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# Sarcopenia and Exercise: Mechanisms, Interactions, and Application of Research Findings

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## summary

Sarcopenia is a multifactorial condition that results in a progressive age-related loss of muscular size and strength. Overall, sarcopenia may result from decreases in or resistance to central nervous system stimulation and anabolic hormones. Although some muscle loss is a normal consequence of the aging, resistance exercise can attenuate much of this loss.

Remarkable scientific and medical advances in the past century have extended the human life span by reducing the incidence of contagious disease. In the past, acute conditions such as rheumatic heart disease, tuberculosis, polio, and whooping cough were major threats to survival. Fortunately, due to the development of antibiotics and immunizations, these diseases no longer pose a significant threat. During the past century, causes of dis-

ease have changed from environment related to lifestyle related.

Advances in technology have reduced the amount of physical activity required to perform daily functions. One of the many conditions believed to be associated with reduced physical activity is sarcopenia. In 1989, Rosenberg coined the term “sarcopenia,” which refers to the loss of muscle mass that occurs with age (19). The name sarcopenia comes from the Greek words “sarca” for flesh and “penia” for loss.

Although some muscle loss is a normal consequence of aging, a reduction in physical activity may accelerate this loss (4, 9, 17, 18, 22, 25). With the reduction in muscle mass, there are corresponding functional losses that lead to immobility, injuries, falls, and, potentially, death (16). The principle of reversibility (“use it or lose it”) definitely applies in the context of sarcopenia (9, 18, 19, 22, 25). This paper will discuss the multiple causes of sarcopenia and the impact of exercise in mediating these causes.

## Sarcopenia: Definition and Prevalence

According to Roubenoff (18), there are no established norms for the loss of muscle mass at which sarcopenia can be diag-

nosed. However, available data suggest that a loss of 40% of baseline lean mass is fatal. Sarcopenia is different from other conditions that result in muscle loss, such as cachexia and wasting.

Roubenoff (17) distinguished between wasting, cachexia, and sarcopenia. Wasting refers to the unintentional loss of weight, including both fat and fat-free mass, and is driven by inadequate dietary intake that results in a negative energy balance. Cachexia refers to the loss of fat-free mass, but with little or no loss of weight, and is driven by inflammatory hormonal responses that result in an elevated metabolic rate and increased protein degradation. Finally, sarcopenia refers specifically to a loss of muscle mass, and is a normal part of the aging process. In contrast to sarcopenia, both wasting and cachexia may occur in the elderly as a result of age-associated diseases but not as a result of normal aging.

Sarcopenia can be compared to the loss of bone mass that occurs with age. Unfortunately, there are no normative data for sarcopenia as there are for osteopenia. Baumgartner et al. (4) has conducted the only population-based study of the relative severity of sarcopenia among an elderly population. Baumgartner and col-

leagues measured appendicular muscle mass by dual-energy X-ray absorptiometry in 833 randomly selected elderly Hispanic and white men and women. Sarcopenia was defined as a muscle mass  $\geq 2$  SD below the mean for young healthy subjects. The prevalence of sarcopenia by this definition increased from 13% to 24% in persons aged 65 to 70 years and to more than 50% of those older than 80 years of age. The prevalence increased in both men and women but was actually higher in men (58%) than in women (45%) older than 75 years of age.

These findings suggest that sarcopenia is different from osteopenia in that men are affected to a greater extent than women. However, because women live longer, women may ultimately suffer the consequences of sarcopenia more than men. Loss of muscle mass can lead to a loss of strength and physical function, which is of primary concern for the elderly. Baumgartner et al. (4) found that sarcopenic women had 3.6 times higher rates of disability, and men had 4.1 times higher rates, compared with subjects who had normal muscle mass. In the sarcopenic subjects, there were significantly greater risks of using a cane or walker and a history of falling. These risks were independent of age, race, obesity, income, alcohol intake, physical activity, current smoking, and comorbidity.

Roubenoff (18) proposed that the severity of sarcopenia is based on a feedback loop that includes physical activity (or inactivity), muscle mass, strength, and physical function. This feedback loop can be driven in either a positive (healthy) or negative (disabling) direction. In the positive direction, physically active individuals are able to preserve muscle mass and strength and thus maintain physical function. In the negative direction, lack of physical activity can accelerate muscle loss, which leads to decreased strength and a greater proportion of maximal effort required to perform any given task. When tasks become uncomfortable due to excessive effort, either these tasks are

abandoned or less-efficient compensatory motor patterns are developed, which creates a progressive cycle of muscle loss, decreased strength, and disability.

Generally speaking, there is a positive relationship between loss of muscle mass and decreased strength. Cross-sectional studies have suggested that the loss of muscle is largely confined to type II fibers—the fast-twitch cells that are responsible for the greatest strength increases (18). Though both aerobic capacity and muscle strength are important determinants of physical function, loss of muscular strength may be more of a limiting factor for the elderly (13).

The ability of an elderly person to perform aerobic activity can be limited by a lack of muscular strength to support their body weight. In this context, muscular strength plays an indirect role in maintaining the health of the cardiovascular system and a direct role in determining functional ability. Understanding the mechanisms of sarcopenia is essential in determining appropriate intervention strategies to maintain muscle mass, strength, and functional ability.

### **Mechanisms of Sarcopenia**

Sarcopenia is likely a multifactorial condition with a range of possible causes. Overall, sarcopenia may result from decreases in or resistance to central nervous system stimulation and anabolic hormones. This section will discuss the proposed mechanisms for sarcopenia under 3 general headings that include neuromuscular factors, hormonal factors, and metabolic factors.

#### **Neuromuscular Factors**

One of the primary causes of sarcopenia is the loss neural input to the muscles. The loss of neurons is a continuous process that occurs throughout life and is currently considered irreversible. Older adults have larger motor units than younger adults. With the loss of motor units, there is an attempt by surviving neurons to compensate for this

loss by “adopting” muscle fibers (7). The loss of motor units results in muscular atrophy and decreased strength.

Lexell et al. (15) studied the vastus lateralis in 43 male cadavers aged 15 to 83 and found that between the ages of 20 and 80, there is a 50% reduction in the total number of fibers. Based on measurements of cross-sectional area, there was a selective loss of fast-twitch type II muscle fibers versus slow-twitch type I muscle fibers. Trappe et al. (23), in a 20-year longitudinal study of distance runners, found that the relatively higher proportion of type I fibers that occurred with aging was independent of rigorous endurance exercise.

It is not known what role resistance exercise, hormone levels, or genetic factors may have in preserving motor unit numbers in the elderly. The role of resistance exercise may be to improve the function of surviving motor units. Frontera et al. (8) demonstrated that 12 weeks of resistance training in older men resulted in increased leg extensor strength of 110% but increased quadriceps cross-sectional area of only 9%. This suggests that the strength gained may have resulted primarily from neurological adaptations, such as increased synchronization of agonist muscle groups and reduced firing of antagonist muscle groups.

In addition to the loss of muscle quantity with age, muscle quality has also been shown to decline. Muscle quality represents the peak force produced normalized to muscle cross-sectional area. Muscle function tests performed on isolated muscle preparations have determined that the decline in muscle quality may be due to a number of structural and compositional changes. These changes may include a disproportionate loss of contractile proteins, increased connective tissue, and increased intramuscular fat (22).

#### **Hormonal Factors**

Several hormones have been shown to be important regulators of muscle protein turnover. This review will focus on

testosterone, growth hormone (GH), and insulin-like growth factor 1 (IGF-1).

Testosterone has potent anabolic effects on muscle. As men age, mean serum testosterone and free serum testosterone have been shown to decline. For example, van den Beld et al. (24) demonstrated that between the ages of 73 and 94, there is a 3% decline per year in free testosterone levels. This decrease is paralleled by a loss of lean muscle mass and strength. In elderly women, testosterone levels also decrease, particularly in the immediate years following menopause. Both estrogen and testosterone can inhibit production of catabolic cytokines, suggesting that the loss of these hormones may result in catabolism of muscle.

Studies reviewed by Greenlund and Nair (9) were inconsistent regarding the effects of testosterone supplementation on changes in muscle mass. Testosterone supplementation was found to be most effective when combined with resistance training. The potential benefits of testosterone supplementation, however, need to be weighed against the negative side effects, which may include increased hematocrit, increased prostate size, and unfavorable lipid profiles.

Currently, the role of GH deficiency in the development of sarcopenia is less understood (19). Secretion of GH from the pituitary stimulates peripheral secretion of “systemic” IGF-1, which then stimulates new muscle growth (10). However, GH production is known to be lower in obese persons. Therefore, fat mass is a major confounder of the relationship between lowered GH and sarcopenia. For example, Roubenoff et al. (20) found an inverse relationship ( $r = -0.67$ ) between serum leptin (a marker of body fatness) and GH production in postmenopausal women.

Similar to testosterone, research examining the effect of GH supplementation on changes in muscle mass has been inconsistent. Many techniques used to measure muscle mass, such as hydrostat-

ic weighing, do not distinguish between water retention and lean tissue growth, which makes determining the effectiveness of GH difficult. GH supplementation is also associated with many potential negative side effects, including fluid retention, carpal tunnel compression, and gynecomastia (9).

A review by Hameed et al. (10) differentiated between “systemic” IGF-1 and “local” IGF-1. As discussed previously, “systemic” IGF-1 is synthesized in the liver as a consequence of GH secretion from the anterior pituitary. However, recent evidence suggests that there is also IGF-1 synthesis that occurs “locally” in skeletal muscle, independent of GH secretion. The “locally” produced IGF-1 may be important for muscular hypertrophy through stimulation of muscle satellite cells.

Muscle satellite cells are immature muscle cells that are activated in response to mechanical loading or damage. When activated, satellite cells fuse with existing fibers and provide new nuclei to fibers undergoing hypertrophy. Resistance exercise may stimulate the production of “local” IGF-1 in skeletal muscle, which may slow the progression of sarcopenia by stimulating new muscle growth.

### **Metabolic Factors**

From the third decade of life to the eighth decade of life, there is approximately a 15% decline in rest metabolic rate (RMR). This translates into burning about 250 kcal less each day. Because of the age-related decline in physical activity and RMR, there is also a decline in total daily energy expenditure (26). This decline in total daily energy expenditure can lead to an accumulation of fat mass, which increases the risk for hypokinesia-related diseases.

In addition to a decline in physical activity, a decline in muscle protein synthesis may contribute to reductions in RMR. Research has shown that the synthesis of mixed muscle proteins is reduced by 30% with age (9). However,

there appears to be some selectivity in the reduction of muscle protein synthesis. For example, Balagopal et al. (2) found that myosin heavy-chain synthesis was decreased 40% in old versus young subjects, but sarcoplasmic protein synthesis was either maintained or increased. A positive correlation was found between myosin heavy-chain synthesis and muscle strength, which suggests that muscle contractile function is partly determined by the ability to produce the necessary proteins.

One reason for reduced protein synthesis is a reduction in the abundance of mRNA, the genetic material that allows for the translation of muscle proteins. Balagopal et al. (3) showed that mRNA levels for myosin heavy-chain (MHC) proteins were significantly reduced with age. This reduction was theorized to occur due to transcriptional or pre-transcriptional defects or instability of mRNA. These changes may explain the decrease in MHC synthesis as well as the preferential atrophy of type II muscle fibers reported to occur with aging.

### **Interactions of Exercise with Sarcopenia**

There is difficulty in determining how much of the reduction in muscle size and strength is due to physical inactivity versus aging per se. However, it is clear that maintaining a pattern of regular exercise is helpful for maintaining muscle mass and strength. This section will discuss studies that have demonstrated the positive effects of exercise in counteracting the age-related effects of sarcopenia.

Schulte and Yarasheski (21) summarized 3 studies that examined the effects of short- and long-term resistance training on strength, rate of muscle protein synthesis, and expression of the myostatin gene. The first study examined the effects of a 2-week resistance-training program on contractile protein synthesis in young (23- to 32-year-old) versus old (78- to 84-year-old) men and women. The older participants were not considered physically

frail, based on the results from a physical performance test. Eight resistance exercises were performed at an intensity of 60–90% of one repetition maximum (1RM) for 2–3 sets per exercise and 8–12 reps per set. Synthesis of MHC and mixed muscle proteins were assessed using muscle samples from the vastus lateralis.

Results demonstrated that before training, mixed and MHC synthesis rates were significantly lower in the 78- to 84-year-old group versus the 23- to 32-year-old group. However, after 2 weeks of resistance exercise, mixed and MHC synthesis rates were directly related and increased similarly in both the young and the old subjects. This study showed the effectiveness of resistance exercise in stimulating acute increases in muscle protein synthesis.

The second study examined the effects of a 6-month resistance-training program on strength and contractile protein synthesis in physically frail 76- to 92-year-old men and women. Physical frailty was assessed using a physical function test and a self-report questionnaire. The resistance exercise program was the same as the one described in the first study (above). Muscle strength testing was conducted on a Cybex (Ronkonkoma, NY) dynamometer and consisted of knee extensor isometric torque production and knee extensor isokinetic torque production at 60 degrees per second.

Results demonstrated increased muscle protein synthesis in the vastus lateralis and increased knee extensor torque production. The men significantly increased isometric strength by 22%, whereas the women significantly increased isokinetic strength by 6%. This study showed that even frail individuals can safely achieve positive benefits from resistance training.

The third study was a cross-sectional study that examined serum myostatin levels in 3 different age groups that included 19- to 35-year-old men and women, 60- to 75-year-old men and women, and 76- to 92-year-old women.

Myostatin is the protein product of the gene that regulates muscle growth. High levels of serum myostatin have been associated with muscle wasting in AIDS patients. Therefore, the authors hypothesized that physically frail elders with sarcopenia may also have high circulating levels of myostatin.

The results demonstrated that serum myostatin levels were significantly greater in the 60- to 75-year-old men and women versus the 19- to 35-year-old men and women. Serum myostatin levels in the 76- to 92-year-old women were significantly greater than both of the younger groups. Overall, serum myostatin levels were inversely related to muscle mass/height<sup>2</sup> ( $r = -0.94$ ). This study suggests that the myostatin gene may have a direct effect on muscle loss with age; however, maintaining physical activity levels can alleviate much of this loss.

A review by Vandervoort and Symons (25) summarized the decreases in concentric, isometric, and eccentric strength that occurs with age. They found that strength decreases for various limb muscle groups were consistently less for eccentric muscle contractions versus either isometric or concentric muscle contractions. Currently, there is no explanation why eccentric strength does not decline to the same extent as isometric and concentric strength. However, a possible functional advantage of eccentric exercise is that, for a given absolute load, the intensity of muscular effort and related cardiovascular response is less. Therefore, learning to use the apparent strength advantage in eccentric contractions may be useful for older adults participating in a resistance exercise program.

LaStayo et al. (14) examined the effects of an 11-week eccentric exercise versus traditional resistance exercise on muscle strength and decreased fall risk in frail elderly subjects. Participants were split into 2 groups that included an eccentric group (ECC) and a traditional group (TRAD). The eccentric group per-

formed lower extremity exercise on a custom-made cycle ergometer powered by a 3-horsepower motor that drove the pedals in a backward rotation.

Subjects attempted to slow down (by resisting) the movement of the pedals. Intensity for this group was assessed using a Borg scale and ranged from “very light” to “somewhat hard.” In contrast, the traditional group performed 3 lower extremity exercises (leg press, leg extension, and mini-squat) using free weights and machines. Intensity for this group was measured in repetitions to fatigue and ranged from 6 to 15. Muscle fiber cross-sectional area (biopsy), strength (knee extension isometric strength), balance (Berg balance scale), stair descending ability (timed-stair descent), and fall risk (timed up and go) were assessed prior to and following the intervention.

Results demonstrated that both groups experienced a significant increase in muscle fiber cross-sectional area (ECC = 60%; TRAD = 41%). However, only the ECC group significantly improved strength (60%), balance (7%), and stair descent ability (21%). The timed up and go task improved in both groups, but only the ECC group went from a high to a low fall risk.

In addition to resistance exercise that promotes eccentric strength, resistance exercise that promotes muscular power may be beneficial for older adults. High muscular power is evidenced by the ability to produce large forces over short periods of time. Muscular power training may be important through improvements in reactive ability, which decreases the risk for falls. Prior studies have demonstrated the effectiveness of resistance-training programs designed to promote muscular power for improving functional ability in older adults (6, 11).

Hruda et al. (11) tested the effectiveness of resistance training aimed at improving muscular power in 25 older adults (ages 76–94 years). Subjects were divid-

ed into a “power” training group ( $n = 18$ ) and a control group ( $n = 7$ ). Subjects were assessed with the following tests prior to and after 10 weeks of training: leg extensor strength and power, 8-ft timed up and go, 30-second chair stand, and 6-m timed walk.

The “power” group performed both seated and standing exercises as quickly as possible to promote muscular power. The seated exercises included the leg cross, hip rotation, ankle rotation, and rising from a seated position. The standing exercises included the heel raise, squat, leg lift, and hamstring curl. Initially, subjects performed a single set to fatigue using only body weight as resistance, but sets were gradually increased, and elastic bands were added for increased resistance. The control group maintained their usual daily activities.

Results demonstrated that the “power” training group improved 25 to 60% on measures of knee extensor strength and power, whereas no improvements were made by the control group. For the functional performance tests, the “power” training group demonstrated improvements of 31% in the 8-ft timed up and go, 66% in the 30-second chair stand, and 33% in the 6-m timed walk. Changes in strength and power were correlated with changes in functional performance. The 8-ft timed up and go and the 6-m timed walk were both significantly related to average concentric power. This study demonstrated that a resistance training program that involves minimal equipment can be effective for improving performance in a variety of functional tasks encountered on a daily basis.

### **Exercise Programming for Sarcopenia**

The following sections will discuss the practical aspects of exercise prescription for sarcopenia.

#### **Resistance Exercise**

Resistance exercise should be the primary focus of a program targeted against sar-

copenia. Other modes of exercise do not provide sufficient overload to produce increases in muscular size and strength. The specifics of a resistance-training program should take into account individual limitations and prior exercise history, especially when working with older adults. A generalized resistance training program for sarcopenia may consist of 4 days per week, with 2 days devoted to eccentric resistance training and 2 days devoted to muscular power training (1, 6, 11, 14).

For the eccentric workouts, the focus should be on obtaining a high level of muscular overload through machine-based exercises. The use of machines is more convenient when performing eccentric workouts with relatively heavy loads. This is because an exercise professional can push or pull against the resistance during the eccentric phase of a repetition to provide additional resistance. Older adults who are not being supervised by an exercise professional can slow down the eccentric phase of a repetition, which increases muscular effort due to reduced momentum.

Exercises should be selected that involve the coordinated contraction of multiple muscle groups, such as the leg press, lat pull-down, chest press, row, and shoulder press. However, the shoulder press may be contraindicated for older adults with degenerative conditions of the rotator cuff muscles or cervical and lumbar vertebrae. Exercises such as these may be performed for 1–3 sets to fatigue (not including warm-up sets) with a resistance equal to 80% of 1RM (1, 6, 11, 14). If eccentric workouts are too intense to begin with, a gradual build-up phase can be incorporated that involves traditional repetitions performed at 60% of 1RM.

For the power-training days, the focus should be on functional movement patterns that emphasize relatively high-velocity repetitions. Free weights and cables that allow for greater freedom of movement should be used, so that movements will be similar to the movement patterns

and forces encountered during activities of daily living. The exercises performed on these days should be dictated by the activities performed during daily living, such as walking up and down stairs, rising from a chair, picking up objects from the floor, and lifting objects overhead.

In order to maximize power output, light resistance should be used that is equal to approximately 30% of 1RM, and repetitions should be performed as quickly as possible (12). Exercises can be performed for up to 3 sets but should not be taken to the point of fatigue. The focus should be on technique and learning efficient and powerful movement patterns.

#### **Aerobic Exercise**

Although resistance training should be the focus of an exercise program targeted against sarcopenia, aerobic exercise should not be neglected. Aerobic exercise is beneficial in regulating fat metabolism; this lowers the risk for several cardiovascular-related diseases (5). To maintain cardiovascular conditioning, aerobic exercise can be performed 3 days per week, ideally on non-resistance-training days. Because older persons may take medications that alter heart rate, the rating of perceived exertion (RPE) may be used to measure exercise intensity. Using the modified Borg 10-point scale, individuals can rate their own intensity level based on their perceived effort. Aerobic exercise should be performed at a low intensity (4–5 RPE) and moderate duration (i.e., 20–30 minutes) so not to interfere with recovery from the resistance workouts.

#### **Conclusion**

Sarcopenia is a multifactorial condition that results in a progressive age-related loss of muscular size and strength. Overall, sarcopenia may result from decreases in or resistance to central nervous system stimulation and anabolic hormones. Although some muscle loss is a normal consequence of aging, maintaining physical activity levels can ward off much of this loss. Research has shown that resistance training is particularly effective in restor-

ing muscular size and strength through increases in muscle protein synthesis and motor unit synchronization. The ability to maintain physical function and independence is heavily influenced by the ability to maintain strength levels. Exercise prescription for sarcopenia should place primary emphasis on resistance exercise with secondary emphasis on aerobic exercise. Older individuals have been shown to respond particularly well to eccentric-type resistance training and muscular power training. ♦

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