Resistance exercise training increases mixed muscle protein synthesis rate in frail women and men ≥76 yr old

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Yarasheski, Kevin E., Jina Pak-Loduca, Debbie L. Hasten, Kathleen A. Obert, Mary Beth Brown, and David R. Sinacore. Resistance exercise training increases mixed muscle protein synthesis rate in frail women and men ≥76 yr old. Am. J. Physiol. 277 (Endocrinol. Metab. 40): E118–E125, 1999.—Muscle atrophy (sarcopenia) in the elderly is associated with a reduced rate of muscle protein synthesis. The purpose of this study was to determine if weight-lifting exercise increases the rate of muscle protein synthesis in physically frail 76- to 92-yr-old women and men. Eight women and 4 men with mild to moderate physical fraility were enrolled in a 3-mo physical therapy program that was followed by 3 mo of supervised weight-lifting exercise. Supervised weight-lifting exercise was performed 3 days/wk at 65–100% of initial 1-repetition maximum on five upper and three lower body exercises. Compared with before resistance training, the in vivo incorporation rate of [13C]leucine into vastus lateralis muscle protein was increased after resistance training in women and men (P < 0.01), although it was unchanged in five 82 ± 2-yr-old control subjects studied two times in 3 mo. Maximum voluntary knee extensor muscle torque production increased in the supervised resistance exercise group. These findings suggest that muscle contractile protein synthetic pathways in physically frail 76- to 92-yr-old women and men respond and adapt to the increased contractile activity associated with progressive resistance exercise training.

SARCOPENIA refers to the undesirable loss of muscle mass that accompanies advancing age. It is associated with muscle weakness, increased fatigability, and a loss of independent function, all characteristics of physical frailty (1, 5, 7–11, 16, 17, 19, 21, 25–27, 31–33). The pathogenesis of sarcopenia is multifactorial, and the primary cause is unclear. Nevertheless, it appears that muscle contractile and mitochondrial protein synthesis rates are reduced with advancing age (1, 16, 19, 20, 25–27, 31, 32). The decrements in contractile and mitochondrial protein synthesis are associated with reduced muscle mass, muscle strength, and endurance capacity (1, 16, 19, 25–27, 31, 32). Therefore, an increase in the rate of muscle protein synthesis should result in an improvement in muscle strength and function and modulate the disability associated with physical frailty.

Progressive resistance exercise training (weight lifting) increased muscle strength, gait velocity, and stair-climbing power in ≥70-yr-old institutionalized physically frail women and men (8–10). Despite this improvement in muscle performance and reduction in physical frailty, the increase in muscle cross-sectional area was modest (2.7%). This suggests that contractile proteins within the muscle cells of physically frail elders have a reduced capacity to hypertrophy in response to weight-lifting exercise training. This is contrary to the observation that weight-lifting exercise increased the rate of mixed-muscle protein synthesis in healthy 64- to 75-yr-old subjects to a similar magnitude as it did in healthy 20- to 30-yr-old subjects (31). Welle et al. (26) reported that 3 mo of progressive resistance exercise training did not increase the rate of myofibrillar protein synthesis in healthy, active 62- to 72-yr-old women and men. The adaptability of muscle protein synthetic pathways to resistance exercise training in ≥76-yr-old physically frail subjects has not been reported.

The purpose was to examine whether weight-lifting exercise training increases muscle protein synthesis rate and maximum voluntary muscle strength in physically frail elderly women and men. The results indicate that 3 mo of supervised resistance exercise training stimulates the in vivo rate of vastus lateralis muscle protein synthesis in physically frail 76- to 92-yr-old women and men.

METHODS

Subjects. Seventeen sedentary 76- to 92-yr-old adults were screened by the Recruitment Core of the Claude Pepper Older Americans Independence Center at Washington University Medical School and enrolled in this study. Eight women and four men were randomly assigned to the supervised exercise program, and four women and one man were assigned to the home exercise program (control group; Table 1). The study was approved by the Human Studies Review Committee at Washington University School of Medicine, and informed consent was obtained after the purpose and procedures were explained to each volunteer.

Before enrollment, volunteers received a physical examination, including a medical history, cognitive function evaluation, physical performance/frailty evaluation, a blood chemistry profile, complete blood cell count, and urinalysis. Each volunteer’s primary care physician authorized his or her participation in the exercise program. Physical frailty was objectively assessed using a physical performance test (e.g., stair climbing speed, walking speed, upper body strength,
balance, lower back range of motion) and subjectively assessed by the participant’s self-reported degree of difficulty with activities of daily living.

Volunteers were excluded if they were taking prescription medications that might affect muscle amino acid metabolism (β-adrenergic blockers, β-agonists, Ca²⁺ channel blockers, corticosteroids) or if they had a metabolic (e.g., diabetes), neuromuscular (Parkinson’s disease, moderate to severe peripheral neuropathy, sciatica), or any disorder that might affect muscle amino acid metabolism, their ability to respond to resistance exercise, or where exercise would be contraindicated (e.g., hypertension or coronary artery disease).

Exercise program. All participants were transported by shuttle bus from their residence to the exercise and testing facilities in the Geriatrics and Gerontology Division at Washington University School of Medicine. Control subjects participated in testing and educational sessions and were prescribed a home exercise program that consisted of light muscle stretching and exercises focused on improving joint range of motion. One day per month, the control subjects were transported to the exercise facility where the group participated in a 1- to 1.5-h supervised stretching and flexibility exercise session. This session was used to direct and assist the control participants with the performance of the home exercises and to provide purposeful interaction between the control participants and the exercise training staff.

The supervised exercise participants attended controlled and prescribed exercise training sessions 3 days/week. For the first 3 mo, all supervised exercise participants followed a stretching and flexibility physical therapy program similar to that of the home exercisers (control group). This supervised program was done 3 days/week and was designed to improve range of motion and familiarize each participant with increased activity. This program was followed by 3 mo of supervised, closely monitored progressive resistance exercise training done 3 days/week. One-repetition maximum (1-RM) voluntary muscle strength was determined in the supervised exercise participants (not controls) on each of eight different commercially available resistance exercise devices (Hoist Equipment) that included bench press, biceps curl, upright row, triceps extension, seated row, leg press, knee extension, and knee flexion. Abdominal muscle exercises and free-weight squats were incorporated into the later stages of the exercise program. An individualized resistance exercise program was designed for each participant based on a percentage of his or her 1-RM. The 1-RM measures were used to adjust the exercise intensity and to corroborate changes in muscle strength determined on a dynamometer. For safety, electrocardiogram and blood pressure were monitored during maximum voluntary strength testing and in some participants during the initial weeks of weight training. Initially, one to two sets of six to eight repetitions of each exercise were completed at 65–75% of 1-RM. This progressed to 3 sets of 8–12 repetitions done at 85–100% of initial 1-RM.

Maximum voluntary muscle strength assessment. Before and at the end of the supervised weight-lifting program, maximum voluntary isometric and isokinetic torque production (ft-lb. at 60°/s) of the knee extensor muscles was determined on a Cybex dynamometer (intermeasure coefficient of variation <10%). Maximal voluntary isometric force production was obtained at 45° of knee flexion. In the home exercise group, the same measures were made after 3 and 6 mo in the program.

Dietary control. For 3 days before initiating the resistance exercise program and for the final 3 days of resistance exercise, all participants consumed meat-free, controlled protein and energy meals supplied to them by the research kitchen on the General Clinical Research Center (GCRC). These meals were delivered to the control subjects or distributed to them in conjunction with other testing visits to the Pepper Center. Meat-free meals were employed to reduce the effects of dietary creatinine and 3-methylhistidine intake on 24-h urinary creatinine excretion measurements used to estimate whole body muscle mass (11, 13) and urinary 3-methylhistidine excretion measurements used as an indicator of myofibrillar proteolysis (14, 24, 28).

Before admission, a research dietitian surveyed each participant’s typical eating habits and designed a 3-day meal plan. The meals provided 1.2–1.3 g protein·kg⁻¹·day⁻¹, 125–165 kJ (30–40 kcal)·kg⁻¹·day⁻¹, 18% of calories from protein, 49% of calories from carbohydrate, and 33% of calories from fat in 3 daily meals with small snacks. The participants were instructed to eat no other food and to eat all food provided. Small amounts not consumed were returned and weighed, and the daily intake record was corrected. Intake was controlled to stabilize body weight and control protein and energy intake to minimize their effects on the measures of whole body and muscle protein metabolism. During the training program, the participants were given instructions on appropriate nutrient and energy intake. During the exercise program, the adequacy of each participant’s dietary intake was monitored by diet recall and, if necessary, adjusted by the research dietitian.

Body composition assessment. Fat-free mass (FFM) was determined using a Hologic QDR-1000/W whole body dual-energy X-ray absorptiometer (Hologic, Waltham, MA). Hologic enhanced whole body analysis software (version 5.71) was used to process the images and determine FFM. Whole body measures of leucine and protein metabolism are expressed per kilogram FFM.

Total body muscle mass was determined from three 24-h urinary creatinine excretion measures. The three daily measures were averaged, and total body muscle mass was calculated by assuming 1 g urinary creatinine excreted/day is equivalent to 20 kg muscle mass (11, 13). Urinary 3-methylhistidine concentration was determined in the three 24-h urine collections. These measures were averaged, and urine 3-methylhistidine excretion was expressed per millimolar creatinine excreted in 24 h.

Urinary creatinine and 3-methylhistidine concentration were determined using a stable isotope dilution assay and gas chromatography-electron impact quadrupole mass spectrometry (Hewlett-Packard 5890 GC and 5970 mass selective detector, EI-GC-MS; unpublished observations). To a 1-ml aliquot of each 24-h urine collection, 1.99 μmol of guanido-[¹³C]creatinine and 540 nmol of N-[¹³C]methylhistidine (MassTrace, Woburn, MA) were added as internal standards. A small amount (400 units) of urease (type III; Sigma-Aldrich, St. Louis, MO) was added to remove urinary urea by conversion to ammonia and carbon dioxide (23). The urease reaction was buffered with ~99% CO₂ gas injected into the sealed

Table 1. Subjects’ baseline characteristics

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Supervised Exercise Group</th>
<th>Control Group</th>
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<tbody>
<tr>
<td></td>
<td>Women</td>
<td>Men</td>
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<tr>
<td>Age, yr</td>
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<td>82±2</td>
</tr>
<tr>
<td>Height, cm</td>
<td>160±3</td>
<td>173±2</td>
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<tr>
<td>Weight, kg</td>
<td>59±3</td>
<td>95±6</td>
</tr>
<tr>
<td>Fat-free mass, kg</td>
<td>38±8</td>
<td>15</td>
</tr>
<tr>
<td>Muscle mass, kg</td>
<td>14±2</td>
<td>0.3</td>
</tr>
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</table>

Values are means ± SE; n, no. of subjects.
reaction vial. The tertiary butyldimethylsilyl derivative (N-methyl-N(tert-butyldimethylsilyl)-trifluoroacetamide + 1% tert-butyldimethylchlorosilane; Regis Chromatography, Morton-grove, IL) of creatinine and 3-methylhistidine was formed (4, 18, 24). The samples were injected onto a DB-1 capillary column (J & W Scientific, Folsom, CA), and methane was the carrier gas. The intensity of the ions at mass-to-charge ratio (m/z) 298 and 299 for creatinine and m/z 238 and 239 for 3-methylhistidine was monitored and quantitated in a single-sample injection onto the GC-MS.

Whole body and skeletal muscle leucine kinetics. Participants were admitted to the GCRC on the evening of the third day of the controlled meal plan. For the supervised exercise group, this occurred 3 h after the most recent exercise session, whereas the control participants were permitted to do their home stretching exercise program within 24 h of admission to the GCRC. In the supervised exercise group, the GCRC admissions for the measures of whole body and skeletal muscle leucine metabolism were done on the following two occasions: (1) at the conclusion of the 3-mo supervised stretching program and just before enrollment in the weight-training exercise program and (2) at the conclusion of 3 mo of supervised resistance exercise training. In the home exercise control subjects, these measures were made (1) at the conclusion of 3 mo of the home stretching exercise program and (2) 3 mo later, when they were still doing the home stretching exercise program.

Amino acid metabolism was determined before starting the resistance exercise program and ~3 h after the final resistance exercise session. At 1800, a baseline intravenous blood sample was obtained, and a primed (7.58 µmol/kg) 14-h constant intravenous infusion (7.58 µmol · kg⁻¹ · h⁻¹) of L-[¹³C]leucine (99 atom%; MassTrace) was initiated. A controlled protein and calorie, meat-free dinner meal was provided after all baseline samples were obtained. The plasma leucine rate of appearance (R_p, estimate of whole body proteolytic rate), the rate of exhaled ¹³CO₂ (estimate of whole body leucine oxidation rate), the nonoxidative leucine disposal rate (estimate of whole body protein synthesis rate), and the fractional rate of mixed skeletal muscle protein synthesis were determined in the overnight-fasted condition (1, 3, 12, 15, 17, 25–33). These determinations were made using blood, breath, and muscle tissue samples obtained at the end of the 14-h infusion.

In blood samples taken before and at 30-min intervals during the last 2.5 h of the overnight [¹³C]leucine infusion (0600–0800), plasma α-ketoglutaric acid (KIC) was isolated and chemically derivatized, and α-[¹³C]KIC abundance was determined using EI-GC-MS (22, 28). The plasma [¹³C]KIC enrichment (mol% excess) at equilibrium was used to calculate the rate of whole body protein breakdown (1, 3, 12, 17, 25–27, 29–33) and was used as an indication of the precursor pool [¹³C] enrichment for the calculation of the fractional rate of muscle protein synthesis (12, 17, 25–33). Exhaled breath samples were collected in 20-ml evacuated tubes (Becton-Dickinson, East Rutherford, NJ) before and at the end of the [¹³C]leucine infusion (0800). These breath samples were analyzed for [¹³C]O₂ enrichment (atom % excess) using EI-GC-MS (12, 29, 32, 33). Fifteen-minute measures of CO₂ production (µmol/min) and CO₂ consumption (mL/min) were made before starting the infusion and at 0700 using an open circuit indirect calorimeter (DeltaTrac Metabolic Monitor; Sensormedics, Fullerton, CA). These measures were used to determine the rate of whole body leucine oxidation (15, 28).

To assess the in vivo rate of incorporation of leucine into mixed muscle protein, muscle [¹³C]leucine enrichment was measured using gas chromatography-combustion-isotope ratio mass spectrometry (1, 12, 29–33) in two muscle samples (~10–20 mg wet wt) removed from the vastus lateralis. One sample was removed ~1.5–2 h after the [¹³C]leucine infusion began, and a second sample was removed from the contralateral vastus lateralis at the end of the infusion (0800). Whole body and skeletal muscle protein kinetics were calculated as described previously (1, 12, 15–17, 25–33). The absolute rate of muscle protein synthesis (mg protein synthesized·kg muscle mass⁻¹·h⁻¹) was calculated using the fractional synthesis rate (%/h) of vastus lateralis muscle protein and by assuming 19% of total body muscle mass is protein. This was expressed per whole body muscle mass to normalize for the difference in muscle mass between men and women.

Statistics. Data are expressed as means ± SE. Baseline measurements were subtracted from final measurements (end supervised exercise or home exercise period), and the difference was compared among the three groups using one-way ANOVA. When a significant interaction was identified (P < 0.05), a Student-Newman-Keuls post hoc analysis was used to determine which baseline-to-final changes differed. Baseline measures were compared with final measures using a paired t-test with Bonferroni correction for multiple comparisons.

RESULTS

Whole body muscle mass was unchanged (from baseline to final) in the home exercise group (0.0 ± 0.5 kg). The exercise-induced increments in whole body muscle mass were greater in the women (1.0 ± 0.6 kg) and men (2.2 ± 0.2 kg) in the supervised exercise group than in the home exercise group (P < 0.05; Table 2). Small increments in FFM were noted in the supervised exercise group of women but not in the supervised exercise group of men.

The maximum voluntary isometric torque production for the knee extensor muscles of the women in supervised exercise increased more than in the home exercise group (P < 0.05; Table 3). Maximum voluntary isokinetic force production at 60% for the knee extensor muscles of the men in the supervised exercise group increased more than in the home exercise control group (P < 0.05). The determination of 1-RM on the leg press, knee extension, leg flexor, and seated rowing exercises increased in the supervised exercise group of women by

Table 2. Baseline and final body composition parameters in supervised exercise and home exercise groups

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<tr>
<th>Group</th>
<th>Initial</th>
<th>Final</th>
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<tr>
<td>Home exercise</td>
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<tr>
<td>Weight</td>
<td>62.8±4.2</td>
<td>64.3±4.0</td>
</tr>
<tr>
<td>FFM</td>
<td>39.3±3.5</td>
<td>40.6±4.0</td>
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<tr>
<td>Muscle mass</td>
<td>17.5±1.7</td>
<td>17.5±1.5</td>
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<tr>
<td>Supervised exercise group of women</td>
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<td></td>
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<tr>
<td>Weight</td>
<td>59.3±2.6</td>
<td>59.8±2.6</td>
</tr>
<tr>
<td>FFM</td>
<td>38.8±1.5</td>
<td>39.8±1.6</td>
</tr>
<tr>
<td>Muscle mass</td>
<td>14.2±0.7</td>
<td>15.2±0.5*</td>
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<tr>
<td>Supervised exercise group of men</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Weight</td>
<td>95.0±7.6</td>
<td>94.6±8.0</td>
</tr>
<tr>
<td>FFM</td>
<td>59.7±1.3</td>
<td>59.4±1.0</td>
</tr>
<tr>
<td>Muscle mass</td>
<td>30.3±2.4</td>
<td>32.5±2.4*</td>
</tr>
</tbody>
</table>

Values are means ± SE. Units are kg. FFM, fat-free mass. Muscle mass was determined by averaging the 3 determinations of 24-h urinary creatinine excretion. The increase in muscle mass (final – initial) was greater in the women and men who did supervised exercise than in the home exercise control group (P < 0.05).
35 ± 7, 39 ± 4, 16 ± 7, and 12 ± 4%, respectively. In the men, 1-RM on these exercises increased 27 ± 4, 42 ± 24, 6 ± 6, and 18 ± 4%, respectively.

The resistance exercise-induced increase in total body muscle mass was accompanied by greater increments in the fractional and absolute rates of vastus lateralis muscle protein synthesis in the women and men enrolled in the supervised exercise program (Fig. 1). The fractional and absolute rates of muscle protein synthesis were unchanged in the home exercise control group. The baseline rate of mixed muscle protein synthesis was identical in all three groups (0.050–0.056%/h or 96–106 mg protein·kg muscle mass⁻¹·h⁻¹) but was elevated compared with rates determined previously in 60- to 72-yr-old men and women (1, 12, 16, 19, 25, 31).

Despite the large increase in the fractional rate of vastus lateralis muscle protein synthesis in the supervised exercise groups, the rate of whole body protein synthesis only tended to increase after resistance training (93 ± 3 to 96 ± 4 µmol·kg FFM⁻¹·h⁻¹; P > 0.05; Fig. 2). The rates of whole body protein breakdown (plasma leucine $R_\mathrm{a}$) and leucine oxidation were similar among the three groups and were not altered after 3 mo of resistance training or 3 mo of home stretching exercise (Fig. 2). Twenty-four-hour urinary 3-methylhistidine excretion (µM) is expressed per millimolar urinary creati-

Table 3. Maximum voluntary isometric and isokinetic torque production (ft-lb.) of the knee extensor muscles

<table>
<thead>
<tr>
<th></th>
<th>Initial</th>
<th>Final</th>
<th>Change</th>
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<tr>
<td>Home exercise control group 0%</td>
<td>65 ± 12</td>
<td>65 ± 13</td>
<td>0 ± 3</td>
</tr>
<tr>
<td></td>
<td>60%</td>
<td>58 ± 9</td>
<td>60 ± 9</td>
</tr>
<tr>
<td>Supervised exercise group of women 0%</td>
<td>65 ± 5</td>
<td>71 ± 7</td>
<td>6 ± 6</td>
</tr>
<tr>
<td></td>
<td>60%</td>
<td>60 ± 3</td>
<td>66 ± 4</td>
</tr>
<tr>
<td>Supervised exercise group of men 0%</td>
<td>96 ± 6</td>
<td>118 ± 4</td>
<td>22 ± 3*</td>
</tr>
<tr>
<td></td>
<td>60%</td>
<td>88 ± 7</td>
<td>95 ± 5</td>
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Values are means ± SE. The increase in maximum voluntary knee extensor isometric force production in the women was greater than control, and the maximum voluntary knee extensor isokinetic force production at 60% in the men was greater than control (*P < 0.05).

Fig. 1. In vivo vastus lateralis muscle protein synthesis rate expressed in mg muscle protein synthesized·kg whole body muscle mass⁻¹·h⁻¹ was increased after 3 mo of progressive resistance exercise training in the supervised exercise groups of women and men, whereas it was unchanged in the home exercise group. Symbols indicate individual participants. Increments in muscle protein synthesis rate (change = final − baseline) were greater in the supervised exercise groups than in the home exercise control group (*P < 0.01).

Fig. 2. Whole body proteolysis rate (A), protein synthesis rate (B), and leucine oxidation rate (C; µmol·kg fat-free mass (FFM)⁻¹·h⁻¹) were unchanged after 3 mo of weight-lifting exercise training in physically frail women and men. $R_\mathrm{a}$, rate of appearance.
nine excretion to normalize for gender differences in whole body muscle mass (Fig. 3). There was a trend toward a greater increase (P > 0.05) in urinary 3-methylhistidine excretion in the women (0.7 ± 0.3 µM/mM) and men (0.8 ± 0.3 µM/mM) in the supervised exercise group than in the home exercise control group (0.1 ± 0.1 µM/mM).

**DISCUSSION**

These findings indicate that 3 mo of supervised progressive weight-lifting exercise stimulates the in vivo rate of vastus lateralis (mixed) muscle protein synthesis and increases maximum voluntary knee extensor muscle torque production in physically frail 76- to 92-yr-old women and men. This suggests that skeletal muscle contractile proteins in 76- to 92-yr-old physically frail elders retain the ability to increase the rate of muscle protein synthesis in response to progressive weight-lifting exercise training. This adaptation should also involve an increase in the rate of myofibrillar protein turnover, as suggested by the slight increase in 3-methylhistidine excreted in the urine per kilogram muscle mass. Over the 3-mo exercise period, small increments in myofibrillar protein synthesis would be expected, because if the increased rate of muscle protein synthesis was not counterbalanced by an increased rate of myofibrillar proteolysis, then muscle protein mass would have increased much more than the 1–2 kg observed in the supervised exercise groups. Unfortunately, the small increments in myofibrillar protein breakdown may not be easily detected using 24-h urinary 3-methylhistidine excretion, even when meat-free meals are consumed for 3 days and complete 24-h urine voids are obtained (11, 14, 25–27, 31). Although controversial, the mild increase in urinary 3-methylhistidine excretion may not be an adequate indicator of the rate of myofibrillar proteolysis (11, 14, 25–27, 31), especially in the individual muscle (vastus lateralis) in which the rate of muscle protein synthesis was determined. It has been suggested that 24-h urinary 3-methylhistidine is excreted in proportion to the quantity of muscle mass (11). In the present study, the small increase in 3-methylhistidine excretion may simply reflect the 1- to 2-kg increase in muscle mass observed in the supervised exercise groups.

Two weeks of weight-lifting exercise have been reported to increase the in vivo rate of vastus lateralis muscle protein synthesis in healthy 60- to 72-yr-old men and women (31). After 16 wk of progressive resistance exercise training, maximum voluntary knee extensor muscle strength was increased 12–22%, and the rate of mixed muscle protein synthesis measured in the fed condition was increased 48% in 64- to 75-yr-old men (32). The current findings extend these observations to an older more physically frail group of women and men. The findings indicate that skeletal muscle proteins maintain the ability to adapt to increased contractile demand even in 76- to 92-yr-old physically frail women and men.

Welle et al. (26) reported that the in vivo rate of vastus lateralis myofibrillar protein synthesis was not increased in 62- to 72-yr-old men and women at the end of a 3-mo progressive resistance exercise training program. The most plausible reason for the discrepancy between the findings of Welle et al. (26) and our findings is that the exercise intensity for the quadriceps muscle group was greater in our study. Our supervised exercise participants performed three sets of two to three different exercises for the quadriceps muscle group 3 days/wk for 3 mo. Welle et al. (26) used only three sets of one exercise for the quadriceps (knee extension), performed 3 days/wk for 3 mo.

Other minor differences in study design and exercise protocol exist between these two reports. They have been clearly described and are unlikely to account for the different findings (26). For example, our participants are fed a small meal at the start of the [13C]leucine infusion, whereas Welle et al. (25–27) determined myofibrillar protein synthesis after a prolonged 12-h fast plus 5-h infusion. In our studies, it is possible that increased circulating concentrations of insulin and substrates might have affected muscle amino acid balance, however, only during the initial few hours of the infusion when insulin was elevated. This represents only a small portion of the 14-h tracer infusion study because plasma insulin concentrations returned to baseline even before the 12- to 14-h time period when the second muscle sample was obtained. Although controversial, our approach is supported by the fact that most in vivo human tracer studies report that insulin reduces the rate of human muscle proteolysis more than it increases the rate of muscle protein synthesis (2, 5, 20). Finally, if we had delayed the determination of the rate of muscle protein synthesis until the day after the final exercise session, we may not have observed an exercise training-induced increase in muscle protein synthesis rate. However, prior evidence suggests that acute exercise-induced increments in muscle protein synthesis rate persist for up to 48 h after exercise (6, 31).

![Fig. 3. Twenty-four hour urinary 3-methylhistidine excretion (µM/mM creatinine) was not significantly greater when final was compared with baseline determinations in any of the groups. In the supervised exercise groups, daily excretion of 3-methylhistidine/creatinine tended to increase (+ 5.4%), whereas no increase (+ 0.8%) was observed in the control group.](image-url)
Fiatarone et al. (8–10) reported that weight-lifting exercise training increased maximum voluntary thigh muscle strength in institutionalized physically frail men and women, but the increase in thigh muscle cross-sectional area was much smaller than the increase in strength. This suggests that the large increase in muscle strength represented primarily a neurological adaptation to weight training, whereas there was a very small metabolic (muscle protein accretion, hypertrophy) adaptation to resistance exercise in the frail elderly. The present findings confirm that vastus lateralis muscle protein synthesis responds favorably to 3 mo of supervised weight-training exercise in 76- to 92-yr-old physically frail women and men. The increase in muscle strength that accompanies the weight-lifting exercise in frail elders is a result of both improved neurological (motor unit) recruitment patterns and an increase in the rate of synthesis of muscle proteins. Maintaining the progressive resistance training program over a longer period of time (≥3 mo) would presumably further increase muscle mass and improve physical function in frail elders.

Based on previous reports, we anticipated that the baseline rates of mixed muscle protein synthesis in these physically frail ≥76-yr-old men and women would be equivalent to or less than the 60- to 75-yr-old men and women previously studied (1, 12, 19, 25–27, 31). We found that the baseline rates of mixed muscle protein synthesis were the same in all three groups but greater than previously observed in 60- to 75-yr-old men and women (31). The most likely explanation is that the home and supervised stretching exercise program that was done by all participants for 3 mo before the baseline determination of vastus lateralis muscle protein synthesis was of sufficient intensity to elevate the rate of mixed protein synthesis in the physically inactive vastus lateralis muscles of frail elders. It is possible that physical frailty and very old age is associated with an increase in the rate of muscle protein synthesis, perhaps as a protective response to prevent against accelerated muscle protein wasting. It is also possible that the mixed muscle proteins isolated from the vastus lateralis muscle samples obtained from 76- to 92-yr-old men and women contained a protein (e.g., sarcoplasmic, mitochondrial, enzymatic) with a very high rate of synthesis. If these or other proteins have synthetic rates that are faster than contractile proteins and they were present in the muscle sample before hydrolysis and quantitation of [13C]leucine abundance, then they will confound the measure of “mixed” muscle protein synthesis rate. It is also possible that the use of plasma α-[13C]KIC (rather than muscle tissue free [13C]leucine) as a surrogate measure for the enrichment of the true in vivo precursor pool for vastus lateralis muscle protein synthesis in physically frail elders was inappropriate (1, 16, 19). However, in the current study, this measure would be confounded because the [13C]leucine infused during the initial study was still present in vastus lateralis muscle proteins during the final study (3 mo later). For this reason and so that we can compare our current findings with previous studies, we have used the plasma α-[13C]KIC abundance to calculate the in vivo rates of vastus lateralis mixed muscle protein synthesis. Also, all of our participants were of similar age; therefore, it would be unlikely that the tissue [13C]leucine abundance would have differed much between the groups (1, 16, 19).

In fact, the muscle tissue [13C]leucine abundance would be predicted to be lower than the plasma α-[13C]KIC abundance, and this would proportionally increase the calculated rate of vastus lateralis mixed muscle protein synthesis. It is likely that a combination of the above factors explains the greater-than-anticipated baseline rate of mixed muscle protein synthesis observed in these frail elders.

Despite the increased rate of mixed muscle protein synthesis induced by the supervised exercise program, the fasting rate of nonoxidative leucine disposal determined in the whole body (a reflection of protein synthesis in all body proteins) and the whole body rate of leucine oxidation and the Ra of leucine into the plasma compartment (a reflection of proteolysis in all body proteins) were not increased after supervised exercise. Welle et al. (26) have reported that the fasting rates of whole body proteolysis and nonoxidative leucine disposal were increased ~10% in 22- to 31-yr-old women and men after 3 mo of resistance training, but they were not increased after training in 62- to 72-yr-old women and men. We have reported no increase in fasting whole body leucine kinetic rates after resistance exercise training in young and older men and women (31). This probably reflects the fact that muscle protein synthesis represents only 20–25% of the whole body protein synthesis rate in young healthy subjects and slightly less in the elderly subjects (1, 12, 16, 17, 19, 31). The contractile muscle protein synthesis and breakdown rates are slow (relative to other body proteins) and comprise a small portion of the average turnover rate of all the body proteins. Our finding also supports the notion that advancing age alters the rate of turnover of specific body proteins differently (1, 5, 16, 19, 20, 31).

We found that the fasting whole body leucine kinetic parameters in physically frail 76- to 92-yr-old men and women (when expressed per kg FFM) were identical to healthy 20- to 30-yr-old and 62- to 74-yr-old adults previously studied (12, 31, 33). This implies that, after an overnight fast, the overall turnover of body proteins is maintained remarkably constant with advancing age but that specific protein pools in the aging body (muscle, liver, visceral organs) undergo substantial changes in protein quantity and quality. This finding is in agreement with Welle et al. (25–27) but contradictory to that of Falak et al. (1) who reported that 52 ± 1- and 77 ± 2-yr-old women and men have lower rates of whole body leucine flux and nonoxidative leucine disposal than 23 ± 1-yr-old men and women. In this report (1), the young men and women had an inordinately high rate of whole body leucine flux (150 ± 7 µmol·kg FFM⁻¹·h⁻¹) and nonoxidative leucine disposal (112 ± 5 µmol·kg FFM⁻¹·h⁻¹) and a low FFM (45 ± 4 kg; 16.5 kg/m²). Previously (12, 31, 33), we studied healthy 23-
to 32-yr-old men and women with higher FFMs (52–59 kg; 17.3–17.7 kg/m²) and reported lower whole body leucine kinetic rates after an overnight fast (129–130 and 96–100 µmol·kg FFM⁻¹·h⁻¹). Taken together, it appears plausible that the discrepancy between whole body protein kinetic rates expressed per kilogram FFM in the current and previous studies may be due to differences in the amount of lean tissue in the young controls used as the comparison group for the older subjects in previous studies (1, 12, 19, 25–27, 31, 33).

In summary, supervised progressive resistance exercise training increased the in vivo rate of vastus lateralis muscle protein synthesis and the maximum voluntary knee extensor muscle torque production capabilities in 76- to 92-yr-old physically frail women and men. Supervised weight-lifting exercise was well tolerated by these older women and men. As in healthy 60- to 73-yr-old men and women, muscle protein synthetic pathways maintain the ability to be activated by the increased contractile activity associated with progressive resistance exercise training.

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