Effects of resistance training on insulin-like growth factor-I and IGF binding proteins

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ABSTRACT

BORST, S. E., D. V. DE HOYOS, L. GARZARELLA, K. VINCENT, B. H. POLLOCK, D. T. LOWENTHAL, and M. L. POLLOCK. Effects of resistance training on insulin-like growth factor-I and IGF binding proteins. Med. Sci. Sports Exerc., Vol. 33, No. 4, 2001, pp. 648–653. Purpose: Our goal was to determine the effects of resistance training on circulating IGF-I and on two of its major binding proteins, IGFBP-1 and IGFBP-3. Additional goals were to compare the time course of hormonal changes with the time course of strength changes and to determine the effect of training volume on the extent of hormonal changes. Methods: Thirty-one men and women (mean age = 37 ± 7 yr) completed a 25-wk, 3 d·wk-1 program in which they performed single-set resistance training (1-SET, N = 11), multiple-set resistance training (3-SET, N = 11), or no exercise (Control, N = 9). Training did not alter IGFBP-1. Increases in IGF-I were significantly higher in the 3-SET group compared to 1-SET during the first 13 wk of resistance training. Results: Circulating IGF-I increased by approximately 20% in both the 1-SET and 3-SET groups (P = 0.041). No further increases occurred between 13 and 25 wk. In the 3-SET group, IGFBP-3 decreased 20% between 13 and 25 wk (P = 0.008). Conclusions: These findings indicate that increased circulating IGF-I may, at least in part, mediate increases in strength that result from resistance training. Key Words: TRAINING VOLUME, STRENGTH TRAINING, WEIGHT TRAINING

The growth hormone/insulin-like growth factor (GH/IGF) pathway plays an important role in the maintenance of skeletal muscle mass and function in adults (1,29). The GH/IGF pathway may also play a role in exercise-induced strength increases. It is well established that circulating GH is elevated for approximately 60 min after a single bout of resistance exercise (9–11,17–22,25,31,39). IGF-I, the major mediator of GH action, does not increase in the first 2 h after resistance exercise (19). However, such an increase may occur later, because injected GH causes an elevation in IGF-I with a delay of some 16 h (4).

From studies to date, it is not clear whether we would expect GH secretion during exercise to be of sufficient magnitude as to cause a significant long-term elevation of IGF-I. In some studies, the amount of GH secreted during exercise was small compared with nighttime GH secretion (1,20–22,39). In others, the amount of GH secreted during exercise is substantial compared to nighttime secretion (17–22). In the present study, our purpose was to determine the longitudinal relationship between changes in circulating IGF-I and IGF binding proteins (IGFBPs) and the increases in strength that occur as a result of intensive resistance training. The impact of training volume on strength gains remains controversial. Some groups report that multiple-set training produces greater strength gains than does single-set training (2,18,23) and other groups report no difference (14,36). For this reason, we chose also to assess the impact of training volume on IGF-I and IGFBPs.

METHODS

A total of 31 healthy, sedentary men, and women aged 25–50 yr were recruited for this research protocol. Subjects were stratified by sex and initial leg strength into one of three groups: single-set resistance training (1-SET, N = 11), multiple-set resistance training (3-SET, N = 11 per group), or nonexercising (Control, N = 9). The protocol was approved by the University of Florida Human Subjects Committee, and written informed consent was obtained. Potential subjects were excluded if they participated in an organized sports or physical activity more than 1 h·wk-1 or had participated in a resistance training program within the previous year. Subjects were screened by interview and, for those over 40 yr of age, a graded treadmill exercise test was performed. The following exclusion criteria were employed: cardiovascular disease, orthopedic limitations, pregnancy, and dementia.

Measurement of strength. As a measure of combined upper- and lower-body muscular strength, a one-repetition maximum (1-RM) was assessed for both chest press and leg extension at training weeks 0, 13, and 25. A
1-RM was defined as the maximum amount of weight that could be lifted one time through a full range of motion, using good form. Each subject completed a standard, general warm-up before 1-RM testing. For the 1-RM test, each subject began by lifting a light load (<50% of 1-RM). With a rest period of at least 2 min between lifts, the load was increased in stages so that the 1-RM could be determined in three to five attempts. Percent changes occurring with training in the 1-RM for chest press and leg extension were averaged as a measure of the change in overall strength. Testing was performed with dynamic, variable-resistance training machines (MedX Industries, Ocala, FL).

Resistance training protocol. Each subject reported to the University of Florida Center for Exercise Center and trained 3 d·wk⁻¹ for a total of 25 wk. Each session, including testing, lasted 20–90 min and consisted of a 5-min warm-up/stretching period, the training period, and a 5-min cool-down period. For the 1-SET training group performed a circuit of one set of each of the following exercises. The 3-SET training group performed a circuit of 1 set of each exercise, followed by two more circuits: torso flexion, leg extension, leg curl, chest press, seated row, triceps extension, and biceps curl.

Training was performed using the same machines as were used for 1-RM testing. All training sessions were supervised by staff trained in the principles of resistance training. For the initial training session, training loads were set at 70% of 1-RM on chest press and leg extension and 60% of 1-RM on the other exercises. For subsequent sessions, the training loads were adjusted so that subjects performed 8–12 repetitions to muscular failure on each set. When subjects were able to perform 12 or more repetitions for a given exercise, the weight was increased by 1.8–2.7 kg for the next session. When subjects were able to perform 12 or more repetitions for a given exercise, the training load was increased by 1.8–2.7 kg for the next session. Each repetition was performed in a controlled manner with 2 s in the concentric phase and 3 s in the eccentric phase.

Training sessions were supervised and subjects adhered closely to the protocol. Each repetition was performed through the entire range of motion of which the subject was capable. A rest period of 2 min was allowed between sets.

Hormone assays. Serum IGF-I, IGFBP-3, and IGFBP-1 were measured in triplicate as we have previously described (33). Blood was drawn from a subject three times; at 0, 13, and 25 wk of resistance training. For each subject, blood was drawn at the same time of day (±2 h) on all three occasions. At the time of blood draw, subjects had abstained from food, nicotine, and caffeine for at least 4 h and had not engaged in strenuous physical activity within the previous 24 h. IGF-I was measured by radioimmunoassay using [¹²⁵I]-[N-Met]human IGF-I and IGF-I antisera (UB2-495) obtained through the National Institute of Diabetes and Digestive and Kidney Diseases Hormone Program. IGFBPs were removed by acid-ethanol extraction and centrifugation. Bound and free [¹²⁵I]-IGF-I were separated by incubation with goat anti-rabbit gamma globulin and normal rabbit serum, followed by centrifugation. IGFBPs were assessed in whole serum using immunoradiometric assay kits obtained from Diagnostic Systems Laboratories (Webster, TX).

Statistical analysis. Statistical analyses were performed using the general linear model procedure (PROC GLM) of the Statistical Analysis System (32). Hormonal changes were assessed by one-way, repeated measures ANOVA of the serum concentrations at 0, 13, and 25 wk. Strength changes were assessed by one-way ANOVA of % differences occurring between 0 and 13 wk of training and between 0 and 25 wk. Probability values reported are for two-sided comparisons with \( P = 0.05 \) defined as the threshold of significance. Data are reported as means ± SE or means ± SD.

RESULTS

Baseline data. At baseline, the 1-SET and 3-SET resistance training groups did not significantly differ with respect to age, height, weight, circulating IGF-I, IGFBP-3, IGFBP-1, or 1-RM strength. (Table 1).

Muscular strength. Resistance training was associated with increased strength (sum of 1-RM for chest press and leg extension see Fig. 1, \( P = 0.0001 \)). Most of the increase occurred during the first 13 wk of training, with a smaller, nonsignificant increase occurred between 13 and 25 wk (\( P = 0.136 \)). In nonexercising controls, 1-RM strength did not change (257.6 ± 36.9 kg at wk 0 and 263.4 ± 36.6 kg at 13 wk).

<table>
<thead>
<tr>
<th>Baseline Values for Subjects Assigned to 1-SET and 3-SET Resistance Training (RT) Groups.</th>
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<tr>
<td><strong>Control</strong></td>
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<td><strong>Age (yr)</strong></td>
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<td><strong>Height (cm)</strong></td>
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<td><strong>Weight (kg)</strong></td>
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<td><strong>IGF-I (ng·mL⁻¹)</strong></td>
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<td><strong>IGFBP-1 (ng·mL⁻¹)</strong></td>
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Values are mean ± SD. N for Control = 9 (4 men, 5 women), N for 1-SET = 11 (6 men, 5 women), and N for 3-SET = 11 (7 men, 4 women), except N for 1-SET IGF-I = 10. LE, leg extension; CP, chest press.

FIGURE 1—Effect of 3- and 1-SET resistance training on strength. Increases in strength are expressed as the mean percentage increases in the sum of 1-RM leg extension and chest press. * \( P < 0.05 \) vs wk 0. # \( P < 0.05 \) vs 1-SET. Values are means ± SE, \( N = 10–11 \).
wk, \( P = 0.920 \)). Absolute strength increases (expressed as % increase over baseline) were approximately 50% greater in the 3-SET group than in the 1-SET group (\( P = 0.013 \)). 1-RM strength was 83.6% greater in men compared with women (\( P = 0.0001 \)). Strength increases due to resistance training were greater in men when expressed as kg (\( P = 0.0151 \)). However, strength increase were similar between the sexes when expressed as percent increase (\( P = 0.80 \)).

**IGF-I.** Resistance training was associated with a significant increase in circulating IGF-I after 13 wk (see Fig. 2, \( P = 0.041, N = 14 \)). In the 1-SET training group, IGF-I increased 20.5% during the first half of the study, with no further increase during the second half. Similarly, in the 3-SET group, IGF-I increased 18.5% during the first half of the study with no change during the second half. Increases in IGF-I at 13 wk were not significantly different in response to 3-SET versus 1-SET training (\( P = 0.6618, N = 14 \)). IGF-I was not significantly different in response to 25 wk of training versus 13 wk (\( 15.8 \pm 6.9 \) at 0 wk and 22.6 \( \pm 11.4 \) at 25 wk, \( N = 9, P = 0.63 \)). IGF-I was higher in women than in men before training (21.9 \( \pm 6.20 \) ng·mL\(^{-1} \) at 0 wk and 8.10 \( \pm 2.90 \) ng·mL\(^{-1} \) at 25 wk, \( N = 9, P = 0.039 \)).

**DISCUSSION**

We found that 25 wk of resistance training caused a 20% increase in circulating IGF-I. All of that increase occurred during the first 13 wk of training, and increases were similar

**FIGURE 2—Effect of 3- and 1-SET resistance training on circulating IGF-I.** Both 1-SET and 3-SET training significantly elevated IGF-I at 13 wk and at 25 wk \( * P < 0.05 \) vs 0 wk. Values are means \( \pm SE, N = 9–11 \).

**FIGURE 3—Effect of 3- and 1-SET resistance training on circulating IGFBP-3.** IGFBP-3 was significantly reduced in the 3-SET group during the second half of the study. \( * P < 0.05 \). Values are means \( \pm SE, N = 10–11 \).

**FIGURE 4—Effect of 3- and 1-SET resistance training on circulating IGFBP-1.** IGFBP-1 levels were not significantly affected by training. Values are means \( \pm SE, N = 10–11 \).
between the 1-SET and 3-SET training groups. Between 13 and 25 wk, 3-SET training also caused a 20% reduction in IGFBP-3.

We measured IGF-I as a marker for the status of the GH/IGF pathway because of its relatively low diurnal variation. In contrast, GH is secreted in several large pulses occurring mainly during REM sleep. Because of its short half-life, circulating GH levels are quite low during the day. Although daytime GH levels are stable (15,38), daytime IGF-I levels are of greater physiological significance.

We measured the impact of resistance training on IGFBPs because of their potential to alter IGF-I action. IGF-I binds to as many as 10 distinct serum proteins, with IGFBP-3 by far the most abundant (3,28). IGFBP-3 both protects IGF-I from degradation and lowers the free concentration of IGF-I (3,8). The net effect of altered IGFBP-3 concentration has not been assessed in vivo. However, in muscle cell culture it appears that the net effect of all IGFBPs is to reduce IGF-I action, as evidenced by the fact that des(1-3)IGF-I, which does not bind IGFBPs, is a 10-fold more potent mitogen than is native IGF-I (34). We observed a decrease in IGFBP-3 in the 3-SET resistance training group during the second half of training. This may have contributed to strength increases by increasing the concentration of free IGF-I. IGFBP-1 is increased acutely by resistance exercise (7) and may play a role in the exercise-induced reversal of insulin-resistance that occurs in rats (24). However, we found no change in resting levels of IGFBP-1 over the course of training.

There is emerging evidence that the GH/IGF pathway may play an important role in muscle hypertrophy and strength gains resulting from resistance training. One possible mechanism for this role is that training increases GH secretion, leading to increased hepatic production of IGF-I and elevated circulating IGF-I. IGF-I stimulates muscle IGF type I receptors, increasing protein synthesis (3,35). A second possible mechanism is that resistance training increases GH secretion and that GH directly stimulates endogenous muscle production of IGF-I, which causes muscle hypertrophy in an autocrine fashion (11). A third possibility, which cannot be ruled out, is that exercise increases muscle production of IGF-I independently of circulating GH or IGF-I. This concept is supported by the work of De Vol et al. (5) in a rat model. Soleus muscle hypertrophy was induced by increased work load after cutting the tendons to the gastrocnemius and plantaris muscles. Both the hypertrophy and increased muscle content of mRNA for IGF-I occurred in hypophysectomized rats, and thus were independent of circulating GH.

In the present study, most of the increase in 1-RM strength occurred during the first 13 wk of training. We observed a similar time course for training-induced increases in IGF-I. In contrast, the effects of training volume on IGF-I and strength were not similar. 1-SET and 3-SET training caused similar increases in IGF-I, whereas 3-SET training caused approximately 50% greater strength increases. However, the latter finding does not argue against a role for circulating IGF-I in mediating training-induced strength gains. Strength gains may be brought about by a number of other factors as well, including muscle IGF-I and IGFBPs, testosterone, insulin, and neural adaptation (12,13,16). These factors may be affected in different proportion by 1-SET vs 3-SET resistance training.

A number of factors are known to affect the magnitude of GH secretion during and immediately after resistance exercise. Kraemer et al. found have found that GH secretion during resistance exercise to be increased by the following factors: higher training volume (21), the use of a hypertrophy exercise protocol (10 RM, 1-min rest between sets) rather than a strength protocol (5 RM, 3-min rest) (20), and the use of a high-calorie nutritional supplement 2 h before exercise (17). Gotshalk et al. (10) reported that GH secretion was greater in response to multi-set resistance exercise, compared with one-set exercise. In contrast, we found that in chronic resistance training, 1-SET training may be a maximal stimulus for increasing IGF-I. Our subjects kept a record of their food intake and no changes with training were observed in either in the amount or composition of the diet. Djarova et al. (6) found that breath-holding stimulates GH secretion. Although our subjects were taught to exhale during exertion, a Valsalva effect does occur during resistance exercise and may have contributed to GH secretion.

It is not clear to what extent the increase in IGF-I that we observed is caused by GH secreted during exercise as opposed to increased nocturnal secretion of GH. Kraemer et al. (19) reported that IGF-I is not elevated 24 h after a single bout of heavy resistance exercise, despite a marked elevation of GH during and immediately after exercise. If such an increase in IGF-I were to occur, 24 h would have been the appropriate time to look for it, as IGF-I has been shown to be elevated at this time after GH injection (4). We also measured IGF-I in blood samples taken 24 h after last exercise, and so the increase could be due to GH secreted either during exercise or at night.

GH is elevated during resistance exercise and for approximately 60 min after (11,17–22,25,31,39). Peak GH concentrations usually range from 2 to 20 ng·mL⁻¹, although one group reported a GH peak as high as 40 ng·mL⁻¹ (25). Integrated 24-h GH concentrations have been estimated to be 3200 ng × min·mL in people aged 25 yr (17) and 4000 ng × min·mL⁻¹ in women aged 19–40 yr (40). Although the above studies of resistance exercise-induced GH secretion did not integrate serum GH profiles, it can be estimated that GH secreted during a single bout of resistance exercise represents anywhere from 2 to 15% of the total 24-h GH. In the present study, we observed that resistance training caused an approximately 20% increase in circulating IGF-I, and it is not clear whether GH secreted during the training sessions would be expected to be of sufficient magnitude to account for this increase.

In contrast to our finding that resistance training causes an increase in circulating IGF-I, numerous cross-sectional studies have failed to clearly establish a close correlation between circulating IGF-I and either strength or fitness (13,27,30). In some cases, no correlation was found (13,27),
and in others, the correlation was weak (30). However, a problem with these studies is the high interindividual variation in IGF-I, particularly in elderly subjects. The absolute GH decreases dramatically (1,37).

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