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Muscle tissue changes with aging

Elena Volpi, **Reza Nazemi**, and **Satoshi Fujita**
Division of Endocrinology and Diabetes, Department of Medicine, University of Southern California, Los Angeles, California, USA

Abstract

Purpose of review—This review article focuses on the changes that occur in muscle with age, specifically the involuntary loss of muscle mass, strength and function, termed sarcopenia. Particular emphasis is given to the metabolic alterations that characterize sarcopenia, and to the potentially treatable causes of this condition, including age-related endocrine and nutritional changes, and inactivity.

Recent findings—Recent data reported include those regarding the potential role of insulin resistance in the development of sarcopenia, the potential role of androgens and growth hormone in the treatment of this condition, the usefulness of exercise including both resistance and aerobic training to improve muscle growth and function, and, finally, the possible use of nutritional manipulations to improve muscle mass.

Summary—Sarcopenia is likely a multifactorial condition that impairs physical function and predisposes to disability. It may be prevented or treated with lifestyle interventions and pharmacological treatment. Further long-term investigations are needed, however, to ascertain what type and combinations of interventions are the most efficacious in improving muscle mass and function in older people.

Keywords

aging; muscle; sarcopenia; nutrition; exercise; hormones; metabolism

Introduction

One of the most striking effects of age is the involuntary loss of muscle mass, strength, and function, termed sarcopenia [1–3]. Muscle mass decreases approximately 3–8% per decade after the age of 30 and this rate of decline is even higher after the age of 60 [4,5]. This involuntary loss of muscle mass, strength, and function is a fundamental cause of and contributor to disability in older people. This is because sarcopenia increases the risks of falls and vulnerability to injury and, consequently, can lead to functional dependence and disability [6,7]. A decrease in muscle mass is also accompanied by a progressive increase in fat mass and consequently changes in body composition, and is associated with an increased incidence of insulin resistance in the elderly [1,4,5,8]. Furthermore, bone density decreases, joint stiffness increases, and there is a small reduction in stature (kyphosis). All these changes have probable implications for several conditions, including type 2 diabetes, obesity, heart disease, and osteoporosis.

Correspondence to Elena Volpi MD PhD, Division of Endocrinology and Diabetes, 1333 San Pablo St., BMT-B11, Los Angeles, CA 90033, USA, Tel: +1 323 442 2839; fax: +1 323 442 2809; e-mail: volpi@usc.edu.

Potential causes of sarcopenia

The etiology of sarcopenia is not clearly understood, but several mechanisms have been proposed. At the cellular level, specific age-related alterations include a reduction in muscle cell number, muscle twitch time and twitch force, sarcoplasmic reticulum volume and calcium pumping capacity [2,9]. Sarcomere spacing becomes disorganized, muscle nuclei become centralized along the muscle fiber, the plasma membrane of muscle becomes less excitable, and there is a significant increase in fat accumulation within and around the muscle cells. Neuromuscular alterations include a decrease in the nervous firing rate to muscle, the number of motor neurons, and the regenerative abilities of the nervous tissue. Motor unit size also increases [2]. Further, aging is associated with changes in satellite cell number and recruitment, an indication and potential cause of reduced muscle growth [10–12].

Biochemical and metabolic changes also occur in muscle with aging. Mitochondrial DNA deletion mutations subsequent to oxidative damage and reduced mitochondrial protein synthesis have been reported and are probably linked with a reduction in glycolytic and oxidative enzyme activities, creatine phosphate and ATP stores within the muscle cell, mitochondrial volume, and a slight reduction in overall metabolic rate (~10%) [13–16]. These metabolic changes in muscle contribute to the overall physical fitness capacity of the elderly and are an important component of the reduction of around 30% in the ability to utilize oxygen during exercise (i.e. VO_{2max}).

Initial studies on a small number of elderly people have also suggested that aging is associated with a reduction in the basal muscle protein synthesis, which might have been responsible for the progressive reduction in muscle mass [17–21]. More recent data obtained in the largest cohort of healthy older men, however, did not confirm the earlier reports and concluded that differences in basal muscle protein turnover between elderly and young men cannot explain muscle loss with age, suggesting that future research should focus on responses to specific stimuli, such as nutrition, exercise, or disease [22].

Besides the muscle-specific alterations highlighted above, other age-related changes in endocrine function or responsiveness to hormonal stimuli, nutrition or responsiveness to nutrients, and physical activity may be responsible for the development and worsening of sarcopenia [23–30]. Most likely, sarcopenia is a multifactorial problem. Among all its potential causes, however, a reduction in endocrine function, physical activity and appropriate nutrition are potentially treatable with behavioral interventions or pharmacological agents, and for this reason will be discussed in this review.

Endocrine changes relevant to sarcopenia

A variety of hormonal changes are seen during the aging process that may contribute to muscle loss with aging. We have selected the most important changes in relation to their effect on skeletal muscle.

The primary and most potent anabolic steroid is testosterone. In about 60% of men over the age of 65, testosterone levels decrease to below the normal youthful values, in a process termed andropause [31]. Unlike the rapid decrease in estradiol seen with menopause, testosterone concentrations gradually decrease throughout the aging process [31]. Since testosterone increases muscle protein synthesis, muscle mass and strength [32,33], it has been proposed that the decrease in testosterone may cause a decrease in muscle protein synthesis and result in a loss of muscle mass. With this in mind, several studies have examined the effect of testosterone replacement therapy in men with overt hypogonadism or testosterone concentrations at the lower-normal range. Testosterone was administered via

injection, transdermal patch, or dermal gel [24,34–38]. From these studies it was shown that testosterone replacement to mid-normal levels resulted in a significant increase in muscle mass, muscle strength, muscle protein synthesis and bone density. These results thus suggest that andropause may be a player in the development of sarcopenia, and highlight that testosterone therapy may lead to a reversal or attenuation of sarcopenia. Testosterone is currently not recommended for the treatment of sarcopenia, however, and a careful evaluation of the potential benefits and potential risks (e.g. increased prostate-specific antigen, hematocrit and cardiovascular risk) should be performed before making such a recommendation [39].

In women, estradiol levels abruptly decrease during menopause [31]. Very little information is available regarding the role of menopause in sarcopenia. It appears that muscle mass is not affected by the decrease in estrogens. Cross-sectional studies evaluating the effects of age on lean body mass and appendicular muscle mass have shown that the rate of decline of muscle mass in women does not increase after menopause, suggesting a marginal role, if any, of this event in the development of sarcopenia in women [5]. Hormone replacement therapy, however, can significantly increase serum steroid hormone binding globulin, which leads to a significant decrease in serum free testosterone levels in women [40]. Low serum free testosterone levels in women are associated with a lower muscle mass. Therefore, hormone replacement therapy may play a role in further reducing, rather than increasing, muscle mass in older women.

The growth hormone/insulin-like growth factor-I axis also exhibits a gradual decline during normal aging [31]. Although providing growth hormone replacement therapy to growth hormone deficient adults resulted in an increase in muscle mass, some studies have shown no effect on muscle strength [41–46]. Growth hormone replacement therapy in the elderly appears to be beneficial for lowering fat mass, improving blood lipid profiles and increasing lean body mass, but these changes may not lead to an increase in muscle strength and function. In fact, muscle strength only increased when growth hormone was given to elderly men undergoing a weight-training program as compared with growth hormone replacement therapy alone, or when sex hormone replacement therapy was given in conjunction with growth hormone [41,46]. It is also important to underscore that the methodologies used to measure body composition may be affected by water retention. Thus, an increase in muscle mass with a reduction of fat mass with no change in strength following growth hormone therapy should be interpreted with caution because growth hormone notoriously increases water retention, which can be misinterpreted as an increase in lean body mass. As for testosterone, growth hormone replacement is not currently recommended for the treatment of sarcopenia due to both the results of the published studies and the potentially serious side effects (arthralgia, edema, insulin resistance, cardiovascular risk, etc.) [41].

The concentrations of dehydroepiandrosterone in the blood also decrease gradually with normal aging (adrenopause) [31]. In fact, levels may be up to five times lower in very old men as compared with younger men. Oral supplementation of dehydroepiandrosterone in older persons does restore levels to youthful values, increases insulin-like growth factor-I levels in men and women, increases estrogens in men, and increases testosterone in women [47–50]. However, no changes in lean body mass were detected and HDL-cholesterol levels significantly decreased [47,49]. Nonetheless, muscle strength was increased in older men (but not women) undergoing dehydroepiandrosterone supplementation in one particular study [48]. Recently, a very large study in older individuals showed that dehydroepiandrosterone replacement therapy has no effect on muscle size, strength or function [50]. Thus, the importance of adrenopause in the development of sarcopenia remains to be demonstrated.

The ability of muscle tissue to respond to insulin is an important aspect of overall insulin sensitivity. The incidences of insulin resistance and type 2 diabetes increase with aging and sarcopenia may play an important role. Most studies have reported that the prevalence of insulin resistance and glucose intolerance is higher in older individuals when the data are reported per unit of body mass, but these differences disappear if the data are corrected by lean body mass [51–55]. This suggests that the changes in body composition may drive the increase in insulin resistance with age. Although insulin is usually considered in the context of its ability to increase glucose uptake into cells, there is emerging evidence that insulin resistance of muscle and whole body protein metabolism in the elderly may be an important contributor to sarcopenia [29,56]. For example, when glucose is ingested with a regular meal, the subsequent increase in insulin concentrations has a negative effect on muscle protein synthesis only in older individuals [29]. This implies that with normal aging the ability of muscle cells to properly respond to circulating insulin (by increasing muscle protein synthesis) is impaired.

Physical activity and sarcopenia

Another important contributor to sarcopenia is inactivity. Although it is difficult to causally determine the relative importance of a sedentary lifestyle in the development of sarcopenia, it is very well known that short-term muscle inactivity severely reduces muscle mass and strength even in young individuals. Typical examples are bed rest and weightlessness [57,58]. It is also recognized that these muscle changes can be counteracted by exercise, typically resistance exercise [59]. Several authors have reported that acute resistance exercise increases myofibrillar muscle protein synthesis both in young and older adults [20,21]. Progressive resistance exercise training has also been shown to induce muscle hypertrophy and increase strength in elderly and physically frail adults [12,19,60–66]. Despite the clear efficacy in increasing muscle mass, strength and function, however, resistance exercise training may be a difficult intervention to implement in community-indwelling older individuals due to the necessity of specific equipment and supervision, the possibility that it may not be indicated in certain conditions frequently found in older patients (e.g. hypertension, stroke), and the fact that weight lifting may not be an appealing activity for sedentary elders.

Aerobic exercise has been shown in several studies to improve VO_{2max}, mitochondrial density and activity, insulin sensitivity and energy expenditure in young and older individuals [67–69]. Two studies have also shown that prolonged and intense aerobic exercise can increase muscle protein synthesis in young active individuals [70–71]. Recent preliminary data suggest that aerobicexercise (40% VO_{2max}) can also acutely increase muscle protein synthesis in healthy, independent older people [72]. Although aerobic exercise does not induce obvious muscle hypertrophy, some studies have shown that intense aerobic exercise training can induce some degree of hypertrophy, as indicated by increased calf circumference, muscle fiber area, and satellite cell activation [73,74]. The characteristic physique of marathon runners, the epitome of aerobic exercisers, may cast doubts about the anabolic efficacy on aerobic exercise. It is important to underscore, however, that the muscles of these athletes, although not hypertrophic, do not lack strength and power as do the muscles of sarcopenic older adults. In fact, muscle mass is not the only determinant of muscle function, and aerobic exercise training may have important positive effects on neuromuscular adaptations and, consequently, muscle quality especially in individuals who were sedentary and sarcopenic prior to the exercise intervention. In fact, muscle quality has been shown to improve significantly with resistance training in older people and in younger people with muscle wasting [75,76].

Thus, both resistance and aerobic exercise can be very useful to counteract sarcopenia and the associated metabolic alterations of the muscle.

Nutrition and sarcopenia

Malnutrition leads to muscle wasting. It has been shown that aging is associated with a progressive reduction in food intake, which predisposes to energy-protein malnutrition [30]. Further, older people may voluntarily reduce their protein intake in order to comply with reduced fat and cholesterol diets. Recent studies [77] suggest that the protein requirements of older individuals may be higher (~1 g/kg/day) than the level currently recommended by the Institute of Medicine (0.8 g/kg/day) [78]. Thus, nutritional interventions are appealing potential means for the prevention and treatment of sarcopenia of the elderly due to the easy applicability and safety. Amino acids from ingested protein directly stimulate muscle protein synthesis [79]. Interestingly, healthy elderly individuals respond to an amino acid stimulus with an increase in muscle protein synthesis that is not significantly different from the effect observed in their younger counterparts [80–82]. However, attempts to increase muscle mass, strength, and muscle protein synthesis with commercial nutritional supplements or high-protein diets have been largely unsuccessful [83,84]. Although an earlier and smaller study reported increases in muscle mass with nutritional supplementation [85], in a much larger cohort of frail elderly individuals, Fiatarone *et al*. [60] reported increases in muscle mass and strength associated with resistance exercise but not with nutritional supplementation. Furthermore, nutritional supplementation or high-protein meals added to resistance exercise did not result in an increase in muscle mass, strength, or muscle protein synthesis as compared with exercise alone [60,83,84]. There are at least two possible explanations for the inability of nutritional supplements or increased protein intake to enhance muscle growth and strength. First, the presence of carbohydrate in a nutritional supplement for the elderly is not beneficial [29], and may in fact impair the anabolic response of muscle proteins to the positive effect of amino acids alone [80,81]. These data are consistent with findings in old rats, indicating that muscle protein synthesis is blunted during balanced feeding [28]. Because both the commercial supplements and the high-protein diets previously tested in older adults contained carbohydrate, this alone might provide a sufficient explanation as to the ineffectiveness of those interventions [60,83,84]. Second, it has been reported that older adults who were given supplements in the absence of increases in physical activity decreased their dietary intake, so that their total daily energy intake remained unchanged [60]. This indicates that nutritional supplements for the elderly would be better considered as dietary substitutes. Consequently, if the nutrient content of the supplement is little different from that of the normal diet, it is likely that the supplementation will be ineffective. Hence, a nutritional supplement for the prevention or treatment of sarcopenia should only contain the nutrients that are absolutely necessary for the stimulation of muscle protein anabolism, in order to achieve the highest anabolic efficiency (anabolic effect per unit of energy). Data from young adults suggest that essential amino acids are mostly responsible for the amino acid-induced stimulation of muscle protein synthesis [86,87], whereas nonessential amino acids do not appear to exert any significant effect even when given at very high doses [87]. Recent studies show that this is also true for older people. In fact, essential amino acids are primarily responsible for the amino acid stimulation of muscle protein anabolism in healthy elderly individuals, whereas nonessential amino acids are apparently not required [82]. Specifically, the intake of 18 g of essential amino acids alone or in combination with 22 g of nonessential amino acids increased net muscle protein anabolism. The magnitude of the anabolic effect of both supplements was similar. It is important to consider, however, that whereas the essential amino acid content and composition of both supplements was identical, the balanced amino acid supplement delivered more than twice as much energy and amino-nitrogen as the essential amino acid supplement.

Nonessential amino acids comprise a significant portion of dietary proteins, including the high-quality proteins (e.g. whey, egg) that are typically used to supplement protein-poor diets. Since nonessential amino acids do not appear to be necessary for the acute stimulation of muscle protein anabolism in older people, high-quality proteins may still be inadequate for a dose-effective prolonged treatment of sarcopenia, given the excessive amount of calories that they provide in the form of nonessential amino acids. Thus, the elimination of any source of energy that does not stimulate protein anabolism, including nonessential amino acids and carbohydrate, should not decrease the long-term anabolic effect of the essential amino acid supplement for the elderly, while significantly decreasing its total caloric content. However, there are no data regarding the efficacy of prolonged supplementation with a highly efficient mixture of essential amino acids on muscle growth in the elderly. Therefore, long-term randomized clinical trials are necessary to clearly assess whether highly efficient nutritional supplements can effectively improve muscle mass in sarcopenic older individuals.

Conclusion

Sarcopenia is a multifactorial process. A reduction in endocrine function, physical activity and inadequate nutrition all play an important role in the reduction of muscle mass with normal aging. Testosterone replacement therapy could be a useful intervention in hypogonadal older men for increasing muscle mass and strength, although it is not currently recommended. Hormone replacement therapy for menopause, adrenopause or somatopause appears to have a marginal or no positive effect on muscle mass and strength. Exercise training and proper nutrition can have dramatic effects on muscle mass and strength. An optimal intervention program may include an exercise-training schedule that incorporates both resistance and aerobic exercise with adequate intake of total calories and protein. This would not only improve muscle mass and strength, but it would also reduce insulin resistance, which is more prevalent in the elderly. Providing a nutritional supplement of only amino acids or protein might also be beneficial to promote muscle growth by stimulating muscle protein synthesis and increasing the total daily caloric intake, but further investigations are needed.

Fortunately, aged muscle is still very plastic and can respond to anabolic stimuli by increasing its mass and strength. This knowledge is vital for designing interventions to reverse or attenuate the loss of muscle mass with aging and to improve functional abilities in the elderly.

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