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Understanding Sarcopenia Development: A Role for Healthy Behaviors

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Abstract

For decades the biomedical community has documented the accelerated loss of muscle mass that occurs with advancing aging, termed sarcopenia. The timely review article ("Attenuation of Adverse Effects of Aging on Skeletal Muscle by Regular Exercise and Nutritional Support") by Arthur Leon presents our current state of knowledge on the biological processes responsible for age-induced loss of muscle mass and function. This loss of skeletal muscle has critical health implications as it can negatively affect morbidity and mortality. A significant theme throughout the review is that a lifelong commitment to regular physical activity and good dietary habits is extremely important to combat age related reductions in muscle mass and function. However, multi-targeted therapeutic approaches, in conjunction with nutrition and exercise, may be beneficial to prevent or treat sarcopenia. Additionally, while significant progress has been made in our understanding of the molecular and biochemical contributors to sarcopenia, further research using well-controlled clinical trials are needed to determine the long-term benefit of exercise and nutrition on aging skeletal muscle.

Keywords

Aging; skeletal muscle; sarcopenia

For decades the biomedical community has documented the accelerated loss of muscle mass that occurs with advancing age, termed *sarcopenia*. While early discussions were focused on legitimate concerns involving decreased quality of life and functional capacity caused by muscle mass loss, the past 2 decades have established that the quantity and metabolic quality of our muscle mass can directly influence mortality and morbidity. Skeletal muscle's impact on overall health has served to up the ante for improving our mechanistic understanding of muscle wasting with disease, disuse, and aging. The accompanying article "Attenuation of Adverse Effects of Aging on Skeletal Muscle by regular Exercise and Nutritional Support" by Arthur Leon presents our current state of knowledge on the biological processes responsible for age-induced loss of muscle function. Furthermore, the article discusses evidence for the therapeutic values of exercise and nutrition interventions to reduce the risk of sarcopenia and also to manage the condition. The emphasis on the success of behavioral

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interventions related to exercise and nutrition is timely, as pharmaceutical interventions are currently limited and fraught with potential secondary effects that could negatively influence older individuals and any comorbidities that may be present.

While skeletal muscle mass is a defining feature of sarcopenia, it does not encompass the totality of skeletal muscle's importance with the aging process. It is now well accepted that important health benefits involve skeletal muscle's metabolic and endocrine functions.[1] Skeletal muscle has a well-defined structure and function relationship with the purpose of turning chemical energy to mechanical work, but this conversion encompasses an amazingly complex metabolic regulation involving substrate selection and utilization that is subject to both systemic and internal regulation. Initially, the article clearly defines how muscle mass is critical for movement, which is tightly coupled with metabolism and metabolic rate. The article then focuses on the important complexity of muscle metabolism as it relates to glucose and fat utilization. Beyond influencing metabolic rate, which is a focus of many obesity researchers, skeletal muscle metabolic functions involving glucose and fat utilization have clear influences on a host of health-related parameters involved with aging or chronic disease. The ability of muscle to efficiency partition substrate availability for energy has been termed muscle "quality". The metabolic quality of muscle involves the function or dysfunction of skeletal muscle mitochondria in the production of ATP.[2] As highlighted later in the review, mitochondria dysfunction has the potential to be involved in several cellular changes occurring with age.

The article also updates our understanding of several skeletal muscle function and plasticity changes associated with aging. Muscle fiber-type shifts relate to both metabolism and contractile function.[3] The article makes a strong case for decrements in muscle function associated with power production that is a more prominent feature of aging than decreased muscle endurance capacity. The preferential atrophy and decreased number of type II glycolytic fibers likely have important roles in this functional change. Type II fibers have also been reported to be more susceptible to atrophy that occurs with disease, such as cancer, heart failure, and kidney failure, when compared to type I myofibers.[4] Research is still necessary to resolve the mechanisms driving type II wasting susceptibility. However, sensitivity to inflammatory signaling, increased reactive oxygen species (ROS), mitochondrial dysfunction, calcium dysregulation, and neuromuscular junction changes have all been investigated and proposed as mechanisms for this selective wasting. Interestingly, disuse has often been associated with age-related sarcopenia. However, oxidative myofibers are known to exhibit more sensitivity to use when compared to glycolytic myofibers, and decreased use induces a shift toward a more glycolytic phenotype, which is the reverse of accepted age-related changes. Additionally, disuse is not associated with some of the same systemic disruptions that are known to occur with wasting diseases and aging. Further work is needed to understand the potential interaction between aging, muscle disuse, and underlying comorbidities that contribute to the progressive loss of muscle mass.

The muscle satellite cell and other muscle precursor cells have been widely investigated for their role in sarcopenia, and also the decline in aged muscle's ability to successfully regenerate. This has spawned research related to both the muscle satellite cell content, disrupted mitotic activity regulation, and inability to fuse with existing myofibers. While

there is wide acceptance that aging reduces satellite cell number in humans and preclinical rodent models, the implications of this change have recently become open for debate. Recent research ablating satellite cells in mouse skeletal muscle has not increased the susceptibility to develop sarcopenia.[5] While methodological and age-related questions remain for these preclinical findings, the implications are that the satellite cell's role in myofiber atrophy and age-induced fiber-type shifts may not be as clear cut as previously discussed. Additionally, the senescent satellite cells in aged muscle may be more related to the muscle microenvironment that involves cytokine and growth factor availability to regulate satellite cell mitotic activity.[6]

The review also updates our understanding of molecular and biochemical stimuli that have the potential to regulate the progression of sarcopenia. The potential contribution of these stimuli to the wasting process is explained in detail, as is the potential for these mechanisms to serve as a therapeutic target to prevent or treat sarcopenia. The review highlights how sarcopenia can be regulated by many factors, and this multifactorial nature demonstrates how one unifying aging mechanism is not likely to emerge in a heterogeneous aging population, which is also true of many chronic wasting diseases. Related to molecular and biochemical contributors, the review discusses several intracellular processes that have been associated with aging-induced decrements in muscle mass. Special emphasis is placed on the contributions of oxidative stress and the accumulation of damaged muscle proteins to the development of sarcopenia. Related to oxidative stress, the review highlights the imbalance between the production of ROS and antioxidant defense system. The potential for an imbalance in ROS production needs further investigation. Interestingly, using antioxidants as an anti-aging therapy may have undesired implications since ROS have also been shown to be important in signaling related to exercise and metabolism.[7] A more important implication for ROS production may be correcting dysfunctional mitochondria, which also suggests a role for mitophagy to remove the dysfunctional mitochondria. Interestingly, increased mitochondrial turnover through the mitophagy process has been linked to an important benefit of aerobic exercise.[2] The past several years has seen an interest in autophagy's role in muscle dysfunction with aging and disease. The regulation of autophagy, lysosomal degradation of organelles and cellular structures, is central for the removal of damaged proteins and organelles that may accumulate and lead to cellular dysfunction.

The systemic environment has a well-established role in regulating skeletal muscle mass and metabolism. Age-related systemic changes have been investigated for decades for both their role in regulating sarcopenia and also as a therapeutic target to prevent or attenuate sarcopenia. The review discusses several important and topical age-related changes that have been associated with muscle mass loss. Emphasis is placed on reduced anabolic hormone activity (ie, hypogonadism), increased systemic inflammation and insulin resistance, and reduced muscle blood flow. Many of these changes are also associated with muscle wasting in other pathophysiological conditions. A decline in circulating sex steroids can lead to the loss of skeletal muscle mass, which can have severe deleterious metabolic and functional implications. Low testosterone levels are associated with decreased muscle mass and strength, while testosterone replacement can improve muscle mass and strength in men.[8] The positive effects of androgens on muscle mass have been attributed to improved muscle protein synthesis in humans and preclinical models.[9,10] In contrast to the anabolic effects of

androgens, there is significant evidence that loss of estrogen function can promote metabolic dysfunction and increase the risk of chronic disease in women. Recent evidence suggests that skeletal muscle estrogen receptor-α is critical for the maintenance of mitochondrial function and whole body metabolic homeostasis in females.[11] Therefore, while sex steroids may have differential effects on muscle mass and metabolism, strategies to maintain or activate these signaling pathways may be of therapeutic benefit in minimizing the age-related changes in muscle quality.

As discussed in the review, resistance exercise training is an effective treatment to counteract the loss of skeletal muscle mass and strength in many wasting conditions. Resistance exercise training increases muscle mass and strength, muscle fiber diameter, and myofibrillar protein synthesis. In addition, parameters related to whole-body and metabolic health such as bone mineral density, resting insulin levels, insulin sensitivity, and basal metabolic rate are also improved by resistance exercise training.[1,12] Interestingly, while aged individuals demonstrate a blunted anabolic response to a single bout of resistance exercise,[13] aged muscle is responsive to exercise training. While the loss of skeletal muscle mass with aging is associated with type II muscle fiber atrophy, resistance exercise training can increase type II muscle fiber cross-sectional area in both male and female individuals.[14,15] Importantly, the improvements in muscle fiber size are associated with improved physical performance and function. Given that muscle strength is inversely associated with all-cause mortality,[16] the overall health benefits of resistance training extend farther than just mass and function. Resistance exercise training significantly improves metabolic health in the elderly, as evident by improved whole-body insulin sensitivity and glycemic control following training.[14] Collectively, there is sufficient evidence to suggest that resistance exercise training exercise should be performed throughout all stages of life and is extremely important in elderly individuals.

In addition to regular physical activity and/or exercise training, the review highlights that appropriate nutritional strategies should be adopted to reduce muscle mass loss during aging. These strategies include obtaining adequate food energy intake (ie, daily calories), increasing daily protein intake, maintaining adequate vitamin D levels, and eating sufficient food-derived antioxidants. Due to decreased appetite with aging, maintaining a sufficient caloric intake should be an important goal for healthy aging. We agree that caloric restriction has positive effects in animal models of aging, but care needs to be taken to avoid malnutrition in human aging. In addition to maintaining sufficient energy intake, research also indicates aged individuals may need to examine their protein intake. Aging has been associated with a blunted protein synthetic response to protein intake, termed *anabolic resistance*.[17] Several potential contributors to anabolic resistance include decreased digestion and absorption, postprandial amino acid availability, postprandial muscle uptake of dietary amino acids, and postprandial amino acid delivery. Interestingly, physical activity can enhance muscle sensitivity to feeding, as physical activity performed prior to food intake can improve postprandial muscle protein synthesis rates.[17] Thus, habitual physical activity appears to have benefits for maintaining a normal anabolic response to feeding during aging. While not discussed in the current review, other potential nutritional supplements that have been shown to attenuate muscle loss with aging include β-hydroxy-β-methylbutyrate (HMB) and creatine.[18,19] In most circumstances, supplementation combined with resistance training

resulted in greater skeletal muscle adaptations when as compared to resistance training alone. While these supplements can significantly increase mass and strength in young individuals, the efficacy and proposed mechanisms of these supplements on aging muscle will require future investigation.

In summary, the timely review by Arthur Leon presents our current state of knowledge on the biological processes responsible for age-induced loss of muscle mass and function. This loss of skeletal muscle has critical health implications as it can negatively affect morbidity and mortality. A significant theme throughout the review is that a lifelong commitment to regular physical activity and good dietary habits is extremely important to combat age-related reductions in muscle mass and function. However, multi-targeted therapeutic approaches, in conjunction with nutrition and exercise, may be beneficial to prevent or treat sarcopenia. Although significant progress has been made in our understanding of the molecular and biochemical contributors to sarcopenia, further research using well-controlled clinical trials are needed to determine the long-term benefit of exercise and nutrition on aging skeletal muscle.

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