Physical and psychological capabilities during substitution therapy with recombinant growth hormone in adults with growth hormone deficiency

Marie Degerblad¹, Ove Almkvist², Roland Grunditz¹, Kerstin Hall¹, Lennart Kaijser³, Evert Knutsson¹, Hans Ringertz⁵ and Marja Thorén¹

¹ Departments of Endocrinology¹, Clinical Physiology¹, Neurophysiology¹ and Radiology³, Karolinska Hospital, and Department of Psychiatry², S:t Görans Hospital, Stockholm, Sweden

Abstract. In a double-blind cross-over study with recombinant methionyl growth hormone (GH) and placebo during 12 weeks, the effect of GH substitution therapy (0.5-0.6 IU · kg⁻¹ · week⁻¹) on physical performance, muscle strength, bone mineral density, and mood and cognitive functions was investigated in 6 GH-deficient adults. During GH substitution serum concentrations of insulin-like growth factor-I and procollagen-III peptide increased in all 6 patients, whereas concentrations of serum urea decreased. Five of the patients identified the GH period and reported improved well-being with increased mental alertness and vitality and improved physical capacity and muscle strength. There was, however, no change of the isokinetic muscle strength during GH substitution therapy, and the working capacity on the bicycle ergometer was just slightly improved in some patients. The bone mineral density was low and unchanged in all patients. Mood and cognitive functions did not change during GH therapy. A reversible fluid retention was observed in one patient during the GH period. In conclusion, short-term GH substitution therapy to GH-deficient adults induced a subjective improvement of general well-being. Longer treatment periods will be necessary to establish the effect on physical capacity, muscle strength, bone mineral density, and mood and cognitive functions.

In patients with hypopituitarism, GH is only given during the period of longitudinal growth. Patients with panhypopituitarism acquired at adult age, for example after pituitary surgery, who receive replacement therapy with cortisone, thyroxine and gonadal steroids, often do not appear to be completely restored to previous health and display low vitality, muscle weakness and fatigue. In adults with pituitary insufficiency since childhood, these symptoms are even more pronounced and in addition they often report problems associated with hypoglycemia. The latter group of patients often has received GH substitution therapy during their growth period, but owing to earlier limited supplies of the hormone and sometimes late diagnosis, they may have been without substitution therapy for long periods during childhood and adolescence.

Furthermore, the anabolic actions of GH seem to be of importance for the preservation of the skeleton and there may be a risk that many years of GH deficiency will result in osteoporosis. Low bone mineral density has been observed in panhypopituitarism both in children (3,4) and in adults (Grunditz et al. 1990, unpublished observations).

The development of recombinant DNA technology has now allowed production of sufficient quantities of GH and treatment of adult GH deficient patients has become possible. This means that clinical studies can now be performed on the effect of GH substitution therapy to adults with hypopituitarism. In a pilot study by Almkvist et al. (5), sub-
stitution therapy during one month produced some improvement of certain cognitive functions during treatment. Westphal et al. (6) reported improved physical capacity, decreased subcutaneous fat and increased comfort during GH substitution therapy. In a recent study, Jørgensen et al. (7) found a significant increase in exercise capacity and a small increase in isometric muscle strength. Salomon et al. (8) found fat mass decreased and lean body mass and basal metabolic rate increased after six months replacement therapy.

The aim of the present study was to evaluate the effects of growth hormone substitution therapy in adults with special emphasis on physical working capacity, muscle strength, bone mineral density, and cognitive functions and mood.

Patients and Methods

Six patients with hypopituitarism, 3 women and 3 men, aged 20-38 years, participated in the study (Table 1). They all had their regular medical check-ups at the Department of Endocrinology and were asked to participate in the study because of symptoms that could be attributed to GH-deficiency. The symptoms were general fatigue, low physical capacity and endurance, and poor muscle strength. One patient also had hypoglycemic attacks. They were all socially well adjusted and were able to carry out normal daily activities. All had at least average intellectual capacity according to two standardized tests concerning reasoning and vocabulary (9). Five of the patients were working full time. One patient had not been working since one year owing to back pain and muscular fatigue.

Five of the patients had panhypopituitarism of different origin acquired in childhood. They received concomitant substitution therapy with cortisol acetate, thyroxine, and testosterone or estrogen/progesterone. One of them in addition received substitution therapy with desmopressin because of diabetes insipidus. These five patients had earlier received GH substitution therapy during some periods, but in no case during the previous five years. The sixth patient had an isolated partial GH deficiency after stereotactic irradiation to an ACTH-producing pituitary adenoma five years earlier. Pituitary function had been preserved until 18 months after treatment, when signs of GH deficiency occurred and a subnormal serum IGF-I level (76 µg/l) was found (10,11). He had never received GH substitution therapy.

The height was 146-159 cm in the 3 women and 161-169 cm in the 3 men. Body mass index (BMI) was 17.7-22.9 (mean 19.4) kg/m².

Informed consent was obtained from each subject and the investigation was approved by the Ethical Committee at Karolinska Hospital and the Swedish Board of Health and Welfare.

Confirmation of GH deficiency

Before entry into the study, the GH deficiency was confirmed in each subject. In all 6 patients, arginine-insulin tests (arginine-HCl 10%, 0.5 g/kg; insulin 0.05 IU/kg) were performed. With adequate hypoglycemia, 4 patients showed no increase in GH concentration. Two patients (No. 3 and 6) showed a small GH response (0.6 and 3.4 µg/l, respectively) with the same magnitude as their spontaneous GH peaks. In 5 of the patients, plasma samples for 12-h GH profiles were collected by a withdrawal pump at 20-min intervals during the night 19.00-07.00 h (12). In 3 of the 5 patients, the GH concentration was below 0.2 µg/l in all 36 samples collected. The 2 patients that showed GH response in the insulin-arginine test had

<table>
<thead>
<tr>
<th>Patient No.</th>
<th>Sex</th>
<th>Age (years)</th>
<th>Height (cm)</th>
<th>Weight (kg)</th>
<th>Etiology of GH deficiency</th>
<th>Previous GH treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>f</td>
<td>36</td>
<td>145.5</td>
<td>42</td>
<td>Idiopathic</td>
<td>1963-1964</td>
</tr>
<tr>
<td>2</td>
<td>f</td>
<td>26</td>
<td>159.0</td>
<td>58</td>
<td>Craniohypophyngioma</td>
<td>1977-1979</td>
</tr>
<tr>
<td>3</td>
<td>f</td>
<td>30</td>
<td>149.5</td>
<td>40</td>
<td>Idiopathic</td>
<td>1969-1974</td>
</tr>
<tr>
<td>4</td>
<td>m</td>
<td>24</td>
<td>164.5</td>
<td>48</td>
<td>Idiopathic</td>
<td>1972-1982</td>
</tr>
<tr>
<td>5</td>
<td>m</td>
<td>38</td>
<td>161.0</td>
<td>48</td>
<td>Perinatal asphyxia</td>
<td>1963-1964</td>
</tr>
<tr>
<td>6</td>
<td>m</td>
<td>20</td>
<td>169.0</td>
<td>56</td>
<td>Congenital toxoplasmosis</td>
<td>1965-1967</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Cushing's disease</td>
<td>1968-1970</td>
</tr>
</tbody>
</table>

All patients except No. 6 received substitution with cortisol acetate, thyroxine, and testosterone or estrogen/progesterone. Patient No. 2 also received desmopressin.
detectable, but low, GH levels in all samples during the night (range 0.2-0.6 and 0.3-4.2 µg/l, respectively). A GHRH (1-29)NH₂ test was also performed in each patient. After injection of 100 µg GHRH(1-29)NH₂, 5 of the patients showed increased GH concentration with maximum levels 0.6-12 µg/l, indicating a disturbed hypothalamo-pituitary axis. One patient (No. 5) had undetectable GH concentration both before and after the injection.

In patients No. 1-5 the concentrations of IGF-I were 23-56 µg/l and in patient No. 6, who demonstrated partial GH deficiency, 200 µg/l. The relatively high value in the latter patient compared with earlier measurements could be explained by the fact that he was in late puberty at the time of study.

**Study design**

The study was performed as a randomized, double-blind, cross-over trial. Recombinant methionyl-GH (somatrem, Somatonorm®, KabiVitrum AB) or placebo was administered for 12 weeks with a wash-out period of at least 12 weeks. Somatrem/placebo was self-administered at a dose of 4 IU sc, 6 or 7 nights a week depending on body weight, corresponding to a dose of 0.5-0.6 IU · kg⁻¹ · week⁻¹.

**Tests**

**Laboratory tests.** At the start and at 6 and 12 weeks of each treatment period, routine laboratory tests were performed, including blood glucose, serum urea, phosphate, and alkaline phosphatase.

Measurements were also performed of serum IGF-I, 25 kD insulin-like growth factor binding protein (25 kD IGFBP), procollagen-III peptide, and antibodies against GH.

At the start and at the end of each treatment period, the following investigations were performed:

**Physical working capacity.** Physical exercise tests were performed on a bicycle ergometer (Siemens Elema, Sweden) with stepwise increasing loads of 4-min duration. From the heart rates, the work intensity corresponding to heart rate 170 (W₁₇₀) and the maximal oxygen uptake (VO₂max) was calculated and correction made for individual maximal heart rate (13). The maximal load which could be tolerated for 4 min (W₉₀) was also calculated. In case the subject stopped before 4 min of a load, W₉₀ was taken as the highest load completed plus the fraction of the next load increase which corresponded to the time (14). The working capacity of the patients was compared with a randomly selected Swedish material (15).

**Muscle strength.** Dynamic muscle strength was determined with an isokinetic dynamometer (Cybex II) modified for control of acceleration and correction for gravitational forces (16), or with Kin-Com II dynamic dynamometer (Chattecx Corp) in which these modifications are not needed. Torque was determined in voluntary knee extensions and flexions (15-90°) at maximal effort at three velocities (30, 60 and 120°/s). Each movement was repeated at least three times and measurements accepted only when variability in repeated tests was less than 15%. Torque was averaged from the three repeated measurements in a computer for each angular position. Torque at an angular position of 45° was used for comparisons with normal values (17). Mean torque for each angular position was used to compare muscle strength at start and end of each treatment period.

**Bone mineral density.** Bone mineral density was measured on the distal parts of the forearms by single photon absorptiometry with radioactive source ¹⁰⁹ᵐT (Nuclear Data 1100 rectilinear scanning) derived from the method originally described by Sorensen & Cameron (18). The measurement starts at a point where the distance between ulna and radius is 8 ± 0.8 mm. The first 6 scans, 4 mm apart, are made proximal to the starting point and measure predominantly cortical bone. The next 4 scans, 2 mm apart, are made distal to the starting point and measure mainly trabecular bone. The values are given as mean values for right and left arm, proximal and distal measurements, respectively, and expressed as arbitrary units. The values are corrected for bone width of radius and ulna at the starting point which compensates for differences in skeletal size (19). The results in the patients were compared with those in 25 healthy females aged 22-45 years and 11 healthy males aged 22-40 years.

**Psychological tests.** Emotional status was assessed by two sets of mood scales. The profile of mood scales (POMS) questionnaire (20) evaluates 5 mood variables: tension, depression, anger, fatigue, and confusion. The Sjöberg mood questionnaire (21) evaluates 6 variables: activity, social orientation, control, extraversion, calmness, and pleasantness. Cognitive functions were assessed by psychometric tests: verbal learning (22), non-verbal learning (23), and attention, the latter function evaluated by a reaction time test and by a symbol-digit substitution test (24). In addition, a finger-tapping test (25) was performed recording motor speed of dominant and non-dominant hand as well as alternating hands.

The testing procedures were performed by the same psychologist (OA).

**Assays**

Plasma GH was analysed by RIA using polyclonal antibodies (26). The detection limit was 0.2 µg/l with intra- and inter-assay coefficients of variation of 3 and 10%, respectively. IGF-I in serum was measured by RIA after acid dissociation from IGFBP and separation on gel chromatography as described by Bang et al. (27). The detection limit was 0.5 µg/l and the intra-assay coefficient of variation 12% including separation step. The normal range in healthy males and females aged 20-40 years was 94-322 µg/l. Serum concentration of 25 kD IGFBP was analysed by a RIA developed by Póvoa et al. (28). The sensitivity was 3 µg/l and intra- and inter-assay coefficients of variation were 3 and 11%, respectively. The mean and
95% confidence limits of 25 kD IGFBP in morning samples of fasting healthy adults (20-66 years) were 34 and 15-79 µg/l, respectively (29). Procollagen-III peptide concentration in serum was analysed by a commercial RIA kit (Behring-Werke AG, Marburg, FRG). Normal range in adults was 2-15 µg/l. Antibodies against GH were analysed by KabiVitrum AB using RIA method 405-02.

Statistics
Values are expressed as mean ± SEM. The result at onset and end of each treatment period was compared by using Student's t-test. In the same way, the results at the end of the GH and the placebo periods were compared. For each of the mood scales and the cognitive tests, a three-way analysis of variance was performed (2 treatment orders × 2 types of treatment × 2 times of testing). A p-value <0.05 was considered significant.

Results

Subjective effects
After the study, 5 of 6 patients correctly identified the periods with somatrem and placebo. The positive subjective effects of GH substitution therapy reported included "generally improved well-being" characterized by increased mental alertness and vitality, less fatigue, increased physical capacity and endurance, and improved muscle strength; furthermore, improved appetite with increased food intake. The reduced waistline stated by the patients was confirmed in each subject (73.7 ± 1.9 cm vs 71.5 ± 1.9 cm). In the patient with hypoglycemic problems, the symptoms disappeared completely during GH substitution therapy.

Adverse reactions
The 5 patients who correctly identified the GH period did not report any adverse reactions to the GH therapy. The sixth patient (No. 1) showed a tendency to general fluid retention, especially obvious in fingers and face, and a weight gain of 4 kg. She also experienced arthralgia in her finger joints. The symptoms completely disappeared after the GH treatment period.

Objective assessment
GH substitution therapy was accompanied by decreased serum urea levels and increased serum procollagen-III peptide and IGF-I concentrations in all patients (Fig. 1). The mean serum urea concentrations before and after 12 weeks were 5.0 ± 0.5 and 3.2 ± 0.4 mmol/l, and the mean concentrations of serum procollagen-III peptide 12.3 ± 1.0 and 44.5 ± 18.2 µg/l, respectively. The mean increase in serum IGF-I levels was 161.7 ± 27.3 µg/l. As previously indicated (21), 3 of the 6 patients demonstrated high morning serum levels of 25 kD IGFBP with 90, 150 and 160 µg/l before GH substitution. After the treatment, their morning serum

Fig. 1.
Serum concentrations of IGF-I, procollagen-III peptide and urea before (■) and after 12 weeks (□) GH substitution therapy.
levels had normalized to 48, 18 and 82 μg/l, respectively. The remaining 3 patients had normal morning fasting levels (24, 40 and 36 μg/l) and showed no significant change after GH therapy. No change in the serum concentrations of urea, procollagen-III peptide or IGF-I was seen during the placebo period. The serum activity of alkaline phosphatase did not change during placebo or substitution period. No antibodies against GH were detectable in any patient before or after GH treatment. The fasting blood glucose and serum phosphate concentrations showed no difference between the periods of GH substitution therapy and placebo.

During GH substitution, 2 patients gained 4 kg in weight. In the other four, the change ranged between –2 and +2 kg. During the placebo period, the weight changed between –2 and +2 kg.

In the cycle ergometer test, W\textsubscript{max} was within normal limits in relation to body weight in 2 women (140 and 75 W, respectively) and 2 men (200 and 140 W). It was moderately reduced in one man (90 W) and extremely reduced in one woman (22 W), mainly owing to osteoarthritis of one hip. W\textsubscript{170} corrected for weight could be calculated in 5 patients and was normal in 4 of them and 25% below average in one man, i.e. in the lower range. Maximal heart rate was normal in 4 of the patients. It was lower than normal in the man with moderately reduced W\textsubscript{max}, who stopped exercise because of leg tiredness, and in the woman with osteoarthritis (Table 2). During GH substitution therapy, heart rate at rest increased significantly in all 6 patients, with a mean increase of 16 beats/min (basal range 52-78 beats/min, during GH therapy 60-102 beats/min). The bicycle ergometer test during GH substitution could only be performed in 5 patients since one patient had slightly injured a leg. Maximal heart rate during work increased in 3 of 5 patients and was unchanged in 2. W\textsubscript{max} corrected for weight increased in 3 of 5 patients, was unchanged in one and decreased in one. VO\textsubscript{2} corrected for weight increased slightly in 4 and decreased in one patient. W\textsubscript{170} corrected for weight could only be calculated in 4 patients and was not systematically altered (Table 2). During the placebo period, the physical capacity was unchanged in all patients.

The results from the isokinetic muscle force measurements were not reproducible in one female patient (No. 1) and were withdrawn. With the preset speed of 30°/s, the torque (mean of right and left leg) at an angular position of 45° was in the male patients (No. 4, 5, and 6) 57, 41 and 51Nm during flexion (normal values 34-134 Nm) and 106, 104 and 66 Nm during extension (normal values 100-268 Nm). The corresponding force in two of the female patients (No. 2 and 3) was 19 and 40 Nm during flexion (normal values 23-67 Nm) and 52 and 98 Nm during extension (normal values 73-213 Nm).

There was no change in the isokinetic muscle strength during placebo and GH substitution therapy. The mean maximal torque during flexion at 30, 60 and 120° was 51 ± 7, 48 ± 8, and 45 ± 8 Nm before and 54 ± 7, 52 ± 10, and 49 ± 8 Nm during GH substitution. The mean maximal torque during extension at the same speeds was 115 ± 17, 108 ± 17, and 95 ± 14 Nm before and 101 ± 16, 91 ± 15, and 86 ± 14 Nm during therapy.

The evaluation of bone mineral density showed

Table 2.

Changes in working capacity after 12 weeks GH substitution therapy.

<table>
<thead>
<tr>
<th>Patient No.</th>
<th>Heart rate at rest (beats/min)</th>
<th>Maximal heart rate (beats/min)</th>
<th>W\textsubscript{max} (W)</th>
<th>W\textsubscript{max} (W/kg)</th>
<th>W\textsubscript{170} (W)</th>
<th>W\textsubscript{170} (W/kg)</th>
<th>VO\textsubscript{2} (ml/kg\textsuperscript{-1}·min\textsuperscript{-1})</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>basal GH Δ</td>
<td>basal GH Δ</td>
<td>basal</td>
<td>basal GH Δ</td>
<td>basal</td>
<td>basal</td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>78 +24 127+21</td>
<td>22 +16</td>
<td>0.52 +0.31</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>18 +3</td>
</tr>
<tr>
<td>2</td>
<td>62 +30 200-6</td>
<td>140 +10</td>
<td>2.41 +0.27</td>
<td>95 +15</td>
<td>1.64 +0.32</td>
<td>29 +5</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>74 +16 180+13</td>
<td>75 +15</td>
<td>1.88 +0.37</td>
<td>75 ±0</td>
<td>1.88 ±0</td>
<td>32 +4</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>60 +8 196-1</td>
<td>140 +10</td>
<td>2.92 –0.03</td>
<td>105 -10</td>
<td>2.19 –0.36</td>
<td>40 –8</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>52 +8 145+15</td>
<td>90 –7</td>
<td>1.88 –0.22</td>
<td>105 –10</td>
<td>2.19 –0.29</td>
<td>24 +1</td>
<td></td>
</tr>
</tbody>
</table>
low values in each patient. In the three women, bone mineral density was 0.95 – 1.03 units at the proximal site and 0.49 – 0.64 at the distal site. In the normal healthy females the range was 1.21 – 1.67 (mean 1.36 ± 0.02) and 0.80 – 1.32 (0.95 ± 0.02) units, respectively. In the 3 men, the values were 1.20 – 1.40 at the proximal site and 0.96 – 0.98 units at the distal site. In the healthy males, the range was 1.53 – 1.98 (mean 1.74 ± 0.05) and 1.15 – 1.68 (1.33 ± 0.05) units, respectively. Bone mineral density was unchanged in all patients at the end of the GH and placebo periods.

All patients showed average basal results in the psychological tests. There were no significant differences, neither between the results at onset and end of each treatment period nor between the two different treatment periods in the self-reported mood scales (Table 3) and in the cognitive tests. The result in the reaction time test was before GH therapy 18.72 ± 0.95 s and after 18.80 ± 0.91. The corresponding values for the placebo period were 19.72 ± 0.99 and 20.07 ± 0.83 s. In the symbol digit substitution test, the result before GH treatment was 235.8 ± 14.0 ms and at the end of the period 238.5 ± 18.2. Before and after the placebo period, the values were 232.2 ± 11.8 and 233.7 ± 15.0 ms, respectively. Analysis of variance did not give any significant changes or order of treatment effects. Individual patients improved the results in some tests during GH treatment, but there was, however, also an improvement seen during placebo. In the finger-tapping test, the motor speed was unaltered in all patients during both periods.

**Discussion**

Like most patients with hypopituitarism (30,31), the adult patients with hypopituitarism in the present study were able to carry out normal daily activities. They suffered, however, from general fatigue, low physical capacity, and muscle weakness. Yet, the dynamic working capacity was rather normal in relation to body weight in all patients except one, in whom the reduced capacity was explained by hip disease. The torque during isokinetic flexion and extension was below the mean for healthy adults in all subjects investigated. The levels were below –2SD in one patient during flexion and in 2 patients during extension. It cannot be excluded, however, that the comparatively low levels recorded are due to difference in body height between the patients and the normal subjects.

Five out of 6 patients very easily identified the periods with growth hormone and placebo and experienced positive effects of GH therapy. A generally increased well-being was reported, with increased mental alertness and vitality, better muscle strength, physical capacity, and endurance. The problems with hypoglycemic episodes completely disappeared during GH therapy. Even the families and friends of the patients confirmed the positive effects of GH substitution therapy. Three of the patients expressed strong wishes to continue the GH therapy in spite of the inconvenience with daily injections.

**Table 3.**

**Evaluation of mood.**

<table>
<thead>
<tr>
<th>Sjöberg*</th>
<th>Basal</th>
<th>GH</th>
<th>Basal</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Activity</td>
<td>2.78</td>
<td>2.97</td>
<td>2.70</td>
<td>2.60</td>
</tr>
<tr>
<td></td>
<td>±0.23</td>
<td>±0.28</td>
<td>±0.20</td>
<td>±0.18</td>
</tr>
<tr>
<td>Social</td>
<td>3.12</td>
<td>2.92</td>
<td>2.83</td>
<td>2.95</td>
</tr>
<tr>
<td>orientation</td>
<td>±0.13</td>
<td>±0.18</td>
<td>±0.12</td>
<td>±0.19</td>
</tr>
<tr>
<td>Control</td>
<td>2.77</td>
<td>2.97</td>
<td>2.70</td>
<td>2.72</td>
</tr>
<tr>
<td></td>
<td>±0.19</td>
<td>±0.17</td>
<td>±0.16</td>
<td>±0.19</td>
</tr>
<tr>
<td>Extraversion</td>
<td>2.70</td>
<td>2.82</td>
<td>2.67</td>
<td>2.57</td>
</tr>
<tr>
<td></td>
<td>±0.12</td>
<td>±0.11</td>
<td>±0.08</td>
<td>±0.07</td>
</tr>
<tr>
<td>Calmness</td>
<td>2.53</td>
<td>2.70</td>
<td>2.60</td>
<td>2.42</td>
</tr>
<tr>
<td></td>
<td>±0.26</td>
<td>±0.14</td>
<td>±0.13</td>
<td>±0.17</td>
</tr>
<tr>
<td>Pleasantness</td>
<td>2.93</td>
<td>2.76</td>
<td>2.55</td>
<td>2.58</td>
</tr>
<tr>
<td></td>
<td>±0.16</td>
<td>±0.28</td>
<td>±0.12</td>
<td>±0.19</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>POMS**</th>
<th>Basal</th>
<th>GH</th>
<th>Basal</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tension</td>
<td>2.67</td>
<td>2.65</td>
<td>2.60</td>
<td>2.77</td>
</tr>
<tr>
<td></td>
<td>±0.26</td>
<td>±0.25</td>
<td>±0.21</td>
<td>±0.29</td>
</tr>
<tr>
<td>Depression</td>
<td>2.17</td>
<td>1.93</td>
<td>2.47</td>
<td>2.55</td>
</tr>
<tr>
<td></td>
<td>±0.20</td>
<td>±0.24</td>
<td>±0.42</td>
<td>±0.39</td>
</tr>
<tr>
<td>Anger</td>
<td>1.97</td>
<td>2.10</td>
<td>2.13</td>
<td>2.50</td>
</tr>
<tr>
<td></td>
<td>±0.23</td>
<td>±0.27</td>
<td>±0.39</td>
<td>±0.30</td>
</tr>
<tr>
<td>Fatigue</td>
<td>2.77</td>
<td>2.50</td>
<td>2.97</td>
<td>2.93</td>
</tr>
<tr>
<td></td>
<td>±0.24</td>
<td>±0.44</td>
<td>±0.34</td>
<td>±0.23</td>
</tr>
<tr>
<td>Confusion</td>
<td>2.20</td>
<td>2.40</td>
<td>2.73</td>
<td>2.58</td>
</tr>
<tr>
<td></td>
<td>±0.28</td>
<td>±0.35</td>
<td>±0.31</td>
<td>±0.30</td>
</tr>
</tbody>
</table>

Values are given as mean ± SEM.

* Higher points indicate better mood

** Lower points indicate better mood
In spite of the improvement in physical capacity and muscle strength reported by the patients, the test results showed a rather small improvement in working capacity on the bicycle ergometer. One possible reason is that the increased mental alertness produced by the treatment made them tolerate physical stress better. Furthermore, it is not to be expected that substitution therapy not including a physical training programme would increase physical working capacity substantially in patients with a rather normal capacity. However, the heart rate at rest increased significantly in all patients, indicating a direct or indirect cardiovascular effect.

There was no change in the maximal voluntary knee flexion and extension. This is, however, not contradictory to the subjectively reported improvement in muscle strength, since the maximal torque is seldom used in daily life and never in exercise during longer periods or during dynamic bicycle work.

The low bone mass, measured as bone mineral density in the forearm, did not change after 12 weeks of GH substitution therapy. Most likely the treatment period was too short. Data concerning GH substitution effect on the skeleton of GH-deficient adults are sparse and time-effect relationship is not known.

The generally increased vitality and alertness reported by the patients were not demonstrated in the tests of mood and cognitive functions. This can be explained by the difficulty as to optimizing the measurement of subtle changes of mood and cognitive functions. In the tests of verbal and non-verbal learning, there were large interindividual variations, and some of the patients had basal scores close to the upper limit, which made a proper evaluation of a potential improvement impossible.

The rise in both serum IGF-I and procollagen-III peptide levels during GH substitution therapy in our adult patients was consistent with previous findings in GH-deficient children (32,33). This indicates that both peptides may be useful as markers during GH therapy also in adults. There was, however, no correlation between the increase in IGF-I and in procollagen-III peptide.

Fluid retention was registered in one of the patients. This side-effect of GH therapy has earlier been noticed in children some months after initiation of therapy. Increase in extracellular water during the first 12 months of GH substitution therapy was shown by four-compartment analysis of body composition in hypopituitary patients (34). In patients with acromegaly, increased total body water, plasma volume, extracellular fluid, and exchangeable sodium have been demonstrated by normalization after successful treatment of the GH hypersecretion (34-37). The mechanism has been considered to be sodium retention owing to augmented sodium pump activity (38). For practical reasons, our patients received one GH-ampoule of 4 IU se 6 or 7 nights a week to obtain a dose corresponding to 0.5-0.6 IU kg⁻¹ · week⁻¹. The patient who had fluid retention received a dose of 0.1 IU kg⁻¹ · day⁻¹ 6 days a week. The same dose, however, was also given to one of the other women without any problems of fluid retention, indicating an individual sensitivity to develop this adverse reaction. Further studies will be needed to find the right dose of GH to each individual patient.

In conclusion, short-term GH substitution therapy to GH-deficient adults induced a generally improved well-being, which encourages further trials. Longer treatment periods seem necessary to definitely establish the effect on physical capacity, muscle strength, bone mineral density, and mood and cognitive functions before substitution therapy can be recommended to GH-deficient adults. The high financial costs also emphasize the need of further clinical trials.

Acknowledgments

The present study was supported by grants from the Karolinska Institute, The Swedish Medical Research Council, Svenska Sällskapet för Medicinsk Forskning, Nordisk Insulin Foundation, Magnus Bergvall Foundation, and Clas Groschinskyss minnesfond.

We gratefully acknowledge help and advice from assistant professor Hans-Eric Sjöberg in evaluating bone mass. The authors appreciate the kind supply of Somatorm® from KabiVitrum AB, Stockholm, Sweden. The Department of Clinical Chemistry, Karolinska Hospital, is acknowledged for their help in analysing routine chemical tests and serum procollagen-III peptide.

References

2. Zadik Z, Chalew SA, McCarter RJ, Meistas M, Kowarski AA. The influence of age on the 24-hour in-


Received March 29th, 1990.
Accepted May 9th, 1990.

Dr M. Degerblad,
Department of Endocrinology,
Karolinska Hospital,
P. O. Box 60500,
S-104 01 Stockholm,
Sweden.