Effects of Testosterone and Resistance Training in Men with Chronic Obstructive Pulmonary Disease

Richard Casaburi, Shalender Bhasin, Louis Cosentino, Janos Porszasz, Attila Somfay, Michael I. Lewis, Mario Fournier, and Thomas W. Storer

Division of Endocrinology and Molecular Medicine, Drew University of Medicine and Science; Division of Pulmonary and Critical Care Medicine, Cedars-Sinai Medical Center, Los Angeles; Rehabilitation Clinical Trials Center, Los Angeles Biomedical Research Institute at Harbor-UCLA Medical Center and Exercise Sciences Laboratory, El Camino College, Torrance, California

Dysfunction of the muscles of ambulation contributes to exercise intolerance in chronic obstructive pulmonary disease (COPD). Men with COPD have high prevalence of low testosterone levels, which may contribute to muscle weakness. We determined effects of testosterone supplementation (100 mg of testosterone enanthate injected weekly) with or without resistance training (45 minutes three times weekly) on body composition and muscle function in 47 men with COPD (mean FEV_1 = 40% predicted) and low testosterone levels (mean = 320 ng/dl). Subjects were randomized to 10 weeks of placebo injections + no training, testosterone injections + no training, placebo injections + resistance training, or testosterone injections + resistance training. Testosterone injections yielded a mean increase of 271 ng/dl in the nadir serum testosterone concentration (to the middle of the normal range for young men). The lean body mass (by dual-energy X-ray absorptiometry) increase averaged 2.3 kg with testosterone alone and 3.3 kg with combined testosterone and resistance training ($p < 0.001$). Increase in one-repetition maximum leg press strength averaged 17.2% with testosterone alone, 17.4% with resistance training alone, and 26.8% with testosterone + resistance training ($p < 0.001$). Interventions were well tolerated with no abnormalities in safety measures. Further studies are required to determine long-term benefits of adding testosterone supplementation and resistance training to rehabilitative programs for carefully screened men with COPD and low testosterone levels.

Keywords: androgenic steroid; inflammation; muscle mass; strength

Patients with chronic obstructive pulmonary disease (COPD) often have exercise intolerance as their chief complaint (1). In recent years, it has become clear that dysfunction of the muscles of ambulation contributes to exercise intolerance in these patients (2). This is of great importance, as muscle dysfunction is potentially remediable. In particular, rehabilitative programs of exercise training have been shown to increase exercise tolerance substantially (3). Endurance training and resistance training (employing maneuvers in which muscles exert or resist force to improve strength) have both been found to be effective. However, the benefits of these two types of programs are distinct: endurance training increases endurance (e.g., walking, climbing stairs), whereas resistance training increases strength (e.g., standing from a sitting position, maintaining balance), although modest crossover effects can be seen in some measures of strength and endurance (4). This difference is related to the distinctly different effects of these two interventions on muscle structure and biochemistry: for example, endurance training increases muscle capillarity and aerobic enzyme concentrations without much hypertrophy, and resistance training increases muscle fiber cross-sectional area without much increase in capillarity or aerobic enzyme concentration.

There has been a search for pharmacologic approaches to improving muscle strength and endurance that might be of benefit to patients with chronic disease. To date, no drugs clearly capable of increasing muscular endurance have been identified. However, the androgenic steroids have been shown to induce changes in the muscles of ambulation at least superficially similar to those seen with resistance training (5). Both in hypogonadal and healthy young men, testosterone supplementation increases muscle mass and improves maximal voluntary muscle strength (6–8). A few clinical studies of androgen supplementation in COPD have been published and have generally shown modest improvements in muscle mass, but without unequivocal improvements in either muscle strength or endurance (9–11).

It was our aim to determine whether testosterone supplementation might have the potential to be an appropriate adjunctive treatment during a program of pulmonary rehabilitation specifically directed at improving muscle mass and muscle function. Because the appropriate replacement dose for women has not been defined, we restricted our study to men with COPD. We therefore conducted a randomized, placebo-controlled, 10-week trial of replacement doses of testosterone enanthate. We compared the effects of this intervention with those of a standardized rigorous program of resistance training of the lower extremities and determined whether testosterone amplified the benefits of resistance training. Principal outcome measures included a change from baseline in body composition and muscle strength. In addition, the hormonal responses, changes in the levels of circulating indices of inflammation, and a number of safety measures were evaluated. Some of the results of this study have been previously reported in the form of an abstract (12).

METHODS

Additional method detail is provided in the online supplement.

Subjects

We enrolled 53 men with stable COPD. Entry criteria included age 55 to 80 years, FEV_1 of 60% predicted or less (13), and FEV_1 to vital capacity ratio of 60% or less. Screening serum testosterone was 400 ng/dl or less (in the lower range for healthy older men). Exclusion criteria included significant cardiovascular or orthopedic impairments, body weight of less

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Correspondence and requests for reprints should be addressed to Richard Casaburi, Ph.D., M.D., Division of Respiratory and Critical Care Physiology and Medicine, Los Angeles Biomedical Research Institute, Building RB2, 1124 West Carson Street, Torrance, CA 90502. E-mail: casaburi@ucla.edu

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than 75% or more than 130% of ideal, symptomatic benign prostatic hypertrophy, prostate cancer history, serum prostate specific antigen of more than 4 μg/L, or hemoglobin of more than 16 g/dl. The institutional review board approved the study, and written informed consent was obtained.

Study Design

Subjects were randomized to (*1*) placebo injections and no training, (*2*) testosterone injections and no training, (*3*) placebo injections and resistance exercise training, or (*4*) testosterone injections and resistance exercise training. Study personnel were blinded to whether subjects received testosterone or placebo. Subjects underwent a testing battery before and after a 10-week intervention.

Interventions

Testosterone supplementation. Subjects received 100 mg/week of testosterone enanthate in sesame oil (Delatestryl) or placebo (sesame oil) intramuscularly for 10 weeks. This testosterone dose was intended to raise nadir serum testosterone to the middle of the normal range for healthy young men (450–850 ng/dl). Testosterone levels were measured immediately before the second injection, and dosage alterations were made by an unblinded investigator.

Resistance training focused on muscles of ambulation. An exercise trainer supervised three sessions per week. Training consisted of seated leg press, seated leg curl, seated leg extension, standing calf raise, and seated ankle dorsiflexion. Subjects performed three sets of each exercise per session. For the first 4 weeks, the training target was 3 sets of 12 repetitions at 60% of pretraining one-repetition maximum. Intensity was increased when subjects completed all 36 repetitions of a given exercise. When 3 sets of 12 repetitions were again achieved, loads were increased. After 4 weeks of training, one repetition maximum values were reassessed and used for the remaining 6 weeks. Subjects performed four sets of 8–10 repetitions, using 80% of the new one-repetition maximum for each training exercise; the intensity was subsequently advanced as tolerated.

Dietary intake. Subjects were instructed to consume a eumetabolic diet. Based on three 3-day food diaries, dietitians reinforced caloric goal advice.

Outcome Measures

Body composition analysis. Dual-energy X-ray absorptiometry (Hologic 4500) provided regional assessment of bone, fat, nonfat nonbone (i.e., lean), and total body mass (14).

Muscle strength and local muscle fatigability. The seated leg press was chosen because it is a closed kinematic chain exercise predominantly testing the quadriceps muscle (although minor contributions of the hamstrings and gluteus maximus are also involved). The quadriceps were studied because dysfunction is associated with impaired gait speed, balance, stair climbing, and rising from a chair in the elderly (15). Muscle strength was evaluated by a one-repetition maximum (16) for bilateral seated leg press (Keiser Sport, Fresno, CA), a pneumatic device that provides increasing resistance through the range of motion; the value assigned for a maneuver is the peak force. Subjects underwent increasing lifts leading to the one-repetition maximum. To assess quadriceps fatigability (17), subjects performed as many seated leg press repetitions as possible using 80% of the preintervention one-repetition maximum. Subjects repeated both strength and local muscle fatigability tests 2 to 7 days later; the higher of the two values was used.

Whole-body exercise endurance. Cardiopulmonary exercise testing was performed on an electronically braked cycle ergometer (Ergoline 800; SensorMedics, Yorba Linda, CA) using a standard method (Vmax; SensorMedics) (18). In incremental testing, the work rate increased at 5 or 10 watts per minute. After 45 minutes of rest, patients performed constant work rate testing at 80% of peak work rate achieved in preintervention incremental testing. Both tests terminated when the subject was unable to maintain pedaling rate, despite encouragement.

Pulmonary function testing/arterial blood gas analysis. Testing was conducted 10 minutes or more after albuterol inhalation. Spirometry, maximum voluntary ventilation, functional residual capacity (by plethysmography), and diffusing capacity were measured by standard techniques (19–21). Respiratory muscle strength was assessed (in triplicate) by a maximal inspiratory effort from residual volume (22). Resting arterial blood gas analysis was performed using radial artery blood (model 1640; Instrumentation Laboratories, Lexington, MA).

Blood assays. Serum testosterone, free testosterone, estradiol, insulin-like growth factor-1, and insulin-like growth factor binding protein-3 levels were measured by previously validated immunoassays (23–26). Serum luteinizing hormone and follicle-stimulating hormone were measured by immunometric assays (23). Serum prostate specific antigen was measured using the Tandem-R monoclonal immunoradiometric assay (Hybritech, San Diego, CA). Inflammatory mediators interleukin-6 and tumor necrosis factor-α were measured by solid phase enzyme-linked immunosorbent assay (R&D Systems, Minneapolis, MN). C-reactive protein, produced by the liver in response to inflammation, was measured by turbidimetric immunoassay (Wako Chemicals, Richmond, VA) (27). Complete blood counts, blood chemistry panels, liver function tests, and lipid panels were performed by standard techniques.

Safety measures. Serum prostate specific antigen levels were measured at entry, Week 5, and intervention end; values of more than 0.75 μg/L above baseline on two consecutive measurements prompted treatment discontinuation. Digital prostate examinations were performed at entry, Week 5, and intervention end. Hemoglobin levels were measured at entry and five times during the intervention; values of more than 18 g/dl led to injection discontinuation.

Data Analysis

Descriptive statistics for each group for pretraining and post-training responses were generated in Excel spread sheets (Microsoft, Redmond, WA). Pretreatment values and the difference between pretreatment and post-treatment responses were analyzed by analysis of variance (SigmaStat 2.0; Jandel, San Rafael, CA). The Student-Newman-Keuls method was used if overall analysis of variance was significant. Linear regression and Pearson correlation analyses defined relationships among variables. The type I error was 0.05. Variation about the mean is expressed as standard deviation in text and tables and standard error in figures.

RESULTS

Eighty-five men with COPD were screened for this study. The distribution of their testosterone levels at screening is presented in Figure E1 in the online supplement. Forty percent of these men had serum testosterone levels below the lower limit of the normal range for healthy young men (300 ng/dl); an additional 16% had low normal testosterone levels (300–400 ng/dl). Eighty-six percent had testosterone levels below the mean level for healthy young men (585 ng/dl).

Of the 53 patients randomized, 47 completed the protocol: 11 in the testosterone + strength training group and 12 in each of the other three groups. Of the noncompleters, one (in the testosterone + training group) was discontinued because of noncompliance with the protocol and five because of non–protocol-related health problems (two in the testosterone + training group and one each in the other three groups). None of these subjects received chronic oral corticosteroid treatment during the intervention. Patients in the training groups completed at least 25 of the scheduled 30 sessions; those receiving testosterone averaged 27.5 sessions, and those receiving placebo averaged 28.1 sessions. Patients tolerated the interventions well, and no adverse events related to either training or testosterone supplementation were recorded.

Demographics and Lung Function

Table 1 lists subject characteristics, pulmonary function, and blood gas results on study entry. There were no significant differences in any of these variables among study groups. Patients averaged 67 years of age and were mildly above ideal body weight. FEV_1 averaged 40% predicted, indicating severe COPD. On average, patients were hyperinflated with reduced diffusing capacity. Blood gas analysis showed that, on average, arterial Po_2 was mildly reduced, and there was mild carbon dioxide retention. As anticipated, the interventions did not yield significant changes

TABLE 1. DEMOGRAPHICS, PULMONARY FUNCTION, AND ARTERIAL BLOOD GAS RESULTS AT STUDY ENTRY (MEAN ± SD)

	Placebo + No Training (*n* = 12)	Testosterone + No Training (*n* = 12)	Placebo + Resistance Training (*n* = 12)	Testosterone + Resistance Training (*n* = 11)
Age, yr	67.7 ± 8.7	66.6 ± 7.5	68.9 ± 9.8	66.4 ± 7.2
Height, cm	175.9 ± 6.8	178.0 ± 8.1	173.4 ± 5.4	175.7 ± 6.7
Weight, kg	81.4 ± 14.0	85.0 ± 17.5	82.9 ± 20.4	89.3 ± 24.2
FEV_1, L	1.25 ± 0.42	1.50 ± 0.66	1.14 ± 0.32	1.39 ± 0.46
FEV_1, % predicted	38.6 ± 12.1	43.0 ± 15.4	35.9 ± 9.2	42.4 ± 11.9
FEV_1/VC	41.4 ± 10.3	42.3 ± 14.5	35.8 ± 7.2	45.9 ± 12.7
TLC, L	7.88 ± 1.83	8.25 ± 1.02	8.33 ± 1.43	7.64 ± 1.45
$D_{L_{CO}}$, ml/min/mm Hg	13.6 ± 4.5	13.1 ± 6.0	11.9 ± 5.3	13.1 ± 7.4
Pa_{O_2}, mm Hg	69.6 ± 7.9	68.9 ± 10.4	73.0 ± 16.6	65.6 ± 17.3
Pa_{CO_2}, mm Hg	44.8 ± 4.5	45.0 ± 8.6	44.0 ± 6.7	46.2 ± 6.1
pHa	7.43 ± 0.02	7.42 ± 0.04	7.42 ± 0.03	7.41 ± 0.03

Definition of abbreviations: $D_{L_{CO}}$ = single-breath diffusing capacity for carbon monoxide; pHa = arterial negative logarithm of hydrogen ion concentration; TLC = total lung capacity.

in pulmonary function and blood gas variables (*see* Table E1 in the online supplement). Average differences between preintervention and postintervention values did not differ significantly among groups with the sole exception of a mild decrease in Pa_{O_2} (averaging 9.4 ± 11.4 mm Hg) in the placebo + resistance training group.

Endocrine Responses

Table 2 presents the hormonal responses and also the responses of three circulating indicators of inflammation at study entry. At entry, there were no significant differences among groups for any of these variables. Per protocol design, average testosterone (and free testosterone) values were low. (Because the values in Table 2 record the values just before initiation of the intervention rather than at screening, some subjects who had lower serum testosterone levels at screening had testosterone values exceeding 400 ng/dl just before treatment initiation.) Both luteinizing hormone and follicle-stimulating hormone were, on average, low. Figure E2 in the online supplement demonstrates that four subjects (8%) with low testosterone levels manifested elevated luteinizing hormone and follicle-stimulating hormone concentrations; these men with hypergonadotropic hypogonadism likely had primary testicular dysfunction. The remaining 92% of men with low testosterone concentrations had low or inappropriately normal luteinizing hormone concentrations; these men with hypogonadotropic hypogonadism likely had a defect at the hypothalamic–pituitary level, although an additional defect at the testicular level cannot be excluded. Insulin-like growth factor-1 is the predominant mediator of growth hormone's anabolic effects on muscle, and insulin-like growth factor binding protein-3 is the predominant plasma binding protein for this hormone. In the subjects studied, serum insulin-like growth factor-1 levels were low, but insulin-like growth factor binding protein-3 concentrations were within the normal range.

Figure 1 shows the hormonal responses to the interventions in the four groups (preintervention and postintervention values are presented in tabular form in Table E2 of the online supplement). Each panel shows the nadir levels (obtained just before the next injection) during the intervention. In the two groups receiving placebo injections, there were no significant changes in total or free testosterone or in luteinizing or follicle-stimulating hormone from preintervention values. In the two groups receiving testosterone enanthate, both total and free testosterone levels were increased significantly above preintervention values; the increase in testosterone level averaged 293 ng/dl in the testosterone + no training group and 248 ng/dl in the testosterone + resistance training group. However, average nadir testosterone levels remained well within the normal range seen in healthy young men. In the two groups receiving testosterone injections, Figure 1 shows that both luteinizing and follicle-stimulating hormones were suppressed to very low levels. This reflects the inhibitory effects of the elevated testosterone levels on pituitary secretion; presumably, these low circulating luteinizing and follicle-stimulating hormone levels inhibited endogenous testosterone secretion by the testes. Changes in insulin-like growth factor-1 and insulin-like growth factor binding protein-3 did not differ among the four groups (Table E2).

Table 2 lists the study entry levels of three indicators of inflammatory state. Interleukin-6 is a cytokine that contributes to the systemic effects of inflammation. Average circulating interleukin-6 levels (Table 2) were mildly above those of healthy normal subjects (mean = 1.8 pg/ml) with this assay; 5 of the 47

TABLE 2. CIRCULATING HORMONAL AND INFLAMMATORY MEDIATOR LEVELS AT STUDY ENTRY (MEAN ± SD)

	Placebo + No Training	Testosterone + No Training	Placebo + Resistance Training	Testosterone + Resistance Training
Testosterone, ng/dL	302 ± 154	302 ± 89	277 ± 106	408 ± 139
Free testosterone, pg/ml	39.2 ± 20.6	39.6 ± 13.8	29.1 ± 13.0	41.5 ± 12.3
Luteinizing hormone, IU/L	5.50 ± 6.99	4.25 ± 2.91	7.71 ± 11.41	4.79 ± 2.11
Follicle-stimulating hormone, IU/L	13.02 ± 24.45	7.27 ± 9.17	14.01 ± 22.18	7.63 ± 8.83
Insulin-like growth factor-1, ng/ml	170 ± 89	239 ± 97	173 ± 93	224 ± 191
Insulin-like growth factor binding protein-3, ng/ml	2.71 ± 0.56	3.19 ± 1.15	2.70 ± 1.02	2.48 ± 1.00
Interleukin-6, pg/ml	4.00 ± 1.87	5.38 ± 4.89	4.92 ± 5.10	9.30 ± 11.88
Tumor necrosis factor-α, pg/ml	3.15 ± 2.52	3.98 ± 3.27	2.99 ± 1.64	4.96 ± 3.30
C-reactive protein, mg/L	7.89 ± 8.34	5.23 ± 5.18	3.96 ± 4.51	6.53 ± 6.67

subjects' levels were above the upper limit of normal (10 pg/ml). Tumor necrosis factor-α is a cytokine that is a nonspecific inflammatory mediator and is responsible for many of the systemic consequences of severe infection. The circulating levels of tumor necrosis factor-α were mildly elevated with respect to healthy normal subjects (mean = 2.1 pg/ml) with this assay; 17 of the 47 subject's levels were above the upper limit of normal (4.7 pg/ml). C-reactive protein is an acute-phase protein produced by the liver in response to inflammation and infection. Again, average circulating levels in the study subjects were mildly above the upper limit of the normal range for the assay (3 mg/L), with 17 subjects' levels above this value. Therefore, the subjects in this study manifested signs of a mild inflammatory state. None of the study groups demonstrated significant changes in any of these three markers of inflammation (*see* Table E2 in the online supplement), indicating that neither resistance training nor testosterone supplementation appreciably modulated the state of inflammation.

Body Composition Responses

Subjects were weighed weekly during the intervention; the time course of body weight change from the preintervention level is shown in Figure 2 for each of the four groups. Both groups receiving placebo injections had little weight change during the intervention. In contrast, both groups receiving testosterone had steady (and similar) weight gain, averaging roughly 2 kg by the end of the study period. Whole-body dual-energy X-ray absorptiometry allows determination of the nature and the regional distribution (arms, trunk, legs) of body composition changes. Table 3 presents the regional as well as total fat and lean mass before and after the intervention in each of the four study groups. Figure 3 plots selected body composition changes from baseline. Both groups receiving testosterone supplementation experienced significant lean mass increases in the arms (averaging approximately 6.5%), the trunk (averaging approximately 4%), and the legs (averaging approximately 7%), yielding a total lean mass increase averaging approximately 5.5%. Changes in lean mass tended to be greater in the testosterone + training group than in the testosterone + no training group, but these differences failed to achieve statistical significance. In the two groups receiving testosterone, fat mass tended to decrease in all regions, but this achieved statistical significance for only the legs (averaging approximately 5%); total fat mass decreased by approximately 5%. Thus, the increase in body weight in the groups receiving testosterone was the net result of an increase in lean body mass coupled with a decrease in fat. There was a significant correlation between the change in testosterone levels and the change in lean body mass for the individuals in the nontraining groups (placebo + no training and testosterone + no training) ($r = 0.52$, $p < 0.01$) (Figure E3 in the online supplement).

In the two groups receiving placebo, the only significant body composition change was an average 3% increase in leg lean mass in the placebo + resistance training group. Thus, the leg resistance training program was associated with a modest local increase in muscle mass.

Local Muscle Strength and Whole-body Exercise Endurance

Table 4 presents the preintervention and postintervention values for each study group for measures of quadriceps strength and

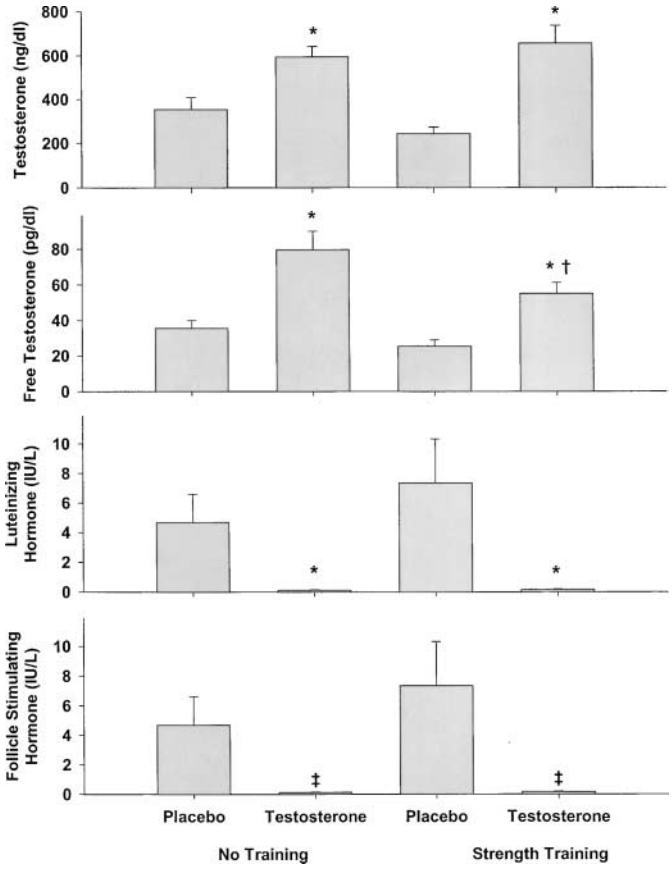

Figure 1. Hormonal levels from venous blood samples drawn immediately before weekly injections (nadir levels) for the four study groups (from left to right: placebo + no training, n = 12; testosterone + no training, n = 12; placebo + resistance training, n = 12; testosterone + resistance training, n = 11). Testosterone and free testosterone levels are increased in the groups receiving testosterone but not placebo. Testosterone supplementation results in near complete suppression of circulating levels of luteinizing and follicle-stimulating hormone. *Response to intervention significantly different from nontestosterone groups. †Response to intervention significantly different from testosterone + no training group. ‡Response to intervention significantly different from placebo + resistance training group.

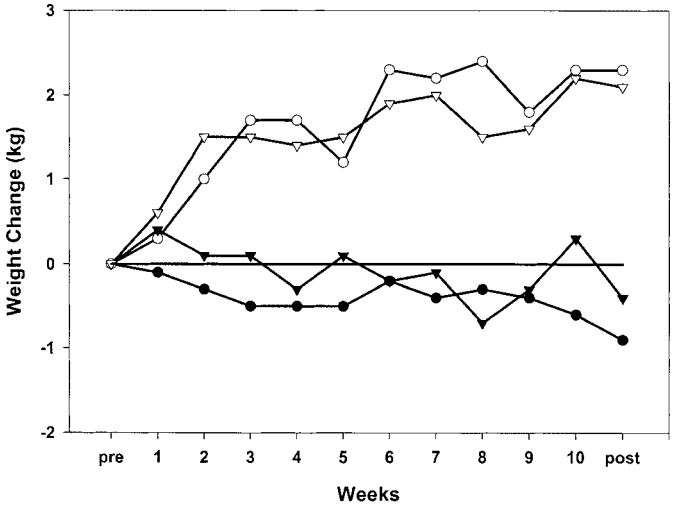

Figure 2. Time course of average body weight change with respect to preintervention values in the four study groups. *Closed circles* = placebo + no training. *Open circles* = testosterone + no training. *Closed triangles* = placebo + resistance training. *Open triangles* = testosterone + resistance training. Groups receiving testosterone supplementation but not groups receiving placebo experienced a steady gain of weight over the course of the intervention.

TABLE 3. BODY COMPOSITION (IN KG) RESPONSES TO THE INTERVENTIONS (MEAN ± SD)

	Placebo + No Training		Testosterone + No Training		Placebo + Resistance Training		Testosterone + Resistance Training	
	Before	After	Before	After	Before	After	Before	After
Arm fat	2.88 ± 1.00	2.62 ± 0.92	2.73 ± 1.11	2.63 ± 1.04	3.33 ± 2.20	3.01 ± 2.13	3.40 ± 2.32	3.11 ± 2.15
Arm lean	6.32 ± 0.92	6.19 ± 1.05	6.96 ± 1.23	7.36* ± 1.27	6.66 ± 1.37	6.51 ± 1.43	6.73 ± 1.25	7.23* ± 1.72
Trunk fat	12.78 ± 4.41	13.12 ± 4.51	13.27 ± 5.33	12.72 ± 5.24	13.47 ± 6.98	13.58 ± 7.76	15.92 ± 9.61	15.25 ± 10.24
Trunk lean	26.38 ± 3.23	26.49 ± 2.54	27.68 ± 4.04	28.50† ± 4.15	27.82 ± 4.48	27.67 ± 4.54	28.12 ± 5.18	29.50* ± 5.12
Leg fat	7.48 ± 2.99	7.32 ± 2.87	7.76 ± 2.77	7.39* ± 2.76	6.76 ± 2.71	6.83 ± 2.78	8.04 ± 3.90	7.59* ± 4.07
Leg lean	16.31 ± 2.97	16.12 ± 2.93	17.40 ± 3.35	18.47‡ ± 3.47	16.46 ± 2.59	16.95‡ ± 2.88	17.48 ± 3.48	18.89* ± 3.80
Total fat	23.14 ± 7.86	23.06 ± 7.71	23.76 ± 8.97	22.75* ± 8.69	23.56 ± 11.43	23.43 ± 12.18	27.36 ± 15.48	25.95* ± 16.14
Total lean	49.01 ± 6.88	48.80 ± 6.27	52.04 ± 8.26	54.34* ± 8.47	50.94 ± 8.24	51.14 ± 8.53	52.33 ± 9.48	55.62* ± 10.10
% Fat	30.60 ± 7.41	30.58 ± 6.94	29.53 ± 6.68	27.76† ± 6.07	29.48 ± 6.95	28.83 ± 7.78	31.35 ± 10.08	28.39* ± 10.36

* Response to intervention significantly different from nontestosterone groups.
† Response to intervention significantly different from placebo + strength training group.
‡ Response to intervention significantly different from placebo + no training group.

fatigability, respiratory muscle strength, and whole-body exercise endurance in cardiopulmonary exercise testing. There were no significant differences among groups for any of these variables at initial testing. Maximum inspiratory pressure was reduced, averaging approximately 62% of predicted (22), indicating inspiratory muscle weakness. Peak oxygen uptake in the incremental exercise test averaged 56% of predicted (18), indicating substantial endurance exercise intolerance.

Figure 4 plots the change in response to the interventions of two measures of quadriceps function. One repetition maximum did not increase significantly in the control (placebo + no training group) but increased in the testosterone + no training, placebo + resistance training, and testosterone + resistance training groups by an average of 17%, 17%, and 27%, respectively. Similarly, leg press repetitions to failure at 80% of the preintervention one-repetition maximum, a measure of quadriceps fatigability, increased significantly with respect to the control group in the three groups receiving active treatment by an average of 17%, 45%, and 81%, respectively. Thus, leg press strength and fatigability increased significantly with each of the two interventions. In the group receiving the combined intervention, the increase in both measures was significantly greater than in the testosterone + no training group and tended to be greater than seen in the placebo + strength training group. Among all subjects studied, there was a significant correlation between the change in lean leg mass and the percentage increase in one repetition maximum leg press ($r = 0.46$, $p < 0.005$) (Figure E4 in the online supplement). In contrast to the measures of leg strength, peak inspiratory pressure, a measure of inspiratory muscle strength, did not increase in any of the study groups.

Measurements obtained during cardiopulmonary exercise testing derived from preintervention and postintervention incremental and constant work rate cardiopulmonary exercise testing are presented in Table 4. No significant changes with respect to the control group were seen in any of these measures in the testosterone + no training or the placebo + resistance training groups, with the exception of a mild decrease in peak work rate in the testosterone + no training group. In the combined intervention group, however, small but statistically significant increases were seen in peak oxygen uptake, peak work rate, and lactic acidosis threshold (averaging 6%, 6%, and 4%, respectively) in the incremental exercise test; the increase in the duration of the constant work rate test just failed to achieve significance (overall analysis of variance, $p = 0.064$).

Safety Measures

Table E3 in the online supplement presents the average preintervention and postintervention values for each of the four study groups for hemoglobin, serum creatinine, liver enzymes (alanine aminotransferase, aspartate aminotransferase, and γ-glutamyltranspeptidase), alkaline phosphatase, prostate specific antigen, cholesterol, and high-density lipoprotein cholesterol. There were no significant differences among groups for any of these measures at baseline. With the exception of hemoglobin, the interventions engendered no significant changes in any of these variables in any of the study groups. In the testosterone + no training and the testosterone + resistance training groups, the average hemoglobin level increased by 0.98 ± 0.96 and 0.97 ± 0.88 g/dl (i.e., roughly 7%). In only one subject did hemoglobin exceed 18 g/dl (this occurred at the end of the intervention period; the hemoglobin level decreased during postintervention observation).

DISCUSSION

Our results show that replacement doses of testosterone increase lean body mass and strength in men with severe COPD and low testosterone levels; strength improvement is amplified by concomitant resistance training. This is the first demonstration that strength increases accompany androgenic steroid supplementation in COPD and raises the possibility that testosterone supplementation may be appropriate therapy in conjunction with rehabilitative programs for patients with muscle weakness. However, further research is needed to assess long-term benefits and to search for adverse effects in a larger patient sample before firm recommendations can be made.

Muscle weakness is common in patients with advanced COPD (28–30). Muscle mass is reduced not only in underweight, but in normal or overweight patients, as well. Weakness and reduced muscle mass correlate with decreased functionality and quality of life (29, 31). Leg muscle biopsy has shown marked abnormalities compared with age-matched healthy control subjects, including low aerobic enzyme levels (32, 33), capillary density, type I fiber fraction, and fiber cross-sectional area (34). The mechanism of COPD muscle dysfunction is likely multifactorial (2, 35, 36). Deconditioning, malnutrition, corticosteroid myopathy (37, 38), muscle inflammation (39), and perhaps a COPD-specific myopathy may be involved.

An additional mechanism of poor muscle function in COPD relates to circulating levels of hormones anabolic to skeletal muscle. Both growth hormone and the androgenic steroids stimulate muscle growth. In men, testosterone levels decline with age (40, 41). This decline has been linked to sexual dysfunction (42), osteopenia (43), memory loss (44), as well as muscle weakness and atrophy (45). Evidence is accumulating that testosterone levels are low in men with COPD (46, 47); hypothesized

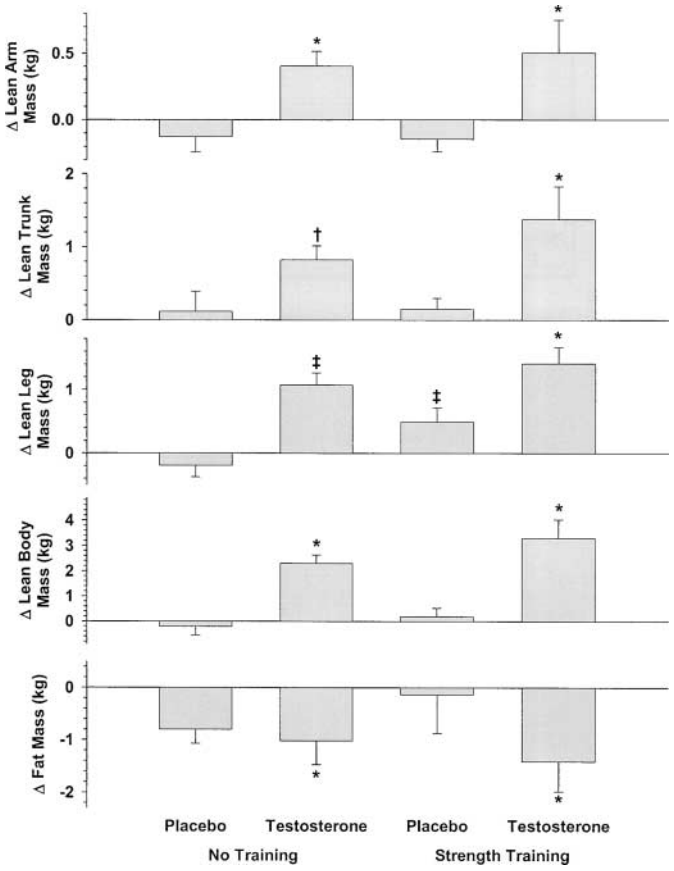

Figure 3. Regional and total body composition changes resulting from the interventions in the four study groups determined by dual-emission X-ray absorptiometry. Study groups are presented as in Figure 1. The regional (arm, trunk, lean, and total) lean mass increases in the groups receiving testosterone supplementation. In the group undergoing a resistance training program targeting the legs, but not receiving testosterone supplementation, lean mass increases only in the legs. Total fat mass decreases in both groups receiving testosterone. *Response to intervention significantly different from nontestosterone groups. †Response to intervention significantly different from placebo + resistance training group. ‡Response to intervention significantly different from placebo + no training group.

mechanisms include chronic hypoxia (48, 49), corticosteroid therapy (50), and chronic illness (51).

That testosterone supplementation increases muscle mass and strength in healthy men was firmly established by a study with a design similar to this study. Supraphysiologic testosterone supplementation for 10 weeks yielded 5% muscle mass and 13% one-repetition maximum squat exercise increase; these gains were additive to those of resistance training (7). More recently, 61 men were randomized to receive one of five testosterone doses for 20 weeks (8). Both lean body mass and muscle strength increased in proportion to the testosterone dose. The group receiving the highest dose (600 mg/week) experienced a 7.9-kg increase in lean mass and a 76.5-kg increase in one-repetition maximum leg press strength.

Hypogonadal men increase muscle mass and strength when testosterone replacement returns testosterone levels to the normal range (6). Accumulating evidence indicates that older men with mildly low testosterone levels respond to testosterone supplementation with increased muscle mass and strength (52, 53). Recent studies demonstrate that replacement testosterone doses increase muscle mass and strength in men with human immunodeficiency virus wasting syndrome (54, 55).

Three studies of androgenic steroid supplementation in COPD have been reported. Schols and colleagues (9) administered nutritional supplementation with and without nandrolone decanoate for 8 weeks to male and female patients with COPD. Weight gain was approximately 1.5 kg in both groups, but weight gain was mostly fat mass in the nutrition-alone group and mostly lean mass in the nandrolone + nutrition group. No differences were detected in maximum inspiratory pressure and 12-minute walking distance between treatment groups. Ferreira and colleagues (10) studied underweight patients with COPD for 27 weeks; half received oral stanozolol and half placebo. The stanozolol group increased lean mass by 2.5 kg. Neither the stanozolol group nor the placebo group increased maximum inspiratory pressure, 6-minute walk distance, or peak oxygen uptake. Yeh and colleagues (11) administered 4 months of oral oxandrolone to underweight COPD men and women. Weight gain averaged 2.1 kg (predominately lean tissue). Neither maximum inspiratory pressure nor 6-minute walk distance increased significantly.

The lack of improvement in functionality has tended to temper enthusiasm for anabolic hormone supplementation in COPD. However, previous studies used testosterone analogues rather than testosterone itself. Doses of these analogues may have been too low; testosterone supplementation allows direct assessment of increase in circulating levels. These can be compared with levels seen in healthy individuals. Furthermore, functional outcomes chosen in previous studies were likely suboptimal. Maximum inspiratory pressure, an index of respiratory muscle strength, is very effort and motivation dependent. Walking distance and peak oxygen uptake are measures of whole-body exercise endurance. Testosterone supplementation has repeatedly failed to improve whole-body endurance exercise performance in healthy young subjects (56). We recently reported responses of vastus lateralis muscle structure and biochemistry (assessed by needle biopsy) to testosterone supplementation in young men (5). Testosterone induced increases in muscle fiber size, but not capillarity density. These features are similar to resistance training, but markedly different from endurance training where increased capillarity enhances muscle oxygen delivery (1).

In this study, we compared the effects of testosterone given in replacement doses to a rigorous program of resistance training. We chose to include normal as well as underweight subjects, as low muscle strength is seen in both groups. Leg press one-repetition maximum values averaged 46% of values obtained in healthy young men using an identical apparatus (57). Participants manifested low testosterone levels that, in most cases, were likely a result of both inadequate testicular function and inadequate pituitary gonadotropin secretion (Figure E1). Testosterone supplementation yielded nadir circulating levels in the normal range for healthy young men (Figure 1). Pituitary secretion of luteinizing hormone and follicle-stimulating hormone was inhibited at this dose. Circulating levels of insulin-like growth factor-1 were not altered, although it has been demonstrated that testosterone supplementation upregulates intramuscular insulin-like growth factor-1 gene expression (52, 58). Although the range of inflammatory mediators that we assayed does not constitute a comprehensive battery, as a group, these subjects manifested evidence of a mild inflammatory state consistent with the findings of Schols and colleagues (59) and Takabatake and colleagues (60), but not with the findings of DiFrancia and colleagues (61) who found dramatically elevated tumor necrosis factor-α levels in underweight patients with COPD.

Testosterone supplementation produced lean body mass increases detectable in all body regions. The 2.3-kg lean mass

TABLE 4. QUADRICEPS STRENGTH AND FATIGABILITY, RESPIRATORY MUSCLE STRENGTH, AND CARDIOPULMONARY EXERCISE TEST RESPONSES BEFORE AND AFTER THE INTERVENTIONS (MEAN ± SD)

	Placebo + No Training		Testosterone + No Training		Placebo + Resistance Training		Testosterone + Resistance Training	
	Before	After	Before	After	Before	After	Before	After
Leg press one-repetition maximum, kg	268 ± 62	274 ± 66	264 ± 89	296* ± 73	296 ± 96	344* ± 98	270 ± 141	329† ± 167
Leg press fatigue, repetitions	14.7 ± 3.6	14.4 ± 7.5	14.2 ± 6.3	16.5* ± 7.2	15.5 ± 11.9	22.5* ± 6.4	12.6 ± 3.6	23.6† ± 10.8
Maximum inspiratory pressure, cm H_2O	68.5 ± 19.0	68.5 ± 16.7	76.4 ± 24.0	83.4 ± 20.5	75.8 ± 30.3	80.8 ± 35.8	69.5 ± 19.4	67.7 ± 24.4
Peak oxygen uptake, L/min	1.10 ± 0.40	1.04 ± 0.35	1.15 ± 0.38	1.05 ± 0.37	1.13 ± 0.39	1.14 ± 0.36	1.10 ± 0.32	1.16† ± 0.39
Peak work rate, W	66.8 ± 34.6	70.0 ± 32.8	77.2 ± 26.8	70.9* ± 28.4	82.8 ± 42.0	82.5 ± 38.1	73.4 ± 30.2	77.6‡ ± 30.8
Lactic acidosis threshold, L/min	1.00 ± 0.19	0.96 ± 0.28	0.87 ± 0.25	0.88 ± 0.32	1.03 ± 0.27	0.98 ± 0.28	0.82 ± 0.25	0.85* ± 0.25
Constant work rate duration, min	4.9 ± 2.0	4.8 ± 1.9	5.0 ± 0.9	5.3 ± 2.4	8.0 ± 4.9	6.8 ± 4.1	6.3 ± 2.0	8.7 ± 5.4

* Response to intervention significantly different from placebo + no training group.
† Response to intervention significantly different from nontraining groups.
‡ Response to intervention significantly different from testosterone + no training group.

increase in the testosterone + no training group and 3.3 kg in the testosterone + resistance training group is greater than seen in previous androgenic steroid studies in COPD (9–11). This increase is somewhat smaller than seen in a study of similar design performed in healthy young subjects (3.2 and 6.1 kg, respectively), but testosterone dose was sixfold higher (7). Muscle dysfunction in COPD apparently does not render muscle unresponsive to the hypertrophic effects of testosterone supplementation. Because the dose–response curve for testosterone supplementation is essentially linear through doses much higher than used in this study (9), doses of testosterone enanthate higher than 100 mg/week might yield larger increases in lean body mass (albeit at increased adverse effect risk). Body fat mass decreased by approximately 5% (1.2 kg) in subjects receiving testosterone supplementation, consistent with testosterone's known lipolytic effects (62).

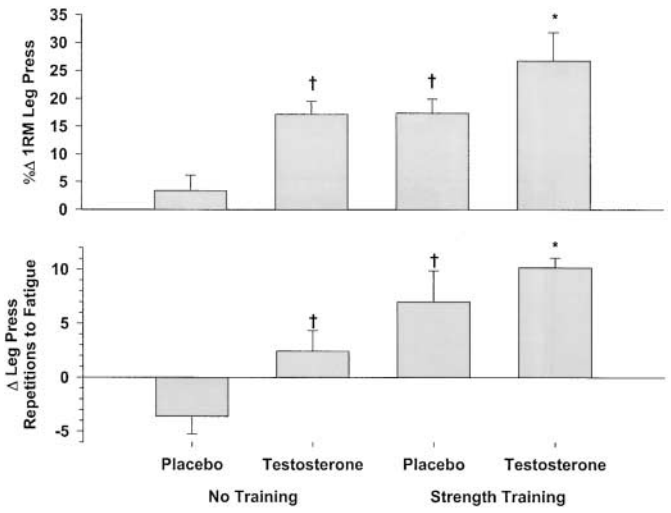

Figure 4. Percentage changes in one-repetition maximum (1RM) of the leg press (a measure of leg extension strength) and in the number of repetitions of the leg press exercise tolerated at a weight equal to 80% of the subject's preintervention one-repetition maximum (a measure of the fatigability of the leg extensors) in the four study groups. Study groups are presented as in Figure 1. Both resistance training and testosterone supplementation increase both leg strength and repetitions to fatigue; the combined intervention tends to yield increases greater than either intervention alone. * Response to intervention significantly different from nontraining groups. † Response to intervention significantly different from placebo + no training group.

Testosterone supplementation produced increased leg extensor strength, muscles important for everyday functional activities (e.g., rising from a chair, maintaining balance). Resistance to fatigue of this muscle group was also enhanced. However, as anticipated (mentioned previously here), whole-body exercise endurance was not enhanced (Table 4). Furthermore, maximum inspiratory pressure was not significantly increased. It is conceivable that variability in this measurement caused us to miss a modest effect; alternately, the respiratory muscles may be relatively "well trained" in COPD and have limited potential for further strengthening.

Adverse effects of testosterone supplementation at this dose and for this duration were not detected, suggesting that replacement doses can be safely administered in carefully screened and monitored patients. At substantially higher doses, reductions in high-density lipoprotein cholesterol (7, 8) are seen. Personality changes ("steroid rage") are only seen at very high doses (63). Liver function test abnormalities have been observed almost exclusively with high doses of orally administered 17-alkylated steroids (11). There is agreement that testosterone does not cause prostate cancer; however, many older men harbor microscopic foci of cancer that remain subclinical. We do not know whether testosterone replacement causes these subclinical cancer foci to become clinically overt, although a long duration failed to show this (64). Testosterone replacement of healthy, hypogonadal men is associated with a small increase in serum prostate-specific antigen level. As seen in this study, modest hematocrit increases (mediated by stimulation of erythropoietin secretion) are seen with testosterone supplementation (7, 8), although overt polycythemia is rare (65).

There is growing appreciation that resistance training has an important role in rehabilitative COPD therapy. Several studies have demonstrated that muscle strength can be improved by resistance training (66). In the placebo + resistance training group in this study, muscle mass increase was limited to the trained limbs (the legs) and tended to be lower than seen in the testosterone + no training group (Figure 3). In contrast, strength increase was similar in the group receiving resistance training and the group receiving testosterone (Figure 4). These findings are consistent with our study in healthy young men demonstrating that specific tension (strength per muscle cross-sectional area) was increased by resistance training but not testosterone administration (57).

The combined intervention (testosterone + resistance training) tended to yield superior muscle mass and strength gains than either intervention alone. A statistically significant increase in whole-body exercise endurance in the incremental exercise test was detected (Table 4), but it is doubtful whether the

magnitude was clinically important. Clearly, endurance exercise programs yield superior endurance benefits (67, 68) and are the preferred way to induce whole-body exercise endurance gains.

In summary, administering replacement testosterone doses for 10 weeks increased lean body mass and leg muscle strength in men with moderate to severe COPD and low testosterone levels. Resistance training of the legs yielded similar benefits and the combination tended to be additive. These interventions may be appropriate for inclusion in rehabilitative programs for carefully screened men with COPD. Because low muscle mass is a predictor of mortality in COPD (69), effects of these anabolic interventions on survival should be investigated. Further research is needed to confirm the safety of testosterone supplementation in COPD and to see whether higher doses or long-term treatment can be recommended. Another priority will be to conduct studies in women with COPD to determine whether gains in muscle mass and strength can be realized at testosterone doses not yielding unacceptable virilizing side effects.

Conflict of Interest Statement: R.C. is on the Biotechnology General Corporation (BTG) National Advisory Board (honorarium $750 to date) and has also been site principal investigator in a multicentered trial of Oxandrolone (an oral steroid) in COPD sponsored by BTG (total payments to site of approximately $75,000), and BTG has donated testosterone enanthate for this project (value approximately $700) and also markets Oxandrolone; S.B. has received research grant support from Solvay Pharmaceuticals ($600,000) and ALZA Corporation ($150,000) and has served on Solvay's Advisory Board and served as a consultant ($5,500) and has given lectures that have been sponsored by BTG, Solvay, Watson, and ALZA Corporation ($10,000), and these corporations manufacture testosterone analogues or delivery systems for testosterone or its analogues; L.C. does not have a financial relationship with a commercial entity that has an interest in the subject of this manuscript; J.P. does not have a financial relationship with a commercial entity that has an interest in the subject of this manuscript; A.S. does not have a financial relationship with a commercial entity that has an interest in the subject of this manuscript; M.I.L. does not have a financial relationship with a commercial entity that has an interest in the subject of this manuscript; M.F. does not have a financial relationship with a commercial entity that has an interest in the subject of this manuscript; T.W.S. does not have a financial relationship with a commercial entity that has an interest in the subject of this manuscript.

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