Effect of Growth Hormone (hGH) Replacement Therapy on Physical Work Capacity and Cardiac and Pulmonary Function in Patients with hGH Deficiency Acquired in Adulthood

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ABSTRACT

The effects of 6 months of replacement therapy with recombinant human GH (hGH) on physical work capacity and cardiac structure and function were investigated in 20 patients with hGH deficiency of adult onset in a double blind, placebo-controlled trial. The GH dose of 12.5 μg/kg BW was self-administered daily sc. Oxygen consumption (VO_2), CO_2 production, and ventilatory volumes were measured during exercise on a bicycle spiroergometer. M-Mode echocardiography was performed using standard techniques. The VO_2 max data, expressed per kg BW (mL/min·kg BW) showed a significant increase from 23.2 ± 2.4 to 30.0 ± 2.3 ($P < 0.01$) in the hGH-treated group, whereas the VO_2 max data, expressed per lean body mass (milliliters per min/kg lean body mass) did not change significantly in either group. Maximal O_2 pulse (milliliters per beat) increased significantly from 15.2 ± 5.6 to 19.6 ± 3.3 mL/beat ($P < 0.01$), but remained constant in the placebo group. The maximal power output (watts $\pm$ SE) increased significantly ($P < 0.01$) from 192.5 ± 13.5 to 227.5 ± 11.5 in the hGH-treated group, but remained constant in the placebo group. Cardiac structure (left ventricular posterior wall, interventricular septum thickness, left ventricular mass, left ventricular end-systolic dimension, and left ventricular end-diastolic dimension) as well as echocardiographically assessed cardiac function did not change significantly after 6 months of treatment in either group. We conclude that hGH replacement in hGH-deficient adults improves oxygen uptake and exercise capacity. These improvements in pulmonary parameters might be due to an increase in respiratory muscle strength and partly to the changes in muscle volume *per se* observed during hGH replacement therapy. Furthermore, an increased cardiac output might contribute to the improvement in exercise performance during hGH treatment.

According to our data, hGH replacement therapy leads to an improvement of exercise capacity and maximal oxygen uptake, but has no significant effect on cardiac structure. (*J Clin Endocrinol Metab* **80:** 552–557, 1995)

G H IS SECRETED from the anterior lobe of the pituitary gland throughout life, although the amounts released gradually decline with increasing age (1, 2). The physiological importance of sustained GH secretion in adulthood is still poorly understood. In children with GH deficiency, treatment with GH, besides promotion of longitudinal bone growth, has important effects on body composition (3, 4). In adults, GH deficiency is associated with a reduction in lean body mass and an increase in body fat mass (5). Furthermore, adults with panhypopituitarism often do not feel well despite adequate hormone replacement therapy with thyroid hormone and adrenal and sex steroids, but not GH. In a recent study, Bengtsson and co-workers (6) showed that human GH (hGH) replacement therapy in hGH-deficient adults results in marked alterations in body composition, especially a considerable loss of body fat and an increase in muscle volume. Whether these changes observed during hGH therapy will cause functional improvements and, therefore, will justify the cost (7) of the replacement therapy is a matter of controversial discussion. We performed a double blind, placebo-controlled trial of hGH replacement therapy in 20 patients suffering from GH deficiency acquired in adulthood. The aim of our study was to evaluate whether the alterations in body composition observed during hGH replacement therapy lead to improved exercise capacity and power output and, therefore, are beneficial for our patients in performing their daily tasks. We report the effects of hGH treatment on pulmonary parameters and physical work capacity in adults with GH deficiency after a 6-month treatment period.

A recent study (8) suggests that GH replacement therapy in GH-deficient adults might affect cardiac function and structure. As cardiac function is an important determinant of exercise performance, we additionally investigated the effects of hGH on these cardiac parameters in our patients.

Methods

Twenty patients, ranging in age from 27–60 yr (15 males and 5 females), with a mean body mass index of 30.2 kg/m² participated in the study. All patients had acquired GH deficiency during adulthood, generally as a consequence of treatment for pituitary tumors, and received stable hormone replacement with corticosteroid, T_4, and gonadal steroids for at least 12 months before entry into the trial (Table 1). With the exception of 1 male subject in the hGH-treated group, who did not require gonadal steroid replacement therapy, all of our patients received adequate and constant gonadal steroid replacement therapy for 12 months before and during the trial. To minimize the influence of different gonadal steroid levels, all of the female patients were studied

TABLE 1. Clinical details of subjects

	Placebo group (n = 10)	Verum group (n = 10)
Mean age (yr)	45.1	44.2
Range (yr)	27–60	28–60
Sex (M/F)	6/4	9/1
Known duration of GH deficiency (yr)	8	6
Chromophobe adenoma	2	4
Prolactinoma	1	1
Craniopharyngioma	2	2
Others[a]	5	3
Ht (cm)	170.2 ± 3.3	172.6 ± 2.6
Wt (kg)	86.3 ± 5.4	90.8 ± 3.6
BMI (kg/m^2)	29.9 ± 0.5	30.4 ± 0.5
Basal IGF-I (ng/mL)	55.8 ± 10.4	62.4 ± 11.6

Data are presented as the mean ± SE.

[a] Others include one Sheehan syndrome, one empty sella syndrome, one Histiocytosis X and traumatic brain injuries.

during the first half of an artificial menstrual cycle. Male patients were studied in the second week of a 3-week dose interval.

Smoking habits (only three of the patients in the verum group were occasional smokers of fewer than five cigarettes per day; none of the placebo group) were unchanged during the trial and played a minor role in our patients. The nature of the trial was explained to the patients, and their written informed consents were obtained. The study protocol was approved by the local ethics committee. Entry criteria included insulin-like growth factor (IGF-I) levels [measured by the method of Blum *et al.* (9)] below 120 ng/mL and a hGH stimulation test (insulin tolerance test or arginine infusion (30 g) in the case of contraindications to insulin tolerance test), with a peak GH response below 2 ng/mL. Biosynthetic hGH was given in the double blind, placebo-controlled trial over a treatment period of 6 months. GH was self-administered sc daily before bedtime in a dose of 12.5 µg/kg BW. Study material, labeled identically for hGH- and placebo-containing vials, was provided by Eli Lilly Co. (Erl Wood, United Kingdom). Randomization of the 20 patients to study numbers was performed by Eli Lilly Co. Exercise tests were performed at baseline and after 6 months of treatment. The tests were performed in the morning, and standard replacement therapy was taken in the morning of the visit before the tests started. Venous blood samples were taken after an overnight fast.

After all patients had completed the 6-month, double blind, placebo-controlled period, IGF-I levels were analyzed, and those 10 patients showing a marked increase in IGF-I levels during treatment were concluded to have received GH (verum), whereas those showing no alteration in IGF-I levels were concluded to have received placebo. The replacement trial is being continued in a single blinded manner, *i.e.* the patients are still blinded.

Exercise test

Height and weight was measured on the day of the visit. Patients were positioned on a cycle ergometer in a semirecumbent position and requested to pedal with a frequency of 40–50 rpm. Clips were fitted, and the seat height was adjusted. Before starting the measurements, the patients had a resting period for steady state ventilation. O_2 consumption (VO_2), CO_2 production (VCO_2) from a mixing chamber, and ventilatory volumes as well as heart frequency and blood pressure were measured with an Ergotest machine (Fa. Jäger, Würzburg, Hochberg, Germany). This machine uses infrared CO_2 and paramagnetic O_2 analyzers and a turbine pneumotachygraph, recording every 15 s. Calibration against standard gases (16% O_2 and 4% CO_2), volume (1000 mL), operating temperature, and barometric pressure was performed immediately before each test. Data analyses were performed with the J-Lab-system, using a RSX-DEC System (Fa. Jäger). The work rate was set at 50 watts for the first minute and was increased by 25 watts every minute until an exhaustion-limited maximum was reached. Heart rate was recorded by surface electrocardiography during the entire exercise period. Blood pressure was measured in 1-min intervals. O_2 pulse was defined as VO_2 max divided by heart rate and reflects an approximation

of stroke volume, under the assumption that arterio-venous O_2 content differs little between individuals at maximal exercise.

The ventilatory anaerobic threshold was calculated from a diagram of VO_2 *vs.* VCO_2 and minute ventilation. Manual curve fitting was performed by one observer blinded to the origin of the graph being assessed.

Measurements of lean body mass were performed with a total body potassium-40 γ-counter. The measurements of total body potassium were compared with predicted normal values according to sex, age, height, and weight (10). Lean body mass was calculated on the assumption that there is 60 mmol potassium/kg lean body mass in women and 66 mmol/kg lean body mass in men (11).

Echocardiography

Transthoracic echocardiograms were obtained with subjects in the left lateral decubitus position. All echocardiograms were performed by the same investigator, blinded to the treatment code, using a commercially available electronic sector scanner (SSH 40, Toshiba Medical Systems Europe, Delft, The Netherlands) with a 2.5-megahertz phased array transducer. Two-dimensional guided M-mode recordings were obtained from the parasternal window. From the M-mode recording, the following measurements were made using American Society of Echocardiography standards (12): interventricular septal thickness, posterior wall thickness, left ventricular end-diastolic dimension (LVEDD), and left ventricular end-systolic dimension (LVESD). Left ventricular mass (LVM) was calculated from the M-mode measurements using the formula modified by Devereux *et al.* (13) and was indexed to body surface area. The echocardiographic examination and the exercise test were performed on the same day.

Statistics

Results were expressed as the mean ± SE. Statistical analysis within each of the two treatment groups was performed with a paired Wilcoxon test; $P < 0.05$ was considered significant. Differences in the mean values between both groups at baseline were compared by Mann-Whitney U test; $P < 0.05$ was again considered significant. The interassay coefficients of variation for the response variables for IGF-I measurement, ventilation parameters, cardiac parameters, and lean body mass measurement were all below 10%.

Results

Effects of treatment with hGH

Fasting serum concentrations of IGF-I and lean body mass. IGF-I levels (±SE), as measured by the method of Blum *et al.* (9), increased from 62.4 ± 11.6 to 303.1 ± 48.9 ng/mL ($P < 0.005$) in 10 of our patients, but remained constant in 10 others (from 55.8 ± 10.4 to 58.8 ± 9.5 ng/mL). Lean body mass (±SE) increased in the verum group from 52 ± 1.9 to 56.6 ± 2 kg ($P < 0.01$), but remained constant in the placebo group (from 47 ± 3.9 to 49.9 ± 3.1 kg).

Maximal oxygen consumption (VO_2 max), maximal O_2 pulse, exercise time, anaerobic threshold, and maximal power output. The VO_2 max (±SE) increased significantly from 1.9 ± 0.2 to 2.6 ± 0.18 L/min ($P < 0.01$) in the group treated with hGH, whereas in the placebo group, no significant changes (from 1.9 ± 0.18 to 2.2 ± 0.18 L/min) could be detected.

The data, expressed per kg BW (±SE) showed a significant increase in VO_2 max from 23.2 ± 2.4 to 30 ± 2.3 L/min·kg BW ($P < 0.005$) after a 6-month GH treatment period in the verum group, but there was no significant increase in the placebo group (from 22.2 ± 1.9 to 25.6 ± 2.0). When expressed as a percentage of the expected value, the VO_2 max

per kg BW increased significantly in the verum group from 81.8 ± 10.2% to 110.8 ± 7.9% ($P < 0.005$), but showed no significant increase in the placebo group (from 84.6 ± 5.9% to 98.1 ± 8.1%; Fig. 1).

Maximal O_2 pulse (±SE) increased significantly from 15.2 ± 5.6 to 19.6 ± 3.3 mL/beat ($P < 0.01$ in the hGH-treated group), but remained constant in the placebo group (14.3 ± 1.2 to 16.3 ± 1.1 mL/beat; Fig. 1).

The VO_2 max data, expressed per kg lean body mass did not change significantly in either group (hGH, from 39.8 ± 9.4 to 44.1 ± 6.6 mL/min·kg; placebo, from 41.4 ± 16.8 to 44.8 ± 11.2 mL/min·kg).

The maximal power output (±SE) achievable by the patients increased significantly from 192.5 ± 13.5 to 227.5 ± 11.5 watts ($P < 0.01$) after 6 months in the verum group, but
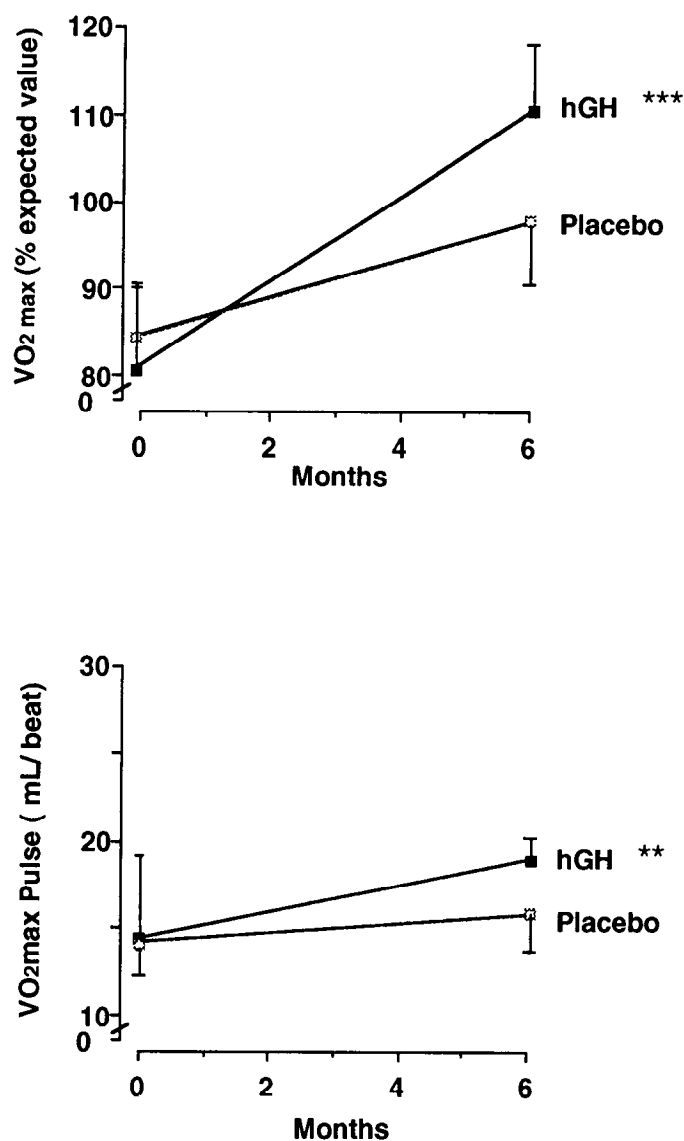
showed no significant changes (from 187.5 ± 16.8 to 192.5 ± 14.9 watts) in the placebo group (Fig. 2).

The same result was found when the power output data were expressed per kg BW [hGH, 2.2 ± 0.17 and 2.4 ± 0.18 ($P < 0.01$); placebo, 2.1 ± 0.19 and 2.1 ± 0.13 at 0 and 6 months, respectively]. When the data were expressed as watts per kg lean body mass, no significant change could be detected in either group (hGH, 3.7 ± 0.3 and 3.5 ± 0.3; placebo, 3.8 ± 0.2 and 3.8 ± 0.1 at 0 and 6 months, respectively; Table 2).

The exercise time (±SE) sustained and, thereby, the total work performed by the patients under the protocol specified in *Materials and Methods* increased significantly in the verum group from 6.35 ± 0.6 to 6.77 ± 0.5 watts ($P < 0.05$), whereas there were no significant changes in the placebo group (from 6.05 ± 0.7 to 6.17 ± 0.6).

The product of power output and operating time (watts × min ±SE) showed a significant increase in the verum group from 1274.4 ± 201 to 1439.1 ± 198 ($P < 0.05$) after 6 months of treatment, whereas in the placebo group, no significant change (from 1182 ± 204.9 to 1212.6 ± 197) was found.

The maximal ventilation (±SE) increased significantly in the verum group from 53.4 ± 6.3 to 59.4 ± 6.0 L/min ($P < 0.05$), whereas in the placebo group, no significant changes could be observed (from 50.5 ± 5.3 to 53.9 ± 5.7 L/min; Table 2).

Changes in the anaerobic threshold, expressed per kg BW, showed the same results. The anaerobic threshold (±SE) increased in the hGH group significantly from 16.88 ± 1.8 to 20.44 ± 1.7 mL/min·kg ($P < 0.01$) as well as in the placebo group, where we found a smaller, but significant, increase from 16.04 ± 1.0 to 18.42 ± 1.2 mL/min·kg ($P < 0.05$).

Cardiac parameters and blood pressure

Before treatment, no patient had values for wall thicknesses or chamber dimension outside the adult reference range of our clinic. After the 6 months of treatment, no significant changes were noted concerning the measured left ventricular posterior wall, left atrium, or interventricular septum thickness or the LVESD, LVEDD, or fractional short-
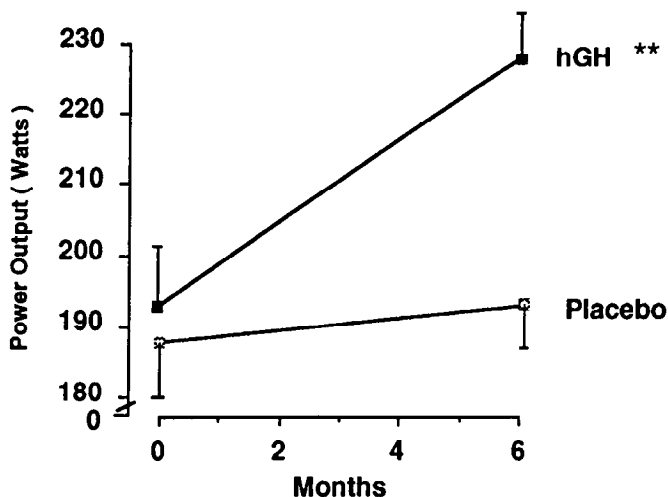

FIG. 1. Changes in maximal O_2 uptake, expressed as a percentage of the expected value (*top*) and changes in maximal O_2 pulse (*bottom*) after GH treatment (*closed symbols*) or placebo (*open symbols*). Values are the mean ± SE. No significant differences existed between groups at baseline: **, $P < 0.01$; ***, $P < 0.005$.

FIG. 2. Changes in maximal power output after GH treatment (*closed symbols*) or placebo (*open symbols*). No significant differences existed between groups at baseline: **, $P < 0.01$.

TABLE 2. Maximal ventilation, anaerobic threshold, maximal power output

Treatment	Baseline	6 months	P
Maximal ventilation (L/min)			
rhGH	53.4 ± 6.3	59.4 ± 6.0	<0.05
Placebo	50.5 ± 5.3	53.9 ± 5.7	NS
Anaerobic threshold/kg BW (mL/min·kg)			
rhGH	16.9 ± 1.8	20.4 ± 1.7	<0.01
Placebo	16.04 ± 1.0	18.4 ± 1.2	0.05
Maximal power output (watts)			
rhGH	192.5 ± 13.5	227.5 ± 11.5	<0.01
Placebo	187.5 ± 16.8	192.5 ± 14.9	NS
Maximal power output BW (watts/kg)			
rhGH	2.2 ± 0.17	2.4 ± 0.18	<0.01
Placebo	2.1 ± 0.19	2.1 ± 0.13	NS
Maximal power output/lean body mass (watts/kg)			
rhGH	3.7 ± 0.3	3.5 ± 0.3	NS
Placebo	3.8 ± 0.2	3.8 ± 0.1	NS
Exercise time (min)			
rhGH	6.35 ± 0.6	6.77 ± 0.5	<0.05
Placebo	6.05 ± 0.7	6.17 ± 0.6	NS

Values are the mean ± SE. No significant differences existed between groups at baseline.

TABLE 3. Echocardiographic results

Treatment	Baseline	6 months	P
IVS (mm)			
rhGH	9.3 ± 1.1	9.3 ± 1.1	NS
Placebo	9.3 ± 0.7	9.6 ± 0.6	NS
LVPW (mm)			
rhGH	8.0 ± 0.8	8.3 ± 0.8	NS
Placebo	8.0 ± 0.6	8.6 ± 0.5	NS
LV-ESD (mm)			
rhGH	31.8 ± 1.2	32.3 ± 1.1	NS
Placebo	31.7 ± 2.2	31.1 ± 2.1	NS
LV-EDD (mm)			
rhGH	48.7 ± 1.5	49.2 ± 1.5	NS
Placebo	48.9 ± 2.7	48.9 ± 2.1	NS
FS (%)			
rhGH	35.3 ± 0.8	35.2 ± 1.0	NS
Placebo	35.7 ± 1.5	36.7 ± 1.7	NS
LVM (g)			
rhGH	148.1 ± 24.5	153.9 ± 25.2	NS
Placebo	158.9 ± 30.3	156.4 ± 17.2	NS
LA (mm)			
rhGH	38.0 ± 0.8	37.8 ± 1.1	NS
Placebo	38.5 ± 0.8	39.5 ± 0.9	NS
LVM/body surface area (g/m²)			
rhGH	73.8 ± 9.7	77.2 ± 10.8	0.058
Placebo	63.1 ± 6.7	66.7 ± 6.6	NS

Values are the mean ± SE. No significant differences existed between groups at baseline. $P < 0.05$ was considered significant. LVM/body surface area shows a trend to increase during hGH replacement therapy. IVS, interventricular septum; LVPW, left ventricular posterior wall; LV-ESD, left ventricular end-systolic dimension; LVEDD, left ventricular end-diastolic dimension; FS, fractional shortening; LVM, left ventricular mass; LA, left atrium.

ening (FS; Table 3). LVM (±SE) increased slightly, but not statistically significantly, from 148.1 ± 24.5 to 153.9 ± 25.2 g. When expressed as LVM per body surface area, we found a tendency ($P = 0.058$) to higher values only in the verum group after 6 months of treatment (from 73.8 ± 9.7 to 77.2 ±

10.8 g/m²). It should be noted that in only 60% of the patients was a reliable echocardiographic result obtained, because of technical difficulties due to the high BMI of the patients. The maximal systolic (from 188.6 ± 9.3 to 194 ± 14.2 mm Hg) and diastolic (from 105 ± 5.5 to 104.7 ± 5.4 mm Hg) blood pressures as well as the maximal heart rate (from 140.9 ± 5.8 to 144 ± 6.9 beats/min) showed no significant change in either group after 6 months of hGH treatment.

Side-effects. Transient side-effects were observed only in the verum group in four patients, during the first 6 weeks of treatment. All four patients developed edema. Three of these four patients also reported muscle pain, and two of them fatigue. In two patients, the hGH dose was reduced to 6.25 μg/kg BW·day, and in all patients, the side-effects dissolved within 3–6 weeks.

Discussion

Over the 6-month period of hGH replacement, IGF-I levels increased in 10 patients with proven hGH deficiency, but remained constant in the 10 placebo-treated patients. Our findings of an increase of 5 kg in lean body mass, as assessed by potassium-40 counting, is in good agreement with previous reports (5). This increase in lean body mass reflects, in particular, muscle mass. Studies in normal subjects (14) have shown that GH increases muscle protein synthesis, as also demonstrated by the St. Thomas group (15). Joergensen *et al.* (16) reported that the increase in lean body mass is combined with an increase in isometric muscle strength.

Little is known concerning the effects of hGH replacement therapy on static and maximal respiratory function. Initial studies (17–19) could not detect an effect of hGH on these parameters.

Furthermore, our data show that GH deficiency in adults is associated with a decrease in the pulmonary parameters measured by spiroergometry compared to those in a reference population (20), and parameters reverted to normal during hGH replacement. Especially the data for VO₂ max per kg BW increased from levels below the normal range to even slightly above the normal range, and this increase in VO₂ max was associated with improved power output.

The improvement in VO₂ max was even more pronounced when corrected for total body weight. When related to lean body mass, however, no alterations in VO₂ max could be demonstrated in either group. These results underline the fact that the increase in lean body mass is an important factor for the improvement of VO₂ max (21), especially as the VO₂ max during maximal exercise occurs almost exclusively in the exercising muscles as blood is shunted away from the splanchnic bed (22).

According to the data of Joergensen *et al.* (16), the increase in lean body mass especially reflects an increase in muscle tissue and, therefore, might result in an increase in respiratory muscle strength. The fact that we could find an increase in the maximal ventilation volume supports the assumption that the increase in respiratory muscle strength during hGH treatment might partially influence the maximal oxygen uptake. The changes during hGH treatment in muscle volume *per se* might play an important role in the changes in VO₂

max. In this context, it is interesting to note that Fleg and Laketta (23) showed that the age-related muscle loss is associated with a progressive decline in VO_2 max.

As our patients received adequate and constant hormone replacement therapy with T_4, glucocorticoids, and gonadal steroids for 12 months before and during the trial, we conclude that the changes observed are not influenced by the standard replacement therapy, especially the glucocorticoid or testosterone therapy in male patients, but are caused by hGH. Our patients were advised not to change their diets or daily activities, but they were not restricted in this respect. The analysis of the daily activity questionnaires showed no significant increase in daily activity during the 6 months of treatment in either group. During the 6-month treatment period, the patients reported no change in daily diet.

It is our opinion that both direct metabolic effects of hGH as well as possible indirect psychological effects (24), leading to increased physical activity, may have contributed to the increase in power output. The anaerobic threshold showed a significant increase in both groups, but with a higher increment in the hGH-treated group. The remarkable increase in the anaerobic threshold, especially in the verum group, might be due to the improved oxygen consumption under hGH replacement.

The increase in the O_2 pulse in the group treated with hGH underlines the positive effect of hGH on the cardio-pulmonary exercise performance and might contribute to the improvement in exercise capacity during hGH treatment. The fact that the maximal O_2 pulse increased significantly during hGH treatment could be explained by an increased cardiac output under the assumption that arterio-venous O_2 content is not altered by hGH treatment, an idea that requires confirmation. This is an indirect conclusion, as we did not measure the arterio-venous O_2 content difference. Our data show a significant increase in oxygen uptake per heartbeat under hGH treatment, and this effect might be due to increased peripheral oxygen consumption or might be explained by an increased cardiac output and, therefore, reflects an increased stroke volume.

The assumption that GH increases cardiac output in GH-deficient patients is supported by the findings of Merola *et al.* (25), who described a decreased ejection fraction in GH-deficient adults. Furthermore, Cuneo *et al.*(26) could show in one case the increase in cardiac output in a patient with dilated cardiomyopathy, and Thuesen *et al.* (27) showed an increase in cardiac output in normal subjects during hGH treatment. We, therefore, examined cardiac structure by echocardiography.

In contrast to previous results, we could not detect any significant changes measured by echocardiography concerning either the cardiac function or the cardiac structure of our patients. The only changes were a slight, but not significant, increase in the LVM, as expressed per body surface area. Cuneo and co-workers (8) described an increase in left ventricular myocardial mass after 6 months of hGH treatment of GH-deficient adults as well as an increase in stroke volume. The other parameters (LVESD, FS, and wall thickness) showed no significant differences after hGH treatment. The discrepancy between our data and those of Cuneo *et al.* (8) might be explained by the lower hGH dosage used in our

study. This suggestion is supported by the data from the Aarhus group (16), who could not detect any changes in the left ventricular wall mass using a hGH dosage comparable to that we used.

According to Cuneo *et al.* (28), the increase in stroke volume after hGH treatment may reflect increased preload (Starling effect) due to the sodium-retaining effect of hGH, which results in an increased circulating blood volume. It appears that in our study this effect played a minor role, as LVEDD determined by echocardiography did not increase during hGH treatment.

Furthermore, it is important to note that left ventricular dimensions and wall thicknesses were within normal limits before and after treatment in our study group. According to these data, we conclude that hGH in physiological replacement dosage does not change cardiac structure and seems not to affect myocardial structure, as observed in acromegaly (29). Concerning cardiac function, on the other hand, according to our O_2 pulse data, hGH might increase stroke volume, a fact that has been reported previously by others (26). We cannot comment on this observation by using echocardiographic measurements, because we do not consider the FS determined echocardiographically to be a reliable parameter for stroke volume.

The observation that hGH does not change the cardiac structure, but does affect cardiac stroke volume, might be explained by the fact that hGH therapy also alters the muscle fiber metabolism (30). Furthermore, the increase in VO_2 max and in the anaerobic threshold during hGH therapy might be influenced by changes in energy metabolism.

Press (31) showed that GH enhances carbohydrate metabolism and muscle and hepatic glycogen stores. Lipid metabolism seems to play no role in the increase in exercise performance (32, 33).

To our knowledge, no data exist concerning changes in the oxygen transport capacity of erythrocytes during hGH therapy. We did not detect changes in the whole erythrocyte mass in either group (data not shown), and this parameter seems to play a minor role in the observed improvement in VO_2 max.

The highly significant increases in the exercise time and power output suggest that the beneficial effects of hGH treatment on pulmonary parameters (VO_2 max and anaerobic threshold) improve physical work capacity. It is, therefore, conceivable that tasks of every day life can be performed by the patients with more ease.

In summary, according to our data, adults with GH deficiency acquired in adulthood show decreased VO_2 max compared to that in a reference population, which can be normalized by hGH replacement therapy. Furthermore, during hGH treatment, we found a significant increase in lean body mass. After 6 months of treatment with hGH, exercise performance, as well as VO_2 max, anaerobic threshold, and O_2 pulse improved significantly. Cardiac structure showed no significant changes during our low dosage hGH replacement regimen, whereas functional improvements, probably due to improved muscle metabolism, might contribute to the improved exercise performance.

As the increase in lean body mass in our study parallels the improvement in VO_2 max and exercise performance, we

conclude that the increase in muscle mass is a major reason for these observations. Investigations over longer study periods are mandatory to arrive at further conclusions concerning the effects of hGH in adults on body composition and exercise performance, especially with respect to possible adverse long term effects, which were not observed in this study.

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