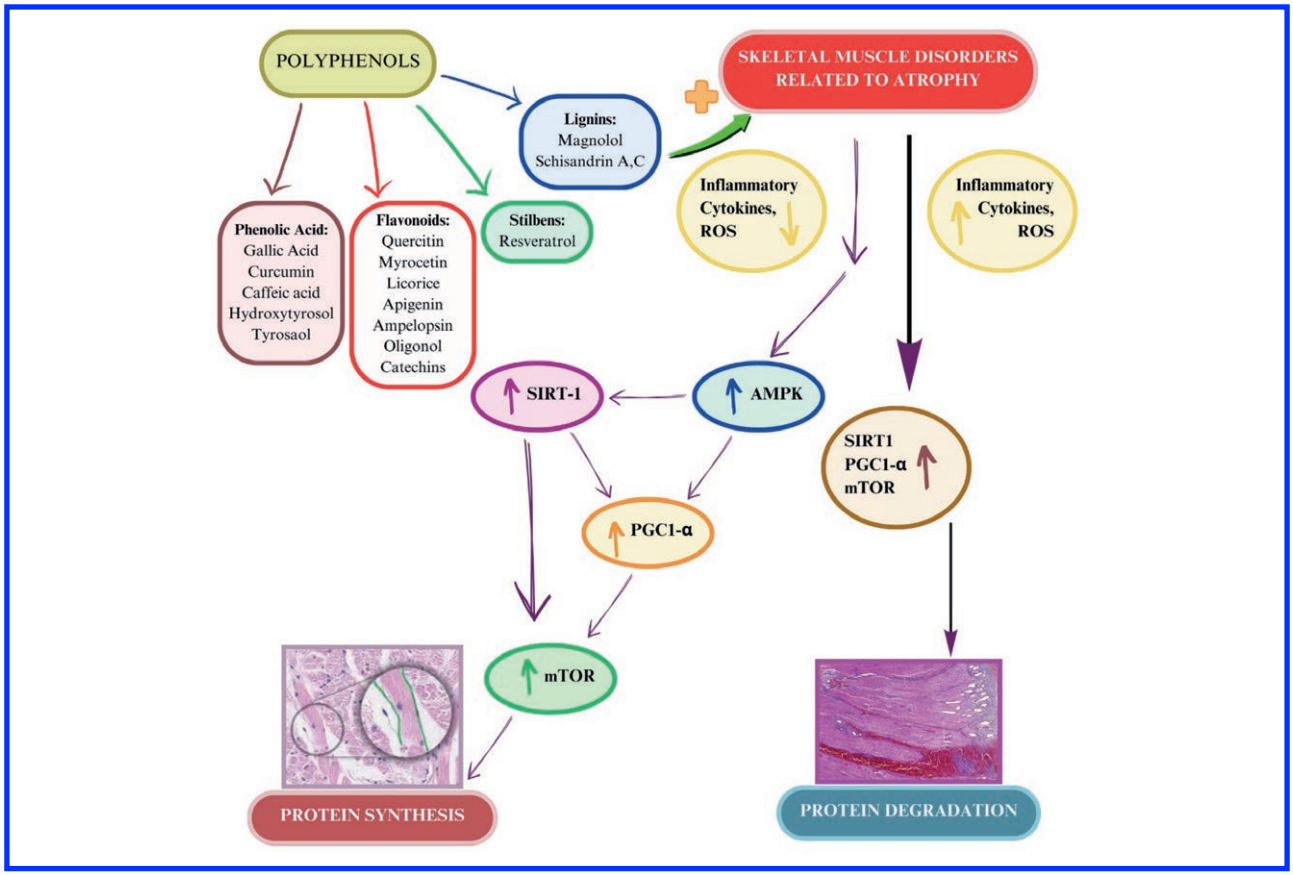


***Figure 6.*** *Polyphenol-rich diet for skeletal muscle disorders.*

***Table 1.*** *Comparative analysis of physical activity and dietary interventions.*

| Intervention | Effect on muscle atrophy | Strength of evidence | Limitations | Citations |
|---|---|---|---|---|
| Improved physical activity via exercise | - Induces autophagy in skeletal muscle and adipose tissues [modulates mTOR and ubiquitin-proteosome pathways]<br>- Reduces sarcopenia | Strong [Clinical studies in geriatric population] | Risk of bone fractures during exercise | [11] |
| Anaerobic exercise {Moderate intensity: $VO_2$ max [70%] and heart rate [80%]} | - Cardiovascular fitness by the regulation of vascular tone [production of endothelial nitric oxide<br>- Elevates heat shock proteins in muscle fibers | Strong [human and rodent efficacy trials] | Requires costly personalized training programs | [34] |
| Exercise-induced preconditioning of skeletal muscles | - Improves the ratio of cardiac and skeletal muscle's bioenergetic enzymes to enhance activity<br>- Prevent muscle wasting stimulated by DOX | Moderate [Community surveys] | May be ineffective if applied for short-time duration | [9] |

To be continued on next page

***Table 1.*** *Continued from previous page.*

| | | | | |
|---|---|---|---|---|
| Bioactive exogenous peptides [NPN_1 pepetide] | - Immune-boosting impact by increase in antioxidant potential of muscles | Strong [murine-model study] | Further quality evaluation of peptide is required for consumer acceptance | [27] |
| Plant-based proteins [plant-based diets] | - Increase muscle protein synthesis<br>- Strengthening skeletal muscles | Moderate [evidence-based human efficacy] | The plant protein bioavailability may be challenge due to lower digestibility and lower quantity of essential amino acids | [35] |
| Protein-rich whole food | - Enhance intramuscular anabolic signaling<br>- Tissue remodeling | Strong [Human study] | Reduce diet diversification | [36] |
| Grape polyphenol supplementation | - Protect against oxidative stress induced by KEAP1 signaling pathway in skeletal muscles | Strong [cell culture and animal studies] | Isolated supplements may be costly alternative to whole foods | [37] |
| Ascorbic acid | - Reduce catalase activity to mitigate overload-induced skeletal muscle hypertrophy<br>- Increased expression of anabolic and proliferative genes | Strong [*in vitro* and *in vivo* studies] | Overload on kidneys | [38] |

## Conclusions

Skeletal muscle atrophy, characterized by significant muscle mass loss, leads to an increased morbidity rate and, thus, may diminish the quality of life. Muscle atrophy is often associated with an imbalance in protein degradation and synthesis due to multiple underlying factors such as genetic predisposition, ageing, inflammation, and trauma. Protein degradation involves signal transduction pathways such as the ubiquitin protein degradation system and autophagy, while the mTOR pathway is used for muscle protein synthesis. Although multiple targets are found to be beneficial for skeletal muscle atrophy, such as activin type-IIB receptor and β2-adrenoceptor, no effective pharmacological drug has been discovered yet. The public health burden of the immobile population demands novel strategies to combat skeletal muscle atrophy. This may include the development of medicines with exercise-mimicking effects, and inhibitory properties of muscle degradation pathways. Diet diversification has proved to be an effective protective mechanism in multiple muscle disorders. Improved physical activity in the geriatric population is crucial to treating skeletal muscle atrophy and, thus, increases ADL performance in later years of life.

However, there is a pressing need to fund large-scale evidence-based trials based on modern machine learning techniques (AI-driven nutrition). Unfortunately, the high cost of highly equipped tools and instruments place a barrier in research activities at local level. For this purpose, collaborative efforts are essential between multiple stakeholders from diverse areas of origin *i.e.* clinical dietitians, government entities, scientists, NGOs, agronomists, data analysts, and public health nutritionists. Furthermore, the blend of traditional dietary intake and modern isolation techniques is the major novel initiative neglected so far. This will ensure consumer acceptance and optimal provision of nutrients. Additionally, entrepreneurial platforms for commercialization of consumer-friendly food products must be initiated in future. The incorporation of lifestyle modifications through diet and physical activity helps to mitigate comorbidities in all age groups. This in return may reduce the burden on health and food sectors, thus, strengthening a country's economy.

## List of abbreviations

ADLs, Activities of Daily Life
AI-driven nutrition, Artificial Intelligence Nutrition
PEM, Protein Energy Malnutrition
UPP, Ubiquitin-Proteasome Pathway
UPS, Ubiquitin-Proteasome System
MPS, Muscle Protein Synthesis
NADPH, Nicotinamide Adenine Dinucleotide Phosphate
ROS, Reactive Oxygen Species
DOX, Doxorubicin-induced skeletal muscle atrophy
ADP, Adenosine Diphosphate

SR, Sarcoplasmic Reticulum
HSP72 levels, Heat Shock Protein 72
MEKK4, Mitogen-activated protein kinase kinase 4
Gadd45α, Growth Arrest and DNA Damage-inducible 45 alpha
TFAM, Mitochondrial Transcription Factor A
SOD, Superoxide Dismutase
MV, Mechanical Ventilation-induced diaphragmatic atrophy
EAA, Essential Amino Acids
KEAP, Kelch-like ECH-associated protein signaling pathway
mTOR, Mammalian Target of Rapamycin

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## Conflict of interest

The authors have no financial nor non-financial interests to declare.

## Contributions

IA, conceptualization, data curation, formal analysis, methodology, writing - original draft, resources; AR, writing - review & editing; SN, project administration; FS, data analysis via formal software, writing - review & editing.

## Data availability

The data supporting this review can be accessed via hyperlinks (DOI/accession numbers) of previously published literature listed in the references.

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