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Mini Review

Neurological Aspects of Sarcopenia: A Comprehensive Update on Pathophysiology, Diagnosis, and Therapeutic Advances

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Abstract

Sarcopenia is an age-related disorder characterized by progressive and generalized loss of skeletal muscle tissue. This condition affects approximately 9.9-40.4% of older adults, 2-34% of outpatients, and about 56% of hospitalized patients. Sarcopenia is classified into primary and secondary types, with primary sarcopenia resulting from the natural aging process and secondary sarcopenia caused by various factors such as sedentary lifestyle, disease, and nutrition. The pathophysiology of sarcopenia involves cellular mechanisms, including genetic alterations, telomere erosion, and proteostasis disruption. Mitochondrial dysfunction, epigenetic modifications, and metabolic factors also contribute to the condition. Neurological aspects, such as motor neuron loss and sodium channel dysfunction, play a crucial role in the development of sarcopenia. Prevention and treatment strategies include exercise interventions, nutritional strategies, and pharmacological interventions. Vitamin D supplementation, testosterone replacement therapy, and selective androgen receptor modulators (SARMs) are among the treatments explored. However, these treatments come with potential side effects, highlighting the need for further research and evaluation.

Keywords: sarcopenia, skeletal muscle, cachexia, frailty, neurodegeneration

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1. Introduction

Human lifestyle has evolved significantly over recent centuries, leading to increased life expectancy [1]. However, aging, as a natural and irreversible biological process, accounts for a considerable proportion of diseases and mortality in human societies. Aging is a primary cause of decreased physiological function in body organs, ultimately resulting in death [2]. Skeletal muscle tissue, comprising 40-50% of the mammalian and human body, is one of the largest organs [3]. During aging, the human skeletal muscle mass undergoes atrophy, with estimates suggesting that after age 30, the body experiences an annual decrease of 0.1% to 0.5% in skeletal muscle volume, or 3-8% per decade [5, 4]. Numerous studies have investigated the onset age of skeletal muscle volume reduction in sarcopenia, with some variation. However, most studies indicate that the rate of muscle atrophy and volume reduction accelerates after age 65 or 70, sometimes leading to mortality in elderly individuals [4 –7].

This phenomenon, known as sarcopenia, is a major age-related disorder. A more comprehensive definition of sarcopenia is the progressive and generalized loss of skeletal muscle tissue, resulting in decreased muscle quality and strength in affected patients compared to healthy age-matched individuals [8 –10]. Studies have shown that the prevalence of sarcopenia is approximately 9.9-40.4% in older adults, 2-34% in outpatients, and about 56% in hospitalized patients, representing a high proportion of the population [11–14]. In sarcopenic patients, reduced muscle function can lead to impaired daily activities, falls, decreased physical performance, increased hospitalization, higher healthcare costs, and ultimately, poor quality of life and even death [9]. Given the relatively high prevalence of this condition in society, its impact on patients' functional abilities, and the associated healthcare costs for patients, hospitals, and communities, studying sarcopenia is crucial for understanding its pathophysiology, prevention, and treatment.

2. Types of Sarcopenias

Sarcopenia is classified into two main categories, primary and secondary sarcopenia (Table 1) [15]. The primary sarcopenia is associated with the natural aging process, without any specific underlying cause other than aging itself. Secondary sarcopenia is caused by various factors, including sedentary lifestyle, immobility, and lack of physical activity, which are called activity-related factors. Other factors that can cause sarcopenia are disease-related factors and nutrition-related factors. Disease-related factors are advanced organ failure, inflammatory diseases, malignancies, and endocrine disorders. Among nutrition-related factors, inadequate dietary intake, malabsorption, gastrointestinal disorders, and use of medications that may cause anorexia are the main causes [15, 16].

In an alternative classification of sarcopenia based on the duration of an individual's involvement with muscular problems, there are two categories: acute sarcopenia and chronic sarcopenia. According to this

Table 1: The classification of sarcopenia based on its underlying causes includes.

Type of disease	Causes	Pathways
Primary sarcopenia	Age-related causes	Reduction in skeletal muscle mass and volume during the aging process
		Degeneration of parts of the brain related to skeletal muscles during the aging process
		Reduction of motor neurons in number and size during the aging process
		Reduction in satellite cell numbers and their regenerative capacity during neural repair
Secondary sarcopenia	Nutrition-related causes	Malnutrition is one of the significant factors contributing to decreased muscle mass and volume, especially during aging
	Physical activity-related causes	Reduced activity and sedentary lifestyle are important factors contributing to sarcopenia
	Disease-related causes	Diseases related to telomere deletions on chromosomes
		Genetic and epigenetic changes
		Reduction in testosterone levels due to aging
		Diabetes and decreased levels of the enzyme peroxiredoxin 6
		Mitochondrial disorders and increased reactive oxygen species levels
		Diseases related to neurological disorders and neural analysis

classification, sarcopenia lasting less than 6 months is referred to as acute sarcopenia. Acute sarcopenia typically occurs due to one or more underlying factors or acute-onset diseases. On the other hand, chronic sarcopenia develops progressively and persistently due to chronic background conditions, with a duration of involvement exceeding 6 months [17]. Given the broad spectrum of sarcopenia-related diseases and their similarities to other skeletal muscle disorders in the elderly population, differential diagnosis becomes crucial.

3. Differential Diagnosis

Among these related conditions are malnutrition, cachexia, frailty, and neuromuscular disorders that often manifest in older individuals [18–21]. Neuromuscular disorders, such as amyotrophic lateral sclerosis (ALS), which involve motor neurons, represent a specific type of inflammatory myopathy. Two subtypes of this disorder—namely, inclusion body myositis and myotonic dystrophy—exhibit delayed onset compared to other related familial disorders and can present with symptoms similar to sarcopenia in older age [21–24].

Of particular interest are malnutrition and cachexia, which share significant similarities with sarcopenia. Recent studies have emphasized that the primary focus of malnutrition definitions is muscle mass reduction [25]. In contrast, the updated definitions of sarcopenia (known as EWGSOP2, developed by the European Working Group on Sarcopenia in Older People in 2019) emphasize muscle function as the key criterion [17]. Consequently, the presence of reduced muscle mass in a patient without a corresponding decline in muscle strength or function may be more indicative of malnutrition than sarcopenia. Conversely, the combination of reduced muscle mass and impaired muscle function is suggestive of sarcopenia [26].

Cachexia is defined as severe weight loss accompanied by muscle wasting. It is associated with underlying conditions such as HIV, cancer, and organ failure. Studies have revealed significant overlap between the definitions of cachexia and sarcopenia, particularly in recent definitions. Both conditions involve a reduction in muscle mass, and they can coexist concurrently in a single patient, especially when there is a decrease in overall skeletal muscle volume [27, 28]. Distinguishing between cachexia and sarcopenia warrants attention to accompanying factors and relevant signs related to skeletal muscles. Sarcopenia arises due to direct factors affecting skeletal muscle, including reduced motor neuron function, decreased anabolic hormone levels, and impaired protein synthesis [29, 30]. In the pathophysiology of cachexia, complex and multifactorial processes come into play, such as increased inflammation, altered metabolism, and changes in endocrine and neural glands. Cachexia often occurs alongside underlying diseases, as previously mentioned. Metabolic hyperactivity is frequently observed in these cases, resulting in an energy imbalance at the systemic level. Clinically, when evaluating patients with reduced muscle mass and involvement of inflammatory processes and cytokines, suspicion tends to lean more towards cachexia than sarcopenia [29–32]. Another distinguishing feature lies in the impact on overall body weight: sarcopenia does not necessarily lead to generalized weight loss, but it does contribute to an increased fat-to-muscle ratio, a phenomenon termed “sarcopenic obesity” [9, 33]. In contrast, cachexia, particularly in advanced and severe stages, is characterized by both overall weight loss and noticeable reductions in both muscle and fat mass [9, 29, 34]. Given the substantial similarities between sarcopenia and cachexia, some studies propose that any individual with cachexia could be considered as having secondary sarcopenia. However, most patients with sarcopenia cannot be classified as cachexic. Therefore, sarcopenia may serve as a clinical indicator of the cachexia wasting syndrome [9, 29].

4. Pathophysiology of Sarcopenia: Cellular Mechanisms and Implications

The primary cause underlying age-related muscle decline and consequent development of sarcopenia is cellular damage. This damage encompasses genetic alterations resulting from an individual’s lifestyle, genetic instability, telomere erosion, and ultimately disruption of proteostasis (Figure **1**) [35].

Cellular injury predominantly affects skeletal muscle cells, particularly satellite cells—the regenerative units responsible for skeletal muscle repair throughout the body. Although the precise genetic factors driving sarcopenia remain incompletely understood, studies suggest that genetic damage associated with aging and telomere attrition within satellite cells leads to impaired regenerative capacity and, ultimately, contributes to sarcopenia [35, 36]. Among influential factors affecting satellite cells, testosterone levels play a crucial role. Testosterone not only activates these cells but also influences protein synthesis, thereby promoting muscle strength and mass. Annual declines of approximately 1-2% in testosterone levels occur in both men and women and may contribute to the development of sarcopenia [38, 38].

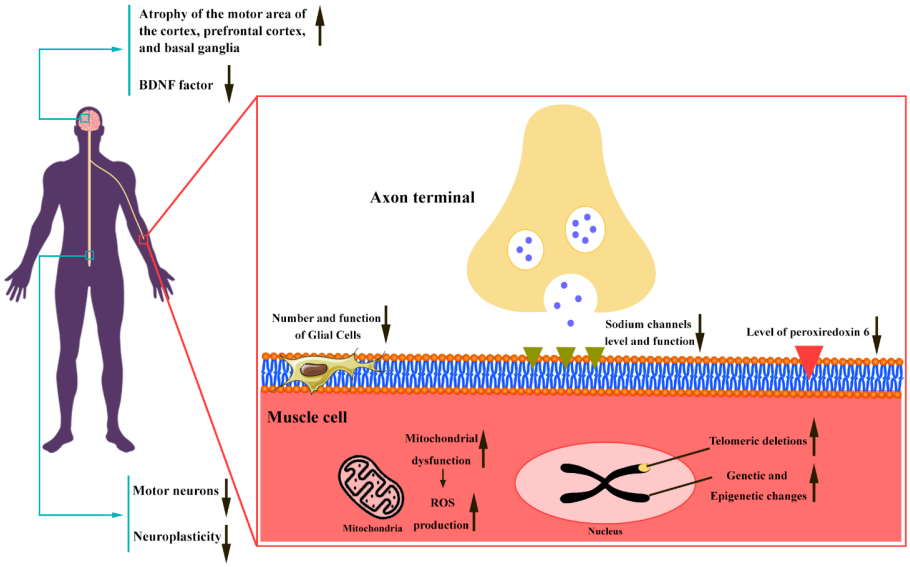

Figure 1: A summary of the mechanisms underlying sarcopenia related to the aging process.

Other contributors to sarcopenia include deficiencies in antioxidant enzymes, such as peroxiredoxin 6, and the loss of function of the Bmall circadian clock gene [39, 40]. Previous studies have demonstrated that reduced levels of peroxiredoxin 6 in mice lead to increased cellular aging. Additionally, this enzyme deficiency results in shortened telomeres and activation of the p53/p21 pathway—an essential mechanism in cellular senescence [39]. Peroxiredoxin 6 is implicated not only in glucose metabolism regulation and insulin secretion but also in insulin resistance within skeletal muscle [41]. Furthermore, cellular deficits in this enzyme lead to the activation of stress-responsive genes and proteins within the endoplasmic reticulum, ultimately culminating in increased production of reactive oxygen species (ROS) [39, 42]. Studies have also highlighted the positive impact of peroxiredoxin 6 on insulin reuptake in skeletal muscle. Reduced enzyme levels can diminish insulin secretion, impair insulin-related signaling, and ultimately reduce glucose reabsorption by muscle cells [39, 41]. This phenomenon is particularly relevant in diabetic patients, emphasizing the role of diabetes as an underlying condition in sarcopenia [43]. Collectively, these factors underscore the critical role of the antioxidant enzyme peroxiredoxin 6 in aging, oxidative stress, and diabetes—all of which contribute to skeletal muscle damage and sarcopenia [32, 44].

5. Mitochondrial Dysfunction, Epigenetics, and Metabolic Factors in Sarcopenia

Problems related to mitochondria contribute to cellular energy disruption and increased intracellular reactive oxygen species (ROS) production. In damaged muscle cells, dysfunctional mitochondria—devoid of function—are eliminated through mechanisms such as mitophagy (the unfolded protein response within the sarcoplasmic reticulum), vesicle release, protein degradation, and the ubiquitin-proteasome system.

Disruption of any of these mechanisms leads to the persistence of damaged mitochondria and elevated cellular oxidative stress [44, 45].

Circadian clock genes (CCGs) play a crucial role in skeletal muscle physiology, structure, and metabolism [40]. Specifically, the gene Bmal1, a CCG, has been evaluated in relation to skeletal muscle impairments and sarcopenia [40, 46]. Studies have shown that Bmal1 deficiency results in reduced mitochondrial density, altered mitochondrial respiration, fiber type changes, sarcomere structural disturbances, and functional limitations in muscle cells. Collectively, these alterations ultimately contribute to sarcopenia [40, 47].

Epigenetic modifications significantly impact sarcopenia. MicroRNAs and gene methylation patterns have been implicated in age-related muscle issues [48–51]. MicroRNAs, in particular, play a prominent role in improving function and mitigating muscle loss associated with aging [50].

Perturbations in cellular metabolism due to aging contribute to sarcopenia. Cellular nutrient sensing, including the deregulation of growth-related hormones such as insulin-like growth factor 1 (IGF-1) and mechanical growth factors (MGF), affects protein synthesis in muscle cells. Lower serum levels of IGF-1 and MGF have been associated with reduced muscle mass and strength, especially in older individuals with sarcopenia [52–54].

The cumulative effect of the mentioned pathophysiological processes damages skeletal muscle tissue, fatigues precursor stem cells, and alters intercellular communication. Satellite cells, fundamental for skeletal muscle regeneration, are particularly affected. Consequently, sarcopenia results from decreased muscle mass, impaired satellite cell function, and compromised tissue regeneration [55, 56].

6. Neurological Aspects of Sarcopenia

In this comprehensive review, we'll explore the effects of the neuromuscular system on the development of sarcopenia (Figure **1**). The reduction in muscle mass significantly impacts muscle strength during the aging process [57]. Achieving a complete muscle contraction involves various components of both the central and peripheral nervous systems.

7. Central Nervous System Involvement

The motor area of the brain's cortex plays a crucial role in the voluntary movement of skeletal muscles. It coordinates closely with the prefrontal cortex, basal ganglia, and cerebellum. Studies indicate that these brain regions are particularly susceptible to atrophy during aging. Such atrophy can lead to impaired motor neuron function and decreased muscle strength [57, 58]. Additionally, spinal cord involvement may contribute to sarcopenia. Spinal cord impairments fall into two main categories: reduced motor neuron numbers and issues specific to each neuron. Around the age of 60, approximately one-fourth to half of motor neurons are lost, affecting overall motor neuron function. Peripheral neurons also experience

reduced axon size and myelin sheath thickness, leading to decreased nerve conduction speed at the spinal level [59–61]. Interestingly, motor neuron loss does not correlate directly with reduced muscle strength. Other secondary factors come into play later, contributing to sarcopenia [58, 60].

8. Sodium Channels and Neuromuscular Function

Sodium channels also play a role in neuromuscular function. Studies have shown that the capacity for sodium uptake and the duration of sodium channel opening decrease with age at the motor plate level. This mechanism contributes to fatigue and reduced strength in individuals [62]. Another phenomenon observed in aging motor neurons is the loss or damage of larger motor neurons. Larger motor neurons are more susceptible to loss/damage, and their reduction leads to compensatory recruitment of smaller motor neurons, ultimately resulting in decreased fast-twitch muscle speed [63, 64].

9. Brain-Derived Neurotrophic Factor

Brain-Derived Neurotrophic Factor (BDNF), a neurotrophic factor, plays a significant role in neural cell division, synaptic plasticity, and DNA remodeling [65, 66]. It is secreted during muscle contractions and enhances oxidation and muscle fiber activity. However, BDNF levels decline with age. This reduction affects protein synthesis in muscles and disrupts the regulatory factors involved in muscle remodeling. Ultimately, it contributes to muscle atrophy [65, 67]. Boosting BDNF production by the brain could potentially strengthen muscle activity and delay the onset of sarcopenia [58, 68]. In summary, the interplay between the nervous system and muscle health is intricate. Understanding these neurological aspects is crucial for addressing sarcopenia effectively.

10. Prevention and Treatment

10.1. Drug-based treatments

Previous studies have highlighted vitamin D as an effective solution for preventing sarcopenia. Specifically, the active form of vitamin D, 1,25(OH)2D, has a significant impact on reducing the expression of genes associated with muscle atrophy, enhancing protein synthesis in muscle cells, promoting muscle hypertrophy, and effecting skeletal muscle mitochondria and oxidative stress. Notably, 1,25(OH)2D influences the FOXO1 gene, a critical player in muscle atrophy [69]. Studies have indicated that the expression of this gene is involved in inducing muscle atrophy, and its pathophysiology is associated with malnutrition, physical inactivity, and cancer. This occurs through the ubiquitin-proteasome system, leading to increased protein degradation and ultimately resulting in autophagy [70, 71]. By targeting

FOXO1, it suppresses genes like cathepsin L and atrogin-1, both involved in muscle protein breakdown [72]. Recent research by Yang and colleagues (2020) emphasized that physical inactivity and vitamin D deficiency exacerbate sarcopenia in older individuals [73]. Additionally, vitamin D has been implicated in muscle hypertrophy through the (mammalian target of rapamycin complex 1) mTORC1 pathway [74].

As previously mentioned, inflammation within muscle tissue is a key factor in the onset of sarcopenia. Dysfunctional mitochondria within muscle cells contribute to this inflammation by producing reactive oxygen species (ROS), leading to tissue damage. Studies have shown that 1,25(OH)2D can enhance oxidative phosphorylation in muscle mitochondria, increasing oxygen consumption and improving mitochondrial function. These effects collectively reduce ROS production [75-77]. While vitamin D has demonstrated positive effects on muscle strength (as previously mentioned) [37], its role in treating sarcopenia remains somewhat ambiguous [78].

One of the initial treatments for sarcopenia involved testosterone replacement therapy [37]. As testosterone declines with age in both men and women, it can contribute to sarcopenia. Treatment with testosterone has shown significant effects on muscle mass, strength, and overall performance. However, it comes with potential side effects such as muscle damage, fluid retention, increased hematocrit, and cardiovascular risks. To address these issues, selective androgen receptor modulators (SARMs) have been explored. SARMs primarily impact muscle size and mass, with minimal effects on muscle strength. However, some SARMs may still carry risks related to cardiovascular health [79].

Among the drugs mentioned, ghrelin, growth hormone, myostatin inhibitors, and activin-2 inhibitors play significant roles in addressing sarcopenia. Except for the last category, all these treatments contribute to increasing muscle mass. Some of these drugs, such as ghrelin, may also impact muscle strength. However, they come with specific side effects; for instance, the side effects of ghrelin include fatigue, vascular fibrillation, and respiratory-vascular issues [37, 79]. For growth hormone, the side effects are joint pain (arthralgia), muscle pain, edema, carpal tunnel syndrome, and hyperglycemia [37, 79]. Myostatin and activin-2 inhibitors drugs may lead to side effects like cachexia, aseptic meningitis, telangiectasia, alterations in gonadotropin levels, hyperkalemia, and hypotension. Additionally, myostatin inhibitors can cause cramps and numbness [37]. In summary, while various drugs have been introduced for sarcopenia treatment, selecting an appropriate treatment and dosage requires further evaluation.

10.2. Effects of resistance training and sarcopenia

Numerous studies have shown that resistance training effectively improves muscle strength, physical function, and body composition in older adults with conditions like frailty and sarcopenia [80]. Significant enhancements were observed in both handgrip and lower-limb strength, with isometric and dynamic measurements showing concordant improvements [81]. Furthermore, resistance training exhibited positive effects on various aspects of physical function, including agility, gait, balance, and functional tasks. These

functional improvements are hypothesized to be associated with gains in lower-limb strength, which is crucial for activities of daily living [82, 83]. The studies also indicate that resistance training positively influenced body composition, reducing fat mass and increasing muscle mass, potentially mitigating the risk of comorbidities such as metabolic syndrome in older adults [84].

Resistance training induces subtle neuroplastic changes encompassing both cortical and subcortical regions, resulting in enhanced motoneuron activation. These neural adaptations are hypothesized to be significant contributors to the observed increases in muscular strength following a resistance training regimen [85]. Based on these findings, the recommended resistance training protocol for older adults with sarcopenia includes moderate to high-intensity exercises (>60% 1RM), performed three times per week, with 2-3 sets of 8-12 repetitions per movement. The mode of exercise should be tailored to individual capabilities, with elastic resistance bands potentially offering a safer alternative to weight machines for this population [86]. Resistance training is associated with enhancements in appendicular skeletal muscle mass index (ASMI), physical performance measures, and select biochemical markers including insulin-like growth factor 1 (IGF-1), prealbumin, and hemoglobin levels. Additionally, positive changes in body composition were observed [87]. Longitudinal engagement in resistance training is emphasized as crucial for combating age-related muscle strength decline [88, 89].

11. Personalized Approach

While various treatments have been explored, the selection of the most suitable treatment for sarcopenia should consider the individual's specific needs, potential side effects, and the balance between increasing muscle mass and improving muscle strength, as the role of vitamin D in treating sarcopenia remains somewhat ambiguous [37, 79].

The current study provides a comprehensive overview of sarcopenia, its pathophysiology, and future prospects for research. It emphasizes the significance of sarcopenia as a major age-related disorder, with a high prevalence in older adults, outpatients, and hospitalized patients. As such, the authors stress the need for studying sarcopenia to understand its pathophysiology, prevention, and treatment, given its impact on patients' functional abilities and associated healthcare costs. To that end, the review highlights the importance of the neuromuscular system in the development of sarcopenia, emphasizing the effects of the central nervous system, sodium channels, and neurotrophic factors on muscle health. It also provides a comprehensive differential diagnosis of sarcopenia, distinguishing it from related conditions such as malnutrition, cachexia, frailty, and neuromuscular disorders—a crucial distinction for accurate diagnosis and targeted treatment. The review also explores potential preventive and treatment strategies for sarcopenia, focusing on vitamin D supplementation, selective androgen receptor modulators (SARMs), and emerging pharmacological treatments. The authors emphasize the need for a personalized approach

in selecting the most suitable treatment, considering individual needs, potential side effects, and the balance between increasing muscle mass and improving muscle strength.

The strength of this review lies in its detailed examination of the cellular mechanisms underlying sarcopenia, including the role of cellular damage, mitochondrial dysfunction, epigenetic modifications, and metabolic factors. The detailed examination of cellular processes and the neuromuscular system provides valuable insights into the pathophysiology of sarcopenia. The review also highlights the importance of accurate diagnosis and personalized treatment approaches, emphasizing the need for further research to address this major age-related disorder.

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Declaration

Conflict of Interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Authors' Contribution

Conceptualization: Mohammad Reza Kalantar Hormozi, Neshat Afshari, and Alireza Afshar; **methodology:** Mohammad Reza Kalantar Hormozi, Neshat Afshari, and Alireza Afshar; **software:** Faezeh Hajeb and Alireza Afshar; **validation:** Neshat Afshari and Alireza Afshar; **investigation**: Robab Bahreini and Faezeh Hajeb; **resources:** Mohammad Reza Kalantar Hormozi; **data curation**: Alireza Afshar; **original draft**: Mohammad Reza Kalantar Hormozi and Alireza Afshar; **review and editing**: Mohammad Reza Kalantar Hormozi, Robab Bahreini, Faezeh Hajeb, Neshat Afshari, and Alireza Afshar; **visualization:** Robab Bahreini; **supervision**: Neshat Afshari and Alireza Afshar; **project administration**: Neshat Afshari and Alireza Afshar

Availability of Data and Materials

The datasets used and/or analyzed during the current study are available from the corresponding author upon reasonable request.

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