Two Years of Growth Hormone (GH) Treatment Increase Isometric and Isokinetic Muscle Strength in GH-Deficient Adults*

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ABSTRACT

GH deficiency in adults is associated with reduced muscle mass and muscle strength. The objective of this trial was to follow the effect of 2 yr of GH treatment in GH-deficient adults on muscle performance in relation to a reference population. Knee extensor and flexor strengths for isometric and isokinetic concentric muscle strength were measured using a Kin-Com dynamometer. Hand-grip strength was measured in both hands. The fatigue index was calculated as the percent reduction in peak torque at 50 repeated isokinetic knee extensions. Superimposed, single twitch electrical stimulation was performed. The GH-deficient subjects had lower isometric knee extensor, knee flexor, and hand-grip strength than the reference population. Two years of GH treatment increased and normalized the mean isometric knee extensor and flexor strengths. The concentric knee flexor and extensor strength at an angular velocity of \( \pi \) rad/s increased, as did the concentric knee flexor strength at an angular velocity of \( \sqrt{3} \) rad/s. The increase in muscle strength was more marked in younger patients and in patients with lower initial muscle strength than predicted. Quadriceps endurance decreased, whereas the effect of superimposing single twitches on isometric contraction and hand-grip strength was unaffected by the GH treatment. Two years of GH therapy in GH-deficient adults increased and normalized isokinetic and isometric muscle strength studied in proximal muscle groups. Hand-grip strength and the degree of lack of maximal motor unit activation on voluntary isometric knee extensor force did not change. The dynamic local muscle fatigue index decreased. (J Clin Endocrinol Metab 82: 2877–2884, 1997)

THE SYNDROME of GH deficiency in adults is associated with reduced muscle mass and muscle strength (1). In addition, the discontinuation of GH treatment in young adults with GH deficiency reduced maximal voluntary isometric muscle strength, muscle size, and muscle fiber area (2), thereby indicating the importance of GH in adults for the maintenance of muscle mass and strength. Furthermore, the contractile properties of the muscle in GH-deficient adults could be disrupted in a manner suggesting a higher proportion of fast twitch, type 2 muscle fibers (3).

The administration of GH to GH-deficient adults for 6–18 months has been shown to increase the lean body mass, muscle volume, and maximal voluntary isometric muscle strength (2–6). In hypophysectomized rats, the administration of GH increased and restored the proportion of slow twitch, fatigue-resistant, type 1 muscle fibers (7), but this effect has not been demonstrated in two small studies of GH-deficient adults (8, 9). The contractile properties of the muscle in GH-deficient adults may, however, change in response to GH in a manner that suggests an increase in the proportion of type 1 muscle fibers (3).

The anabolic action of GH is not only restricted to GH deficiency, as GH treatment increased fat-free mass in athletes (10), healthy young untrained men (11), and elderly men (12, 13). Combined with resistance exercise training in young men, GH enhanced the increase in fat-free mass, total body water, and positive whole body protein balance compared with the effect of exercise alone. However, the fractional quadriceps muscle protein synthesis and isometric and concentric knee flexor and knee extensor muscle strength were not enhanced by combining GH treatment and training (11). This indicates that the additional lean tissue in response to GH was not skeletal muscle and that factors other than anabolic ones, stimulated by exercise, may be of more importance to muscle strength in GH-sufficient adults.

Muscle endurance is rarely studied in GH deficiency. Cuneo et al. demonstrated that the shoulder abduction fatigue index, calculated from 10 maximal voluntary shoulder abductions performed within 1 min, was lower than expected in GH-deficient adults and was not affected by 6 months of GH treatment (6). In contrast, general endurance measured by bicycle ergonometry increased in response to GH treatment (14, 15).

Knowledge of the long term effects of GH treatment on muscle function in GH-deficient adults is limited. This information is important, as patients with acromegaly have muscles that appear to be hypertrophied but may be functionally impaired (16), indicating that exposure to overly high levels of GH for a long period of time may have a deleterious effect on muscle function.

The primary objective of this trial was to study the effects


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of long term GH treatment in GH-deficient adults on isometric and isokinetic muscle strength and local muscle endurance. This was achieved by performing repeated measurements of muscle function for the quadriceps, hamstrings, and hand-grip for a period of 2 yr in a large heterogeneous cohort of GH-deficient adults in terms of age and sex. Results from the GH-deficient patients were compared with muscle function in a reference population. The secondary objective of this trial was to explore possible predictive background factors for the treatment response.

**Subjects and Methods**

**Patients**

Fifty-six adults with known pituitary deficiency and with a mean age of 45 yr (range, 19–74 yr) participated (Table 1). The diagnosis of GH deficiency was based on a maximum peak GH response of less than 1.7 \( \mu \text{g/L (5 mIU/L)} \) during insulin-induced hypoglycemia (blood glucose, \( \leq 2.2 \text{nmol/L (1.1 mmol/L)} \)). When required, patients received adequate and stable replacement therapy with glucocorticoids, thyroid hormone, gonadal steroids, and desmopressin. The replacement therapy was kept constant during the entire study period. The patients were not receiving any other medication that could affect muscle performance.

**Reference population**

In 1994 and 1995, 144 men and women, aged 40–79 yr, selected at random from the population census of the city of Göteborg, were invited to participate in a study measuring muscle function. A physical examination was performed to exclude any orthopedic problems, neurological deficits, and hypertension. At least 1 person of each age was tested. The subjects formed 10-yr cohorts; 40–49, 50–59, 60–69, and 70–79 yr for each sex. The numbers of men/women tested were 16/19, 20/15, 18/27, and 15/14 in increasing age.

Comparisons with the reference population were made by applying a predicted value for muscle function to each GH-deficient patient. The predicted value was obtained by calculating a mean value for each muscle test in each 10-yr cohort of men and women in the reference population. Patients younger than 40 yr of age (13 men and 4 women) were given a predicted value from the cohort of healthy controls aged 40–49 yr, assuming no major change in muscle strength in previous adult age periods (17). This assumption might, however, overestimate the muscle strength in relation to normal in the young GH-deficient men and women with GH deficiency treated with GH for 2 yr.

**TABLE 1.** Clinical characteristics of the cohort of 56 men and women with GH deficiency treated with GH for 2 yr

<table>
<thead>
<tr>
<th>Patient characteristics</th>
<th>All</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of patients; men/women</td>
<td>56; 35/21</td>
</tr>
<tr>
<td>Mean age ± SEM (yr (range))</td>
<td>45 ± 2 (19–74)</td>
</tr>
<tr>
<td>Known duration of pituitary deficiency ± SEM (yr (range))</td>
<td>9 ± 1 (1–39)*</td>
</tr>
<tr>
<td>Causes of pituitary deficiency</td>
<td>Nonsecreting pituitary adenoma 28, Prolactinoma 2, Craniopharyngioma 7, Idiopathic 5, Other 14</td>
</tr>
<tr>
<td>Hormone replacement therapy</td>
<td>Cortisone acetate 37, Levothyroxine 47, Sex steroids 46, Isolated GH deficiency 7</td>
</tr>
</tbody>
</table>

* Five patients had childhood-onset GH deficiency.

**Study protocol**

This study is an ongoing, open label treatment trial of the administration of recombinant human GH in GH-deficient adults. This report has analyzed the effects on consecutive patients treated with recombinant human GH for 2 yr.

During the first 4 weeks of treatment, the daily GH dose was 4.8 \( \mu \text{g/kg (0.1 U/kg BW-week)} \), and the target dose thereafter was 12 \( \mu \text{g/kg/day (0.25 U/kg BW-week)} \). The dose was reduced in the event of side-effects and on an individual basis if the serum IGF-I concentration was higher than age- and sex-adjusted, population-based reference values (19). As a result, after 2 yr of treatment, the average daily GH dose was reduced from 0.76 ± 0.04 to 0.62 ± 0.03 mg.

The patients were studied as out-patients. At the start and after 6, 12, and 24 months of GH treatment, physical and laboratory examinations were performed, including measurements of muscle function. Body weight was measured in the morning to the nearest 0.1 kg, and body height was measured barefoot to the nearest 0.01 m. No effort was made to influence the patients’ activity level during the study period.

Informed consent was obtained from all patients. The study was approved by the ethics committee at the University of Göteborg and the Swedish Medical Products Agency (Uppsala, Sweden).

**Measurements of muscle function**

Knee extensor and flexor strengths for isometric contraction at a knee angle of \( \pi/3 \text{ rad (60°)} \) and for isokinetic concentric muscle action at angular velocities of \( \pi/3 \text{ rad/s} \) and \( \pi \text{ rad/s} \) (180°/s) were measured using a Kin-Com dynamometer (Chattecx Co., Chattanooga, TN). The subjects were positioned sitting in the test chair with a hip angle of \( \pi/2 \text{ rad (90°)} \). The knee joint axis was approximated to be the center of the quadriceps muscle and the ankle joint at \( \pi/2 \text{ rad} \). The trunk, hip, and thigh were strapped down to avoid involuntary movements. Warming-up submaximal exercise was performed on a bicycle ergometer for 5 min before the muscle tests. The torque values were recorded with a computerized system using compensation for the weight of the lower leg and the lever arm. After submaximal isometric knee extension for further warm-up and familiarization, three curves were recorded, and the highest peak torque values are reported. The methodological errors in duplicate measurements for isometric muscle strength and isokinetic muscle strength at an angular velocity of \( \pi/3 \text{ rad/s} \) and \( \pi \text{ rad/s} \) were 9%, 8%, and 8%, respectively (20). Right and left hand-grip strengths were measured using an electronic grip force measurement instrument that measures the maximum momentary force and the mean force over a set period of 10 s in Newtons (N). The methodological error between duplicate determinations was 4.4–9.1% (21). Verbal instructions were given to encourage maximal force production.

Local muscle endurance in the quadriceps was measured as the percent reduction (fatigue index) in peak torque between the first and the last 3 knee extensions in a series of 50 maximal voluntary concentric contractions with an angle of velocity of \( \pi \text{ rad/s} \). The subjects were instructed to perform repeated extensions with maximal effort and to resume the starting position passively between each contraction. The methodological error was 1.4% from duplicate determinations (22).

During isometric muscle contractions (the technique was not available for dynamic activity), superimposed single twitch electrical stimulation was given through the percutaneous stimulation of the quadriceps muscle, as described by Rutherford et al. (23) and previously used in our laboratory by Thomeé et al. (24), to estimate the degree of activation of motor units at maximal voluntary contraction. A specially developed electrical stimulator monitored by a PC software program (AB Detektor, Göteborg, Sweden) was used, connected to 5 × 10-cm electrodes placed over the vastus medialis and rectus femoris muscles. Two stimuli, square wave pulses, 0.1 s in duration, were used, with 1 s between each twitch. With the muscles relaxed, the stimuli were first given at increasing voltages up to the maximal stimulation effect, usually obtained at around 150 volts. The maximal level of stimulation was then increased by superimposing twitches on approximately 30%, 50%, 70%, and 100% of maximal voluntary isometric activation for 4 s, with an interval of about 1 min between each level. The subjects were asked to keep to the various activation levels as closely as possibly by matching the effect.
according to the level indicated on the screen. Extrapolations from linear regression analyses were made using the additional torque from the superimposed switches as a dependent variable to calculate any possible additional torque at true maximal isometric contraction (24).

Body composition

Total body potassium was measured by counting the emission of 1.46 MeV γ-radiation from the naturally occurring 40K isotope in a high sensitive 3π whole body counter with a coefficient of variation of 2.2% (25). Body cell mass was calculated on the assumption that there is a constant intracellular potassium/nitrogen ratio of 3 mmol potassium/g nitrogen and a protein content equal to 25% of the body cell mass (26).

Total body nitrogen was measured by in vivo neutron activation. This method is based on the capture of low energy (thermal) neutrons by N nuclei. A Cf source was used to produce the neutrons. The patients were irradiated from below by a 15 cm3 neutron activation field. The angle of π/3 rad increased by 7.4 ± 4.6% and 9.8 ± 1.8%, respectively, during the 2 yr of GH treatment. Concentric knee extensor strength at an angular velocity of π/3 rad/s increased by 6.5 ± 2.0%, and concentric knee-flexor strength at angular velocities of π/3 rad/s and π rad/s increased by 16.2 ± 3.1% and 12.6 ± 3.3%, respectively. Peak hand-grip strength demonstrated a tendency to increase, whereas concentric knee extensor strength at an angular velocity of π/3 rad/s and average hand-grip strength during 10 s did not increase in response to the 2 yr of GH treatment.

Concentric knee extensor strength at an angular velocity of π/3 rad/s and left hand-grip (peak and average over 10 s) tended to decrease transiently from 157, 362, and 310 N, respectively, at baseline to 150 (CI, 146–164), 335 (CI, 293–372), and 288 (CI, 255–321) N, respectively, at 6 months.

At baseline, positive correlations were found between isometric knee flexor strength and lean body mass (r = 0.82; P < 0.001) and serum IGF-I concentration (r = 0.39; P < 0.01), and inverse correlations were found between isometric knee flexor strength and age (r = −0.31; P < 0.05) and the duration of pituitary deficiency (r = −0.37; P < 0.01). In a standard multiple regression analysis using isometric knee flexor strength as a dependent variable and body cell mass, age, serum IGF-I concentration, and duration of pituitary deficiency as independent variables (r = 0.83; P < 0.001), body cell mass (β = 0.83; P < 0.001) eliminated the influence of the other factors. During the 2 yr of GH treatment, an inverse correlation was found between the increment in isometric knee flexor strength and age (r = −0.28; P < 0.05), whereas no significant correlations were found between the increment in isometric knee flexor strength and the change in serum IGF-I concentration (r = 0.23; P = 0.1) or the change in body cell mass (r = 0.04; P = 0.8). Both at baseline and during GH treatment, isometric knee extensor strength demonstrated a similar correlation with age, duration of treatment, and serum IGF-I as isometric knee flexor strength (data not shown). However, in contrast with isometric knee flexor strength, a positive correlation was found between the increment in isometric knee extensor strength and the increment in body cell mass (r = 0.31; P < 0.05).

As estimated from the superimposition of single twitches on isometric contractions in 30 patients, the 2-yr course of GH treatment did not alter the estimated torque at maximal motor unit activation, which was 113–120% of the torque at

### TABLE 2. Measurement of serum IGF-I concentration and body cell mass from total body potassium and total body nitrogen from in vivo neutron activation in 56 adults with GH deficiency receiving GH treatment for 2 yr

<table>
<thead>
<tr>
<th>Variable</th>
<th>Baseline</th>
<th>6 months</th>
<th>12 months</th>
<th>24 months</th>
<th>Mean of the βi (CI)a</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serum IGF-I (µg/L)</td>
<td>109 ± 9</td>
<td>386 ± 21</td>
<td>359 ± 19</td>
<td>322 ± 16</td>
<td>6.576 (5.278–7.874)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Body cell mass (kg)</td>
<td>30.2 ± 1.3</td>
<td>32.0 ± 1.4</td>
<td>31.5 ± 1.4</td>
<td>32.4 ± 1.3</td>
<td>0.090 (0.036–0.144)</td>
<td>0.002</td>
</tr>
<tr>
<td>Total body nitrogen (kg)</td>
<td>1.84 ± 0.07</td>
<td>1.92 ± 0.07</td>
<td>1.99 ± 0.08</td>
<td>2.04 ± 0.08</td>
<td>0.011 (0.007–0.014)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

All values are expressed as the mean ± SEM.

a βi is the estimated coefficient of the slope for the individual regression line reflecting the individual response to treatment. CI represents the 95% confidence interval of the mean response to treatment.
maximal voluntary contraction, representing the absence of maximal muscle activation both before and after GH treatment (Table 3).

**Quadriceps muscle endurance**

At baseline, muscle strength values before and after 50 concentric knee extensions, hand-grip strength (Newton; N), and estimated torque at maximal motor unit activation using the single twitch superimposition (% of maximal voluntary isometric torque) in 56 adults with GH deficiency receiving GH treatment for 2 yr

<table>
<thead>
<tr>
<th>Variable</th>
<th>Baseline</th>
<th>6 months</th>
<th>12 months</th>
<th>24 months</th>
<th>Mean of the βi (CI)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Knee extension</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Isometric</td>
<td>195 ± 10</td>
<td>190 ± 9</td>
<td>199 ± 9</td>
<td>202 ± 9</td>
<td>0.393 (0.036–0.750)</td>
<td>0.035</td>
</tr>
<tr>
<td>Concentric π/3 rad/s</td>
<td>157 ± 8</td>
<td>150 ± 7</td>
<td>153 ± 8</td>
<td>156 ± 7</td>
<td>0.097 (–0.181–0.375)</td>
<td>0.5</td>
</tr>
<tr>
<td>Concentric π rad/s</td>
<td>117 ± 6</td>
<td>118 ± 5</td>
<td>122 ± 6</td>
<td>123 ± 6</td>
<td>0.291 (0.101–0.481)</td>
<td>0.004</td>
</tr>
<tr>
<td>Knee flexion</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Isometric</td>
<td>73 ± 4</td>
<td>76 ± 4</td>
<td>82 ± 4</td>
<td>83 ± 4</td>
<td>0.412 (0.255–0.569)</td>
<td>P &lt; 0.001</td>
</tr>
<tr>
<td>Concentric π/3 rad/s</td>
<td>77 ± 4</td>
<td>79 ± 4</td>
<td>84 ± 4</td>
<td>84 ± 4</td>
<td>0.251 (0.100–0.402)</td>
<td>0.002</td>
</tr>
<tr>
<td>Concentric π rad/s</td>
<td>60 ± 3</td>
<td>61 ± 4</td>
<td>63 ± 3</td>
<td>65 ± 3</td>
<td>0.201 (0.074–0.328)</td>
<td>0.003</td>
</tr>
<tr>
<td>Fatigue index</td>
<td>37 ± 2</td>
<td>39 ± 2</td>
<td>41 ± 2</td>
<td>43 ± 2</td>
<td>0.256 (0.109–0.403)</td>
<td>0.001</td>
</tr>
<tr>
<td>Hand-grip strength, right Peak</td>
<td>375 ± 18</td>
<td>368 ± 19</td>
<td>385 ± 19</td>
<td>391 ± 20</td>
<td>0.656 (–0.038–1.350)</td>
<td>0.07</td>
</tr>
<tr>
<td>Average 10 s</td>
<td>329 ± 18</td>
<td>314 ± 17</td>
<td>329 ± 18</td>
<td>335 ± 18</td>
<td>0.390 (–0.285–1.075)</td>
<td>0.3</td>
</tr>
<tr>
<td>Hand-grip strength, left Peak</td>
<td>362 ± 20</td>
<td>335 ± 19</td>
<td>354 ± 20</td>
<td>366 ± 20</td>
<td>0.552 (–0.002–1.106)</td>
<td>0.09</td>
</tr>
<tr>
<td>Average 10 s</td>
<td>310 ± 19</td>
<td>288 ± 17</td>
<td>298 ± 17</td>
<td>310 ± 17</td>
<td>0.428 (–0.138–0.994)</td>
<td>0.1</td>
</tr>
<tr>
<td>Estimated torque at maximal</td>
<td></td>
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<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>motor unit activation</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Knee extension</td>
<td>113 ± 3</td>
<td>117 ± 4</td>
<td>117 ± 5</td>
<td>120 ± 5</td>
<td>0.123 (–0.237–0.483)</td>
<td>0.5</td>
</tr>
</tbody>
</table>

All values are expressed as the mean ± SEM.

* βi is the estimated coefficient of the slope for the individual regression line reflecting the individual response to treatment. CI represents the 95% confidence interval of the mean response to treatment.

The baseline isometric and isokinetic muscle strength in all measured muscle groups was lower in women than in men (P < 0.001), whereas the fatigue index was similar (data not shown). During treatment, the men responded with a more marked increment in total body nitrogen (P < 0.05), whereas changes in muscle strength, quadriceps endurance, and measurements from the superimposed electrical stimulation were similar in women and men (data not shown).

**Muscle function in comparison with reference population**

Before treatment, isometric muscle strength in both the quadriceps and hamstring muscle groups was lower than that in the reference population (Fig. 1). The concentric muscle strength in the knee extensor and knee flexor at an angular velocity of π/3 rad/s and the concentric muscle strength in the knee flexor at an angular velocity of π rad/s was in the lower normal range, whereas the concentric knee extensor strength at an angular velocity of π rad/s was within the upper normal range (Fig. 2). The right peak hand-grip strength was 83% (CI, 78–87), and the right average 10-s hand-grip strength was 81% (CI, 75–86) of the healthy control values. The corresponding values for the left hand-grip were similar.

After 2 yr of GH treatment, muscle function was within the normal range in all tests performed, except for the hand-grip, where muscle strength was still lower than normal [for the right hand; peak strength, 86% (CI, 80–91) and average 10-s strength, 81% (CI, 76–87), respectively].

There was an inverse correlation between the ratio of observed/predicted muscle strength at baseline and the change in muscle strength in terms of isometric knee extension, isometric knee flexor, concentric knee flexor at an angular velocity of π/3 rad/s, and concentric knee extensor at an angular velocity of π rad/s (r = −0.41, P < 0.01; r = −0.36, P < 0.01; r = −0.40, P < 0.01; and r = −0.44, P < 0.001,
respectively), indicating a more marked increase in muscle strength in patients with lower than predicted muscle function at baseline (Fig. 3).

The fatigue index in the control population was 39% (CI, 37–41). The fatigue index in the GH-deficient adults was in the low normal range, i.e. 37% (CI, 33–41) at baseline. After 2 yr of GH treatment, however, the fatigue index was 43% (CI, 39–47), i.e. in the high normal range.

Discussion

We have shown that 2 yr of GH treatment in GH-deficient adults increased maximal voluntary isometric and isokinetic muscle torque and that this increment was more marked in younger patients and in patients with lower initial muscle strength than predicted for current age and sex. The dynamic local muscle endurance, however, was found to decrease in response to GH treatment.

There is convincing evidence that GH and IGF-I have a regulatory effect on muscle morphology, function, and metabolism (28). The IGF-I content of the skeletal muscle at both the protein and messenger ribonucleic acid levels is dependent on GH as well as on other stimuli (29). In rats, high intensity exercise or GH alone has a minimal effect on the mass of unloaded muscle, whereas a combination of the two produces a strong interactive effect (30), implying that the endocrine action of GH/IGF-I and the paracrine/autocrine action of IGF-I, possibly stimulated by the neuromuscular activity loading, are both important for muscle size and function.

In agreement with previous reports (3, 5, 6, 31, 32), this group of GH-deficient adults had reduced isometric muscle strength compared with a group of healthy controls. It has been suggested that this is an effect of reduced muscle cross-sectional area in GH-deficient adults (32). However, Cuneo et al. also found that the peak torque per muscle area in the quadriceps was reduced (1), suggesting that contractile properties and neural activation are responsible for the reduction in muscle strength. Compared with the reference population, the ability of GH-deficient subjects to perform a maximum
voluntary isokinetic muscle torque was somewhat better than the isometric performance. Furthermore, in the present study, the distal muscles in the arm in particular displayed low muscle strength compared with controls, whereas another study found that the reduction in hand-grip strength and quadriceps strength was proportional (32). These discrepancies between the studies could be an effect of large individual variations in muscle strength and the small cohort of patients in the previous study.

Like other researchers (4–6, 31), we found that GH treatment increased the isometric quadriceps strength. The increment in isometric knee-flexor strength was, however, more homogeneous and more marked. The transient decrease in isometric knee extensor strength demonstrated after 6 months of treatment and the absence of a significant increment in hand-grip strength and quadriceps strength was proportional (32). This could be an effect of the occurrence of arthralgia, peripheral edema, and carpal tunnel affection in the initial phase of GH treatment using the present initial doses of GH (33).

Two previous studies measuring dynamic muscle strength in GH-deficient adults were unable to demonstrate changes in isokinetic muscle strength in the quadriceps and hamstrings after 12 weeks (34) and 6 months (35) of GH treatment, respectively. We studied the isokinetic muscle strength at different speeds of movement in both the quadriceps and hamstring muscles during more prolonged GH treatment. Both concentric knee extensor and knee flexor strengths at an angular velocity of \( \pi \text{ rad/s} \) increased in response to GH treatment, whereas concentric knee extensor muscle strength at an angular velocity of \( \pi/3 \text{ rad/s} \) did not.

Muscle strength can be assumed to be closely associated with the muscle cross-sectional area (36), although there are large individual variations (37), which can probably be explained by factors such as variations in neural activation and differences in contractile properties and force transmission. In our study, the increment in body cell mass, which is highly correlated to the thigh muscle cross-sectional area (6), demonstrated a different pattern of change in response to GH than the increment in muscle strength.

This could be an effect of changes in the intracellular potassium concentration and/or hydration of body cell mass (38) or could be a true disproportional change in muscle mass and strength. Moreover, the more marked increase in total body nitrogen compared with total body potassium suggests that the anabolic effects are not merely skeletal, but are also an effect of increased extracellular proteins. Our results from superimposed single twitch electrical stimulation do not indicate that the level of activation of motor units at voluntary maximal muscle effort was altered during the period of GH treatment. The fairly slight lack of maximal activation at baseline did not change during GH treatment and would, therefore, not contribute to the recorded change in isometric strength. However, we have not studied motor unit activation at maximal voluntary effort in the dynamic activity. In the present study, a linear regression was used. As recently reported (39), however, the use of a shallow hyperbolic curve for the relationship between the extra force generated by the superimposed twitch and the voluntary muscle force increases the accuracy of the estimation of maximal quadriceps muscle strength, but only slightly. However, any such change in the estimation would not alter the conclusion of no effect of GH treatment on maximal muscle activation.

We have previously demonstrated large individual variations in the response to GH in terms of changes in body composition (40). In the same way as in that study, the young responded best. Those patients who obtained the best anabolic effect demonstrated the most pronounced increase in muscle strength and the smallest reduction in local muscle endurance. Furthermore, the most pronounced effect was obtained in patients with lower baseline muscle strength than that predicted for current age and sex, whereas the effect obtained in subjects with normal baseline muscle strength was less marked. This observation is of importance because the doses used in this cohort of GH-deficient patients did not result in any short term supraphysiological effect on muscle strength. This indicates that GH administration for a short
period in healthy adults with normal muscle strength will not result in any further gain in muscle strength (11, 12, 41, 42).

Although muscle mass and peak voluntary muscle torque increased in response to GH treatment, the ability to sustain muscle strength during repeated contraction of the quadriceps muscle decreased. It thus appears that the increase in maximal muscle force production during GH treatment does not result in the maintenance of the capacity to produce force at repeated contractions. This is probably best explained by local changes in the muscle (22, 43) during the 2 yr of GH treatment. A lack of parallel metabolic adaptation in the muscle in terms of muscle glucose storage and utilization, oxidative enzyme activity, and capillarization are all conceivable explanations. If a change in fiber composition had occurred in the direction of a larger proportion of slow twitch, fatigue-resistant, type I fibers, as has previously been suggested (3, 7), this might have resulted in improved local muscle endurance (22). The adult patient with previously untreated GH deficiency has adapted to a sedentary lifestyle (44) that might contribute to their low muscle mass and muscle strength. The daily activity was not significantly affected by GH treatment in a 6-month placebo-controlled trial (14), although a self-perceived improvement in energy and general well-being was obtained in response to treatment (45). Reduced local muscle endurance in response to GH treatment contrasts with the increased exercise performance noted in response to GH treatment (15), thereby suggesting that this effect might be the result of increased cardiac performance. The optimal regimen for increasing muscle function in the GH-deficient adult would be GH replacement in combination with exercise, including endurance training, which would improve neural activation and also activate the autocrine/paracrine action of IGF-I in the muscle (30, 46), which might be of more importance than the circulating levels of serum IGF-I for the metabolic adaptation of the muscle.

Two years of GH treatment increased both isometric and isokinetic muscle strength studied in proximal muscle groups in GH-deficient adults. The effect first appeared after 12–24 months of treatment, but was sustained over time. The discordance between the increment in body cell mass and muscle strength and the deterioration in quadriceps endurance suggests that factors other than merely anabolic ones are involved in the mechanisms through which GH acts on muscle function. These factors are still unclear, but metabolic studies of the effect of GH on muscle may elucidate the underlying mechanisms. Furthermore, the long term results in terms of the reaction of muscle function in response to GH are of importance in view of the uncertainty relating to GH doses in GH-deficient adults and the known myopathy observed in long-standing acromegaly.

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References

5. Rutherford OM, Beshyah SA, Johnston DG. 1994 Quadriceps strength before and after growth hormone replacement in hypopituitary adults: relationship to changes in lean body mass and IGF-I. Endocrinol Metab. 7:41–47.
Nominations for the Eli Lilly HypoCCS Award

The Eli Lilly HypoCCS Award will be given annually in recognition of clinical and/or basic scientific achievements in the field of hypothalamus/pituitary diseases and their impact on peripheral receptive tissues or organs.

The award consists of a certificate and a financial reward of U.S. $20,000 and will be presented on the occasion of the next annual HypoCCS Symposium in Sevilla, Spain on May 8–9, 1998. The recipient will be invited to give a lecture and submit a manuscript that will be published in the proceedings of the HypoCCS Symposium.

Nominations by individuals or groups should be in the form of:

1. A covering statement of no more than 1000 words, in English, defining the way in which the candidate has significantly contributed during the last 5 years to the advancement of knowledge in the field of the hypothalamus/pituitary axis (biochemistry, molecular biology, morphology, physiology, pathophysiology, diseases, etc.) and related end-tissues or end-organs.

2. A curriculum vitae of the candidate, including bibliography.

3. Nominees should be less than 45 years of age as of December 31, 1997.

4. Self-nominations will not be accepted.

Nominations should be sent to: Pierre C. Sizonenko, Chairman Award Jury, Division of Biology of Growth and Reproduction, Department of Pediatrics, HUG, 1211 Geneva 14, Switzerland. Fax: +4122-382-4588; E-mail: pisi@diogenes.hcuge.ch.

Nominations must be received or postmarked by November 15, 1997.