Resistance Training Alters Plasma Myostatin but not IGF-1 in Healthy Men

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ABSTRACT

WALKER, K. S., R. KAMBADUR, M. SHARMA, and H. K. SMITH. Resistance Training Alters Plasma Myostatin but not IGF-1 in Healthy Men. Med. Sci. Sports Exerc., Vol. 36, No. 5, pp. 787–793, 2004. Purpose: We determined and compared the magnitude of changes in resting plasma myostatin and IGF-1, muscle strength, and size in response to whole body or local muscle resistance training in healthy men. Methods: Volunteers performed high-intensity resistance exercise of major muscle groups of the whole body (N = 11), or of the elbow flexors only (N = 6), twice per week for 10 wk. Strength was assessed by elbow flexor one-repetition maximum (1-RM) and repetitions at 80% of 1-RM, muscle cross-sectional area by MRI, and plasma IGF-1 by RIA and myostatin by Western analyses, before and after the training program. Results: In subjects of both groups, elbow flexor 1-RM and cross-sectional area increased (P < 0.05) by 30 ± 8% (mean ± SD) and 12 ± 4%, respectively. Individual changes in myostatin ranged from 5.9 to −56.9%, with a mean decrease of 20 ± 16%, whereas IGF-1 did not change from pre- to posttraining. There were no significant differences in any of the responses of the subjects between the two training programs. Conclusion: Myostatin may play a role in exercise-induced increases in muscle size, its circulating levels decreasing with resistance training in healthy men. Exercise of the whole body versus the elbow flexors alone did not provide a supplementary stimulus in altering resting plasma IGF-1 or myostatin, or in increasing muscle strength or size. Thus, by default, growth factor responses local to the muscle may be more important than circulating factors in contributing to muscle hypertrophy with resistance training. Key Words: EXERCISE, MUSCLE HYPERTROPHY, STRENGTH, GROWTH FACTORS

Myostatin and insulin-like growth factor-1 (IGF-1) are both produced in skeletal muscle, available in the circulation, and act in opposite manners as regulators of overload-induced adult muscle hypertrophy. This study examined changes in the resting plasma levels of these growth factors and increases in muscle strength and size resulting from resistance exercise training in healthy adult men.

Myostatin is a negative growth and differentiating factor expressed specifically in developing and mature skeletal muscle. Targeted disruption or mutation of the gene results in a dramatic increase in skeletal muscle mass during development (19). Myostatin is processed in, and then secreted from, the cell. It acts in an autocrine or paracrine manner by reentry through cell surface receptors (13) but also reaches the circulation (6,9).

The concentration of circulating myostatin has been reported as inversely correlated with indices of fat-free mass in a cross-sectional comparison of HIV-infected men with pronounced weight loss, HIV-infected men, and healthy controls (6). Serum myostatin was also inversely correlated with total body muscle mass in relation to height in older versus younger adult males and females (24,27). Elevated circulating levels of myostatin have also been associated with muscle atrophy due to prolonged bed rest and thyroxine administration (28). Such observations indicate that the level of circulating myostatin may have a role in regulating changes in muscle size.

As yet, no study has reported whether changes in circulating myostatin levels might occur concurrent with increases in muscle mass, or specifically, with muscle hypertrophy resulting from resistance exercise training. Because myostatin is present at detectable levels in the circulation of healthy adults (6) and in highly trained athletes with large lean body mass (our unpublished observations), we reasoned that there would be scope for a decrease in myostatin in the circulation, and that such a decrease might have physiological relevance to muscle hypertrophy with resistance

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exercise training. Recent evidence that myostatin mRNA levels are lower after resistance training (22) suggests a decreased transcription and/or stability of the mRNA in the muscle. At the simplest, a reduction in myostatin mRNA is in fitting with the possibility of a reduced translational output, i.e., less myostatin protein in the cell, which in turn might result in a reduced secretion of the processed mature myostatin into the circulation. Less available myostatin to be taken up by muscle would reduce its inhibitory effects on muscle growth, and thereby facilitate hypertrophy of the tissue.

In contrast, IGF-1 is a known positive modulator of muscle growth. It is produced in the liver and in skeletal muscle and has known endocrine and autocrine-paracrine roles (1,4,21). Muscle IGF-1 receptor ligation initiates signaling cascades and subsequent mitogenic and myogenic responses. However, chronic increases in circulating IGF-1 with resistance exercise training and the resultant muscle hypertrophy have been reported in some (2,14), but not all (11,16), studies. The IGF-1 responses appear specific to particulars of the training program, and the age, training status, and initial muscle mass and IGF-1 levels of subjects.

Both IGF-1 and myostatin therefore have potential to exert their effects local to their synthesis as well as acting upon (re)uptake from the circulation (1,13). Both growth factors affect the cell cycle: IGF-1 by promoting, and myostatin by inhibiting myoblast proliferation and differentiation (4,17). The anabolic effects of IGF-1 (e.g., enhanced translational efficiency/protein synthesis) are also well established, whereas additional regulatory roles for myostatin are emerging. Because of their similar yet opposite-acting influence, we considered whether inverse changes in the circulating levels of these factors would occur in concert with muscle hypertrophy due to resistance training.

Secondly, it is known that the amount of muscle mass used and the volume (intensity, sets, and repetitions) of resistance exercise performed affects the extent of acute circulating endocrine and metabolic responses (7,10,12). These responses are believed to contribute to the training-induced gains in strength and size of the exercised muscles.

We postulated that exercise of a larger muscle mass, and hence total volume of resistance exercise, would provide a greater stimulus for circulating factors, particularly liver-derived IGF-1, than that of exercise of a limited muscle mass. Therefore, we compared the results of training the elbow flexor muscle group with that of the same training followed by exercises for other major muscle groups. The results were interpreted as reflecting, respectively, the effects of responses local to the exercised muscle, and of local and systemic whole body responses combined. We thereby attempted to determine the contributions of local and circulating IGF-1 and myostatin to muscle hypertrophy associated with resistance training.

The objectives of this study were therefore to determine and compare the magnitude of changes in resting plasma myostatin and IGF-1, muscle strength as determined by one-repetition maximum (1-RM) and repetitions at 80% of 1-RM, and hypertrophy as determined by increases in muscle cross-sectional area, in response to 10 wk of whole body or single muscle group resistance training in healthy adult men.

We anticipated, firstly, that resting plasma myostatin would be reduced, and IGF-1 increased, and that these changes would be accompanied by gains in muscle size and strength of the single muscle group. Secondly, we expected that exercise training of a larger total muscle mass as compared with the single muscle group alone would result in correspondingly greater changes in myostatin and IGF-1, and increases in strength and cross-sectional area of the single muscle group.

METHODS

Experimental design and approach to the problem. To address our objectives, we used a longitudinal experimental design in which subjects were assessed before and after the completion of one of two different resistance exercise-training programs designed to induce muscle hypertrophy. This enabled, firstly, the evaluation of within-subject changes in the dependent variables with resistance training. The two training programs involved either the training of the elbow flexors only or the whole body, and therefore differed in the amount of muscle mass used and total training volume. These programs were designed to reflect, respectively, the effects of responses local to the exercised muscle, or of local and systemic responses combined. Thus, comparisons of the training responses between the two groups enabled the evaluation of the contributions of local and circulating IGF-1 and myostatin to changes in muscle strength and size with resistance training.

Subjects. Twenty men were recruited to begin this study. All procedures were approved by the University of Auckland Human Subjects Ethics Committee, and written informed consent was obtained from all participants. Subjects were screened for inclusion by gender, age (18–45 yr), and prior experience with resistance training, but not within the previous 6 months. Those included had no orthopaedic limitations or positive responses to the Physical Activity Readiness Questionnaire (Canadian Society for Exercise Physiology, Ottawa, Canada).

Resistance training program. Subjects were randomly allocated to one of two training programs: elbow flexor (N = 8), consisting of three exercises for the elbow flexors, or whole body (N = 12), consisting of the same three exercises for the elbow flexors followed by six exercises of other major muscle groups (Table 1). For both groups, the first elbow flexion exercise performed throughout the program was a unilateral dumbbell curl performed on a seated preacher curl bench. This exercise was also used for muscle strength and endurance testing (described below). Both groups trained twice per week for 10 wk.

Both training groups were prescribed the same number of sets per exercise and repetitions per set as follows: three sets of 10–12 repetitions maximum (RM) during the first 3 wk, four sets of 8–10 RM from weeks 4–6, and four sets of 6–8 RM for the final 4 wk of training. Resistance were selected such that the minimum number of repetitions could be
performed and the last repetition was difficult to complete. When more than the prescribed number of repetitions could be completed, the resistance was increased to bring the number of repetitions back within the RM range. Rest intervals between sets and exercises were 2–3 min.

Muscle strength and muscle endurance. Each subject’s 1-RM and the number of repetitions that could be performed with 80% of the pretraining 1-RM with each arm during unilateral elbow flexion were assessed before (pretraining) and after (posttraining) the training program.

Muscle cross-sectional area (CSA). To obtain cross-sectional images of the upper arms, magnetic resonance imaging (MRI) was performed using a 0.2-T system with a 150-mm-diameter coil and 150 × 150 mm field of view (Neche Ortho 8000, Innervation MRI Ltd., London, UK). Pulse sequences for spin-echo T1-weighted images were performed with a repetition time of 100 ms, an echo time of 5 ms and a signal acquisition, scan matrix and reconstruction matrix of 256 pixels. Subjects were scanned while resting supine with the arm in a horizontal position. Images were acquired at the anatomically defined (ISAK biceps skinfold site) biceps brachii. The CSA of the elbow flexors, elbow extensor muscle group and the circumference of the arm were determined from these images using commercial image analysis software (ImagePro Plus, Media Cybernetics, Silver Spring, MD). The coefficient of variation of repeated measures of elbow flexor CSA from the same image was <2%. Images of both upper arms were obtained one to three days before the first testing session (pretraining) and the same day or the day before the final testing session (posttraining).

Blood sampling. Venous blood samples were taken from each subject before the first testing session, before the first training session (both pretraining) and after the final training session but before the final testing session (posttraining). Subjects were tested at approximately the same time of day on each occasion, and were asked to refrain from eating and drinking alcohol or caffeinated beverages for 4 h beforehand. Microsamples were taken from the sample and analyzed for hematocrit concentration in duplicate by the microcapillary tube centrifugation method. The remaining sample was then centrifuged and the plasma frozen at −80°C until use.

Plasma IGF-1. Total plasma IGF-1 was measured in duplicate with a standard radioimmunoassay kit protocol (Nichols Institute Diagnostics, San Juan Capistrano, CA). The sample IGF-1 concentrations were determined from a curve generated from standards run concurrently. The standard curve was based on five IGF-1 concentrations ranging from 30 to 1200 ng·mL⁻¹, with a reported sensitivity of 6 ng·mL⁻¹. The kit has an intra-assay variation of 3.3% (CV) and an interassay variation of 10.3%.

Plasma myostatin. Differences in plasma myostatin levels were determined by Western blot analyses. Pre- and posttraining plasma samples from each subject were loaded onto precast, 4–12% gradient SDS-polyacrylamide gels (Invitrogen) and the proteins separated by electrophoresis. Protein was electrophoretically transferred to a nitrocellulose blotting membrane and equal loading and uniformity of transfer visually confirmed by Ponceau Red staining. The membranes were then incubated serially with antmyostatin antisera diluted 1:2,000 and horseradish peroxidase-conjugated goat antirabbit IgG secondary antibodies (Dako Corporation, Denmark). The membrane was washed and horseradish peroxidase activity detected using a chemiluminescent reagent (ECL, PerkinElmer Life Sciences) according to the manufacturer’s protocol. Digital images of the developed film were captured, and the optical density of the myostatin-immunoreactive band running at approximately 28 kDa, corrected for background density, was determined using image analysis software (Bio-Rad). The change in myostatin with training was calculated for each subject as the quotient of the optical density of the posttraining sample minus that of the pretraining sample, and that of the pretraining sample.

The primary antibody was raised against purified recombinant bovine myostatin protein as previously described (25). The antibody recognizes human myostatin as there is a high degree of sequence homology between the two species (18). Proteolytic processing of myostatin in the cell produces a latency-associated peptide and a mature peptide, both of which are secreted into the extracellular space and then into plasma. Our polyclonal antibody recognizes both forms of the protein, but the clones are of low titer for the latent form and have a stronger binding for the mature portion.

Statistics. Data are presented as mean ± SD. Paired Student’s t-tests or, for nonparametric data, Wilcoxon signed rank tests were used to determine differences between pre- and posttraining myostatin, IGF-1 and muscle strength, endurance, and CSA. Student’s t-tests were used to
compare the relative (percentage) change from pre- to post-training between the two training groups. Statistical significance was accepted at \( P \leq 0.05 \).

RESULTS

Subjects. Subjects ranged in age from 22 to 38 (31.3 ± 4.9) yr. Their mean height was 182.7 ± 5.9 cm. The subjects' body mass increased by a small margin from pre- to posttraining (91.2 ± 13.6 to 92.1 ± 13.9 kg, \( P < 0.05 \)). Two subjects failed to complete the training program, citing the time commitment as a reason, and one further subject was removed from the study due to noncompliance with the prescribed training. Data from these subjects were not included in the analyses. All other subjects completed the 20 training sessions within the prescribed guidelines.

Muscle strength and endurance. Significant overall \((N = 17)\) increases in elbow flexor 1-RM \((17.7 \pm 3.3\) to \(23.0 \pm 4.3\) kg; \( P < 0.001 \); Fig. 1) and the number of repetitions at \(80\%\) of the pretraining 1-RM \((11 \pm 3\) to \(26 \pm 6\); \( P < 0.001 \)) were found after training. The increase in 1-RM expressed relative to pretraining values was \(30.5 \pm 8.3\%\). The increase in the number of repetitions at \(80\%\) of the pretraining 1-RM expressed relative to pretraining values was highly variable yet large in all subjects \((153 \pm 90\%)\). However, the relative magnitude of the increases in strength did not differ between the elbow flexor and whole body programs \((29.8 \pm 5.0\%\) and \(30.9 \pm 9.8\%\), respectively, \( P = 0.79 \)). Similarly, the relative increases in muscular endurance were not different between the two training programs \((132 \pm 41\%\) and \(164 \pm 108\%\), respectively, \( P = 0.96 \)).

Muscle cross-sectional area. Data are presented from 14 subjects as one subject did not satisfy the safety criteria for the MRI, and in one scan of each of two subjects, the margins of each muscle were not sufficiently clear for quantification of the muscle area. The overall mean elbow flexor CSA increased with training \((1681 \pm 278\) to \(1874 \pm 310\ mm^2, P < 0.001; \) Fig. 2), but the relative increases in CSA were not different between the two training programs \((12.6 \pm 3.2\%\) and \(10.9 \pm 5.2\%,\) respectively \( P = 0.50 \)).

Changes in plasma IGF-1. There was no overall change in resting IGF-1 from pre- to posttraining \((198 \pm 38\) to \(193 \pm 39\ ng\cdot mL^{-1}, P = 0.83)\). The relative changes with training were not different between subjects in the elbow flexor and whole body training programs \((1 \pm 10\%\) and \(-4 \pm 10\%,\) respectively, \( P = 0.35)\).

Changes in plasma myostatin. The relative change in plasma myostatin for all subjects ranged from \(+5.9\) to \(-56.9\%,\) with a mean of \(-20.3 \pm 16.2\%\). The relative changes with training were not different between the two training programs (Fig. 3).

On the Western blots, mature myostatin was detected as a 28-kDa band (Fig. 4) rather than the theoretical 12.5 kDa. This could be due to posttranslational modifications or dimerization of mature myostatin. Based on its reactivity with the antibody, our previous observations using the same

FIGURE 1—Elbow flexor one-repetition maximum in subjects before (open bars) and after (hatched bars) performing elbow flexor only \((N = 6)\) or whole body \((N = 11)\) resistance training for 10 wk. There was a significant effect of training in all subjects combined \((P < 0.001)\) but no significant difference in the changes with training, expressed relative to pretraining values, between the two groups \((P = 0.79)\).

FIGURE 2—Elbow flexor muscle cross-sectional area in subjects before (open bars) and after (hatched bars) performing elbow flexor only or whole body resistance training for 10 wk. There was a significant effect of training in all subjects combined \((P < 0.001)\) but no significant difference in the changes with training, expressed relative to pretraining values, between the two groups \((P = 0.50)\).

FIGURE 3—Change in plasma myostatin relative to pretraining values in subjects performing whole body or elbow flexor resistance training for 10 wk. There was no significant difference between groups \((P = 0.28)\).
antibody and the work of others (6), the band quantified was regarded as the biologically active mature form of myostatin.

Any binding in the circulation of mature myostatin with its latent form or other proteins such as follistatin-related gene (9) would be destroyed during preparation of the plasma samples. The latent form of myostatin migrates as 36–39 kDa and is detected by our antibody in Western blots of bovine muscle (25). However, no such band was detected in the plasma samples of the present study, suggesting that, compared with mature myostatin, relatively little of the latent peptide reached or remained in the circulation. Regardless, our determinations were of the total amount of mature myostatin in the plasma.

DISCUSSION

The observed increases in elbow flexor muscle strength, endurance, and CSA of subjects of both training groups were as expected based on the nature of the exercise performed (10). The extent of the overall increase in elbow flexor 1-RM was within the range of that observed in men after longer periods (12–20 wk) of training (23–46%; 3,15,20), despite training only twice as opposed to 3× wk⁻¹. However, our subjects performed two- to threefold the total number of sets per session using the elbow flexors as compared with the studies of O’Hagan et al. (20) and Cureton et al. (3), and a similar number to that used by McCall et al. (15). The intensity used in the present study was higher during the final 4 wk of training than in the previously cited studies, and in combination with the larger number of sets per session may account for the shorter training timeframe to achieve similar relative gains in strength, despite the lower training frequency.

The mean increase in elbow flexor CSA was also of similar magnitude to the 10% reported in the previously cited study of McCall et al. (15) and less than the 15–16% achieved by the training described above (3,20) for longer duration (16–20 wk). As with the increase in strength, the greater volume per session and intensity of the training in the present program resulted in comparable gains.

That there were no differences in the changes in muscle strength or CSA between the training programs is consistent with the principle of specificity of training as it applies to resistance exercise: the adaptations of a muscle or muscle group are specific to the nature (primarily the intensity and volume) of the exercise performed by the muscle(s) involved.

We had anticipated an increase in resting plasma IGF-1 with resistance training because of the factor’s anabolic properties and influence on muscle hypertrophy (1). Furthermore, modest (~15–20%) increases in IGF-1 after resistance training using multiple sets and exercises, 3× wk⁻¹, for 12–25 wk have been seen in adult men (2) and women (14). However, the presently observed lack of change in the growth factor has also occurred previously, after 10–12 wk of resistance training similarly designed to induce muscle hypertrophy in adult males (11,16). Due to the multiple factors inherent in different resistance training programs, it is difficult to resolve these discrepancies. However, the lack of change in IGF-1 may be attributable to the shorter program duration in comparison with studies in which changes were found (2,14). Although the rest intervals between sets and exercises and the frequency of training in the present study differed from that of prior studies, consistency in these factors in such studies has also led to discrepant results (2,11,14,16).

The observed lack of change in resting plasma IGF-1 with training suggests a minor or only transitory, noncumulative importance of the circulating, predominantly liver-derived, peptide to the muscle hypertrophy seen. That no change in IGF-1 was seen with either training program suggests that the amount of muscle mass exercised was either unimportant, or, if the acute IGF-1 responses did differ between the exercise programs, then the effect thereof was not sufficient to mediate differences in muscle hypertrophy. This lack of IGF-1 response in all subjects and the lack of difference between the two training groups, by default, imply that any effects of IGF-1 in increasing muscle size and strength could be attributed to autocrine-paracrine action of IGF-1 or its variant(s) (5) produced within the exercising muscle. IGF-1 in the circulation has been accepted as a marker of the activity of the growth-hormone-IGF-1 system, yet the difficulty of the interpretation of its relevance when measured on its own is now being demonstrated (2). Clearly, the various components and processes of the IGF-1 system need also be considered in the determination of the influence of circulating IGF-1 on muscle hypertrophy.

This study provides the first evidence that a reduction in circulating myostatin occurs with exercise-induced muscle hypertrophy in healthy humans, an observation consistent with the inhibitory role of this protein in the regulation of muscle growth.

Previously, evidence of a role for circulating myostatin has been based on associations between the amount of muscle mass or muscle size and myostatin levels, or increases in the protein concentration with muscle atrophy, in sedentary or physically compromised individuals. Serum myostatin concentration has been shown to be inversely correlated with total body muscle mass/height² in cross-sectional studies of physically frail elderly, and healthy, middle-aged and young, men and women (24,27). Similarly, a 12% increase in plasma myostatin has been shown with a mean 2.2 kg loss of lean body mass, including appendicular skeletal muscle, after 25-d bed rest with triiodothyronine treatment in adult men (28). The present observations of a
20% mean decrease in plasma myostatin with a 12% mean increase in muscle CSA suggest that the association extends above that during muscle loss to healthy individuals with increases in muscle mass above sedentary control levels. We are unable to explain why the reduction in myostatin did not differ between the two training programs. We can only suggest that there may exist a threshold effect of a minimum of resistance exercise and exercising muscle mass needed to effect this change, and that this was met by the elbow flexor training program.

The relative changes in plasma myostatin within an individual may be more important than the absolute amount of the protein. Circulating myostatin concentration, as determined by radioimmunoassay, in healthy untrained men has a greater than threefold range (7,27,28). However, significantly higher mean myostatin concentrations have been shown in HIV-positive men with muscle wasting than in healthy controls (6), and in healthy older as compared with younger men (27). Similarly, the 12% increase in myostatin coinciding with lean body mass loss during 25 d of bed rest, although statistically significant, was only approximately one-third of the SD of the values among subjects (28). Data from the present study indicate that even a modest, relative decrease in myostatin coincides with only a modest increase in muscle size.

The mechanism by which plasma myostatin decreased cannot be determined from our data. Yet, based on the existing literature, it is most logical that the reduced plasma myostatin reflects a reduced production or processing of the protein. Circulating myostatin concentration, as determined by radioimmunoassay, in healthy untrained men has a greater than threefold range (7,27,28). However, significantly higher mean myostatin concentrations have been shown in HIV-positive men with muscle wasting than in healthy controls (6), and in healthy older as compared with younger men (27). Similarly, the 12% increase in myostatin coinciding with lean body mass loss during 25 d of bed rest, although statistically significant, was only approximately one-third of the SD of the values among subjects (28). Data from the present study indicate that even a modest, relative decrease in myostatin coincides with only a modest increase in muscle size.

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A direct or causal nature of the relationship between myostatin and enhanced adult muscle size has only recently been demonstrated in mice by postnatal inactivation of the gene (8) and the administration of a neutralizing antibody to the protein (26). An association between the expression of myostatin and muscle hypertrophy, that is, increases in muscle size above that during muscle loss to healthy individuals with increases in muscle mass above sedentary control levels. We are unable to explain why the reduction in myostatin did not differ between the two training programs. We can only suggest that there may exist a threshold effect of a minimum of resistance exercise and exercising muscle mass needed to effect this change, and that this was met by the elbow flexor training program.

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REFERENCES


