BRIEF REPORT

A 10-Year, Prospective Study of the Metabolic Effects of Growth Hormone Replacement in Adults

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Context: Only a few studies have investigated the effects of GH replacement in adults for more than 5 yr.

Objective/Design/Patients: In a prospective, open-label, single-center study, the effects of 10-yr GH replacement were determined. Eighty-seven consecutive patients (52 men and 35 women), with a mean age of 44.1 (range 22–74) yr with adult-onset GH deficiency (GHD) were included.

Results: The initial mean dose of GH (0.98 mg/d) was reduced during the study and at yr 10 was 0.47 mg/d. The mean IGF-I SD score increased from −1.81 at baseline to 1.29 at study end. The absolute reduction in total body fat was transient. However, after correction for age and sex using a four-compartment model, the reduction in body fat was sustained during the 10-yr study period. There was a sustained improvement in serum lipid profile and after 10 yr, and blood glycosylated hemoglobin level was reduced. The treatment responses in IGF-I SD score, serum high-density lipoprotein cholesterol level, and body composition as measured using dual-energy x-ray absorptiometry were more marked in men, whereas women had a more marked reduction in blood glycosylated hemoglobin level.

Conclusion: The effect on the absolute amount of body fat was seen early and was transient, which could be due to the normal aging of the patients. The effects on metabolic indices were detected later, but they were sustained and even progressive throughout the study period.

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A FEW STUDIES have shown that the reduction in body fat and the increase in lean mass observed during short-term GH replacement are sustained during prolonged (5–7 yr) treatment (1–4). The effects on circulating lipids observed in short-term studies are maintained in studies with 5–10 yr of GH replacement therapy (2, 4, 5). Although the long-term effect by GH replacement on glucose homeostasis is still controversial (2–4, 6), the risk of type 2 diabetes mellitus does not appear to be increased in adults with normal body mass index (BMI) (4, 6).

The aim of this study was to investigate the efficacy of 10-yr GH replacement therapy in patients with adulthood onset GH deficiency (GHD).

Patients and Methods

Patients

Eighty-seven patients (52 men), mean age 44.1 (range 22–74) yr, with adult-onset pituitary disease were included 1990–1994. The causes of the pituitary deficiency were nonsecreting pituitary adenoma (n = 48), secreting pituitary adenoma, (n = 18), craniopharyngioma (n = 10), empty sella (n = 3), Sheehan’s syndrome (n = 3), cholesteatoma (n = 1), trauma (n = 1), meningioma (n = 1), and idiopathic (n = 2). The patients had previously been treated with pituitary surgery (n = 45), combined pituitary surgery and radiotherapy (n = 31), and only pituitary radiotherapy (n = 1). In 73 patients, the GHD was verified with a peak GH less than 3 µg/liter during insulin-induced hypoglycemia. In 14 patients with multiple anterior pituitary deficiencies, the diagnosis was based on measurements of 24-h GH secretion (n = 12) or a peak GH less than 1.5 µg/liter during a glucagon stimulation test (n = 2). At baseline, nine patients had isolated GHD and eight, 14, and 36 patients had one, two, and three additional pituitary hormonal deficiencies, respectively. In addition, 23 patients had diabetes insipidus. When required, these patients received replacement therapy with glucocorticoids, thyroid hormone, gonadal steroids, and desmopressin. However, at study start 58%, and at study end 64.5%, respectively, of the gonadotropin-deficient women received estrogen replacement.

Ethical considerations

Informed written consent was obtained from all patients. The study was approved by the local ethical committee of Sahlgrenska University Hospital, Göteborg, Sweden.

Study protocol

This is an ongoing, prospective, open-label treatment trial. The initial target dose of GH in the first 64 patients was 11.9 µg/kg/d (0.25 IU/kg/wk). The dose was gradually lowered and individualized when the weight based dose regimen was abandoned (7). In the remaining 23 patients, the GH dose was individualized from study start (7). The mean dose of GH is shown in Table 1. The dose of GH (milligrams per day) was similar in both sexes, but adjusted for body weight, the mean GH dose was higher in women (data not shown).

At baseline and then after 1, 2, 3, 4, 5, 7, and 10 yr, physical and laboratory examinations were performed including measurements of body composition and metabolic indices. In addition, dose titration and safety monitoring were performed during visits every third month throughout the first year and every sixth month thereafter.
Go¨therstro¨m et al. • GH Effects on Metabolism in Adults

TABLE 1. The dose of GH, body composition, and metabolic indices during 10-yr GH therapy in 87 GHD adults

<table>
<thead>
<tr>
<th>Metric</th>
<th>Baseline</th>
<th>1 yr</th>
<th>2 yr</th>
<th>3 yr</th>
<th>4 yr</th>
<th>5 yr</th>
<th>6 yr</th>
<th>7 yr</th>
<th>8 yr</th>
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<tbody>
<tr>
<td>Dose of GH (mg/d)</td>
<td>0.98 (0.02)</td>
<td>0.66 (0.03)*</td>
<td>0.53 (0.02)*</td>
<td>0.50 (0.02)*</td>
<td>0.48 (0.02)*</td>
<td>0.47 (0.03)*</td>
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<tr>
<td>IGF-1 sd score</td>
<td>-1.81 (0.12)</td>
<td>3.10 (0.28)*</td>
<td>2.25 (0.25)*</td>
<td>1.88 (0.24)*</td>
<td>1.51 (0.19)*</td>
<td>1.29 (0.25)*</td>
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<td>BMI (kg/m²)</td>
<td>27.8 (0.7)</td>
<td>27.3 (0.5)</td>
<td>27.7 (0.5)</td>
<td>27.9 (0.5)</td>
<td>28.0 (0.7)*</td>
<td>28.1 (0.7)*</td>
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<td>DEXA</td>
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<tr>
<td>Body fat (kg)</td>
<td>26.3 (1.0)</td>
<td>23.6 (1.1)*</td>
<td>25.2 (1.0)</td>
<td>25.2 (1.1)</td>
<td>25.9 (1.1)</td>
<td>25.9 (1.1)</td>
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<tr>
<td>Lean body mass (kg)</td>
<td>50.0 (1.4)</td>
<td>52.7 (1.5)*</td>
<td>52.6 (1.5)*</td>
<td>53.0 (1.5)*</td>
<td>53.4 (1.6)*</td>
<td>53.2 (1.5)*</td>
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<tr>
<td>Four-compartment model</td>
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<tr>
<td>Body fat (kg)</td>
<td>25.5 (1.1)</td>
<td>22.5 (1.2)*</td>
<td>22.7 (1.1)*</td>
<td>22.6 (1.2)*</td>
<td>20.9 (1.1)*</td>
<td>21.5 (1.1)*</td>
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<tr>
<td>Lean body mass (kg)</td>
<td>115.4 (2.6)</td>
<td>97.6 (2.9)*</td>
<td>95.9 (2.4)*</td>
<td>93.3 (2.7)*</td>
<td>84.8 (2.6)*</td>
<td>86.7 (2.8)*</td>
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<tr>
<td>BCM (kg)</td>
<td>30.6 (0.9)</td>
<td>32.1 (0.9)*</td>
<td>32.1 (0.9)*</td>
<td>31.7 (0.9)*</td>
<td>31.3 (0.8)*</td>
<td>31.3 (0.8)*</td>
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<tr>
<td>B ECM (pred, %)</td>
<td>100.2 (2.4)</td>
<td>105.2 (2.0)*</td>
<td>105.7 (1.9)*</td>
<td>105.0 (1.8)*</td>
<td>104.6 (1.8)*</td>
<td>106.3 (1.8)*</td>
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<td>ECW (kg)</td>
<td>17.8 (0.6)</td>
<td>19.6 (0.6)*</td>
<td>20.4 (0.6)*</td>
<td>21.5 (0.6)*</td>
<td>24.0 (0.7)*</td>
<td>22.8 (0.6)*</td>
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<tr>
<td>ECW% (pred, %)</td>
<td>94.2 (1.8)</td>
<td>103.2 (1.9)</td>
<td>102.9 (3.5)</td>
<td>110.8 (1.6)</td>
<td>122.3 (3.3)*</td>
<td>117.1 (1.9)*</td>
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<td>Five-compartment model</td>
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<tr>
<td>Body fat (kg)</td>
<td>23.7 (1.2)</td>
<td>19.8 (1.3)*</td>
<td>20.4 (1.2)*</td>
<td>21.4 (1.4)*</td>
<td>22.1 (1.3)</td>
<td>22.6 (1.2)</td>
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<tr>
<td>Metabolic indices</td>
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<td>Serum TC (mmol/liter)</td>
<td>5.90 (0.10)</td>
<td>5.80 (0.10)</td>
<td>5.60 (0.10)*</td>
<td>5.40 (0.10)*</td>
<td>5.53 (0.12)*</td>
<td>5.37 (0.12)*</td>
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<tr>
<td>Serum HDL-C (mmol/liter)</td>
<td>1.21 (0.04)</td>
<td>1.28 (0.04)</td>
<td>1.28 (0.04)*</td>
<td>1.30 (0.04)</td>
<td>1.32 (0.04)*</td>
<td>1.36 (0.04)*</td>
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<tr>
<td>Serum LDL-C (mmol/liter)</td>
<td>3.89 (0.10)</td>
<td>3.66 (0.11)*</td>
<td>3.60 (0.11)*</td>
<td>3.39 (0.10)</td>
<td>3.47 (0.10)*</td>
<td>3.22 (0.10)*</td>
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<tr>
<td>Blood glucose (mmol/liter)</td>
<td>4.00 (0.10)</td>
<td>4.30 (0.10)*</td>
<td>4.30 (0.10)*</td>
<td>4.30 (0.10)*</td>
<td>4.57 (0.08)*</td>
<td>4.86 (0.09)*</td>
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<tr>
<td>Blood HbA1c (%)</td>
<td>4.90 (0.10)</td>
<td>5.10 (0.10)*</td>
<td>5.00 (0.07)</td>
<td>4.90 (0.10)</td>
<td>4.72 (0.09)*</td>
<td>4.59 (0.09)*</td>
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</table>

All values are shown as the mean (SEM). BF, Body fat; BCM, body cell mass; ECW, extracellular water; TC, total cholesterol; LDL-C, low density lipoprotein cholesterol; BF%, an individual’s observed/predicted body fat values ratio; BCM%, an individual’s observed/predicted body cell mass values ratio; ECW%, an individual’s observed/predicted extracellular water values ratio; BF chem, body fat values according to the five-compartment model.

* P < 0.001 (vs. baseline).
* P < 0.01.
* P < 0.05.

Measurements of body composition and biochemical methods

The methods used for body composition measurements [dual-energy x-ray absorptiometry (DEXA), four- and five-compartment models, total body potassium, total body water, and total body nitrogen] are similar to those previously described (2). All biochemical assays were similar as those previously described (2).

Statistical methods

Values are presented as the mean (SEM). The statistical analyses were performed using ANOVA and are similar to those previously described (2).

Results

Body composition

The mean IGF-1 sd score as well as BMI increased (Table 1). Systolic and diastolic blood pressure were unaffected (data not shown). There were sustained increases in lean mass (Table 1). The reduction in body fat was transient as measured using DEXA or the five-compartment model, whereas it was sustained as determined using the four-compartment model (Table 1). There was a sustained increase in total body potassium and transient increases in nitrogen, protein, and glycogen in the total body (data not shown).

Metabolic indices

Serum cholesterol concentration was improved (Table 1). Serum triglyceride and insulin concentrations were unchanged (data not shown). Fasting blood glucose concentration was increased (Table 1). In contrast, after 7 and 10 yr of GH replacement, blood glycosylated hemoglobin (HbA1c) concentration was reduced as compared with baseline (Table 1).

Gender differences

Gender differences in terms of IGF-1 sd score, total body fat, and lean body mass as determined using DEXA, and blood HbA1c level are shown in Fig. 1. In addition, men had a more marked treatment response in serum high-density lipoprotein cholesterol (HDL-C) concentration (P < 0.01 vs. women; data not shown). The responses in other variables were similar in both genders (data not shown).

Loss to follow-up and adverse events

Nine patients were not followed up for 10 yr [lost to follow-up (n = 2), lack of compliance (n = 1), adverse events (n = 6)].

Four of the patients that did not complete the 10 yr of therapy had died after 3, 5, 6, and 7 yr, respectively, of GH replacement. The causes of death were renal carcinoma (58-yr-old man), cancer in the omentum (likely colonic cancer; 63-yr-old man), pulmonary edema due to a probable myocardial infarction (53-yr-old man), and cerebral infarction (55-yr-old man that had previously received conventional pituitary radiation therapy). Two patients were discontinued after 8 and 9.5 yr, respectively, due to malignant tumor in the urinary bladder combined with a cerebral infarction (71-yr-old woman who had not received conventional pituitary radiation therapy) and chronic lymphatic leukemia (54-yr-old woman).

One patient received insulin treatment due to diabetes mellitus diagnosed before the study start. In four patients, a
diagnosis of type 2 diabetes mellitus was made between 1 and 6.5 yr. Three of these patients, with BMI between 32 and 38 kg/m², received oral treatment due to the type 2 diabetes mellitus after 4, 6, and 7 yr, respectively, of GH replacement. In addition, two of these patients had angina pectoris after 1 and 5 yr of study, respectively. Six patients received oral lipid lowering treatment due to hyperlipidemia that was initiated between 5 and 8.5 yr.

**Discussion**

In this study, the dose of GH was based on body weight at initiation of treatment in 64 of the 87 patients. In these patients, the GH dose was gradually lowered and individualized, whereas in the remaining 23 patients, the GH dose was individualized from the beginning. After 10 yr, the mean GH dose was approximately half that used at initiation of therapy. However, also the individualized GH dosing resulted in overtreatment as body fat was supranormalized as measured using the four-compartment model (87% of predicted).

The reduction in body fat was transient as assessed using DEXA or the five-compartment model, whereas it was sustained as measured using the four-compartment model (87% of predicted).

The reduction in body fat was transient as assessed using DEXA or the five-compartment model, whereas it was sustained as measured using the four-compartment model. A difference of a similar type has also previously been observed between these methods of body composition estimation (2).

In the present study, it could be hypothesized that in terms of absolute values, the reduction of total body fat was transient but after correction for the age-related increase in body fat in the background population using the four-compartment model, the reduction in body fat was sustained over the 10 yr.

In this study, as in most previous studies (8–11), the GH replacement improved serum lipid profile and thereby likely the cardiovascular risk in the patients. The improvement of serum lipid profile was even progressive except for serum triglyceride concentration, which was unaffected by the 10 yr GH therapy.

The increase in fasting blood glucose concentration could, at least to some extent, be an effect of the normal aging of the patients. In northern Sweden, in 2000 normal subjects, mean fasting glucose increased with increasing age (12). However, in contrast, after an initial deterioration, blood HbA1c level was improved after 7 and 10 yr of GH replacement. This discrepancy between increased blood glucose level and decreased blood HbA1c level could suggest that a blood glucose measurement in the morning after a sc GH injection at bedtime do not reflect 24-h glucose homeostasis in GHD adults receiving GH replacement. We have previously observed a similar discrepancy between fasting morning blood glucose level and blood HbA1c level in our 5-yr follow-up, and this discrepancy was extensively discussed in that publication (2).

In three patients, all with a BMI of 32–38 kg/m², oral treatment was initiated due to type 2 diabetes mellitus. Larger studies than the present one are needed to evaluate the risk of type 2 diabetes mellitus in nonobese as well as in obese GHD patients receiving GH treatment. However, one report, including 5120 GHD adults, suggested that GH replacement did not affect the risk of type 2 diabetes mellitus in GHD adults with normal BMI (6).

Four patients died during the study period (one death per approximately 210 patient-years). This is in line with the results of a study in which overall mortality was one death per 195 patient-years (13). This was lower than that previ-
uously observed by Rosén and Bengtsson in hypopituitary patients without GH substitution (one death per 96 patient-years) (14). Furthermore, in the present study, a malignant disease was observed in four patients. The present study population was too small for a meaningful evaluation of mortality or malignant disease during GH replacement. In a previous study, we evaluated all patients receiving GH replacement at our center (also patients with GH replacement < 10 yr were included) (15). In that study, we found similar risk of mortality or malignant disease during GH replacement as that in the background population (15), but this needs to be confirmed in further studies.

The GHD men had, as also previously observed in several previous studies with shorter duration (2, 16, 17), a more marked response to GH replacement in terms of IGF-I sd score, changes in body composition as measured using DEXA, and serum HDL-C level. In contrast, the reduction in blood HbA1c concentration was less marked in men, which may be a consequence of the slight overtreatment with GH in men as indicated by relatively high IGF-I sd scores and sustained supranormalization of total body fat as measured using the four-compartment model.

The normal aging of the GHD patients during this 10-yr trial probably affected several of the end points studied. However, although this is an uncontrolled study, most end points, except possibly for fasting blood glucose concentration, were changed in an opposite direction as that normally seen during aging.

In conclusion, 10 yr of GH replacement in adults produced approximately similar effects as that observed in studies with shorter duration of treatment. The effect on body fat was seen early and was transient as measured using DEXA and the five-compartment model, possibly due to the normal aging of the patients. The effects on metabolic indices were detected later, but they were sustained and even progressive throughout the study. Women had a less marked treatment response than men in IGF-I sd score, body fat, and lean body mass as estimated using DEXA and serum HDL-C level, but they had a more beneficial response in blood HbA1c level.

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References


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