Administration of Growth Hormone to Underweight Patients with Chronic Obstructive Pulmonary Disease: A Prospective, Randomized, Controlled Study

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Patients with chronic obstructive pulmonary disease (COPD) often develop weight loss, which is associated with increased mortality. Recombinant human growth hormone (rhGH) treatment has been proposed to improve nitrogen balance and to increase muscle strength in these patients. The aim of this study was to assess the effects of rhGH administration on the nutritional status, resting metabolism, muscle strength, exercise tolerance, dyspnea, and subjective well-being of underweight patients with stable COPD. Sixteen patients attending a pulmonary rehabilitation program (age: 66 ± 9 yr; weight: 77 ± 6% of ideal body weight; FEV₁: 39 ± 13% of predicted) were randomly treated daily with either 0.15 IU/kg rhGH or placebo during 3 wk in a double-blind fashion. Measurements were made at the beginning (D0) and at the end (D21) of treatment and 2 mo later (D81). Body weight was similar in the two groups during the study, but lean body mass was significantly higher in the rhGH group at D21 (p < 0.01) and D81 (p < 0.05). The increase in lean body mass was 2.3 ± 1.6 kg in the rhGH group and 1.1 ± 0.9 kg in the control group at D21 and 1.9 ± 1.6 kg in the rhGH group and 0.7 ± 2.1 kg in the control group at D81. At D21, the resting energy expenditure was increased in the rhGH group (107.8% of D0, p < 0.001 compared with the control group). At D21 and D81, the changes in maximal respiratory pressures, handgrip strength, maximal exercise capacity, and subjective well-being were similar in the two groups. At D21, the 6-min walking distance decreased in the rhGH group (−13 ± 31%) and increased in the control group (+10 ± 14%; p < 0.01). We conclude that the daily administration of 0.15 IU/kg rhGH during 3 wk increases lean body mass but does not improve muscle strength or exercise tolerance in underweight patients with COPD. Burdet L, de Muralt B, Schutz Y, Pichard C, Fitting J-W. Administration of growth hormone to underweight patients with chronic obstructive pulmonary disease: a prospective, randomized, controlled study.


Patients with chronic obstructive pulmonary disease (COPD) often present a certain degree of protein-calorie malnutrition. This malnutrition is associated with a higher mortality that is independent of the degree of airway obstruction (1). A reduction of respiratory muscle mass and function is recognized as a particularly deleterious consequence of malnutrition. The loss of diaphragm muscle mass and maximal force in undernutrition has been demonstrated in human (2, 3) and animal (4, 5) studies. A reduction in diaphragmatic strength is of clinical importance in COPD patients because it brings them close to the threshold of diaphragmatic fatigue in case of increased respiratory load (6). In addition, limb muscle weakness contributes to exercise limitation in COPD (7). Thus, apart from inactivity and corticosteroid treatment, malnutrition represents another important cause of reduced muscle mass and function in these patients.

Because malnutrition appears to be deleterious in COPD patients, attempts have been made to improve energy balance by oral nutritional support. This was assessed by several controlled studies (8–13). Weight gain and improvement in muscle function could only be achieved with marked increase in caloric intake, and several studies failed to show a benefit of nutritional supplementation (10–12). The prominent reason was the patients' inability to increase their energy intake sufficiently, mainly because of bloating, satiety, and dyspnea.

The difficulties encountered in nutritional support have led investigators to envisage alternative methods, in particular adjuvant treatment with recombinant human growth hormone (rhGH). Administration of this hormone induces lipolysis, protein anabolism, and muscle growth, either directly or through insulin-like growth factor-1 (IGF-1) (14, 15). Thus, rhGH administration has been shown to improve nitrogen
balance in various clinical settings: in postoperative patients (16), critically ill patients (17), AIDS patients (18), patients with hypoproteic diet (19), patients with corticosteroid treatment (20), and healthy elderly men (21). Two studies reported the effects of rhGH in undernourished patients with COPD. Suchner and associates (22) found that the administration of rhGH during 8 d (0.03 mg/kg/d subcutaneously for 4 d plus 0.06 mg/kg/d for another 4 d) failed to increase peripheral or respiratory muscle strength. These patients were not engaged in a rehabilitation program, and the study did not specify whether they were receiving corticosteroids. Pape and colleagues (23) reported an increase in inspiratory muscle strength after 3 wk of treatment (0.05 mg/kg/d subcutaneously). These patients were not engaged in a rehabilitation program and did not receive corticosteroids. However, none of the latter two studies was placebo-controlled.

The aim of our study was to assess the effects of administration of rhGH on nutritional status, resting metabolism, peripheral and respiratory muscle strength, exercise tolerance, dyspnea, and subjective well-being in underweight patients with COPD in stable clinical state and following a pulmonary rehabilitation program.

METHODS

Subjects

Study subjects were selected among COPD patients in stable clinical state attending a program of pulmonary rehabilitation as inpatients in the Rolle Hospital. Inclusion criteria for COPD were defined as an FEV₁/FVC ratio > 70% of predicted value and an increase in FEV₁ > 10% of predicted value after inhalation of 400 μg of albuterol. Patients were eligible if their body weight was > 90% of ideal body weight as defined by the midpoint of the weight range for height in the table of the Metropolitan Life Insurance Company (24). Sixteen patients were studied. None of them was suffering from known diabetes, cancer, or digestive or renal failure. None had unstable cardiac condition or edema. Thyroid hormone levels (TSH, free T4) were normal in all patients. All were pyrexial during the measurement sessions.

None of the patients was receiving continuous oxygen therapy or systemic corticosteroid therapy. Two patients of the control group had not receive corticosteroids. However, none of the latter two patients who fulfilled the inclusion criteria and who consented to the study continued the usual drug treatment and followed a rehabilitation program. The usual treatment consisted of inhaled bronchodilators and corticosteroids

Methods

During a 3-wk pulmonary rehabilitation course in the Rolle Hospital, patients who fulfilled the inclusion criteria and who consented to the study continued their usual drug treatment and followed a rehabilitation program, including exercise training. The usual treatment consisted of inhaled β₂-agonists and anticholinergics in all patients, theophylline derives from

Blood Tests

Serum levels of IGF-1 were measured by radioimmunoassay (Biochem ImmunoSystems, Freiburg, Germany). Serum levels of insulin were measured by radioimmunoassay after acid-ethanol extraction. Serum levels of theophylline were measured with a fluorophotometer (TDx; Abbott Laboratories, Chicago, IL).

Nutritional Status

Height was measured to the nearest 0.5 cm with the subject standing barefoot. At each measurement session, all the patients were weighed barefoot with light clothing to the nearest 0.1 kg on the same beam scale. The body mass index was calculated by dividing the body weight by the height squared and expressed in kilograms per square meter. Body composition was assessed by dual-energy X-ray absorptiometry (DEXA) (QDR-2000; Hologic, Waltham, MA), which calculates the lean body mass, fat mass, and bone mineral mass (25). The X-ray source provided two levels of switching energy (70 and 140 kVp), allowing for optimal discrimination between tissues. The scanning time lasted 12 to 18 min, depending on the surface scanned. Body compartments were calculated with the Enhanced A ray Whole Body 5.7 software version.

Energy Expenditure

REE was measured by indirect calorimetry with a transparent ventilated hood placed over the head of the patient. A constant fraction of the air flowing through the hood was collected for analysis by an indirect calorimetry device (DeltaTrac; Datex Instrumentarium Corp., Helsinki, Finland). Oxygen concentration was measured by a paramagnetic oxygen sensor, and carbon dioxide concentration by an infrared sensor. The device was calibrated immediately before each measurement with a reference gas mixture. Each measurement was performed in the supine position after an overnight fast. A short initiation calorimetry, time was allowed for measured values to stabilize, and R E E then measured over a 20-min period of steady state.

Pulmonary Function Tests

Lung volumes were measured by body plethysmography and forced expiratory flow rates were measured by a mass flow anemometer (Sensormedics 6200 A; Utah; U.S.A.). Carbon monoxide transfer factor was measured by the single-breath technique (Sensormedics 6200 A; Utah; U.S.A.). A total of 201 blood gases were measured at rest by a blood gas analyzer (ABL 520; Radiometer, Copenhagen, Denmark). Reference values of pulmonary function tests were those proposed by Quanjer (26).

Muscle Strength

Peripheral muscle strength was measured by the maximal voluntary handgrip maneuver (Vigorimeter; M artin, Tuttlingen, Germany). The patients performed four maneuvers on each side with at least a 1-min interval between each maneuver. If the greatest pressure was obtained with the fourth maneuver, additional measurements were made until no further increase was seen in order to avoid a learning effect. The average of the best values on the left and right sides was reported. Respiratory muscle strength was measured during maximal voluntary efforts against occluded airways (Chest Scientific Instruments Ltd, Westerham, UK) (27). Maximal inspiratory pressure (MIP) and maximal expiratory pressure (MEP) were measured from functional resid-
Exercise Tolerance
The exercise tolerance was assessed with a 6-min walking test, by measuring the maximal distance walked during 6 min at the patient’s own pace. Two practice runs were performed before the beginning of the study to avoid bias from a learning effect. The exercise tolerance was also assessed by a progressive exercise test on a cycle ergometer, with 10-W increments every minute until symptom limitation. The oxygen concentration in expired air was measured by a paramagnetic sensor and the carbon dioxide concentration was measured by an infrared sensor (E O S Sprint; J aeger, Würzburg, Germany). A practice run was performed before the beginning of the study. From D0 to D21, the daily life activity was assessed by reading daily a pedometer worn by the patient during the whole day, which is an indirect estimate of overall activity (28), and by calculating the area under the curve from D0 to D21 for both groups.

Subjective Well-being
From D0 to D21, the global sensation of dyspnea during daily life activities was measured each day with a visual analogue scale. During measurement sessions at D0, D21, and D81, the dyspnea at rest was assessed by the patient on a Borg scale (29), the self-assessment of exercise tolerance was measured by the oxygen-cost diagram (30), and the score obtained on the Hospital Anxiety and Depression (H A D) scale (31) was calculated.

Statistical Analysis
The baseline characteristics of the patients were compared between the groups by two-tailed unpaired t test. Serum levels of hormones and glucose, parameters of nutritional status and body composition, R E E, pulmonary function tests, change in functional parameters, and parameters of quality of life were compared by A N O V A for repeated measures. Daily activity and caloric intake during treatment period were compared between groups by two-tailed unpaired t test. All analyses were done using the JMP program (S A S Institute, Inc., Cary, N C). Significance was determined at the 5% level. A ll reported values are means (SD).

RESULTS
Sixteen patients completed the study, eight in the rhGH group and eight in the control group. Their physical characteristics are presented in Table 1.

Blood Analysis
At D0, serum levels of albumin were 44.0 ± 2.5 g/L in the control group and 42.6 ± 2.9 g/L in the rhGH group (p = NS). All individual values were in the normal range, the lowest being 37 g/L. The serum levels of theophylline in patients taking this medication were similar in both groups: 7.1 ± 6.4 mg/L in four patients in the control group and 6.1 ± 3.4 mg/L in five patients in the rhGH group (p = NS). Serum level of IGF-1, insulin, and glucose are presented in Table 2. Four patients of the control group had baseline IGF-1 values below 1 and 25 µg/L below the normal inferior limit, three patients of the rhGH group had baseline IGF-1 values between 10 and 34 µg/L below the normal inferior limit. The fasting serum level of glucose increased during rhGH treatment, reached 7.4 and 9.9 mmol/L in two patients of the rhGH group at D21 and returned to pretreatment value at D81.

Nutritional Status and Body Composition
The baseline nutritional parameters of the patients are shown in Table 1. There was no difference between the two groups of patients. Body weight was not different between the two groups at D0, D21, and D81. Lean body mass was similar in the two groups at D0 but was significantly higher in the rhGH group at D21 (p < 0.01) and at D81 (p < 0.05). The increase in lean body mass was 2.3 ± 1.6 kg in the rhGH group and 1.1 ± 0.9 kg in the control group at D21 and 1.9 ± 1.6 kg in the rhGH group and 0.7 ± 2.1 kg in the control group at D81. The changes in weight and in lean body mass in both groups during the study period are illustrated in Figure 1.

Energy Expenditure and Intake
R E E at D0 was 25.6 ± 2.8 kcal/kg/d in the control group and 27.5 ± 2.7 kcal/kg/d in the rhGH group (p = NS). This represented 114.8 ± 14.7% of predicted value according to H arris and Benedict (32) for the 16 patients. The mean values of R E E in the study period in both groups are displayed in Figure 2. There was no difference between both groups at D0 and D81, but at D21, the R E E was increased in the rhGH group compared with the control group (p < 0.001) and represented

<table>
<thead>
<tr>
<th>TABLE 1</th>
<th>PHYSICAL CHARACTERISTICS OF THE PATIENTS</th>
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<tbody>
<tr>
<td></td>
<td>Control Group</td>
</tr>
<tr>
<td>Sex, male/female</td>
<td>7/1</td>
</tr>
<tr>
<td>Age, yr</td>
<td>65.3 (8.2)</td>
</tr>
<tr>
<td>Height, cm</td>
<td>169 (8)</td>
</tr>
<tr>
<td>Weight, kg</td>
<td>48.8 (3.6)</td>
</tr>
<tr>
<td>Weight, % of ideal body weight</td>
<td>76 (5)</td>
</tr>
<tr>
<td>Body mass index, kg/m²</td>
<td>17.2 (1.0)</td>
</tr>
<tr>
<td>Lean body mass, kg</td>
<td>40.0 (5.6)</td>
</tr>
</tbody>
</table>

Definition of abbreviations: rhGH = recombinant human growth hormone. Values are means (SD).

<table>
<thead>
<tr>
<th>TABLE 2</th>
<th>SERUM LEVELS OF IGF-1, INSULIN, AND GLUCOSE</th>
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<tbody>
<tr>
<td></td>
<td>IGF-1 (µg/L)</td>
</tr>
<tr>
<td></td>
<td>Control Group</td>
</tr>
<tr>
<td>Day of Study</td>
<td></td>
</tr>
<tr>
<td>D0</td>
<td>72 (48)</td>
</tr>
<tr>
<td>D7</td>
<td>75 (4)</td>
</tr>
<tr>
<td>D14</td>
<td>84 (6)</td>
</tr>
<tr>
<td>D21</td>
<td>87 (5)</td>
</tr>
<tr>
<td>D81</td>
<td>73 (28)</td>
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</tbody>
</table>

Definition of abbreviations: IGF-1 = insulin-like growth factor-1; rhGH = recombinant human growth hormone. Values are means (SD). n = 8 in each treatment group.
During the treatment period, the caloric intake was 45.0 ± 6.4 kcal/kg/d in the control group and 39.9 ± 6.4 kcal/kg/d in the rhGH group (p = NS). This represented 183 ± 26% of REE in the control group and 153 ± 33% of REE in the rhGH group (p = 0.06).

**Pulmonary Function Tests**

The results of the pulmonary function tests at D0 are presented in Table 3. There was no difference between the two groups of patients. On the basis of a DLCO < 60% of predicted value, seven patients of the control group and six patients of the rhGH group could be classified as emphysematous. Three patients in each group were hypoxemic (PaO2 < 60 mm Hg). Two patients were hypercapnic (PaCO2 > 45 mm Hg) in the control group, and none in the rhGH group. There was no change in lung volumes, forced expiratory flows, and arterial blood gases during the study period.

**Muscle Strength and Exercise Tolerance**

Considering all maneuvers performed by each patient, the average within-session coefficient of variation was 11.5 ± 6.2% for MIP, 11.9 ± 6.9% for MEP, and 5.3 ± 2.8% for handgrip strength. The measured respiratory and handgrip strength, the maximal walking distance in 6 min, and the peak power and VO2 at baseline are presented in Table 3. There was no difference between the two groups of patients. The percentage of change in MIP and MEP, handgrip strength, maximal walking distance in 6 min, and peak VO2 at the end of treatment period (D21) versus baseline (D0) are shown in Table 4. The changes were similar in the two groups, except for 6-min walking distance, which increased in the control group and decreased in the rhGH group (p < 0.01). Over the 3-wk period, the daily

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**Figure 1.** (Upper panel) Change in body weight from Day 0 to Day 21 and Day 81. (Lower panel) Change in lean body mass from Day 0 to Day 21 and Day 81. rhGH = recombinant human growth hormone. Values are means and SD. n = 8 in each treatment group.

**Figure 2.** Resting energy expenditure at Day 0, Day 21, and Day 81. Values are means and SD. n = 8 in each treatment group.

**Table 3**

<table>
<thead>
<tr>
<th>FUNCTIONAL PARAMETERS AT BASELINE</th>
<th>Control Group</th>
<th>rhGH Group</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>FEV1, L</td>
<td>1.19 (0.43)</td>
<td>0.96 (0.26)</td>
<td>NS</td>
</tr>
<tr>
<td>FEV1, % of predicted</td>
<td>42 (12)</td>
<td>37 (15)</td>
<td>NS</td>
</tr>
<tr>
<td>FEV1/FVC, % of predicted</td>
<td>34 (6)</td>
<td>31 (6)</td>
<td>NS</td>
</tr>
<tr>
<td>FRC, % of predicted</td>
<td>173 (27)</td>
<td>193 (36)</td>
<td>NS</td>
</tr>
<tr>
<td>RV, % of predicted</td>
<td>158 (44)</td>
<td>193 (62)</td>
<td>NS</td>
</tr>
<tr>
<td>RV/TLC, % of predicted</td>
<td>127 (29)</td>
<td>144 (30)</td>
<td>NS</td>
</tr>
<tr>
<td>TLC, % of predicted</td>
<td>119 (11)</td>
<td>126 (16)</td>
<td>NS</td>
</tr>
<tr>
<td>DlCO, % of predicted</td>
<td>41 (16)</td>
<td>42 (20)</td>
<td>NS</td>
</tr>
<tr>
<td>PaO2, mm Hg</td>
<td>65 (12)</td>
<td>64 (8)</td>
<td>NS</td>
</tr>
<tr>
<td>PaCO2, mm Hg</td>
<td>41 (5)</td>
<td>40 (3)</td>
<td>NS</td>
</tr>
<tr>
<td>MIP, cm H2O</td>
<td>58 (13)</td>
<td>51 (16)</td>
<td>NS</td>
</tr>
<tr>
<td>MEP, cm H2O</td>
<td>84 (24)</td>
<td>81 (32)</td>
<td>NS</td>
</tr>
<tr>
<td>Handgrip strength, mm Hg</td>
<td>502 (127)</td>
<td>435 (127)</td>
<td>NS</td>
</tr>
<tr>
<td>6-min walking distance, m</td>
<td>456 (155)</td>
<td>397 (81)</td>
<td>NS</td>
</tr>
<tr>
<td>Power max, W</td>
<td>62 (13)*</td>
<td>44 (11)</td>
<td>NS</td>
</tr>
<tr>
<td>Peak VO2, ml/min</td>
<td>920 (160)*</td>
<td>710 (110)</td>
<td>NS</td>
</tr>
</tbody>
</table>

Definition of abbreviations: rhGH = recombinant human growth hormone; DLCO = carbon monoxide transfer factor; MIP = maximal inspiratory pressure; MEP = maximal expiratory pressure; Power max = maximal power performed on cycle incremental test; Peak VO2 = peak oxygen consumption attained on cycle incremental test.

Values are means (SD). All measurements made at 400 m above sea level.
* n = 5.
activity assessed by the pedometer was 2.4 ± 1.9 arbitrary units/d in the control group and 1.2 ± 0.8 arbitrary units/d in the rhGH group (p = NS).

Subjective Well-being
In each group, the mean value of the global sensation of dyspnea assessed by visual analogue scale during the last 4 d of treatment was similar to the mean value during the first 4 d of treatment. A s well, the scores of Borg scale at rest, oxygen-cost diagram, and H A D scale were not different between both groups at D 0 and at D 21.

DISCUSSION
This study showed the following effects after the administration of rhGH during 3 wk to underweight patients with stable COPD: (1) an increase in lean body mass; (2) a raised R E E; (3) no effect on respiratory or peripheral muscle strength; (4) no effect on maximal power during an incremental exercise test; (5) a decrease of maximal distance walked in 6 min; and (6) no effect on the sensation of dyspnea or on the H A D score.

Nutritional Status
In this study, body composition was analyzed by D E X A. B ody composition can be measured by different techniques, such as isotope dilution, hydrodensitometry, and total body potassium (33), but these methods are not easily applicable in patients. D E X A has been validated against these methods and is now considered as one of the reference methods for body composition analysis (25).

The increase in lean body mass in patients receiving rhGH was selective, since this treatment had no impact on body weight. This result is in accordance with the known stimulating effect of growth hormone on protein anabolism and lipolysis (14, 15). In addition to the lack of effect of rhGH on body weight, there was no difference in caloric intake between the two groups, which demonstrates that the effect of rhGH was not mediated by stimulating appetite.

However, rhGH can induce salt and water retention, which would also lead to an increase in body weight and/or lean body mass measured by D E X A. We do not think that this was an important cause of increase in lean body mass in our patients because there was no clinical evidence of fluid retention and because the lean body mass remained increased 2 mo after discontinuation of rhGH treatment.

Resting Energy Expenditure
A t baseline, R E E was slightly elevated in these patients, as frequently observed in patients with stable COPD (34–36). R E E was further increased by 7.6% at the end of rhGH treatment. The thermogenic effect of rhGH is related to an increase in oxygen consumption and in carbon dioxide production and is the result of increased protein turnover and lipolysis and free fatty acid oxidation. Ponting and coworkers (37) reported a 21% increase of R E E after 7 d of daily administration of a larger dose of rhGH (0.1 mg/kg) in patients on full intravenous nutritional support.

Muscle Strength
A t the end of the treatment, the changes in peripheral and respiratory muscle strength were similar in the rhGH and control groups. Because lung volumes did not change during the study, this factor did not interfere with maximal respiratory pressures. Three previous studies examined the effect of rhGH administration on muscle strength in COPD patients. Suchner and associates (22) could demonstrate no effect on grip strength, MIP, or MEP after 8 d of rhGH administration in underweight, COPD patients under total parenteral nutrition. In contrast, Pape and colleagues (23) reported a 27% increase in MIP after 3 wk of daily administration of 0.05 mg/kg rhGH. However, the latter study was not placebo-controlled. In our study, we used the same dose and duration of rhGH administration. The maximal respiratory pressures tended to be slightly higher at D 21 than at baseline, but the difference was not significant and no difference existed between the rhGH group and the control group. Finally, Pichard and coworkers (17) assessed peripheral muscle function measured by electrical stimulation of the adductor pollicis in patients requiring prolonged mechanical ventilation for acute respiratory failure, half of them suffering from COPD. After 12 d of treatment, no difference in thumb muscle strength and fatigability was observed between the rhGH and control groups. Taken together, these studies show that peripheral and respiratory muscle strength is not improved by the administration of 1 to 3 wk of rhGH in COPD patients.

Recently, Schols and associates (38) reported the effects of adding another anabolic agent, nandrolone decanoate, to nutritional support in COPD patients. Their results showed some similarity to ours: whereas adding nandrolone induced a proportionately greater gain in fat-free mass, the slight increase in MIP was similar in patients treated with nutritional intervention and nandrolone or with nutritional intervention alone.

Exercise Tolerance
T o our knowledge, this is the first study assessing the effects of rhGH on exercise performance in COPD patients. We found no favorable effect of rhGH on maximal power during a symptom-limited incremental exercise test. M oreover, the maximal distance walked in 6 min decreased after rhGH administration, suggesting an adverse effect on exercise tolerance in these patients. The results of these tests depend on the collaboration of the patient, and we tried to minimize this possible confounding effect by the design mentioned above. Furthermore, practice runs were performed before the beginning of the study in order to avoid bias from a learning effect. The discrepancy between the maximal incremental test and the 6-min walking test may be explained by the greater sensitivity of submaximal tests to detect changes in exercise capacity. Thus, the 6-min walking test may have detected an adverse effect of GH therapy which could not be detected by the maximal incremental test.
Possible Mechanisms Underlying the Observed Effects

The observed increase in lean body mass suggests an increase in muscle mass, because muscles represent the main component of lean body mass. However, this effect did not lead to an increase in strength and exercise performance. In the absence of any favorable trend, it is unlikely that a larger number of patients in each group would have permitted detection of a clinically significant improvement after rhGH administration. This lack of functional improvement could stem from an inadequate scheme of administration of the drug, inadequate metabolic response, lack of correlation between protein anabolism and muscle function, or adverse effects of the drug.

The route, frequency, and timing of administration of rhGH may play an important role in the efficacy of the treatment (39, 40). Different studies suggest that the metabolic response to rhGH is enhanced by the subcutaneous route, by daily injections, and by administration in the evening rather than in the morning (39). A corollary of our study was that an improvement in muscle strength can only be achieved on nitrogen balance and protein anabolism. In our study, the rhGH group showed a beneficial effect of rhGH on MIP in undernourished patients with COPD.

The plasma levels of IGF-1 reported in Table 3 were similar in the two groups at baseline, and they significantly increased during rhGH treatment. The baseline levels of IGF-1 of our underweight patients were low. However, compared with Pape’s study (23), the increase in IGF-1 during G H therapy was similar in absolute values (+154 versus +150 ng/ml in Pape’s study) and was higher in relative values (+277% versus +200% in Pape’s study). It should also be noted that no functional benefit was found by Pichard and coworkers (17) despite a massive increase in IGF-1 levels (+340%). Therefore, we think that the lack of functional benefit observed in our study is probably not due to an insufficient increment in IGF-1 levels. The duration of the treatment does not seem too short in our study, as a positive nitrogen balance is known to occur already after 1 wk of treatment (37). Thus, although nitrogen balance was not measured in our study, it is likely that our patients treated by rhGH presented a positive nitrogen balance, as suggested by the increase in lean body mass. We cannot exclude that a longer period of therapy could induce a larger increase in limb and respiratory muscle mass. However, this would expose patients to a high risk of clinically significant side effects, as noted by Papadakis and associates (21). Patients included in this study did not receive systemic corticosteroid treatment, since this factor may alter the effect of rhGH on nitrogen balance and protein anabolism.

It can be hypothesized that a threshold increment in muscle mass is required to obtain an improvement in muscle strength. Previous nutritional intervention studies in COPD have shown that an improvement in muscle strength can only be achieved in patients who gain weight. In our study, the rhGH group showed a gain of body weight and lean body mass similar to those of studies achieving improvement in respiratory and limb muscle strength by nutritional support alone or combined with anabolic steroids (13, 38). Thus, assuming that the gain in lean body mass consisted of muscle, an increase in respiratory and peripheral muscle strength could be expected in our study.

The lack of improvement in muscle function could be explained by another hypothesis. The protein-sparing effect of rhGH could result in a redistribution of protein toward central organs rather than toward muscle tissue. Our patients underwent a rehabilitation program with upper and lower limb muscular training, which should have promoted muscle growth and improvement in muscle function, but the relative increase in mass of muscles and other organs was not documented. Further studies should assess if specific muscular training in addition to the administration of rhGH could favor increased protein anabolism in muscles rather than in other organs and bring a sizable effect on muscle function.

The question may be raised whether a larger dose of rhGH should be administered to obtain a beneficial effect and whether this larger dose would be tolerated. Well-known side effects of rhGH include local reactions to injection, salt and water retention, and impairment of glucose metabolism. Our patients tolerated well the injections of rhGH, and none of them developed edema. A slight transitory increase of fasting glucose level was noticed during the treatment, but no patient developed diabetes. Whether a higher dose of rhGH would induce significant water retention or glucose metabolism impairment is not known. We suspect that another side effect may prevent the administration of higher doses of rhGH to patients with COPD. As mentioned above, rhGH induced an increase in R E E. This is related to an increase in oxygen consumption and carbon dioxide production. In normal subjects, increased carbon dioxide is easily eliminated by increasing alveolar ventilation. In patients with severe COPD, elimination of supplemental carbon dioxide may be costly or impossible and may lead to an increased dyspnea, to an impaired exercise tolerance, or to carbon dioxide retention. Although resting dyspnea and arterial PCO2 remained stable, the 6-min walking distance fell in the group of patients treated by rhGH. The observation of the most severely obstructed patient during the study supports this hypothesis. During the 3 wk of rhGH treatment, he developed a progressive increase in dyspnea and decreased exercise tolerance, without any other sign of pulmonary exacerbation. His FEV1 remained stable, but his R E E increased by 13% at the end of the treatment period. His dyspnea decreased within a few days after discontinuation of rhGH administration. We speculate that his worsening dyspnea and exercise capacity was due to an intolerance to increased carbon dioxide production. Although this report is anecdotal, it suggests that administration of a higher dose of rhGH could be deleterious in patients with severe COPD and should be attempted with caution.

In conclusion, the daily administration of 0.15 IU/kg rhGH to undernourished patients with COPD during a 3-wk in-hospital rehabilitation course induced an increase in lean body mass but no improvement in peripheral or respiratory muscular strength nor in exercise performance. Further studies should determine if intensive specific muscular training in addition to drug treatment could lead to an improved performance. Furthermore, the dose-response effect of this treatment should likely be studied in patients with moderate airway obstruction, as severely obstructed patients may not tolerate the increase in carbon dioxide load induced by rhGH treatment.

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