Anabolic growth hormone action improves submaximal measures of physical performance in patients with HIV-associated wasting

John G. Esposito,1 Scott G. Thomas,1,2 Lori Kingdon,3 and Shereen Ezzat3,4
1Graduate Department of Rehabilitation Science, Faculty of Medicine; 2Graduate Department of Exercise Sciences, Faculty of Physical Education and Health; 3Department of Medicine, Faculty of Medicine, University of Toronto; and 4Freeman Centre for Endocrine Oncology, Mount Sinai Hospital, Toronto, Ontario, Canada

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Esposito, John G., Scott G. Thomas, Lori Kingdon, and Shereen Ezzat. Anabolic growth hormone action improves submaximal measures of physical performance in patients with HIV-associated wasting: a randomized, double-blind, placebo-controlled crossover trial. Am J Physiol Endocrinol Metab 289: E494–E503, 2005—First published May 10, 2005; doi:10.1152/ajpendo.00013.2005.—Growth hormone (GH) treatment reverses the muscle loss allegedly responsible for diminished aerobic capacity and increased fatigue in patients with HIV-associated wasting. This study examined whether submaximal measures of physical performance can be used as objective measures of the functional impact of GH treatment-induced anabolism. We randomized 27 HIV-positive men [mean (SD) age, 43.9 (7.2) yr; body mass, 71.9 (10.4) kg; BMI, 23.1 (2.8) kg/m²] with unintentional weight loss despite antiretroviral therapy to receive GH (6 mg) or placebo in a double-blinded, placebo-controlled, cross-over trial. VO2 peak, ventilatory threshold (VeT), 6-min walk test (6MWT) distance and work, profile of mood states (POMS) fatigue and vigor scores, and Nottingham health profile (NHP) energy and physical mobility scores were measured. LBM significantly increased after 3 mo of GH treatment vs. placebo (means ± SE, 3.7 ± 0.6 vs. 0.3 ± 0.4 kg; P < 0.001). VeT significantly improved (17.6 ± 3.7 vs. −5.9 ± 2.5%; P < 0.001), but VO2 peak did not change significantly. 6MWT distance improved (24.9 ± 9.7 vs. 19.9 ± 11.6 m; P < 0.05) and 6MWT work increased significantly more after 3 mo of GH treatment (33.3 ± 8.8 vs. 16.5 ± 7.5 kJ; P < 0.05). POMS scores of fatigue and vigor and the NHP score of energy improved, yet the changes were not statistically significant. GH treatment improved VeT linearly to the increase in LBM (r = 0.43, P = 0.037) and 6MWT work (r = 0.51, P = 0.008), and the increase in 6MWT work correlated with increase in LBM (r = 0.45, P = 0.024). Improvement in 6MWT work above the median (27.3 kJ) showed a decrease in fatigue (r = −0.62, P = 0.024). We concluded that GH treatment-induced LBM gains in HIV-associated wasting were functionally relevant, as determined by effort-independent submaximal measures of cardiopulmonary exercise testing.

human immunodeficiency virus wasting syndrome; human growth hormone; endocrine; exercise; physical fitness; fatigue

PROGRESSIVE INVOLUNTARY WEIGHT LOSS is among the most debilitating complications in patients with human immunodeficiency virus (HIV). Moreover, it is the loss of lean body mass (LBM) that is intimately associated with increased morbidity and mortality (44, 55, 58, 64). Although highly active antiretroviral therapy (HAART) has led to significant reductions in HIV-related mortality (43), HIV-associated wasting remains of clinical concern (57). Muscle wasting is associated with impaired strength and functional performance (24) and is alleged to be the underlying cause of increased fatigue among such patients. Additionally, diminished aerobic capacity in this patient population is well demonstrated by clinical exercise testing (14, 31, 32, 36, 46, 47, 53). Due to the strong association between HIV-associated muscle wasting and survival, as well as the concomitant diminutions of aerobic capacity and functional status, there has been considerable interest in targeted interventions.

The beneficial effects of recombinant human growth hormone (rhGH) in a variety of age-related and nonage-related catabolic conditions (7, 9, 23, 61) has prompted interest in the use of this treatment in the area of HIV-associated wasting. rhGH treatment-mediated improvements in exercise physiological and functional performance have been documented in patients with adult growth hormone deficiency (41, 49, 65). It is well known that in patients with HIV, rhGH treatment increases LBM, reduces total body fat (TBF) (34, 39, 50), and ameliorates lipodystrophy (27, 62). The impact of rhGH administration on physical performance has been measured using cycle (39) and treadmill ergometry (50). However, those performance measures are limited in assessing physiological status by their effort-dependent nature, as well as in assessing functional status by their uncertain relation to activities of daily living (21).

Using cardiopulmonary exercise testing and the gas exchange analyses thereof, we have recently demonstrated that rhGH treatment transiently increases peripheral muscle oxygen extraction and utilization during exercise in male patients with HIV-associated wasting (20), thereby providing insight into one of the mechanisms responsible for improved exercise performance after rhGH treatment in these patients. However, there have been no studies using cardiopulmonary exercise testing in tandem with functional walk tests to determine their ability to measure the impact of rhGH treatment on physical performance in patients with HIV-associated wasting. Therefore, we extend our previous findings (20) and herein present a randomized, double-blinded, placebo-controlled study. The primary purpose of the study was to assess the ability of submaximal measures of exercise physiological performance obtained from sophisticated gas exchange methodology and functional measurements of the simple 6-min walk test (6MWT) to reflect the impact of rhGH-induced changes in body composition and subjective perception of fatigue in patients with HIV-associated wasting.
METHODS

Patients

Thirty male patients (20–70 yr old) with documented HIV-associated wasting, defined as unintentional weight loss of ≥10% over the preceding 12 mo, were selected for inclusion in the study. Patients had to have been receiving a stable regimen of antiretroviral therapy for ≥1 mo before study entry and were to continue with the same regimen for the duration of the study. Patients must not have had rhGH treatment for ≥2 yr or received systemic glucocorticoids for ≥6 mo before study entry. Those already receiving androgenic agents (i.e., testosterone) had to be receiving them for ≥6 mo continuously before entry and were to continue for the duration of the study.

Patients were excluded from the study if any of the following criteria were fulfilled: 1) the presence of chronic severe kidney disease (serum creatinine ≥2.25× the upper limit of normal range and/or repeated positive tests for hematuria and/or proteinuria); 2) the presence of chronic severe liver disease (serum γ-glutamyl aminotransferase and/or aspartate aminotransferase and/or alanine aminotransferase ≥2.5× the upper limit of normal range); 3) the presence of impaired glucose tolerance (fasting glucose ≥110 mg/dl); 4) the presence or history of malignancy; 5) unstable hypertension (systolic blood pressure >160 mmHg or diastolic blood pressure >100 mmHg); 6) acute or severe illness during the 6 mo before study entry; 7) the presence of any concomitant disease, intercurrent illness, or resultant therapy that could interfere either with the patient’s compliance with the study; or 8) known active drug addiction, including alcoholism or use of drugs for nontherapeutic purposes.

Study Design

The study was reviewed and approved by local ethics review committees. After written and informed consent was obtained, the referred patients underwent a prestudy evaluation for eligibility that was completed within 1 mo of proposed study entry, which included a physical examination (i.e., weight, height, electrocardiogram, chest X-ray, routine hematology, blood biochemistry and urinalysis, and routine ophthalmology) and medical history assessment. Eligible patients were then studied for 9 mo in a randomized, double-blinded, placebo-controlled, two-period cross-over trial (Fig. 1) from November 2001 to June 2003. Treatment consisted of rhGH or placebo, which was self-administered as a nightly subcutaneous injection, at a dose of 6 mg/day. The rhGH (Serostim) was provided by Serono (Rockland, MA) and was identical to placebo in preparation and packaging. The 2-period × 2-group trial was an A/B-B/A design. Participants were randomized to receive either drug A, rhGH, or drug B, placebo, for 3 mo (period 1). After a 3-mo washout period, participants crossed over to receive the alternative treatment for 3 mo (period 2). Participants randomized to group 1 received drug A (rhGH) in period 1 and drug B (placebo) in period 2 (A/B); the treatment order for group 2 was B/A. Compliance was assessed from returned vials and self-reporting cards. Dose reduction was permitted if side effects were alleged to have been a consequence of rhGH treatment. All measurements were made on six major study visits (months 0, 1, 3, 6, 7, and 9). Patients attended the Exercise Physiology Laboratory at 0900 after an overnight fast. Baseline measurements (months 0 and 6) preceded each treatment period, and identical procedures were undertaken for both periods. In addition, 2 wk after the start of each period, patients were clinically examined for safety (i.e., routine hematology, blood biochemistry, and urinalysis and monitoring of adverse events). Participants were asked not to alter their physical activity throughout the study; this was monitored with the use of patient diaries. The randomization code was computer generated at month 0, after baseline measurements were completed. Unblinding occurred after full completion of the trial by all participants.

Outcome Measurements

Serum insulin-like growth factor I concentration. Serum levels of GH (Quest Diagnostics, San Juan Capistrano, CA) and insulin-like growth factor I (IGF-I) (Diagnostics Systems Laboratories, Webster, TX) were measured using immunoassays according to the manufacturers’ protocols.

Body composition assessment. Body mass and stature were measured to the nearest 0.1 kg and 0.5 cm, respectively, with light clothing and without shoes. Body mass index (BMI) was calculated as body mass divided by the square of stature. Anthropometric measurements (circumferences, skinfold thicknesses) were made by the same observer according to established protocols (16a, 35). The subscapular and suprailliac thicknesses were added to give the sum of trunk skinfolds (SOTS), and the thicknesses from all five sites were summed to obtain the total sum of skinfolds (SOS) (16a).

Total body water (TBW) and body cell mass (BCM) were estimated by whole body bioelectrical impedance analysis, with the patient in the supine position, using a multifrequency (5 kHz to 1 MHz) spectrum analyzer (Hydra ECF/ICF model 4200; Xitron Technologies, San Diego, CA). The software provided by the manufacturer was used to estimate TBW and BCM.

Body composition (whole body) estimates of LBM, TBF, and bone mineral content were derived through dual energy X-ray absorptiometry using a Lunar DPX-L Plus bone densitometer (model 2288; Lunar, Madison, WI).

Cardiopulmonary Exercise Testing

All exercise tests were performed on a Trackmaster treadmill (model TMX425; Full Vision, Newton, KS), using a continuous, progressive pseudoramp (small step increases) protocol to symptom-limited maximum and assessed by the same trained researcher. This
was a walking protocol for all patients, and the initial treadmill velocity based on the level of physical activity and fitness of each patient was set low to ensure accurate estimation of ventilatory threshold (VeT). Maximum velocity and grade increments varied between patients, ranging from 1.8 to 3.5 mph and 1.0 to 2.0%, respectively, and grade was increased every minute once maximum velocity was attained (usually within 5 min at 0% grade). For 3 min of rest before actual walking and throughout the exercise test, expired gas was analyzed by open-circuit spirometry using a MOXUS Modular V̇O₂ System (AEI Technologies, Naperville, IL). Data were processed and expressed in 20-s averages for heart rate (HR), oxygen consumption (V̇O₂), carbon dioxide production (V̇CO₂), respiratory exchange ratio (RER; V̇CO₂/V̇O₂), expired ventilation (V̇E), respiratory frequency, and tidal volume. HR was determined using a Polar monitor (Polar Electro Oy, Kempele, Finland), and blood pressure was measured every 2 min by automated auscultation (Tango Exercise Stress BP Monitor, SunTech Medical Instruments, Morrisville, NC). After every minute of exercise, patients were shown a revised Borg scale and were asked to indicate their current rating of perceived exertion (RPE) on a scale of “0 = nothing at all” to “10 = very, very severe”. Measurements included maximum oxygen uptake (V̇O₂ peak) and VeT, and maximum heart rate (HRpeak). V̇O₂ peak was simply the highest V̇O₂ achieved for a presumed maximal exercise effort. A noninvasive method was used to estimate VeT from ventilatory equivalents for oxygen (VeO₂/V̇E) and carbon dioxide (VeCO₂/V̇E), as previously described (16). VeT was identified as V̇O₂ at the point of inflection, where VeO₂/V̇E was lowest and then increased progressively with further increases in treadmill work rate, whereas VeCO₂/V̇E reached a plateau or declined. The modified V-slope method (8), in which V̇CO₂ is plotted as a function of V̇O₂, noting where V̇CO₂ reaches 10% in all cases, and the mean value was taken as the VeT. HRpeak was compared with maximum predicted heart rate, which was calculated as 220 minus age in years.

6MWT

Each 6MWT was conducted according to a standardized protocol (13) by the same examiner. Patients performed the test ≥2 h after the maximal treadmill exercise test along an indoor corridor. The test was timed using a stopwatch, and HR was recorded before the test. The examiner walked 10 m behind the patients with a mechanical pedometer to measure distance and used standardized statements of encouragement every minute such as, “You are doing well,” or “Keep up the good work.” Total distance, HR, and RPE were recorded at the end of the test. The work performed during the 6MWT was calculated by the following equation,

walk work = (body mass · gravity · distance)/1,000

where walk work is measured in kilojoules, body mass is measured in kilograms, the force of gravity is a constant of 9.8 m/s², and distance is the total distance in meters covered by the patient in 6 min (28).

Profile of Mood States

The self-report profile of mood states (POMS) questionnaire (37) is widely used to assess transient mood states in six domains: depression, anger, vigor, fatigue, and confusion. Patients read 65 words or brief phrases that described their feelings during the previous week and day that they completed the inventory. Responses to each phrase were recorded on a 5-point Likert scale, ranging from “0 = not at all” to “4 = extremely.” Responses were summed to obtain scores for each of the six domains.

Nottingham Health Profile

The self-report Nottingham health profile (NHP) (30) was used as an adjunct questionnaire to the POMS. The 38 dichotomous yes/no items of the NHP reflect the patient’s degree of distress within several domains, including physical mobility and energy level.

Statistical Analyses

All statistical analyses were performed using SigmaStat for Windows (version 2.03; SPSS, Chicago, IL). A paired difference in VeT of 1.75 ml·kg⁻¹·min⁻¹ with an SD of 2.0 ml·kg⁻¹·min⁻¹ can be detected with a power of 80% for a sample size of 24. A dropout rate of 20% was assumed; therefore, an initial sample size of 30 was recruited. Data are expressed as means ± SE unless otherwise stated. Differences in baseline characteristics between groups 1 and 2 were analyzed using a two-sample t-test. All measures were examined for equality of carry-over effects, using a two-sample t-test of patient totals for period 1 plus period 2 values at P < 0.10 (25). When there was no evidence of a carry-over effect, the two patient groups were combined, and repeated-measures ANOVA was used to examine within-treatment (from baseline to 1 and 3 mo of placebo and rhGH) and between-treatment (rhGH vs. placebo) differences. Post hoc comparisons were made using Student-Newman-Keuls tests. Correlations were evaluated using the Pearson product moment correlation coefficient determined from simple linear regression analyses. All reported P values are two-sided, and the level of significance was P < 0.05.

RESULTS

Patient Characteristics

Thirty male patients met inclusion criteria and gave informed consent to participate in the study. Two patients, one from each group, withdrew before completion of the study on account of arthralgia and headaches, and another from group 1 died from a cerebrovascular accident during the washout period. Therefore, 27 patients completed the 9-mo trial. One patient (from group 1) did not complete measurements at the 1-mo visit and neither did three patients (two from group 1 and one from group 2) at the 7-mo visit. Blinded dose reduction to 3 mg/day was required in 10 patients as a result of side effects (arthralgia) during the rhGH treatment period. Thus the actual mean (SD) dose administered was 74.5 (17.5) mg/day. Thus the actual mean (SD) dose administered was 74.5 (17.5) mg/day. There was also no significant difference in body mass between patients, ranging from 1.8 to 3.5 mph and 1.0 to 2.0%. Each 6MWT was conducted according to a standardized protocol (13) by the same examiner. Patients performed the test ≥2 h after the maximal treadmill exercise test along an indoor corridor. The test was timed using a stopwatch, and HR was recorded before the test. The examiner walked 10 m behind the patients with a mechanical pedometer to measure distance and used standardized statements of encouragement every minute such as, “You are doing well,” or “Keep up the good work.” Total distance, HR, and RPE were recorded at the end of the test. The work performed during the 6MWT was calculated by the following equation,

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Serum IGF-I Concentration

Circulating IGF-I concentrations at study entry were within normal range in 85% (23/27) of the patients. Four patients had concentrations exceeding the upper limit of the age-specific reference range (ages 30–39 yr, 40–280 μg/l; ages 40–49 yr, 40–256 μg/l; ages 50–59 yr, 66–310 μg/l; ages 60–69 yr, 118–314 μg/l). IGF-I concentration significantly increased after 1 mo of rhGH treatment vs. 1 mo of placebo (624.5 ± 66.0 vs. −1.0 ± 12.8 μg/l, P < 0.001). Due to dose reduction necessitated by side effects (arthralgia), IGF-I levels declined (P < 0.05) but remained significantly elevated above baseline
after 3 mo of rhGH treatment relative to placebo (331.7 ± 37.6 vs. −4.6 ± 12.4 μg/l, P < 0.001; Fig. 2A).

Body Composition

Changes in anthropometric and body composition variables are shown in Table 2. Body mass significantly increased after 1 mo of rhGH treatment vs. 1 mo of placebo (3.1 ± 0.5 vs. 0.1 ± 0.4 kg, P < 0.001), and despite the rhGH dose reduction, body mass remained elevated above baseline after 3 mo of rhGH treatment vs. placebo (2.0 ± 0.7 vs. 0.3 ± 0.5 kg, P < 0.01; Table 2). Waist circumference decreased after rhGH treatment, but the change was not statistically significant (Table 2). On the other hand, hip circumference significantly increased after rhGH treatment vs. placebo (1 mo: 2.0 ± 0.4 vs. −0.2 ± 0.3 cm, P < 0.001; 3 mo: 1.4 ± 0.5 vs. 0.2 ± 0.4 cm, P < 0.01; Table 2). As a result, waist-to-hip ratio significantly decreased after rhGH treatment.

The increases in arm and thigh circumferences after 3 mo of rhGH treatment were statistically significant relative to placebo (0.9 ± 0.3 vs. −0.1 ± 0.2 cm, P < 0.001 and 1.0 ± 0.3 vs. −0.02 ± 0.28 cm, P < 0.001, respectively; Table 2). In addition, the changes in TBW and

Table 1. Demographic and patient characteristics by group at study entry

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Total (n = 27)</th>
<th>Group 1 (n = 13)</th>
<th>Group 2 (n = 14)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, yr</td>
<td>43.9 (7.2)</td>
<td>44.5 (8.5)</td>
<td>43.4 (6.0)</td>
</tr>
<tr>
<td>Body mass, kg</td>
<td>71.9 (10.4)</td>
<td>71.9 (9.0)</td>
<td>71.9 (12.0)</td>
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<tr>
<td>Stature, cm</td>
<td>176.1 (5.8)</td>
<td>176.1 (5.7)</td>
<td>176.1 (6.1)</td>
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<tr>
<td>BM1, kg/m²</td>
<td>23.1 (2.8)</td>
<td>23.2 (2.5)</td>
<td>23.1 (3.1)</td>
</tr>
<tr>
<td>Waist-to-hip ratio</td>
<td>0.98 (0.06)</td>
<td>0.97 (0.06)</td>
<td>0.98 (0.07)</td>
</tr>
<tr>
<td>LBM, kg</td>
<td>60.0 (7.5)</td>
<td>59.8 (5.9)</td>
<td>60.2 (9.0)</td>
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<tr>
<td>TBF, kg</td>
<td>8.4 (4.6)</td>
<td>8.9 (4.3)</td>
<td>8.0 (4.9)</td>
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<tr>
<td>SOS, mm</td>
<td>26.7 (6.7)</td>
<td>28.0 (8.1)</td>
<td>25.4 (5.1)</td>
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<tr>
<td>SOTS, mm</td>
<td>16.4 (4.9)</td>
<td>17.3 (5.8)</td>
<td>15.6 (3.9)</td>
</tr>
<tr>
<td>TBW, L</td>
<td>43.5 (6.9)</td>
<td>43.6 (4.7)</td>
<td>43.4 (8.6)</td>
</tr>
<tr>
<td>BCM, kg</td>
<td>35.9 (6.7)</td>
<td>36.0 (4.5)</td>
<td>35.9 (8.5)</td>
</tr>
<tr>
<td>[IGF-I], μg/l</td>
<td>209.8 (83.0)</td>
<td>211.4 (88.8)</td>
<td>208.3 (80.5)</td>
</tr>
</tbody>
</table>

All values are means (SD). BMI, body mass index; LBM, lean body mass by DEXA (dual energy X-ray absorptiometry); TBF, total body fat by DEXA; SOS, sum of skinfolds; SOTS, sum of trunk skinfolds; TBW, total body water by bioimpedance analyzer (BIA); BCM, body cell mass by BIA; [IGF-I], insulin-like growth factor I concentration.
Table 2. Anthropometric and body composition changes after rhGH and placebo treatment

<table>
<thead>
<tr>
<th></th>
<th>rhGH Treatment</th>
<th></th>
<th>Placebo Treatment</th>
<th></th>
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</thead>
<tbody>
<tr>
<td></td>
<td>Baseline</td>
<td>Change from baseline month 1</td>
<td>Change from baseline month 3</td>
<td>Baseline</td>
</tr>
<tr>
<td>Body mass, kg</td>
<td>71.7±1.9</td>
<td>3.1±0.5†</td>
<td>2.0±0.7*</td>
<td>71.9±2.0</td>
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<tr>
<td>Waist, cm</td>
<td>85.5±1.4</td>
<td>-0.4±0.5</td>
<td>-2.1±0.6</td>
<td>84.8±1.4</td>
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<tr>
<td>Hip, cm</td>
<td>87.6±0.9</td>
<td>2.0±0.4</td>
<td>1.4±0.5*</td>
<td>87.7±1.0</td>
</tr>
<tr>
<td>Arm, cm</td>
<td>28.9±0.6</td>
<td>0.9±0.2†</td>
<td>0.9±0.3†</td>
<td>28.9±0.6</td>
</tr>
<tr>
<td>Thigh, cm</td>
<td>46.8±0.8</td>
<td>1.5±0.3†</td>
<td>1.0±0.3†</td>
<td>46.7±0.8</td>
</tr>
<tr>
<td>TBW, liters</td>
<td>43.9±1.2</td>
<td>3.4±0.4</td>
<td>4.4±0.7†</td>
<td>44.4±1.5</td>
</tr>
<tr>
<td>BCM, kg</td>
<td>36.3±1.2</td>
<td>3.4±0.4</td>
<td>3.2±0.6†</td>
<td>36.9±1.4</td>
</tr>
</tbody>
</table>

All values are means ± SE. †P < 0.01, ‡P < 0.001 for between-treatment difference.

BCM were significantly greater after 3 mo of rhGH treatment than after 3 mo of placebo (4.4 ± 0.7 vs. 0.4 ± 0.5, P < 0.001 and 3.2 ± 0.6 vs. 0.3 ± 0.5 kg, P < 0.001, respectively; Table 2).

Finally, LBM significantly increased after 1 and 3 mo of rhGH treatment relative to placebo (4.5 ± 0.6 vs. -0.1 ± 0.3 kg, P < 0.001 and 3.7 ± 0.6 vs. 0.3 ± 0.4 kg, P < 0.001, respectively; Fig. 2B) and TBF significantly decreased (-1.7 ± 0.3 vs. -0.1 ± 0.3 kg, P < 0.001 and -1.9 ± 0.5 vs. 0.3 ± 0.4 kg, P < 0.001, respectively; Fig. 2C).

Changes in SOS and SOTS were not significantly different between treatments.

Aerobic Capacity

At study entry, \( V_{O2\text{ peak}} \) [34.9 (1.3) ml·kg\(^{-1}\)·min\(^{-1}\)] was significantly lower (P = 0.01) than age-specific normative values [38.4 (0.5) ml·kg\(^{-1}\)·min\(^{-1}\)] (1), and HR\(_{\text{peak}}\) [158.4 (2.9) beats/min] was 10.0 (1.6)% lower (P < 0.001) than age-predicted maximum. After 3 mo of treatment with rhGH, \( V_{O2\text{ peak}} \) and HR\(_{\text{peak}}\) increased to 35.5 (1.0) ml·kg\(^{-1}\)·min\(^{-1}\) and 160.0 (3.1) beats/min, respectively, yet the changes were not statistically significant relative to the changes after placebo [\( V_{O2\text{ peak}} \) and HR\(_{\text{peak}}\) decreased to 33.0 (1.2) ml·kg\(^{-1}\)·min\(^{-1}\) and 154.7 (3.6) beats/min, respectively, after 3 mo of placebo].

VeT at study entry [18.1 (0.7) ml·kg\(^{-1}\)·min\(^{-1}\)] was ~21% lower (P < 0.001) than that predicted for healthy sedentary males of similar age, body mass, and stature (18). After rhGH treatment, VeT significantly improved relative to placebo [1 mo: 1.8 (0.4) vs. -1.3 (0.5) ml·kg\(^{-1}\)·min\(^{-1}\), P < 0.001; 3 mo: 3.0 (0.6) vs. -1.2 (0.5) ml·kg\(^{-1}\)·min\(^{-1}\), P < 0.001] (Fig. 2D).

In addition, VeT as a percentage of \( V_{O2\text{ peak}} \) was 52.4 (1.2)% at study entry and was significantly elevated after rhGH treatment compared with placebo [1 mo: 56.8 (1.1) vs. 49.1 ± 1.4%, P < 0.001; 3 mo: 58.2 (1.4) vs. 51.6 ± 1.6%, P < 0.001]. Changes in RER were not significantly different between treatments.

Functional Status

Distance ambulated during the 6MWT at study entry was 646.2 (18.9) m. Predicted distance for healthy males of similar age, body mass, and stature is 767.3 (10.5) m (19). 6MWT distances between group 1 [677.9 (17.7) m] and group 2 [616.7 (31.2) m] were not significantly different at study entry. Repeated measures analysis within group 2 revealed a significant increase from study entry at all time points (P < 0.01), suggesting a learning effect. Overall, the increases in distance ambulated after rhGH treatment were not significantly greater than those after placebo [1 mo: 12.3 (8.2) vs. 19.5 (9.3) m, P > 0.05; 3 mo: 24.9 (9.7) vs. 19.9 (11.6) m, P > 0.05; Fig. 2E].

Post-6MWT HR at study entry was 122.5 (3.5) beats/min and was significantly higher after 1 mo of rhGH treatment than after 1 mo of placebo [134.9 (3.0) vs. 125.1 (3.3) beats/min, P = 0.003]. The between-treatment difference for post-6MWT HR at 3 mo was not significant [130.7 (3.4) vs. 127.1 (3.4) beats/min, P = 0.095]. Changes in post-6MWT RPE were not significantly different between treatments.

6MWT work at study entry was 455.5 (17.8) kJ. After rhGH treatment, 6MWT work was greater compared with that after placebo [1 mo: 494.5 (20.1) vs. 477.9 (21.9) kJ, P < 0.05; 3 mo: 502.7 (21.0) vs. 483.4 (19.8) kJ, P < 0.05; Fig. 2F].

POMS

Scores on all of the POMS subscales improved after active treatment (Table 3); however, changes in scores were not significant relative to those after placebo. Only the decrease in anger score revealed a within-treatment difference (P < 0.01).

Table 3. POMS subscale scores during rhGH and placebo treatments

<table>
<thead>
<tr>
<th></th>
<th>rhGH Treatment</th>
<th></th>
<th>Placebo Treatment</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Normative</td>
<td>Baseline</td>
<td>Month 1</td>
<td>Month 3</td>
</tr>
<tr>
<td>Tension</td>
<td>7.1±0.4</td>
<td>11.4±2.3</td>
<td>10.3±1.6</td>
<td>8.7±1.0</td>
</tr>
<tr>
<td>Depression</td>
<td>7.5±0.7</td>
<td>14.7±2.3</td>
<td>12.2±2.3</td>
<td>9.5±1.9</td>
</tr>
<tr>
<td>Anger</td>
<td>7.1±0.5</td>
<td>12.2±2.0</td>
<td>8.0±1.7*</td>
<td>6.4±1.2*</td>
</tr>
<tr>
<td>Vigor</td>
<td>19.8±0.5</td>
<td>14.6±1.5</td>
<td>16.0±1.4</td>
<td>16.4±1.4</td>
</tr>
<tr>
<td>Fatigue</td>
<td>7.3±0.4</td>
<td>13.8±1.5</td>
<td>11.7±1.4</td>
<td>10.9±1.4</td>
</tr>
<tr>
<td>Confusion</td>
<td>5.6±0.3</td>
<td>8.3±0.9</td>
<td>8.7±1.0</td>
<td>7.0±0.9</td>
</tr>
</tbody>
</table>

All values are means ± SE. POMS, profile of mood states. *P < 0.01 compared with treatment baseline.
The mean vigor score increased from 14.6 (1.5) to 16.4 (1.4) after 3 mo of rhGH treatment. The expected score for adult males (18–94 yr) is 19.8 (0.5) (42). The mean fatigue score decreased from 13.8 (1.5) to 10.9 (1.4) [normative score = 7.3 (0.4)] (42) over the course of active treatment. Vigor and fatigue scores tended to decrease and increase, respectively, during treatment with placebo.

**NHP**

The mean NHP energy score improved after 3 mo of rhGH treatment, decreasing from 45.2 (8.6) to 27.0 (7.8), and although the score tended to worsen after placebo [38.8 (8.0) to 41.1 (8.6)], the between-treatment difference was not statistically significant. Changes in the NHP physical mobility score were not significant between treatments [10.5 (3.4) to 12.9 (3.0) vs. 6.6 (2.1) to 9.1 (2.6)].

**Correlation and Simple Linear Regression Analyses**

At baseline, 6MWT distance was linearly related to both VeT ($r = 0.43$, $P = 0.024$; Fig. 3A) and $V_{O2peak}$ ($r = 0.57$, $P = 0.002$; Fig. 3B). After 3 mo of rhGH treatment, changes in VeT were related to changes in $V_{O2peak}$ ($r = 0.56$, $P = 0.003$). Increases in LBM and IGF-I concentration were related during rhGH treatment ($r = 0.62$, $P = 0.001$). Furthermore, improvements in VeT from baseline to 3 mo of rhGH treatment were significantly correlated to increases in IGF-I concentration ($r = 0.43$, $P = 0.03$), LBM ($r = 0.43$, $P = 0.037$; Fig. 3C), thigh circumference ($r = 0.40$, $P = 0.043$), and 6MWT work ($r = 0.51$, $P = 0.008$; Fig. 3D). The relationship between changes in VeT and changes in 6MWT distance did not reach statistical significance ($r = 0.36$, $P = 0.067$). At baseline, 6MWT work was linearly related to LBM ($r = 0.73$, $P < 0.001$) and thigh circumference ($r = 0.62$, $P < 0.001$), and improvements in 6MWT work from baseline to 3 mo of rhGH treatment were associated with the increases in LBM ($r = 0.45$, $P = 0.024$; Fig. 3E) and thigh circumference ($r = 0.44$, $P = 0.023$). No significant correlations were observed between measurements of aerobic capacity (and functional status) and POMS scores of fatigue. However, the improvements in 6MWT work and POMS score of fatigue, from baseline to 3 mo of rhGH treatment, were correlated in those patients ($n = 13$) who demonstrated a change greater than or equal to the median.

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**Fig. 3.** Linear regression: VeT and peak $O_2$ uptake ($V_{O2peak}$) on 6MWT distance at baseline. Changes ($\Delta$) in VeT on changes in LBM and 6MWT work, changes in 6MWT work on changes in LBM, and changes in profile of mood states (POMS) fatigue score on changes in 6MWT work after 3 mo of rhGH treatment.
change of 27.3 kJ in 6MWT work \((r = -0.62, P = 0.024; \text{Fig. 3F})\). Furthermore, the relationship between improvements in 6MWT work and NHP energy score was just short of statistical significance \((r = 0.64, P = 0.066)\) in the same subgroup of patients.

**DISCUSSION**

Herein we show that rhGH treatment-induced anabolism in patients with HIV-associated wasting on current-era antiretroviral therapy is functionally meaningful and can be determined from objective, effort-independent measurements of respiratory gas exchange. In turn, the functional nature of this anabolic effect can be assessed by the much simpler and clinically relevant 6MWT. The novelty of the present study is reflected in the confluence of clinically applicable and physiologically validated tools (6MWT and cardiopulmonary exercise testing, respectively) to objectively measure the impact of targeted hormone intervention on physical performance in patients with HIV-associated wasting. This study is the first to uncover an association between improvement in VeT, a submaximal measurement of aerobic capacity obtained from respiratory gas exchange analyses, and the favorable changes in body composition that accompany rhGH treatment in these patients. Moreover, we demonstrate that the rhGH treatment-induced anabolism is associated with improved functional status that relates to a reduced sense of fatigue.

In this study, the considerable increase in VeT after rhGH treatment, relative to placebo treatment, is an important finding in HIV-infected patients with wasting. Treatment with rhGH increases VeT in other patients, such as those with GH deficiency (65). Unlike \(\text{VO}_2\max\), VeT is an effort-independent measurement of physical performance that demarcates the upper limit of a range of exercise intensities that can be accomplished almost entirely aerobically. In HIV-infected patients, who become symptom limited with premature cessation of exercise during cardiopulmonary exercise testing (52), the VeT (which is observed at a submaximal work rate) can be used in place of \(\text{VO}_2\max\) to assist in clinical decision making (3).

VeT below 40% of predicted \(\text{VO}_2\max\) may indicate a limitation in cardiac or pulmonary function, abnormal oxygen delivery to active tissue, and/or intrinsic muscle abnormalities (3). Exercise above VeT results in metabolic acidosis, impaired muscle contraction, hyperventilation, and altered oxygen kinetics (63), all of which contribute to a progressive decrease in exercise tolerance and an inability to sustain performance. VeT is reduced in conditions characterized by excessive fatigue, including heart failure (12), chronic fatigue syndrome (33), chronic pulmonary disease (45), and acromegaly (60). In this study, VeT was significantly lower than that predicted for healthy sedentary males of similar age, body mass, and stature (18), confirming previous reports of reduced VeT in HIV-infected patients compared with healthy controls (31, 47, 53).

Any delay in VeT (shifting to a higher percentage of \(\text{VO}_2\peak\)) that can be attributed to an intervention (drug, exercise training) may add important information concerning the efficacy of the intervention in improving aerobic capacity (40). In view of this, rhGH treatment increased VeT (and \(\text{VO}_2\peak\) to a lesser extent) in our patients and, consequently, VeT as a percentage of \(\text{VO}_2\peak\) shifted toward normal (55%) (63). Because VeT correlates well with daily life activities, such as cumulative hours of exercise and work in a month (56), an increase in VeT attributable to rhGH treatment could potentially influence lifestyle in patients with HIV-associated wasting who demonstrate high and low levels of fatigue and vigor, respectively.

The POMS questionnaire (37) is a reliable and sensitive measure of transient mood states and has been widely used as a research tool in a variety of populations (10, 22, 59). In the present study, the POMS fatigue and vigor scores were higher and lower, respectively, than age- and gender-specific normative scores (42). While changes in self-reported fatigue and vigor did not reach statistical significance, the inclination was one of improvement. Moreover, the decrease in fatigue score and increase in VeT after rhGH treatment supports the notion that fatigue and VeT are physiologically linked. In a study of patients with growth hormone deficiency, the POMS fatigue score decreased by 30% from a baseline score of 14.8 after 3 mo of rhGH treatment (65). In our study, the fatigue score decreased by 21% after 3 mo of rhGH treatment. The discordance may be due to the presence or absence of psychopathologies influencing perception of fatigue in the two patient populations. POMS scores for tension, depression, and confusion remained above normal after rhGH treatment in our HIV-infected patients.

The 6MWT is an easy and inexpensive submaximal exercise test with good measurement properties (validity, reliability, interpretability, responsiveness) (51) that relates more closely to daily activities and quality of life than conventional cardiorespiratory exercise tests (13, 26) and possesses prognostic value (11, 15, 38). It is for this reason that it has become a common test to evaluate functional status and treatment efficacy (4, 6, 29, 54). 6MWT distance correlated moderately, yet significantly, with VeT and \(\text{VO}_2\peak\) at study entry. In spite of the increases in aerobic capacity after rhGH treatment, we did not observe a major increase in 6MWT distance overall. The learning effect that was present in group 2 represents a limitation of this study that may well have precluded a significant treatment effect. On the other hand, the work performed during the 6MWT significantly improved with rhGH treatment, implying that patients were able to walk the same distance with the added body mass. This improvement was also associated with improvements in VeT and, interestingly, improvements in 6MWT work that were greater than or equal to the median change in our patients were also associated with reductions in the POMS score of fatigue. Although distance is the customary measure of the 6MWT, 6MWT work has been proposed as a parameter for evaluation of patients’ fitness if gas exchange measurements are not available (17). Compared with 6MWT distance, 6MWT work correlates significantly better with \(\text{VO}_2\peak\). VeT, and dynamic muscle strength in patients with chronic obstructive pulmonary disease and congestive heart failure (17, 28). Although 6MWT work may be a better reflection of a patient’s exercise capacity, limited literature exists on the interpretability of this measure, and further research is therefore warranted to fully elucidate its clinical utility.

The relationships between measurements of aerobic capacity (VeT and \(\text{VO}_2\peak\)) and functional status (6MWT distance and work) observed in this study call attention to the potential clinical utility of the 6MWT as an adjunct tool for the evalu-
ation of physical performance and treatment efficacy in patients with HIV-associated wasting. However, the strongest indication for the 6MWT is for measuring the response to medical interventions in patients with moderate to severe impairment of functional capacity (2). In this study, distance ambulated during the 6MWT at study entry was reduced compared with that predicted for healthy males of similar age, body mass, and stature (19), yet the reduction (~5%) was presumably not great enough to reflect moderately severe impairment. Moreover, the change in distance walked after rhGH treatment was not clinically significant (a change in 6MWT distance of ≥54 m represents a clinically significant change in functional status) (51), perhaps on account of this lack of impairment. In light of these limitations, a clinically significant change may have been revealed had our patients been more severely disabled.

Treatment with rhGH resulted in a significant increase in LBM (as well as BCM) paralleled by a sizeable decrease in TBF, as previously noted (34, 39, 50). It was our primary intent to examine the impact of these changes in body composition on physical performance. rhGH treatment-induced anabolism, measured as increased LBM (by dual-energy X-ray absorptiometry) and thigh circumference, was positively associated with the improvements in aerobic capacity (VeT) and functional status (6MWT work) in our patients. In the pre-HAART era (50) it was also shown that an increase in treadmill work output was accompanied by rhGH treatment in patients with HIV-associated wasting. Although that study and ours attribute improvement of physical performance to rhGH anabolic action, other potential physiological mechanisms (improved regional distribution of peripheral blood flow, increased numbers of muscle mitochondria, and/or improved respiratory enzyme activity) may concurrently contribute to this improvement. We (20) have recently demonstrated that rhGH treatment transiently increases peripheral muscle oxygen extraction and utilization, yet it is unclear whether this improvement is dependent on or independent of the increased LBM.

Fasting serum concentrations of IGF-I before treatment were within normal range in our patients. We chose a dose (6 mg/day) that we were confident would be effective in improving body composition and, hence, possibly exercise performance in patients with HIV-associated wasting (39, 50). However, our study is limited by the halving of doses, necessitated by arthralgias, in nearly one-third of our patients. These arthralgias were associated with a fourfold increase in IGF-I levels (≤3 times the upper limit of normal) after 1 mo of rhGH treatment. After 3 mo of rhGH treatment, there was a reduction in IGF-I levels and a subsequent resolution of side effects as a result of the rhGH dose reduction. A previous study of HIV-infected patients demonstrated a similar fourfold increase in IGF-I concentrations after 1 mo of rhGH treatment, even with a lower dose of 3 mg/day (34). Yet it is unknown whether a dose of 3 mg/day, administered over 3 mo to such patients, would effect an ergogenic response comparable to that of this study. Nonetheless, elevated concentrations of circulating IGF-I are associated with an increased risk of common cancers (48), and the balance of benefits and risks of rhGH supplementation in patients with HIV-associated wasting has not been fully delineated. Therefore, caution should be exercised in the use of rhGH in these patients.

In conclusion, the administration of rhGH to patients with HIV-associated wasting is followed by favorable changes in aerobic capacity and functional status, owing to rhGH anabolic action. The increase in LBM is functionally relevant, as noted from the improvements in VeT and 6MWT work, and these improvements relate to reduced feelings of fatigue. This study demonstrates that rhGH treatment influences physical performance within a clinically relevant context concurrently validated by physiologically pertinent measurements (from respiratory gas exchange analyses) in the current HAART era. The present findings begin to provide an objective, physiologically based framework with which to assess the impact of hormone treatment in the HIV population.

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The design, execution, data handling, interpretation, and manuscript preparation were entirely the responsibility of the authors.

DISCLOSURES

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