Effect of growth hormone and resistance exercise on muscle growth in young men

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Department of Medicine, Washington University School of Medicine, St. Louis, Missouri 63110; and Department of Anatomy and Physiology, University of Dundee, Dundee DD1 4HN, United Kingdom

Yarasheski, Kevin E., Jill A. Campbell, Kenneth Smith, Michael J. Rennie, John O. Holloszzy, and Dennis M. Bier. Effect of growth hormone and resistance exercise on muscle growth in young men. Am. J. Physiol. 262 (Endocrinol. Metab. 25): E256–E267, 1992.—The purpose of this study was to determine whether growth hormone (GH) administration enhances the muscle anabolism associated with heavy-resistance exercise. Sixteen men (21–34 yr) were assigned randomly to a resistance training plus GH group (n = 7) or to a resistance training plus placebo group (n = 9). For 12 wk, both groups trained all major muscle groups in an identical fashion while receiving 40 μg recombinant human GH·kg⁻¹·day⁻¹ or placebo. Fat-free mass (FFM) and total body water increased (P < 0.05) in both groups but more (P < 0.01) in the GH recipients. Whole body protein synthesis rate increased more (P < 0.03), and whole body protein balance was greater (P = 0.01) in the GH-treated group, but quadriceps muscle protein synthesis rate, torso and limb circumferences, and muscle strength did not increase more in the GH-treated group. In the young men studied, resistance exercise with or without GH resulted in similar increases in muscle size, strength, and muscle protein synthesis, indicating that 1) the larger increase in FFM with GH treatment was probably due to an increase in lean tissue other than skeletal muscle and 2) resistance training supplemented with GH did not further enhance muscle anabolism and function.

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

RECENT EVIDENCE SUGGESTS that short-term growth hormone (GH) treatment acutely increases forearm amino acid uptake (12) and whole body protein synthesis (19) in normal adults. Prolonged GH treatment increases fat-free mass (FFM) in athletes (6) and elderly men (31) and increases muscle mass and strength in GH-deficient adults (7). However, the alterations in the rates of whole body protein synthesis and breakdown that produce an increase in FFM in normal adults during prolonged GH treatment are not known. Furthermore, it is not clear whether the increase in FFM is due to an increase in muscle protein.

Despite clinical observations that acromegalics have larger but not stronger muscles (25), GH administration has been used in conjunction with heavy-resistance exercise training in an effort to maximize skeletal muscle protein anabolism and strength. The protein anabolic effects of resistance exercise training are well documented (21). Besides anecdotal reports, no controlled published study has examined whether GH administration potentiates the anabolic effects of resistance exercise training.

Therefore the purpose of this double-blind placebo-controlled study was to examine whether GH supplementation enhances the anabolic response to resistance exercise training by measuring GH and exercise effects on FFM, muscle strength, the rates of whole body protein turnover, and quadriceps muscle protein synthesis.

METHODS

Eighteen healthy young (21–34 mean 27 ± 1 yr) untrained men of normal height (177 ± 2 cm) and weight (73.7 ± 2.3 kg) were recruited for this study, which was approved by the Human Subjects Review Board at Washington University School of Medicine. Informed consent was obtained after the purpose and procedures were described.

On entry, the subjects underwent a medical history, physical examination, and measures of oral glucose tolerance (OGTT), body composition, muscle strength, an overnight GH profile, and serum insulin-like growth factor I (IGF-I) levels as described below. These were followed by a 10-day controlled diet, at the end of which whole body and skeletal muscle protein kinetics were measured as detailed below.

All subjects then underwent a 12-wk heavy-resistance exercise training program consisting of moderate to high-intensity (75–90% maximum strength) low (4–8)-repetition exercise performed for 4 sets/session 5 days/wk. The weight training was done on Nautilus equipment, involved all major muscle groups, and alternated daily between lower and upper body exercises. Subjects were assigned randomly to the resistance exercise training plus placebo injection (Genentech excipient in sterile water) group (n = 9) or to a group (n = 9) that trained in an identical fashion but received an injection of 40 μg recombinant human GH·kg⁻¹·day⁻¹ (Genentech) after each exercise session. The subcutaneous injections were given 5 days/wk in a double-blind fashion, and their administration was rotated daily among four (2 arm and 2 thigh) injection sites. Injections were administered after each exercise session to match the possible anabolic effects of GH with the enhanced muscle protein synthesis that occurs during recovery from exercise (4).

After 6 wk of treatment, the OGTT and serum IGF-I measures were repeated. After 12 wk of treatment, measures of OGTT, body composition, muscle strength, an overnight GH profile, and serum IGF-I levels were repeated. During the final 10 days of exercise and injections (weeks 11–12), the subjects consumed a controlled protein diet, and whole body and skeletal muscle protein kinetics were measured within 16–20 h of the last exercise session and 13–15 h of the last injection. One month after treatment had ended, the OGTT and serum IGF-I measures were repeated.

Overnight GH profile and serum IGF-I levels. Subjects were admitted to the General Clinical Research Center (GCRC) for an overnight GH profile (2100–1300 h), during which venous blood samples were drawn every 30 min and analyzed for serum GH by radioimmunoassay (18). The final GH profile was done immediately after the daily injection. Serum IGF-I was deter-
The percutaneous muscle biopsy technique was used to remove a sample (50-100 mg) of muscle tissue from the vastus lateralis at the beginning and at the end of the [1-13C]leucine infusion, and the in vivo fractional incorporation rate of leucine into protein (i.e., muscle protein synthesis; %/h) was determined using plasma [14C]KIC as the precursor as previously described (26, 35).

**Statistical analysis.** To assess between-group differences, delta scores (final - initial) were computed for each measure and compared using 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 6 and 12 wk and 1 mo posttreatment, 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, two of the GH recipients developed symptoms of carpal tunnel compression and were withdrawn from the study. This occurred after only 16 injections and exercise sessions in 1 subject and after 9 wk of treatment in another. The symptoms subsided after GH administration and resistance training were discontinued, but one case required several weeks to completely resolve. Therefore the results of 16 young men (9 placebo, 7 GH treated) are reported.

**GH, IGF-I, glucose, and insulin levels.** The area under the serum GH curves averaged 38 ± 6 ng·ml⁻¹·16 h⁻¹ in the placebo group before training and was unchanged (39 ± 11 ng·ml⁻¹·16 h⁻¹) after 12 wk of training. Additionally, serum IGF-I values in the placebo group remained constant before, after 6 and 12 wk of training, and 1 mo after training, averaging 0.76 ± 0.08, 0.72 ± 0.10, 0.80 ± 0.10, and 0.79 ± 0.15 U/ml, respectively. In the GH-treated group, the area under the overnight GH curves averaged 52 ± 10 ng·ml⁻¹·16 h⁻¹ before treatment [not significant (NS) vs. placebo] and increased (P< 0.05) to levels six times greater (250 ± 25 ng·ml⁻¹·16 h⁻¹) than in the placebo group after the last injection. Within 2.5 h after a GH injection, serum GH levels peaked at an average 29.0 ± 1.4 ng/ml and remained >10 ng/ml for 10 h after injection. The elevated GH values were physiologically significant because the average serum IGF-I values in the GH-treated group at 6 and 12 wk of training (2.85 ± 0.56 and 2.78 ± 0.67 U/ml, respectively) were greater (P < 0.001) than in the placebo group but returned to initial levels (0.66 ± 0.13 U/ml) 1 mo after treatment was discontinued.

Fasting plasma glucose and insulin levels were not affected by training or GH treatment (Figs. 1 and 2), and oral glucose tolerance remained normal (NDTG criteria) in all subjects. However, after 12 wk of training, the area under the insulin curve for the placebo group was lower (P < 0.02) than the corresponding pretraining curve. In the GH-treated group, on the other hand, the areas under the glucose curves at 6 and 12 wk of training were greater (P < 0.01) than the initial and 1-mo posttraining areas.

**Body composition.** Initially, the two groups did not differ significantly with respect to height (178 ± 2 cm) or weight (76.0 ± 2.3 vs. 70.6 ± 3.7 kg). After 12 wk of treatment, body weight increased in both groups, but the increment in body weight was not significantly different between groups. By hydrodensitometry, FFM increased significantly in both groups, but the increment was greater (P < 0.01) in the GH-treated group (Table 1). Because FFM is principally water, TBW measured by ²H₂O dilution also increased in both groups, but, again, the increment was greater (P < 0.01) in the GH-treated group (Table 1). The ratio of the increase in...
TBW to increase in FFM at the end of treatment was similar (0.9) in both groups, implying that an equal proportion of fluid was retained per kilogram FFM, but the observed ratio was slightly greater than expected (0.7–0.8; see Ref. 20). On the basis of the observed rapid body weight gain (1.90 ± 0.04 kg) during the first 10 GH injections and the subsequent weight loss (−0.61 ± 0.22 kg) over the weekends when injections were not given, it is likely that a portion of the increment in FFM in the GH group was due to fluid retention. After treatment, the fat mass in the GH group tended to be lower (P = 0.056) than before treatment, but this decrement was not greater than the small change in the placebo group.

Chest and upper arm circumference increased (P < 0.05, Table 1) in both groups, and thigh and midthigh circumferences were greater (P < 0.05) than initially in the GH-treated group. Most importantly, the increments in limb and torso circumference in the GH-treated group were no greater than the increments in the placebo group. However, the tendency toward larger (NS) increments in thigh circumference in the GH-treated group may be due to a greater increment in fluid retention or possibly noncontractile protein (e.g., connective tissue, collagen), because the muscle strength increments in the GH-treated group were no greater than in the placebo group (see below).

Muscle strength improvements. In both groups, muscle strength improved on all weight-lifting exercises (P < 0.01, Table 2), and the relative percent improvement on each exercise (placebo range = 26–73% vs. GH = 33–71%) and average improvement for all exercises (placebo = 50 ± 5% vs. GH = 54 ± 5%) were identical for each group. Furthermore, although the concentric force-producing capabilities of the knee extensor and flexor muscles increased in both groups (Table 3; P < 0.05), these increases and the increments in isometric force production were not greater in the GH-treated group.

Whole body protein turnover and fractional muscle protein synthesis rate. At the completion of training, whole body protein synthesis and breakdown rates were significantly elevated (P < 0.05) in the GH-treated group (Table 4) when measured with the [15N]glycine tracer over the final 3 days of the 10-day controlled diet. The whole body protein synthesis rate increased more (P < 0.03) in the GH-treated group (0.5 ± 0.1 g protein·kg·FFM−1·day−1) than in the placebo group (0.1 ± 0.1 g protein·kg·FFM−1·day−1). In addition, body protein balance (calculated as the difference between synthesis and breakdown rates) increased more (P = 0.01) in the GH-treated group (0.26 ± 0.08 g protein·kg·FFM−1·day−1) than in the placebo group (0.01 ± 0.04 g protein·kg·FFM−1·day−1). Finally, total urinary N decreased more (P < 0.05) in the GH-treated group (−2.3 ± 0.9 mmol·kg·FFM−1·day−1) than in the placebo group (−0.2 ± 0.4 mmol·kg·FFM−1·day−1), providing additional support for a greater increase in protein anabolism in the GH-treated group.

Similar results were obtained from the [13C]leucine tracer experiments conducted in the postabsorptive state (Table 4). In the GH-treated group, the leucine oxidation rate decreased significantly (P < 0.05), whereas the nonoxidative leucine disposal rate (estimated protein
Table 1. Body composition and circumferences

<table>
<thead>
<tr>
<th>Exercise + Placebo</th>
<th>Exercise + GH</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Initial</strong></td>
<td><strong>Final</strong></td>
</tr>
<tr>
<td>Body wt, kg</td>
<td>76.0±2.3</td>
</tr>
<tr>
<td>Fat mass, kg</td>
<td>12.6±1.8</td>
</tr>
<tr>
<td>Fat-free mass, kg</td>
<td>63.4±2.1</td>
</tr>
<tr>
<td>Total body water, liters</td>
<td>46.7±1.5</td>
</tr>
<tr>
<td>Chest, cm</td>
<td>97.7±1.9</td>
</tr>
<tr>
<td>Upper arm, cm</td>
<td>34.6±0.9</td>
</tr>
<tr>
<td>Thigh, cm</td>
<td>57.1±1.2</td>
</tr>
<tr>
<td>Midthigh, cm</td>
<td>54.0±1.0</td>
</tr>
</tbody>
</table>

Values are means ± SE; *P < 0.05 vs. initial; †P < 0.01 vs. initial. § Increase for growth hormone (GH)-treated group greater than (P < 0.01) increase for placebo.

Table 2. Muscle strength improvement

<table>
<thead>
<tr>
<th>Exercise</th>
<th>Exercise + Placebo</th>
<th>Exercise + GH</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td><strong>Initial</strong></td>
<td><strong>Final</strong></td>
</tr>
<tr>
<td>Shoulder press</td>
<td>5.3±0.5</td>
<td>53±6</td>
</tr>
<tr>
<td>Bench press</td>
<td>6.1±0.7</td>
<td>43±6</td>
</tr>
<tr>
<td>Deltoids</td>
<td>4.4±0.3</td>
<td>47±7</td>
</tr>
<tr>
<td>Bicep curl</td>
<td>4.4±0.3</td>
<td>36±3</td>
</tr>
<tr>
<td>Latissimus</td>
<td>6.5±0.4</td>
<td>56±5</td>
</tr>
<tr>
<td>Flys</td>
<td>6.5±0.4</td>
<td>73±8</td>
</tr>
<tr>
<td>Knee extension</td>
<td>9.7±0.0</td>
<td>63±10</td>
</tr>
<tr>
<td>Leg press</td>
<td>4.9±0.7</td>
<td>26±4</td>
</tr>
<tr>
<td>Knee flexion</td>
<td>4.1±0.4</td>
<td>47±8</td>
</tr>
<tr>
<td>Average</td>
<td>5.8±0.6</td>
<td>50±4.8</td>
</tr>
</tbody>
</table>

Values are means ± SE. Final strength score greater (P < 0.01) than initial for all exercises in both groups. Delta scores represent absolute increase in no. of 4.5-kg wts lifted. Average and individual delta and % change scores were not different between groups.

Table 3. Maximum knee extensor and flexor muscle force production

<table>
<thead>
<tr>
<th>Exercise</th>
<th>Exercise + Placebo</th>
<th>Exercise + GH</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td><strong>Initial</strong></td>
<td><strong>Final</strong></td>
</tr>
<tr>
<td>Concentric</td>
<td>212±13</td>
<td>245±10†</td>
</tr>
<tr>
<td>Knee extensors</td>
<td>137±11</td>
<td>155±7*</td>
</tr>
<tr>
<td>Knee flexors</td>
<td>220±13</td>
<td>252±13*</td>
</tr>
<tr>
<td>Isometric</td>
<td>131±8</td>
<td>156±8*</td>
</tr>
</tbody>
</table>

Values are means ± SE. Maximum force (N·m) determined using a Cybex dynamometer. Concentric force measured at 60°/s angular velocity. Isometric force measured at 135° of knee extension. *P < 0.05 vs. initial; †P < 0.01 vs. initial.

DISCUSSION

These findings indicate that prolonged GH treatment, in combination with resistance exercise training, produced no greater increase in muscle strength, size, or fractional muscle protein synthesis rate than an identical exercise program without GH treatment. The GH treatment dose used in this study was two to four times the daily adult GH secretion rate (38) and induced significant elevations in serum IGF-I levels. Thus our results indicate that pharmacological doses of GH given to young men with normal GH secretory function do not enhance skeletal muscle protein accretion or muscle function more than resistance training without GH treatment.

The greater increase in FFM and whole body protein synthesis rate observed in the GH-treated group indicates that these individuals accumulated additional lean tissue. However, on the basis of the greater body water accumulation, and no greater increase in fractional muscle protein synthesis rate, muscle strength, or limb and torso circumferences, it appears unlikely that the additional lean tissue was skeletal muscle. This suggests that, with resistance exercise, muscle protein synthesis is stimulated near some limit, and the addition of another anabolic stimulus (GH) does not further enhance muscle protein synthesis, but other proteins (not activated by exercise) can increase their synthesis rates. Therefore the rationale for the use of GH (administered in the dose regimen described here) to amplify exercise-induced muscle growth, and thus enhance muscle force production, appears to have no foundation in fact.

Both amino acid tracers demonstrated that GH treatment enhanced FFM by increasing the rate of whole body protein synthesis more than the rate of whole body protein breakdown and by reducing the rate of leucine oxidation. One possible interpretation of this finding relates to the ability of GH to increase plasma FFA concentration and the rate of FFA oxidation (28), such...
that other energy substrates are displaced (29). The higher plasma glucose levels and the lower leucine oxidation rate support this notion. Additionally, insulin stimulates amino acid incorporation into protein in humans when amino acid availability is sufficient (13), and thus the contribution of small increments in circulating insulin (or possibly IGF-I) in the GH-treated subjects might also have contributed to the whole body anabolic response observed. However, all the interactions of elevated GH, insulin, glucocorticoids, IGF-I levels, and exercise on whole body protein turnover are not understood completely and need to be elucidated.

In the placebo group, no changes in the whole body protein turnover, synthesis, or catabolic rates were observed. Our data demonstrate, therefore, that after adaptation to resistance training lean tissue accumulates at the same relative rates of protein synthesis, oxidation, and catabolism per kilogram FFM as those measured before initiation of training. It is important to note, however, that these measurements were made after 12 wk of resistance training, and it is possible that changes in body and muscle protein turnover occurred at the beginning of the training program or immediately after an exercise session that were different in magnitude and/or direction from those observed.

The similar changes in fractional muscle protein synthesis rate (placebo = 38%, GH = 46%) were somewhat surprising because, in growing rats, GH-induced muscle growth is well established (16), and it has recently been suggested (11) that human skeletal muscle myosin synthesis is enhanced during a 6-h infusion of methionyl human GH. However, increased levels of muscle myosin mRNA do not always indicate increased synthesis of the protein, and the acute effect of a GH infusion during intravenous hypercaloric feeding, which elevates insulin but not IGF-I levels, may differ from the effects of prolonged GH treatment studied here. Our findings are consistent with others (39) who observed no change in muscle fiber diameter after 6 mo of GH treatment in GH-deficient adults. In addition, if the rate of muscle proteolysis decreased in either of the groups, this can also account for an increase in muscle protein mass. But again, since the increments in muscle strength and accretion were similar for the two groups, it does not appear that muscle proteolysis was affected more in either group.

One possible reason for the lack of an additional anabolic effect of GH in the present study may be that prolonged GH administration induces a downregulation of the muscle GH receptor. Indeed, preliminary measurements of serum GH binding protein in several of our GH-treated subjects suggests that levels of this circulating GH receptor fragment were reduced 15% during GH treatment (K. E. Yarasheski and W. H. Daughaday, unpublished observations). Furthermore, it is conceivable that sustained GH treatment led to downregulation of the muscle IGF-I receptor (10) and to consequent tissue resistance to the anabolic effects of this hormone (36). Moreover, IGF-I can stimulate the secretion of several growth factor binding proteins [e.g., IGFBP-(1—3); see Ref. 24]. Some of these binding proteins potentiate, whereas others inhibit the interaction of IGF-I with its receptor (8). The integral sum of the effects of resistance exercise training and GH administration on these interactions is currently unknown.

Indirectly, our findings suggest that the GH-IGF-I axis plays a minor role in exercise-induced muscle hypertrophy in young men. First, exogenous GH treatment that resulted in a fourfold increase in IGF-I did not further enhance the muscle protein synthesis rate. This is somewhat analogous to several previous observations: 1) not all muscle cell types (especially type 2) are enlarged in acromegalics (25), 2) circulating GH is not necessary for compensatory muscle hypertrophy to occur in overloaded muscles of hypophysectomized rats (15), and 3) the muscle contractile strength of GH-treated rats is not greater than normal (2). Second, significant increases in FFM, muscle size, and strength occurred in the placebo group without a significant increase in serum IGF-I, even though exercise-stimulated GH secretion probably occurred. The possibility still exists that local autocrine or paracrine release of IGF-I contributes more to exercise-induced muscle growth than circulating IGF-I (9). Perhaps other factors (e.g., muscle stretch and/or tension) contribute more to stimulating muscle hypertrophy. Taken collectively, these observations indirectly suggest that exercise training strategies (altering exercise intensity, sets, load, and rest intervals) and nutritional supplements (i.e., amino acids) intended to potentiate GH release from the normally functioning pituitary, even if they do result in elevations in circulating GH and IGF-I, may not be effective muscle growth enhancers. However, our findings do not rule out the possibility that GH administration might increase muscle protein synthesis and strength in healthy elderly individuals with muscle atrophy and low serum GH and IGF-I levels.

GH administration did not markedly alter oral CHO tolerance, perhaps due to the fact that initially these lean young men had excellent CHO tolerance. The return of glucose and insulin levels to normal 1 mo after treatment indicates that GH treatment did not result in
lastling insulin resistance. Increases in glucose and insu-
lin levels with GH treatment are consistent with previous
studies (34), but the increments in the present study are
somewhat lower. In agreement with others (5), resistance
training with an increase in FFM reduced the insulin
response to oral glucose, which implies an improvement
in insulin sensitivity. The present findings suggest that
resistance training may provide some protection against
the insulin resistance typically associated with GH ad-
ministration.

In summary, resistance exercise training with or with-
out GH administration increases FFM and muscle size
and strength. The combination of resistance training and
GH administration is no more effective in increasing
muscle size and strength and the rate of muscle protein
synthesis than resistance training without GH. GH ad-
ministration with resistance training results in a greater
synthesis than resistance training without GH. GH ad-
ministration with resistance training results in a greater
increase in the rate of whole body protein synthesis than
resistance training without GH supplementation, but our
findings suggest that the proteins synthesized are not
skeletal muscle proteins. Resistance exercise training
combined with chronic GH administration in an attempt
to increase muscle anabolism and function was not sup-
ported.

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