Review Article

Exercise, Aging, and Muscle Protein Metabolism

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Age-associated alterations in muscle protein quantity and quality that adversely affect muscle structure, composition, and function have been referred to as sarcopenia. Muscle protein is metabolically active, and the age-associated loss of muscle protein mass is related to a loss of physical function and an inability to perform activities of daily living (physical frailty). It is important to maintain adequate reserves of muscle protein and amino acids as we age. As in all cachectic conditions, sarcopenia can be explained by an imbalance between the rates of muscle protein synthesis and muscle proteolysis, in which net muscle protein balance is negative. This review summarizes evidence that supports the notion that: (a) advancing age and physical frailty are associated with a reduction in the fasting rate of mixed and myosin heavy chain protein synthesis, which contributes to muscle protein wasting in advancing age; (b) this impairment can be corrected because resistance exercise acutely and dramatically increases the rate of muscle protein synthesis in men and women aged 76 years and older; and (c) resistance exercise training maintains a modest increment in the rate of muscle protein synthesis and contributes to muscle hypertrophy and improved muscle strength in frail elderly men and women. The cellular mechanisms responsible for these adaptations, as well as the role of nutrition and hormone replacement in reversing sarcopenia, require further investigation.

Skeletal muscle structure and composition change with advancing age; there is an infiltration of fat and connective tissue, skeletal muscle protein mass, and cross-sectional area decline [see Figure 1 in (1)]. Roubenoff and colleagues (2) refer to these age-associated changes in muscle quantity and quality as sarcopenia. My laboratory has focused on the mechanisms that might explain the loss of muscle protein and gain in connective tissue and fat that occur with advancing age, and the efficacy of exercise training, hormonal, or nutritional interventions for slowing or reversing the muscle-wasting process in aging muscle.

The loss of muscle protein mass with age is related to a loss of function and an inability to perform activities of daily living (3–6). Muscle proteins provide amino acids for other metabolic processes. Therefore, it is important to maintain adequate reserves of muscle amino acids as we age. Muscle wasting in the hip, knee, and ankle muscles contributes to a greater risk of falls and fractures. Maintenance of muscle strength appears to maintain bone mineralization, and this may also reduce fracture risk. 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. The purpose is to describe how advancing age affects the rate of muscle protein synthesis, and how acute and progressive resistance exercise (PRE) training affect muscle contractile protein synthesis rates in women and men aged 76 years and older. I will summarize the findings from two published studies (7,8).

The characteristics of the subjects enrolled in these studies are shown in Table 1. We recruited men and women aged 76 years and older. We used a physical performance test (PPT), maximum O2 consumption test (VO2 max), and a series of questionnaires focused on the participant’s ability to perform activities of daily living (ADL) to evaluate whether each participant was physically frail or not physically frail. The frail elders were randomly assigned to a 12-month supervised exercise training program or a control group (no PRE). We measured the rate of mixed muscle protein synthesis before and after the 3-month PRE portion of this program and hypothesized that PRE would increase muscle mass and muscle protein synthesis rate in frail men and women aged 76 years and older. The nonfrail elders and a group of healthy 23–32-year-old men and women were enrolled in a short, 2-week weight-lifting exercise program. Based on findings from a similar study done on 63–66-year-old men and women (9), we hypothesized that (a) nonfrail elders would have lower myosin heavy chain (MHC), actin, and mixed muscle protein synthesis rates than the healthy young men and women, and (b) weight-lifting exercise would acutely and equivalently increase myosin heavy chain, actin, and mixed muscle protein synthesis rates in nonfrail elders and young men and women. We measured the rate of muscle protein synthesis before and after this short, acute exposure to weight-lifting exercise.

We measured the in vivo fractional rate of muscle protein synthesis by determining the incorporation of an intravenously administered stable isotope-labeled amino acid (13C-leucine) into skeletal muscle proteins (MHC, actin, mixed) (see Figure 1). Subjects were admitted to the General Clinical Research Center (GCRC) at Washington University Medical School following 3 days of controlled protein (1.1–1.4 g/kg/d; 14%–16% total kcal) and energy (31–39 kcal/kg/d) intake. These meals were provided by the GCRC Research Kitchen and contained no meat; estimates
skeletal muscle protein kinetics.

Figure 1. Amino acid infusion protocol used to measure whole body and skeletal muscle protein kinetics.

of whole-body muscle mass and myofibrillar protein degradation were derived from 24-hour urine collection analyzed for creatinine and 3-methylhistidine concentrations. Postexercise $^{13}$C-leucine infusions were performed 3–4 hours following completion of the last exercise session. Blood samples were collected before and at 30-minute intervals during the last 2 hours of the $^{13}$C-leucine infusion. A vastus lateralis muscle sample (100–120 mg) was obtained 1–1½ hours after starting the $^{13}$C-leucine infusion. A second sample was obtained from the contralateral muscle 13–14 hours after starting the $^{13}$C-leucine infusion. Gas chromatography-mass spectrometry was used to measure muscle cytosolic $^{13}$C-leucine, plasma $^{13}$C-leucine, and plasma $^{2}$-ketoisocaproic acid enrichment. Gas chromatography-combustion-isotope ratio mass spectrometry was used to measure $^{13}$C-leucine enrichment in mixed, MHC, and actin proteins isolated from the muscle samples. We isolated MHC and actin proteins using high-salt extraction and polyacrylamide gel electrophoresis (6). The fractional rate of muscle protein synthesis was calculated as described previously (7,8,10).

Maximum voluntary muscle strength (1-repetition maximum [1-RM]) was measured on 8 weight-lifting exercises: chest press, inclined chest press, latissimus pull-down, leg press, knee extension, knee flexion, seated overhead press, and overhead triceps extension. During the acute exercise study, participants completed ten 1–1½-hour weight-lifting sessions in a 2-week period, 2–3 sets/session of the above exercises, 8–12 repetitions/set, 60%–90% of maximum voluntary muscle strength. The prolonged exercise training program consisted of an initial 3 months of supervised range of motion, stretching, and flexibility exercises (3 sessions/wk) that prepared participants for the next 3-month period focused on PRE. In general, the PRE consisted of 3 sessions/week, 1–2 sets/session, 6–8 repetitions/set at 65%–75% 1-RM. The intensity, number of sets, and repetitions were gradually increased so that by the end of the program they were lifting 3 sessions/week, 3 sets/session, 8–12 repetitions/set at 75%–85% 1-RM. Subsequently, this group completed a 3-month aerobic endurance exercise-training program that was supplemented with light weight-lifting and flexibility exercises. Muscle amino acid metabolism was examined before and at the end of the 3-month PRE program. These individuals were living in the community but were not allowed to drive. Therefore, we transported them by bus to and from the training facility 3×/week. The control group of frail elders participated in testing and educational sessions, and were prescribed a home exercise program that consisted of muscle stretching and flexibility exercises. Once a month, they were transported to the exercise facility and participated in a supervised stretching and flexibility exercise session. In the control group, muscle amino acid metabolism was examined 3 and 6 months after starting the home stretching/flexibility exercises.

The basal rates of MHC and mixed muscle protein synthesis were lower in nonfrail 78–84-year-old men and women than in 23–32-year-old healthy young men and women (Figure 2). This suggests that a portion of the muscle-wasting that accompanies advancing age is caused by a reduced rate of incorporation of amino acids into contractile proteins. Whether this is transcriptionally or post-transcriptionally regulated is still debated. Our findings are in contrast to those observed in active healthy older adults (11). The difference in these findings may be due to the fact that we studied frail elderly individuals consuming a controlled meal plan who were admitted to the GCRC for 24 hours prior to determining synthetic rates versus studying physically active, free-living elderly people (12).

Although basal protein synthetic rates were diminished in 78–84-year-old men and women, the rates of protein synthesis significantly increased following an acute (2-week) exposure to weight-lifting exercise in the older individuals to a rate similar to that of the young individuals (Figure 2). This suggests that muscle proteins retain the ability

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Supervised Exercise Group</th>
<th>Control Group</th>
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<tbody>
<tr>
<td></td>
<td>Frail Women</td>
<td>Frail Men</td>
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<tr>
<td>N</td>
<td>8</td>
<td>4</td>
</tr>
<tr>
<td>Age (y)</td>
<td>82 ± 2</td>
<td>82 ± 1</td>
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<tr>
<td>Height (cm)</td>
<td>160 ± 3</td>
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<tr>
<td>Weight (kg)</td>
<td>59.3 ± 2.6</td>
<td>95.0 ± 7.6</td>
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<tr>
<td>Fat-free mass (kg)</td>
<td>38.8 ± 1.5</td>
<td>59.7 ± 1.3</td>
</tr>
<tr>
<td>Muscle mass (kg)</td>
<td>14.2 ± 0.7</td>
<td>30.3 ± 2.4</td>
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Notes: Values are means ± SE.

* $p < .05$ nonfrail older group. From References 7 and 8.
to respond to an acute contraction-induced activation of muscle protein synthetic machinery even in 78–84-year-old men and women. It is interesting that acute resistance exercise increased mixed and actin protein synthesis to similar absolute rates in both 78–84 and 23–32-year-old men and women, suggesting that there may be a biological limit in the magnitude to which resistance exercise can increase the muscle protein synthesis rate that is not diminished by advanced age. In an earlier study, exercise acutely activated muscle protein synthesis in 63–66-year-old men and women (9). It appears that, regardless of age, contractile proteins respond to short-term resistance exercise with an increased rate of protein synthesis. These findings also suggest that the absence of muscle contractile activity (physical inactivity) typical of advancing age contributes to sarcopenia, because the low basal rate of muscle protein synthesis noted in the older men and women was restored to rates similar to young men and women given the same relative amount of resistance exercise.

Urinary 3-methylhistidine excretion estimates of myofibrillar proteolysis were not significantly increased after 2 weeks of resistance exercise in either the younger or older subjects. However, baseline 3-methylhistidine excretion in the older subjects was greater than in the younger subjects, suggesting that increased muscle proteolysis also contributes to sarcopenia. This marker of myofibrillar protein breakdown may not be a specific reflection of proteolysis in the vastus lateralis muscle, where protein synthesis was measured, and therefore may not accurately reflect the effects of short-term resistance exercise on vastus lateralis muscle protein balance. Phillips and colleagues demonstrated that a single bout of resistance exercise increased mixed muscle protein synthesis and breakdown rates in sedentary young men (13,14). The increments in synthesis were larger than the increments in breakdown, such that muscle amino acid balance was increased above baseline following exercise. The exercise-induced increments in synthesis and breakdown were attenuated in resistance-trained young men.

Three months of PRE also augmented the rate of mixed muscle protein synthesis in frail elderly men and women (Figure 3). Whole-body muscle mass was not increased in the control group. Three months of PRE increased muscle mass in the frail women (~1.0 kg) and men (~2.2 kg). Basal mixed muscle protein synthesis was slightly elevated above the rates observed in the acute exercise study because the control subjects and the PRE subjects all did flexibility/stretching exercises for 3 months before the basal measurement of muscle protein synthesis was made (Figure 3). Mixed muscle protein synthesis rate was similar to basal in the control group after 3 additional months of home stretching/flexibility exercises. Mixed muscle protein synthesis rate was increased over basal after PRE in the frail men and women (Figure 3). However, the magnitude of this increase was less than that observed following acute (2 weeks) exercise.

In frail elderly men and women, even the small amount of muscle contractile activity induced by stretching, range of motion, and flexibility exercises was sufficient to elevate basal muscle protein synthesis rate above that observed in sedentary 78–84-year-old individuals. When exercise intensity was increased and included 3 months of PRE, the mixed muscle protein synthesis rate increased significantly more (Figure 3).

Maximum voluntary muscle force production was also increased after PRE in frail elderly men and women.
Isometric force production of the knee extensor muscles was increased 6% in the exercising women, and 7%–22% in exercising men. Three months of PRE improved muscle function in frail elderly men and women.

Based on these observations, we proposed a schematic model for the alterations in muscle protein synthesis and breakdown that are induced by acute and chronic resistance training and might explain muscle hypertrophy (15) (Figure 4). The model predicts that a single bout of weight-lifting exercise dramatically stimulates the rates of muscle protein synthesis and breakdown, but that the increase in breakdown lags behind and is less in magnitude than the increase in synthesis rate. By the time of the next bout of exercise (~48 hr), both synthesis and breakdown have declined to a nadir value, but they do not return to baseline levels. This could explain the higher rate of protein turnover that occurs following exercise. As the exercise bouts are repeated, so are the pulse-wave increments in protein synthesis and breakdown rates, but they reach some threshold value after several repeated exposures. This rate may represent some genetic limit to the magnitude of the pulse increments in synthesis and breakdown rates. After many repeated exercise bouts, the magnitude of the increase in synthesis and breakdown dampens, and a new “steady-state” level of protein turnover is achieved. The small positive difference in muscle protein balance elicited by each repeated exercise-induced pulse in synthesis and breakdown rates begins to accumulate and muscle protein mass begins to increase. So, the increase in muscle protein mass lags behind the acute increases in synthesis and breakdown and requires several weeks of repeated exercise exposure before it is measurable.

What regulates muscle protein synthesis and breakdown rates and muscle mass in elderly people? We have focused on tumor necrosis factor-alpha (TNF-α) and growth and differentiation factor-8 (myostatin)—a proinflammatory cytokine and a growth factor present in skeletal muscle that may be important autocrine or paracrine regulators of muscle protein metabolism. Greiwe and colleagues (16) reported that TNF-α mRNA and protein were upregulated in muscle from frail elderly men and women, that PRE reduced muscle TNF-α protein levels in these frail elders, and that the reduction in muscle TNF-α protein was associated with the PRE-induced increase in muscle protein synthesis rate. These findings suggest that gene expression and protein levels for a marker of chronic inflammation within muscle (TNF-α) are elevated in frail elderly men and women, and that PRE induces a reduction in this marker of inflammation while increasing the rate of muscle protein synthesis. Similarly, others have reported that age-related diseases, disability, and mortality are associated with circulating levels of interleukin-6, another proinflammatory cytokine (17–19).

Some evidence suggests that serum and muscle tissue levels of myostatin are elevated in muscle-wasting conditions (20–23). Recombinant full-length and carboxy-terminal myostatin protein inhibited cell proliferation, DNA synthesis, and protein synthesis in mouse skeletal muscle C2C12 cells (22). Most notable is the muscle-specific myostatin knock-out mouse that develops 2–3 times more muscle mass than the wild-type littermate (23). A potential link between these two regulators of muscle protein synthesis and breakdown has been proposed (24). Whether this pathway contributes to sarcopenia and is attenuated with exercise training should be evaluated.

Roth and colleagues (25,26) have focused on the satellite cells as regulators of the regenerative capacity of muscle in elderly people. On the basis of electron microscope analysis of vastus lateralis muscle samples, they reported that satellite cell populations are not significantly lower in healthy, sedentary 65–75-year-old men and women than in 20–30-year-old young men and women (1.7%–2.8%). These findings contradict those obtained from animal models. However, satellite cell proportions and the number of morphologically active satellite cells increased after 9 weeks × 3 days/week of unilateral knee extension PRE in healthy young and older men and women. These findings suggest that PRE activates muscle satellite cells in older men and women, but that a reduction in satellite cell number or percentage does not explain the reduced capacity for human muscle cells to regenerate or maintain muscle mass with advancing age.

In summary, the fundamental pathogenesis for sarcopenia is only partially understood. Clearly, resistance exercise training is an effective and potent stimulus for restraining sarcopenia. The cellular mechanisms responsible for mediating exercise-induced adaptations, as well as the role of nutrition and hormone replacement in reversing sarcopenia, require further investigation.

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