

## [ Athletic Training ]



# Muscle Changes in Aging: Understanding Sarcopenia

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Muscle physiology in the aging athlete is complex. Sarcopenia, the age-related decrease in lean muscle mass, can alter activity level and affect quality of life. This review addresses the microscopic and macroscopic changes in muscle with age, recognizes contributing factors including nutrition and changes in hormone levels, and identifies potential pharmacologic agents in clinical trial that may aid in the battle of this complex, costly, and disabling problem.

**Level of Evidence:** Level 5.

**Keywords:** sarcopenia; aging athlete; muscle aging; SARMS

As the population continues to age, more and more people choose to remain active much later in life than in the past. These people range from “weekend warriors” to competitive master athletes. Sports medicine practitioners should be knowledgeable about normal physiologic changes as well as injuries to the aging athlete. Sarcopenia, often defined as the age-related decrease in lean body mass,<sup>11</sup> has become a topic of significant investigation since it affects so many people, healthy and ill, and utilizes significant medical resources.<sup>32</sup> The direct costs approached \$18.5 billion in the United States in 2000<sup>22</sup>; by comparison, the annual cost of osteoporotic fractures in 1995 was \$16.3 billion.<sup>31</sup> Successful maintenance activity remains a challenging area of research because of the multifactorial contributions of age, nutrition, hormones, medical comorbidities, and activity level to changes in muscle over time.

There is a spectrum of changes in aging muscle, some of which are normal (age-related sarcopenia) and some of which are not (eg, cancer-related anorexia and cachexia syndrome). Sarcopenia has been more quantitatively defined as a relative muscle mass less than 2 standard deviations below a sex-matched control group aged 18 to 40 years, but the lack of a clear definition has resulted in a wide range of prevalence from 8% to 40%<sup>36</sup> (Table 1). The 2010 European Working Group on Sarcopenia in Older People defined 3 stages of this process<sup>27</sup>: *presarcopenia* is simply loss of muscle mass, *sarcopenia* is muscle loss that occurs in conjunction with loss of strength or physical performance, and *severe sarcopenia* occurs when muscle loss is present with both strength and physical performance loss. This is different from cachexia, which is a

complex metabolic syndrome that is always associated with an underlying illness or inflammatory condition that results in loss of muscle and fat mass. Cachexia involves increases in muscle protein synthesis and degradation, basal metabolic rate and energy expenditure, inflammation, and insulin resistance, but the practicing clinician may have difficulty in distinguishing whether sarcopenia or cachexia is behind the loss of tissue<sup>33</sup> (Table 2). Regardless, the result is a loss of muscle mass, strength, and function.<sup>4,11</sup>

## MUSCLE MASS AND AGING

To understand the gross changes in muscle function with aging, it is important to appreciate the micro- and macrostructural changes in this complex tissue. Our understanding of aging muscle is limited in several respects. It is difficult to evaluate studies of a small number of subjects and changing patterns and designs of investigations. Methods for quantifying longitudinal changes in gross lean muscle mass as well as subcellular adaptations continue to evolve, leading to variable results.

Mitchell et al<sup>27</sup> compared changes in muscle mass as a factor of global changes in body composition with age. Muscle mass decreases with advancing age, with men losing more absolute and relative muscle mass. This seems to be most prevalent in the seventh decade and beyond. Mitchell's group reported a 0.5% to 1.0% loss of muscle mass per year after 70 years of age and a 4.7% loss compared with peak mass in men and 3.7% decrease for women per decade. As a result, 70 years of age has

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Table 1. Definition of terms

Anorexia	5-lb weight loss in the preceding 2 months and/or an estimated daily caloric intake of <20 calories/kg; a desire by the patient to increase his or her appetite and gain weight; the physician's opinion that weight gain would be beneficial for the patient. <sup>29</sup>
Malnutrition	Any condition in which the body does not receive enough nutrients for proper function. It can be a result of starvation, related to a specific deficiency, or when one cannot properly digest or absorb nutrients from the food he or she consumes.
Cachexia	"A complex syndrome characterized by a severe, chronic, unintentional, and progressive weight loss, which is poorly responsive to the usual nutritional support, and may be associated with anorexia, asthenia, and early satiation." <sup>12</sup>
Cancer cachexia	Loss of desire to eat due to cancer, which leads to malnutrition, increases morbidity (illness) and mortality (death), and impinges on the quality of life.
Pre-cachexia	No or very small unintentional weight loss (<5% in 6 months) in the presence of underlying disease with anorexia ("markedly reduced appetite or total aversion to food") and chronic or recurrent inflammatory response. <sup>25,29</sup>
Refractory cachexia	Patient who is procatabolic, unresponsive to anticancer therapy, poor performance status (WHO score of 3 or 4), <3-month expected survival (too sick to receive anticachectic therapy). <sup>25</sup>
Sarcopenia	Loss of muscle mass and muscle strength that is associated with aging. <sup>11</sup>
Sarcopenic obesity	Increased body mass index associated with depleted lean body mass and function. <sup>35,39</sup>

Table 2. Sarcopenia versus cachexia<sup>a</sup>

Sarcopenia	Factor	Cachexia
Mild ↓	Weight	Severe ↓
Normal or ↑	Fat mass	Marked ↓
Moderate loss ↓	Fat-free mass	Marked ↓
↑	Protein degradation	Marked ↑
Not evident	Anorexia	Very evident
Normal or slight ↑	Inflammation	Marked ↑

<sup>a</sup>Modified from Morley and Makin.<sup>28</sup>

been mentioned as the target age for clinical trials addressing sarcopenia.<sup>28</sup> In parallel, strength declines by 10% to 15% per decade up to the age of 70 years, when the loss accelerates to 25% to 40% per decade.<sup>18,21</sup>

As previously mentioned, data from reviews must be carefully interpreted and are specific to the methods used in the original studies. Frontera et al<sup>16</sup> presented one of the more thorough descriptions of aging skeletal muscle mass. They measured the cross-sectional area of the thigh at 2 time points 12 years apart to help quantify muscle mass changes. These male patients

started at  $65.4 \pm 4.2$  years of age and completed the study at  $77.6 \pm 4.0$  years of age. The initial cross-sectional area of all thigh muscles measured at a specific portion of the thigh (which was reproducible at the second time point) was approximately 136 cm<sup>2</sup> at the onset of the study, and at completion, 12 years later, was 116 cm<sup>2</sup>. This was almost a 15% decrease in mass that was statistically significant. Knee extensors and flexors were both significantly smaller and weaker 12 years later. The change in muscle cross-sectional area was an independent predictor of strength at the later time point.

## Metabolic Consequences of Aging

Evans<sup>11</sup> described metabolic changes of aging as a significant contributor to sarcopenia. These changes include a decrease in muscle protein synthesis but little change in degradation. This suggests that muscle turnover and repair capacity is likely decreased with age. This occurs in the setting of increasing insulin resistance and higher percentage body fat mass. In conjunction with a decreasing basal metabolic rate, it is clear that these factors all contribute to the decrease in lean body muscle mass. These interact with decreased physical activity, lower hormone excretion, nutritional deficits, and possibly chronic inflammation, contributing to this complex change in body composition.<sup>2</sup>

Other factors associated with aging are systemic. Muscle, as a highly vascular and metabolically active tissue, is affected by oxygen delivery throughout the body. Endurance capacity declines 10% per decade (as measured by maximal oxygen consumption). Similarly, enzymatic changes in energy production occur with age; anaerobic enzymes seem to remain constant with age, while aerobic energy production is decreased with age.<sup>23</sup>

## Muscle Fiber Type Distribution With Age

Age-related changes in muscle fiber distribution have been identified. Type I fibers are small, slow-contracting, low-tension output fibers with many mitochondria and aerobic enzymes for energy production (Krebs cycle and electron transport chain). These fibers are highly resistant to fatigue and are capable of metabolizing fat for energy expenditure. Type II fibers are much larger and faster contracting fibers that produce large tension output but fatigue quickly. While there is no consensus as to the exact numbers, it is clear that aging leads to an increasing percentage of type I fibers compared to type II.<sup>24</sup> Similarly, general muscle strength decreases with age, possibly related to decreased contribution from the progressively smaller numbers of large tension-producing type II fibers.<sup>17</sup>

## Muscle Fiber Denervation

The reasons behind the age-related increase in type I fiber composition may be due to the trophic influence the motor nerve has on muscle fibers.<sup>3</sup> It is possible that regeneration of previously damaged muscle fibers fails, but this seems unlikely.<sup>1</sup> A more reasonable explanation would be a reorganization of the aging motor unit pool. About one quarter of the motor units are inactive and nonfunctional. While the number of active motor units decreases, each active motor unit pool becomes larger.<sup>5</sup> The increase in the size of the active motor units may be due to new collaterals from the most active motoneurons in the type I pool branching out to the nonfunctioning fibers, which is commonly seen in nerve injury. Therefore, with age, there is less of a contribution to tension output from the higher tension type II fibers because the lower tension-output type I fibers are now more predominant.

Overall, the muscle mass of the elderly is smaller and weaker because of the loss of type II fibers.<sup>23</sup>

## Identifying the Presence of Sarcopenia

There are multiple techniques available to measure muscle mass ranging from chemical composition (total body potassium/nitrogen) to imaging (computed tomography [CT], magnetic resonance imaging [MRI], and dual-energy x-ray absorptiometry [DXA]) to less technically challenging methods such as anthropometry or hydrostatic weighing. Availability, expense, and limitations all contribute to issues related to quantifying the degree of muscle loss.<sup>28</sup> Currently, DXA is the most favored technique. There is no definitive biological marker of sarcopenia, but there are a number of markers that are associated with it, including adipokines, cytokines, antioxidants, evidence of oxidative damage, and apoptosis.<sup>37</sup>

## POSSIBLE INTERVENTIONS TO MINIMIZE SARCOPENIA

### Resistance and Endurance Training

With age, muscle strength and endurance are notably decreased. The decrease in muscle strength is secondary to a diminished muscle mass and protein production. The cross-sectional area of type I and type II fibers decreases with normal aging, and the relative distribution shifts to a slower profile. Decrease in endurance can be due to the reduced number of mitochondria and the subsequent reduction in mitochondrial-based aerobic enzymes.<sup>10</sup> Muscle is at the end of the chain of events in movement, so virtually every step involved from oxygenating the blood to the delivery of oxygen to working muscle may contribute in some manner. The loss of strength, a hallmark feature of aging, may begin with inactivity, but the role of the shift in the fiber profile to a greater fraction of the active tissue being type I must also be considered.

One of the impressive features of skeletal muscle is its plasticity. This ability to adapt to its demands continues throughout the life span, as there are numerous studies that demonstrate the trainability of skeletal muscle and the resulting gains experienced by the elderly. For example, adults between 60 and 80 years of age can experience, with appropriate training, 20% to 30% increase in aerobic fitness, similar to what people far younger achieve.<sup>19,34</sup> The improvements come from central cardiovascular as well as peripheral muscle adaptations.

Muscle is also fully capable of responding to resistance training. For example, men over 66 years of age who trained by lifting 80% of their 1 RM (repetition maximum) for 12 weeks experienced strength gains of approximately 5% per day, which is similar to what is reported in far younger men.<sup>17</sup> Strength is commonly a factor in frailty in older patients, represented as decreased walking speed, sit-to-stand transition time, balance, stair climbing, falls, and more. A resistance training program in a group of subjects where the inclusion criteria was 90 years of age showed that even at this advanced age, strength could be improved (in this group by 175%), as

well as the cross-sectional area of the thigh muscles (by 15%), all leading to improvements in functional mobility.<sup>15</sup>

While the loss of strength and endurance is expected to occur across the age span, it remains important to keep older individuals active. Cardiovascular health is greatly improved with increased activity, and alternately, increased fragility and mortality is associated with less physical activity.<sup>13</sup> Training helps muscle meet the complex demands of increased activity by increased enzymatic protein production and capillary density for higher muscle metabolic demand as well as increased contractile protein production to allow for greater contraction tension. For many patients, the age-related effects on skeletal muscle are largely reversible.<sup>14</sup>

### Beyond Physical Activity

Sarcopenia is a complex process that involves much more than just age-related decreases in physical activity. The interaction of changes in hormone levels and nutrition over the life span strongly contribute to this process and should not be overlooked. Each contributes to the overall loss of skeletal muscle, increase in fatty tissue present in muscle, muscle weakness, and much more. The nature and extent of the contribution by each factor is not known and very likely to be highly individual.

#### Nutrition

One of the more difficult aspects of muscle physiology is nutrition because of the interplay between eating behavior, dietary composition, and digestion. It is difficult to establish a direct link between dietary intake (especially of protein) and increased muscle mass. The physiology of the aging digestive system parallels that of skeletal muscle with regard to reduced function. For a multitude of reasons (physiologic, psychologic, and social), diet also changes with age, often resulting in reductions in protein intake, Vitamin D, and long-chain polyunsaturated fatty acids, deficiencies of which have been linked to decreased muscle function.<sup>6,26,32</sup> Future work into the ideal nutritional needs of individuals in various age groups is still needed to delay, prevent, or reverse sarcopenia. Similarly, research into combined dietary supplementation and exercise regimens for successful aging is currently ongoing.

#### Androgens

The role of sex hormones in muscle physiology is an important topic related to adaptation with age. Androgens are complex steroid-derived hormones that contribute to many aspects of growth in youth, which continues with maintenance of muscle mass and other tissues, including bone, in more mature individuals. Androgen levels decline with age in both men and women. Beginning around the age of 35 years, testosterone levels in men decrease by 1% to 3% per year, while women experience the greatest drop in hormone levels with menopause.<sup>20</sup>

For men, decreasing levels of testosterone over time can lead to a decrease in lean muscle mass and muscle strength, which

may have roles in decreased physical activity, higher fall risk, depression, and other medical problems such as obesity and its role in the development of type II diabetes. With testosterone supplementation, however, it is possible to slow or even reverse this trend. Similarly, in women, lower levels of estrogen lead to decreased muscle mass and increasingly fragile bones, which can contribute to decreased activity levels and can be reversed with hormone replacement therapy.<sup>9,20</sup>

The many benefits of exogenous steroid therapy are unfortunately associated with other more damaging effects. In men, testosterone replacement therapy has been associated with increased rates of prostate cancer, erythrocytosis (hematocrit >50%), adverse cardiovascular events, and a host of other hormonal and emotional adverse events.<sup>20</sup> Similarly, women treated with estrogen replacement have higher rates of cancer and venous thromboembolism. Adverse complications of hormone therapy like those listed have led to research into synthetic hormones that have the beneficial aspects of hormone therapy without the detrimental effects. The current thrust is in selective androgen receptor modulators (SARMs),<sup>9,30</sup> discussed in the following.

#### SARMs and the Future of Sarcopenia Modification

The benefits of maintaining lean mass are apparent to the medical community, and significant efforts are being made to explore options for the medical management of sarcopenia. One direction under investigation is the development of SARMs, which are a synthetic group of compounds that bind to specific areas of androgen receptors on many cell surfaces to activate or inhibit selective functions of the steroid receptors. This selective activation/inhibition could encourage muscle growth while at the same time prevent some of the unwanted aspects of hormone therapy, such as prostate growth in men, and minimize the virilization effects on women. Similarly, for any SARM to become accepted for clinical use in the treatment of sarcopenia, it must not adversely affect the patient's cardiovascular risk profile.<sup>30</sup>

Currently, there are several SARMs in clinical trials. One such example is ostarine, a SARM developed to help with muscle wasting secondary to malignancy. After only 86 days of use, elderly men and women had improved ability to climb stairs and had increased lean body mass. More importantly, men had no increase in prostate-specific antigen levels and women had no increase in hair growth, suggesting the selective androgenic nature of this drug and side effect profiles remain low.<sup>30</sup> However, there is always the potential for misuse of new therapies, especially by people for whom the treatment was not intended. While SARMs can help increase muscle tissue in wasting conditions, including sarcopenia and cachexia, there is potential for athletes to utilize these new products to enhance performance. The World Anti-Doping Agency has added SARMs to its list of banned substances in advance of any specific product on the market. Clinical detection mechanisms are already in place to detect these new compounds.



## CONCLUSION

The American Geriatrics Society has identified sarcopenia to be a geriatric syndrome<sup>8</sup> that needs to be treated with an interdisciplinary approach.<sup>7</sup> Sarcopenia continues to be a challenging problem for the aging population while researchers continue to wrestle with complex issues related to study design and interventions.<sup>38</sup> Between increasing exercise regimens, better nutrition, and hormone modulation, there is great potential to decrease disability associated with age-related changes to muscle. As little as a 10% reduction in the prevalence of sarcopenia has the potential to save \$1.1 billion in US health care costs.<sup>22</sup> High-quality research is needed to continue to better define sarcopenia, validate methods of measurement that help establish clinical norms, and validate biomarkers that qualify and quantify age-related changes to muscle. With better management of the quality of muscle, older individuals may successfully participate in physical activities well into their later years of life with concomitant benefits to cardiovascular function and decreased disability.

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