

Review Article

Sarcopenia: Causes, Consequences, and Preventions

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With the onset of advancing age, muscle tissue is gradually lost, resulting in diminished mass and strength, a condition referred to as sarcopenia. The sequela of sarcopenia often contributes to frailty, decreased independence, and subsequently increased health care costs. The following was adapted from an introduction to the conference “Sarcopenia, Age-Related Muscle Loss—Causes, Consequences, and Prevention,” sponsored by the Kronos Longevity Research Institute in June 2002. This brief review will introduce potential mechanisms that may contribute to sarcopenia, although no one mechanism has yet, and may not completely, define this process. The only agreed-upon intervention from these proceedings was regular physical exercise, stressing weight-training for elderly men and women. However, even those individuals who maintain their fitness through exercise do not appear to be immune to sarcopenia.

WHETHER considered a process, or a disease, discussion of sarcopenia (an age-related loss of muscle mass and strength) first requires an appreciation of the biological process of aging. Is aging an inevitable process, or are there potentially alterable physiological or genetically programmed events occurring? Although no one mechanism has yet unified our understanding of the aging process (1–3), with advancing age, decrements occur in many physiological systems averaging on the order of 2% per year (4), of which several potentially contribute to muscle loss (5). In healthy young adults, under equilibrium conditions, skeletal muscle protein synthesis and degradation is a balanced, dynamic process with no net change occurring in skeletal muscle mass (6,7). During aging, however, muscle tissue is gradually lost, resulting in diminished mass and strength, a condition referred to as sarcopenia (8). The sequela of sarcopenia may contribute to frailty, decreased capacity for independent living, and subsequent increased health care costs. The following review was adapted from June 2002 conference, “Sarcopenia, Age-Related Muscle Loss—Causes, Consequences, and Prevention,” sponsored by the Kronos Longevity Research Institute.

The term *sarcopenia* (from the Greek *sarx* for flesh and *penia* for loss) was first coined by Rosenberg (8) in identifying the age-associated loss of muscle mass and function. Sarcopenia is determined by two factors: the initial amount of muscle mass and the rate at which it declines with age. The rate of muscle loss with age appears to be fairly consistent, approximately 1%–2% per year past the age of 50 years (4,9). But is sarcopenia a normative process of aging, a disability, or a disease? If sarcopenia is an inevitable process occurring over time, at what point does a person lose enough muscle mass to cross a threshold for disability (disease)? A clear relationship exists between loss of muscle strength and loss of independence, contributing to falls, fractures, and nursing home admissions (10,11). However, what is the minimal amount of muscle mass

and strength required to maintain independent living with advancing age? In examining the frailty literature, a loss of 30% of reserve capacity limits normal function, whereas a decrease of 70% results in failure of that system (12). Therefore, what amount of sarcopenia is required to significantly contribute to the condition of frailty and disability?

Who really is sarcopenic? If we compare the muscle mass of body builder turned actor/gubernatorial candidate Arnold Schwarzenegger to that of the 1984 Olympic gold medalist in the 1500-meter run, Sebastian Coe, who is sarcopenic? A 70% reduction in mass is suggested to lead to disability, yet Arnold could afford to lose 70% of his lean body mass and still have greater muscle mass than that of Sebastian. Thus, if we assume that muscle loss rates are similar, then the greater the (starting) reserve capacity the longer it will be before sarcopenia or physical frailty will compromise function.

With advancing age there are significant changes in body composition such that body fat increases while modest losses are observed in muscle mass (13–19). The average adult can expect to gain approximately 1 pound of fat every year between ages 30 to 60, and lose about a half pound of muscle over that same time span; that change in body composition is equivalent to a 15-pound loss of muscle and a 30-pound gain in fat (14). This shift in body composition with advancing age is often masked by relative stability in overall body weight (9,20). As an example, cross-sectional data demonstrates that young healthy men have a body composition of approximately 20% body fat at age 25, whereas in men aged 55 years, body fat was 30%, and greater than 35% in 75-year-old men (6). Muscle mass was fairly stable between the 25- and 55-year-old men, but declined approximately 25% between 50 and 75 years of age (6). Although physical activity and exercise status are important factors in the onset of obesity with age, the decline in muscle mass and gain in body fat are evident even in active older adults (9,21–23). Therefore, how do we

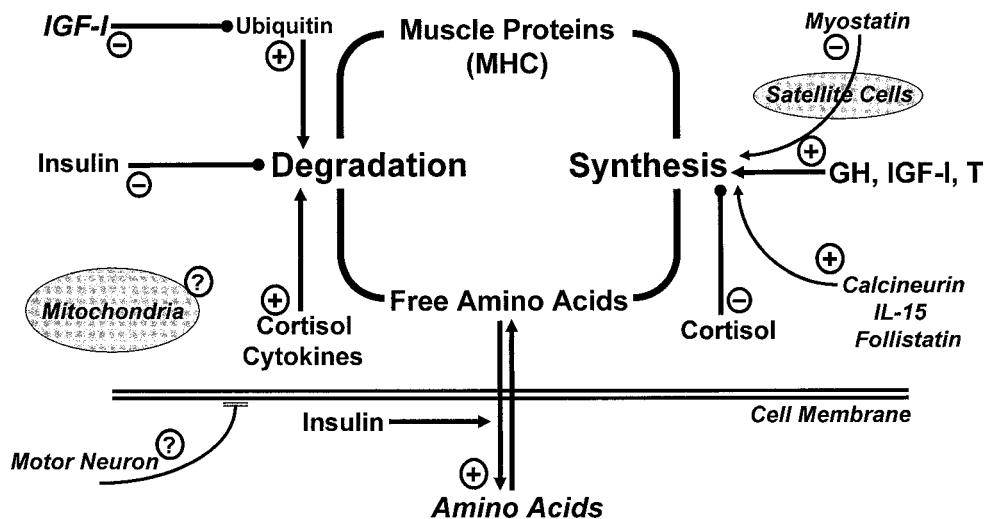


Figure 1. Skeletal muscle protein turnover is a complex regulated process. Several physiological stimuli have been demonstrated to affect either protein synthesis (for hypertrophy or repair) or protein degradation (for controlled atrophy or apoptosis). This process has both extracellular and intracellular regulators. It is suggested that no single mechanism (changing innervation, altered hormonal balance, decreased amino acid availability, or failure to supply adequate energy demands) may solely account for sarcopenia. Therefore, clinical interventions may also need to be multifaceted.

define sarcopenia in the face of changing body composition? In the New Mexico Elder Health Study (24), sarcopenia was defined as a muscle mass index [muscle mass (kg)/height (m)²] less than two standard deviations below the mean of a young reference population. Using this definition 10%–25% of persons under the age of 70 years were sarcopenic, whereas beyond the age of 80 greater than 30% of women and 50% of men were sarcopenic (24,25).

What are the ramifications of losing muscle mass? The consequences of sarcopenia include decreased strength (26,27), metabolic rate (28–31), and maximal oxygen consumption (32). These physiologic decrements in maximal strength and fitness probably contribute to weakness and a loss of independence (33). The loss of aerobic capacity with age is predominantly due to a loss of muscle mass (34). This loss of fitness is also observable in highly active older adults, who continue to exercise regularly, yet display rates of decline are similar to their sedentary peers (35,36). However, fitness remains greater at any age in those who exercise regularly as compared with those who do not.

Much like the underlying causes of aging, the biology of sarcopenia remains elusive. Two key observations associated with sarcopenia include a loss of skeletal muscle fiber number (37) and a change in the cross-sectional area (CSA) of the remaining fibers (38). Various mechanisms have been put forth to explain the change in total muscle mass observed including: (a) a lack of regular physical activity (“use it or lose it”), (b) a change in protein metabolism (a deficit between protein synthesis versus degradation), (c) alterations in the endocrine milieu (decrease in growth hormone (GH) and testosterone and an increase in cortisol and cytokines), (d) a loss of neuromuscular function (denervation versus reinnervation), (e) altered gene expression, and (f) apoptosis; other factors may also contribute in part to sarcopenia (Figure 1).

Figure 1 demonstrates the multifactorial nature of muscle protein balance. Skeletal muscle is a dynamic tissue constantly turning over its proteins to amino acids. Using mathematical modeling and rate constants from the literature, Mader (39) has suggested that approximately 65%–80% of the amino acids are resynthesized into proteins during muscle protein turnover, whereas about 20%–35% of amino acids have to be supplied through the diet, resulting in the average turnover of muscle of 8%–12% per day. For muscle to maintain its mass, the rate of protein synthesis must be in balance with the rates of degradation to amino acids in combination with dietary absorption maintaining the difference in amino acid utilization. For sarcopenia to occur, only small imbalances between synthesis and degradation over many years are necessary to eventually result in a significant loss of muscle mass (40). In young adults, muscle mass accounts for approximately 30% of whole body protein turnover, whereas in elderly persons, muscle mass only represents approximately 20% or less of whole body protein turnover (41). With advancing age, illness, trauma, or inadequate dietary intake of amino acids can all decrease the rates of protein synthesis and ultimately exacerbate the onset of sarcopenia. Alternatively, the oxidized proteins, which increase with advancing age, may not be as efficiently removed by the proteolysis system (ubiquitination and lysosomal degradation) resulting in the accumulation of lipofuscin and cross-linked proteins (5). An age-related accumulation of nonfunctioning proteins that are not efficiently removed from the muscle could increase the amount of noncontractile material in muscle, which might explain why muscle strength declines to a greater degree than total muscle mass in sarcopenia.

Figure 1 also outlines several endocrine mediators of protein metabolism. With advancing age, there is a well-documented increase in insulin resistance that contributes to diabetes. Insulin has long been considered anabolic,

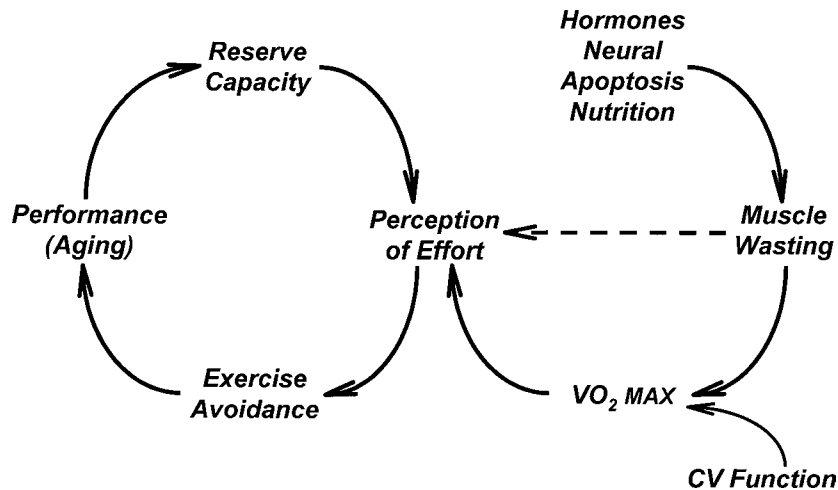


Figure 2. The vicious cycle of sarcopenia might be described as a positive loop: As regular physical activity decreases with age, there is a down-regulation of physiological systems adapting to reduced exercise/stress levels. As cardiovascular and skeletal muscle reserve functions decline, this contributes to an increased relative perception of effort for a similar absolute task as compared to when an individual was younger. If tasks are perceived to be more difficult, this will increase the likelihood for avoidance of physical work. As more physical work is avoided, exercise performance will continue to decline, therefore contributing to additional physiological decrements in an individual's functional reserve capacity, thus leading to more sarcopenia.

primarily by reducing protein degradation (42,43). A recent review of the topic has suggested that insulin can also stimulate protein synthesis (44). One mechanism by which insulin signaling may facilitate amino acid transport into the cell is via stimulating nitric oxide synthase (45). Therefore, insulin resistance with age may contribute to sarcopenia via an inhibition of the nitric oxide cascade resulting in less absorption of available amino acids for protein synthesis. As well, GH, liver-derived insulin-like growth factor (IGF)-I (46), and testosterone (47,48) all decrease with age. Although GH-induced IGF-I production in the liver is the major source of circulating IGF-I, and mediates many GH metabolic effects, local IGF-I production within target tissues, under the influence of both GH and testosterone (49), accounts for greater than 50% of total IGF-I production and appears to be important for stimulating muscle growth and repair (50–53). Cortisol, a potent stimulus to protein catabolism (54–56), increases slightly with age and may contribute to the age-related increase in adiposity (57). Circulating levels of these various hormones are altered by the aging process, all potentially contributing to sarcopenia (46,58–60). How age-related changes in hormone levels that translate to altered molecular signaling pathways, such as the IGF-I pathway in skeletal muscle, may contribute to sarcopenia remains poorly understood.

One molecular pathway of interest involves the suppression of myostatin, a recently discovered member of the transforming growth factor (TGF) superfamily. Myostatin is an autocrine factor that inhibits muscle development (61). Postnatally, myostatin is expressed in varying levels exclusively in skeletal muscle (62,63) and preferentially in fast-type skeletal muscle fibers (63). Age-related loss of skeletal muscle is associated with a selective atrophy of the fast-type skeletal muscle fibers (64). An unanswered question is whether the age-related decline in anabolic hormonal status allows a progressive increase in myostatin expression and could contribute to sarcopenia (65). How-

ever, we recently demonstrated that circulating hormone levels were not related to the expression of myostatin in skeletal muscle (53). Therefore, how myostatin ultimately interacts in sarcopenia remains unclear.

Other mediators of muscle protein turnover and balance include neural activity mediated through the motor neuron. Age-related reductions in muscle mass and strength are also accompanied by a reduction in motor unit (MU) number (66) and histological changes (angulated fibers, fiber-type clumping), which are suggestive of neuronal remodeling (67) in elderly people. Therefore, there has been much debate as to whether the loss of motor neurons precedes that of fiber number loss in sarcopenia. Although a complete and thorough discussion of the changes in MU with age is beyond the scope of this article, the reader is encouraged to reference several excellent reviews of this topic (68–71). Age-related loss of muscle mass has been demonstrated to involve a greater loss of fast-fiber cross-sectional area (37,72,73), which is accompanied by a greater reduction in fast MUs (66). Spinal motor neurons demonstrate similar losses to the muscle motor units, such that little change in motor neurons was observed up to the age of 60 years, yet there was nearly a 70% reduction by the age of 90 in previously healthy individuals postmortem (74). The muscle appears to compensate for this reduction in MUs by hypertrophy of existing smaller and slower MUs that attempt to reinnervate faster fibers and transform them into slower myosin fiber types (66,75), thus partially explaining why slower muscle is preserved in aging. Urbanek (76) recently assessed the issue of whether denervated fibers significantly contributed to the age-related loss of muscle strength and observed that only 11% of specific force decrements were due to denervated fibers.

Lastly, what role does the generation of free radicals and/or alterations in mitochondrial energy status play in sarcopenia? The decline in $VO_{2\text{ max}}$ with age has been primarily attributed to sarcopenia and a reduced cardiac out-

put (34). However, available evidence suggests that mitochondrial metabolism is also adversely affected by age (77) and may contribute to a reduction in $\text{VO}_2 \text{max}$. Aiken and colleagues, and others (78–81), have demonstrated that mitochondrial DNA mutations and deletions are increased in the single fibers of aged skeletal muscle, and the abundance of these abnormal mitochondrial regions increase with age in both rats (79) and nonhuman primates (80). The frequency of mutations is greater in muscles more prone to sarcopenia (79). Human studies have also demonstrated increased numbers of mitochondrial point mutations in older versus younger participants (82). The molecular mechanisms responsible for increased oxidative stress with aging and its impact on cellular function is beyond the scope of this article; however, several excellent reviews (77,78,83–87) are available.

How can we prevent sarcopenia? Nutrition and especially amino acid intake are important to maintain protein turnover, but what amounts and types are optimal remain to be determined. Are vitamin and mineral supplements important or necessary? What about hormone replacement? Should we be giving growth hormone and testosterone to all older men and women? Do the adverse effects offset the benefits? We know that regular exercise is important, but how much is required?

Exercise is beneficial and will decrease body fat, improve reserve capacity, and increase muscle strength (and maybe muscle mass), but why is exercise compliance low in elderly people? Are there factors that prevent older individuals from benefiting from exercise? It could be that sarcopenia has both physiologic factors, as has been discussed, in combination with social issues resulting in older persons not taking up exercise. Figure 2 combines the several issues that contribute to frailty as discussed by Bortz (12) with the physiologic parameters presented in Figure 1. Sarcopenia is a process whereby a loss of reserve capacity will result in an increased sense of effort for a given exercise intensity. We have recently discussed how the individual lactate threshold (a commonly prescribed exercise intensity) increases with age, forcing older individuals to exercise at a greater percentage of their maximal capacity (89). If the perception of exercise effort increases, older individuals will be more likely to avoid exercise. A vicious cycle then begins in that if one avoids exercise, then future performance will continue to decrease, as cardiovascular function and $\text{VO}_2 \text{max}$ will diminish, again feeding back to the increased perception of exercise effort, thus exacerbating sarcopenia.

The physiological and psychological factors that contribute to the process of sarcopenia are multifactorial, occurring over a prolonged time period, possibly with no identifiable single cause or mechanism, potentially explaining this age-related loss of mass and strength in and of itself. However, from our ongoing characterization of active older adults from the University of Southern California longitudinal study on master athletes, we have demonstrated that, although the loss in function that occurs in these individuals (35,36) is similar to sedentary persons, on average, they typically demonstrate fitness and functional reserves similar to individuals 20 years their junior. Therefore, our goal as clinicians should be to advocate exercise yet be aware of the issues that limit compliance (Figure 2). Our goal as researchers should be to

gain an improved understanding of the complex biological factors leading to age-related muscle loss beyond those attributable to a simple decrease in physical activity.

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