Aging of Human Skeletal Muscles

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ABSTRACT

Normal aging in humans is associated with progressive decrease in skeletal muscle mass and strength (sarcopenia) which contributes to frailty and falls. The age associated changes in body composition result from lower levels of anabolic hormones, oxidative damage, neuromuscular alterations and a general decrease in muscle protein turnover. In this review we discuss the potential mechanisms and physical activity as prevention and treatment of sarcopenia.

Key words: aging, muscle, skeletal

Introduction

Sarcopenia is a term invented by Irwin Rosenberg 1988. The Greek word »sarco« refers to flesh and »penia« indicates a deficiency. Sarcopenia is a generic term for the loss of skeletal muscle mass, quality and performance associated with normal aging that can lead to frailty in the elderly. It cannot be considered a disease or a condition that has a clear diagnostic marker. Namely, some older individuals have larger muscles and are stronger than young adults. However, the clearly is a decline in the average muscle mass1,2 and performance3,4 associated with senescence. Sarcopenia appears to begin in the fourth decade of life and accelerates after the age of approximately 75 years5. Because of the great increase in the proportion of the population living long enough that frailty becomes a significant problem, there is much interest in achieving a better scientific understanding of sarcopenia. The hope is that such an understanding will lead to better strategies for preventing or reversing the underlying processes. It occurs in all individuals to some degree as a consequence of aging, but it can be accelerated by a variety of factors including inactivity6, poor nutrition7 and chronic illness8. Sarcopenia is harmful as osteoporosis but less well known. The mechanisms that underline sarcopenia are only beginning to be elucidated. In this article we will discuss the functional consequences of sarcopenia, potential mechanisms and possible methods of prevention and treatment.

Muscle Morphology And Aging

Skeletal muscle consists of different fiber types characterized by their specific myosin heavy chain (MHC) isoforms. In adult human skeletal muscle, using monoclonal antibodies specific to MHC isoforms, three major fiber types can be distinguished: type I, type IIA, and type IIX fibers with predominance of myosin heavy chain 1 (MHC 1), 2a (MHC 2a) and 2x (MHC 2x), respectively. Type I fibers are slow-twitch fatigue resistant fibers with greater oxidative capacity, higher mitochondrial content and greater capillary density. In contrast, the type II fibers are fast-twitch fibers with a high glycolytic capacity. The type II fibers in adult humans are further subdivided into type IIA that have intermediate oxidative and glycolytic capacity and are more fatigue resistant, and type IIX in which predominates glycolytic activity9. In a comprehensive study of the entire vastus lateralis muscle in 43 male cadavers aged 15–83, Lexell et al. (1986) showed that there is an age-related loss in fiber number, and between the ages of 20 and 80 there is about a 50% reduction in the total fiber number. This loss is more rapid after the age of sixty. There is a selective loss of fast-twitch type II fibers as compared to slow-twitch type I muscle fibers10. Some results indicate that arm and leg muscles are not affected in the same way. Loss of muscle strength in leg muscles was about 40% compared with 30% in arm muscles, measured between 30 and 80 years of age11. Recent studies have demonstrated that the mRNA levels of MHC 2a and 2x decrease with age12.

Loss of Motor Neurons / Motor Unit Remodeling

Age related changes in the neuromuscular system might play a role in the onset of sarcopenia. The number
of spinal cord motor neurons and functioning motor units decline with age\textsuperscript{13,14}. This is a continuous process throughout life and is considered irreversible\textsuperscript{15}. Human nerve cells have a predetermined life span and the decline in these cells is dependent on the location in the body, age and presence of disease\textsuperscript{16}. The motor neurons are responsible for sending signals from the brain to the muscles to initiate movement. A motor unit consists of the motor neuron and all of the muscle fibers innervated by that neuron. The number of fibers that a motor neuron innervates depends on the function of that certain muscle. For example, a muscle that requires precise movements, such as muscles of eye, will have motor units with a motor neuron innervating a few muscle fibers. Muscles that require less precise movements and large strength, such as the quadriceps muscle, will have motor units with motor neuron innervating hundreds and possibly over a thousand muscle fibers. The loss of muscle fibers begins with the loss of motor neurons. Morphological changes in the anterior horn of the spinal cord, as well as those in the peripheral axon in older humans and animals, can be accountable for the old-age muscle atrophy. Motor neurons will die with age resulting in a denervation of the muscle fibers within the motor unit. This denervation causes the muscle fibers to atrophy and eventually die, leading to decrease in muscle mass\textsuperscript{13}. When a motor neuron dies, an adjacent motor neuron, usually a slow twitch motor neuron may reinnervate the muscle fibers, preventing atrophy. Aging seems to induce «type grouping», i.e., in young and middle-aged skeletal muscle the fast and slow fibers are distributed in a chessboard fashion, whereas in aged muscle the fibers cluster in groups of either slow or fast cells. This process is called motor unit remodeling. When compared to fast twitch motor units, slow twitch motor units are slower to contract, produce less muscle force. Motor unit remodeling by slow twitch motor neurons leads to less efficient motor units. The remodeled slow twitch motor unit will have less precise control of movements, less force production and slowing of muscle mechanics\textsuperscript{5,13,14}. This may help explain the loss of balance and speed of movement with age. In addition, denervation rates of fast twitch muscle fibers may exceed reinnervation rates by slow twitch motor neurons, further explaining atrophy of fast twitch muscle fibers in elderly\textsuperscript{13}.

Satellite Cells and Aging

The ability of skeletal muscle to grow or become repaired upon injury is principally dependent on a population of progenitor cells called satellite cells. These cells are present between the sarcolemma of the mature fiber and its basal lamina\textsuperscript{16}. Skeletal muscle regenerative capacity has been shown to decline with age\textsuperscript{7,16}, and Carlson (1995) has suggested that a decrease in regeneration potential could contribute to a reduction in muscle mass in older individuals\textsuperscript{28}. Satellite cells are quiescent in normal adult muscle, although they can be induced to proliferate under certain conditions to add myonuclei to existing fibers or to form new muscle fibers. Research in animals has indicated that the number or percentage of satellite cells is significantly diminished in older skeletal muscle, thus providing a potential basis for the decline in muscle regeneration and adaptation potential in older animals\textsuperscript{20–23}. Snow (1977) reported a 50% decrease in satellite cell number between the ages of 8 and 30 months in the soleus muscle of mice and rats, and also suggested that the satellite cells in older muscles were less metabolically active than those of young animals, based on morphological criteria\textsuperscript{23}. Gibson and Schultz (1983) reported similar differences in satellite cell proportions in the extensor digitorum longus muscle between young and old rats but not between adult and old ones\textsuperscript{21}. In addition, several morphological changes have been noted in satellite cells in adult compared to young animals, including decreased quantities of endoplasmatic reticulum, golgi and ribosomes\textsuperscript{22}. Possible changes in satellite cell characteristics in older human skeletal muscle are unclear and the studies that have been completed are associated with limitations in scope and methodology\textsuperscript{24,25}. Schmalbruch and Hellhammer (1976) reported a lower satellite cell proportion (0.6%) in a 75-year-old male compared to a satellite cell proportions (4%) in eight adults between 20 and 34 years of age\textsuperscript{26}. However, no other older subjects were assessed in that investigation. Hikida et al (1998) reported similar proportions of satellite cells (2%) in young and older men\textsuperscript{27}. Perhaps a more important issue than the number of satellite cells is the environment that regulates the activation, proliferation and terminal differentiation of satellite cells\textsuperscript{28–30}.

Protein Synthesis and Aging

Another factor affecting sarcopenia is the rate of muscle protein synthesis. The quality and quantity of protein in the body is maintained by a continuous repair process, which involves both, protein breakdown and synthesis, whose balance determines the protein content in the body\textsuperscript{41}. With age, the changes in whole body protein turnover reflect a decreased synthesis rate rather than an increased catabolic rate\textsuperscript{15}. Additionally, research has consistently reported that muscle protein synthesis rates are lower in older adults when compared to young adults\textsuperscript{13,31–33}. Thus a decrease in muscle protein synthesis will result in the loss of muscle mass.

Hormones, Growth Factors and Cytokines

The underlying biological mechanisms that account for the development of age related sarcopenia are probably complex and not yet sufficiently identified. To some extent, even masters athletes develop sarcopenia and, therefore, biological mechanisms, which are intrinsic to aging and independent of behavior and environment, should be hypothesized.
Aging is associated with several changes in hormonal levels including decrease in the concentrations of growth hormone (GH), testosterone (T), and insulin-like growth factor-I (IGF-I). A decrease in concentrations of these hormones and growth factors may be one of the causes to the development of sarcopenia. GH and IGF-I play a dominant role in the regulation of protein metabolism; GH and T are required for protein maintenance; and IGF-I levels are positively correlated with the muscle protein synthesis rates, specifically myofibrillar protein (actin and myosin filaments)\textsuperscript{30}. A sustained decrease in these hormones and growth factor is linked to a decrease in muscle mass and increase in body fat\textsuperscript{31}. Although these hormones are involved in protein metabolism and maintenance, there is conflicting evidence whether hormone replacement is effective in maintaining or gaining muscle mass\textsuperscript{14}.

As people age, they develop numerous minor ailments (e.g., arthritis, recurrent infections, tumors, pressure ulcers) that result in inflammatory responses. Elevated cytokines, especially interleukin-6 (IL-6), have been associated with a decline in function and frailty in older persons\textsuperscript{32–36}. It is unclear whether the increase in circulating IL-6 levels associated with normal aging is enough to cause muscle atrophy\textsuperscript{36,37}.

**Oxidative Damage**

Normal cellular metabolism generates various radicals (\textit{‘free radicals’}) that can react with proteins, DNA and lipids. These radicals include reactive oxygen and nitrogen species and reactive aldehydes. Reactive oxygen species (ROS) are produced within muscle mitochondria where large quantities of ATP are created by the electron transport chain\textsuperscript{38}. All these reactive elements, but especially the hydroxyl radical, may be harmful producing oxidative damage to other molecular components of the cell including: peroxidation of membrane phospholipids, modification of nuclear DNA or alteration of proteins causing enzymatic changes and proteolysis. The challenge addressed by the ROS to the different cellular components is known as \textit{‘oxidative stress’}\textsuperscript{39–41}. Interestingly, there is no direct evidence that the production of ROS and the rate of oxidative stress increase with age\textsuperscript{42}. How crucial oxidative damage is to muscle function in old age has yet to be investigated.

**Lifestyle Factors**

Sarcopenia is accelerated with a lack of physical activity, especially the lack of overload to the muscle, as in resistance exercise. The amount of physical activity generally declines with age. Physically inactive adults undergo a faster and greater loss of muscle mass than physically active adults. However, sarcopenia is not completely prevented by exercise, as it is also evident, but to a lesser degree, in physically active individuals. It is possible that if the physical activity is not sufficient in intensity and duration to recruit fast twitch muscle fibers it may lead to fast twitch fiber atrophy and the development of sarcopenia\textsuperscript{14}. An additional factor in the development of sarcopenia may be an inadequate energy intake. Many older individuals may not be taking in enough calories and/or protein to sustain their muscle mass\textsuperscript{33}.

Resistance training has been shown to be a powerful intervention in the prevention and treatment of sarcopenia\textsuperscript{29}. Resistance training has been reported to positively influence to the neuromuscular system, hormone concentrations, and protein synthesis rates. According to Roubenhoff (2001) and Roth et al. (2000), a properly designed resistance-training program may increase motor neuron firing rates, improve muscle fiber recruitment, and create a more efficient motor unit\textsuperscript{13,14}. An increased motor neuron firing rate combined with an increased recruitment of muscle fibers would lead to faster muscle contractions and greater force production.

Although protein synthesis rates decrease with age, it is found that progressive resistant training can increase protein synthesis rates in two weeks. Hasten et al. (2000) reported that following a two-week supervised resistance training program muscle protein synthesis rates increased up to 182% from baseline in seven 76–84 year old persons\textsuperscript{31}. Yarasheski and colleagues (1993) also found that muscle protein synthesis rates in older adults (63–66 years old) increased significantly in response to two weeks of resistance training\textsuperscript{44}. In addition, Yarasheski et al (1999) reported that three months of supervised progressive resistance training increased the rate of muscle protein synthesis by approximately 50% in seventeen frail 76–92 year old men and women\textsuperscript{32}. These findings suggest that older men and women retain the ability to increase the rate of muscle protein synthesis in response to acute and long-term progressive resistance training. Furthermore, acute and long-term resistance training increases the number of satellite cells in the trained muscle, leading to faster muscle regeneration\textsuperscript{13}. Exercise, also, may have a direct, positive effect on the inflammatory pathway to sarcopenia\textsuperscript{45}, but these preliminary data should be confirmed in a longitudinal investigation.

**Conclusions**

The frailty of old age has emerged as an important public health problem because it impairs mobility and quality of life, and increases the risk of falls and the utilization of health care resources. Based on already known data, there is good reason to believe that an appropriate combination of hormones and local growth factors would be useful, but much needs to be learned about how to deliver these agents without inducting adverse effects. In fact, while our hopes for future treatment and prevention lay on the discovery of new pharmacological intervention, exercise is currently our sole solid resource.
REFERENCES


STARENJE SKELETNIH MIŠIĆA ČOVJEKA

SAŽETAK

Starenje je u ljudi povezano sa progresivnim smanjenjem mišićne mase i snage (sarkopenija) što dovodi do slabosti i povreda. Tjelene promjene koje se događaju starenjem posljedica su smanjenih razina anaboličkih hormona, oksidentalnog oteženja, neuromuskularnih promjena i općenitog smanjenja metabolizma bjelančevina u mišiću. U ovom preglednom članku raspravljamo o mogućim mehanizmima sarkopenije i ulozi fizičke aktivnosti u njoj prevenziji.