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Review article

Disrupted Circadian Rhythms as a Novel Driver of Sarcopenia: Mechanisms, Evidence, and Future Directions

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Abstract: Sarcopenia, a progressive and generalized skeletal muscle disorder characterized by loss of muscle mass, strength, and function, represents a major public health concern in aging populations. It contributes significantly to frailty, reduced mobility, falls, and mortality among older adults. While multifactorial in origin, emerging research suggests a compelling link between circadian rhythm disruption and the pathogenesis of sarcopenia. Circadian rhythms, governed by the central pacemaker in the suprachiasmatic nucleus (SCN) and regulated by a transcription-translation feedback loop involving core clock genes (BMAL1, CLOCK, PER, and CRY), orchestrate diverse physiological processes including metabolism, inflammation, hormone release, and mitochondrial function. Skeletal muscle harbors its own peripheral clock, which plays a critical role in regulating protein synthesis, glucose utilization, and mitochondrial dynamics. Recent evidence indicates that age-related alterations in circadian rhythms, as well as external circadian disruptions due to shift work, light exposure, or irregular sleep-wake cycles, may contribute to sarcopenia through hormonal dysregulation, chronic inflammation, impaired mitochondrial biogenesis, and reduced autophagy. Animal models with muscle-specific clock gene deletions exhibit muscle atrophy, increased oxidative stress, and reduced regenerative capacity. Epidemiological studies further support a relationship between circadian misalignment and decreased muscle strength and mass in humans. Additionally, interventions such as time-restricted feeding, scheduled exercise, and light therapy show promise in restoring circadian alignment and potentially mitigating muscle loss. This review aims to provide a comprehensive overview of current knowledge on the circadian regulation of skeletal muscle and the implications of circadian disruption for sarcopenia. We explore molecular mechanisms, epidemiological data, experimental studies, and emerging therapeutic strategies. Understanding the interplay between the circadian clock and muscle health may reveal novel approaches for preventing and managing sarcopenia in the aging population.

Keywords: sarcopenia; circadian rhythm; skeletal muscle disorder; aging; muscle health;

1. Introduction

Sarcopenia, as defined by the European Working Group on Sarcopenia in Older People (EWGSOP2), is a progressive and generalized syndrome marked by the decline in skeletal muscle strength, mass, and function, resulting in adverse outcomes such as physical disability, reduced quality of life, and increased mortality [1]. Given its profound impact on patient well-being, sarcopenia shares common challenges with other chronic conditions like cancer, where integrative therapeutic approaches have been shown to enhance quality of life and functional capacity [2,3]. It is increasingly prevalent in aging societies, with estimates suggesting that up to 50% of individuals over the age of 80 may be affected [4]. While sarcopenia has traditionally been

associated with sedentary behavior, nutritional deficiency, hormonal decline, and chronic inflammation, there is growing recognition that biological rhythms—particularly circadian rhythms—may also play a critical role in its pathophysiology [5,6].

Circadian rhythms are endogenously generated biological processes that cycle approximately every 24 hours and regulate a multitude of physiological functions including sleep-wake cycles, metabolism, immune responses, and endocrine signaling [6,7]. These rhythms are maintained by a central clock in the suprachiasmatic nucleus (SCN) of the hypothalamus and are synchronized by environmental cues such as light and food intake. Importantly, nearly every peripheral tissue, including skeletal muscle, possesses its own circadian machinery that operates in coordination with the central clock. The molecular clockwork in cells is driven by transcriptional-translational feedback loops involving core clock genes—BMAL1, CLOCK, PER1/2, CRY1/2—and their downstream targets, which in turn regulate tissue-specific gene expression [8,9].

With aging, circadian rhythmicity deteriorates. Older adults often experience fragmented sleep, delayed or advanced sleep phases, and a blunted amplitude of circadian gene expression. This dysregulation extends to peripheral tissues, including muscle, where it may contribute to impaired protein turnover, altered mitochondrial dynamics, and reduced regenerative potential. Additionally, lifestyle factors that disrupt circadian alignment—such as night shift work, erratic meal timing, and inadequate exposure to natural light—can exacerbate these effects [10,11].

Despite accumulating evidence of a connection between circadian biology and skeletal muscle health, this relationship remains underexplored in the context of sarcopenia. A comprehensive understanding of the gut-muscle-clock axis, hormonal influences, oxidative stress, and inflammatory pathways offers potential for the development of chrono-targeted interventions. The goal of this review is to synthesize current evidence linking circadian disruption to sarcopenia, identify gaps in the literature, and propose potential therapeutic strategies rooted in chronobiology.

2. The Circadian Clock System

Circadian rhythms are intrinsic, approximately 24-hour cycles in physiological processes that enable organisms to anticipate and adapt to regular environmental changes such as the light-dark cycle. These rhythms are regulated by a central pacemaker located in the suprachiasmatic nucleus (SCN) of the hypothalamus and are synchronized to environmental cues, known as zeitgebers. The primary zeitgeber for the central clock is light, detected via specialized retinal ganglion cells projecting to the SCN. In turn, the SCN coordinates peripheral clocks present in almost every cell of the body, including those in liver, adipose tissue, and skeletal muscle [9].

At the molecular level, circadian rhythms are generated and maintained by transcription-translation feedback loops involving a set of core clock genes. The positive arm of the feedback loop involves BMAL1 and CLOCK, which heterodimerize and promote the transcription of Period (PER1, PER2) and Cryptochrome (CRY1, CRY2) genes. The PER and CRY proteins accumulate, translocate to the nucleus, and inhibit the activity of the BMAL1/CLOCK complex, thereby repressing their own transcription and closing the loop. A secondary loop involving nuclear receptors REV-ERBα/β and RORα/β fine-tunes the oscillation of BMAL1 expression and links the clock to metabolic gene regulation[9,12].

In skeletal muscle, the circadian clock regulates tissue-specific transcriptional programs controlling glucose uptake, mitochondrial function, lipid metabolism, protein

synthesis, and myogenic differentiation . For instance, BMAL1 influences the expression of MyoD, a key transcription factor involved in myogenesis [13]. CLOCK proteins modulate mitochondrial biogenesis and oxidative phosphorylation pathways. Additionally, the muscle clock is tightly integrated with systemic signals including feeding patterns, hormonal cues (e.g., insulin, cortisol), and neural input, allowing skeletal muscle to act as both a circadian effector and sensor [8,14].

The disruption of this clock system in skeletal muscle has been shown to induce metabolic inflexibility, increase reactive oxygen species (ROS) production, and impair muscle contractile function. Muscle-specific BMAL1 knockout mice exhibit premature aging phenotypes, including muscle atrophy, reduced muscle strength, and abnormal mitochondrial morphology. These findings underscore the critical role of a functioning circadian clock in muscle homeostasis and suggest that circadian disruption could contribute directly to sarcopenia [13,14].

Importantly, the temporal regulation of muscle function also extends to whole-body physiology. Diurnal variation in muscle strength, exercise capacity, and susceptibility to fatigue has been documented in humans. These fluctuations align with the endogenous rhythm of muscle gene expression and mitochondrial activity [15]. Thus, time-of-day may significantly influence muscle performance and regenerative potential—a concept with implications for the timing of exercise, nutrition, and pharmacologic interventions in sarcopenic patients [14,15].

3. Aging and Circadian Dysregulation

Aging is associated with progressive deterioration of the circadian system, a phenomenon that contributes to a range of physiological dysfunctions, including metabolic disorders, cognitive decline, and immune dysregulation [16]. The SCN, the central pacemaker, undergoes structural and functional changes with age, including decreased neuronal activity, impaired electrical signaling, and reduced responsiveness to light cues. These changes manifest clinically as disrupted sleep patterns, fragmented rest-activity cycles, and advanced or delayed circadian phase syndromes [17,18].

Importantly, peripheral clocks also exhibit age-related alterations. In skeletal muscle, the amplitude of circadian gene oscillation becomes blunted with age. Several studies using transcriptomic and proteomic analyses have shown that aged muscle exhibits altered rhythmicity in genes related to metabolism, protein turnover, and mitochondrial dynamics. For example, the rhythmic expression of genes encoding enzymes in glycolysis, fatty acid oxidation, and the tricarboxylic acid (TCA) cycle is dampened in aged skeletal muscle. This loss of rhythmic coordination may impair metabolic efficiency and contribute to anabolic resistance—a hallmark of sarcopenia [8,14,19].

Additionally, aging disrupts the coupling between the central and peripheral clocks, leading to internal desynchronization [20]. Factors such as reduced physical activity, irregular feeding schedules, and diminished exposure to daylight exacerbate this phenomenon. This decoupling results in asynchronous tissue-specific gene expression and impairs systemic homeostasis. In skeletal muscle, this may manifest as disrupted autophagy, accumulation of damaged proteins and organelles, and decreased responsiveness to anabolic stimuli like exercise or amino acids [14,20].

Hormonal changes associated with aging further compound circadian dysregulation. Secretion of melatonin, a key circadian hormone, declines with age, weakening the signal from the SCN to peripheral tissues. Growth hormone (GH) and insulin-like growth factor-1 (IGF-1), which follow circadian patterns, also decrease with age, im-

pairing muscle protein synthesis and regenerative capacity. Glucocorticoids, particularly cortisol, often exhibit a flattened diurnal curve in older adults, contributing to catabolic signaling in muscle.

These age-associated disruptions to circadian rhythmicity and hormonal signaling establish a pro-sarcopenic environment characterized by increased oxidative stress, chronic inflammation, mitochondrial dysfunction, and impaired protein synthesis. When compounded by lifestyle factors such as poor sleep hygiene or nighttime light exposure, the risk of sarcopenia may be further amplified. Understanding and mitigating circadian dysregulation in aging individuals may thus represent a novel strategy to preserve muscle mass and function across the lifespan.

4. Evidence Linking Circadian Disruption and Sarcopenia

4.1. Epidemiological Evidence

Observational studies in human populations have increasingly pointed to a correlation between circadian rhythm disruption and adverse musculoskeletal outcomes [21-23]. One of the earliest and most cited lines of evidence stems from research on shift workers—individuals whose work schedules deviate from the traditional diurnal pattern. These individuals are chronically exposed to circadian misalignment due to irregular light exposure, altered sleep-wake cycles, and inconsistent eating patterns. Shiftwork can negatively impact skeletal muscle health due to disruptions in circadian rhythms, hormonal imbalances, poor nutrition, and reduced physical activity. The irregular sleep-wake cycles and meal timing associated with shiftwork can impair the body's internal clock, leading to decreased muscle protein synthesis and increased protein breakdown. Hormonal fluctuations, such as elevated cortisol and reduced testosterone levels, further contribute to muscle degradation. Additionally, shiftworkers often experience challenges in maintaining a balanced diet and regular exercise routine, both of which are essential for muscle maintenance. These combined factors suggest that shiftwork may increase the risk of muscle atrophy over time [22].

A large-scale Korean population-based study by Choi et al. (2019) analyzed data from the Korea National Health and Nutrition Examination Survey and found that night-shift workers had a significantly higher prevalence of sarcopenia compared to non-shift workers, even after adjusting for lifestyle confounders such as physical activity, diet, and sleep duration. The association was especially strong among older men, suggesting a possible age and sex interaction in circadian vulnerability. This study supports the hypothesis that circadian misalignment is an independent risk factor for muscle degeneration [22].

Similar trends have been observed in the elderly. Poor sleep quality, a common marker of circadian dysfunction, is associated with reduced muscle strength and physical performance in aging adults. In a study of over 4,000 older adults in China, participants with objectively measured short sleep duration (<6 hours/night) and fragmented sleep exhibited significantly lower appendicular lean mass and grip strength. These findings held true after controlling for comorbidities and physical activity, suggesting a biological pathway between sleep disruption and muscle wasting [23].

Other observational data link irregular meal timing—a disruptor of peripheral circadian rhythms—with impaired muscle function. A study by Farsijani et al. (2023) explored the relationship between chrononutrition behaviors and muscle health in older adults. The study found that certain meal timing patterns, such as an earlier first intake time and a longer eating window, were associated with better muscle mass and function. While this doesn't directly address evening calorie consumption

and physical performance tests, it highlights the significance of meal timing on muscle health in older populations [24].

While causality cannot be inferred from observational studies alone, these findings underscore the potential impact of circadian disruption on sarcopenia risk, independent of traditional risk factors such as diet and activity level.

4.2. Experimental evidence

Experimental studies in animal models have provided mechanistic evidence to support the epidemiological findings [25-29]. Genetically modified mice with deletions or mutations in core clock genes exhibit profound musculoskeletal abnormalities that mirror features of sarcopenia.

The role of BMAL1, a master circadian regulator, has been extensively studied in this context. Kondratov et al. (2006) demonstrated that global BMAL1 knockout mice show premature aging, reduced lifespan, and pronounced sarcopenia-like phenotypes, including decreased muscle mass, muscle fiber atrophy, and reduced contractile strength. Muscle-specific BMAL1 knockout mice also display metabolic impairments, mitochondrial dysfunction, and impaired myogenesis—further supporting a muscle-intrinsic role for circadian regulation [25].

Further insights have come from studies using environmental manipulation to induce circadian misalignment. Mice exposed to chronic phase shifts (e.g., 6-hour advances of the light-dark cycle every few days, mimicking shift work) show decreased muscle mass and fiber size, as well as increased expression of muscle atrophy-related genes like Atrogin-1 and MuRF1. These effects are thought to be mediated by alterations in the muscle's molecular clock, mitochondrial stress, and inflammatory cytokine expression [26-28].

Circadian disruption also impairs muscle regeneration following injury. A study by Andrews et al. (2010) found that the timing of muscle injury relative to the circadian cycle significantly affected regenerative outcomes [13]. Additionally, injuries incurred during the resting phase (subjective night in rodents) led to slower healing and reduced satellite cell activation compared to those sustained during the active phase [29]. These findings suggest that not only maintenance but also repair of muscle tissue is under circadian control [13,28,29].

Animal models have further demonstrated that environmental cues such as feeding and exercise can entrain the muscle clock and restore rhythmicity, suggesting that behavioral interventions may mitigate the effects of genetic or environmental circadian disruption.

4.3 Human Studies

While human interventional studies directly linking circadian misalignment to sarcopenia are limited, several small-scale investigations provide translational insight.

A clinical study conducted by Takahashi et al. (2021) evaluated the effect of controlled light exposure on muscle function in older adults with circadian rhythm sleep disorders. After four weeks of morning bright light therapy, participants showed not only improved sleep quality and circadian phase alignment, but also modest gains in muscle strength and physical performance [9]. Though preliminary, this suggests that restoring circadian rhythm through light entrainment may have peripheral benefits on muscle health [30].

Chrono-nutrition studies have also revealed that the timing of protein intake affects muscle protein synthesis [31,32]. In a crossover trial, older adults who consumed a high-protein breakfast exhibited greater postprandial muscle protein synthesis compared to those who consumed the same meal at dinner, even when total protein intake was held constant [31]. These findings align with the notion that muscle is more responsive to anabolic stimuli during the daytime, when peripheral clock gene expression is optimized for protein turnover.

Exercise-timing studies support a similar conclusion. Resistance training performed in the morning resulted in greater improvements in muscle strength and lean mass compared to evening training among older men [33,34]. This effect may be attributed to synchronization between exercise-induced stimuli and peak expression of clock-controlled genes involved in myogenesis and mitochondrial function.

Moreover, patients with chronic circadian disorders such as advanced sleep phase syndrome (ASPS) or delayed sleep phase syndrome (DSPS) often exhibit higher levels of systemic inflammation, oxidative stress markers, and metabolic dysfunction—all of which are known contributors to muscle catabolism and sarcopenia [35-37].

While more rigorous and large-scale interventional studies are needed, these early human trials and correlational data provide a compelling rationale for circadian-targeted therapies in sarcopenia prevention and management.

5. Mechanisms of Circadian Disruption in Muscle Loss

Understanding the mechanistic links between circadian disruption and muscle atrophy is essential for developing targeted interventions against sarcopenia. Current evidence suggests that several interrelated pathways are involved, including hormonal dysregulation, mitochondrial dysfunction, inflammation and oxidative stress, and impaired autophagy and regeneration. Each of these pathways is influenced by the circadian clock and becomes progressively dysregulated with age and circadian misalignment. The main findings can be seen in *Table 1*.

Table 1. **Mechanisms Linking Circadian Disruption to Muscle Degradation**

Biological Mechanism	Circadian Influence	Impact on Skeletal Muscle
Hormonal Dysregulation	Disrupts secretion of GH, IGF-1, and testosterone; flattens the cortisol rhythm	Blunted anabolic signaling, increased proteolysis, reduced neuromuscular function
Mitochondrial Dysfunction	Reduces mitochondrial biogenesis and ATP production; increases ROS	Decreased endurance, impaired muscle contractility, fatigue, and atrophy
Inflammation and Oxidative Stress	Increases pro-inflammatory cytokines; dampens antioxidant enzyme expression	Promotes catabolic pathways, damages muscle fibers, accelerates muscle loss
Impaired Autophagy & Regeneration	Suppresses autophagic flux and satellite cell activation	Accumulation of damaged proteins, delayed muscle repair and regeneration

5.1. Hormonal Pathways

Skeletal muscle is highly responsive to endocrine signals, many of which are under circadian control. Key anabolic hormones—including growth hormone (GH), testosterone, and insulin-like growth factor-1 (IGF-1)—exhibit diurnal fluctuations that are essential for muscle protein synthesis and maintenance of muscle mass [38,39].

GH, secreted primarily during slow-wave sleep, promotes muscle hypertrophy and facilitates IGF-1 production in peripheral tissues. IGF-1 activates the PI3K-Akt-mTOR pathway, a crucial driver of protein synthesis in skeletal muscle. Circadian disruption, particularly from poor sleep quality or irregular sleep-wake cycles, blunts GH secretion and reduces IGF-1 levels, impairing the muscle's anabolic signaling capacity [38,39]. Moreover, cortisol, a glucocorticoid hormone with catabolic effects on muscle, typically follows a diurnal pattern, peaking in the early morning and declining throughout the day. Circadian misalignment can flatten this curve, leading to elevated cortisol levels during inappropriate times, exacerbating muscle breakdown via activation of the ubiquitin-proteasome pathway [5,40].

Testosterone, another key anabolic hormone, also demonstrates a circadian rhythm, with peak levels occurring during early morning hours. In older men, circadian flattening and overall decline in testosterone secretion contribute significantly to the development of sarcopenia. Sleep deprivation and circadian phase shifts have been shown to suppress testosterone release, reducing protein synthesis and impairing neuromuscular function [41,42].

The combined disruption of these hormonal axes leads to an environment characterized by blunted anabolic signaling and enhanced proteolysis, both of which favor muscle atrophy. These hormonal disturbances may also impair the muscle's response to external stimuli such as resistance exercise or protein intake, a phenomenon known as anabolic resistance [38-43].

5.2. Mitochondrial Dysfunction

Mitochondria are the powerhouses of the cell and play a central role in energy metabolism, redox balance, and apoptosis regulation. Skeletal muscle is highly dependent on mitochondrial function to meet its energy demands, particularly during exercise or repair.

Mitochondrial biogenesis and oxidative phosphorylation are tightly regulated by the circadian clock. CLOCK and BMAL1 have been shown to control the expression of genes involved in mitochondrial metabolism, including nuclear respiratory factors (NRF1/2), peroxisome proliferator-activated receptor gamma coactivator 1-alpha (PGC-1α), and genes encoding components of the electron transport chain. Disruption of clock gene expression leads to diminished mitochondrial content, impaired ATP production, and increased ROS generation [8,13].

Animal studies have shown that muscle-specific disruption of BMAL1 results in abnormal mitochondrial morphology, reduced oxidative enzyme activity, and increased markers of oxidative damage. These changes mirror those observed in aged and sarcopenic muscle, suggesting a mechanistic overlap. Furthermore, circadian misalignment caused by environmental cues such as irregular feeding or light exposure impairs the expression of mitochondrial regulators, contributing to metabolic inflexibility [25].

Mitochondrial dysfunction in skeletal muscle also triggers pro-apoptotic signaling and reduces the muscle's ability to respond to metabolic stressors. This contributes not only to muscle loss but also to increased fatigue and reduced endurance, which further reduce physical activity and exacerbate sarcopenia in a vicious cycle [8,13,25].

5.3. Inflammation and Oxidative Stress

Chronic low-grade inflammation, also known as "inflammaging," is a hallmark of both aging and sarcopenia. Elevated levels of circulating inflammatory cytokines such as TNF-α, IL-6, and CRP have been correlated with reduced muscle mass and

strength in older adults. Importantly, the circadian clock is a key regulator of the immune system and inflammatory responses [44].

The expression of inflammatory genes is subject to circadian regulation. For instance, NF-κB, a central transcription factor in inflammation, shows rhythmic activity modulated by clock genes. Disruption of BMAL1 or CLOCK leads to increased expression of pro-inflammatory cytokines and heightened sensitivity to inflammatory stimuli [45,46].

Circadian misalignment also exacerbates oxidative stress in muscle tissue. The rhythmic expression of antioxidant enzymes such as superoxide dismutase (SOD) and catalase is dampened under disrupted circadian conditions, reducing the muscle's capacity to neutralize ROS. Accumulation of ROS damages cellular proteins, lipids, and DNA, ultimately impairing muscle contractility and regenerative potential [46].

Oxidative stress also activates catabolic pathways such as the FOXO/atrogin-1 axis, which accelerates proteolysis and contributes to muscle wasting. The interplay between oxidative stress and inflammation creates a pro-catabolic environment that promotes sarcopenia, especially in the context of aging [48].

5.4. Impaired Autophagy and Muscle Regeneration

Autophagy is a cellular quality control mechanism responsible for degrading damaged organelles and proteins, thus maintaining cellular homeostasis. In skeletal muscle, autophagy plays a vital role in preserving muscle mass and supporting recovery following injury or stress. Circadian control of autophagy-related genes ensures temporal coordination of muscle repair and regeneration processes [13,49].

Several studies have demonstrated that autophagy is under circadian control, with peak autophagic activity occurring during specific phases of the light-dark cycle. Disruption of circadian timing leads to impaired autophagic flux and accumulation of dysfunctional mitochondria and aggregated proteins—features commonly observed in sarcopenic muscle [13,49,50].

Furthermore, muscle regeneration following injury relies heavily on the activation and proliferation of satellite cells—muscle stem cells that are crucial for growth and repair. Satellite cell activity is also regulated by circadian signals. A recent study by Chatterjee et al. (2021) demonstrated that circadian disruption impairs satellite cell proliferation and myogenic differentiation, resulting in delayed muscle regeneration [49].

These findings suggest that circadian misalignment compromises both the degradation of damaged cellular components and the regenerative response to injury or stress. This double-hit may accelerate the progression of sarcopenia, especially in older adults whose regenerative capacity is already diminished.

6. Potential Therapeutic Interventions

Given the growing evidence linking circadian misalignment with sarcopenia, a range of therapeutic strategies has emerged that aim to restore circadian harmony and, in doing so, preserve or improve muscle mass, strength, and metabolic function. These interventions target both central and peripheral clocks and include chronotherapy, time-restricted feeding, sleep hygiene optimization, light exposure, and exercise timing. While many of these strategies remain under investigation, preliminary data from both animal models and human studies are promising. The findings are summarized in *Table 2*.

Table 2. Circadian-Aligned Interventions for Sarcopenia Management

Intervention Strategy	Mechanism of Action	Preliminary Evidence and Benefits
Time-Restricted Feeding (TRF)	Synchronizes peripheral clocks with feeding cues; enhances metabolic coordination	Preserves lean mass, improves muscle performance in older adults
Light Exposure & Sleep Optimization	Resets central circadian pacemaker (SCN); regulates hormonal output	Morning light improves sleep and muscle strength; enhances melatonin rhythm
Scheduled Exercise	Entrains the muscle clock; aligns training with peak anabolic sensitivity	Morning training yields superior muscle strength and hypertrophy gains
Chronotherapy (Timed Medications)	Aligns hormone or drug administration with biological rhythms	Timed GH/testosterone delivery may improve synthesis and reduce side effects

6.1. Chronotherapy

Chronotherapy refers to the strategic timing of medical treatments or interventions to align with biological rhythms. It is increasingly recognized that the efficacy and tolerability of certain medications vary depending on the time of day they are administered. This concept has been explored in oncology and hypertension management, and is now gaining attention in the field of geriatric muscle health [51].

In the context of sarcopenia, chronotherapy could be applied to optimize the administration of anabolic agents, such as testosterone, GH analogues, or IGF-1 stimulators. For example, administering GH in synchrony with its natural nocturnal peak may enhance muscle protein synthesis and minimize adverse effects. Similarly, the timing of anti-inflammatory treatments might be tailored to suppress pro-inflammatory cytokine expression at their circadian zeniths, potentially attenuating muscle catabolism [52].

Emerging pharmacologic approaches also include the use of compounds that modulate core clock proteins—so-called "clock-enhancing drugs." In animal models, small molecules targeting REV-ERBs and RORs have demonstrated potential to reset circadian rhythms and improve metabolic outcomes. Though these agents are not yet approved for clinical use in sarcopenia, they represent an exciting area of future research [52].

6.2 Time-Restricted Feeding (TRF)

One of the most practical and well-studied interventions for circadian realignment is time-restricted feeding (TRF), a dietary approach that confines food intake to a consistent daily window, typically 8–12 hours. TRF helps synchronize peripheral clocks, including those in skeletal muscle, with environmental light-dark cycles and feeding cues. Unlike caloric restriction, TRF can improve metabolic and musculoskeletal health without reducing energy intake [24,25,29].

Studies in mice have shown that TRF protects against muscle loss and preserves mitochondrial function even under high-fat diet conditions. TRF restores rhythmic gene expression in muscle, improves insulin sensitivity, and enhances muscle repair after injury. In aging rodents, TRF extends lifespan and delays the onset of sarcopenia-like phenotypes [25,26,29].

In humans, evidence is growing to support the role of meal timing in muscle health. A 2020 study involving older adults found that TRF improved muscle performance and reduced fat mass without compromising lean mass. Furthermore, circadian-

aligned protein ingestion (e.g., consuming protein-rich meals earlier in the day) may enhance muscle protein synthesis compared to evening or nighttime consumption, likely due to heightened sensitivity of muscle tissue to anabolic signals during daylight hours [31].

While more randomized controlled trials are needed, TRF represents a low-cost, behaviorally accessible intervention with significant potential to modulate circadian rhythms and combat sarcopenia.

6.3 Sleep Hygiene and Light Exposure

Maintaining high-quality, consolidated sleep is essential for optimal circadian function. Older adults often experience sleep fragmentation, advanced sleep phase, and insomnia—all of which disrupt the SCN's regulatory control over peripheral clocks. Thus, improving sleep quality and reinforcing natural circadian rhythms may help support musculoskeletal health [10,11,18].

Sleep hygiene interventions—such as consistent sleep-wake timing, limiting screen exposure before bed, and creating dark, quiet sleep environments—are foundational. Cognitive behavioral therapy for insomnia (CBT-I) has also been shown to improve muscle-related outcomes indirectly by reducing inflammation and enhancing endocrine regulation [35,38].

Light exposure is another powerful tool for circadian entrainment. The SCN is particularly sensitive to bright light, especially blue wavelengths during the morning hours. Morning light exposure can shift the circadian phase earlier, enhance melatonin secretion, and restore rhythmicity of hormonal outputs. In a small clinical trial, older adults who received daily morning bright light therapy experienced not only improved sleep and mood, but also increased gait speed and muscle strength over four weeks [16,17].

Strategically reducing light exposure at night—particularly from screens and artificial sources—can prevent melatonin suppression and support sleep-mediated anabolic processes. Reducing circadian "light pollution" in nursing homes and elder care settings may offer a simple yet effective intervention for reducing sarcopenia risk [35,47].

6.4 Scheduled Exercise

Physical activity is one of the most effective interventions for both preventing and treating sarcopenia. Beyond its direct anabolic effects, exercise also serves as a potent zeitgeber for peripheral clocks, including the muscle circadian oscillator. The timing of exercise plays a critical role in its ability to reset the clock and optimize metabolic and regenerative pathways [7,13,14].

Animal studies have shown that exercise at different times of day leads to distinct gene expression patterns in muscle. For instance, morning exercise enhances glycolytic pathways, while evening exercise promotes lipid oxidation. Timing exercise to align with circadian phases when muscle sensitivity is highest may amplify the benefits of training [26,34,50].

Human data, though limited, are supportive. A study by Zambon et al. (2022) demonstrated that resistance training in the morning led to greater improvements in muscle strength and lean mass compared to evening sessions in older adults [53]. Another trial found that older individuals who engaged in habitual morning walking exhibited better muscle preservation and physical performance over time than those who exercised later in the day [54].

Combining exercise with other circadian-aligned behaviors—such as TRF and consistent sleep patterns—may yield synergistic benefits. Exercise interventions can also help restore circadian rhythm in individuals suffering from disorders like advanced sleep phase syndrome, further reinforcing a healthy muscle clock [19,24,29].

6.5 Multimodal Interventions and Future Perspectives

Given the interconnected nature of circadian rhythms and muscle health, a multimodal approach combining several circadian-aligned strategies is likely to be most effective. Personalized chronotherapeutic interventions that take into account an individual's chronotype (morningness vs. eveningness), lifestyle, and comorbidities may optimize outcomes [22,24].

Wearable devices capable of tracking activity, sleep, and light exposure in real-time can offer novel insights into circadian rhythm patterns and facilitate tailored recommendations. Integration of digital health tools with behavioral coaching may represent a future direction in sarcopenia management [10,55].

Furthermore, ongoing clinical trials are testing the impact of circadian-aligned interventions—such as time-restricted eating, melatonin supplementation, and bright light therapy—on muscle mass and function in older adults [19,23]. These studies will help clarify the potential of circadian medicine in combating age-related muscle loss.

7. Research Gaps and Future Directions

Despite increasing evidence linking circadian disruption to sarcopenia, the field remains in its infancy. Several critical research gaps must be addressed to fully understand the mechanisms involved and to develop effective, evidence-based interventions.

Most of the current data associating circadian rhythm disruption with sarcopenia in humans are derived from cross-sectional studies or short-term interventional trials. These designs limit causal inference and fail to capture the long-term consequences of chronic circadian misalignment. Longitudinal cohort studies tracking sleep-wake cycles, feeding behaviors, hormonal rhythms, and muscle outcomes across the lifespan are urgently needed. Additionally, studies that begin in midlife and follow individuals into old age could help identify early circadian biomarkers predictive of later sarcopenia risk.

There is currently no gold standard for measuring circadian misalignment in clinical populations. Studies use diverse proxies—including self-reported sleep quality, chronotype questionnaires, actigraphy, and biomarker rhythms—making comparison across studies difficult. Developing and validating standardized tools for assessing circadian rhythm health (e.g., rest-activity phase, melatonin onset, core body temperature rhythms) will improve the reproducibility and reliability of findings.

Furthermore, wearable technology and machine learning approaches could enhance the precision of circadian measurements and allow real-time circadian tracking in naturalistic settings. Integrating such tools in aging and sarcopenia research could reveal novel temporal patterns and personalize interventions.

While animal models have illuminated core mechanisms by which circadian disruption affects muscle physiology, human data remain sparse. Muscle biopsies obtained at different circadian time points could be used to assess diurnal variation in gene expression, mitochondrial function, and regenerative signaling in both young and older adults. Omics-based studies (transcriptomics, metabolomics, proteomics) may

further clarify the molecular signatures of circadian dysregulation in sarcopenic muscle.

Moreover, studies exploring sex differences in circadian-muscle interactions are lacking. Hormonal fluctuations across the menstrual cycle, menopause, and aging may alter circadian biology and muscle responses, necessitating gender-specific research.

Few RCTs have tested whether circadian-aligned interventions—such as time-restricted eating, exercise timing, or light therapy—can prevent or reverse sarcopenia. Most studies to date are small and focus on surrogate outcomes like sleep quality or subjective fatigue.

Future RCTs should evaluate functional endpoints such as muscle mass (via DXA or MRI), strength (grip or isokinetic testing), and physical performance (gait speed, chair stand). These trials should also explore the optimal timing, duration, and combination of interventions, and stratify participants by chronotype or baseline circadian disruption. Ideally, large-scale multicenter trials would evaluate the real-world effectiveness of circadian-based lifestyle modifications in older populations.

Emerging tools such as organoids, circadian reporter cell lines, and CRISPR-based editing of clock genes in human-derived muscle cells offer powerful platforms for studying circadian biology in vitro. These models could help identify druggable targets and test responses to timed stimuli (e.g., nutrients, hormones) under different circadian phases.

Looking forward, precision medicine approaches incorporating chronobiology could become a cornerstone of sarcopenia prevention. Integrating genetic chronotype data, behavioral circadian patterns, and individual responses to timing-based interventions could lead to personalized treatment protocols that optimize muscle maintenance throughout aging.

8. Conclusion

Sarcopenia is a multifactorial condition with significant public health implications, particularly in rapidly aging societies. While traditional factors such as inactivity, malnutrition, and hormonal decline have long been recognized, circadian rhythm disruption represents a novel and underappreciated contributor to muscle degeneration in aging.

This review has synthesized current evidence highlighting the pivotal role of the circadian system in regulating skeletal muscle physiology. From the molecular clock within muscle cells to systemic hormonal rhythms, circadian timing influences protein synthesis, mitochondrial function, inflammation, and regenerative capacity. Disruptions to this temporal regulation—whether from aging itself or lifestyle factors like shift work, sleep loss, or irregular meal timing—can tip the balance toward catabolism and muscle loss.

Emerging human and animal studies underscore the potential of circadian-aligned interventions, including time-restricted feeding, scheduled exercise, light therapy, and sleep optimization, to restore circadian synchrony and support muscle health. While early findings are promising, robust longitudinal studies and randomized trials are needed to clarify causality, define optimal intervention strategies, and guide clinical translation.

The integration of circadian biology into the framework of sarcopenia opens new therapeutic avenues. It challenges researchers and clinicians to think not only about what interventions are used to preserve muscle mass, but also when they are administered. In doing so, we may unlock new opportunities to enhance healthy aging, improve mobility, and reduce disability in older adults.

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