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Review

Disuse-Induced Skeletal Muscle Atrophy: Pathogenesis and Therapeutic Potential of Melatonin

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Abstract

Skeletal muscle is a highly adaptable and plastic tissue essential for voluntary movement, posture, metabolic regulation, and whole-body homeostasis. Nevertheless, extended periods of muscle disuse, whether caused by immobilization, prolonged bed rest, aging, or microgravity, precipitate progressive skeletal muscle atrophy. This pathophysiological process is characterized by pronounced structural degeneration, substantial reductions in muscle mass and contractile strength, and diminished regenerative capacity. The underlying mechanisms involve myofiber atrophy, extracellular matrix remodeling, mitochondrial dysfunction, depletion of satellite cells, and perturbations in muscle homeostasis, all of which collectively impair muscle function and adversely affect quality of life. This review provides a comprehensive overview of skeletal muscle biology, encompassing its structure, development, and postnatal regeneration, and discusses the pathogenesis of disuse-induced skeletal muscle atrophy, focusing on structural alterations, experimental animal models, human studies, and underlying mechanisms. It also evaluates melatonin as a potential therapeutic candidate, owing to its potent antioxidant, anti-inflammatory, and mitochondria-protective properties. Despite extensive investigations into the effects of melatonin across various models of skeletal muscle atrophy, evidence specifically addressing its effects on disuse-induced muscle atrophy remains limited. Accordingly, this review critically synthesizes the available evidence, evaluates methodological limitations, identifies key research gaps, and delineates future research priorities to clarify the therapeutic potential of melatonin in disuse-induced skeletal muscle atrophy.

Keywords: skeletal muscle; disuse-induced muscle atrophy; muscle unloading; structural alterations; mechanisms of muscle wasting; melatonin; muscle regeneration

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1. Introduction

Skeletal muscle is a highly plastic tissue that continuously adapts to mechanical loading and physiological demands. Prolonged reduction in mechanical loading or contractile activity disrupts muscle homeostasis and leads to progressive loss of muscle mass and function. This condition, commonly referred to as disuse-induced muscle atrophy, occurs during prolonged immobilization, bed rest, limb unloading, reduced physical activity, and

other states of mechanical unloading, and represents an important cause of muscle weakness and functional decline [1–5].

Disuse-induced muscle atrophy involves changes at multiple levels, extending from muscle fiber size and composition to extracellular matrix organization, vascular supply, satellite cell activity, myofibrillar and sarcomere integrity, and mitochondrial structure and function [2,6–11]. These alterations are accompanied by reduced anabolic signaling and protein synthesis, activation of proteolytic pathways, oxidative stress, altered calcium homeostasis, mitochondrial dysfunction, and disturbances in endocrine and circadian regulation [12–14]. However, the contributions of these mechanisms vary across muscles, fiber types, experimental models, and stages of disuse. Thus, current evidence supports disuse atrophy as a multifactorial process involving interconnected structural and molecular changes rather than a single dominant pathway.

Melatonin is an endogenous indoleamine with established circadian functions and additional antioxidant, anti-inflammatory, and mitochondrial-regulatory properties [15–19]. These effects provide a biological basis for its potential to counteract the cellular disturbances associated with muscle disuse. Experimental studies have reported protective effects of melatonin against skeletal muscle atrophy, including evidence from an immobilization-related model, with reported effects on muscle condition, morphology, oxidative status, and selected molecular outcomes [20–23]. Nevertheless, the evidence remains heterogeneous because of differences in experimental models, treatment protocols, and outcome measures.

Although previous reviews have addressed various aspects of disuse-induced skeletal muscle atrophy, a comprehensive synthesis integrating structural and ultrastructural alterations with their underlying molecular mechanisms remains lacking, particularly regarding muscle-specific, fiber-type-dependent, and sex-related differences. Moreover, a critical evaluation of the available evidence on melatonin is needed, with particular emphasis on distinguishing findings from direct mechanical disuse models from those obtained in other contexts of skeletal muscle atrophy.

Accordingly, this review therefore aims to characterize the morphological, cellular, ultrastructural, and molecular alterations associated with disuse-induced skeletal muscle atrophy; to critically evaluate the available evidence on melatonin as a potential protective intervention, including its biological actions and proposed mechanisms; and to identify the major limitations and knowledge gaps in the current literature. Taken together, the available evidence indicates that disuse atrophy involves interconnected disturbances across multiple levels of skeletal muscle organization, while melatonin represents a promising, yet incompletely characterized, strategy for mitigating these changes. This is a narrative review rather than a systematic one, so it does not attempt to cover the literature exhaustively.

2. Muscle Structure, Composition, and Physiological Functions

Muscle tissue is composed of highly specialized fibers whose primary physiological role is to generate contractile force. Based on distinct structural and functional characteristics, muscle tissue is broadly classified into three main types: striated skeletal muscle (the voluntary component that constitutes the bulk of total muscle mass), striated cardiac muscle (the specialized involuntary muscle of the heart), and unstriated smooth muscle (the involuntary muscle lining hollow internal organs) [24–27].

Among these variants, skeletal muscle plays a fundamental role in locomotion, posture, and systemic metabolic regulation. This functional breadth makes it one of the most extensively studied tissues, particularly within the contexts of adaptation, regeneration, and pathological conditions such as wasting and atrophy. Skeletal muscle accounts for approximately 40% of total body mass, harbors 50–75% of the body's total protein content, and contributes to 30–50% of whole-body protein turnover. Structurally, healthy skeletal

muscle is a metabolically active tissue composed mainly of water (~75%), proteins (~20%), and a smaller fraction (~5%) of inorganic salts, minerals, lipids, and carbohydrates [3,28,29].

From a mechanical perspective, skeletal muscle functions as a biological transducer, converting chemical energy into mechanical work to generate force, power, maintain structural posture, and produce voluntary movements. These coordinated actions support daily functional activities, facilitate occupational and social interactions, promote systemic health, and preserve long-term functional independence. From a metabolic standpoint, skeletal muscle is a major contributor to basal energy metabolism, acts as a primary physiological reservoir for amino acids and carbohydrates, generates heat during thermoregulation, and consumes the majority of circulating oxygen and fuel substrates during physical activity and exercise [3,30]. Furthermore, during periods of prolonged starvation, this amino acid reservoir serves as a critical substrate source for the synthesis of organ-specific proteins in vital tissues, such as the skin, brain, and heart, while simultaneously maintaining glucose homeostasis [31].

In addition to its structural and metabolic roles, skeletal muscle demonstrates remarkable plasticity, adapting dynamically to changes in activity levels, nutritional state, health conditions, and genetic background [32].

3. Embryonic Development and Postnatal Muscle Regeneration

Skeletal muscles originate from the paraxial mesoderm during embryonic development, where somites segmentally form and differentiate into three primary lineages: the sclerotome (giving rise to vertebrae), the dermatome (forming dermal tissue), and the myotome (forming muscle). Muscle progenitor cells, or myoblasts, originate from mesenchymal stem cells residing within these somites [30,33,34]. While a subset of myoblasts remains localized within the somites to form the spinal musculature, other progenitor populations migrate extensively to drive the morphogenesis of limb and body wall muscles [35,36]. During embryogenesis, these myoblasts undergo a highly coordinated fusion process known as myogenesis, forming multinucleated myofibers that serve as the foundational units of functional skeletal muscle tissue [35].

Following embryogenesis, postnatal skeletal muscle growth, maintenance, and repair transition to distinct cellular mechanisms. A key role in this process is played by satellite cells (SCs), which reside in a quiescent niche located between the basal lamina and the sarcolemma of individual muscle fibers. SCs represent the primary source of postnatal myogenic progenitors and are indispensable for both developmental muscle hypertrophic growth and regenerative responses following adult tissue injury [37].

4. Hierarchical and Ultrastructural Organization

At the macroscopic level, skeletal muscles are firmly anchored to bones via dense connective tissue tendons, which serve as the primary structures for transmitting force during movement. Toward the muscle belly, the tendon transitions into the musculotendinous junction and subsequently continues into the epimysium, a dense connective tissue sheath that envelopes the entire muscle organ. Beneath the epimysium, the muscle belly is subdivided into smaller internal bundles known as fascicles. Each fascicle is separated and supported by the perimysium, which provides structural reinforcement and mechanical isolation. Within each fascicle, individual muscle fibers are encased by a delicate connective tissue matrix termed the endomysium, which is composed primarily of reticular fibers (Figure 1). In healthy tissue, cross-sectional views reveal that muscle fibers exhibit a characteristic polygonal morphology with highly uniform diameters and peripherally located, vesicular nuclei, reflecting a highly ordered architecture [11,38].

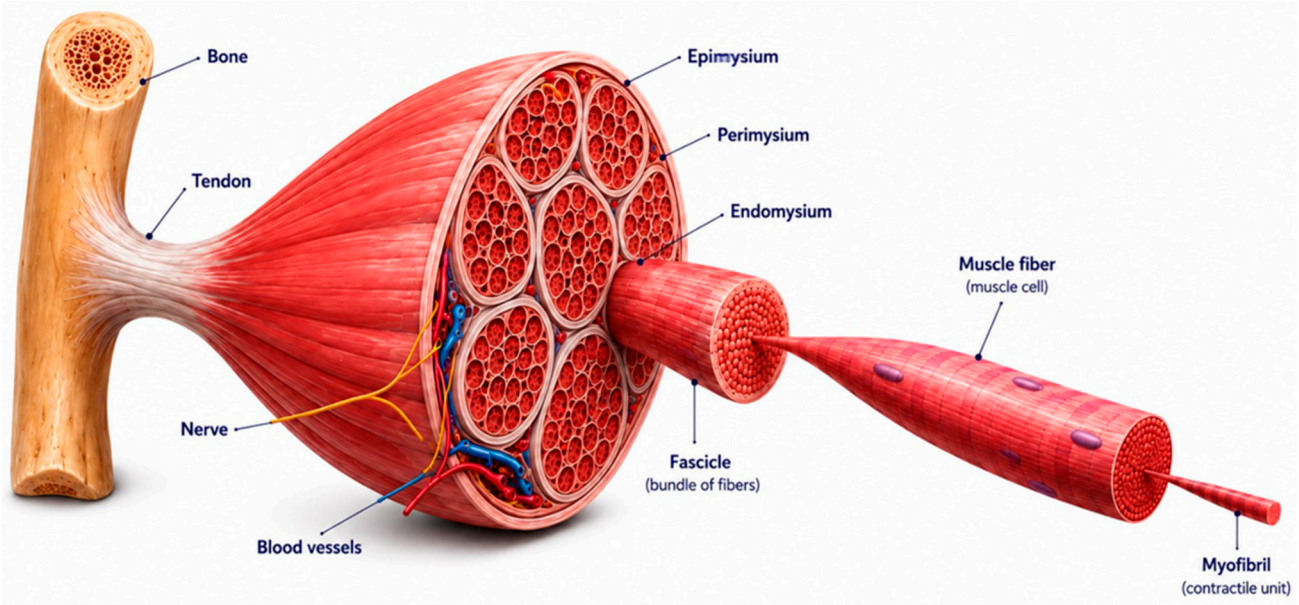

Figure 1. Hierarchical organization of skeletal muscle. Skeletal muscles are organized in a hierarchical manner, extending from the whole muscle to fascicles, individual muscle fibers, and myofibrils. The entire muscle is surrounded by the epimysium and is composed of multiple fascicles, each enclosed by the perimysium. Each fascicle contains numerous multinucleated muscle fibers, which are individually surrounded by the endomysium. Within each muscle fiber, numerous myofibrils are arranged longitudinally and represent the contractile components composed of repeating sarcomeres. Skeletal muscle is connected to bone through tendons and is supplied by blood vessels and nerves.

At the ultrastructural level, each muscle fiber contains numerous cylindrical myofibrils that occupy nearly 80% of the total intracellular volume. These myofibrils represent the core contractile apparatus, composed of interdigitating thick (myosin) and thin (actin) myofilaments organized into repeating units called sarcomeres, which constitute the fundamental structural and functional units of muscle contraction. When viewed longitudinally, skeletal muscle fibers display alternating dark anisotropic (A) bands and light isotropic (I) bands, which generate the characteristic striated appearance under microscopy. The light I band is symmetrically bisected by the dense Z-line (Z-disc), which serves as the anchoring matrix for thin actin filaments and defines the physical boundaries of a single sarcomere (Figure 2). Sarcomere length is relatively conserved within species, typically ranging from 2.0 to 2.5 μm when measured between adjacent Z-discs. Disuse induces radial atrophy of muscle fascicles, partly associated with a reduction in muscle fiber size. However, the ultrastructural mechanisms underlying these changes remain incompletely understood, particularly the potential contributions of myofibrillar atrophy and myofibril hypoplasia. Surrounding these myofibrillar tracks are abundant networks of mitochondria, strategically aligned in rows to satisfy the immense ATP demands of contraction. Mitochondrial adaptations to mechanical unloading include preferential alterations in subsarcolemmal mitochondria compared with intermyofibrillar mitochondria, accompanied by changes in the expression of genes involved in mitochondrial biogenesis and morphology. These are tightly integrated with an extensive sarcoplasmic reticulum (SR), a specialized membranous system that precisely regulates calcium storage, release, and reuptake during excitation-contraction coupling [11,38–41].

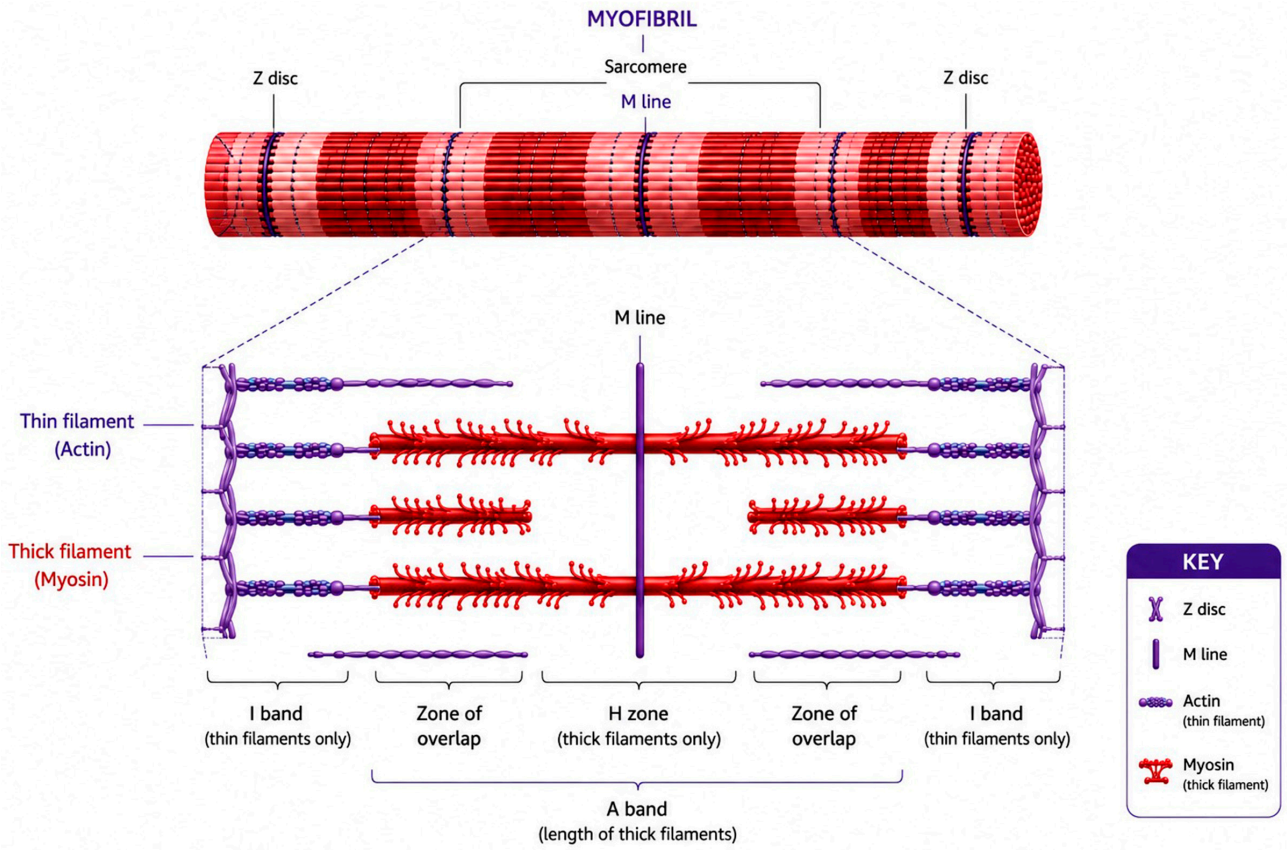

Figure 2. Ultrastructure of the skeletal muscle sarcomere. Schematic representation of the ultrastructural organization of a myofibril, illustrating the repeating sarcomere units. Each sarcomere extends between two Z discs and contains thin actin filaments and thick myosin filaments. The central M line anchors the thick filaments, while the I band contains thin filaments only. The A band corresponds to the entire length of the thick filaments and includes regions of overlap between actin and myosin. The H zone represents the central region containing thick filaments without overlap with thin filaments.

5. Definition, Pathophysiology, and Risk Factors of Disuse-Induced Muscle Atrophy

Skeletal muscle atrophy is a pathological condition characterized by a progressive reduction in muscle mass, accompanied by impaired contractile force, metabolic dysfunction, and compromised functional capacity [42–44]. It represents a widespread clinical complication affecting both humans and animals in response to diverse physiological and pathological stimuli [45,46]. Muscle atrophy can arise from different underlying conditions and may be broadly distinguished according to the nature of the initiating stimulus. Adaptive reductions in muscle size may occur in response to reduced muscle use or mechanical demand, whereas pathological muscle wasting may develop in association with prolonged immobilization, denervation, fasting or inadequate nutritional support, systemic diseases, and other catabolic conditions [42,43,47–49]. Among the different forms of muscle atrophy, disuse atrophy arises primarily from decreased contractile activity and reduced mechanical loading [47,48].

Disuse-induced muscle atrophy should be distinguished from muscle wasting primarily caused by denervation, systemic disease, cancer cachexia, or other pathological conditions in which additional neural, inflammatory, endocrine, metabolic, or nutritional mechanisms contribute to muscle loss [42,48,50–53]. In particular, disease-associated catabolic and inflammatory factors may act synergistically with reduced mechanical loading and amplify the progression of muscle atrophy [48].

The term disuse has been used to describe several experimental and clinical conditions involving reduced mechanical loading, including prolonged bed rest, spaceflight or microgravity, hindlimb suspension, unilateral limb suspension, and limb or joint immobilization. Because these models can impose different mechanical conditions on skeletal muscle, particularly with respect to muscle length and passive tension, Sayed et al. [38] proposed a precise operational definition of disuse. They defined disuse as any condition in which there is a maintenance or reduction in mean passive tension, together with a reduction in mean active tension generated by the muscle. Based on this definition, Sayed et al. [38] focused their review on disuse-induced structural adaptations in otherwise healthy individuals, distinguishing these responses from disease-associated muscle wasting, in which circulating atrophic factors, such as cytokines and cortisol, may provide additional catabolic stimuli. Furthermore, they excluded denervation as a representative model of disuse because it can induce additional pathological events, including muscle fiber death and a concomitant regenerative response, which are rarely observed in other disuse models [38].

Under sustained mechanical unloading, reduced contractile activity disrupts muscle protein homeostasis, resulting in an imbalance between muscle protein synthesis and degradation and a progressive loss of muscle proteins and muscle fiber size [43,48,54]. This response is accompanied by interconnected structural and cellular adaptations involving myofibrillar organization, extracellular matrix remodeling, mitochondrial function, oxidative stress, and intracellular signalling pathways [38,48,55,56]. The magnitude and progression of disuse-induced atrophy can vary according to the duration and degree of unloading and the muscle examined [54].

Disuse atrophy frequently develops in clinical settings involving musculoskeletal trauma (e.g., torn ligaments and bone fractures), spinal cord injuries, degenerative joint diseases, and primary myopathies. It is also a hallmark consequence of prolonged clinical bed rest, joint immobilization using orthopedic casts or limb braces, and exposure to microgravity during spaceflight missions [54,57–59]. Additional systemic risk factors that accelerate wasting include reduced neural activation, chronic low-grade inflammation driven by elevated circulating cytokines, hypercortisolemia (increased glucocorticoids), and protein-energy malnutrition [48,54]. These factors should be considered potential modifiers or aggravating influences rather than defining components of disuse itself, because the defining stimulus of disuse is the sustained reduction in mechanical loading and contractile activity [38,48]. Collectively, these conditions promote progressive muscle wasting and functional deterioration [13].

6. Models of Disuse-Induced Skeletal Muscle Atrophy

6.1. Animal Models of Disuse-Induced Muscle Atrophy

Experimental models of disuse-induced muscle atrophy include hindlimb unloading (HLU) in rodents [60–65], immobilization models in rats and mice [66–71], and unilateral immobilization models that allow comparison with the contralateral limb [72–75]. Other approaches include EDL-specific disuse models [76], gravitational unloading models [77], and reduced cage-volume models [78]. More recent studies have also examined unilateral hindlimb immobilization followed by remobilization to investigate recovery after disuse [79], as well as casting-based hindlimb immobilization [80] and bilateral hindlimb immobilization [81]. Collectively, these models reproduce different forms of mechanical unloading and reduced muscle use and have been used to investigate the structural, molecular, and functional consequences of disuse-induced muscle atrophy. Representative animal studies investigating disuse-induced skeletal muscle atrophy, including the experimental model, duration, muscle examined, principal outcomes, and study limitations, are summarized in Table 1.

Table 1. Representative animal studies investigating disuse-induced skeletal muscle atrophy.

Study	Animal/Model	Disuse Protocol	Main Findings	Limitation
Gao et al. [13]	Rodent disuse models	Reviewed hindlimb unloading and other mechanical unloading models	Mechanical unloading induces substantial skeletal muscle atrophy, particularly in postural slow-twitch muscles such as SOL, involving altered protein turnover and multiple molecular and cellular pathways.	Review study; therefore, it does not provide primary morphological, structural, ultrastructural, or functional data from a single experimental model.
Ohira et al. [60]	Rodent—HLU	Hindlimb unloading and other gravitational unloading/reloading models	The review summarizes evidence that muscle activity (EMG) and neuromuscular responses change rapidly during unloading, including changes in muscle activity and EMG responses during unloading and reloading.	As a review, it does not provide an original experimental protocol or a unified assessment of structural, ultrastructural, molecular, and functional outcomes within the same experimental cohort.
Ohira et al. [61]	Rat—HLU	14 days hindlimb suspension	SOL muscle weight decreased by approximately 34% after 14 days of suspension. A partial shift in MHC expression occurred (about 9% of fibers), while SDH and GPD activities were not significantly changed.	Provided morphological and fiber-level assessments together with MHC-related and enzymatic changes, but did not comprehensively integrate ultrastructural, molecular-signaling, and functional outcomes.
Zhang et al. [65]	Rat—HLU	14 days hindlimb suspension	HLU markedly reduced SOL muscle wet weight (−47.3% in the vehicle group) and the SOL muscle wet weight/body weight ratio (−48.1%), indicating substantial muscle atrophy; TMP treatment attenuated these losses.	Integrated morphological, functional, and protein-level changes, including CSA, fiber-type composition, contractile properties, fatigability, and calpain/MuRF1-related markers, but did not include ultrastructural characterization.
Kyparos et al. [62]	Rat—HLU	Hindlimb unloading	Plantar foot stimulation attenuated HLU-induced loss of muscle fiber CSA in the SOL and medial gastrocnemius.	A countermeasure-focused study limited to histochemical and morphometric assessment of selected muscles and fiber types, without molecular, ultrastructural, or direct functional assessment.
Tsika et al. [63]	Female rats—HLU	6 weeks HLS	HLS reduced PLT and SOL muscle weight and myofibrillar protein, with a shift toward fast myosin isotypes. Steroid treatment partially attenuated muscle and protein loss but did not prevent the isomyosin shift.	Examined muscle mass, myofibrillar protein, and myosin isoform expression, providing structural/protein and molecular information, but without comprehensive histological, ultrastructural, or functional assessment.
Du et al. [76]	Female rats—EDL disuse model	Tail suspension + unilateral plaster-cast immobilization	Combined tail suspension and immobilization caused faster and greater EDL CSA loss than tail suspension alone, with a shift toward glycolytic Type IIB fibers.	Focused mainly on muscle/fiber morphology and fiber-type composition; although combined and suspension-only models were compared, the individual contribution of each disuse component within the combined condition could not be fully isolated. Ultrastructural and functional outcomes were not addressed.
Booth & Seider. [66]	Rat—immobilization	90 days hindlimb immobilization	SOL muscle weight and protein content recovered by 14 days after remobilization, whereas maximal isometric tension required 120 days to recover.	Included biochemical and functional recovery measures, particularly muscle protein, ATP-related parameters, muscle mass, and maximal isometric tension, but provided limited morphological and ultrastructural characterization.

Table 1. *Cont.*

Study	Animal/Model	Disuse Protocol	Main Findings	Limitation
Fournier et al. [71]	Adult female rats—immobilization	28 days bilateral hindlimb immobilization at different muscle lengths	SOL and MG muscle weight decreased when immobilized in shortened or neutral, but not lengthened, positions.	Primarily assessed EMG/IEMG activity across different immobilization positions together with muscle mass, but provided limited molecular, ultrastructural, and direct force-related functional characterization.
Itai et al. [64]	Male rats—HLU	5 weeks hindlimb unloading	SOL mass decreased to 52% and fiber CSA to 22% of control; mass recovered faster than fiber CSA after reloading.	Provided muscle mass, fiber CSA, and histological evidence of recovery, including regenerative fibers, but did not comprehensively examine ultrastructural or molecular mechanisms.
Okita et al. [67]	Male rats—immobilization	4 weeks bilateral ankle immobilization followed by 1- or 3-week remobilization with or without 30 min/day stretching	Immobilization reduced soleus muscle wet weight and Type I and II fiber diameters. Short-duration stretching during remobilization accelerated recovery of Type I fiber diameter after 1 week and both Type I and II fiber diameters after 3 weeks but did not restore the immobilization-induced shift in fiber-type distribution.	Comprehensive morphological and histochemical assessment of the SOL, including muscle weight, fiber diameter, fiber-type distribution, and ankle range of motion, but without molecular, ultrastructural, or direct muscle functional assessment.
Vazeille et al. [68]	Rat—immobilization	Hindlimb immobilization for 4–8 days, followed by 10–40 days recovery	SOL and gastrocnemius showed greater atrophy than EDL and TA. Polyubiquitinated proteins and proteasome activity increased during early atrophy, whereas the ubiquitin–proteasome pathway normalized early during recovery. Mitochondria-associated apoptotic signaling declined later during recovery.	Provided an integrated assessment of muscle morphology together with proteolytic and mitochondria-associated apoptotic pathways; however, ultrastructural changes and direct functional performance were not comprehensively assessed.
Lang et al. [72]	Mouse—unilateral immobilization	Hindlimb immobilization for 5–7 days, followed by recovery at various time points, including 10 days	Immobilization reduced gastrocnemius mass and protein synthesis while increasing proteasome activity and transiently increasing atrogin-1 and MuRF1 expression. During recovery, WT mice restored muscle mass by day 10, whereas mTOR+/− mice showed delayed regrowth associated with impaired protein synthesis, altered mTORC1 signaling, sustained inflammation, and failure of compensatory IGF-I upregulation.	Focused on muscle mass and extensive molecular/protein metabolic mechanisms, but did not include histological or myofiber morphometric assessment, ultrastructural characterization, or direct muscle functional assessment.
Ohira et al. [77]	Rat gravitational unloading models	Reviewed hindlimb unloading and related unloading conditions	Atrophy was greatest in slow extensors, followed by fast extensors and fast flexors; slow muscles were more responsive to unloading.	Review study integrating responses across unloading models; therefore, findings cannot be attributed to a single experimental disuse protocol or used to provide a unified structural, ultrastructural, molecular, and functional assessment.

Table 1. *Cont.*

Study	Animal/Model	Disuse Protocol	Main Findings	Limitation
Onda et al. [69]	Mouse—immobilization	Spiral-wire hindlimb immobilization for 3–10 days	Immobilization reduced SOL and PLT mass and increased MAFbx/atrogin-1 and MuRF1 expression.	Focused on muscle mass and molecular markers of atrophy, particularly MAFbx/atrogin-1 and MuRF1, with limited characterization of morphological, ultrastructural, and functional outcomes.
Okamoto et al. [70]	Male mice—immobilization	Hindlimb immobilization for 3, 7, 14, and 21 days	SOL and PLT showed similar muscle mass loss, but MAFbx/Atrogin-1 and MuRF1 expression were greater in PLT during early atrophy.	Focused on muscle mass, protein content, and time-dependent MAFbx/Atrogin-1 and MuRF1 expression, providing morphological/molecular evidence but limited histological, ultrastructural, and functional assessment.
Kincheloe et al. [73]	Mouse—unilateral immobilization	Hindlimb immobilization for 3–7 days	Increasing protein synthesis did not prevent muscle atrophy, suggesting that compensatory mechanisms may overcome enhanced protein synthesis during disuse.	Extensive molecular assessment, but no histological, fiber-level, structural, ultrastructural, or functional assessment. Although both sexes were included, they were combined after no significant sex differences were detected.
Marmonti et al. [78]	Rat—reduced cage volume	7, 14, or 28 days reduced spontaneous activity	SOL mass decreased by approximately 7.3%, 10.5%, and 13.2% after 7, 14, and 28 days, respectively.	Assessed muscle mass, fiber CSA, and grip force, providing morphological and functional outcomes, but did not include molecular-signaling or ultrastructural characterization.
Rahman et al. [79]	Unilateral hindlimb immobilization followed by remobilization	mt-Keima mice (sex not reported); 7 days immobilization + 7 days remobilization; n = 5–8/group	Immobilization caused fast-fiber atrophy, muscle weakness, increased mitophagic flux, impaired mitochondrial respiration, and increased oxidative stress. Suppression of mitophagy exacerbated IIX/IIB atrophy, supporting a protective role of mitophagy.	Included fiber-type-specific CSA analysis and muscle force/fatigue testing but did not include ultrastructural analysis; the pharmacological modulators (NAC and colchicine) were not mitophagy-specific, limiting mechanistic interpretation; sex and some protocol details were not reported.
Michel, Godwin, Kerr et al. [80]	Hindlimb immobilization by casting	Female Wistar rats (~4 months old); gastrocnemius muscle; 10 days of hindlimb immobilization (HLI, n = 12) vs. sham/control casting (CTL, n = 12)	Immobilization increased CHOP protein expression, nuclear CHOP localization, and CHOP-regulated gene expression, including Gadd34 (~35-fold) and Bax; normalized gastrocnemius weight was reduced by 33.6%. CHOP protein expression was strongly negatively correlated with normalized gastrocnemius weight.	Assessed muscle mass and molecular/biochemical responses, including CHOP expression and related gene markers, but did not include histological/morphometric, functional, or ultrastructural characterization; causal involvement of CHOP was not tested experimentally.
Dalle et al. [74]	Unilateral hindlimb immobilization	Young and old male C57BL/6 mice; 5 days; rimonabant 10 mg/kg/day	Rimonabant partly attenuated gastrocnemius mass loss but unexpectedly increased the reduction in muscle protein synthesis; the mechanism of muscle preservation remained unclear.	Males only and short-term immobilization. Assessment focused mainly on muscle mass, protein synthesis, and molecular markers, without comprehensive structural, ultrastructural, or functional characterization.

Table 1. *Cont.*

Study	Animal/Model	Disuse Protocol	Main Findings	Limitation
Wang et al. [81]	Bilateral hindlimb immobilization	Male C57BL/6J mice; 7 days; $OCN^{-/-}$ and WT; complementary porcine myotubes	Immobilization reduced circulating undercarboxylated OCN by ~70%. OCN deficiency aggravated atrophy, whereas exogenous OCN attenuated atrophy and promoted recovery through the Piezo1–OCN–Gprc6a–Fndc5/Irisin pathway.	Male mice only; although muscle mass, H&E histology, myofiber CSA, molecular signaling, and exercise capacity were assessed, comprehensive ultrastructural characterization was not performed.
Sayed et al. [75]	Male mice; young (4 months) and old (24 months); unilateral hindlimb immobilization	10 days unilateral hindlimb immobilization; TA, EDL, PLT, SOL, GAST, and FDL were assessed from immobilized and contralateral limbs	Immobilization induced muscle mass loss and radial atrophy, with effects varying among muscles and age groups. In SERCA1-positive fibres, fibre atrophy was driven predominantly by a marked reduction in the number of myofibrils per fibre, with a smaller contribution from reduced myofibril CSA.	Male mice only; the study did not assess molecular mechanisms underlying the observed ultrastructural changes, and the cross-sectional nature of the study precludes definitive conclusions about causality or the temporal sequence of the structural adaptations.

Table 1 abbreviations: CSA = cross-sectional area; CHOP = C/EBP homologous protein; EDL = extensor digitorum longus; EMG = electromyography; FDL = flexor digitorum longus; GAS/MG = gastrocnemius/medial gastrocnemius; Gadd34 = growth arrest and DNA damage-inducible 34; H&E = hematoxylin and eosin; HLI = hindlimb immobilization; HLU = hindlimb unloading; HLS = hindlimb suspension; IEMG = integrated electromyography; IIX = type IIX muscle fibers; IIB = type IIB muscle fibers; MAFbx = muscle atrophy F-box/atrogin-1; MHC = myosin heavy chain; mt-Keima = mitochondria-targeted Keima; MuRF1 = muscle RING-finger protein 1; NAC = N-acetylcysteine; OCN = osteocalcin; $OCN^{-/-}$ = osteocalcin knockout; PLT = plantaris; SERCA1 = sarco/endoplasmic reticulum Ca^{2+}-ATPase 1; SOL = soleus; TA = tibialis anterior; TMP = tetramethylpyrazine; WT = wild type.

Evidence from animal disuse models shows that disuse-induced muscle atrophy varies by experimental model, muscle type, fiber characteristics, disuse duration, and recovery period, with muscle-specific differences in structural and molecular responses. However, most studies have assessed selected aspects of atrophy rather than integrating structural, ultrastructural, molecular, and functional outcomes within the same model. Recovery studies further indicate that restoring muscle mass does not necessarily restore structural and functional characteristics. Recent work by Sayed et al. [75] extended disuse research to include quantitative myofibrillar analysis, identifying reduced myofibril number as a major contributor to fiber atrophy. However, the cross-sectional design limited causal and temporal inference, and the molecular mechanisms underlying the ultrastructural changes remain unresolved. Ultimately, the key knowledge gap lies in the limited integration of muscle-level, fiber-level, myofibrillar, molecular, and functional responses, particularly in relation to sex, muscle type, and fiber composition.

6.2. Human Models of Disuse-Induced Muscle Atrophy

Although disuse-induced muscle atrophy is commonly studied in animal models, these findings have substantial implications for human health. Several clinical and experimental conditions involve prolonged mechanical unloading or inactivity that closely resemble experimental models of disuse. In humans, commonly used models include prolonged bed rest [82,83], unilateral lower-limb suspension [68,69,79], limb immobilization [84–89], and spaceflight/microgravity [90–92]. Representative human studies investigating the structural, functional, and molecular consequences of disuse-induced muscle atrophy are summarized in Table 2.

Table 2. Representative human evidence for skeletal muscle atrophy across different atrophy-inducing conditions.

Study	Disuse Model	Participants/Duration	Main Outcomes/Findings	Limitations
Deitrick et al. [85]	Immobilization using bi-valved plaster casts extending from the umbilicus to the toes	4 healthy young men; 6–7 weeks immobilization, preceded by 5–7 weeks control and followed by 4–6 weeks recovery	Increased nitrogen/mineral losses and decreased muscle mass and strength, with a 6.9% reduction in basal metabolic rate. Most changes recovered within 3–4 weeks; exercise tolerance and leg girth required 4–6 weeks.	Very small, male-only sample; historical bilateral lower-limb/pelvic casting model combined with bed rest, limiting comparison with localized disuse models; no direct histological, ultrastructural, or molecular assessment of muscle.
LeBlanc et al. [83]	Continuous bed rest	8 healthy men; 17 weeks bed rest + 8 weeks reambulation	Lean tissue loss was 3.9 ± 2.1 kg, mainly from the lower limbs. Limb muscle volume and thigh/calf strength decreased and recovered rapidly during reambulation.	Small, male-only sample; whole-body bed rest limits separation of local unloading effects from systemic responses; assessment relied on MRI, DPA, nitrogen balance, and muscle performance, without biopsy-based fiber-level structural or molecular analysis.
Alkner & Tesch. [82]	6° head-down-tilt bed rest, with or without resistance exercise	17 healthy men; 90 days	In the bed rest-only group, knee extensor and plantar flexor volume decreased by 18% and 29%, respectively, with 31–60% (knee extension) and 37–56% (plantar flexion) reductions in torque/power and decreased EMG activity. Resistance exercise prevented knee extensor atrophy but only attenuated plantar flexor atrophy (−15%).	Small groups, men only; only knee extensors and plantar flexors assessed; whole-body bed rest (not localized disuse); countermeasure results specific to the exercise device/protocol used.
Widrick et al. [92]	17-day spaceflight	4 male astronauts; 17 days	Soleus type I fibers showed reduced Ca^{2+}-activated force (0.99 → 0.78 mN) and increased unloaded shortening velocity (0.64 → 0.83 fiber lengths/s).	Very small, male-only sample; spaceflight includes factors beyond mechanical unloading, limiting attribution of the observed changes specifically to unloading; in-flight exercise countermeasures may have attenuated the effects; analysis was restricted to soleus type I fibers and a single immediate post-flight time point.
Tesch et al. [91]	17-day spaceflight (STS-78)	4 male astronauts; 17 days	Knee-extensor strength decreased ~10%, while knee-extensor and gluteal CSA decreased ~8%; knee-flexor CSA was largely unchanged.	Very small sample and multiple spaceflight-related physiological influences.
Fitts et al. [90]	Prolonged spaceflight/microgravity	9 ISS crew members; ~180 days	Soleus type I fibers showed marked atrophy, with ~20% reduction in fiber diameter (98 → 79 µm) and ~35% reduction in peak force (0.86 → 0.56 mN); peak power declined across fiber types. Unloaded shortening velocity (V0) decreased by 21% (soleus) and 18% (gastrocnemius) in type I fibers, associated with increased thin filament density.	Small astronaut sample with only pre-flight and immediate post-flight sampling; no longitudinal recovery assessment; the amount of in-flight treadmill exercise was associated with the extent of fiber atrophy, potentially influencing the observed response.

Table 2. *Cont.*

Study	Disuse Model	Participants/Duration	Main Outcomes/Findings	Limitations
Hather et al. [93]	Unilateral lower-limb suspension (ULLS)	8 subjects; 6 weeks	Thigh CSA decreased 12%; knee-extensor and knee-flexor CSA decreased 16% and 7%, respectively. Soleus and gastrocnemius CSA decreased 17% and 26%, respectively; Average vastus lateralis fiber CSA decreased by 14% (type I −12%, type II −15%), with no change in capillary number around fibers.	ULLS prevented weight bearing on the suspended limb but permitted crutch-assisted ambulation and freedom of movement at the ankle, knee, and hip; therefore, it represents unloading rather than complete limb immobilization.
De Boer et al. [94]	Unilateral lower-limb suspension	17 men (9 ULLS, 8 controls); 23 days	Knee-extensor torque decreased 14.8% by day 14 and 21.0% by day 23; CSA decreased 5.2% and 10.0%, respectively. VL fascicle length decreased 7.7% by day 23.	ULLS preserves residual muscle activation and afferent input, so it does not fully reproduce complete immobilization; findings may not generalize to casting-induced disuse.
Yasuda et al. [89]	Unilateral leg immobilization using a knee brace at 60° flexion	27 adults (13 men, 14 women); 14 days	Quadriceps CSA decreased similarly in men and women (5.7% vs. 5.9%) and decreased leg lean mass by 3.7% and 2.7%, respectively. Type I, IIa, and IIx fiber areas decreased by 4.8%, 7.9%, and 10.7% in men and 5.9%, 8.8%, and 10.8% in women, respectively, without fiber-type transformation. Women showed greater losses in specific strength, particularly during slow concentric contractions (16.6% vs. 4.7%) and isometric contractions (17.1% vs. 3.1%; $p = 0.055$), despite similar muscle atrophy.	Short immobilization period (14 days) with no post-immobilization recovery assessment; the knee-brace model did not completely eliminate limb movement or involuntary muscle activity, particularly at the hip; fiber-level analysis was limited to vastus lateralis, and the proposed neural contribution to sex-related strength loss was not directly assessed.
Thom et al. [88]	Lower-limb cast immobilization	8 healthy women; 10 days	Quadriceps CSA decreased 11.8% and 1-RM leg-extension strength 41.6%. SR Ca^{2+} uptake decreased by ~20%, whereas Ca^{2+} release and ATPase activity were unchanged.	Small, female-only sample and short immobilization period.
Psatha et al. [87]	Lower-leg cast immobilization following ankle fracture	18 patients (8 men, 10 women); ~6 weeks	Total muscle volume decreased 17%. CSA losses were greatest in gastrocnemius medialis (23.3%), soleus (19.0%), gastrocnemius lateralis (17.1%), and tibialis anterior (10.7%); contralateral CSA also decreased.	Clinical fracture-related model; earliest assessment was at day 3 in only three patients, with day 5 used as the baseline, potentially missing early atrophy; the contralateral leg also showed significant muscle loss, limiting its use as an unaffected control.
Michel et al. [86]	Unilateral left-leg immobilization using a locking brace and crutches	21 young adults (18–35 y); 16 males and 5 females; 10 resistance-trained and 11 untrained; 2 weeks immobilization + 8 weeks recovery RT	Immobilization reduced VL CSA and mean and type II myofiber CSA, while type I CSA was unchanged, and total RNA decreased. Satellite-cell content was unchanged during immobilization but increased after RT.	Small sample with few females, limiting sex comparisons; findings were limited to young adults and a single muscle (VL).

Table 2. *Cont.*

Study	Disuse Model	Participants/Duration	Main Outcomes/Findings	Limitations
Kilroe et al. [95]	Unilateral lower-limb suspension (ULLS) followed by rehabilitation	16 late-midlife adults (50–65 y): 8 males and 8 postmenopausal females; 7 days ULLS + 7 days rehabilitation	Seven days of unilateral lower-limb suspension reduced muscle protein synthesis by approximately 18% in men and 33% in women and reduced leg-extension 1-RM by 24.2% and 17.1%, respectively, with similar reductions in muscle fiber CSA between sexes. Seven days of resistance-exercise rehabilitation partially restored MPS, fiber size, and strength, but full recovery required a longer rehabilitation period.	Small sample and short rehabilitation period; assessment was limited to VL and did not include ultrastructural characterization.
Ahmadi et al. [84]	Unilateral leg immobilization using a knee brace and crutches; percussive massage as a countermeasure	17 healthy active adults (10 men, 7 women); 10 days; $n = 9$ control and $n = 8$ PM	Immobilization reduced quadriceps/VL size, myofiber CSA, and isometric strength. PM did not prevent these changes but partially preserved fatty-acid-supported mitochondrial respiration.	Small groups and a short 10-day immobilization period limited the ability to assess sex-specific responses; the study primarily evaluated percussive massage as a countermeasure rather than disuse-induced atrophy alone.

Table 2 abbreviations: CSA = cross-sectional area; ISS = International Space Station; MRI = magnetic resonance imaging; RM = repetition maximum; SR = sarcoplasmic reticulum; STS = Space Transportation System; ULLS = unilateral lower-limb suspension; VL = vastus lateralis; MPS = muscle protein synthesis; RNA = ribonucleic acid; mTORC1 = mechanistic target of rapamycin complex 1; DPA = dual-photon absorptiometry; RT = resistance training; 1-RM = one-repetition maximum; EMG = electromyography.

Critical evidence from human disuse models has shown that disuse or immobilization reduces muscle size, fiber cross-sectional area (CSA), and strength, with responses varying according to the unloading model, duration, muscle examined, and fiber type. However, evidence remains heterogeneous across models. Bed rest, spaceflight, unilateral suspension, and limb immobilization differ substantially in the degree of mechanical unloading and residual movement, limiting direct comparisons and making it difficult to distinguish complete immobilization from partial unloading in some cases. It also indicates that structural and functional adaptations are not necessarily proportional. Reductions in muscle CSA may occur alongside substantial strength loss, while recovery of muscle size does not necessarily indicate complete functional recovery. Fiber-type specific responses are also evident, with both type I and type II fibers showing susceptibility depending on the disuse model and muscle examined. Sex-related responses remain insufficiently characterized. Although some studies have included both men and women and reported broadly similar changes, many studies were conducted exclusively in males or females, while others included too few participants of one sex to draw definitive conclusions regarding sex-specific susceptibility. Human evidence establishes disuse-related muscle loss and functional impairment, but it remains limited by small cohorts, heterogeneous unloading paradigms, and restricted structural assessment. Integrated studies that combine muscle morphology, fibre characteristics, ultrastructure, molecular responses, and functional outcomes are therefore needed to clarify how these adaptations interact across different disuse conditions.

7. Cellular Structural, Ultrastructural Alterations, and Functional Impairment During Disuse

7.1. Fiber Atrophy and Myonuclear Apoptosis

At the cellular level, muscle disuse induces a pronounced reduction in total mass by downregulating protein synthesis while concurrently upregulating intracellular proteolytic pathways [96,97]. Histologically, this manifests as marked shrinkage of individual muscle

fibers, widening of the interstitial spaces, fiber splitting, intra-sarcoplasmic vacuolation, and the appearance of pyknotic nuclei [11].

Hindlimb unloading in rodents for 14–21 days caused about 50% loss of SOL muscle mass, mainly due to reduced fiber CSA rather than fiber number [98]. It has been established that unloading for 14 days reduced type I fiber CSA by about 63% and type IIa fiber CSA by about 47% in the SOL muscle [99]. Also, a previous study showed that 14 days of unloading reduced SOL muscle CSA by about 41% and type I fiber diameter by about 25%, with decreased MHC-I expression [100]. Following 4 weeks of unloading, SOL muscle mass and fiber CSA decreased by 39% and 58%, respectively. Concurrently, GAS muscle fibers showed a 51% decrease in CSA, which was accompanied by a 44% decline in single-fiber contractility and a 39% reduction in fatigue resistance [101].

Programmed cell death (apoptosis) serves as an established hallmark of disuse-induced atrophy. Animal models have revealed elevated apoptotic signalling within postural muscles (such as the SOL) during hindlimb suspension protocols. This response is particularly elevated in aged subjects, where classic markers like caspase-3 activation and DNA fragmentation indicate the profound involvement of mitochondrial-mediated apoptotic pathways [102]. Both caspase-dependent and caspase-independent mechanisms drive this apoptotic execution during muscle wasting [103]. While a proportion of true myonuclei undergo apoptosis, thereby lowering local transcriptional and translational capacity, apoptotic changes also heavily compromise resident SCs and interstitial mononuclear cell populations, which exhibit high vulnerability to unloading stress [104,105]. Histological validation via TUNEL staining confirms the presence of apoptotic nuclei across both myonuclear and stromal compartments, confirming the role of targeted cell death in structural muscle remodelling [106]. T These findings collectively demonstrate the contribution of apoptosis to cellular loss during disuse-induced muscle remodelling [11,107].

7.2. Capillary Density and Perfusion Alterations

Muscle disuse is consistently linked to a significant reduction in capillarization, which limits local oxygen and nutrient delivery to recovering muscle fibers. This structural decline is frequently accompanied by microvascular endothelial damage and increased deposition of extracellular connective tissue matrix around the remaining capillaries, further impairing microperfusion [11,108,109]. Interestingly, when normalized against the concurrently shrinking CSA of atrophied fibers, the absolute capillary number has been reported to remain unchanged in some models, suggesting a relative rather than absolute capillary rarefaction [110]. However, immobilization and bed rest models demonstrate early, measurable declines in the absolute capillary-to-fibre ratio, particularly within highly oxidative slow-twitch muscles like the SOL, directly paralleling a drop in local oxidative capacity. Despite this heterogeneous microvascular distribution, resting tissue oxygenation during maximal demand may occasionally appear sufficient, as the relative capillarization still matches or exceeds the drastically diminished oxidative requirements of the atrophied fibers [109].

7.3. Extracellular Matrix Remodelling and Fibrosis

Mechanical unloading promotes early, aberrant remodelling of the extracellular matrix (ECM), resulting in an increased concentration of connective tissue around individual muscle fibers [10,111]. Experimental work demonstrates that immobilization rapidly elevates collagen deposition, manifesting first within the perimysium sheaths before extending deeper into the endomysium. This progressive connective tissue thickening markedly reduces global muscle compliance and drives clinical stiffness [111]. Extensive ECM remodelling and fibrotic infiltration represent the primary drivers of increased passive muscle

stiffness during periods of disuse or aging, which severely limit elasticity and restrict joint range of motion [112]. Modern diagnostic imaging confirms that this connective tissue proliferation increases muscle echo-intensity, a metric that correlates positively with passive tissue stiffness and inversely with voluntary muscle strength [113]. Together, these observations highlight the role of connective tissue accumulation in reducing the flexibility and functional performance of disused muscles.

7.4. Depletion of the Satellite Cell (SC) Niche

While SCs are essential for maintaining muscle homeostasis, their population density and proliferative capacity are severely compromised during disuse atrophy. Mechanistically, SCs' activity is strictly modulated by competing molecular cascades, such as myostatin and insulin-like growth factor 1 (IGF-1) signalling, both of which undergo pathological alterations under unloading conditions [7]. Evidence from rodent hindlimb suspension models demonstrates a severe depletion of $Pax7^+$, $MyoD^+$, and $myogenin^+$ SCs, indicating a near-complete breakdown of normal proliferation and myogenic differentiation capacity [114]. This cellular reduction occurs across both oxidative (e.g., SOL) and glycolytic (e.g., TA) muscles, implying a coordinated, systemic down-regulation across distinct fiber phenotypes [114–116]. Clinical human studies confirm these findings. Short-term bed rest protocols in middle-aged and elderly cohorts induce an abrupt drop in SC abundance, a decline that correlates with a reduction in fiber CSA and accelerated atrophy kinetics [117]. Collectively, these data suggest that disuse compromises the regenerative potential of skeletal muscle by impairing SC content and function, thereby limiting recovery upon physical reloading. The potential role of melatonin in modulating SC activation and regenerative capacity is discussed in Section 10.3.4.

7.5. Myofibrillar Dismantling and Sarcomere Dissolution

Skeletal muscle atrophy involves a gradual, highly ordered dismantling of the internal myofibrillar structure. The early stages of wasting are marked by the selective removal of thick filament-associated accessory proteins, including myosin-binding protein C and myosin light chains, which precede the structural degradation of the primary myosin heavy chains [8]. A pivotal biophysical step in this destructive cascade is the disassembly of the desmin intermediate filament cytoskeleton. The breakdown of desmin disrupts the structural alignment of adjacent Z-bands and thin filaments, rendering them highly vulnerable to subsequent proteasomal degradation. This structural instability accelerates the parallel loss of both actin and myosin filaments [118,119]. The molecular mechanisms underlying proteasomal degradation are discussed in Section 9.2.

Ultimately, progressive sarcomere fragmentation, pronounced Z-line distortion, and the loss of core contractile proteins cause severe weakening and shrinkage of individual muscle fibers [120,121]. Prolonged muscle inactivity further aggravates this ultrastructural damage, resulting in a total loss of myofilament alignment, the disruption of distinct A and I band boundaries, irregular Z-line tearing, and eventual sarcomere dissolution [11]. Ultrastructural evaluations via electron microscopy consistently show shrunken myofibrils and longitudinal filament splitting [122].

Titin (TTN), the giant elastic protein that anchors thick filaments to the Z-disc matrix, plays a central role in preserving sarcomere structural stability. The accelerated degradation of titin during disuse triggers rapid sarcomere disassembly, Z-disc deformation, and immediate contractile force reduction [123]. A recent study demonstrated that disuse atrophy is manifested by blurred A and I bands, irregular Z-lines, and disrupted myofilament organization [11]. Under these weakened conditions, the eccentric overstretching of com-

promised sarcomeres further compounds the physical damage, driving the progressive decline in global muscle function [124].

More recent ultrastructural evidence suggests that disuse-induced fibre atrophy is mediated primarily by a reduction in myofibril number rather than in individual myofibril size. In a 10-day unilateral hindlimb immobilization model in young (4-month-old) and old (24-month-old) mice, Sayed et al. (2026) [75] reported radial atrophy of SERCA1-positive fibres in the soleus, accompanied by a small decrease in myofibril cross-sectional area but a markedly greater decrease in the number of myofibrils per fiber, with near-identical results in the FDL. These changes were blunted in old mice. Together, these findings provide direct ultrastructural evidence that myofibril loss may be a central structural basis of disuse atrophy, one that conventional fibre CSA measurements cannot fully capture.

7.6. Mitochondrial Remodelling and Functional Decline

Mitochondria within atrophic muscle fibers undergo profound structural remodelling that parallels a severe decline in bioenergetic function. Wasting is driven by an imbalance in mitochondrial dynamics, characterized by impaired fusion pathways (regulated by Mfn1/Mfn2 and OPA1) and excessive, runaway fission driven by Drp1 hyperactivation. For instance, a reduction in OPA1 expression destabilizes mitochondrial DNA and accelerates organelle dysfunction [6,9]. Excessive fission fosters widespread mitochondrial fragmentation, which in turn triggers cytochrome c release and activates downstream apoptotic cascades. These fragmented, dysfunctional mitochondria are rapidly cleared via mitophagy, which drastically reduces mitochondrial density and volume within the atrophied fibers [125].

Transmission electron microscopy has demonstrated age-related abnormalities in mitochondrial morphology in human and mouse skeletal muscle, accompanied by progressive accumulation of mitochondrial damage and impaired organelle turnover [126]. Age-related mitochondrial deterioration has been associated with oxidative damage and declining mitochondrial function [127]. In long-lived postmitotic cells, including skeletal muscle, defective mitochondria may progressively accumulate and undergo structural disorganization and enlargement, contributing to the formation of giant mitochondria [126]. Consistent with these observations, ultrastructural examination of skeletal muscle from aged humans and CBA/Ca mice revealed giant mitochondria, irregularly spaced or disrupted cristae, and, in some mitochondria, lamellar or myelin-like structures [128]. Likewise, mitochondrial morphology is altered in the skeletal muscle of aged mice, with larger and less circular subsarcolemmal (SS) mitochondria and longer, more branched intermyofibrillar (IMF) mitochondria, suggesting increased fusion and/or decreased fission [129].

Prolonged inactivity suppresses mitochondrial biogenesis, resulting in reduced volume and functional capacity, directly correlating with diminished ATP production and limited cellular energy availability. This energy crisis suppresses energy-expensive protein synthesis while enhancing proteolytic activity, aggravating muscle wasting [9,130]. The interactions between mitochondrial dysfunction, oxidative stress, and altered protein turnover during disuse are further addressed in Sections 9.2 and 9.3.

7.7. Muscle Quality and Contractile Dysfunction

Importantly, functional impairment during periods of disuse cannot be attributed solely to reductions in muscle mass or fiber cross-sectional area. Evidence from human studies demonstrates that the decline in muscle strength often exceeds the loss in muscle size, indicating the involvement of additional neuromuscular and intrinsic contractile alterations. This disproportionate reduction in strength may be related to decreased neural activation, compromised neuromuscular function, alterations in excitation–contraction cou-

pling, impaired calcium handling, and changes in myofibrillar organization and contractile properties [131,132]. Consequently, muscle quality, particularly specific tension, is an important functional measure of the intrinsic force-generating capacity of muscle, expressed as the maximum force generated per unit of muscle fiber CSA [133,134]. Thus, integrating assessments of muscle force and specific tension with morphometric and ultrastructural analyses is essential for a comprehensive understanding of functional deterioration associated with disuse-induced muscle atrophy.

8. Fiber-Type Classification and Differential Susceptibility to Disuse Atrophy

Skeletal muscle fibers are broadly classified into slow-twitch (type I) and fast-twitch (type II) fibers based on their contraction kinetics, which are primarily determined by the predominant myosin heavy chain (MHC) isoforms expressed within each fiber. Fast-twitch fibers are further subdivided into IIa, IId/x, and IIb phenotypes, exhibiting progressive differences in contraction velocity, force generation, and fatigue resistance [135–138].

Slow-twitch fibers are highly enriched with mitochondria, myoglobin, and oxidative enzymes, reflecting their reliance on oxidative metabolism. In contrast, fast-twitch fibers predominantly utilize glycolytic metabolism, have lower mitochondrial content, and generate rapid, powerful contractions at the expense of reduced fatigue resistance [130,135,139].

Accumulating evidence indicates that these fiber subtypes exhibit distinct vulnerabilities to various atrophic stimuli. Oxidative type I fibers maintain higher basal rates of protein turnover and demonstrate greater resistance to muscle loss induced by fasting compared to glycolytic type II fibers. However, type I fibers are particularly susceptible to atrophy triggered by inactivity, microgravity, and denervation [140–142]. Conversely, type II fibers are more prone to wasting in systemic catabolic states such as cancer cachexia, diabetes, chronic heart failure, and aging [135,143].

Disuse-induced skeletal muscle atrophy is characterized not only by reductions in muscle mass and myofiber CSA but also by significant phenotypic remodeling. The degree of atrophy varies substantially among muscle groups; antigravity muscles like the SOL and GAS experience more pronounced atrophy compared to fast-twitch muscles such as the TA and EDL [13,77]. Additionally, muscles immobilized in a shortened position undergo greater atrophy than those maintained in a lengthened state, highlighting the critical role of mechanical loading and muscle tension in preserving muscle integrity [144–146]. Collectively, these observations demonstrate that the severity of muscle loss during disuse is influenced by unloading magnitude, muscle architecture, and intrinsic fiber composition. A notable feature of disuse atrophy is a slow-to-fast fiber-type transition alongside myofiber atrophy [54,147–150].

Several mechanisms contribute to the heightened susceptibility of slow-twitch muscles to unloading-induced atrophy. Primarily, slow fibers rely heavily on continuous neural activation and mechanical loading to maintain their phenotype. The reduction in neuromuscular activity during disuse rapidly disrupts the signaling pathways essential for preserving slow-fiber gene expression, facilitating atrophy and a slow-to-fast fiber-type switch [151]. Secondly, unloading leads to a marked decline in mitochondrial content and oxidative capacity, especially within the SOL muscle [152,153]. These alterations impair energy metabolism and contribute to increased susceptibility to catabolic remodeling [154].

Thirdly, disuse activates multiple proteolytic pathways that drive muscle protein degradation [13,155–158]. The involvement of these pathways, together with the contribution of oxidative stress to unloading-induced muscle loss, is discussed in Sections 9.2 and 9.3, respectively. Together, these findings underscore the particular vulnerability of slow-twitch muscles

to disuse atrophy, attributable to their dependence on continuous neuromuscular input, oxidative metabolism, and redox-sensitive signaling networks.

It is also essential to differentiate age-related muscle remodeling from adaptations induced by mechanical unloading. While both conditions are associated with reduced physical activity and elevated oxidative stress, aging typically results in preferential atrophy of fast-twitch (type II) muscle fibers, accompanied by motor neuron loss and motor unit remodeling. In contrast, mechanical unloading predominantly induces pronounced atrophy in slow-twitch, antigravity muscles [98,159–161]. These distinctions underscore that muscle deterioration due to aging and that resulting from mechanical unloading are distinct, albeit partially overlapping, processes.

9. Core Molecular Mechanisms of Disuse-Induced Atrophy

9.1. Suppression of Protein Synthesis (Anabolic Blunting)

Muscle protein synthesis declines during disuse, a phenomenon driven by the suppression of the canonical IGF-1/Akt/mTOR signaling cascade, which serves as the master upstream regulator of translation initiation [13,162–167]. Under normal mechanical loading, the binding of insulin-like growth factor 1 (IGF-1) activates a downstream phosphorylation cascade involving insulin receptor substrate 1 (IRS-1), phosphoinositide 3-kinase (PI3K), phosphoinositide-dependent kinase-1 (PDK1), and Akt [163,168–170]. Activated Akt directly upregulates the mechanistic target of rapamycin complex 1 (mTORC1) [171,172], which subsequently phosphorylates downstream anabolic effectors, namely eukaryotic translation initiation factor 4E-binding protein 1 (4E-BP1) and ribosomal protein S6 kinase 1 (S6K1), to drive translation [173].

During mechanical unloading or immobilization, the development of local insulin resistance coupled with a drastic reduction in the phosphorylation of these signaling proteins effectively shuts down this anabolic pathway [164,166,167,174,175]. Additionally, the mechanosensitive focal adhesion kinase (FAK) serves as a critical mechanical sensor modulating Akt-mTOR activity; a reduction in FAK phosphorylation during inactivity further suppresses protein synthesis [176–181]. At the translational level, crucial elongation factors like eukaryotic elongation factor 2 (eEF2) and ribosomal biogenesis are heavily downregulated, limiting cellular translation capacity [182–187].

9.2. Hyperactivation of Proteolytic Pathways

Concurrently, intracellular protein degradation pathways are heavily upregulated during disuse atrophy. The most prominent degradative system is the ubiquitin-proteasome system (UPS), which is strictly regulated by the muscle-specific E3 ubiquitin ligases Atrogin-1 (MAFbx) and muscle RING finger 1 (MuRF1) [188,189]. These ligases function by specifically tagging structural, sarcomeric, and contractile proteins with ubiquitin chains, targeting them for destruction within the 26S proteasome core. The transcription of these atrogenes rises rapidly during the early phases of disuse, denervation, or metabolic stress. This process is controlled by the Akt/FOXO axis. When upstream Akt signalling is suppressed, forkhead box O (FOXO) transcription factors are dephosphorylated, allowing them to translocate into the nucleus where they directly stimulate atrogenes transcription [162,189–191]. Experimental models demonstrate that the targeted inhibition of MuRF1 significantly preserves muscle mass, confirming its central role in atrophy progression [188].

In addition to the UPS, three other interconnected proteolytic systems cooperate to drive muscle breakdown during disuse [13]: (1) Calpains: Calcium-dependent non-lysosomal cysteine proteases that initiate the degradation process by cleaving anchoring proteins to release myofilaments from the sarcomere matrix [192–194]. (2) Caspase-3: An executioner protease that actively participates in both apoptotic signalling and the direct cleavage

of myofibrillar structures, further feeding substrates into the UPS [194]. (3) Autophagy-Lysosomal Pathway: Hyperactivated alongside the UPS to clear larger protein aggregates and intact organelles like mitochondria [195]. The structural consequences of these proteolytic processes, particularly myofibrillar dismantling and sarcomere disruption, are described in Section 7.5.

9.3. Oxidative Stress and Intracellular Calcium Overload

Mitochondrial-derived ROS and intracellular calcium overload serve as critical upstream triggers that simultaneously enhance muscle proteolysis and inhibit protein synthesis during disuse. Excess intracellular ROS promotes insulin resistance, activates catabolic proteolytic pathways, and biochemically modifies myofibrillar proteins to increase their susceptibility to proteasomal degradation [13,196–198]. This oxidative stress-induced muscle atrophy occurs across diverse pathological conditions, including aging, disuse, diabetes, denervation, and cancer cachexia [199]. Because muscle mitochondria are damaged by chronic ROS production, lipid peroxidation within the mitochondrial membranes intensifies, generating a destructive feedback loop that compounds organelle damage. In parallel, the disruption of intracellular calcium homeostasis leads to persistent calcium accumulation, which activates calpains and induces apoptosis-related caspases, exacerbating muscle loss [14]. The associated mitochondrial structural and functional alterations during disuse are described in Section 7.6.

9.4. Endocrine and Circadian Regulation

9.4.1. Glucocorticoid Signalling

Elevated circulating glucocorticoids (such as cortisol) act as potent systemic promoters of muscle wasting [200]. Mechanistically, the activation of the intracellular glucocorticoid receptor induces the expression of two key target genes: REDD1 (Regulated in Development and DNA Damage Response 1) and KLF15 (Kruppel-like Factor 15). Together, REDD1 and KLF15 inhibit downstream mTOR signalling and enhance catabolic pathways via the coordinated regulation of FoxO1, Atrogin-1, and MuRF1 expression [201,202]. Glucocorticoids, often working in synergy with pro-inflammatory cytokines like tumour necrosis factor-alpha (TNF-α), accelerate proteolysis by stimulating both the ubiquitin-proteasome and autophagy-lysosomal pathways while suppressing muscle protein synthesis. This endocrine axis is highly active during systemic stress and disease states [5,200].

9.4.2. Clock Genes and Circadian Regulation (Melatonin Axis)

Circadian regulators, such as the core clock proteins BMAL1 and CLOCK, control muscle metabolism, mitochondrial quality control, and the physiological rhythms of fiber growth. The experimental loss of BMAL1 severely impairs mitochondrial biogenesis and normal protein turnover, which accelerates muscle atrophy. Similarly, the circadian secretion of hormones influences muscle homeostasis. While diurnal cortisol peaks promote catabolism, nocturnal melatonin secretion provides essential mitochondrial protection and enhances antioxidant defences within skeletal muscle tissue [12,203–207]. These findings highlight circadian regulation as an important mechanism governing skeletal muscle atrophy.

The principal molecular and cellular mechanisms contributing to disuse-induced skeletal muscle atrophy discussed in this section are summarized in Figure 3.

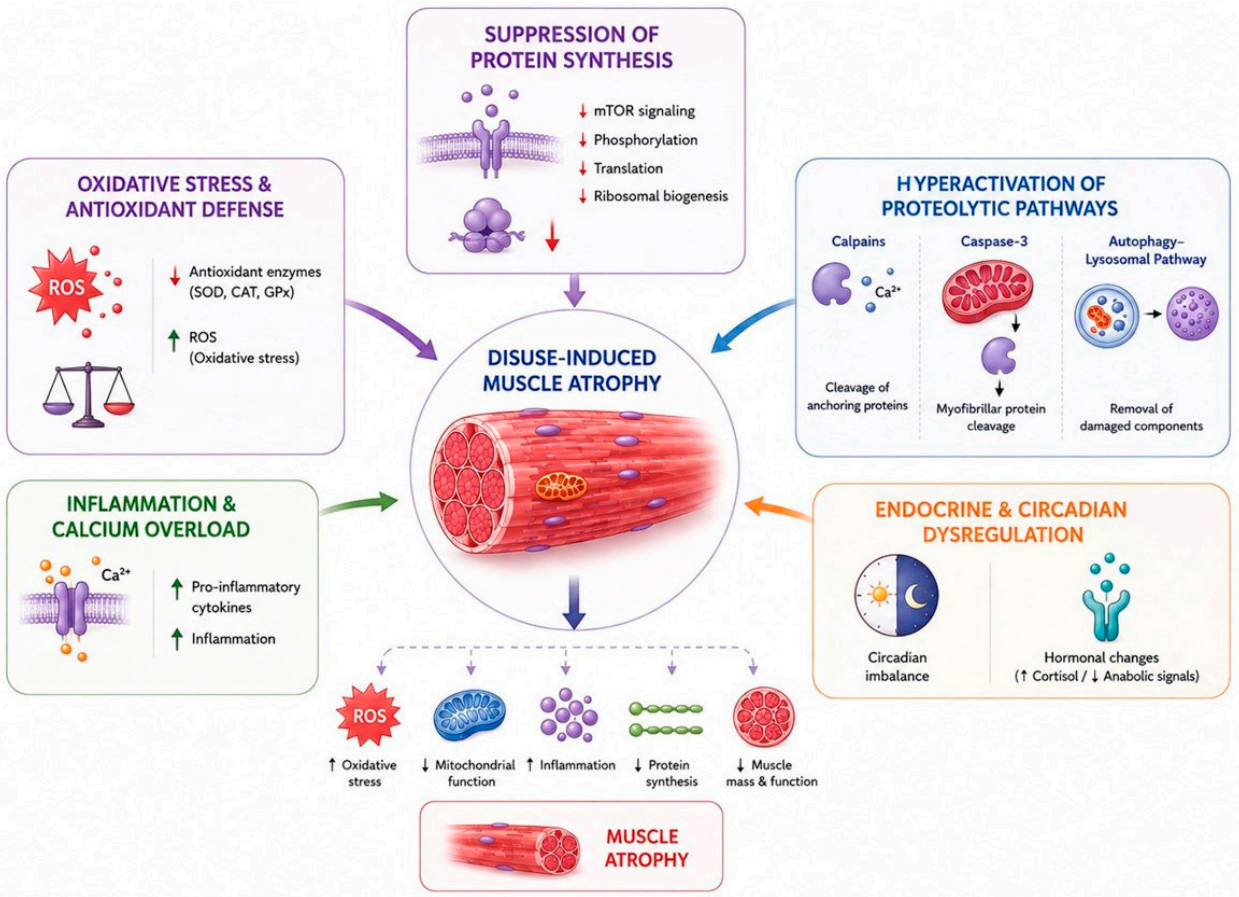

Figure 3. Integrated molecular mechanisms underlying disuse-induced skeletal muscle atrophy. Skeletal muscle unloading disrupts proteostatic homeostasis by suppressing anabolic signaling and protein synthesis while enhancing proteolytic pathways. Reduced protein synthesis, activation of calpain-dependent proteolysis, and alterations in autophagy-related processes have been experimentally demonstrated in disuse models. Oxidative stress, intracellular Ca^{2+} dysregulation, and mitochondrial alterations have also been documented experimentally, although their extent and contribution vary among models. In contrast, the involvement of inflammatory signaling and endocrine–circadian dysregulation remains less consistently established in uncomplicated mechanical disuse and is supported partly by indirect evidence or findings from other catabolic conditions. These interconnected mechanisms may contribute to myofiber remodeling, alterations in myonuclear content, and progressive deterioration of skeletal muscle mass and function. Thus, the mechanisms illustrated differ in the strength of their experimental support and should not be interpreted as equally established. ↑: increased; ↓: decreased.

10. Melatonin: Secretion, Function, Mechanisms of Action, and Role in Skeletal Muscle Atrophy

10.1. Secretion

Melatonin, or 5-methoxy-N-acetyltryptamine, was first isolated from bovine pineal glands in 1958 by Aaron Lerner. It is the principal hormone secreted by the pineal gland during the night and plays a central role in circadian rhythm regulation, sleep modulation, and diverse physiological processes [208,209]. Besides the pineal gland, melatonin production occurs extrapituitarily (extrapineal sources) in various tissues, including the retina, gastrointestinal tract, bone marrow cells, platelets, lymphocytes, Harderian gland, and cerebellum [208,210–212]. Moreover, melatonin has also been detected in several edible sources, including plants, eggs, and fish, suggesting its potential role as a nutraceutical compound with broad physiological relevance [206,213].

At the physiological level, pineal melatonin is synthesized at night under the control of the suprachiasmatic nucleus (SCN) in synchrony with the light–dark cycle, while mitochondria serve as a primary site for its synthesis within cells [204]. Melatonin is synthesized from serotonin in a two-step process by the sequential action of the pivotal enzymes aralkylamine N-acetyltransferase (AANAT) and acetylserotonin O-methyltransferase (ASMT) [214,215]. AANAT and ASMT are expressed at very high levels only in the pineal gland and are essential to the well-established physiological function of the pineal gland, namely, melatonin synthesis. Pineal synthesis of melatonin accounts for circulating levels of melatonin, which increase at night due to an increase in AANAT activity, whereas ASMT activity varies little on a 24-h basis in the mammalian pineal gland [215,216].

10.2. Function

Functionally, melatonin operates as a potent endogenous synchronizer of circadian rhythms by acting on the SCN, thereby regulating the sleep–wake cycle and coordinating peripheral oscillators in tissues such as skeletal muscle, liver, pancreas, and others [208,217,218]. In addition to its circadian functions, melatonin exerts several biological actions relevant to skeletal muscle physiology and protection against atrophy, as discussed below.

10.3. Mechanisms of Action in Skeletal Muscle

Melatonin exerts diverse biological effects through multiple, interconnected mechanisms relevant to skeletal muscle physiology and protection against atrophy. These mechanisms include antioxidant and anti-inflammatory actions, mitochondrial protection, modulation of cell signaling pathways, regulation of proteolysis, SC promotion, and anti-apoptotic effects. The following subsections detail these key mechanisms.

10.3.1. Antioxidant and Anti-Inflammatory Effects

Melatonin functions as a potent free radical scavenger, neutralizing ROS and reactive nitrogen species (RNS) that contribute to oxidative stress in skeletal muscle. It also stimulates endogenous antioxidant enzymes such as superoxide dismutase (SOD) and catalase (CAT), thereby enhancing the muscle's resilience against oxidative damage. Besides its antioxidant capacity, melatonin exhibits anti-inflammatory actions by inhibiting pro-inflammatory signaling pathways, including the nuclear translocation of NF-κB, resulting in reduced production of cytokines like IL-6 and TNF-α [219–225].

10.3.2. Mitochondrial Protection and Bioenergetics

A critical feature of melatonin's mechanism is the preservation of mitochondrial structure and function. Melatonin maintains mitochondrial membrane integrity, reduces lipid peroxidation of mitochondrial components such as cardiolipin, and prevents mitochondrial swelling under stress conditions. It promotes mitochondrial biogenesis and dynamics by upregulating key regulators such as PGC-1α, NRF-1, and TFAM, and corrects imbalances in mitochondrial fission and fusion by modulating proteins like Fis1 and DRP1. These effects ensure adequate ATP production and oxidative capacity essential for muscle metabolism and endurance [206,226]. Also, the mechanisms of melatonin as a mitochondrial protector not only relate to its excellent free radical scavenging capacity but also to its function as a signalling molecule to upregulate gene expression of antioxidant enzymes and a spectrum of stress-responsive genes [227].

10.3.3. Modulation of Cell Signaling Pathways

Melatonin influences multiple signaling cascades that govern muscle mass and regeneration. It has been reported to inhibit muscle-specific ubiquitin ligases MuRF1 and Atrogin-1

(MAFbx), key mediators of protein degradation in muscle atrophy, thereby potentially counteracting the proteolytic mechanisms described in Section 9.2. Concurrently, melatonin activates anabolic pathways, particularly the IGF-1 and PI3K/Akt signaling axis, promoting muscle hypertrophy and protein synthesis. Additional signaling modulation involves regulation of Wnt/β-catenin pathways and microRNA activity (e.g., downregulation of miR-3475-3p), which contribute to SCs' function and muscle differentiation [21,228,229].

10.3.4. Promotion of SC Activation and Muscle Regeneration

Melatonin enhances the activation, proliferation, and differentiation of skeletal muscle SCs, which are essential for muscle repair and regeneration [221,230]. It increases the expression of myogenic regulatory factors such as Pax7, MyoD, and myogenin, facilitating effective myogenesis. These effects may contribute to improved muscle regeneration following injury, as demonstrated in glycerol-induced muscle injury models [228]. However, whether SC-mediated regenerative effects of melatonin contribute directly to the attenuation of mechanical-disuse-induced muscle atrophy remains to be established [228].

10.3.5. Anti-Apoptotic Effects

In relation to the apoptotic changes associated with disuse-induced muscle atrophy (Section 7.1), melatonin exerts significant anti-apoptotic activity by upregulating anti-apoptotic proteins like Bcl-2 and suppressing pro-apoptotic factors, including caspases and MAPK pathways [231–234]. It prevents mitochondrial cytochrome c release, thus inhibiting intrinsic apoptotic signaling in muscle fibers exposed to injury or oxidative stress. This protective effect preserves muscle cell viability and supports functional muscle maintenance during stress conditions [232,235–237].

The principal mechanisms underlying the protective effects of melatonin against disuse-induced skeletal muscle atrophy discussed in this section are summarized in Figure 4.

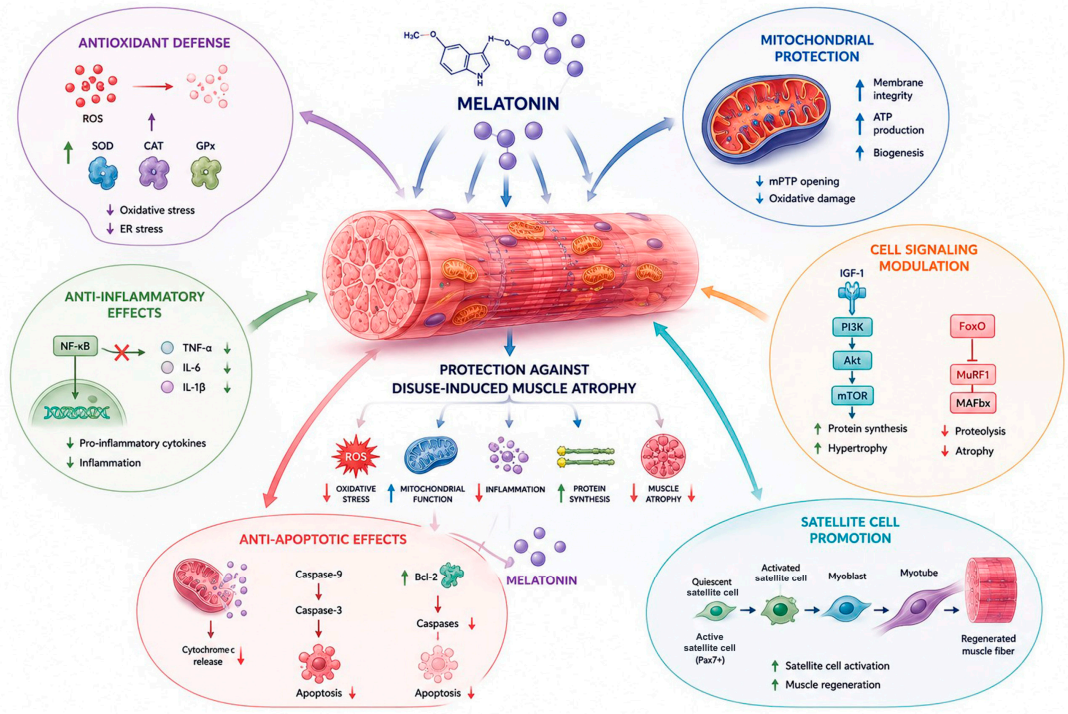

Figure 4. Proposed mechanisms underlying the protective effects of melatonin against disuse-induced skeletal muscle atrophy. Melatonin may exert protective effects through antioxidant defense,

mitochondrial protection, anti-inflammatory activity, modulation of intracellular signaling, inhibition of apoptosis, and promotion of satellite cell activity. Among these mechanisms, antioxidant effects and changes in selected atrophy-related signaling markers (increased IGF-1R and reduced MAFbx expression) have been experimentally demonstrated in a skeletal muscle immobilization model. In contrast, the proposed mitochondrial, anti-inflammatory, anti-apoptotic, and satellite cell-related effects are supported mainly by findings from other experimental muscle conditions or indirect mechanistic evidence and have not been comprehensively established in mechanical disuse models. Accordingly, these pathways represent potential mechanisms of melatonin action rather than fully confirmed effects in disuse-induced muscle atrophy. ↑: increased; ↓: decreased.

10.3.6. Therapeutic and Protective Applications of Melatonin

Beyond its physiological role, melatonin has demonstrated broad therapeutic and protective potential, primarily in experimental models. Literature reviews report its activity against several parasites, including Plasmodium, Toxoplasma gondii, and Trypanosoma cruzi, through mechanisms involving modulation of calcium levels and/or the host immune response; in vitro efficacy has also been described against Leishmania infantum [238]. In streptozotocin-induced diabetic rats, melatonin attenuated pancreatic and hepatic alterations, increased pancreatic β-cell area, and reduced hepatic alpha-fetoprotein expression [239]. Another study using a similar diabetic rat model demonstrated improvements in serobiochemical abnormalities as well as cardiac and renal vascular and cellular alterations following melatonin administration [240]. septic mice, melatonin was shown to attenuate the septic inflammatory response and counteract NLRP3 inflammasome activation [241]. In rats subjected to tongue irradiation, oral melatonin gel protected the small intestine by preserving mitochondrial function, suppressing NF-κB/NLRP3 signaling, reducing apoptosis, and facilitating mucosal recovery [242]. In an MPTP-induced zebrafish embryo model of Parkinson-like disease, melatonin prevented and reversed the pathological phenotype, restoring the parkin/PINK1/DJ-1/MUL1 network and motor activity [243]. In aged mice, oral melatonin attenuated cardiac sarcopenic changes by preserving cardiomyocyte structure and number, improving mitochondrial architecture, and reducing apoptosis and IL-1α/IL-6 expression [244].

Melatonin also appears relevant to skeletal muscle: in resistance-trained athletes, four weeks of supplementation reduced oxidative stress and biochemical markers of exercise-induced muscle damage [245], while in male and female skeletal muscle-specific inducible Bmal1-knockout mice, melatonin ameliorated sarcopenic alterations [246]. In concert, these findings suggest that melatonin possesses broad protective potential across infectious, metabolic, inflammatory, neurodegenerative, and tissue injury conditions, as well as skeletal muscle disorders.

10.4. Evidence for the Effects of Melatonin on Skeletal Muscle

10.4.1. Experimental Animal Studies Showing Melatonin's Effect Against Muscle Atrophy

A growing body of experimental evidence from animal models suggests that melatonin may exert protective and therapeutic effects on skeletal muscle under different pathological and stress-related conditions. These effects have been investigated using diverse experimental models and treatment protocols, with reported outcomes including muscle preservation, attenuation of oxidative stress and inflammation, enhancement of regeneration, and maintenance of tissue integrity. Studies involving immobilization-related models have provided relevant evidence of the potential protective effects of melatonin against muscle alterations [20,247]. Other studies have demonstrated its potential protective effects in age-related muscle alterations [248–251]. Additional evidence comes from other experimental models, including sarcopenic obesity [252], mitochondrial dysfunction and muscle fiber adaptation [253], injury-associated muscle changes [254], fibromyalgia-

associated muscle alterations [255], and neurological or systemic disease-associated muscle atrophy [21,229,256]. For example, Song et al. [253] reported that melatonin enhanced mitochondrial biogenesis and function, reduced mitochondrial apoptosis, and promoted oxidative muscle-fiber formation through the AKT/BAD/BCL-XL pathway. Nevertheless, findings from non-disuse models should be interpreted as indirect evidence of the potential muscle-protective actions of melatonin rather than direct evidence of its efficacy against mechanical disuse-induced muscle atrophy. The characteristics and principal findings of representative animal studies are summarized in Table 3 [20,21,229,247–252,254–258].

Table 3. Experimental animal studies investigating the effects of melatonin against skeletal muscle atrophy and related outcomes.

Study	Atrophy Model/Cause	Animal/Model	Melatonin Intervention	Main Findings	Limitation
Mostafa & Samir. [247]	Immobilization-induced muscle atrophy	Male Wistar albino rats; soleus muscle	Melatonin (10 mg/kg, SC) given once daily (morning or night) or twice daily, concurrently during the 7-day immobilization period (preventive intervention).	Nighttime and twice-daily treatment reduced MAFbx/MuRF1 and increased IGF-1R and antioxidant capacity.	Administration schedule comparison rather than dose–response assessment; restricted to male rats and soleus muscle; histological, MHC-related, and molecular/antioxidant outcomes assessed, but no ultrastructural or direct functional assessment.
Abd Allah & Mahmoud. [20]	Chronic immobilization stress-induced muscle atrophy (trunk restraint 90 min/day for 6 weeks)	Rats subjected to chronic immobilization stress	Melatonin administered during the 6 weeks of chronic immobilization-stress protocol (preventive intervention).	Reduced oxidative stress and atrogin-1 expression and improved Na^+/K^+-ATPase activity.	Chronic immobilization stress model involving systemic stress rather than localized limb unloading; single treatment regimen; molecular and physiological outcomes assessed, but fiber-level morphology, ultrastructure, and direct contractile function were not characterized.
Sayed et al. [249]	Age-related sarcopenia	C57BL/6J female mice	Oral melatonin providing 10 mg/kg/day for 2 months before sacrifice in aged mice; treatment was given to already aged animals (including 24-month-old mice) (therapeutic intervention).	Preserved muscle architecture, fiber number, mitochondrial integrity, and activity.	Age-associated sarcopenia rather than mechanical disuse; female mice and gastrocnemius muscle only; single melatonin dose without dose–response assessment; functional assessment based on locomotor activity and treadmill endurance rather than direct contractile testing; comprehensive morphological and ultrastructural characterization, but no mechanical-disuse model or comparison across muscle types.
Zhu et al. [251]	Age-related sarcopenia	Aged mice; aging-induced satellite-cell model in vitro	30 mg/kg/day i.p., daily during the last 3 months of life, initiated at 19–21 months (therapeutic intervention).	Preserved muscle mass and strength and reduced fibrosis via TGF-β1/Smad2/3 signaling.	Age-related sarcopenia rather than mechanical disuse; single melatonin dose without dose–response assessment; no ultrastructural or direct contractile assessment; the D-gal-induced satellite-cell senescence model does not fully recapitulate natural aging; limited availability and proliferative capacity of SCs from old mice restricted direct studies; and the primary cellular targets of melatonin remain unresolved.

Table 3. *Cont.*

Study	Atrophy Model/Cause	Animal/Model	Melatonin Intervention	Main Findings	Limitation
Fang et al. [248]	Age-relate sarcopenia	Middle-aged mice	5 or 10 mg/kg/day for 2 months in middle-aged mice (therapeutic intervention).	Improved grip strength, running performance, muscle weights, and GA fiber CSA; improved mitochondrial morphology/function and oxidative status; reduced ATROGIN-1/MURF-1 and enhanced the PGC-1α/TFAM pathway; 10 mg/kg was more effective than 5 mg/kg.	Two-dose comparison provided dose range information but not formal dose optimization; aging-associated sarcopenia model rather than mechanical disuse; morphological, fiber-level, biochemical, and functional outcomes assessed; ultrastructural assessment not confirmed.
Zhou et al. [250]	Age-related sarcopenia	Aged C57BL/6J male mice	10 mg/kg/day for 16 weeks, beginning at 20 months and continuing to 24 months) (therapeutic intervention).	Improved muscle mass, strength, and fiber CSA through a putative gut–muscle axis.	Single treatment regimen; age-associated sarcopenia model rather than localized mechanical disuse; morphological, fiber-level, molecular/multi-omics, and functional outcomes assessed, but no ultrastructural characterization.

Table 3 abbreviations: CSA = cross-sectional area; i.p. = intraperitoneal; IGF-1R = insulin-like growth factor-1 receptor; MAFbx = muscle atrophy F-box/atrogin-1; MHC = myosin heavy chain; MuRF1 = muscle RING-finger protein 1; Na^+/K^+-ATPase = sodium–potassium adenosine triphosphatase; s.c. = subcutaneous; TGF-β1 = transforming growth factor beta 1.

Critical evidence from melatonin intervention studies has shown that across a range of atrophy models, melatonin generally exhibits muscle-protective effects by modulating proteolysis, oxidative stress, apoptosis, mitochondrial function, and associated signaling pathways. However, direct evidence supporting its efficacy in localized mechanical disuse remains limited. Considerable heterogeneity in dosing regimens, routes of administration, treatment durations, and preventive versus therapeutic protocols complicates dose–response comparisons and hinders the standardization of treatment protocols. Furthermore, comprehensive ultrastructural analyses and systematic sex-specific comparisons are rarely performed. In general, the available evidence supports a potential protective role for melatonin in skeletal muscle atrophy, but direct evidence in localized mechanical disuse models is scarce. The heterogeneity of experimental protocols and the limited integration of structural, ultrastructural, molecular, and functional outcomes underscore the need for standardized immobilization-based studies to determine melatonin efficacy across sex, muscle type, fiber composition, dose, and timing of treatment.

10.4.2. Human Studies Investigating the Effects of Melatonin on Skeletal Muscle

Given the well-established structural and functional consequences of skeletal muscle disuse in humans, increasing attention has been directed toward potential interventions that may preserve muscle integrity and function. Melatonin has emerged as a potential candidate because of its reported antioxidant, anti-inflammatory, and muscle-protective properties. However, human evidence regarding its effects on skeletal muscle remains relatively limited compared with the extensive preclinical literature [259–263]. Representative human studies examining the effects of melatonin on skeletal muscle-related outcomes are summarized in Table 4.

Table 4. Human studies investigating the effects of melatonin on skeletal muscle-related outcomes.

Study	Participants /Model	Melatonin Intervention	Duration/Timing	Main Muscle-Related Findings	Limitations
Rondanelli et al. [259]	159 elderly sarcopenic patients (42 men, 117 women)	Placebo, melatonin (M; 1 mg/day), essential amino acids (eAA; 4 g/day), or eAA + M (4 g eAA + 1 mg M/day)	4 weeks; M administered 30 min before sleep (therapeutic intervention)	eAA + M increased total FFM vs. placebo and M alone, but not vs. eAA alone. M alone reduced albumin levels, with no significant changes in muscle strength or inflammatory markers.	Short intervention; independent effect of M difficult to distinguish from eAA; no muscle fiber morphology, CSA, histological, or ultrastructural assessment was performed.
Cheikh et al. [260]	14 healthy, trained male teenage athletes	Single 10 mg oral dose	Acute crossover study; M administered at 22:00 after late-evening exhaustive exercise, with testing repeated the next morning at 07:30; (post-exercise/recovery treatment)	M improved next-morning sprint performance and attenuated exercise-induced leukocytosis, inflammation, lipid peroxidation, and muscle/hepatic damage markers.	Small, male-only adolescent sample; acute single-dose design; exercise-induced muscle stress rather than disuse; No muscle mass, fiber morphology, CSA, histological, or ultrastructural assessment was performed.
Farjallah et al. [261]	20 soccer players (10 M, 10 placebo)	5 mg oral M nightly	6-day intensive training camp; M administered daily during the intensive training period (representing concurrent/preventive treatment)	M reduced oxidative stress, leukocytosis, and cellular-damage markers and attenuated deterioration in repeated-sprint performance.	Small sample and short intervention; trained athlete population; exercise-induced muscle stress rather than immobilization/disuse; no muscle mass, fiber morphology, CSA, histological, or ultrastructural assessment was performed.
Ben Dhia et al. [262]	23 people with obesity (9 men, 14 women)	Single 3 mg dose before high-intensity interval exercise (HIIE)	Acute; two experimental sessions (HIIE + placebo vs. HIIE + M); M administered before HIIE (representing a preventive/pre-exercise intervention)	M attenuated exercise-induced inflammation, muscle/hepatic damage, and lipid/protein peroxidation, while increasing thiol and catalase levels.	Small sample; acute single-dose design; obesity population; exercise-induced muscle damage rather than disuse; no muscle mass, fiber morphology, CSA, histological, or ultrastructural assessment was performed.
Mahdi et al. [263]	12 trained males (21.92 ± 2.84 years)	Single 6 mg dose the night before exercise	Acute randomized crossover study; M administered the night before the exercise test (representing a preventive/pre-exercise intervention), with recovery outcomes assessed up to 72 h after the exercise test	M improved next-day high-intensity exercise performance, enhanced perceived recovery status (PRS), and reduced delayed-onset muscle soreness (DOMS). No significant effects were observed on sleep parameters or blood markers.	Very small, male-only trained sample; acute single-dose design; exercise recovery model rather than disuse-induced atrophy; no direct assessment of muscle mass, fiber CSA, or regeneration.

Table 4 abbreviations: CSA = cross-sectional area; DOMS = delayed-onset muscle soreness; eAA = essential amino acids; FFM = fat-free mass; HIIE = high-intensity interval exercise; M = melatonin; PRS = perceived recovery status.

Critical evidence from human melatonin studies has shown that Human studies provide limited and heterogeneous evidence for melatonin-related skeletal muscle benefits. Reported effects include improved exercise performance or recovery and attenuation of oxidative, inflammatory, and muscle damage responses, whereas evidence for direct preservation of muscle mass or fiber morphology is limited. The evidence is predominantly derived from exercise-induced muscle stress or established sarcopenia, rather than mechanical disuse or immobilization. Consequently, these findings cannot be considered direct evidence that melatonin prevents or reverses immobilization-induced muscle atrophy. Treatment

protocols are highly heterogeneous, ranging from single acute doses administered before or after exercise to short-term daily administration in sarcopenic individuals. Differences in dose, timing, treatment duration, and clinical context limit direct comparison and prevent identification of an optimal regimen. Sex and population representation are also limited, with several studies restricted to trained males, whereas only some included both sexes. Moreover, most studies did not directly assess muscle mass, fiber CSA, fiber morphology, or ultrastructure. Human evidence supports potential antioxidant, anti-inflammatory, and recovery-related effects of melatonin, but direct evidence for its effects on disuse-induced skeletal-muscle atrophy remains insufficient. Studies using established immobilization or unloading models with direct structural and functional muscle outcomes are needed to determine its translational relevance.

11. Methodological Limitations and Research Gaps

Skeletal muscle atrophy arises from a range of distinct conditions, including mechanical disuse, aging, denervation, systemic disease, and trauma. Although these conditions share certain downstream features, such as reduced muscle mass and impaired function, their initiating stimuli and cellular responses differ. Consequently, findings from one atrophy etiology cannot necessarily be extrapolated to another. The main limitations of the current literature involve model heterogeneity, incomplete structural assessment, biological variability, lack of mechanistic integration, and limited evidence for melatonin in the context of mechanical disuse.

11.1. Heterogeneity of Atrophy Etiology and Experimental Models

Disuse models are not interchangeable. Hindlimb unloading and limb immobilization alter mechanical loading, but may impose different mechanical conditions on specific muscles, while denervation and neurological injury introduce additional neural and pathological factors. Even among immobilization studies, differences in duration, limb involvement, joint position, fixation method, extent of movement restriction, and muscle selection can all influence the degree of atrophy. Greater methodological standardization is therefore needed to improve comparability and interpretation across studies.

11.2. Structural and Ultrastructural Assessment Gaps

Many studies examine selected outcomes such as muscle mass, fiber size, apoptosis, extracellular matrix remodeling, or mitochondrial structure rather than integrating multiple structural levels within the same experimental model. Consequently, the progression from muscle loss to microscopic and ultrastructural remodeling remains incompletely defined. Recent advances, such as fluorescence imaging of myofibrils and image deconvolution (FIM-ID), have enabled the quantitative characterization of myofibrillar architecture and provided evidence that reduced myofibril number, rather than myofibril size, may be a key determinant of fiber atrophy during disuse. However, this level of resolution remains uncommon in the broader disuse literature, and it is unclear whether this relationship is consistent across different disuse models, muscle types, and recovery time points. Longitudinal studies integrating structural, molecular, and functional assessments are needed to clarify the temporal relationships between these changes and the recovery process.

11.3. Fiber-Type, Muscle-Specific, and Sex-Related Variability

Disuse studies have predominantly focused on slow-twitch postural muscles, particularly the soleus, resulting in their overrepresentation in the literature. However, susceptibility to disuse-induced atrophy is influenced by muscle architecture, baseline activity, fiber composition, and joint position, which are not consistently incorporated into experimental

designs. This limits the generalizability of findings from individual muscles and leaves muscle-specific responses among muscles with different fiber compositions insufficiently characterized under comparable conditions.

Although slow-to-fast fiber-type transitions during unloading are well established, their association with muscle-specific structural and ultrastructural changes remains inadequately defined. Moreover, sex is inconsistently addressed, and the interactions among sex, muscle type, and fiber composition have not been thoroughly investigated within a common experimental framework. Thus, the combined influence of these factors on structural and ultrastructural responses to immobilization remains insufficiently understood.

11.4. Mechanistic Integration Gaps

Although protein turnover, oxidative stress, calcium dysregulation, mitochondrial dysfunction, inflammation, and apoptosis have each been implicated in disuse atrophy, they are often investigated in isolation. The relationships of these mechanisms with myofibrillar organization, extracellular matrix remodeling, and mitochondrial structural changes remain insufficiently integrated. Clarifying these relationships may help distinguish primary mechanisms from downstream consequences.

11.5. Limitations and Heterogeneity of the Melatonin Evidence

The evidence supporting the anti-atrophic effects of melatonin is derived from a wide array of experimental models, including aging-related sarcopenia, neurological injury, muscle trauma, chronic immobilization stress, and localized immobilization. Given that these conditions involve distinct pathophysiological mechanisms, the protective effects observed in models of sarcopenia, stroke, or muscle trauma cannot be directly extrapolated to mechanically induced disuse. Consequently, while the collective evidence points toward a potential protective role for melatonin, its efficacy remains inconsistent across different atrophy models.

The existing literature is further characterized by considerable heterogeneity in melatonin dosing, route of administration, timing, treatment duration, and dosing schedules, all of which may contribute to the variability in outcomes reported across studies and species. Additionally, many investigations focus on isolated molecular or cellular mechanisms without integrating these findings with comprehensive structural and functional assessments, thereby limiting the ability to determine whether molecular effects correspond to meaningful preservation of muscle morphology and function.

Clinical evidence in humans remains limited and largely indirect, as most studies have focused on sarcopenia and exercise-induced muscle damage or recovery, rather than on immobilization or mechanical disuse. To date, no clinical study has directly evaluated melatonin as an intervention for immobilization or disuse-induced skeletal muscle atrophy in humans, underscoring a significant translational gap. Consequently, the current evidence for melatonin is constrained by heterogeneity in atrophy models, intervention protocols, and outcome measures, as well as by a paucity of direct evidence in the context of mechanically induced disuse.

11.6. Direct-Evidence Limitations for Melatonin in Mechanical Disuse

Among the studies identified in this review, direct evidence for the effects of melatonin during immobilization remains limited. Mostafa and Samir [247] reported protective effects of melatonin following seven days of hindlimb immobilization in male rats; however, their investigation was restricted to the soleus muscle and focused on selected histological and molecular outcomes. Abd Allah and Mahmoud [20] examined melatonin in a chronic immobilization-stress model, but this paradigm involved systemic stress rather than local-

ized limb immobilization. Neither study included both sexes, multiple muscle phenotypes, or provided comprehensive structural and ultrastructural analyses.

The available literature does not appear to include a study combining melatonin treatment with controlled unilateral hindlimb immobilization while simultaneously comparing both sexes and muscles with different fiber-type compositions. Furthermore, the available direct evidence lacks integrated assessment of muscle morphology, fiber characteristics, extracellular matrix remodeling, myofibrillar and sarcomeric organization, apoptosis, and mitochondrial ultrastructure within a single mechanical disuse model.

11.7. Research Gap and Rationale for the Current Study

The central unresolved question is whether melatonin can attenuate mechanically induced skeletal muscle atrophy while preserving structural integrity, and whether this response varies according to sex, muscle type, and fiber composition. Although disuse-induced muscle atrophy studies have revealed a range of structural, cellular, and molecular alterations, these findings have not been sufficiently integrated across the hierarchical levels of muscle organization. Likewise, the evidence supporting the protective effects of melatonin is predominantly derived from heterogeneous atrophy models, thereby limiting its direct relevance to localized mechanical disuse. While the limited number of immobilization studies suggests potential protective effects, they do not comprehensively address sex- and muscle-specific variability, nor do they integrate morphological and ultrastructural outcomes within a unified experimental framework. The principal research gap, therefore, lies in the absence of a controlled experimental model that simultaneously investigates localized mechanical disuse across sex, muscle type, and fiber composition, and determines whether melatonin can modify the associated structural and biological changes.

11.8. Clinical and Broader Significance

Closing the gaps identified above has implications for understanding structural and functional recovery after skeletal muscle disuse. Determining whether fiber atrophy reflects changes in myofibrillar number, size, or organization could sharpen the assessment of structural recovery. Likewise, a dissociation between the recovery of muscle mass and that of fiber-level or functional properties would underscore the limitations of relying on muscle mass alone as a recovery endpoint.

Muscle and sex-specific differences in susceptibility to disuse may also guide more individualized prevention and rehabilitation strategies, for example, in the timing or type of intervention. Finally, the protective effects of melatonin in experimental models justify further investigation as a potential adjunctive strategy for disuse-induced muscle atrophy; however, most evidence derives from animal studies, and its clinical efficacy in mechanical disuse remains to be established.

11.9. Future Research Directions

11.9.1. Structural and Methodological Priorities

Future studies should integrate morphological, histological, ultrastructural, molecular, and functional assessments within the same experimental model. Building on recent ultrastructural evidence, future work should further quantify myofibrillar and sarcomeric remodeling and integrate these findings with molecular and functional outcomes. Experimental designs should also include both sexes and multiple muscles representing different fiber compositions, while longitudinal approaches covering immobilization, reloading, and recovery phases are needed to clarify the temporal progression of structural and functional changes.

11.9.2. Mechanistic Priorities

Future research should integrate analyses of protein turnover, oxidative stress, mitochondrial dysfunction, calcium homeostasis, inflammation, and apoptosis with structural remodeling. Such approaches should determine whether these mechanisms differ according to biological sex, muscle type, fiber composition, and duration of disuse, thereby clarifying the factors that contribute to differential muscle susceptibility and recovery.

11.9.3. Melatonin-Specific Priorities

Future studies should standardize melatonin dose, route, timing, and treatment duration and establish dose–response relationships. Preventive administration should be clearly distinguished from treatment of established atrophy, with direct comparisons between these approaches where feasible. Melatonin should also be evaluated in well-characterized mechanical disuse models, with assessment extending beyond muscle mass to include structural and ultrastructural preservation, functional investigations, and molecular studies. Finally, investigations should be extended to clinically relevant human immobilization and disuse settings, incorporating functional outcomes alongside structural and biochemical measures to determine whether experimentally observed benefits translate into meaningful clinical effects.

12. Conclusions

Disuse-induced skeletal muscle atrophy is a dynamic and multifactorial process in which mechanical unloading progressively disrupts muscle mass, fiber integrity, extracellular matrix organization, satellite cell function, myofibrillar architecture, and mitochondrial homeostasis through interconnected molecular pathways. The magnitude of these changes depends on the type and duration of disuse, the muscle examined, and its fiber composition, highlighting the need to consider structural and fiber-specific responses when interpreting experimental findings. Melatonin has been investigated for its potential effects on several of the pathways involved in this process, with experimental evidence supporting antioxidant, anti-inflammatory, mitochondrial-protective, and regenerative effects across different models of muscle wasting. However, direct evidence for its ability to preserve the structural and ultrastructural integrity of skeletal muscle during disuse remains limited. Further well-controlled studies integrating quantitative morphometry with histological, ultrastructural, and mechanism-related outcomes are therefore needed to define the extent and mechanisms of melatonin-mediated protection against disuse-induced muscle atrophy.

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