Effect of growth hormone and resistance exercise on muscle growth and strength in older men

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Yarasheski, Kevin E., Jeffrey J. Zachwieja, Jill A. Campbell, and Dennis M. Bier. Effect of growth hormone and resistance exercise on muscle growth and strength in older men. *Am. J. Physiol.* 268 (*Endocrinol. Metab.* 31): E268–E276, 1995.—The purpose of this study was to determine whether growth hormone (GH) administration enhances the muscle protein anabolism associated with heavy-resistance exercise training in older men. Twenty-three healthy, sedentary men (67 ± 1 yr) with low serum insulin-like growth factor I levels followed a 16-wk progressive resistance exercise program (75–90% max strength, 4 days/wk) after random assignment to either a GH (12.5–24 $\mu g \cdot kg^{-1} \cdot day^{-1}$; $n = 8$) or placebo ($n = 15$) group. Fat-free mass (FFM) and total body water increased more in the GH group. Whole body protein synthesis and breakdown rates increased in the GH group after treatment. However, increments in vastus lateralis muscle protein synthesis rate, urinary creatinine excretion, and training-specific isotonic and isokinetic muscle strength were similar in both groups, while 24-h urinary 3-methylhistidine excretion was unchanged after treatment. These observations suggest that resistance exercise training improved muscle strength and anabolism in older men, but these improvements were not enhanced when exercise was combined with daily GH administration. The greater increase in FFM with GH treatment may have been due to an increase in noncontractile protein and fluid retention.

aging; muscle hypertrophy; somatotropin; insulin-like growth factor I; protein-amino acid metabolism; stable isotope tracers

ADVANCING AGE is associated with undesirable decrements in muscle protein mass, strength, and bone mineral density as well as an increase in body fat mass (9). These anthropometric changes result in part from physical inactivity (4, 15, 16, 37, 42), hyposecretion of and insensitivity to anabolic hormones, particularly growth hormone (GH; Ref. 32), insulin-like growth factor I (IGF-I; Ref. 8), testosterone (35), and insulin (20). Improving muscle protein anabolism in the elderly is essential to maintain physical function and independence and to circumvent disability and frailty in this population. Consequently, exercise and replacement hormone therapy have been proposed as protein anabolic interventions for the elderly.

The anabolic properties of GH are currently under investigation. For example, a 6-h intra-arterial infusion of recombinant human GH (rhGH) improved forearm amino acid (phenylalanine) balance in normal volunteers (18), and 7 days of GH administration increased nitrogen retention and the rate of whole body protein synthesis in fed young adults (25). Additionally, nitrogen retention was increased in older men and women after 10 days of GH treatment (28). More prolonged periods of GH administration (6 wk-6 mo) increased fat-free mass (FFM) and reduced body fat in well-trained young men and women (10), increased muscle mass and strength in GH-deficient adults (11), and increased FFM and reduced fat mass in elderly men (32). However, it is not clear whether the GH-induced increase in FFM in the elderly is due to an increase in contractile protein (i.e., skeletal muscle), which results in functional improvements in muscle strength.

The anabolic benefits of heavy-resistance exercise training (i.e., weight lifting) for both young and elderly are well established (4, 15, 16, 27, 37, 42). Consequently, combining anabolic hormone therapy with resistance exercise training in the elderly may reduce body fat mass and increase muscle mass and strength more effectively than resistance exercise or GH therapy alone.

When young previously sedentary or experienced weight lifters supplemented their weight-training programs with daily GH injections, muscle protein synthesis and strength were not enhanced any more than in a group of comparably trained men receiving placebo injections (14, 38, 41). However, these observations do not rule out the possibility that healthy older men with muscle atrophy, weakness, and lower serum GH and IGF-I levels might increase muscle mass and strength more when GH administration and resistance exercise training are combined.

Therefore the purpose of this study was to determine whether daily GH treatment during a 16-wk resistance exercise-training program results in a greater increment in FFM, muscle strength, whole body and skeletal muscle protein synthesis rate, or a greater reduction in fat mass and myofibrillar protein breakdown rate in older men than an identical training program without GH supplementation.

METHODS

Subjects. Twenty-three sedentary, healthy elderly (64–75 yr) men were enrolled in this study, which was approved by the Human Studies Review Board at Washington University School of Medicine. 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, blood chemistry profile (SMA-12), complete blood cell count, and urinalysis and were required to pass an oral glucose tolerance test (NDDG criteria; Ref. 30) and a Bruce treadmill graded exercise test. These tests were used to exclude volunteers with cardiovascular, metabolic, or neuromuscular disease.

Exercise program. All subjects then followed a 16-wk supervised progressive resistance exercise-training program consisting of moderate to high-intensity (75–90% max strength) low-repetition (5–10) exercise, completing four sets of each

exercise per session and four sessions per week. The weight-training exercises involved all major muscle groups, alternated daily between lower (leg press, knee flexion, knee extension) and upper body exercises (biceps curl, shoulder press, deltoid lifts, bench press, latissimus pullover, arm cross) and were done on Nautilus equipment.

Subjects were assigned randomly to the resistance exercise-training plus placebo injection group (Genentech excipient in sterile water; $n = 15$) or to a group ($n = 8$) that trained in an identical manner but received a daily injection of rhGH (Genentech; Table 1). The first two subjects in this group received 24 μg rhGH·kg^{-1}·day^{-1}, but this was reduced to 18 μg rhGH·kg^{-1}·day^{-1} for the next two subjects and further reduced to 12.5 μg rhGH·kg^{-1}·day^{-1} for the remaining four subjects because of the prevalence of side effects (see RESULTS) that resulted in subject attrition at the two higher doses (40). The subcutaneous injections were given in the afternoon (1500–1800 h) 7 days/wk in a double-blind fashion, and their administration was rotated daily among four injection sites (2 arms and 2 thighs). Injections were administered after each exercise session to match the potential anabolic effects of GH with the acute increase in muscle protein synthesis that follows exercise (6).

Dietary control. Before and for the final 6 days of exercise, 10 placebo and 6 GH recipients consumed a 6-day controlled protein diet. On *day 6*, whole body and skeletal muscle protein kinetics were determined during an intravenous infusion of [1-^{13}C]leucine (see below). The meals for the first 3 days of this controlled protein diet contained no meat, and 24-h urinary excretion of creatinine and 3-methylhistidine were measured [interassay coefficient of variation (CV) 3.2 and 3.8%, respectively] for the estimation of muscle mass and myofibrillar protein breakdown (23, 42).

A research dietitian designed the 6-day meal plan to provide 1.5 g protein·kg^{-1}·day^{-1}, 130–163 kJ (31–39 kcal)·kg body wt^{-1}·day^{-1}, 18% of calories from protein, 52% from carbohydrate, and 30% from fat. The meals were prepared in the Research Kitchen and served to each subject at the General Clinical Research Center (GCRC). The subjects were instructed to eat no other food and to eat all the food provided. Any small amount not consumed was weighed, and the daily intake record was corrected. During the training program the subjects returned to their normal eating habits, but their dietary intake was monitored by the research dietitian using 3-day records and adjusted if necessary. Calculated from these records, on average the subjects were consuming 1.5 g protein·kg^{-1}·day^{-1}, 96–171 kJ (23–41 kcal)·kg^{-1}·day^{-1}, 19% of calories from protein, 50% from carbohydrate, and 31% from fat, a composition no different from the controlled diet and no different between the two groups.

Whole body protein turnover and muscle protein synthesis rate. On the evening of the 6th day of the controlled meal plan, before the start of the exercise program (initial) and ~3 h after the final exercise session and injection (final), the subjects (10 placebo and 6 GH recipients) were admitted to the GCRC (1800 h), where a primed (7.58 μmol/kg) constant intravenous infusion (7.58 μmol·kg^{-1}·h^{-1}) of [1-^{13}C]leucine (~99 atom%, Tracer Technologies, Somerville, MA) was used to estimate the rates of whole body protein breakdown, synthesis, and amino acid oxidation using the reciprocal pool approach (1) and to determine the fractional rate of skeletal muscle protein synthesis (29, 39). The remaining subjects (5 placebo and 2 GH) were not willing to consent to this test on the basis of the invasiveness of the muscle biopsy technique or the stringency of the dietary control, urine collections, or hospital admissions. To enroll a sufficient number of subjects, the volunteers who declined to participate in these aspects of the study underwent the same exercise-training program and injection regimen but had only measures of muscle strength, body composition, and serum IGF-I.

The measures of whole body protein kinetics were made *1*) during the overnight (1800–0600 h) fast and *2*) while the subjects were fed during the last 6 h of the leucine infusion (0600–1200 h). To approximate the fed state while minimizing the perturbations in plasma and breath isotopic enrichments during the tracer infusion, the subjects were fed a portion (1/12) of their daily breakfast and lunch meals at 30-min intervals (38). These meals were identical in composition to those consumed during the 6-day meal plan.

In blood samples taken before and at 30-min intervals during the last 2.5 h of the overnight fasted and fed portions of the [^{13}C]leucine infusion, plasma α-ketoisocaproic acid was isolated, chemically derivatized, and analyzed using positive chemical ionization gas chromatography-mass spectrometry (Ref. 33; interassay CV = 1%). The plasma α-[^{13}C]ketoisocaproic acid enrichment (atom% excess, APE) was used to calculate the rate of whole body protein turnover (systemic leucine rate of appearance in μmol·kg FFM^{-1}·h^{-1}; Ref. 1) and was used as the precursor pool enrichment for the calculation of the fractional rate of muscle protein synthesis (29, 36, 39). In addition, exhaled breath samples were collected into 15-ml evacuated tubes (Terumo Medical) before and at the end of the fasted and fed portions of the [^{13}C]leucine infusion. These breath samples were analyzed for $^{13}CO_2$ enrichment (APE) using isotope ratio mass spectrometry (interassay CV < 1%) and in conjunction with 15-min measures of CO_2 production (ml/min) made at the same time points using indirect calorimetry (interassay CV = 9%) to determine the rate of whole body amino acid oxidation.

To assess the in vivo rate of incorporation of leucine into mixed muscle protein, muscle [^{13}C]leucine enrichment was measured using gas chromatography-combustion-isotope ratio mass spectrometry (Ref. 39; interassay CV = 3%) in two muscle samples (~15–30 mg wet wt) removed from the vastus lateralis, one sample removed ~1.5–2 h after the [^{13}C]leucine infusion began and a second sample removed from the contralateral vastus lateralis at the end of the infusion.

Body composition. Before and at 8 and 16 wk of treatment, body density, fat mass, and FFM were determined by hydrodensitometry using methods previously described (5, 38). Before and after 16 wk of treatment, total body water (TBW) was determined using the dilution of deuterium oxide in body fluid. Plasma samples taken before and 2, 3, and 4 h after oral administration (250 mg ^2H_2O/kg) were analyzed for ^2H_2O abundance using proton magnetic resonance spectroscopy (interassay CV = 6.3%), and TBW was calculated as previously described (31).

Muscle strength assessment. Before and at the end of 16 wk of treatment, muscle strength was determined from the maximum amount of weight lifted on each of the Nautilus

Table 1. *Descriptive characteristics*

Measure	Exercise + Placebo	Exercise + GH
n	15	8
Age, yr	66.4 ± 0.4	66.5 ± 1.2
Ht, cm	174 ± 1	179 ± 1
Wt, kg	78.7 ± 1.6	78.3 ± 0.8
%Body fat	29.9 ± 0.9	26.9 ± 1.2
Fat-free mass, kg	55.1 ± 1.0	57.2 ± 0.9
Muscle mass, kg	27.3 ± 0.6	30.1 ± 0.4

Values are means ± SE. Muscle mass was determined by 24-h urinary creatinine excretion in 10 placebo and 5 growth hormone (GH) recipients consuming a 3-day meat-free diet.

exercise devices (1-repetition max) and as the maximum force (N·m) produced by the knee flexor and extensor muscles during maximum voluntary isokinetic (60°/s) and isometric contractions on a Cybex dynamometer (intermeasure CV < 10%).

Circulating hormone levels. Before and at 8 and 16 wk of treatment and 1 mo after treatment ended serum IGF-I and antibodies to rhGH were determined in a blood sample collected after an overnight fast 16 h after the previous injection. The concentration of IGF-I was determined by radioimmunoassay after extraction from its binding proteins (13).

Statistical analysis. To assess between group differences, Δ scores (final − initial) were computed for each measure and compared using the Student's *t*-test. To determine whether changes existed within a group, the initial and final measures were compared using a paired *t*-test. When measures were made initially at 8 and 16 wk, a two-group repeated-measures analysis of variance with Tukey's analysis of individual comparisons was used. Means ± SE are reported.

RESULTS

During the study, GH treatment was discontinued in several subjects because they reported symptoms of carpal tunnel compression, arthralgia, and fluid retention localized to the hands and feet (see Ref. 40). None of the GH recipients developed antibodies to rhGH. Overall, 8 of 13 GH recipients completed 16 wk of treatment, but the GH dose was not the same for all subjects. Two of the first four subjects receiving 24 μg GH·kg^{-1}·day^{-1} reported numbness and a tingling sensation in both hands, especially in the evening, and were removed from the study. The GH dose was reduced to 18 μg GH·kg^{-1}·day^{-1}, where two of the next four recipients reported similar symptoms and were removed from the study. Finally, the GH dose was reduced to 12.5 μg·kg^{-1}·day^{-1}, and one of the final five recipients reported similar symptoms and was removed from the study. Despite the variation in GH dose, the anthropometric, muscle strength, and serum IGF-I responses of the GH recipients were similar, and no relationship between initial IGF-I or change in IGF-I and increments in FFM or muscle strength were observed (Table 2). The initial serum IGF-I levels of the five GH recipients who did not complete the study because they reported symptoms of carpal tunnel compression were 225, 214, 165, 109, and 76 ng/ml. This wide range suggests that there was no relationship between initial IGF-I concentration and the development of side effects.

Table 2. *Individual subject responses to GH treatment*

Subj No.	Initial IGF-I, ng/ml	GH Dose, μg·kg^{-1}·day^{-1}	ΔIGF-I, ng/ml	ΔFFM, kg	ΔStrength
1	107	24	187	5.7	4.4
2	162	24	221	8.0	3.9
3	228	18	196	3.0	5.8
4	26.9	18	139	6.6	4.1
5	110	12.5	183	2.7	6.5
6	83	12.5	103	4.6	3.5
7	66.9	12.5	181	3.3	5.1
8	110	12.5	120	4.2	5.4

Initial insulin-like growth factor-I (IGF-I) vs. Δstrength: $r = 0.22$, $P = 0.41$; ΔIGF-I vs. Δstrength: $r = 0.26$, $P = 0.53$; initial IGF-I vs. Δfat-free mass (FFM): $r = -0.16$, $P = 0.71$; ΔIGF-I vs. ΔFFM: $r = 0.14$, $P = 0.74$. ΔStrength was calculated as average improvement in 1-repetition maximum strength (no. of plates lifted) for all 9 Nautilus exercises.

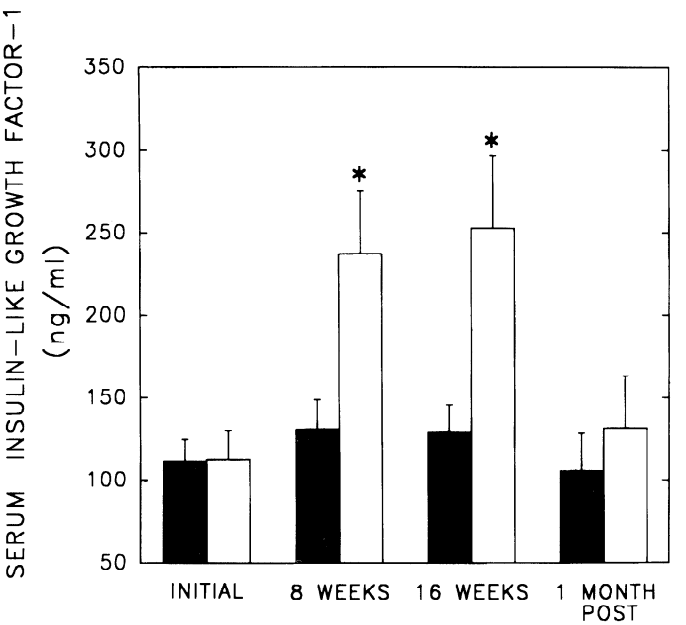

Fig. 1. Serum insulin-like growth factor I (IGF-I) concentrations in elderly men before, during (8 and 16 wk), and 1 mo after a resistance exercise-training program combined with either daily placebo (filled bars) or growth hormone (GH) administration (open bars). Initial serum IGF-I levels in both groups were lower than normal. *$P < 0.05$ vs. placebo group and vs. initial and 1 mo post for GH group.

Serum IGF-I concentrations. The normal adult range for serum IGF-I concentration is 124–450 ng/ml (8), and on average both groups had lower than normal serum IGF-I concentrations (GH group 113 ± 18, placebo 112 ± 14 ng/ml; Fig. 1). Individually, nine subjects in the placebo group and seven in the GH group had initial IGF-I concentrations ≤125 ng/ml. After 8 and 16 wk of resistance exercise training, circulating IGF-I concentrations were not changed in the placebo group, but in the GH group serum IGF-I concentrations were twofold greater than initial, twofold greater than in the placebo group ($P < 0.005$; Fig. 1), and returned to pretreatment levels within 1 mo after GH was discontinued.

Body composition. Initially, the two groups did not differ with respect to age, height, weight, and body composition (Table 1). At the end of 16 wk of treatment, body weight was unchanged in the placebo group as the result of an increase in FFM ($P = 0.003$), which was equivalent to the decrease in fat mass ($P = 0.006$; Table 3). In the GH recipients, the small increment in body weight ($P = 0.06$) was greater than in the placebo group ($P = 0.02$) and was the result of an increase in FFM ($P = 0.001$) greater than the increase in the placebo group ($P = 0.007$) and a decrease in fat mass ($P = 0.02$) not different from the fat loss observed in the placebo group (Table 3). In the GH-treated group, most of the increase in FFM (4.0 kg, 83%) and decrease in fat mass (−1.9 kg, 73%) occurred within the first 8 wk of treatment, and only a small additional increase in FFM

Table 3. *Body composition in older men before and after 16 wk of resistance exercise with and without daily GH treatment*

Measure	Exercise + Placebo			Exercise + GH		
	Initial	Final	Δ	Initial	Final	Δ
Body wt, kg	78.7 ± 1.6	78.7 ± 1.7	0 ± 0.5	78.3 ± 0.8	80.5 ± 1.1	2.2 ± 0.9*
Fat mass, kg	23.6 ± 1.0	21.5 ± 1.0†	−2.1 ± 0.6	21.1 ± 1.0	18.5 ± 1.4†	−2.6 ± 0.8
FFM, kg	55.1 ± 1.0	57.2 ± 1.1‡	2.1 ± 0.6	57.2 ± 0.9	62.0 ± 0.9‡	4.8 ± 0.6*
TBW, liters	39.2 ± 1.1	40.2 ± 0.9	1.0 ± 0.5	41.7 ± 0.9	45.6 ± 1.5†	3.9 ± 1.0*
Muscle mass, kg	27.3 ± 0.6	28.6 ± 1.2	1.3 ± 0.7	30.1 ± 0.4	32.4 ± 0.5	2.3 ± 0.2

Values are means ± SE. Total body water (TBW) was determined by ^2H_2O dilution in 9 placebo and 7 GH recipients. * Increase for GH group greater than ($P \leq 0.02$) increase for placebo group. †$P \leq 0.01$ vs. initial. ‡$P \leq 0.001$ vs. initial.

(0.8 kg, 17%) and decrease in fat mass (−0.7 kg, 27%) occurred during the final 8 wk.

FFM is principally water, and TBW also increased more ($P = 0.02$) in the GH than in the placebo group. The ratio of the change in TBW to the change in FFM after treatment was greater in the GH (0.81) than in the placebo group (0.52), suggesting that the amount of fluid retained in the GH group was out of proportion to the increase in FFM compared with that in the placebo group.

Finally, similar increments in the urinary creatinine excretion estimates of muscle mass were observed in both groups of older men ($P = 0.2$). In addition, it is likely that the estimate of muscle mass in the GH group was artifactually elevated because GH treatment increased TBW and has been reported to increase glomerular filtration rate and renal plasma flow (24). On the basis of inulin and *p*-aminohippurate clearance measures, we estimate that GH/IGF-I may increase creatinine excretion by 20–25% (Miller and Yarasheski, unpublished observation).

Whole body protein kinetics. In the GH group, the final whole body protein kinetic rates are expressed per kilogram of FFM corrected for the increase in TBW (Table 4). Initially, the two groups had similar whole body protein kinetic rates measured in both the fasted and fed experiments. In the placebo-treated group, the final rates of protein turnover, breakdown, oxidation, and synthesis were not different from initial in both the overnight fasted and fed conditions. In the GH group, the fasted rate of whole body protein synthesis was increased ($P < 0.05$), and there was a trend toward an increased rate of whole body protein breakdown ($P = 0.09$) after treatment. In the fed experiments, GH treatment increased whole body protein breakdown and synthesis rates ($P < 0.04$), but the difference between the synthesis rate and the breakdown rate (net anabolism) measured after treatment (42 ± 6 μmol·kg $FFM^{-1}\cdot h^{-1}$) was not different from that measured initially (43 ± 3 μmol·kg $FFM^{-1}\cdot h^{-1}$).

Muscle protein synthesis rate. The fractional rate of vastus lateralis muscle protein synthesis increased from 0.060 ± 0.012%/h before to 0.089 ± 0.009%/h after training in the placebo group ($P < 0.001$) and from 0.051 ± 0.006 to 0.092 ± 0.014%/h in the GH group ($P = 0.04$; Fig. 2). The increment in muscle protein synthesis rate was not different between the two groups (0.03 ± 0.01%/h placebo vs. 0.04 ± 0.02%/h GH).

Urinary 3-methylhistidine excretion. This indirect estimate of myofibrillar protein breakdown was not different between the two groups when measured on 2 days before treatment and was not different from initial when measured after 16 wk of exercise with or without GH (Table 5).

Muscle strength. Initial muscle strength on all nine of the resistance exercises was similar in the two groups of older men (Table 6). Muscle strength (1-repetition max) increased on all nine of the resistance exercises in both groups ($P = 0.01$); however, the strength increment (%increase above initial) on each exercise was not greater in the GH-treated group (Fig. 3). In addition, the average strength increment on all nine exercises was similar for both groups (60 ± 8% placebo vs. 57 ± 7% GH) and similar in magnitude to the strength increments observed in young men (50 ± 5% placebo vs. 54 ± 5% GH) after a 12-wk resistive exercise program using the same measures of strength improvement and identical exercises (Fig. 3). The similar increment in muscle strength for the young and old men occurred despite the fact that the young men were initially much stronger

Table 4. *Fasted and fed whole body amino acid kinetics measured in older men before and at end of 16 wk of exercise with or without GH treatment*

	Kinetic Rates, μmol·kg $FFM^{-1}\cdot h^{-1}$			
	Exercise + Placebo		Exercise + GH	
	Initial	Final	Initial	Final
	Fasted			
Breakdown	140 ± 5	142 ± 5	140 ± 4	153 ± 6
Oxidation	33.2 ± 1.8	31.9 ± 1.8	34.4 ± 3.4	29.9 ± 3.2
Synthesis	106 ± 5	110 ± 4	106 ± 4	123 ± 5*
	Fed			
Intake	114 ± 6	113 ± 6	114 ± 6	113 ± 4
Turnover	178 ± 7	186 ± 5	192 ± 6	210 ± 7*
Breakdown	64.2 ± 7.6	73.7 ± 7.3	78.3 ± 4.4	96.4 ± 6.6*
Oxidation	62.4 ± 5.1	67.5 ± 3.8	70.9 ± 5.4	71.0 ± 6.2
Synthesis	116 ± 4	119 ± 5	121 ± 5	139 ± 7†

Values are means ± SE. Final kinetic rates in GH group are expressed per kg FFM corrected for increase in TBW. Breakdown rates were estimated from plasma leucine appearance rate using reciprocal pool approach and accounting for dietary leucine intake rate during fed experiment, oxidation rates were estimated from the rate of $^{13}CO_2$ production, and synthesis rates were calculated as nonoxidative disposal of leucine (see METHODS and Ref 1). *$P < 0.04$ vs. initial. †$P \leq 0.003$ vs. initial.

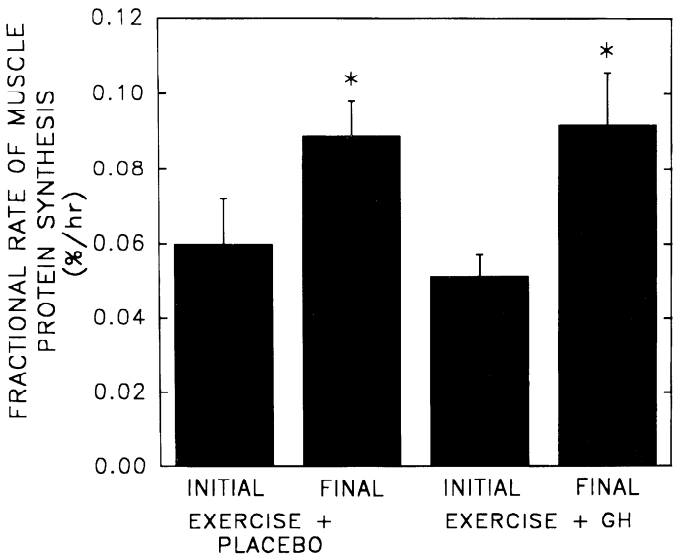

Fig. 2. Fractional rate of vastus lateralis muscle protein synthesis in older men before and after 16 wk of resistive exercise with or without daily GH supplementation. Increase in muscle protein synthesis was similar in both groups. *$P < 0.04$ vs. initial.

($P < 0.05$) than the older men when measured on the same resistance exercise devices (Table 6). In general, when young and older men were compared, there was less difference in initial lower body muscle strength (25–41%) than upper body muscle strength (21–184%; Table 6).

Finally, when upper and lower body strength measures were made at 4-wk intervals during the treatment period, the rate of strength gain was similar in both groups of older men, and the rate had not plateaued at the end of the training program. These observations are illustrated for a representative upper body exercise in Fig. 4.

In accord with the findings from the isotonic measures of maximum voluntary strength made before and after treatment, both groups experienced similar significant increments ($P < 0.01$) in knee extensor and flexor muscle force production on the isokinetic muscle strength test, but only knee extensor muscle force increased ($P < 0.01$) in both groups during isometric contractions (Table 7). In fact, the percentage improvement in knee flexor strength in the placebo group during an isometric contraction was greater than in the GH group ($P = 0.04$).

Table 5. *Urinary 3-methylhistidine excretion measured in older men before and at end of 16 wk of exercise with or without GH treatment*

Treatment	3-Methylhistidine, μmol·mmol creatinine^{-1}·day^{-1}			
	Initial		Final	
	Day 2	*Day 3*	*Day 2*	*Day 3*
Exercise + placebo	15.4 ± 0.9	14.0 ± 0.9	14.6 ± 1.0	14.2 ± 0.6
Exercise + GH	16.1 ± 1.1	13.6 ± 2.3	15.6 ± 1.0	15.1 ± 0.7

Values are means ± SE. 3-Methylhistidine excretion measured in 10 placebo and 5 GH recipients on 2nd and 3rd day of meat-free diet.

Table 6. *Initial maximum voluntary muscle strength in young and elderly men*

Exercise	Maximum No. of 4.5-kg Weights Lifted		
	Exercise + placebo	Exercise + GH	Young men
Leg press	15.1 ± 0.7	14.1 ± 0.8	17.6 ± 0.8
Biceps curl	9.7 ± 0.5	9.7 ± 0.4	12.8 ± 0.4
Deltoid	8.0 ± 0.4	7.1 ± 0.5	9.7 ± 0.4
Latissimus	9.2 ± 0.4	9.5 ± 0.6	11.1 ± 0.4
Bench press	9.6 ± 0.4	9.6 ± 0.4	14.8 ± 0.7
Knee extension	13.0 ± 0.8	14.4 ± 1.0	16.5 ± 1.1
Arm cross	5.9 ± 0.4	6.6 ± 0.4	9.8 ± 0.6
Knee flexion	6.4 ± 0.6	6.6 ± 0.7	9.0 ± 0.6
Shoulder press	4.1 ± 0.4	3.9 ± 0.3	11.1 ± 0.7

Values are means ± SE representing maximum no. of 4.5 kg weights lifted (1-repetition max). Muscle strength for sedentary young men ($n = 14$, Ref. 38) is greater ($P < 0.05$) than for older men on all exercises.

DISCUSSION

These observations suggest that in older men with low serum IGF-I concentrations, muscle atrophy, and weakness, daily GH treatment in combination with 16 wk of resistance exercise training produced no greater increase in muscle protein synthesis, muscle mass, or strength and no greater decrease in body fat or myofibrillar protein breakdown than an identical exercise program without GH supplementation. The GH dose was reduced from 24 to 12.5 μg GH·kg^{-1}·day^{-1} because several subjects developed side effects. However, serum IGF-I concentration, the putative regulator of the anabolic actions of GH, was significantly elevated in all GH recipients. These observations imply that equivalent increments in resistive exercise-induced muscle strength and hypertrophy occur in older men, regardless of the circulating IGF-I concentration, and support the previous reports that elevations in circulating GH and IGF-I

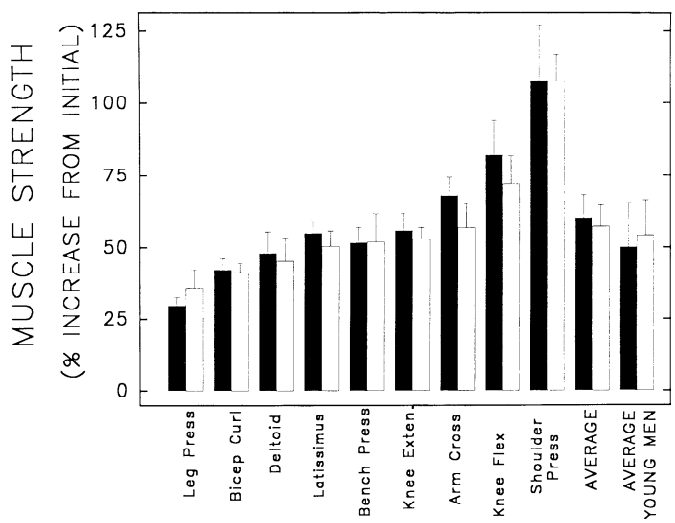

Fig. 3. Muscle strength improvement measured as %increase in 1-repetition maximum determined on all 9 resistance exercises for both placebo (filled bars) and GH-treated (open bars) groups. Also shown is average strength improvement on all 9 exercises for both groups of older men and 2 groups of young men (21–34 yr) treated with GH or placebo and similarly trained (from Ref. 38).

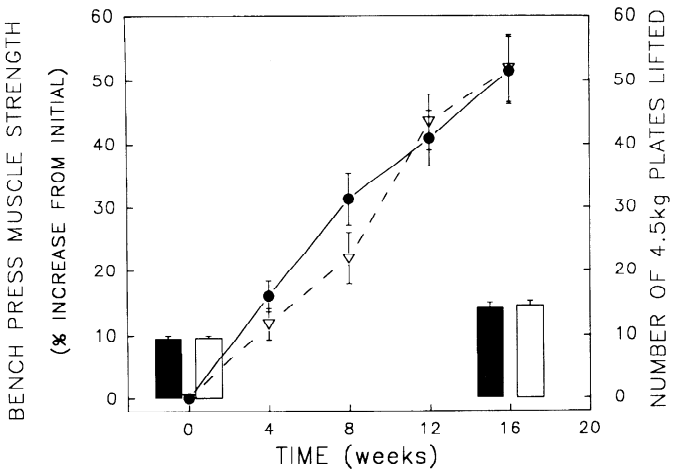

Fig. 4. Rate of increase in upper body muscle strength determined from measures of 1-repetition maximum made every 4 wk on bench-press exercise in both placebo (●) and GH-treated (▽) groups. Bars indicate that both groups had similar absolute muscle strength (no. of plates lifted) before and after treatment.

are not required for the protein anabolic effects of resistive exercise to be achieved (2, 14, 21, 38). The prospect that local autocrine or paracrine release of IGF-I contributes more to exercise-induced muscle growth than circulating IGF-I still exists.

The greater increase in FFM in the GH group as well as the nitrogen retention associated with GH treatment (10, 28) suggests that some additional lean tissue anabolism occurred with GH treatment. However, on the basis of *1*) the similar increments in the rate of muscle protein synthesis, without a decrease in the estimate of myofibrillar protein breakdown, and *2*) the similar increments in muscle strength determined for several muscle groups and across several types of muscle contraction, it appears doubtful that the additional lean tissue accretion which occurred in the GH group was contractile protein.

On the basis of the larger increment in TBW observed in the GH group, it is likely that a portion of the additional lean tissue determined from the measure of body density was a consequence of fluid retention. In addition, the possibility that connective tissue protein accumulated is also implied by the development of carpal tunnel compression in several of these and other GH recipients (38, 40), a possibility that requires further study. The possibility that the rate of albumin synthesis was enhanced and contributed to the increase in nitrogen retention during GH treatment has recently been dismissed (43). Finally, these findings suggest that, even in older men with low serum IGF-I levels, resistance exercise training increases muscle strength and growth near some maximal rate of accumulation and that prolonged daily GH supplementation (in the above doses) does not further enhance muscle growth or strength.

The possibility that prolonged daily GH administration triggered insensitivity to the protein anabolic actions of GH (22, 34) by some interaction among tissue GH and IGF-I receptors and binding proteins and their regulatory hormones (insulin, Ref. 19) and proteases (3, 12) requires further examination. Indirect support for this possibility comes from the current observation that most of the increase in FFM in the GH group occurred within the first 8 wk of treatment, and thereafter no substantial increase in FFM occurred.

These findings do not suggest that GH has no beneficial effects in the elderly, just that when given daily in this dose range in combination with muscle-building exercise no additional increase in muscle strength occurred over that achieved using resistance exercise training without GH supplementation. It is possible that a different GH dose regimen, given at a different time of day without resistance exercise, might result in a greater anabolic response.

The changes in whole body and skeletal muscle protein kinetics that accompany exercise-induced muscle hypertrophy in the elderly have not been clearly described. In older men and women, the fractional rate of vastus lateralis muscle protein synthesis increased markedly (150%) after only 2 wk of resistance exercise, and estimated rates of whole body and myofibrillar protein breakdown were unchanged (42). In the present study, 16 wk of resistance exercise training increased the rate of muscle protein synthesis ~50%. If either of these increments in the rate of muscle protein synthesis are extrapolated over a 16-wk resistance exercise-training program, the increase in muscle mass would greatly exceed any reported exercise-induced increment in

Table 7. *Maximum knee extensor and flexor muscle force production in elderly men*

Measure	Maximum Force, N·m					
	Exercise + placebo			Exercise + GH		
	Initial	Final	%Δ	Initial	Final	%Δ
			Isokinetic			
Knee extensors	145 ± 2	162 ± 4*	12 ± 2	158 ± 3	177 ± 6†	12 ± 3
Knee flexors	101 ± 3	118 ± 4*	17 ± 4‡	122 ± 4	129 ± 5†	6 ± 1
			Isometric			
Knee extensors	159 ± 5	193 ± 6*	22 ± 4	178 ± 7	209 ± 8†	18 ± 5
Knee flexors	103 ± 3	107 ± 3	5 ± 3	118 ± 6	123 ± 5	4 ± 4

Values are means ± SE. Maximum force was determined using a Cybex dynamometer. Isokinetic force measured at 60°/s angular velocity. Isometric force measured at 135° of knee extension. *$P \leq 0.001$ vs. initial. †$P \leq 0.01$ vs. initial. ‡Percent increase for placebo group greater than percent increase for GH group ($P = 0.04$).

muscle mass (27). It is therefore possible that these increments in muscle protein synthesis represent an acute stimulatory effect of the most recent exercise session (6) but still imply that exercise-induced muscle hypertrophy results primarily from increments in the rate of muscle protein synthesis. However, it is still possible that rapid acute increments in myofibrillar protein breakdown occur immediately after exercise and were not detected by the indirect measure of myofibrillar protein breakdown using 24-h urinary 3-methylhistidine excretion.

In support of this, Frontera and co-workers (16) reported a 40% increase in urinary 3-methylhistidine-creatinine excretion in elderly men (60–72 yr) after 12 wk of resistance exercise training (3 days/wk, 3 sets/day, 8 repetitions/set at 80% of one-repetition maximum measured weekly) localized to the extensor and flexor muscles of both knee joints. Whether resistance exercise increases myofibrillar protein breakdown and whether urinary 3-methylhistidine-creatinine excretion is an adequate indicator of this process is still debated in the literature (26). The only obvious differences between our study and the previous study possibly explaining the different 3-methylhistidine-creatinine results are that *1*) we found a small increase in creatinine excretion with resistance training, whereas the earlier study did not, and *2*) we trained all major upper and lower body muscle groups 4 days/wk in an alternating fashion (e.g., upper body on Monday and Thursday, lower body on Tuesday and Friday), which may have given the muscles adequate time to recover between training sessions (72 h), whereas the exercise program in the previous study focused exclusively on training the knee extensor and flexor muscles with 48-h recovery between sessions. In addition, in the earlier study (16), one-repetition maximum measures of muscle strength were made every week. This frequency of high-intensity (80%) resistance exercise combined with weekly measures of one-repetition maximum localized solely to the knee extensor and flexor muscles may have resulted in a greater myofibrillar protein turnover and an increase in 3-methylhistidine excretion.

Despite the exercise-induced increment in the fractional rate of muscle protein synthesis, no changes in whole body protein kinetics were observed in the placebo group. This may be due to the slow synthetic rate of muscle protein (1–3%/day) relative to other body proteins and the small contribution muscle protein turnover makes to whole body protein turnover (25–30%; Refs. 17, 29). In the placebo group, the fasted and fed whole body protein kinetic data suggest that after 16 wk of resistance training whole body protein metabolism occurred at the same rate per unit FFM as before training.

The strength improvements observed for the different types of muscle contraction in these older men are comparable to those achieved by younger men (21–34 yr) during a similar resistance exercise program. This supports the notion that skeletal muscle contractile protein retains the ability to respond to the anabolic stimulus of resistance exercise, even in previously sedentary elderly men (64–75 yr) with low serum IGF-I levels. This does not imply that strength gains in the elderly are solely due to an increase in contractile protein, because the neurological adaptations to resistance exercise have been shown to contribute to the strength improvements observed in older men (4, 16). Our findings from the isokinetic measures of maximum force production and training-specific measures of one-repetition maximum are entirely consistent with this concept.

In addition, the observation that upper body muscle strength was still increasing after 16 wk of exercise (Fig. 4) suggests that the potential exists for further upper body strength gains in these older men beyond those observed after 16 wk of training. The potential for upper body strength improvement may be greater than lower body strength improvement in the elderly, because upper body strength seems to decline more than lower body strength with advancing age (Table 6).

Finally, because of the variability associated with the measures of muscle protein synthesis, urinary creatinine and 3-methylhistidine excretion, and the relatively few number of subjects studied, the possibility of making a type II error is high when only these measures are considered. However, if the increase in muscle mass was greater in the GH-treated group than in the placebo group, then the GH recipients should have had greater improvements in isotonic, isometric, or isokinetic muscle strength. This was clearly not the case. Furthermore, the extensive series of measures of muscle strength improvement has a high degree of power, and the possibility of a type II error when conclusions are based on the strength measures is remote. Therefore, when all measures (strength, muscle protein synthesis, urinary creatinine, and 3-methylhistidine) are considered together, they support the conclusion that GH administration (in doses used in this study) during a 16-wk resistance exercise program did not enhance muscle strength and anabolism in elderly men more than exercise without GH supplementation.

In summary, sedentary elderly men with low serum IGF-I gained the anabolic and functional benefits of 16 wk of resistance exercise training. Their increments in lean tissue and muscle strength are similar to those achieved by previously sedentary young men trained in a similar manner and suggest that, with advancing age, skeletal muscles maintain their ability to respond to muscle-building exercise despite low serum IGF-I concentrations. Additionally, when resistance exercise was combined with daily GH treatment, fat loss was similar and FFM increased more, but this lean tissue did not appear to be contractile protein, because increments in maximum isokinetic, isotonic, and isometric muscle strength and the rate of muscle protein synthesis were not greater than in the placebo group. Therefore the decline in muscle strength associated with aging can be opposed with resistive exercise, but this functional adaptation was not augmented by daily GH supplementation (12.5–24 $\mu g\ GH \cdot kg^{-1} \cdot day^{-1}$).

Brigid Dodson, Barbara Wilhelm, the GCRC nurses, dietitians, and staff provided excellent technical assistance.

Genentech provided rhGH for these studies.

This project was supported by National Institutes of Health Grants AG-00444, AG-05562, AG-00078, RR-00036, and RR-00954.

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Received 22 July 1994; accepted in final form 26 September 1994.

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