Long-term growth hormone treatment in growth hormone deficient adults

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Abstract. Growth hormone treatment in GH-deficient adults has proved beneficial in recent short-term trials, but long-term results have not yet been reported. Thirteen GH-deficient adults (4 females, 9 males; mean (SEM)

\[ \text{age 26.4 (1.7) years}, \]

who had completed 4 months of GH therapy in a double-blind placebo-controlled cross-over study were followed, for further 16.1 (0.8) months of uninterrupted GH therapy in an open design. A significant mean increase of 1.3 cm in linear height was recorded, whereas body mass index remained unchanged. Mean muscle volume of the thigh, estimated by computerized tomography, increased significantly compared with that of the initial placebo period (p<0.01), and a slight decrease was recorded in adipose tissue volume of the thigh (p=0.10) and subscapular skinfold thickness (p=0.10). Still, the muscle to fat ratio of the thigh was significantly lower compared with that of normal subjects (72.6/27.4 vs 77.9/22.1) (p<0.01). The mean isometric strength of the quadriceps muscles increased significantly during long-term GH therapy (p<0.01), but remained lower compared with that of normal subjects (1.66 (0.10) to 2.13 (0.11) Nm/kg body weight). Exercise capacity performed on a bicycle ergometer increased significantly after long-term therapy (p<0.05), but still did not reach the values seen in normal subjects (22.5 (3.4) vs 37.4 (4.2) watt \cdot \text{min}\cdot \text{kg}^{-1}). No adverse reactions were recorded during long-term therapy and hemoglobin A\(_1c\) remained unchanged. These data suggest that long-term GH replacement therapy in GH-deficient adults has beneficial effects on several physiological features which are subnormal in these patients.

The primary goal of growth hormone therapy has been to increase linear height in GH-deficient children. The criterion for termination of therapy varies from attainment of a certain target height (1-3) to complete cessation of longitudinal growth or fusion of epiphyses (3-5). Neither of these criteria is in accordance with normal physiology, since GH secretion continues in adulthood although at a declining rate (6). The limited supply of pituitary GH necessitated a very restrictive use, but the advent of biosynthetic GH enables new indications, such as GH deficiency in adults, to be explored. There are only limited data on the consequences of adult GH deficiency, but retrospective surveys point at varying degrees of psycho-social maladjustment (3,7) and also an increased mortality (8) of such patients. Recently, two controlled studies of GH replacement therapy for 4-6 months in GH-deficient adults reported beneficial effects on features such as body composition, muscle strength, exercise capacity, and psychological well-being, all of which were abnormal during placebo treatment (9-11).

In order to examine more long-term effects of GH therapy in GH-deficient adults we continued a double-blind protocol (9) as an open study of 16 months of uninterrupted GH therapy.

Patients and Methods

The GH-deficient patients in the present study had all participated in a double-blind placebo-controlled cross-over study on the effects of 4 months GH therapy (9).
The diagnosis had been established by means of 2 classic GH stimulation tests and all the patients had in childhood been treated with GH in an average weekly dose of 12 IU. Twenty-one patients completed the initial trial after which all of them were offered renewed GH treatment in an open study, which was agreed upon by 13 of the patients (4 females, 9 males). Eight patients did not participate for the following reasons: the inconvenience of injections and, in particular, the frequent in- and outpatient visits required by the study protocol (N=6); plans of pregnancy, which was considered an exclusion criterion (N=1); emigration as part of an educational programme (N=1). A mean (SEM) period of 7.5 (1.0) months had elapsed between termination of GH treatment in the cross-over study and start of GH treatment in the open study. The mean (SEM) age of the patients at the time of the last investigation was 26.4 (1.7) years.

The patients were studied after at least 1 year of uninterrupted GH therapy with a mean (SEM) duration of 16.1 (0.8) months, during which they had been seen regularly at the outpatient clinic. In the open study, the patients treated themselves with daily sc injections (at 20.00 h) of GH (Norditropin® Novo Nordisk, Denmark) in a median replacement dose of 2.9 IU/m² (range 1.2-3.8 IU/m²).

Muscle and adipose tissue volume were measured by computerised tomography (CT). The area scanned was a 0.8 cm cross-sectional slice of the mid thigh region. The exact point of measurement was the same on each occasion as established on a scanogram of the region at the first examination of the patients. In addition, the subscapular skinfold thickness was measured by means of a caliper.

The maximal isometric strength of the right and left quadriceps muscle was recorded by means of an electronic dynamometer and was calculated as the torque exerted about the axis of the knee joint (mean of 3 measurements). To measure exercise capacity bicycle exercise was done with an initial workload of 50 W which was increased by 50 W every 3 min until exhaustion. Blood pressure and heart rate were measured at rest and immediately after exercise. A fasting morning blood sample was drawn at the end of the study period for measurements of serum IGF-I. In addition HbA₁c was analysed. Finally, body weight and linear height were recorded. More detailed information on the investigative procedures have been published previously (9).

For comparison, all of the above described measurements except HbA₁c were also performed in healthy, untreated subjects. Twenty-one healthy subjects underwent measurements of conventional anthropometrics, serum IGF-I, and muscle strength, and 13 of these subjects also had a CT scan of their thighs (Table 1). Another group of 24 subjects performed the exercise test. Both groups matched the patients as regards age and sex.

The data obtained in the open long-term study were compared with the corresponding data from the GH and placebo period of the initial cross-over study by means of two-way analysis of variance (ANOVA). If this test yielded a significant difference (p<0.05), the Newman-Keul’s test was used for post hoc analysis. In addition, the variables obtained in the long-term study were compared with the reference group by means of an unpaired Student’s t-test (two-tailed). Unless otherwise stated, results are given as mean and SEM.

The study was approved by the regional ethical committee and the Danish Health Authorities.

### Results

Serum IGF-I increased significantly during GH therapy in the cross-over study. A further increase, which did not reach statistical significance (p=0.06), was recorded during long-term GH therapy (Table 1). Hemoglobin A₁c remained unchanged during the entire study period (Table 1). No adverse reactions were recorded during long-term GH therapy.

A small but significant increase in linear height of the patients was recorded at the end of the study period, whereas body weight only increased insignificantly (Table 1). Body mass index (BMI) remained unchanged and did not differ from that of the control group (N=21). Mean muscle volume of both thighs increased during long-term GH therapy (p<0.01) and was significantly higher compared with that during the placebo period (p<0.01), whereas the increase compared with that during the short-term GH period did not quite reach significance (Fig. 1). The decrease in adipose tissue volume of the thighs and subscapular skinfold thickness after long-term GH therapy was not statistically significant compared with any previous measurements (Fig. 1). The muscle to fat ratio of the thighs increased significantly during long-term GH therapy compared with both values in the cross-over study, but the ratio still remained significantly lower than that of the control group (p<0.01) (Table 1).

The mean isometric muscle strength of the right and left quadriceps, which did not change during the cross-over study, increased significantly during long-term GH therapy (p<0.01). Fig. 2 depicts the changes in muscle strength in the patients during the trial as compared with the control group. The values are given as muscle strength/body weight in order to allow a comparison between the patients and the control group. Even with this correction,
Table 1.
Clinical details and effects of GH on physiological features of the patients as compared with normal untreated subjects.

<table>
<thead>
<tr>
<th></th>
<th>Mean (SEM)</th>
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<tbody>
<tr>
<td></td>
<td>Placebo</td>
</tr>
<tr>
<td>Age (years)</td>
<td>24.4 (1.7)</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>165.1 (3.8)</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>59.1 (3.4)</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>21.6 (0.9)</td>
</tr>
<tr>
<td>Serum IGF-I (µg/l)</td>
<td>104 (14)</td>
</tr>
<tr>
<td>HbA1c (%)</td>
<td>5.1 (0.1)</td>
</tr>
<tr>
<td>Subscapular skinfold (mm)</td>
<td>15 (2)</td>
</tr>
<tr>
<td>Muscle/fat ratio</td>
<td>64.0/36.0</td>
</tr>
</tbody>
</table>

*Significantly different (p<0.01) when comparing patient results (two-way ANOVA). # Significantly different (p<0.01) when comparing long-term GH and normal subjects.

The muscle strength of the patients after long-term GH therapy was significantly lower (p<0.01) than that of the control group (Fig. 2). Exercise capacity also increased significantly following long-term GH therapy with both values in the cross-over study (p<0.05). When corrected for body weight, exercise capacity was significantly lower in all the patients compared with the control group (p<0.01) (Fig. 2). In the cross-over study heart rate, both at rest and during exercise, was higher following GH therapy than during the placebo period, whereas during long-term GH therapy, the levels were intermediate to the two previous measurements (data not shown).

Discussion

This study is the first to report results of long-term GH therapy in GH-deficient adults. A significant increase in muscle to fat ratio, isometric muscle strength, and exercise capacity was recorded when compared with previous measurements in the same patients during both short-term GH and placebo therapy. These achievements represented only a partial normalization when compared with an untreated group of healthy subjects.

It would have strengthened the long-term study had it included a placebo-treated patient group, but that was not feasible. It is, however, very unlikely that the observed effects reflected natural changes with time, since both lean body mass, maximal isometric strength and exercise capacity decline with age already from the onset of early adulthood (12-14). It is more conceivable that the benefits represent a true treatment effect. The small but significant increase in linear height was unexpected although delayed puberty is a common feature in
GH-deficient patients. The finding emphasizes that the duration of GH therapy today is arbitrary.

A number of short-term studies of GH therapy in GH-deficient adults have emerged within the last two years (9,10,15,16). The results and conclusions are strikingly similar in terms of a normalization/improvement in body composition indices and physical capabilities. Furthermore, improved psychological well-being has been reported in two of the studies (11,15). The present long-term data support and extend these findings. The adverse reactions reported so far consist of moderate fluid retention (9,10), which is dose-dependent and in most cases transient as supported by the fact that such complaints were not reported in this long-term study. Theoretically, impairment of glucose tolerance could be suspected on the basis of the well-known insulin antagonistic actions of GH (17). HbA1c however, remained unchanged in the present study.

Surveys in adults with untreated GH deficiency point at various degrees of psycho-social maladjustments (3,7). A recent epidemiological study reported significantly increased overall mortality of hypopituitary patients, which could be ascribed to premature cardiovascular deaths (myocardial infarction and cardiac failure), in spite of adequate replacement therapy with thyroxine, sex steroids and corticosteroids (8). The increased mortality was not correlated with known variables such as duration or nature of disease or degree of pituitary insufficiency. Untreated GH deficiency was forwarded as a putative explanation by the authors (8). This hypothesis is indirectly supported by the observation of a lowering of plasma cholesterol and waist to hip ratio during GH therapy in GH-deficient adults (10), since high levels of these features are associated with increased cardiovascular morbidity (18). Furthermore, GH administration has been reported to increase myocardial contractility in both normal subjects and GH-deficient adults (9,19,20). On the other hand, GH excess (21) and hyperinsulinemia (22) have also been associated with increased cardiovascular morbidity in epidemiological studies, indicating that long-term GH should be used with caution and probably only at replacement doses.

At any rate, the data by Rosén & Bengtsson (8) clearly imply that current treatment of adult hypopituitarism needs to be improved.

In conclusion, the present results indicate that GH replacement therapy in GH-deficient adults offer significant benefits, also when given for a relatively long time, without significant adverse reactions. Therefore, GH treatment should be considered in these patients, at least for some years or decades after cessation of linear growth.

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References


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