The utility of resistance exercise training and amino acid supplementation for reversing age-associated decrements in muscle protein mass and function
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Advancing age is associated with reduced skeletal muscle protein synthesis, altered expression of and chemical modifications to muscle proteins, reduced muscle strength, muscle strength per unit muscle mass and muscle power (sarcopenia). These age-associated impairments in the quantity and quality of contractile protein contribute to physical disability and frailty, a loss of independent function, the risk of falling and fractures, and escalating health-care costs. Progressive resistance exercise training is a potent, non-pharmacologic, efficacious therapy for the impairment in muscle quantity and quality in middle age and physically frail adults. Evidence is accumulating that dietary amino acid supplementation may also improve muscle protein balance in the elderly. Several potential cellular mechanisms for the loss of muscle protein and resistance exercise-induced improvements in muscle quantity and quality in elderly adults are reviewed. Curr Opin Clin Nutr Metab Care 3:489–495. © 2000 Lippincott Williams & Wilkins.

Introduction

Without exception, all organisms undergo senescence. The pathogenesis of this involves genetic, behavioral, hormonal, nutritional, neurologic, and metabolic alterations and interactions. Undesirable aspects of human senescence include: a decrease in skeletal muscle protein mass, reduced contractile capabilities and muscle quality, the altered expression of and chemical and structural modifications to muscle proteins, and an increase in the relative proportion of intramuscular adipose and connective tissue [1–3]. Contractile protein loss comprises the majority of the age-related loss of mass, but neuromuscular alterations cannot be ignored. Recent evidence indicates that muscle power and muscle force relative to the amount of muscle protein decline with age. Regulators of muscle quantity and quality are particularly susceptible to the aging process. These regulators and useful countermeasures (e.g. nutrition and exercise) need to be identified, tested, and incorporated into successful aging programs.

Figure 1 [4] depicts the reduction in thigh muscle cross-sectional area that occurs with advancing age and physical inactivity. Most obvious is the reduction in muscle area, the increase in subcutaneous and intramuscular adipose area, and the infiltration of adipose and connective tissue into the muscle with advancing age. Table 1 lists the potential reasons for preserving muscle protein mass and contractile function during the aging process.

Aging alters muscle protein synthesis, morphology, strength, power and quality

Several excellent reviews and commentaries on the importance of reducing muscle protein loss and maintaining muscle strength, power, quality, and physical function in the elderly have appeared [1–9]. Our understanding of the factors that regulate contractile protein properties, the synthesis and breakdown rates, and how to modulate these factors in the elderly is still evolving. Stable isotope tracer dilution methods combined with mass spectrometric detection techniques have been extremely useful for examining in-vivo muscle protein kinetics. The incorporation rate of $^2$H-, $^{18}$O-, $^{13}$C-, $^{15}$N-amino acids into different muscle protein fractions (myofibrillar, mitochondrial, sarcoplasmic, and enzymatic) can be quantitated using gas chromatography-quadrupole or magnetic sector gas isotope ratio mass spectrometry.
This approach has contributed to our understanding of age-, nutrition-, or exercise-induced alterations in muscle amino acid balance [3,10–20,21].

As in all cachectic conditions, sarcopenia can be explained by an imbalance between the rates of muscle protein synthesis and muscle protein breakdown, in which net muscle protein balance is negative [3,10–13]. When determined after an overnight fast, the in-vivo rates of mixed muscle (myofibrillar + mitochondrial + sarcoplasmic) and myosin heavy chain (MHC) protein synthesis were reduced in 60–70-year-old and 78–92-year-old men and women in comparison to 20–32-year-old adults [11–14]. The potential artifact introduced by measuring the ‘mixed’ (rather than the specific) muscle protein synthesis rate may be minor, because both mixed and myofibrillar protein synthetic rates were found to be approximately 30% lower in 60–70-year-old than in men and women under 35 years of age [12–13].

MHC proteins (all isoforms combined) have been isolated from the myofibrillar protein fraction and the rate of MHC protein synthesis was reduced in 52 ± 1-year-old, 77 ± 2-year-old [3,10] and 78–84-year-old men and women [14]. The mitochondrial protein synthesis rate declined in a similar pattern [11]. The sarcoplasmic protein synthetic rate was not reduced from young to middle or old age [10]. This suggests that the synthetic rates of contractile and mitochondrial proteins are especially susceptible to increasing age, while the synthesis of soluble cytosolic proteins does not appear to be altered.

The age-associated reduction in the MHC synthetic rate suggests an impaired ability to remodel key contractile proteins, which may contribute to impaired muscle contractile function or muscle quality, while reducing the quantity of skeletal muscle protein [10]. A positive correlation ($r = 0.41–0.58$) between the vastus lateralis MHC synthetic rate and the lower extremity isokinetic or concentric muscle strength per unit thigh muscle mass [10] supports a link between muscle biochemistry and function with advancing age. An altered expression of MHC isoforms probably explains the age-associated reduction in type II muscle fiber percentage and size [4], but whether this is mediated by endocrine, neuromuscular, metabolic, or contractile actions is not clear.

Based on the cross-sectional studies of Hurley et al. [7,8,25,26,27,28], it is clear that the maximum voluntary isometric, concentric, and eccentric muscle force of the knee extensors declines with advancing age.
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(from 20 to 93 years) in a similar fashion in both men and women [25**,26]. Maximum voluntary concentric and eccentric muscle force per unit muscle area also declines with age (muscle quality) [25**,26]. There is a difference in the rate and extent of the decline in muscle quality depending on gender, arm versus leg muscles, and concentric versus eccentric measures of peak force production.

Recent reports suggest that muscular power, the ability to produce force rapidly, is another muscle quality that declines with advancing age (even more so than muscle strength) [29–32]. The loss of muscle power contributes to age-associated impairments in physical function [32*], can be improved with progressive resistance exercise training [33*], and may be linked to the age-related decrease in type II muscle fiber percentage and size [5]. Power-specific muscle contractions and exercises might need to be incorporated into progressive resistance exercise training programs for the elderly [6,33*].

Sarcopenia is characterized by a loss of muscle protein mass, strength, power, and quality that combine to impair physical function. More longitudinal studies are needed to confirm the decrements in muscle protein synthesis, mass, strength, power, and quality derived from cross-sectional studies of women and men across different ages. A mass spectrometric analysis of protein modifications and alterations in protein structure, as well as synthetic and proteolytic rates, will enhance our understanding of the age-associated alteration in the regulators of muscle protein quantity and quality. Novel isolation and mass spectrometric measurement techniques will be developed for important targets such as myosin heavy and light chain isoforms, actin, troponin, the DNA proliferation rate [34], the expression of autocrine growth factors (insulin-like growth factor-1 and transforming growth factor-β) [35], proteolytic processes and enzymes (ubiquitin–proteasome, caspases, calpains, cathepsins, and lysosomal enzymes) [36,37] and specific enzymes of energy transduction (e.g. ATPase and cytochrome oxidase) in muscle samples acquired from ageing men and women.

Effect of acute and prolonged resistance exercise on muscle protein synthesis and strength

Following an acute resistance exercise session, the vastus lateralis muscle protein fractional synthesis and breakdown rates are increased in healthy young subjects [11–14,18,19].

Time course studies have found that the rate of mixed muscle protein synthesis is elevated for 36–48 h after a bout of resistance exercise [18,19]. In one study, the acute exercise-induced increase in mixed muscle protein synthetic rate was mediated through post-transcriptional events [16], probably due to an improved efficiency of mRNA translation after resistance exercise [22*].

The rate of vastus lateralis muscle proteolysis was elevated for up to 24 h following eight sets of eight repetitions at 80% of one-repetition maximum resistance exercise and returned to baseline by 48 h in young women and men [19]. In the same study, the mixed muscle protein synthesis rate was elevated at 4, 24, and 48 h following resistance exercise. Both rates were augmented in the immediate postexercise period, but the time frames differed. Net muscle protein balance was more positive for 2 days following the acute bout of resistance exercise. This contributes to the protein accretion that occurs when resistance exercise sessions are chronically repeated (during training).

Several potential translational regulators of and intracellular signaling pathways for rodent gastrocnemius muscle protein synthesis are altered hours after a resistance exercise session [38,39*]. Between 12 and 24 h after resistance exercise, muscle protein synthesis was elevated, and muscle phosphatidylinositol 3-kinase, p70S6k, eukaryotic initiation factor-2B, and to a lesser extent 4E-binding protein 1 (eIF2B, eIF4E-binding protein 1), phosphorylation and activity were elevated during this time frame. These findings implicate specific steps in the phosphorylation signaling pathways, the regulation of mRNA translation initiation, and the formation of polyribosomes for mRNA translation by peptide chain initiation factors as important rate-limiting steps in the acute activation of protein synthesis following resistance exercise. Probing these pathways in aging human muscle before and after exercise should be an important initiative.

In summary, progressive resistance exercise training increases muscle protein mass and strength in young men and women. The increase in muscle protein mass is attributable to an acute and chronic increment in muscle protein turnover such that the rate of muscle protein synthesis exceeds muscle proteolysis [19,41]. Coincident with the increase in muscle protein are increases in maximum voluntary muscle strength and muscle fiber hypertrophy.

Effect of resistance training on protein synthesis, muscle morphology, strength, power, and quality in the elderly

The magnitude of the acute exercise-induced increase in mixed and MHC protein synthesis was similar in 23–32-year-old, 63–66-year-old, and 78–83-year-old men and women [12–14], suggesting that the capacity of the muscle protein synthetic machinery to respond to resistance exercise is preserved until very old age.
When older adults adhere to an optimally designed resistance exercise training program, the rate of mixed muscle protein synthesis increases, muscle strength increases, muscle protein mass increases, muscle quality and power increase, and physical function improves [5–9, 12–14, 23, 25**, 28**, 29, 33*, 42–44, 45*, 46–50, 56]. Several of these studies are summarized in Table 2.

Evidence indicates that resistance exercise training induces muscle hypertrophy and increases the rate of muscle protein synthesis in middle-aged, elderly, and physically frail adults. The vastus lateralis mixed muscle protein synthetic rate increased after just 2 weeks of whole-body resistance exercise (5 days per week of 2–4 sets each of 4–10 repetitions at 60–90% of one-repetition maximum) in healthy 24-year-old and 63–66-year-old men and women [13]. The baseline mixed muscle protein synthesis rate was lower in the elderly than in the young. Following resistance exercise, mixed muscle protein synthesis increased similarly in the young and elderly subjects.

Using a similar protocol, 2 weeks of resistance exercise increased the myosin heavy chain (105%) and mixed muscle protein synthetic rates (182%) in 78–84-year-old men and women [14]. The skeletal muscles of middle-aged (63–66-year) and very old (>76-year) men and women retain the ability to rapidly respond to a resistance exercise session and activate the protein synthetic machinery. This is similar to what occurs following acute resistance exercise in the muscles of young, healthy men and women.

The exercise-induced stimulation of muscle protein synthesis in the elderly and in the young appears to be mediated via a similar mechanism. Three sessions of resistance exercise increased vastus lateralis myofibrillar protein synthesis (30%) in 62–75-year-old men and women without a compensatory increase in total RNA, actin, or MHC mRNA [22*]. This suggests that the acute exercise-induced stimulation of muscle protein synthesis in the elderly is mediated through post-transcriptional mechanisms.

Prolonged periods of progressive resistance exercise training increase the rate of mixed muscle protein synthesis in mild-to-moderate physically frail 76–92-year-old men and women [23]. Physical frailty was assessed using a physical performance test and questionnaires that evaluated difficulties with activities of daily living. Following 3 months of supervised progressive resistance exercise training (65–100% of the initial one-repetition maximum), the vastus lateralis mixed muscle protein synthetic rate increased in men and women. Whole-body muscle mass

### Table 2. Resistance exercise- or nutrition-induced alterations in muscle protein kinetics, mass, and strength in the elderly

<table>
<thead>
<tr>
<th>Intervention</th>
<th>Ref.</th>
<th>Protocol</th>
<th>Age (years)</th>
<th>Muscle protein synthesis</th>
<th>Muscle protein breakdown</th>
<th>Muscle mass</th>
<th>Muscle strength</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acute resistance exercise</td>
<td>[14]</td>
<td>2 weeks, 2–3 sets, 8–12 reps, 60–90% 1RM</td>
<td>78–84</td>
<td>↑</td>
<td>→</td>
<td>ND</td>
<td>ND</td>
</tr>
<tr>
<td>Acute resistance exercise</td>
<td>[13]</td>
<td>2 weeks, 2–4 sets, 4–10 reps, 60–90% 1RM</td>
<td>63–66</td>
<td>↑</td>
<td>→</td>
<td>→</td>
<td>ND</td>
</tr>
<tr>
<td>Resistance exercise training</td>
<td>[23]</td>
<td>12 weeks, 3 sets, 8–12 reps, 65–100% 1RM</td>
<td>76–92</td>
<td>↑</td>
<td>→</td>
<td>↑</td>
<td>↑</td>
</tr>
<tr>
<td>Resistance exercise training</td>
<td>[56]</td>
<td>12 weeks, 3 sets, 8 reps, 80%–3RM</td>
<td>62–72</td>
<td>→</td>
<td>→</td>
<td>→</td>
<td>↑</td>
</tr>
<tr>
<td>Resistance exercise training</td>
<td>[28**]</td>
<td>9 weeks, 3 sets, 5–10 reps, 5–10RM–unilateral leg training</td>
<td>65–75</td>
<td>ND</td>
<td>ND</td>
<td>↑ Men only</td>
<td>↑</td>
</tr>
<tr>
<td>Resistance exercise training</td>
<td>[48*, 49]</td>
<td>16 weeks, 3 sets, 6–8 reps, 85–90% 1RM</td>
<td>60–75</td>
<td>Nuclei/muscle cell → Nuclei/mm fiber length → Type I, IIA, IIB areas ↑</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Acute resistance exercise + 0.6–2.4 g protein/kg/day</td>
<td>[51]</td>
<td>3 days, 4–5 sets, 10 reps, 80% 1RM</td>
<td>62–72</td>
<td>↑ No additional increase with higher protein intake</td>
<td>ND</td>
<td>ND</td>
<td>ND</td>
</tr>
<tr>
<td>Intravenous amino acid supplements</td>
<td>[20]</td>
<td>148.5 mg amino acids/kg at rest</td>
<td>71 ± 2</td>
<td>↑</td>
<td>→</td>
<td>ND</td>
<td>ND</td>
</tr>
<tr>
<td>Oral amino acid supplements</td>
<td>[21**]</td>
<td>40 g amino acids at rest</td>
<td>71 ± 2</td>
<td>↑</td>
<td>→</td>
<td>ND</td>
<td>ND</td>
</tr>
</tbody>
</table>

ND = not determined in this study. 1RM = 1-repetition maximum. ↑ = increase, ↓ = decrease, → = no change.
increased in both women (1.0 kg) and men (2.2 kg). The maximum voluntary isokinetic torque production (60%) increased in the women (10%) and in the men (23%).

This suggests that chronic resistance exercise training increases the rate of mixed muscle protein synthesis in physically frail men and women. The magnitude is less than that observed following an acute (2-week) exposure to resistance exercise, implying that the initial increase in the rate of muscle protein synthesis is attenuated when the resistance exercise sessions continue for several weeks. Phillips et al. [41] reached a similar conclusion. They reported that resistance exercise training reduced the acute exercise-induced increase in muscle protein synthesis in 25±3-year-old women and men. These findings also suggest that the age-associated loss in muscle protein mass can be restrained with regular resistance exercise training.

The functional benefits of resistance exercise training were evaluated in a large-scale trial of 72–98-year-old physically frail nursing home residents [44]. Lower extremity resistance exercise training increased muscle strength (113%), gait velocity (12%), stair-climbing power (28%), level of spontaneous physical activity, and thigh muscle cross-sectional area (2.7%).

Resistance exercise training induces an alteration in myosin isomorph expression in elderly muscles. Twelve weeks of resistance exercise training increased type II muscle fiber area (12–27%) in the vastus lateralis of 65–72-year-old men [47], reduced type IIB (−9%) and increased type IIa (5%) fiber percentages, increased the cross-sectional area of all fiber types (34–52%), and increased the maximum voluntary strength 50–84% [48,49]. Similarly, 12 weeks of unilateral resistance exercise training for the elbow flexors increased type II muscle fiber area (30%) and one-repetition maximum strength (48%) in 60–70-year-old men [50].

Resistance exercise training-induced increases in muscle protein synthesis, mass, and strength in the elderly are well documented. Recent studies have reported that resistance exercise training improves muscular power and the maximum voluntary muscle force generated per amount of muscle tissue (muscle quality) in the elderly [25,28,33]. It is clear that novel exercise therapies for geriatric patients should focus not just on increasing muscle mass and strength, but also on improving muscle power and quality [6,8,9]. These latter properties of muscle integrate alterations in neural innervation, speed of movement, and differences in contractile and non-contractile protein composition in the muscles of elderly adults, and may provide more information about mechanisms causing sarcopenia.

Amino acid supplementation with or without exercise increases muscle protein synthesis in the elderly

Recent evidence suggests that providing more amino acids to muscle, especially during the post-resistance exercise period, may augment the exercise-induced increase in muscle protein synthesis. Most of this work has been done on healthy young subjects. Welle et al. [51] reported that high protein meals (0.6–2.4 g protein/kg per day) did not enhance the myofibrillar protein synthesis rate following three sessions of resistance exercise in 62–75-year-old men and women. Conversely, Volpi et al. [20] reported that an intravenous infusion of amino acids (10% Travasol + glutamine) increased the rate of mixed muscle protein synthesis (100%) in healthy 71±2-year-old men. Oral supplementation with essential amino acids increased the rate of mixed muscle protein synthesis by 70% in 71±2-year-old men and women [21].

In sedentary young men, the intravenous infusion of a balanced amino acid mixture increased (by 141%) the resting rate of muscle protein synthesis [52]. When this amino acid mixture was administered following a bout of leg resistance exercise, the rate of muscle protein synthesis was increased still further (by 241%) [52]. These observations suggest that exogenous amino acid supplementation following resistance exercise may augment the stimulatory effect of exercise on muscle protein synthesis rate. Whether this effect persists with repeated exposure and further improves muscle quantity and quality in the elderly remains to be determined.

Conclusion

Contractile protein synthesis rates, mass, strength, power, and force production per unit area of muscle decrease with advancing age. Many factors interact to cause these decrements. Evidence favors prescribing resistance exercise training to older adults without any contraindication to regular exercise. Muscle proteins in older adults maintain the ability to respond to acute and chronic resistance exercise by activating the rate of mixed muscle and MHC protein synthesis, increasing muscle mass, muscle power, and muscle quality, much the same as exercise activates these processes in young men and women.

Research should focus on identifying and quantifying the signals and biochemical processes that regulate the balance between contractile protein synthetic and proteolytic processes in the muscles of older adults. Interventions should focus on increasing muscle protein quantity, strength, and muscular power, improving the quality of muscle proteins and their contractile characteristics, and maintaining independent physical function in the elderly. Resistance exercise training may not
be feasible in all elders and may not extend life span, but it may extend the years of independent living and improve quality of life in advancing age.

The sequencing of the human genome has helped to identify genes that might contribute to the senescent process, but the current proteomics era will exponentially increase our understanding of the pathogenesis of advancing age, the age-associated alterations in skeletal muscle protein expression, function, structure, and chemical modifications that might explain pathogenesis, and potential therapeutic targets that might amend the senescent protein (especially muscle) phenotype.

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**References and recommended reading**

Papers of particular interest, published within the annual period of review, have been highlighted as:

- of special interest
- of outstanding interest


Exercise, ageing and muscle protein

Myostatin is one of several homologous growth factors that are recently discovered members of the TGF-β family of genes. The underexpression of myostatin in transgenic mice and several agricultural species with myostatin gene mutations has been attributed to massive muscle hypertrophy. In this preliminary report, the authors have expressed and isolated human myostatin protein from bacterial/insect cell lines. The isolates were incubated with growing cultures of a fibroblast cell line. Myostatin and a myostatin carboxy-peptide fragment inhibited proliferation and protein synthesis in mouse C2C12 muscle cells. Endocrine Society, Vancouver BC, 2000. Abstr. 1022.

This implies that resistance exercise-induced increments in the muscle protein synthetic rate are mediated by activation of the PI-3 kinase pathway and RNA transcription initiation factors. In rodents, the phosphorylation and activation of eukaryotic initiation factors (especially eIF2B) increases following resistance exercise. These increments correspond temporally with increases in the mixed muscle protein synthetic rate. This implies that resistance exercise-induced increments in the muscle protein synthetic rate are mediated by activation of the PI-3 kinase pathway and RNA transcription initiation factors.


