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Unraveling the Multifactorial Etiology and the Potential Strategies to Overcome Sarcopenia

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ABSTRACT

Sarcopenia, characterized by the decline of skeletal muscle mass and function, can have severe consequences for older adults, including disability and frailty. The condition is also linked to various diseases, increased insulin resistance, fatigue, falls, and mortality. Factors such as obesity and myosteatosis (fat infiltration into muscle) play a significant role in driving sarcopenia, particularly in morbidly obese individuals who also have low muscle mass, known as sarcopenic obesity. The Framingham study found additional limitations in function and mobility in individuals with sarcopenic obesity. This literature review aims to provide the potential causes of sarcopenia, with a specific focus on middle-aged adults, the biological processes that lead to muscle loss, methods to mitigate its effects, and how physical activity and nutrition can aid in recovery.

KEYWORDS: Myosteatosis, sarcopenia, skeletal muscle mass, middle-age adult sarcopenia, lipofuscin

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INTRODUCTION

Sarcopenia has been characterized as a condition associated with the general decline of skeletal muscle mass and function[1, 2]. Given that 60% of body mass is entirely composed of muscle mass, any change relating to pathology regarding this essential metabolically active tissue can have immense consequences on the older adult [3]. The consequences of sarcopenia are generally considered to be especially damaging to older adults [3]. The noticeable reduction in strength and ability to function concomitant with sarcopenia can be a major factor in influencing various health outcomes including disability and frailty [4]. Sarcopenia also plays a major role in the numerous states of both acute and chronic diseases, increased insulin resistance, fatigue, falls, and mortality [3]. Sarcopenia is also heavily associated with conditions relating to joints, tendons, muscles, ligaments, bones, and muscles, especially rheumatoid arthritis (RA) in women [5]. Despite how the aging process directly increases the risk of sarcopenia, it is becoming more evident that other factors including obesity and fat infiltration into skeletal muscle (myosteatosis) play a major role in driving the disease. This phenomenon, called sarcopenic obesity is a new characterization of obesity that involves morbidly obese individuals who have low skeletal muscle mass [6]. It is usually grouped together with sarcopenia and substantially influences a portion of those older adults thought to have sarcopenia [2]. Interestingly, additional limitations in function and mobility associated with sarcopenic obesity have recently been brought to light in the Framingham study [7]. In the Health, Aging and Body Composition Study, researchers repeatedly examined the same individuals over an eight-year period and realized that increased fat mass was associated with lower muscle quality [8]. The rate of loss of lean muscle mass was also accelerated [8]. This literature review aims to review the possible causes of sarcopenia, the biological processes that result in rapid loss of skeletal muscle mass, methods that people have used to reduce the disease's effect on their well-being, and how increased physical activity and nutrition intake can positively influence the recovery of sarcopenia.

ETIOLOGY OF SARCOPENIA

Sarcopenia is commonly regarded as a disease that can be caused by multiple factors [3]. For instance, the activation of inflammatory pathways due to the injuring of tissues by various causes including bacteria, heat, and trauma [3]. Likewise, environmental causes and hormonal changes play a major part in triggering sarcopenia [9]. Additionally, the recent understanding of the series of actions in cells that lead to the maintenance of skeletal muscles has concluded that tissue growth factor (TGF)-β signaling, the clearing of

infected cells, and the functional decline of mitochondria could be contributing to the cause of sarcopenia [10].

Factors involving environmental causes of the disease are generally divided between insufficient nutritional intake and reduced physical activity [11]. Older individuals are significantly less active compared to adolescents because of long-term diseases which cause pain or fatigue [12]. Moreover, inadequate protein intake and excessive calorie surplus increase the risk of sarcopenic obesity and heavily contribute to sarcopenia in older adults. In short, the environmental factors mentioned all aid in the decline in skeletal muscle mass and function [13].

First, fewer neuromuscular junctions can reduce the ability for signals to travel from motor nerves to muscles [6]. This results in a substantial drop out of type-II muscle fibers which are responsible for strength [6]. The decline in fast-twitch muscle fibers is considered to be a major contributor to muscle decline relating to the aging process [14]. Recent studies done on mice have shown a significantly high number of denervated neuromuscular junctions in older female mice and a reduction of type-II muscle fibers such as in the extensor digitorum longus [6]. Surprisingly, the number of motor neurons in the spinal cord that supplies nerves to this area is not decreased [6]. This shows that the substantial increase in the percentage of neuromuscular junctions that lack nerve supply can be caused by a decline in the number of axons rather than a change relating to the nerve body [6, 15]. Overall, it is possible that this decline in neuromuscular junctions can potentially impact the loss of muscular tissue and strength in humans [16]. The C-terminal agrin fragment has been used as a screening measurement to aid in diagnosing this reduction [4]. Second, the sudden drop in hormones that are responsible for the maintenance of muscle tissue including Dehydroepiandrosterone sulfate, testosterone, and estrogen is a factor that contributes to the development of sarcopenia [17]. Third, the activation of the inflammation pathways can also have a major effect on sarcopenia [16]. These pathways can be activated by many factors. For instance, disease and aging causes [4]. Additionally, a study conducted on older women has shown a steep decline in walking ability, as well as a high chance of developing physical disability in individuals who have certain serum levels of the inflammatory cytokine interleukin-6 [14, 18]. A decline in skeletal muscle mass is seen in these older women [19]. Inflammation in older adults can stem from a variety of different reasons including chronic diseases which play a role in activating inflammatory pathways [20, 21]. This in turn can negatively impact muscle regeneration and contribute to the development of sarcopenia [22]. Finally, as we age it becomes more difficult for our bodies to repair and replace muscle tissue [13]. The motility of skeletal muscle stem cells in older individuals is significantly lower than in younger people [13]. This is mostly due to low levels of integrin expression [23, 24].

BIOLOGICAL MECHANISMS OF SARCOPENIA: FROM MOLECULAR TO HISTOLOGICAL LEVEL

The underlying mechanisms of sarcopenia are not fully understood, however, multiple biological factors have been identified to contribute to its development [24]. These include an imbalance in oxidative stress, inflammation in muscle fibers, hormonal imbalances, deficiencies in vitamin E, and impairment in stem cell function [6, 24]. This section will briefly discuss the most common mechanisms related to the development of sarcopenia including oxidative stress (an imbalance between the production and gradual gathering of ROS and the body's ability to detoxify these reactive products), muscle fiber inflammation that is unable to be clinically observed, the inability to regulate certain hormones e.g., testosterone and growth hormone, vitamin E deficiency, proteolysis pathway, and involvement of stem (satellite) cells. By understanding the mechanisms that are involved in the development of sarcopenia, we proceed to create strategies to intervene with the disease [16, 25, 26].

From a histological and physiological perspective, skeletal muscle is composed of various types of fibers, with type I and type II fibers being the most prevalent [2]. Type II fibers, also known as fast-twitch fibers, possess high glycolytic potential, lower oxidative capacity, and a quick response, making them suitable for muscle strength and short-duration anaerobic activities. In contrast, type I fibers, also known as slow-twitch fibers, are characterized by a high density of capillaries, myoglobin, and mitochondria, which allows them to better supply oxygen and nutrients to the muscle, thereby improving muscular endurance and aerobic activities [27].

Sarcopenia is a condition that is characterized by shrinkage and decreased activation of the muscles in the lower extremities in comparison to those in the upper limbs [26]. Furthermore, research has shown that the muscles in the lower limbs of older individuals are smaller and contain more fat and connective tissue than those of younger individuals [28]. This condition is caused by a reduction in both the number and size of muscle fibers, particularly type II fibers, and is partially due to a slow, stem cell-dependent myogenic process [4]. As a result, these changes can lead to decreased energy production, poor muscle repair, and limited muscle regeneration. Additionally, these changes can manifest as a decline in physical performance, such as difficulty with activities such as walking up stairs or running, as well as early onset of fatigue, all of which can negatively impact one's quality of life and increase dependence on others [29].

Research has shown that there is a connection and interdependence between various factors related to sarcopenia [15]. These factors can act as causes, effects, or outcomes of one another [30]. Some of these mechanisms have a positive correlation, while others have a negative correlation [30]. Generally, skeletal muscle can "die" through different molecular pathways [30]. Sarcopenia, as a normal physiological process, is associated with a significant

increase in the levels of inflammatory molecules in both blood serum and within and outside of cells [31]. The aging process, which induces oxidative stress and degradation of damaged mitochondria, promotes the accumulation of lipofuscin, which is a marker of fiber oxidative damage [32]. The accumulation of lipofuscin, is recognized as the hallmark pigment of aging muscle [32]. Lipofuscin is an intralysosomal substance made up of cross-linked protein residues and lipid per oxidized molecules and it is recognized as a hallmark pigment of aging muscle [32]. This intracellular waste material interferes with muscle metabolism and muscle contraction [32].

Imbalance between the production of reactive oxygen and nitrogen species and antioxidants and nitrogen defense molecules can result in oxidative stress [33]. This can lead to a chain reaction of inflammatory molecules being released within fibers, including myokines such as tumor necrosis factor-α (TNF-α), interleukin-6 (IL-6), and interleukin-1 (IL-1), which can contribute to age-related sarcopenia through the activation of the ubiquitin-protease system and the activation of myofiber signaling pathways that lead to muscle apoptosis [34]. Additionally, it is suggested that cytokines may also contribute to anabolic resistance by hindering the anabolic effects mediated by insulin growth factor-1 (IGF-1), and by involving in growth hormone resistance which limits IGF-I availability [17]. Other potential factors and mechanisms that have been suggested to lead to sarcopenia include TGF-β-activated kinase (TAK)-1, C-reactive protein, a significant reduction of dihydropyridine (DHP)-sensitive Ca_2^+ (the decrease of Ca_2^+ available for mechanical responses in aged skeletal muscle is due to DHP receptor (DHPR)-ryanodine receptor (RyR) uncoupling); and the stress of sarcoplasmic reticulum due to accumulation of unfolded or misfolded proteins like heat shock proteins [15, 29].

EFFORTS TO MANAGE SARCOPENIA

The multifactorial nature of sarcopenia, a condition that affects millions of older adults, has been widely studied, but most current therapies focus on addressing environmental factors such as physical activity and nutrition [35]. Despite this, pharmaceutical companies and researchers continue to prioritize the development of new treatments for sarcopenia due to its high incidence and association with functional decline and chronic disease [36]. Despite the lack of large-scale clinical studies, interventions utilizing diet and resistance training have shown significant improvements in muscle protein synthesis and functional capacity in older adults [37]. Even the frailest and oldest nursing home patients displayed considerable functional improvement due to diet and resistance training in clinical intervention studies. Recent clinical trials demonstrate this through considerable improvements in muscle protein synthesis in older persons who engage in physical exercise and obtain proper nutrition [1]. Additionally, organizations continue to investigate the optimal modes of exercise for preventing and treating sarcopenia, which may target satellite cell dysfunction, neuromuscular junction deterioration, and mitochondrial biogenesis [28]. Current pharmacological treatments for sarcopenia have had limited success, but future developments may target specific molecular pathways such as the angiotensin system, apoptosis, and mitochondrial function [38].

In order to advance research on sarcopenia, a consensus definition must be established for use across various studies and populations to evaluate the safety and efficacy of treatments. The International Working Group on Sarcopenia has recommended guidelines for clinical trial design, emphasizing the importance of measuring muscle mass, strength, and functional performance in order to establish a valid diagnostic screening methodology for sarcopenia [6, 17, 39 ,40]. The EWGSOP also recommends including these measurements in any clinical definition to aid in replication across multiple populations and incorporation into geriatric medicine [41, 42].

PHYSICAL ACTIVITY ASSOCIATIONS WITH SARCOPENIA AND SARCOPENIC OBESITY IN MIDDLE-AGED AND ELDERLY PERSONS

This cross-sectional study investigated the relationships between levels of physical activity and obesity, sarcopenia, and sarcopenic obesity in a large and heterogeneous population [20]. In general, favourable relationships were reported for obesity and obesity-related characteristics in middle-aged and older persons, particularly those who exercised 3 times per week [43]. However, sarcopenia-related features were adversely associated with greater activity frequencies, and a positive association between sarcopenia-related traits and exercise frequencies was detected only after correcting for body mass index [44]. Additionally, among older girls and males, only those exercising 3 times per week were less likely to develop obesity and sarcopenic obesity than those without regular exercise [45]. However, regular exercise 1 to 2 times per week was not associated with reducing the disease risk. Middle-aged people who exercised 1 to 2 times per week and older persons who exercised regularly did not have reduced sarcopenia. The outcomes of this study may imply that older persons should be encouraged to engage in physical activity and exercise to counteract the effects of obesity and sarcopenia [46]. The complicated relationships between physical activity, weight loss, and muscle maintenance must be investigated further in the elderly to optimize the advantages of exercise [47].

Increased adiposity may be a persistent physical overload stimulation on the antigravity muscles, such as the quadriceps and calf, increasing muscular size and strength. In addition, weight loss has been shown to hasten sarcopenia in older persons [48]. Therefore, it is plausible that exercise-induced weight reduction may limit the effect of physical loading of body weight on lean mass, particularly when

accompanied by dietary restraint or poor dietary choice [49]. Meanwhile, significant increases in muscle growth could only be accomplished by increasing resistance training or weight gain through increased calorie and protein consumption [50]. The preservation of muscle mass may have been overlooked in middle-aged and older individuals due to a prevalent focus on addressing obesity as a public health crisis [51]. n order to optimize both body composition and overall health outcomes, research into physical activity and exercise regimens must be conducted in a holistic manner [39].

The existing literature on the impact of physical exercise on grip strength in older adults is inconsistent [34]. Studies have shown that those who participate in exercise interventions that place a greater emphasis on resistance training and have a higher frequency of exercise per week have reported an increase in grip strength [52]. After controlling for confounding variables, it has been found that a higher exercise frequency is positively associated with grip strength in middle-aged males [20, 53]. Similar results have been observed in middle-aged females when controlling for body weight, but no correlation was detected in older individuals. The cross-sectional nature of the current study, which found no correlation between exercise frequency and grip strength in older adults, suggests that the specific type of exercise may have been overlooked in this population [54].

The findings of this study contradict previous conclusions that physical exercise has a negative correlation with sarcopenia [55]. For older males and females, exercising less than three times per week was not associated with a reduced risk of obesity or sarcopenic obesity, and any exercise frequency was not associated with a reduced risk of sarcopenia [56]. This discrepancy in findings may be due to previous studies failing to differentiate between sarcopenia and sarcopenic obesity or being conducted in different populations. Additionally, the EWGSOP2 has revised the definition of sarcopenia to promote early identification and treatment, and the most recent criteria for sarcopenia were adopted in this study [42, 57]. These findings may suggest that older individuals require exercise programs to maintain and develop muscle mass and strength, and that older adults with sarcopenia may not engage in regular exercise [4, 40, 58].

CONCLUSION

Sarcopenia is a significant clinical issue that affects millions of seniors. Despite its widespread occurrence, no standard definition has been established. The causes include a decrease in hormones and the number of neuromuscular connections, an increase in inflammation, a decrease in physical activity, and poor nutrition. Changes in mitochondrial biology, the angiotensin system, and apoptosis are some of the more recent molecular findings that may influence sarcopenia. Overall, even though there are therapies for sarcopenia which utilize exercise and dietary therapy to reduce the effects of the disease and improve the quality of life of older individuals, the absence of a standardized definition for sarcopenia has hampered the development of pharmaceuticals since it makes it difficult to distinguish between sarcopenic obesity and sarcopenia that correlates with the aging process.

Conflict of Interest

Author declares no conflict of interest.

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