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ORIGINAL ARTICLE

The effects of five-year growth hormone replacement therapy on muscle strength in elderly hypopituitary patients

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Summary

Objective Little is known of the long-term effects of GH replacement therapy on muscle strength in elderly adults with adult onset GH deficiency (GHD). In this study, the effects of 5 years of GH replacement therapy on muscle function were determined in adults over 60 years of age with adult onset GHD.

Design A prospective, open-label, single-centre study.

Patients Twenty-six (12 male and 14 female) consecutive hypopituitary adults with adult onset GHD, mean age 65·0 (range 61–74) years.

Measurements Upper leg muscle strength was measured using a Kin-Com dynamometer. Right and left handgrip strength were measured using an electronic grip force instrument.

Results The mean insulin-like growth factor-I (IGF-I) SD score increased from −1·10 at baseline to 1·21 at end of the study. Body weight was unchanged during the 5-year study. A sustained increase in lean body mass and a sustained reduction of body fat was observed as measured using dual-energy X-ray absorptiometry (DEXA). The GH replacement therapy induced a sustained increase in isometric (60) knee flexor strength. After statistical correction for age and sex variables using observed/predicted value ratios, a sustained increase was also observed in concentric knee flexor strength at an angular velocity of 60 /s, concentric knee extensor strength at 60 /s and 180 /s, and peak right handgrip strength. At baseline, knee flexor strength was 90–96% of predicted, knee extensor strength was 85–87% of predicted, and hand-grip strength was 74–80% of predicted values. At study end, knee flexor strength was 98–106% of predicted, knee extensor strength was 90–100% of predicted, and hand-grip strength was 80–87% of predicted values.

Conclusion Elderly patients with adult onset GH deficiency had decreased baseline muscle strength also after correction for age and sex. The 5-year GH replacement therapy normalized knee flexor strength and improved, but did not fully normalize, knee extensor strength and handgrip strength.

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Introduction

Untreated adult GH deficiency (GHD) is characterized by abnormal body composition with increased fat mass and decreased lean body mass.[1] Studies using both a fixed dose of GH based on body weight and lower individualized GH dosing have shown that GH replacement normalizes body composition in GHD adults.[1–6]

GHD adults of various ages have reduced isometric muscle strength as compared with healthy controls.[2,7,8] Isokinetic muscle strength and local muscle endurance is reduced or in the lower normal range.[7] Replacement with GH increases maximum voluntary isometric and isokinetic strength, changes that become apparent after approximately 1 year of therapy.[2,7–14] The increase in muscle strength during GH replacement is seen regardless whether the GHD is of childhood or adulthood onset although, the magnitude of the increase in muscle strength may be greater in GHD adults who have childhood onset GHD.[15] However, local muscle endurance has been transiently decreased during the first year of GH replacement in adults.[8,14]

Studies have shown clear differences in terms of GH secretion,[16] body fat,[17] and biochemical bone markers[18,19] between elderly GHD patients and normal elderly subjects. Fat-free mass and bone mineral density of elderly GHD patients, however, are not different from those seen in healthy subjects.[17,18] Elderly GHD patients have a similar response to GH replacement therapy in terms of body fat and quality of life as young or middle-aged GHD patients do.[19,20] However, little is known of the baseline status and the effect of GH replacement therapy in elderly GHD adults in terms of muscle strength.

In this single-centre, prospective, open-label study, baseline status and the effects of 5 years of GH replacement therapy on muscle performance were determined in 26 consecutive hypopituitary patients over 60 years of age with adult onset GHD.

	Male	Female	Total
Nonsecreting pituitary adenoma	8	8	16
Hormone-secreting pituitary adenoma	2	3	5
Craniopharyngioma	1	1	2
Empty sella	1	1	2
Pituitary apoplexy	0	1	1

	Baseline			Study end		
Number of deficiencies	Male	Female	Total	Male	Female	Total
One additional deficiency	2	3	5	2	2	4
Two additional deficiencies	3	2	5	2	2	4
Three additional deficiencies	7	9	16	8	10	18
Diabetes insipidus	3	2	5	3	2	5

Table 1. Causes of pituitary deficiency and the type of pituitary deficiency in the study population of 26 elderly patients over 60 years with adult onset GH deficiency (GHD). No patient had isolated GHD

Subjects and methods

Patients

Twenty-six (12 male and 14 female) hypopituitary patients with adult onset GHD were included in the study between 1991 and 1995. The patients' mean age was 65·0 (0·7; range 61–74) and all were diagnosed of pituitary disease or other pituitary hormonal deficiency. The pituitary deficiency was mainly caused by pituitary tumours or their treatment (Table 1). Twenty-one of the patients had been treated surgically and 17 had received radiotherapy. Most patients have multiple anterior pituitary deficiencies (Table 1). Possibly due to late effects of radiotherapy, several patients have more anterior pituitary deficiencies at study end as compared with baseline (Table 1). In 25 patients, the diagnosis of GHD was based on a maximum peak GH response of less than 3 g/l (gmU/l) during insulin-induced hypoglycaemia (blood glucose ≤ 2·2 mmol/l; $n = 24$) or during a combined GH-releasing hormone-pyridostigmine stimulation test ($n = 1$). In one patient with three additional anterior pituitary hormonal deficiencies, a stimulation test was not performed.

When required, patients received replacement therapy with glucocorticoids, thyroid hormone, gonadal steroids and desmopressin throughout the study period. ACTH-deficient patients received a standard dose (25 mg/day) of cortisone acetate and hypogonadal males received a standard dose (250 mg im) of testosterone enantate every 4th week. Two of the 14 females received oestrogen replacement therapy.

The level of physical activity was not measured throughout the study but none of the patients reported participating in group activities on regular basis or mild to moderate strength training alone. Side effects were mild and were mostly related to fluid retention.

Two patients died during the study period [pneumonia ($n = 1$) and myocardial infarction ($n = 1$)]. Three patients discontinued from the study due to adverse events [prostate cancer ($n = 1$) and epileptic seizures ($n = 2$)], and one patient was excluded due to lack of compliance. All patients were, however, retained in the statistical analysis as the last observed value for each variable was carried forward according to the intention-to-treat approach used.

Study protocol

This is an ongoing, prospective, open-label treatment trial of the administration of recombinant human GH in adult patients with GHD. Twenty-six consecutive elderly patients with adult onset GHD were treated with GH for 5 years. The initial target dose of GH in the first 12 patients was 11·9 g/kg/day (0·25 IU/kg/week). The dose was gradually lowered and individualized when the weight-based dose regimen was abandoned.[21] In the remaining 14 patients, the dose of GH was individualized from the beginning with the aim of normalizing IGF-I SD score and body composition, as estimated using the four-compartment model, in each patient.[21]

At baseline and after each year of treatment, physical examinations including measurements of body composition and muscle strength were performed. Titration of the dose of GH was performed every 3rd month during the 1st year and every 6th month thereafter. 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.

Ethical considerations

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).

Body composition

Dual-energy X-ray absorptiometry (DEXA) (Lunar DPX-L, Lunar Corp., Madison, Wisconsin, USA; software version 1·3) was used to measure lean body mass (LBM) and body fat (BF_{DEXA}).[22] The relative error for LBM was 1·5%.

Body cell mass (BCM), extra cellular water (ECW), and body fat (BF) were estimated using a four-compartment model based on total body potassium (TBK) and total body water (TBW) assessments.[23] TBK was assessed using a whole body counter [coefficient of variation (CV) = 2·2%] and TBW was determined by the isotope dilution of tritiated water (CV = 3·2%). Normative values for the four-compartment model were from body composition studies of 476 healthy individuals.[23]

Table 2. The dose of GH during 5 years of GH substitution in 26 elderly GH deficient patients over 60 years of age and the effects of this treatment on serum IGF-I, IGF-I SD score, and body height, weight and BMI. All values are shown as the mean (SEM). The statistical analyses are based on a one-way ANOVA followed by post hoc Student's Newman–Keuls test

	Baseline	1 year	2 years	3 years	4 years	5 years
Dose of GH (mg/day)	0·73 (0·07)	0·40 (0·03)***	0·40 (0·03)***	0·36 (0·02)***	0·36 (0·02)***	0·36 (0·02)***
Serum IGF-I (g/l)	88 (10)	246 (13)***	234 (22)***	232 (20)***	220 (21)***	202 (18)***
IGF-I SD score	−1·10 (0·20)	2·06 (0·46)***	1·69 (0·46)***	1·72 (0·41)***	1·54 (0·44)***	1·21 (0·39)***
Body height (cm)	168·8 (2·3)	168·8 (2·3)	168·7 (2·3)	168·5 (2·3)	168·5 (2·3)	168·4 (2·3)*
Body weight (kg)	75·4 (2·4)	74·3 (2·5)	74·7 (2·3)	75·2 (2·5)	74·9 (2·4)	74·5 (2·3)
BMI (kg/m^2)	26·6 (0·9)	26·2 (0·9)	26·4 (0·9)	26·6 (0·9)	26·6 (0·9)	26·4 (0·9)

*$P < 0·05$; ***$P < 0·001$ (*vs.* baseline).

An individual observed/predicted values ratio could then be calculated for BCM (BCM%), ECW (ECW%) and BF (BF%).

Total body nitrogen (TBN) was measured by *in vivo* neutron activation with a measurement error of approximately 4%.[24,25]

Measurements of muscle function

Isometric knee-extensor and flexor strength at knee angles of 60 (π/3 rad), and isokinetic muscle strength at angular velocities of 60 / s (π/3 rad/s) and 180 /s (π rad/s), were measured using a Kin-Com dynamometer (Chattecx Co., Chattanooga, TN).[8,26–28] Gravity correction was used for isokinetic muscle strength.[8,26–28] The patients were positioned sitting in the test chair with a hip angle of 90 (π/2 rad). The knee-joint axis was approximated to the Kin-Com measuring axis. The lower leg was secured to the Kin-Com shin pad at 3 cm proximal to the insertion of the anterior tibialis muscle with the ankle joint at 90 . 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 prior to the muscle tests. The methodological errors in duplicate measurements for isometric muscle strength and isokinetic muscle strength at angular velocities of 60 /s and 180 /s were 9%, 8% and 8%, respectively.[8,26–28]

Right and left handgrip strength was measured using an electronic grip force instrument (Grippit®, AB Detector, Göteborg, Sweden), which measures the maximum momentary force and the mean force over a set period of 10 s in Newtons. The methodological error between duplicate determinations was between 4·4% and 9·1%.[8,27,29]

Local muscle endurance in the quadriceps muscle was measured as the percentage reduction (fatigue index) in peak torque between the first and the last three knee extensions in a series of 50 maximal voluntary isokinetic contractions with an angle of velocity of 180 / s (π rad/s). The methodological error was 1·4% from duplicate determinations.[8,27,30]

Muscle strength values from a normal population

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

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-year cohort of male and female in the reference population (in the present study, only the 60–69 and 70–79 years intervals were relevant). The observed/predicted percentages for each patient were then calculated. Mean body height [1·69 (0·02) m], mean body weight [74·0 (2·5) kg], and mean BMI [25·9 (0·8) kg/m^2] in the reference population were similar to the present study population [baseline: mean body height 1·69 (0·02) m, mean body weight 75·4 (2·4) kg, mean BMI 26·6 (0·9); Table 2].

Biochemical assays

Serum IGF-I concentration was determined by a hydrochloric acid-ethanol extraction radioimmunoassay (RIA) using authentic IGF-I for labelling (Nichols Institute Diagnostics, San Juan Capistrano, CA, USA). Interassay and intra-assay CVs were 5·4% and 6·9%, respectively, at a mean serum IGF-I concentration of 126 g/l, and 4·6% and 4·7%, respectively, at a mean serum IGF-I concentration of 327 g/l. The detection limit of the assay was 13·5 g/l. The individual serum IGF-I-values were compared with age and sex-adjusted values obtained from a reference population of 197 male and 195 female.[31] The individual IGF-I SD scores could then be calculated as described previously.[32]

Statistical methods

All the descriptive statistical results are presented as the mean (SEM). For all variables, within-group differences were calculated using a one-way analysis of variance (ANOVA), with all data obtained from all time points and with time as the independent variable. Post-hoc analysis was performed using Student's Newman–Keuls test. Between-group differences (men *vs.* women) were calculated by a one-way ANOVA, with all data obtained from all time points, and with gender as the independent variable. In order to eliminate for baseline differences, data were transformed as percent change or change from baseline before the analyses of between-group differences. All analyses were performed using an intention-to-treat approach (based on

Table 3. The effects of 5-year GH replacement therapy on body composition as measured using DEXA and the four-compartment model in 26 elderly GHD patients over 60 years. All values are shown as the mean (SEM). The statistical analyses are based on a one-way ANOVA followed by post hoc Student's Newman–Keuls test

	Baseline	1 year	2 years	3 years	4 years	5 years
DEXA						
Body fat (kg)	26·3 (1·7)	24·1 (1·7)**	24·3 (1·6)**	24·3 (1·7)**	24·2 (1·6)*	23·7 (1·6)**
Lean body mass (kg)	46·6 (2·1)	47·8 (2·2)**	47·7 (2·2)**	48·0 (2·2)**	47·9 (2·3)**	48·0 (2·2)**
Four-compartment model						
BF (kg)	22·9 (1·6)	20·6 (1·8)	20·7 (1·6)	21·5 (1·9)	22·0 (2·0)	21·0 (1·8)
BF% (% of pred)	105·1 (4·1)	95·1 (4·7)*	93·7 (3·8)*	94·9 (4·1)*	96·6 (5·3)*	94·7 (4·4)*
BCM (kg)	25·2 (1·2)	26·1 (1·3)	26·1 (1·3)	26·1 (1·3)	25·7 (1·4)	25·2 (1·3)
BCM% (% of pred)	101·2 (3·8)	105·1 (4·5)*	106·0 (4·6)**	105·9 (4·4)**	104·6 (4·5)*	103·8 (4·9)*
ECW (kg)	18·6 (1·0)	19·1 (0·9)	19·3 (0·7)	19·2 (0·9)	19·2 (1·0)	20·0 (0·9)
ECW% (% of pred)	107·9 (5·9)	111·2 (4·6)	111·1 (3·3)	110·0 (5·3)	110·0 (6·5)	115·1 (6·1)
TBN (kg)	1·57 (0·07)	1·62 (0·07)	1·64 (0·08)	1·63 (0·08)	1·60 (0·09)	1·57 (0·08)
TBK (mmol)	3057 (146)	3131 (162)	3145 (157·0)	3127 (157)	3081 (165)	3023 (159)
TBN/TBK (10^{-5} kg/mmol)	50·7 (0·6)	51·7 (1·0)	51·4 (1·0)	50·7 (0·8)	51·3 (1·2)	51·3 (0·94)

*$P < 0{\cdot}05$; **$P < 0{\cdot}01$ (*vs.* baseline).

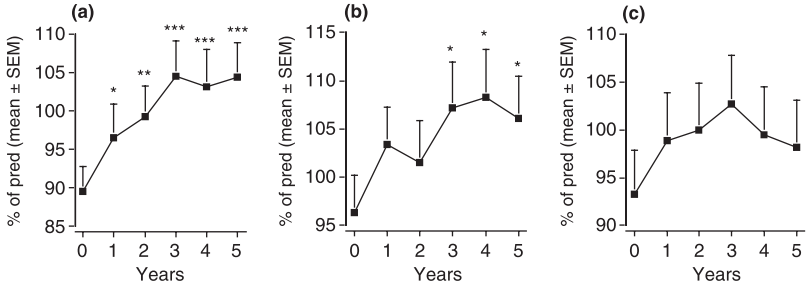

Fig. 1 Observed/predicted value ratios for (a) isometric 60 (b) concentric 60 /s, and (c) concentric 180 /s knee flexor strength in 26 elderly GHD patients above 60 years during 5 years of GH replacement therapy. The vertical bars indicate the SE for the mean values shown. *$P < 0{\cdot}05$; **$P < 0{\cdot}01$; ***$P < 0{\cdot}001$ *vs.* baseline.

the last observation carried forward principle). Correlations were calculated using Pearson's linear regression coefficient. A two-tailed $P < 0{\cdot}05$ was considered significant.

Results

GH dose, IGF-I SD score, and body composition

The mean dose of GH decreased during the first 2 years of the study (Table 2). The mean IGF-I SD score increased from −1·10 at baseline to 1·21 at study end (Table 2). Body weight was unchanged during the 5-year study (Table 2).

The GH therapy induced a sustained reduction in body fat, and a sustained increase in lean mass, as measured using DEXA (Table 3). As measured using the four-compartment model, BF, BCM, and ECW were unchanged (Table 3). However, after statistical correction for age and sex variables, there was a sustained decrease in BF%, and a sustained increase in BCM% (Table 3). TBN, TBK and TBN/TBK ratio were not significantly affected by the GH replacement therapy (Table 3).

Muscle strength

The GH replacement therapy induced a sustained increase in isometric (60) knee flexor strength (Table 4). Other measurements of muscle performance, including the fatigue index (expressed as the percentage reduction in torque at 50 repeated isokinetic knee extensions), were unaffected (Table 4). After statistical correction for age and sex variables using observed/predicted value ratios, however, a sustained increase was also observed in concentric knee flexor strength at an angular velocity at 60 /s (Fig. 1), concentric knee extensor strength at 60 /s and 180 /s (Table 5), and peak right handgrip strength (Fig. 2).

At baseline, concentric knee flexor strength at angular velocities of 60 /s and 180 /s and the fatigue index were similar to the reference population whereas all other variables reflecting muscle performance were lower in the elderly GHD patients than that in the reference population (data not shown). At study end, isometric (60) knee flexor strength, concentric knee flexor strength at 60 /s and 180 /s, concentric knee extensor strength at 180 /s, and the fatigue index were similar to the reference population whereas all other measurements of muscle performance were lower in the elderly GHD patients (data not shown).

Gender differences

The dose of GH (mg/day as well as adjusted for body weight) was similar in both sexes (data not shown). The increase in IGF-I SD score was, however, more marked in men (data not shown). Age

Table 4. Measurements of isometric and isokinetic strength in knee flexion and extension, hand-grip strength, and the fatigue index during 5 years of GH replacement in 26 elderly GHD patients over 60 years. All values are shown as the mean (SEM). The statistical analyses are based on a one-way ANOVA followed by post hoc Student's Newman–Keuls test

	Baseline	1 year	2 years	3 years	4 years	5 years
Knee flexion						
Isometric 60 (Nm)	55·0 (3·7)	59·0 (4·6)**	60·1 (4·4)**	60·9 (4·3)**	59·7 (4·3)*	59·0 (4·3)*
Concentric 60 /s (Nm)	57·0 (4·1)	60·2 (4·2)	58·5 (4·2)	59·3 (4·3)	60·1 (4·5)	57·8 (4·5)
Concentric 180 /s (Nm)	78·2 (3·0)	82·3 (3·4)	82·1 (3·5)	81·4 (3·4)	81·2 (3·7)	80·3 (3·6)
Knee extension						
Isometric 60 (Nm)	136·0 (9·0)	135·5 (9·8)	137·6 (10·2)	135·0 (9·9)	133·5 (8·9)	133·2 (9·1)
Concentric 60 /s (Nm)	109·9 (6·8)	113·1 (7·0)	113·0 (7·8)	111·4 (7·3)	113·0 (7·5)	109·9 (7·1)
Concentric 180 /s (Nm)	41·2 (5·0)	43·2 (6·0)	43·3 (6·2)	42·6 (5·7)	41·6 (5·8)	40·4 (5·5)
Grip strength, right hand						
Peak (N)	282·6 (20·1)	282·0 (22·5)	290·7 (22·8)	294·8 (23·2)	297·2 (23·5)	297·3 (24·0)
Average 10 s (N)	236·1 (18·9)	232·1 (19·9)	239·3 (20·6)	246·4 (21·6)	241·3 (21·0)	245·0 (21·8)
Grip strength, left hand						
Peak (N)	266·1 (19·9)	253·9 (21·5)	256·0 (19·4)	261·8 (22·0)	265·9 (22·0)	268·5 (23·2)
Average 10 s (N)	226·3 (17·7)	212·9 (18·5)	218·9 (17·2)	218·6 (18·1)	225·2 (18·8)	219·8 (18·9)
Fatigue index (% reduction of peak torque)	39·4 (2·8)	40·4 (1·8)	41·7 (2·3)	40·8 (2·2)	41·7 (2·2)	40·1 (2·3)

*$P < 0{\cdot}05$; **$P < 0{\cdot}01$ (*vs.* baseline).

Table 5. Knee extensor strength, left handgrip strength, and the fatigue index, expressed as percent of predicted, during 5-year GH replacement therapy in 26 GHD patients above 60 years. All values are shown as the mean (SEM). The statistical analyses are based on a one-way ANOVA followed by post hoc Student's Newman–Keuls test

	Baseline	1 year	2 years	3 years	4 years	5 years
Knee extension						
Isometric 60 (% of pred)	84·6 (3·5)	85·3 (4·3)	87·0 (4·3)	87·6 (4·0)	87·9 (3·9)	90·0 (4·1)
Concentric 60 /s (% of pred)	86·0 (3·1)	89·0 (3·1)	89·4 (3·9)	90·4 (3·2)	92·5 (3·7)*	92·1 (3·6)*
Concentric 180 /s (% of pred)	87·1 (3·6)	92·7 (4·2)	93·0 (4·1)	96·6 (3·9)**	97·2 (4·2)**	99·6 (4·0)***
Grip strength, left hand						
Peak (% of pred)	80·3 (3·3)	76·4 (4·1)	78·4 (3·2)	81·1 (3·4)	83·2 (3·8)	84·6 (3·8)
Average 10 s (% of pred)	77·5 (3·4)	72·9 (4·4)	76·1 (3·3)	77·6 (3·6)	80·3 (3·8)	79·8 (4·1)
Fatigue index						
(% of pred)	93·8 (6·6)	96·1 (4·4)	99·2 (5·5)	97·4 (5·2)	100·2 (5·1)	96·2 (5·4)

*$P \leq 0{\cdot}05$; **$P < 0{\cdot}01$; ***$P < 0{\cdot}001$ (*vs.* baseline).

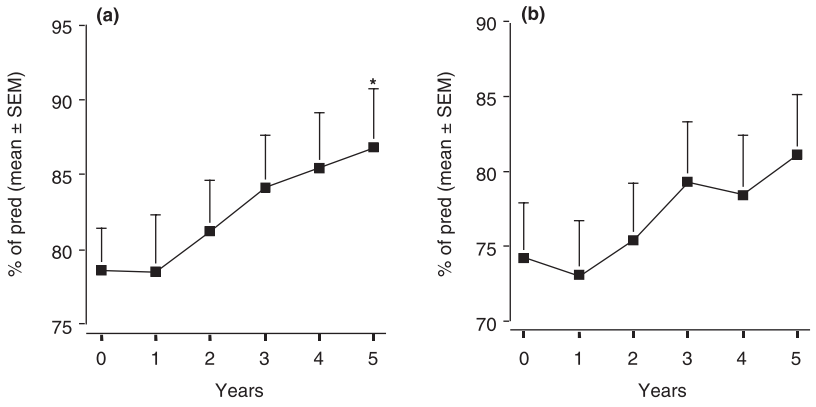

Fig. 2 Observed/predicted value ratios for right-hand peak grip strength (a) and average 10 sec grip strength (b) in 26 elderly GHD patients above 60 years during 5 years of GH replacement therapy. The vertical bars indicate the SE for the mean values shown. *$P < 0{\cdot}05$.

and sex-adjusted muscle strength values were similar in men and women throughout the treatment, except for isokinetic (60 /s) knee flexor strength, which was lower in women ($P < 0{\cdot}05$). The response to treatment (change from baseline) in all variables reflecting body composition or muscle performance was similar among men and women (data not shown).

Comparisons between male and female receiving and not receiving sex steroid replacement were not meaningful due to small subgroups (only one male did not receive testosterone treatment and only two females received oestrogen treatment).

Correlation analysis

Absolute values of baseline muscle strength were not correlated with the percent change in the variables after 5 years of GH replacement therapy. Observed/predicted value ratios (muscle strength statistically corrected for age and sex) of concentric (60 /s) knee flexor strength ($r = -0{\cdot}49$, $P < 0{\cdot}05$), peak right handgrip strength ($r = -0{\cdot}51$, $P < 0{\cdot}05$), peak left handgrip strength ($r = -0{\cdot}49$, $P < 0{\cdot}05$), and average 10 s left handgrip strength ($r = -0{\cdot}50$, $P < 0{\cdot}05$) were, however, inversely correlated with the percent change at study end in the variables. This means that those patients with the lowest observed/predicted muscle strength in these variables at baseline had the greatest response to treatment. The absolute value as well as the observed/predicted value ratio of the fatigue index was inversely correlated with the percent change after 5 years ($r = -0{\cdot}70$, $P < 0{\cdot}001$ and $r = -0{\cdot}71$, $P < 0{\cdot}001$). Therefore, the patients with highest fatigue index at baseline had the lowest increase in the fatigue index.

At baseline serum IGF-I concentration was positively correlated with isometric (60) and concentric (60 /s) knee flexor strength ($r = 0{\cdot}46$, $P < 0{\cdot}05$ and $r = 0{\cdot}42$, $P < 0{\cdot}05$, respectively). At study end, the percent change or absolute change in serum IGF-I concentration was not correlated with the percent change or absolute change in any variable reflecting muscle strength.

There was no correlation between age at baseline and the percent change or absolute change in IGF-1 or IGF-I SD score, body composition, or muscle performance (data not shown).

Discussion

This single-centre, prospective, open-label study is the first one that has determined the long-term effect of GH replacement in elderly GH-deficient patients on muscle strength. It shows that elderly hypopituitary patients with GHD have reduced muscle strength. The 5-year GH replacement normalized knee flexor strength and improved, but did not fully normalize, knee extensor strength and right handgrip strength.

At baseline, as measured using the four-compartment model, body fat statistically corrected for age and sex in the elderly GHD patients (105% of predicted) was increased. In line with the results of a previous study by Toogood *et al.*,[17] body cell mass was similar in the GHD adult patients and the reference population. The GH replacement therapy in the elderly hypopituitary patients reduced body fat as measured using DEXA. At study end, as measured using the four-compartment model, body fat in the elderly GHD patients (95% of predicted) was even lower than that in the reference population, suggesting that the dose of GH in this study was a little too high.

GH replacement in the elderly GHD patients increased lean mass as measured using DEXA. In contrast to the previous findings in younger GHD patients,[6,33] there was no significant change in TBN. As measured using the four-compartment model, the absolute value of BCM was unchanged whereas after statistical correction for age and sex variables using an observed/predicted values ratio, BCM% was increased. The reason for the different results in lean mass as measured using DEXA, TBN, and the four-compartment model in response to GH replacement in elderly adults is unclear. It could be argued that the increase in lean mass in the elderly GHD patients, as measured using DEXA, was partly due to increased hydration of the lean mass. On the other hand, previous studies have shown that the increased muscle strength during GH replacement was due to increased muscle mass whereas there was no major change in muscle morphology[10,13,34] Therefore, as there was an increase in muscle strength in the present study, it is unlikely that the increase in lean mass as measured using DEXA was only the result of increased hydration of lean mass.

After statistical correction for age and sex variables, adults with GHD over the age of 60 showed reduced muscle strength. Baseline isometric knee flexor strength was 90–96%, baseline knee extensor strength was 85–87%, and baseline handgrip strength was 74–80% of predicted values. GH replacement therapy normalized knee flexor strength whereas knee extensor and handgrip strength were not fully normalized. The lower effect on handgrip strength is in line with the previous finding in younger GHD patients that GH replacement therapy induced a greater increase in proximal than distal muscle mass.[8,35] A larger effect by GH on proximal leg muscle strength than handgrip strength could therefore be anticipated. Furthermore, the lack of full normalization of muscle performance by GH replacement in this study could suggest that the deficiency or insufficient treatment of other anterior pituitary hormones was also of importance for the decreased muscle strength in the elderly hypopituitary patients. The consequences of testosterone deficiency in men and oestrogen deficiency in women were not, however, possible to evaluate since only one man did not receive testosterone treatment and only two women received oestrogen treatment.

GH replacement has been shown to increase well-being and physical activity in young,[33,36] as well as in elderly GHD patients.[20] In middle-aged GHD patients who have not undergone GH replacement, a resistance training program increased muscle power.[37] In trials on healthy elderly males,[38,39] there was a GH-independent increase in local muscle performance as a result of increased physical exercise.[38,39] This was an uncontrolled study. Furthermore, the activity level of the patients was not controlled or measured. A possible increase in physical activity in the elderly GHD patients in the present study could have contributed to the increase in muscle strength and possibly also to the different responses in different muscle groups. In probable support of this, the results of several studies suggest that the activity level is of more importance for leg muscle than handgrip strength.[40–42] Finally, as this was an uncontrolled study, the possibility can not be ruled out that there was an increase in physical activity due to factors other than GH, such as the patients' expectations or their increased care.

The GH replacement therapy not only induced a moderate increase in absolute muscle strength in elderly hypopituitary patients, but it also provided protection from the age-related decline in muscle strength. Data from the reference population indicate a reduction in muscle strength of approximately 7% over a 5-year period.[27] In the present study, the maximum effect of the GH replacement therapy in terms of absolute muscle strength values was observed after approximately 2–3 years of treatment. However, when using observed/predicted values ratios, thereby statistically correcting for age and sex, the effect on muscle strength was maintained throughout the 5 year study.

We sought predictors of treatment response and found inverse relationships between age and sex-adjusted baseline levels and the changes in concentric (60 /s) knee flexor strength, peak handgrip strength and average 10 s handgrip strength. Although this could be due to regression towards the mean, it may suggest that patients with low baseline muscle strength in relation to normative data had the greatest response to treatment. Furthermore, these findings imply that GH will not increase muscle strength in elderly patients beyond the upper normal level. In support of this, at study end, knee flexion strength was 98–106% of predicted, knee extension strength was 90–100% of predicted, and handgrip strength was 80–87% of predicted.

At baseline, serum IGF-I concentration was positively correlated with isometric (60) and concentric (60 /s) knee flexor strength. This is in line with previous observations that GH as well as IGF-I are of importance for muscle morphology, function, and metabolism.[8,43] Furthermore, in a study by Ekman *et al*.,[44] hypopituitary patients with the largest changes in IGF-I in response to GH replacement had better biomechanical output than patients with small changes in IGF-I. No correlation, however, was found in the present study between the change in serum IGF-I concentration and the change in any measure of muscle function. This suggests that circulating IGF-I levels were not of major importance for the obtained response in muscle strength.

Baseline age- and sex-adjusted muscle strength was similar among male and female except for concentric (60 /s) knee flexor strength, which was lower in females. Studies in younger GHD adults have shown lower muscle strength in GHD females (also after correction for age and sex) in most measures of muscle strength.[14] Furthermore, in younger GHD adults, males have a more marked treatment response in TBN and TBN/TBK ratio,[14,33] which was not observed in the present study. The present study cohort was smaller than those in the studies on younger GHD adults,[14,33] and the statistical power could therefore be weaker in this study. It is, however, possible that gender differences in TBN and muscle strength could be smaller in older than in younger GHD adults. Androgen deficiency could be of smaller importance in elderly GHD females. Moreover, only a very small portion of the females in this study ($n = 2$) had oestrogen treatment. Oral oestrogen treatment might reduce protein synthesis during GH treatment.[45]

In conclusion, the results of this single-centre, prospective, open-label study show that elderly hypopituitary patients above 60 years of age with GH deficiency experience decreased muscle strength. Five years of GH replacement therapy increased muscle strength and also reversed the age-related decline in muscle strength. Proximal leg muscle groups responded more markedly to GH replacement than distal arm muscle groups. The present results suggest that GH replacement in elderly GHD patients is useful in order to preserve and increase muscle strength.

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