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Exercise capacity and hormonal response in adults with childhood onset growth hormone deficiency during long-term somatropin treatment

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Summary Growth hormone (GH) deficiency in adults in associated with reduced muscular strength and peak oxygen uptake (peak Vo_2). How these variables are influenced by long-term somatropin therapy in adults with childhood onset GH-deficiency has not been precisely defined. The effect of somatropin treatment in 20 childhood onset GH-deficient adults on muscular strength, maximal exercise capacity, and hormonal response to exercise were therefore examined in a double-blind placebo-controlled study with recombinant human GH (rhGH, 12 μg/kg/day) for 6 months, followed by 36 months of open-labeled uninterrupted therapy, after which treatment was stopped for 9 months.

After 6 months of treatment, exercise capacity increased significantly, as assessed by time to exhaustion [mean change (95% CI) 0.8 (0.2, 1.4) min, $P<0.05$], total (accumulated) work [11.6 (0.8, 22.4) kJ, $P<0.05$] and peak Vo_2 [2.6 (0.3, 4.9) ml/kg/min, $P<0.01$], whereas no significant changes were observed during placebo. This effect on exercise capacity remained unchanged during long-term somatropin treatment, mainly due to increased capacity among patients with isolated GH deficiency. Nine months after stopping treatment, peak Vo_2 decreased by 11% from 32.8 ± 2.5 to 29.1 ± 2.1 ml/kg/min ($P<0.05$). Maximal muscular handgrip strength was not affected by treatment. Long-term GH therapy resulted in decreased respiratory exchange value (R value) at rest and during exercise ($P<0.001$), suggesting a metabolic role with increased fat combustion. Resting and submaximal noradrenaline levels decreased during somatropin treatment ($P<0.05$), while no effect was observed for other exercise-induced hormonal responses, including adrenaline, insulin, prolactin, renin, and ACTH.

We conclude that somatropin therapy to childhood onset GH deficient adults has a favourable effect on exercise capacity and may have a potentially beneficial effect on plasma catecholamines.

INTRODUCTION

Previous studies with recombinant human somatropin therapy in growth hormone deficient adults have demonstrated an increase in lean body and muscle mass [1–3], increased physical exercise performance [4–6], and improved quality of life [3]. However, most studies with GH therapy have been performed in adult onset GH-deficient patients, with less experience in adult patients with childhood onset GH-deficiency. The discrimination between these two groups seems to be of practical clinical interest since clinical and biochemical variables and responses to therapy are different [7].

Attanasio *et al.*[7] recently demonstrated that patients with adult onset GH-deficiency increased physical mobility and energy levels after GH treatment, while no consistent effects were observed among those with childhood onset GH-deficiency. More objective variables of

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exercise capacity, such as maximal workload or time to exhaustion have been reported to be increased during GH therapy in both groups [3,4,6], but gas exchange variables and maximal oxygen uptake have not been reported in childhood onset GH-deficiency.

The purpose of the present study was therefore to examine the effect of long-term somatropin treatment in childhood onset GH-deficient adults on muscular strength and exercise capacity assessed by peak oxygen uptake. Additionally, since cardiac structure and function may deteriorate after stopping treatment with GH [8], hemodynamic and gas exchange variables were re-examined 9 months after stopping of somatropin therapy. Since GH-deficiency is known to alter body composition and fuel metabolism, we also measured catecholamines and insulin during the exercise test, and hypothesized that GH-substitution therapy might modulate these responses. Lastly, we wanted to assess whether GH-deficiency and subsequent substitution therapy influenced the normal exercise-induced increase in prolactin and ACTH secretion.

MATERIALS AND METHODS

Patients

The present study was a single-center study performed as a part of a larger multicenter study, as previously reported [7]. Twenty adult patients (5 females and 15 males) with childhood onset GH-deficiency participated in the study. Their clinical characteristics are given in Table 1. All had previously received pituitary GH treatment during childhood (in the early 1960s and 1970s), but none had received GH treatment during the last 2 years. Nine patients had isolated GH deficiency (isolated GHD) (male/female:8/1), while 11 had multiple pituitary hormone deficiencies (MPHD) (male/female: 7/4). The latter group received stable and clinically appropriate substitutional treatment with corticosteroids (n=4), thyroxine (n=8), and sex steroids (n=7). Diagnosis of GH deficiency was performed by means of peak GH serum levels of <5 ng/ml during standard stimulation tests.

Table 1 Clinical characteristics of the patients.

	Mean ± SE	Range
Number	20	
Age (years)	30 ± 2	18–48
Height (cm)	165 ± 2	148–181
Weight (kg)	67 ± 4	44–104
BMI (kg/m^2)	24.3 ± 0.9	18.5–34.4
Time since GH stopped (years)	10.7 ± 1.7	2–26
Duration of GH treatment (years)	8.6 ± 0.9	2–18

Because of lack of GH in the 1960s and 1970s, the diagnosis of GH deficiency had been established by at least three stimulation tests: all had insulin hypoglycemia before the start of GH treatment in childhood, and 1 year after this treatment was stopped. GH deficiency was also confirmed in adulthood before the present study with clonidine (5 μg/kg body weight).

The patients were randomized to two groups. One received rhGH (Humatrope, Eli Lilly & Co, IN, USA), and the other received placebo diluted with the same solution as for rhGH as a daily subcutaneous injection at bedtime for 6 months. Four out nine of patients with isolated GHD, 5 out of 11 patients with MPHD, and 1 out 5 women started with rhGH. The dose of rhGH was 6.25 μg/kg/day for 4 weeks, which thereafter was increased to 12.5 μg/kg/day. On completion of the randomized phase of the study, to avoid breaking the study code, all patients were treated with 6.25 μg/kg/day for 4 weeks. Thereafter, all patients were treated with 12.5 μg/kg/day for 36 months. The serum IGF-I was determined at each visit. In patients in whom IGF-I increased to levels higher than 350 ng/ml, which is the upper normal range, the somatropin dose was adjusted. In patients with subnormal IGF-I (lower than 140 ng/ml), the somatropin dose was increased in order to achieve IGF-I levels within the levels of 140–350 ng/ml. With these dosages, no complications were observed. All patients were re-examined after 9 months without somatropin treatment.

The protocol was approved by The Regional Ethics Committee at the University of Oslo, and all patients gave written informed consent.

Methods

Studies were performed at baseline (two tests with a 1-week interval), after 6, 12, 18 and 24 months of treatment, at the end of treatment (36–42 months of active treatment), and 9 months after termination of somatropin treatment.

Exercise tests were performed using an electromagnetically-braked cycle ergometer, in the morning after an overnight fast. Each subject rested for a period of 15 min before baseline recordings were obtained. During exercise, pedal rate was kept constant at 60 rpm, with stage duration of 2 min. Workload was initiated between 20 and 50 W, with subsequent increments ranging from 20 to 50 W in order to obtain exercise duration of approximately 10 min [9,10]. Exercise was terminated at exhaustion (defined as the inability to pedal at 60 rpm).

In a subgroup of 10 randomly selected patients, a cannula was placed into an antecubital vein for blood sampling at baseline, after 12 and 18 months of treatment for hormonal analysis. This part of the study did not contain a placebo control. Venous blood was sampled at rest, and

during submaximal (stage 3, approximately 60% of peak Vo_2), and maximal exercise. Plasma was immediately separated and frozen at −80°C for later analysis for catecholamines, renin, insulin, ACTH, prolactin and growth hormone.

Pulmonary oxygen uptake (Vo_2) was measured using an open-circuit technique (EOS/SPRINT, E. Jaeger, Germany). Heart rate (HR) was recorded from an electrocardiogram and blood pressure (BP) with a semi-automatic-recorder (Ergo-metrics 900, Ergoline, Germany) before exercise, during each stage of exercise (during the last 30 s at each stage), at maximum exercise and after 1, 2 and 4 min of recovery.

Maximal handgrip strength in both hands was measured with a strain gauge dynamometer (Martin Vigorometer, Germany), and the average of three consecutive measurements was used in the calculation.

Blood plasma was analysed by standard methods. Lactate was determined using a commercial system (Monotest, Boehringer Mannheim Diagnostics). Catecholamines were evaluated using HPLC (Waters Instruments) with an electrochemical detector. Reagents were delivered by Chromsystems, Munchen, Germany. Hormones were measured with immunoradiometric assays: GH (in-house method with antibodies from Medix Biochemical, Kauniainen, Finland), ACTH (Nichols Inst. Diagnostics, San Juan Capistrano, CA, USA); with radioimmunoassay: insulin (antibodies from Linco Research, St Louis, MO, USA); and with immunofluorometric assay: prolactin (Delfia; Pharmacia Diagnostics, Uppsala, Sweden). Renin was measured with an in-house radioimmunoassay of angiotensin I produced during incubation.

Statistical analysis

The results are expressed as means and SE, while changes are expressed as mean with associated 95% confidence interval (95% CI). Comparison between the groups were carried out by using analysis of variance (ANOVA) with the mean of the two baseline values as cavariate. In order to study and compare the development during treatment, ANOVA with repeated measurements and trace analysis was used. If the ANOVA demonstrated a statistically significant effect, *post-hoc* (multiple comparisons) statistics were employed using the Student–Newman–Keul's test. In the analysis of baseline values, the results were expressed as simple regression plots and limits of agreement, with an index of agreement (AI) defined as 1− [2SD (baseline 1−baseline 2)/Mean (baseline 1−baseline 2)] [11,12]. A positive value close to 1 indicates sufficient or good agreement [12]. For the variables obtained during exercise, the area under the curve was calculated using the Trapezoid method. For the hormonal analysis, in the paired situation, multiple analysis of variance (MANOVA) were performed à priori and, if significant, Wilcoxon's rank sum test for paired data was performed à posterior. Relations between variables were tested using Spearman's rank correlation test. $P<0.05$ was considered statistically significant.

RESULTS

All patients completed the double-blind period. Three dropped out after 1 year because of the inconvenience of follow up, and one patient was excluded from the study after 2 years because of impaired glucose tolerance as assessed by $HbA1_c$. The weight of the patients increased significantly during somatropin treatment (Table 3). Analysis of the two baseline data demonstrated sufficient agreement for all measured variables except diastolic blood pressure in which comparisons of the two baseline periods indicates doubtful repeatability. For example, the AI for the two baseline tests was 0.79 for peak Vo_2, with mean (SD) difference of −0.07 (0.18) l/min. Accordingly, the two baseline data sets were combined in further analysis, and the mean of the two baseline sets reported.

Exercise capacity

Baseline peak Vo_2 revealed an exercise capacity of approximately 85% of predicted values [13], slightly lower among patients with MPHD (80 ± 5.5%) than those with isolated GHD (92 ± 6%), although the difference was not statistically significant. There was no significant correlation between peak Vo_2 at baseline and any of the measured variables (including age, height, weight, HR, BP, time from previous GH treatment, and stimulated IGF-I), except a negative correlation between peak Vo_2 and BMI ($R=-0.60$, $P<0.01$).

During the double-blind period (6 months), exercise capacity assessed by exercise duration ($P<0.05$), total (accumulated) work ($P<0.05$) and peak Vo_2 ($P<0.01$) increased significantly during somatropin treatment, while no changes were observed during placebo (Table 2). Accordingly, the changes observed for total work and peak Vo_2 during GH treatment were significantly different from placebo ($P<0.05$) (Table 2). During subsequent open-label treatment, exercise capacity increased or remained stable. Nine months after stopping treatment, peak Vo_2 decreased by 11% from 32.8 ± 2.5 to 29.1 ± 2.1 ml/kg/min ($P<0.05$) (Table 3, Fig.1).

None of the baseline characteristics except type of deficiency (i.e. isolated GHD vs MPHD) could predict an increase in peak Vo_2 during treatment. In patients with isolated GHD peak Vo_2 increased from 2.21 (0.19) l/min to 2.51 (0.23) l/min ($P<0.05$) and 2.67 (0.31) l/min ($P<0.05$) after 0.5 and 3–3.5 years of somatropin

Table 2 Exercise capacity, maximal gas exchange and hemodynamic variables during 6 months treatment with somatropin (rhGH) and (n=10) or placebo (n=10).

	Treatment	baseline	Change after 6 months
Time to exhaustion (min)	GH	10.1 ± 0.4	0.8 (0.2,1.4)*
	Placebo	10.1 ± 0.4	0.0 (–0.6, 0.6)
Accumulated work (kJ)	GH	61 ± 10	12 (1,22)†,‡
	Placebo	61 ± 6	–1 (–6,4)
Peak Vo_2 (1/min)	GH	2.2 ± 0.2	0.2 (0.1,0.4)†, ‡
	Placebo	2.2 ± 0.2	–0.1 (–0.3, 0.02)
Peak Vo_2 (ml/min/kg)	GH	31.6 ± 2.2	2.6 (0.3, 4.9) †, ‡
	Placebo	33.7 ± 2.4	–1.7 (–3.9,0.5)
R value	GH	1.18 ± 0.03	0.06 (0.01,0.11)*
	Placebo	1.22 ± 0.01	0.03 (–0.02,0.08)
Ventilation (1/min)	GH	72 ± 5	7 (2,13)*
	Placebo	71 ± 7	5 (–7,18)
Heart rate (bpm)	GH	176 ± 3	11 (–9,30)
	Placebo	172 ± 5	2 (–4,7)
Systolic BP (mmHg)	GH	181 ± 6	14 (1,27)*
	Placebo	175 ± 8	15 (5,24)*

Values are given as mean ± SE, and mean change with 95% CI. Vo_2, oxygen uptake; *R* value, respiratory exchange value. *P<0.05, †P<0.01: significant change during treatment; ‡P<0.01: significant difference from placebo treatment.

Table 3 Weight, exercise capacity, gas exchange and hemodynamic variables at baseline and changes observed during treatment with somatropin (rhGH), and 9 months after end of treatment.

	Baseline (n=20)	18 months (n=17)	42 months (n=16)	After stopping (n=16)
Weight (kg)	67.8 ± 3.7	1.2 (–2.2,4.6)	3.5 (0.0,6.9)*	5.3 (1.9,8.7)*
Time to exhaustion (min)	10.1 ± 0.3	1.2 (0.3,2.0)*	0.6 (–0.3,1.4)	–0.1 (–1.0,0.8)
Accumulated work (kJ)	61 ± 5	17 (6.29)*	11 (0.4,23)*	4 (–7,16)
Peak Vo_2 (l/min)	2.2 ± 0.1	–0.04 (–0.25,0.16)	0.12 (–0.08,0.32)	–0.10(–0.30,0.11)†
Peak Vo_2 (ml/min/kg)	33.0 ± 1.8	–1.2 (–4.2,1.9)	0.08 (–0.3,3.1)	–3.3(–6.3,–0.2)*,†
$R\,value_{rest}$	0.86 ± 0.01	–0.07 (–0.12,–0.02)*	–0.08 (–0.13, –0.03)*	–0.06 (–0.12, –0.02
$R\,value_{max}$	1.20 ± 0.02	–0.04 (–0.11, 0.04)	–0.11 (–0.19, –0.014)*	–0.09 (–0.17, –0.02)*
Ventilation rest (l/min)	10 ± 0.3	–1.7 (–3.4,0.0)	–1.2 (–2.9,0.5)	–1.9 (–3.7,–0.2)*
Ventilation max (l/min)	73 ± 4	0.6 (9.6, –10.8)	2.8 (7.4,–13.0)	0.8 (9.9,–10.9)
HR_{rest} (bpm)	83 ± 3	–1.2 (–8.8,6.4)	–1.6 (–9.1,6.0)	–6.8 (–14.4,0.8)
HR_{max} (bpm)	174 ± 3	1 (–16,18)	2 (–15,19)	2 (–18,15)
Systolic BP_{rest} (mmHg)	113 ± 4	–3.2 (–12.7, 6.4)	0.2 (–9.4,9.7)	1.1 (–8.4,10.7)
Systolic BP_{max} (mmHg)	173 ± 6	23 (9,38)*	22 (7,36)*	20 (5,35)*

Values are given as mean ± SE, and mean change with 95% CI. Vo_2, oxygen uptake; *R* value, respiratory quotient. *Significant change from baseline during treatment. †P<0.01 compared with end of treatment (42 months).

treatment, respectively, while no significant effect was observed during GH therapy among those with MPHD (Fig. 1). In fact, 7 of the 9 patients with isolated GHD increased peak Vo_2 by more than 1.0 ml/kg/min during the first year of treatment with GH, compared with only 3 out of 11 with MPHD (P=0.07).

Hemodynamic and gas exchange variables

Maximal ventilation, respiratory exchange value (*R* value) and systolic BP increased slightly during GH treatment in the double-blind period, while other gas exchange data and HR remained unchanged (Table 2).

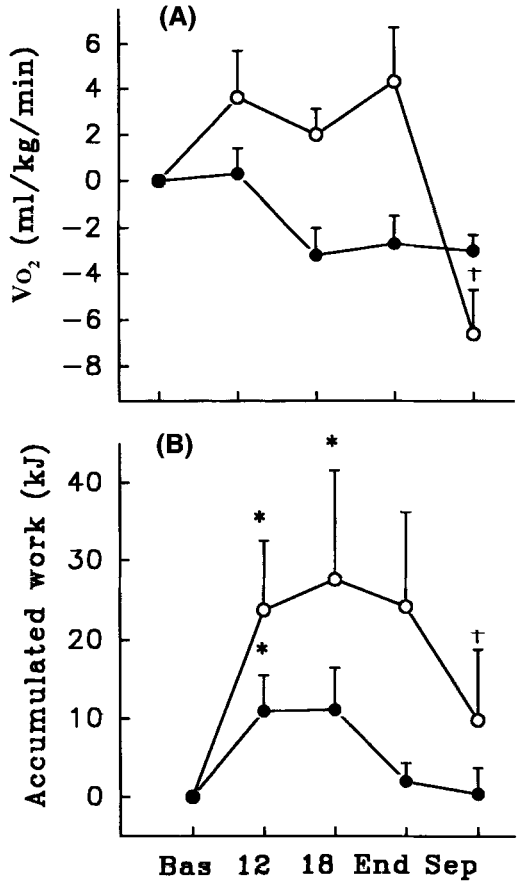

Fig. 1 Change in peak oxygen uptake (peak Vo_2) (A) and accumulated work (B) during treatment with rhGH after 12, 18 and 36–42 (End) months, and after termination of treatment for 9 months (Sep) among patients with isolated growth hormone deficiency (IGHD, n=9; ○) and multiple pituitary hormone deficiencies (MPHD, n=11; ●). Results are given as means ± SE. *P<0.05: change from baseline. †P<0.05: change after stopping treatment.

Also, during open treatment with GH, the measured variables remained unchanged at baseline, during submaximal and maximal exercise, except for decreased R values at all levels, and increased maximal systolic BP (Table 3).

Muscular strength

Maximal handgrip strength was not significantly changed during the double-blind period or during subsequent GH treatment.

Lactate and hormonal response to exercise

Plasma lactate increased from 1.4 ± 0.1 mmol/l at rest to 8.0 ± 1.3 mmol/l at peak exercise during baseline. This response did not change with treatment. Plasma levels of adrenaline, noradrenaline and renin all exceeded upper normal values at baseline (Table 4) [14]. There was no

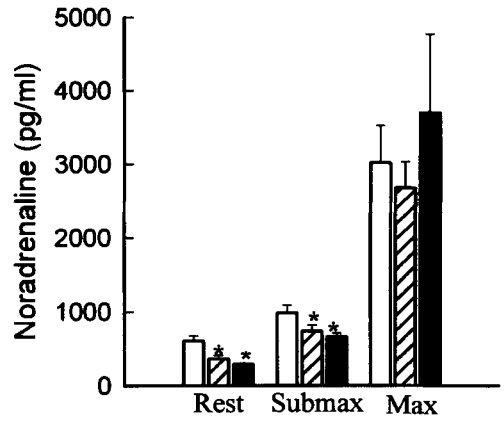

Fig. 2 Plasma noradrenaline concentrations at baseline (□) and after 12 ▨ and 18 months (■) of treatment with rhGH at rest and during submaximal (Stage 3, corresponding to approximately 60% of Vo_2 max) and maximal exercise. Results are given as means ± SE. *significant difference after treatment.

significant correlation between baseline catecholamine levels and clinical or hemodynamic parameters (heart rate and blood pressure).

The individual hormonal responses to exercise were variable, but overall an expected increase in catecholamines and renin, a decrease in insulin, and unchanged ACTH and prolactin levels were observed (Table 4). Growth hormone was hardly detectable at baseline and increased from 0.34 (0.04) (range 0.3–0.7) ng/ml at baseline to 0.76 (0.35) (range 0.30–3.7) ng/ml at maximal exercise (NS). Twelve and 18 months of GH treatment caused significantly reduced noradrenaline levels at rest and submaximal exercise (both P<0.01), reduced renin levels at submaximal and maximal exercise (both P<0.05), and a tendency for reduced resting adrenaline levels (Table 4, Fig. 2). Prolactin levels were decreased at 12 months (P<0.05), but not after 18 months of treatment, while ACTH and insulin remained unchanged (Table 4). There was no apparent difference in these responses between those with isolated GHD and those with MPHD, except for ACTH that hardly increased during exercise among patients with MPHD compared with an expected increase among isolated GHD [change from baseline to maximal exercise: 8 (7) vs 91 (59) ng/l in the two groups, respectively], although the difference was not statistically different, probably because of small sample size.

DISCUSSION

Previous studies on GH deficiency in adult onset GH-deficiency have demonstrated increased peak Vo_2 and muscular strength during short-term somatropin substitution [4,6]. The present study confirms these

Table 4 Plasma hormones at rest and during submaximal and maximal exercise observed at baseline and changes after 12 and 18 months treatment with somatropin (rhGH).

	Baseline (n=10)	12 months (n=9)	18 months (n=9)
Adrenaline (pg/ml)			
Rest	106 ± 30	–31 (–71,8)	–39 (–80,2)
Submax	176 ± 36	–38 (–125,49)	–8 (–166,150)
Max	738 ± 256	119 (–766,1004)	623 (–374,1620)
Noradrenaline (pg/ml)			
Rest	573 ± 75	–215 (–360,–71)†	–328 (–504,–151)†
Submax	960 ± 116	–224 (–453,5)	–319 (–526,–111)†
Max	3196 ± 540	–309 (–1320,701)	504 (–1341,2351)
Insulin (pmol/l)			
Rest	135 ± 26	8 (–67,84)	–15 (–69,39)
Submax	129 ± 32	2 (–71,75)	–41 (–103,22)
Max	99 ± 23	7 (–33,47)	–37 (–85,11)
ACTH (ng/l)			
Rest	48 ± 13	–16 (–46,13)	–8 (–38,22)
Submax	77 ± 33	–43 (–124,37)	–33 (–104,38)
Max	94 ± 33	–33 (–104,36)	–42 (–116,33)
Prolactin (mIE/l)			
Rest	179 ± 41	–80 (–143,–17)*	–61 (–143,22)
Submax	181 ± 40	–76 (–135,–18)*	–61 (–142,20)
Max	194 ± 43	–80 (–143,–17)*	–60 (–161,40)
Renin (nmol/l/h)			
Rest	1.0 ± 0.2	–0.2 (–0.6,0.2)	–0.5 (–1.2,0.2)
Submax	2.2 ± 0.6	–1.1 (–2.1,0.0)	–1.5 (–2.8,–0.0)*
Max	3.7 ± 0.7	–1.2 (–2.2,–0.2)*	–1.0 (–2.2,0.2)

Values are given as mean ± SE, and mean change with 95% CI during treatment. *P<0.05 from baseline; †P<0.01 from baseline.

observations in childhood onset GH deficiency, and expand them by showing preserved exercise capacity during long-term treatment and with a clinically-relevant deterioration after treatment was stopped. Muscular strength was, however, unchanged.

The majority of our patients had reduced exercise capacity, similar to that previously described in patients with acquired GH deficiency [4,6]. Body mass index was negatively correlated to peak Vo_2, while age, time since somatropin substitution and basal IGF-I levels did not correlate.

Somatropin treatment increased peak Vo_2 after 6 months, which then remained unchanged during long-term treatment, and was followed by a drop in peak Vo_2 of 10–15% after stopping treatment, in many cases associated with clinical judgement of psychological discomfort. Overall, the increase in exercise capacity during the first 6 months was somewhat less (approximately 9%) than reported by Cuneo *et al.*[4] (24% increase) and by Nass *et al.*[6] (37% increase) in patients with acquired GH deficiency. The reason for this is probably partly related to onset of GH deficiency, but could also be related to type of deficiency, since we could only observe a significant increase in peak Vo_2 among patients with isolated GH deficiency. Except for type of GH deficiency, no single parameter including gender predicted an increase in peak oxygen uptake in the present study. Thus, it appears that both onset of and type of GH deficiency might be the major determinants for increased exercise capacity during rhGH treatment. The reason for a better response to treatment among patients with isolated GHD compared with MPHD is unknown, but might be related to insufficient ACTH response to exercise or inadequate sex steroid replacement therapy among MPHD patients.

The reason for increased exercise capacity during GH treatment cannot be explained by the present study, but may be due to improvement in central or peripheral factors. Increased muscle mass and strength, increased O_2

delivery due to increased cardiac output or peripheral extraction, altered metabolism or a combination could explain increased exercise capacity. Although increased muscular strength has been reported during GH treatment in adult onset GH-deficiency [3,6], this was not confirmed in the present study, although only investigated by handgrip test. The reason for these discrepant results is unknown, but may be due to different study populations [7]. Although some studies have reported on increased maximal HR [3] or increased left ventricular end diastolic volume [15], we could not detect any changes in resting or maximal HR on echocardiographic data (unpublished data). It has not been examined if peripheral O_2 delivery is changed during GH therapy.

To what extent changes in metabolism contribute to increased exercise capacity is not known. However, in the present study, somatropin treatment resulted in an initial increase in the respiratory exchange ratio at rest and during exercise during the first 6 months of treatment, with a subsequent decrease during long-term treatment. This could suggest that GH therapy have a differential effect on fuel metabolism during short- and long-term treatment. We cannot make any exact conclusions from our data regarding the mechanism for this, but the initial increase in *R* value could be due to enhanced carbohydrate metabolism [16], while a lipolytic effect of GH may be more important during long-term treatment, although the reduced catecholamine levels as observed in the present study may contribute.

Treatment with somatropin resulted in reduced noradrenaline levels at baseline and submaximal exercise and decreased renin response to exercise. The explanation for this is unclear. It may partly be attributed to reduced anxiety during follow up, but a proper resting phase was introduced before baseline blood sampling in the patient population who were familiar with the procedures, and anxiety probably does not explain decreased levels at submaximal exercise. Changes in water content with increased extracellular volume could partly explained the difference, but the magnitude of catecholamine change cannot be explained by volume expansion. Whatever the mechanism of interaction between GH and noradrenaline, further investigations in a larger population is needed, as one could speculate that the relatively high baseline noradrenaline levels could contribute to the well-known known increased cardiovascular mortality in this patient group [17].

One limitation of the present study is that long-term treatment was not blinded. However, we tried to control for factors that could alter our conclusions. Patients with multiple pituitary deficiencies received optimal substitutional treatment for at least 12 months prior to the study, and all medication was kept constant during the trial. All patients were familiar with exercise testing and two baseline tests demonstrated good reproducibility, and all tests were conducted by the same staff throughout the study. Moreover, the main conclusion, namely increased or preserved exercise capacity, was observed also during the initial double-blind period. With regard to the last exercise test, after stopping treatment, effort was made to encourage the patients to exercise in the usual fashion and no difference in maximal *R*-value was observed.

In conclusion, the present study demonstrates that adults with GH deficiency have reduced exercise tolerance and muscular strength. Both short- and long-term treatment with somatropin improved and preserved exercise capacity, whereas muscle strength remained unchanged. Associated reduced noradrenaline levels may be of clinical interest, but are not explained in this study. The sudden decline in exercise capacity after termination of treatment suggest that continuous treatment will benefit this population.

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