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 (VO₂), CO₂ production, and ventilatory volumes were measured during exercise on a bicycle spiroergometer. M-Mode echocardiography was performed using standard techniques. The VO₂ 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 VO₂ max data, expressed per lean body mass (milliliters per minute/kg lean body mass) did not change significantly in either group. Maximal O₂ 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 ± SE) increased significantly (P < 0.01) from 192.5 ± 13.5 to 227.5 ± 11.5 watts 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 echo-cardiographically 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)

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Exercise test

This machine uses infrared CO₂ and paramagnetic O₂, operating temperature, and barometric pressure was performed immediately before each test. Data analyses were performed with the J-Lab 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. Defined as VO₂ max divided by heart rate and reflects an approximation of stroke volume, under the assumption that arterio-venous O₂ content differs little between individuals at maximal exercise.

The ventilatory anaerobic threshold was calculated from a diagram of VO₂ vs. VCO₂ 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

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

Fastig 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 (VO₂ max), maximal O₂ pulse, exercise time, anaerobic threshold, and maximal power output. The VO₂ 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 VO₂ max from 23.2 ± 2.4 to 30.2 ± 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 VO₂ 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 shortening.
increasing (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
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 O2 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 VO2 max and 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 VO2 max.

The highly significant increases in the exercise time and power output suggest that the beneficial effects of hGH treatment on pulmonary parameters (VO2 max and anaerobic threshold) improve physical work capacity. It is, therefore, conceivable that tasks of everyday 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 VO2 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 VO2 max, anaerobic threshold, and O2 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 VO2 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 bGH 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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