

Sarcopenia – Mechanisms and Treatments

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ABSTRACT

Background: Sarcopenia is a consequence of aging. This atrophic event is responsible for decrease in strength and associated functional deficits seen in the aging adult. **Purpose:** This paper reviews: (1) the mechanisms contributing to sarcopenia, (2) the impact of age-related changes in muscle composition on 3 processes integral to muscle function, (3) the efficacy of pharmaceuticals and over-the-counter nutritional supplements in the management of sarcopenia, (4) experimental use of pharmaceutical regulation of myostatin to increase muscle mass and strength in animal models, and (5) efficacy of resistance training as a means of maintaining or recovering muscle mass and strength. **Methods:** PubMed was searched for relevant research articles using the following descriptors: sarcopenia, aging, muscle mass, muscle performance, muscle strength, myostatin, testosterone, growth hormone, dehydroepiandrosterone, hormone replacement, nutrition, resistance training, and endurance training. **Results:** Sarcopenia is mediated by multiple mechanisms, including alpha-motor neuron death, altered hormone concentrations, increased inflammation, and altered nutritional status. Age-related changes within muscle likely affect processes integral to muscle function. These changes negatively influence muscle performance directly or by contributing to sarcopenia. Pharmaceutical or supplement interventions to treat sarcopenia have not proved encouraging to date, either lacking or providing limited efficacy, along with the potential for negative health consequences. In contrast, resistance training has proven safe and highly effective for increasing muscle mass and strength in aging adults. **Conclusion:** Sarcopenia is a multifactorial consequence of aging that will affect many adults. Resistance training is the most effective and safe intervention to attenuate or recover some of the loss of muscle mass and strength that accompanies aging.

Key Words: aging muscle, sarcopenia, resistance training

INTRODUCTION

The word sarcopenia, meaning “loss of flesh,” was first used in 1988 to describe the loss of skeletal muscle mass with aging.¹ The striking decline in muscle mass in the later decades of life is related to loss of strength and changes in function.^{1,2} Sarcopenia is associated with functional impairments in tasks such as standing up from a chair and lifting 10 pounds, and physical

disabilities such as performing home chores and personal care.² Changes in function play a role in the increase in weakness, falls, and fractures and increased tendency for nursing home admissions and loss of independence.¹ For physical therapists concerned with diminished function, strength loss should be of great concern.

Sarcopenia has predominately been studied in muscle groups that would be associated with functional impairment and physical disability in the literature cited here. There does not appear to be any published evidence that sarcopenia is selective with respect to specific muscles or muscle groups.

Underlying age-related contributors to sarcopenia include disuse atrophy associated with inactivity, changes in the nervous system (ie, loss of alpha-motor neurons), hormonal changes, inflammatory effects, altered caloric intake, and changes muscle physiology and composition (see review^{3,4}). It has not been determined that one particular contributor is predominately responsible for sarcopenia.

The degree of muscle mass loss dictates whether or not an individual is considered sarcopenic. A number of techniques aid in determining muscle mass including dual-energy X-ray absorptiometry, computed tomography scanning, magnetic resonance imaging, and ultrasonography. Although there is no universal objective definition of sarcopenia, Baumgartner et al defined sarcopenia as appendicular (extremity) muscle mass (kg)/height² (m²) being less than two standard deviations below a young reference group consisting of individuals between ages 18 to 40 years.⁵ Applying this criterion in their study, 19% of men and 34% of women between 70 and 74 years were sarcopenic and 55% of men and 52% of women over 80 years were sarcopenic.⁵

CAUSES OF SARCOPENIA

Muscle is highly adaptable and responds to many given stresses, especially physical activity and inactivity. Muscles atrophy in response to decreased contractile activity, which results in diminished force output. If aging adults are sedentary, declining physical activity may be partially responsible for sarcopenic changes. Type I (slow) muscle fibers that are predominant in postural muscles appear most susceptible to inactivity.⁴ Muscle disuse, however, is not the only contributor to sarcopenia.

Changes in the aging nervous system influence sarcopenia through the loss of motor units, which correlates with diminished strength.^{6,7} A motor unit consists of a single alpha-motor neuron and all of the muscle fibers it innervates. The body's compensatory mechanism to the loss of the alpha-motor neurons is to produce neural cell adhesion molecules (NCAM) at the neuromuscular junction to attract regenerating axons to the abandoned muscle cells. Neural cell adhesion molecules increase in aged muscle, suggesting that remodeling is occurring following age-related denervation as alpha-motor neurons

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decline in number.⁸ As a result of this remodeling, motor unit size increases, ie, an individual neuron innervates more muscle fibers, resulting in fewer motor units. This reorganization of the nervous system with larger motor units may be, in part, responsible for less precise motor control and coordination often noted by physical therapists working with aging adults.⁹

Levels of testosterone and growth hormone (GH) drop later in life. These hormonal changes may impact muscle growth and maintenance. Lower testosterone levels are due to an age-related drop in Leydig cell function in the testes.¹⁰ Testosterone is an anabolic hormone that influences protein synthesis. There is evidence that men with sarcopenia have lower testosterone levels than men without sarcopenia.¹¹ Growth hormone, which also has a positive influence on muscle protein synthesis, also declines with age.¹² This decline is a result of a change in GH secretory burst frequency and the GH secretory rate.¹²

Inflammatory markers and their role in sarcopenia have recently attracted interest of not only researchers, but clinicians, too.¹³ Inflammatory processes common in older adults are rheumatoid arthritis and osteoarthritis; both have increased production of cytokines.¹⁴ Cytokines are catabolic agents that trigger muscle wasting. Of particular interest is interleukin-6 (IL-6) cytokine that has elevated concentrations in older individuals.¹⁵ High concentrations of IL-6 correlate with movement disabilities, slower walking speed, and lower grip strength.^{16,17} Dehydroepiandrosterone (DHEA), a sex-hormone precursor, inhibits IL-6 production. As DHEA levels drop with age, its inhibitory influence on IL-6 production becomes attenuated.¹⁸

The catabolic role of IL-6 in sarcopenia may be exacerbated in individuals who are overweight or obese because elevated levels of IL-6 have also been correlated with increased abdominal fat.¹⁷ In addition, lower levels of testosterone and GH have been correlated with increased fat mass.^{19,20} Consequently, body fat may play a role in sarcopenia by influencing hormones and cytokines that affect muscle mass. Individuals with increased body fat may have disguised sarcopenia, giving rise to the term “sarcopenic obesity.”¹⁷

Interestingly, elevated IL-6 production appears to play a role in anorexia (loss of appetite).²¹ Loss of appetite is a major concern in older adults as insufficient nutrient intake can contribute to muscle loss. Consequently, IL-6 may mediate sarcopenia directly via its catabolic effects on muscle and indirectly as diminished appetite increasing the risk of malnutrition. Research suggests that the present recommended daily allowance for protein (0.8g/kg/day) is not adequate to meet the protein needs in older persons, especially for maintaining muscle mass by exercise.²² Albumin, a protein marker of nutritional status, declines with age and this correlates with a reduction in muscle mass.²³ Physical therapists suspecting a patient is sarcopenic may consider referral to a physician who can test for sarcopenia and make any other referrals warranted.

AGE-RELATED CHANGES IN MUSCLE

Sarcopenia and age-related muscle composition changes are due, in part, to a lower rate of protein synthesis rather than an increased rate of protein degradation. Although

quantitatively there is no increase in protein degradation, the quality of the protein often decreases secondary to accumulation of oxidative damage from free radicals. The Free Radical Theory of Aging suggests that the aging process results from an accumulation of oxidatively modified proteins and DNA.²⁴ Oxidative damage accumulated over time contributes to the decline in physiologic function. Muscle proteins that can be affected by aging are integral to 3 processes involved in muscle contraction: excitation-contraction coupling, cross-bridge cycling, and ATP production.

Excitation-contraction Coupling

Excitation-contraction coupling is the process responsible for translating the motor nerve signal into a muscle contraction after synapse at the neuromuscular junction. Several different proteins in the muscle cell play a role in changing the concentration of cytosolic calcium to initiate and conclude muscle contraction. The neural signal for contraction is translated into an action potential in the muscle cell membrane activating proteins in a cascade of events that culminates in calcium release from the sarcoplasmic reticulum, the storehouse of calcium in the muscle cell. The calcium is released through the ryanodine receptor, the calcium release channel in the sarcoplasmic reticulum. The resulting increase in cytosolic calcium initiates muscle contraction. Calcium binds to troponin allowing for actin-myosin interaction which produces force. Contraction continues until the calcium-ATPase (Ca-ATPase), a protein that pumps the calcium back into the sarcoplasmic reticulum, lowers cytosolic calcium concentration and the muscle relaxes. With age, 2 key proteins involved in the excitation-contraction coupling process, the ryanodine receptor and the Ca-ATPase, are altered.^{25,26} These alterations may contribute to the increased time to peak contraction and increased time to relaxation seen in aged human muscle fibers.^{27,28}

The ryanodine receptor, the calcium release channel in skeletal muscle, remains in the cell longer in aged muscle before being replaced by new copies of the protein.²⁵ This slower turnover rate allows more time for this protein to accumulate oxidative damage which could contribute to altered function. Also, there is an uncoupling of the signal for the release of calcium in Type II (fast) muscle fibers. This results in a reduced amount of calcium to initiate muscle contraction and is, in part, responsible for the increased time to peak contraction.²⁷ Increased time to peak contraction would decrease the rate of force development and impact power and the force-velocity relationship. Power is a strong predictor of functional status in aged women.²⁹

The Ca-ATPase also has a slower turnover rate in aged muscle, and consequently more opportunity to be damaged by free radicals.²⁵ The Ca-ATPase in Type I muscle fibers are oxidatively damaged in aged rats and Ca-ATPase activity is reduced when the Ca-ATPase is oxidized.^{26,30} This finding may be particularly important because aged individuals with sarcopenia have a shift toward more Type I muscle fibers. Impairment of Ca-ATPase activity would allow cytosolic calcium concentrations to remain elevated which will increase half relaxation time. Increased half relaxation time would increase the time between successive contractions.

Cross-bridge Cycling

Cross bridge cycling, the process that produces force in the muscle, involves the contractile protein myosin. Myosin is the predominate protein contributing to muscle mass. Myosin has several forms corresponding to different fiber types, ie, Type I myosin in Type I muscle fibers. With advancing age, the rate of myosin protein synthesis slows contributing to the development of sarcopenia.³¹ An age-related shift of Type II fibers to Type I fibers and atrophy of Type II fibers contributes to increased contraction time, reduced strength, and decreased size of aged muscle fibers.³²⁻³⁴ The shift to Type I fibers is supported by a fall in Type II myosin gene expression.³⁵

Independent from the shifts in myosin isoforms, age-related structural changes and chemical changes in myosin alter its function and contributes to decreased force production. Structural changes in Type II myosin contribute diminished specific tension during isometric contractions in aged rat muscle.³⁶ Lowe et al found that during concentric contractions, myosin-ATPase activity is slower in aged Type II rat muscle fibers.³⁷ There is evidence that oxidation may contribute to the chemical changes in myosin responsible for the diminished myosin ATPase activity in aged muscle.³⁸ These structural and chemical changes seen in myosin from aged muscle contribute to the decreased strength and increased time to contraction.

ATP Production

Muscle contraction is dependent on the production of ATP in the mitochondria. Since ATP is used for almost all reactions in the cell including muscle contraction, changes in mitochondria size, the DNA inside the mitochondria, and mitochondrial proteins directly effect muscle contraction in aged muscle. With age, mitochondrial DNA content and protein synthesis are lower leading to a reduction in mitochondrial proteins.^{39,40} In addition to the fall in number of mitochondrial proteins, the proteins have reduced activity.⁴⁰ This reduction in mitochondrial proteins and their activity results in a 50% decrease in oxidative capacity and ATP available for muscle contraction, which in turn contributes to age-associated reduction of aerobic capacity.⁴¹

The fall in mitochondrial DNA content, protein synthesis, and protein activity seen with age maybe associated with free radical production and oxidative damage to DNA and mitochondrial proteins.⁴² Common sites of oxidative damage in muscle cells are nuclear and mitochondrial DNA. While damaged nuclear DNA is quickly repaired, damaged mitochondrial DNA is not easily repaired (see review⁴³). Extensive oxidative damage to mitochondrial DNA can accumulate over years diminishing the amount of functional mitochondrial DNA. This damage results in decreased levels of functional mitochondrial protein.⁴² Oxidative damage to mitochondrial proteins also diminishes ATP production and oxidative capacity in aged muscle.⁴²

PHARMACOLOGICAL INTERVENTIONS

Health care professionals should be aware of pharmacological interventions that may influence the development or progression of sarcopenia. The benefits of some treatments include increased muscle mass and functional strength gains, but there are also potential adverse effects to be considered. This review addresses 2 hormone treatments (testosterone and GH), one over-the-counter supplement (DHEA), and the potential treatment of a protein that regulates muscle growth (myostatin) (Table 1).

Testosterone

Because diminished levels of sex hormones are associated with sarcopenia, testosterone administration in elderly men has been examined as a pharmacological therapy to preserve muscle mass and minimize loss of strength.⁴⁴ Testosterone is a steroid hormone that promotes the development of secondary sexual characteristics in males including muscle growth. Administration of testosterone to the level of circulating testosterone seen in young men increased muscle mass but did not result in functional gains in strength.⁴⁵ Recent studies suggest administration of supraphysiological dosages of testosterone to elderly men may significantly increase lower extremity strength as well as lean muscle mass.⁴⁴

Although there are significant increases in strength among elderly males when given high doses of testosterone, the potential risks may outweigh the benefits. Risks associated with testosterone therapy in older men include aggressive behavior, thrombotic complications, sleep apnea, peripheral edema, gynecomastia, and the increased risk of prostate cancer.⁴⁶

Growth Hormone

As serum GH levels drop with aging, the role GH plays in many processes in the body is impacted.¹² Growth hormone supplementation for anti-aging has become a multimillion-dollar industry.⁴⁷ Vance has suggested that one third of GH prescriptions in the United States are for indications not approved by the FDA which includes anti-aging and athletic enhancement.⁴⁷

Although GH administration in the elderly appears to improve body composition as evidenced as increased muscle mass, decreased fat mass, and reduced rate of bone demineralization, a strong body of evidence suggests that GH supplementation does not result in strength gains, increases in functional capacity, or positive metabolic changes.^{48,49} The adverse effects associated with GH supplementation are significant and are reported

Table 1. Pharmacological Interventions for Sarcopenia

Treatment	Targeted Action	Result	Side Effects
Testosterone	Increased protein synthesis	High doses increase muscle mass and strength	Aggressive behavior, thrombosis, sleep apnea, peripheral edema, gynecomastia, increased risk of prostate cancer
Growth hormone	Increased muscle mass, decreased body fat	Increased muscle mass but no increase in strength or function	Arthralgia, carpal tunnel syndrome, edema, glucose intolerance, diabetes, increased risk of some cancers
Dehydroepiandrosterone (DHEA)	Increased levels of testosterone	No increase in muscle mass or strength	None known
Myostatin regulation	Decreased inhibition of muscle mass	Increased muscle mass and strength in animal studies	Unknown

at a high rate with treatment. Such adverse effects include carpal tunnel syndrome, edema, arthralgia, glucose intolerance, and diabetes.⁴⁸

Dehydroepiandrosterone

Dehydroepiandrosterone (DHEA) is marketed as a nutritional supplement and is available over-the-counter in health-food stores. Unlike testosterone and estrogen, DHEA is a hormone precursor which is converted to sex hormones at specific target tissues.⁵⁰ The relationship between DHEA levels and testosterone/estrogen levels in the human body has been of particular interest.

Since DHEA is a precursor in the biosynthesis of sex hormones such as testosterone and estrogen, DHEA supplementation in both males and females could potentially aid in increasing muscle mass and strength without the potential risks associated with testosterone and estrogen therapy. Supplementation of DHEA in aged men and women resulted in an increase in bone density, testosterone and estradiol levels, libido parameters, but no changes in muscle size, strength, or function.^{51,52} Researchers evaluating DHEA use in aging adults suggest that its effects should be evaluated over a longer period of time, and it might be more efficacious if the DHEA dosage administered resulted in circulating androgen levels exceeding those of young, healthy adults.⁵²

While there are few known adverse effects associated with DHEA supplementation, most studies have failed to demonstrate gains in muscle size or strength that would address concerns about sarcopenia. Although DHEA may provide the consumer with other benefits such as increased bone density and sex hormone levels which may counter other factors involved with aging, it has not yet been proven to counter sarcopenia.

Myostatin Regulation

Myostatin is a key protein in regulating muscle growth; when myostatin is inhibited, muscle hypertrophy occurs.⁵³ Myostatin and its effects on muscle hypertrophy is a novel topic in the scientific community. While animal studies have been enlightening, there has been only one study of myostatin regulation in humans published to date.⁵⁴ The potential regulation of myostatin to ameliorate the adverse effects of muscle mass and strength loss not only seen in sarcopenia and other muscle wasting pathologies is appealing. There are various proposed methods of inhibiting myostatin in muscle which would aid muscle hypertrophy. Three methods being evaluated are through direct genetic deletion of myostatin, administration of follistatin, and administration of anti-myostatin antibodies.

In mice, deletion of the myostatin gene resulted muscle mass increases through hypertrophy and hyperplasia, with as much as a 2.5-fold increase in individual muscle mass compared to control mice.⁵³ Another study targeted follistatin, a protein that binds to and antagonizes myostatin, thus, diminishing myostatin's role in controlling muscle size.⁵⁵ In mice over expressing follistatin a similar increase (3-fold) in muscle mass was seen compared to control mice.⁵⁵ Another method used to inhibit myostatin is through anti-myostatin antibodies; injection of anti-myostatin antibodies in mice demonstrated a 20% increase in muscle mass and strength increases over a 4-week period.⁵⁶

Increased myostatin levels in human muscle would potentially explain part of the fall in muscle mass associated with aging. Of two studies looking at myostatin mRNA in aged human muscle, one found an increase in myostatin mRNA while the other found no difference in myostatin mRNA compared to young controls.^{57,58} One human study manipulating myostatin has been conducted using a recombinant human antibody on patients with muscular dystrophy.⁵⁴ The results of this study suggest that this approach may be a promising treatment to stimulate muscle growth in muscular dystrophy.⁵⁴ Other myostatin inhibitors are being investigated for sarcopenia and other muscle-wasting disorders such as cachexia by pharmaceutical companies.⁵⁴

CLINICAL STRATEGIES FOR FIGHTING SARCOPENIA

Physical therapists routinely use resistance training as an intervention. Resistance training is recognized as the most safe and effective method of combating sarcopenia and maintaining strength and function in the elderly population. Skeletal muscle responds to resistance exercise with increased protein synthesis and muscle hypertrophy leading to increased muscle strength, regardless of age.^{59,60} The degree of muscle response, however, may vary depending on age. In general, older subjects may experience smaller absolute strength gains than their younger counterparts, but have similar percentage strength increases.⁶⁰ Overall, high-intensity resistance training programs of 70% to 90% of 1-Repetition Maximum (RM) resulted in substantial strength gains in aging adults (see review⁶¹).

There is a widespread agreement as to the benefits of resistance training for aging adults, but the optimal specific exercise parameters remain unclear. In a comparison of single to multi-set resistance training programs, it was shown that the multi-set group had greater muscle strength and endurance gains than those who only performed a single set of each exercise. Nevertheless, the single-set group acquired significant gains in muscle strength, endurance, and physical performance measures over their baseline, indicating that single-set programs may be sufficient to reduce sarcopenic muscle strength decline.⁶²

The number of exercises, repetitions, sets, intensity, frequency, etc. could be modified to an infinite number of combinations, but the general consensus from a review of the literature is that some resistance training is better than no training at all for reducing the effects of sarcopenia. A scientific review and guidelines for resistance training in healthy, older adults is described in the American College of Sports Medicine's Position Stand, "Progression Models in Resistance Training for Healthy Adults."⁶³ They recommend an "individualized" process in resistance training prescription and caution be taken with the aging adult as to the rate of progression.⁶³

Injury may be a concern of some clinicians when prescribing high intensity resistance exercise to their aging adult patients, especially those who are frail or significantly deconditioned; however, most studies have shown that resistance training can be performed safely in both community and nursing home settings. Compared to low-intensity resistance training, high-intensity resistance training produced greater strength gains and was as safe and well-tolerated by elderly men who were frail.^{64,65}

Increases in strength resulting from resistance training can positively affect the functional status and self-reported quality of life in the elderly.²⁹

Resistance training may also positively impact some of the hormonal contributors to sarcopenia. Resistance exercise can lead to acute increases in the amount of testosterone and GH in both young and aging adults, though this increase may be slightly attenuated with age.⁶⁶ This acute rise in anabolic hormone levels may be an important factor for increases in muscle size and strength associated with resistance training. Higher hormone levels post-exercise, however, are acute and are not sufficiently persistent to impact long-term baseline circulating hormone levels.⁶⁷

Chronic endurance training has been shown to delay the decline in muscle strength and fiber type changes associated with sarcopenia until 70 years of age.⁶⁸ After age 70, peak isokinetic concentric torque of the leg extensor muscles began to diminish. Endurance exercise, ie, exercise sustained for a period of time, must be at a sufficiently high intensity and frequency to prevent this decline. In aging adults aged 68 to 92 years, leisure activity such as gardening or walking alone did not enough to prevent sarcopenic changes over a three year period.⁶⁹ Endurance training may be most beneficial when performed along with some resistance training, as resistance exercise improves muscle force generation and Type II fiber hypertrophy in aging adults.^{59,60}

Exercise not only positively affects muscle contractile properties but impacts on neural properties of muscle function as well. It is generally accepted that muscle response to strength training occurs in 2 stages, the first stage involving muscle strength gains without noticeable muscle hypertrophy that are typically attributed to neural adaptations.⁷⁰ These neural adaptations may include increased neural output from the CNS, more effective motor unit synchronization, changes in motor unit recruitment, decreased antagonist co-contraction, and increased maximal motor unit discharge rate (see review⁷⁰).

Another benefit of increasing activity levels in aging adults is to combat increases of IL-6 that occur with inflammatory process associated with aging. Higher levels of physical activity associated with exercise and active lifestyles have been shown to significantly decrease inflammatory cytokine concentrations such as IL-6 in older adults.⁷¹ High levels of IL-6 have been correlated with diminished muscle function related to strength and movement.^{16,17}

Inadequate nutrition can compound the problem of sarcopenia in older adults. The question has been raised as to what effect exercise has on appetite. A review by Blundell and King found that 19% of studies reported an increase in energy intake after exercise, 16% showed a lessening in appetite after exercise, and 65% showed no change in food intake in response to physical activity.⁷² The scientific evidence, while inconclusive, tends to suggest that increased physical activity does not have a significant effect on energy intake.

SUMMARY

Overall, there appear to be natural neuronal, musculoskeletal, hormonal, and metabolic changes with aging that contribute to sarcopenia. Disuse atrophy and inactivity compound the

problem. Multiple mechanisms contribute to decline in muscle mass and force production. Supplements and hormone treatments appear to have little value in strength gains, but some aid in muscle hypertrophy. Future pharmaceutical management of muscle wasting is being studied in animals and has promise for fighting sarcopenia and muscle wasting pathologies. Resistance exercises are beneficial in delaying deleterious effects of sarcopenia such as loss of muscle mass, which often results in a reduction of strength. Diminishing the effects of sarcopenia should result in longer independent living and shorter rehabilitations when necessary.

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