Treatment with oxandrolone and the durability of its effects in older men

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1Division of Infectious Diseases, Department of Medicine, 2General Clinical Research Center, and 3Department of Radiology, Keck School of Medicine, and 4Department of Biokinesiology and Physical Therapy, University of Southern California, Los Angeles, California 90033; and 5Divisions of Metabolism, Endocrinology and Lipid Research and Cell Biology and Physiology, Department of Internal Medicine, Washington University School of Medicine, St. Louis, Missouri 63110

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Schroeder, E. Todd, Ling Zheng, Kevin E. Yarasheski, Dajun Qian, Yolanda Stewart, Carla Flores, Carmen Martinez, Michael Terk, and Fred R. Sattler. Treatment with oxandrolone and the durability of its effects in older men. J Appl Physiol 96: 1055–1062, 2004.—We investigated the effects of the anabolic androgen, oxandrolone, on lean body mass (LBM), muscle mass, fat, and maximum voluntary muscle strength, and we determined the durability of its effects after treatment was stopped. Thirty-two healthy men, aged 60–78 yr, were randomized to receive 20 mg oxandrolone/day (n = 20) or placebo (n = 12) for 12 wk. Body composition [dual-energy X-ray absorptiometry (DEXA), magnetic resonance imaging, and 1H2O dilution] and muscle strength [1 repetition maximum (1 RM)] were evaluated at baseline and after 12 wk of treatment; body composition (DEXA) and 1-RM strength were then assessed 12 wk after treatment was discontinued (week 24). At week 12, oxandrolone increased LBM by 3.0 ± 1.5 kg (P < 0.001), total body water by 2.9 ± 3.7 kg (P = 0.002), and proximal thigh muscle area by 12.4 ± 8.4 cm2 (P < 0.001); these increases were greater (P < 0.003) than in the placebo group. Oxandrolone increased 1-RM strength for leg press by 6.7 ± 6.4% (P < 0.001), leg flexion by 7.0 ± 7.8% (P < 0.001), chest press by 9.3 ± 6.7% (P < 0.001), and latissimus pull-down exercises by 5.1 ± 9.1% (P = 0.02); these increases were greater than placebo. Oxandrolone reduced total (−1.9 ± 1.0 kg) and trunk fat (−1.3 ± 0.6 kg; P < 0.001), and these decreases were greater (P < 0.001) than placebo. Twelve weeks after oxandrolone was discontinued (week 24), the increments in LBM and muscle mass were no longer different from baseline (P > 0.15). However, the decreases in total and trunk fat were sustained (−1.5 ± 1.8, P = 0.001 and −1.0 ± 1.1 kg, P < 0.001, respectively). Thus oxandrolone induced short-term improvements in LBM, muscle area, and strength, while reducing whole body and trunk adiposity. Anabolic improvements were lost 12 wk after discontinuing oxandrolone, whereas improvements in fat mass were largely sustained.

lean body mass; muscle mass; dual-energy X-ray absorptiometry; magnetic resonance imaging

ADVANCING AGE IS ASSOCIATED with a progressive loss of muscle mass (sarcopenia), skeletal muscle strength, and physical function (1, 2, 9, 14, 19). Sarcopenia increases the risk for frailty, falls, fractures, dependency, and depression (34, 36). Advancing age is also associated with increases in fat mass, particularly central adiposity, which increases the risk for insulin resistance, hypertension, dyslipidemia, and impaired fibrinolysis (metabolic syndrome) (37). The metabolic syndrome pre-disposes older persons to accelerated atherosclerosis and Type 2 diabetes.

The contribution of age-associated hormonal alterations to these adverse health consequences is unclear. Both cross-sectional (15, 28, 51) and longitudinal (17, 30) studies have shown that serum total and free concentrations of testosterone decline with advancing age in men. Testosterone regulates muscle mass and fat mass, but the relationship between gonadal hormone status and age-associated alterations in body composition, skeletal muscle strength, and metabolic disorders in older persons is uncertain. There is some evidence that bioavailable testosterone levels (free and the fraction loosely bound to albumin) correlate with skeletal muscle mass and muscle strength in different ethnic populations (3, 35).

Testosterone treatment in hypogonadal young men increases lean tissue (4, 7, 20, 45, 53, 54) and muscle strength (4, 54) and decreases fat mass (4, 20, 54). Despite evidence that supplemental testosterone increases myofibrillar protein synthesis rate in older men (11, 52), its effects on body composition and muscle function in these men are less clear (22, 31, 44, 46, 50, 51). In the largest studies, in which older relatively hypogonadal men received testosterone replacement for 1 and 3 yr, respectively, lean body mass (LBM) was only modestly increased (1.0 and 1.9 kg, respectively) (22, 46), and the effects on muscle strength were variable. Only three studies have shown increases in lower extremity maximum voluntary force (11, 22, 52). By contrast, in a controlled study of 108 older men randomized to receive placebo or testosterone (46), upper extremity grip strength and lower extremity isokinetic strength were unchanged with testosterone (50). Similarly, the effects of testosterone on fat mass have been variable with either no change or only modest reductions achieved (11, 21, 31, 46, 51, 52).

The variability in outcomes in older men may be related to the different delivery strategies for testosterone (intramuscular vs. transdermal delivery), dose (200 mg biweekly vs. 5 mg/day), change in testosterone levels in response to therapy, duration of treatment (4 wk vs. 3 yr), different methods to assess body composition [bioelectrical impedance analysis, dual-energy X-ray absorptiometry (DEXA), magnetic resonance imaging (MRI), hydrostatic weighing], as well as measures of muscle strength (handheld dynamometers, isokinetic dynamometers, free weights, or pneumatic resistance devices).

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Moreover, with one exception, these studies did not directly assess changes in muscle mass or muscle cross-sectional area (CSA).

Oxandrolone is a potent, oral anabolic androgen that is approved for the treatment of weight loss due to known medical or unexplained causes (43, 48). We evaluated whether the licensed dose of oxandrolone increases muscle mass and muscle strength and reduces body fat mass in older men at risk for sarcopenia and metabolic complications. Moreover, we followed these men for 12 wk after discontinuing oxandrolone to evaluate the durability of the alterations in body composition and muscle strength. We hypothesized that oxandrolone would increase LBM, muscle area, and muscle strength, and reduce whole body and central adiposity in older men, and that these benefits would not be fully sustained.

METHODS

Study Design

This was a single-center, investigator-initiated, double-blind, placebo-controlled investigation to determine the magnitude and durability of effects of a potent, convenient to administer anabolic androgen, oxandrolone (Oxandrin). The study was performed at the University of Southern California National Center for Research Resources-funded General Clinical Research Center, with the exception that skeletal muscle strength was assessed at the Clinical Exercise Research Center in the Department of Biokinesiology and Physical Therapy of the University. The study design and informed consent were approved and annually reviewed by the Institutional Review Board of the Los Angeles County-University of Southern California Medical Center.

Study Population

Men ≥60 yr old were recruited from the Los Angeles communities surrounding the University of Southern California Health Sciences Campus. To be eligible for the study, subjects had to have a body mass index ≤35 kg/m², repeated resting blood pressure <180/95 mmHg, prostate-specific antigen (PSA) ≤4.1 ng/ml, serum hematocrit ≤50%, alanine aminotransferase (ALT) less than three times the upper limit of normal, and serum creatinine ≤1.5 mg/dl. Subjects with untreated endocrine abnormalities (e.g., diabetes, hypothyroidism), active inflammatory conditions, or cardiac problems (heart failure, myocardial infarction, or angina) in the proceeding 3 mo were excluded. An incremental treadmill exercise test with 12-lead electrocardiogram and blood pressure monitoring to achieve a heart rate ≥85% of age-predicted maximum was administered before resistance exercise testing to identify subjects at possible risk for exercise induced ischemia, abnormalities in cardiac rhythm, or abnormal blood pressure responses.

Study Interventions

Eligible subjects were randomized in a 2:1 manner to receive either the licensed oral dose of oxandrolone (Oxandrin, Savient Pharmaceuticals, East Brunswick, NJ) of 20 mg/day (10 mg twice daily) or matching placebo for 12 wk. Twenty milligrams were chosen because this is the Food and Drug Administration-licensed dose for treatment of weight loss or inability to maintain normal body weight. Subjects returned for a follow-up evaluation at study week 24 (12 wk after stopping study treatment). Adherence was monitored by tablet count at each study visit.

Safety Monitoring

Complete blood counts, comprehensive chemistries with tests of renal and hepatic function, and PSA were measured at baseline and weeks 6, 12, and 24. Additionally, liver function tests were obtained at weeks 3 and 9.

Body Composition by DEXA

Whole body DEXA scans (Hologic QDR-4500, version 7.2 software, Waltham, MA) were performed at baseline and weeks 12 and 24 to quantify LBM and fat mass. One blinded, experienced technician (C. Flores) performed and analyzed the scans. The coefficient of variation (CV) for repeated measures was <1% for lean and fat mass.

Muscle CSA

CSA of the dominant thigh muscles was assessed by using proton MRI at baseline and week 12 (but not week 24). 1H-MRI was performed by using a 1.5-T GE Signa-LX scanner with the body coil used as both transmitter and receiver. Nine axial images of the thigh were acquired after obtaining a longitudinal relaxation time-weighted coronal scout image (relaxation time-weighted longitudinal repetition time/echo time 300/echo time) that was used to identify the exact anatomic location for the axial images. The slice thickness was 7.5 mm with a 1.5-mm gap. The field of view was 24 × 24 cm with a 254 × 128-pixel matrix. One signal average was used.

Thigh muscle CSA was measured at the junction of the proximal and middle third of the femur in the dominant leg, because greater relative increases in CSA of the proximal quadriceps have been reported after anabolic interventions (32). Pixels associated with intramuscular fat, bone, and major arteries, veins, and nerves were subtracted from the image (using Scion Image, version Beta 4.0.2 software, Scion). Muscle CSA was measured by setting a pixel intensity threshold value that distinguished fat from muscle pixels. This allowed adipose tissue to be differentiated from other more optically dense lean tissue (muscle, nerve, and blood vessels). Total thigh muscle CSA was calculated after area of the fat tissue was removed automatically and area of the femur, nerve tissue, and blood vessels were removed manually. The same investigator (E. T. Schroeder) blinded to treatment located the region of interest, set the threshold value and performed the image analyses. The CV for repeated measures of total thigh CSA was <1%.

Total Body Water

Total body water (TBW) was determined at baseline and week 12 by using 3H2O dilution. Subjects ingested 3H2O (Cambridge Isotopes Laboratory; 0.25 g/kg), and isotope dilution was estimated from plasma samples obtained at −15 min, 0, 3, and 4 h. Our laboratory has previously determined that steady-state 3H enrichment is achieved in plasma and maintained between 120 and 240 min (58). The dilution of tracer, corrected for the exchange of hydrogen with other body hydrogen pools (~4%), provides a measure of tracer dilution space, which is equivalent to TBW volume. Plasma samples were analyzed for 3H2O abundance using proton magnetic resonance spectroscopy and d4-tert-butanol as an internal standard (interassay CV = 6.3%) (16). TBW was calculated from the average of the 3- and 4-h 3H enrichments in plasma water by using the following formula: TBW = dose (16/18 × g of 3H2O/deuterium enrichment, where TBW is expressed as 3H dilution space/1.04 (57).

Evaluation of Muscle Strength

Maximal voluntary muscle strength was assessed by using the one-repetition maximum (1-RM) method (13) at baseline and weeks 12 and 24. The 1 RM was defined as the greatest resistance that could be moved through a defined range of motion with the use of proper technique. Before strength testing, subjects warmed up on a cycle ergometer or by walking for 5 min. Maximum voluntary strength was determined for the bilateral leg press, leg flexion, latissimus pull-down, and chest press exercises on Keiser A-300 pneumatic equipment (Keiser, Fresno, CA). The leg press and chest press machines
only displayed units of measure in newtons. The newton measurement of force cannot accurately be converted to kilograms, and therefore the strength data are reported in newtons for these two machines. To accommodate for familiarization and learning of the testing procedures, baseline strength was assessed twice within 1 wk before study therapy was initiated. The greatest 1 RM measured for each exercise during the two pretreatment testing sessions was used as the baseline value for maximal voluntary muscle strength. The technician was blinded to the subjects’ treatment.

Nutritional Assessment

Subjects recorded dietary intake on 3 consecutive days, including 2 weekdays and 1 weekend day in the week before baseline and weeks 12 and 24. Subjects were counseled that the days should be chosen to include usual activities and typical eating patterns. A licensed nutritionist (C. Martinez) reviewed all dietary entries with the subjects. This information was entered into the Nutritionist V software (First Data Bank, San Bruno, CA) and analyzed for total energy intake, macronutrients, and types of fat. Subjects were counseled not to change their routine dietary habits during the course of the study.

Measurement of Hormones and C-Reactive Protein

Total testosterone concentration (ng/dl) was measured by the Los Angeles County-University of Southern California Medical Center Clinical Diagnostic Laboratory (Endocrinology Section) by using Diagnostic Products Coat-A-Count at baseline and week 24, 12 wk after the oxandrolone intervention was completed. This competitive radioimmunoassay uses a solid-phase polyclonal antibody. The CV for total testosterone was ≤7.7%. We did not measure testosterone levels at week 12 because semisynthetic androgens, including oxandrolone, cross-react in these testosterone assays. Luteinizing hormone (LH) concentration (IU/ml) was measured by using a microparticle enzyme immunoassay (AxSYM; Abbott Diagnostics), at baseline and study weeks 12 and 24. The CV for LH was ≤5.0%. Statistical analyses are presented in Tables 1–3 and the text as means ± SD.

Statistical Considerations

The study was conservatively powered at 80% to detect a difference in means between the oxandrolone and placebo group of 1.36 times the common SD, using a two-sample t-test with a Bonferroni-adjusted P = 0.0008, with 20 in oxandrolone group and 12 in placebo group. For total LBM by DEXA scanning, this sample size will be able to detect a mean difference of 2 kg, assuming the common SD is 1.47 kg. For the maximum voluntary skeletal muscle strength of the leg press exercise (which typically has the greatest variance of the exercises tested in this study), this sample size will be able to detect a mean relative difference of 6.8%, assuming the common standard deviation of 5.0%. Statistical analyses are presented in Tables 1–3 and the text as means ± SD.

For the main outcome variables, a two (oxandrolone and placebo group) by three (baseline, week 12, and week 24) repeated-measures ANOVA was used to statistically compare mean differences within subjects and between groups. Greenhouse-Geisser adjustment was used to justify the assumption of sphericity. When a significant group × time interaction was found, the changes from baseline to week 12 and the changes from baseline to week 24 between and within groups were compared by independent t-tests and paired t-tests, respectively. All post hoc tests were performed with Bonferroni adjustment for six possible comparisons. Baseline characteristic and the changes in safety evaluation from baseline to week 12 were compared between oxandrolone and placebo groups by using an independent t-test. All statistical testing was performed at a two-sided 5% level of significance (0.83% for each post hoc t-test) by using Statistical Analysis System version 8.0 (SAS Institute, Cary, NC).

RESULTS

Subjects

Thirty-four eligible subjects were enrolled and randomized to either oxandrolone (n = 22) or placebo (n = 12). One subject randomized to receive oxandrolone elected not to participate after providing informed consent; however, he did not start the study drug. A second subject randomized to receive oxandrolone completed study therapy through week 12 but did not return for follow-up at week 24. This subject could not be contacted until well after he missed the week 24 evaluation; he indicated that he had not had adverse events but had been too busy to make his appointment. Therefore, 32 subjects completed all aspects of the study and were included in the final analysis. On the basis of tablet count, these subjects were adherent to their assigned treatment (94.0 ± 7.4% of all pills prescribed with no difference between the groups).

Baseline characteristics were similar in the two study groups (Table 1), except that serum PSA levels were greater (P = 0.009) in the oxandrolone group. Baseline energy, protein, carbohydrate, and fat intakes were similar between the two groups.

Changes in Body Composition

LBM. There was a significant (P < 0.001) group × time interaction for total LBM. After 12 wk, LBM increased significantly (P < 0.001) in the oxandrolone group (3.0 ± 1.5 kg), and this increase in LBM was greater (P < 0.001) than the small change (0.0 ± 1.4 kg; P = 0.91) in the placebo group (Fig. 1). At week 24, LBM (56.5 ± 6.3 kg) had returned to baseline (56.0 ± 5.9 kg) in the oxandrolone group (P = 0.15).

Table 1. Baseline characteristics of the study population

<table>
<thead>
<tr>
<th></th>
<th>Oxandrolone (n = 20)</th>
<th>Placebo (n = 12)</th>
<th>P Value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, yr</td>
<td>72.8 ± 6.9</td>
<td>71.5 ± 3.2</td>
<td>0.49</td>
</tr>
<tr>
<td>DEXA weight, kg</td>
<td>81.3 ± 13.3</td>
<td>84.8 ± 8.9</td>
<td>0.43</td>
</tr>
<tr>
<td>DEXA LBM, kg</td>
<td>56.5 ± 5.6</td>
<td>58.3 ± 5.9</td>
<td>0.47</td>
</tr>
<tr>
<td>DEXA fat mass, kg</td>
<td>23.5 ± 7.7</td>
<td>23.7 ± 4.4</td>
<td>0.51</td>
</tr>
<tr>
<td>BMI, kg/m²</td>
<td>27.5 ± 3.5</td>
<td>29.1 ± 2.9</td>
<td>0.20</td>
</tr>
<tr>
<td>Caloric intake, kcal/kg</td>
<td>25.8 ± 6.3</td>
<td>25.6 ± 4.5</td>
<td>0.87</td>
</tr>
<tr>
<td>Intake of protein, g/kg</td>
<td>1.2 ± 0.4</td>
<td>1.1 ± 0.1</td>
<td>0.97</td>
</tr>
<tr>
<td>Intake of carbohydrate, g/kg</td>
<td>3.0 ± 0.6</td>
<td>3.2 ± 0.7</td>
<td>0.47</td>
</tr>
<tr>
<td>Intake of fat, g/kg</td>
<td>1.0 ± 0.3</td>
<td>1.0 ± 0.3</td>
<td>0.94</td>
</tr>
<tr>
<td>Hematocrit, %</td>
<td>42.9 ± 2.2</td>
<td>42.6 ± 3.4</td>
<td>0.82</td>
</tr>
<tr>
<td>Creatinine, mg/dl</td>
<td>1.5 ± 1.3</td>
<td>1.2 ± 0.4</td>
<td>0.34</td>
</tr>
<tr>
<td>Albumin, g/dl</td>
<td>4.0 ± 0.2</td>
<td>4.2 ± 0.2</td>
<td>0.07</td>
</tr>
<tr>
<td>ALT, U/l</td>
<td>38.0 ± 7.0</td>
<td>38.0 ± 4.4</td>
<td>0.83</td>
</tr>
<tr>
<td>Ultrasonisive CRP, mg/l</td>
<td>1.4 ± 1.0</td>
<td>2.3 ± 2.7</td>
<td>0.21</td>
</tr>
<tr>
<td>PSA, ng/ml</td>
<td>2.4 ± 1.1</td>
<td>1.3 ± 0.8</td>
<td>0.009</td>
</tr>
<tr>
<td>Total testosterone, µg/dl</td>
<td>369 ± 147</td>
<td>357 ± 153</td>
<td>0.83</td>
</tr>
<tr>
<td>Luteinizing hormone, U/l</td>
<td>8.5 ± 7.1</td>
<td>6.5 ± 6.7</td>
<td>0.51</td>
</tr>
<tr>
<td>Total cholesterol, mg/dl</td>
<td>186 ± 31.1</td>
<td>186 ± 34.3</td>
<td>0.97</td>
</tr>
</tbody>
</table>

Values are means ± 1 SD; n, number of subjects. DEXA, dual-energy X-ray absorptiometry; LBM, lean body mass; BMI, body mass index; ALT, alanine aminotransferase; CRP, C-reactive protein; PSA, prostate-specific antigen. *P value obtained by independent t-test.
In the placebo group, the change from baseline in LBM was not significant at either 12 or 24 wk.

Thigh muscle CSA. Oxandrolone increased the thigh muscle area (12.4 ± 8.4 cm², \( P < 0.001 \); Fig. 2), whereas placebo did not (1.4 ± 6.9 cm²). After 12 wk, the increase in thigh muscle area was greater in the oxandrolone group than in the placebo group (\( P = 0.002 \)). Thigh muscle area was not measured at week 24.

TBW. Oxandrolone increased TBW (2.9 ± 3.7 kg; \( P = 0.002 \)), whereas placebo did not (−0.6 ± 2.8 kg; \( P = 0.47 \)). After 12 wk, the increase in TBW tended to be greater in the oxandrolone group than in the placebo group (\( P = 0.07 \)). TBW was not measured at week 24.

Fat mass. There was a significant (\( P = 0.03 \)) group × time interaction for total fat mass. Oxandrolone reduced whole body fat mass (−1.9 ± 1.0 kg, \( P < 0.001 \); Fig. 3A) and trunk fat mass (−1.3 ± 0.6 kg, \( P < 0.001 \); Fig. 3B), whereas placebo did not (whole body = −0.2 ± 1.0 kg, \( P = 0.58 \); trunk = 0.0 ± 0.7 kg; \( P = 0.87 \)). The decreases in whole body and trunk fat mass were greater in the oxandrolone group than in the placebo group (\( P < 0.001 \)). After oxandrolone was discontinued (week 24), whole body and trunk fat were still less than baseline (−1.5 ± 1.8 kg, \( P = 0.001 \); −1.0 ± 1.1 kg, \( P < 0.001 \), respectively).

Changes in Maximal Voluntary Strength

There was a significant group × time interaction for chest press (\( P < 0.001 \)), leg press (\( P = 0.009 \)), leg flexion (\( P = 0.01 \)), and latissimus pull-down (\( P = 0.04 \)). After 12 wk, the relative (Fig. 4) and absolute (Table 2) increases in maximal voluntary strength were greater for subjects receiving oxandrolone. These increases were significantly different from the placebo group for leg press and chest press and approached significance for leg flexion and latissimus pull-down, even with our very conservative Bonferroni adjustment. For leg press, relative strength increased by 6.7 ± 6.4% (\( P < 0.001 \)), for leg flexion by 7.0 ± 7.8% (\( P < 0.001 \)), for chest press by 9.3 ± 6.7% (\( P < 0.001 \)), and for latissimus pull-down by 5.1 ± 9.1% (\( P = 0.02 \), not significant with Bonferroni adjustment) in the group receiving oxandrolone (Fig. 4), whereas there were no significant changes in the placebo group. By week 24, the relative and absolute maximal voluntary strength were similar to baseline values in both the oxandrolone and placebo groups (Table 2, Fig. 4).

Nutrition and Exercise

Nutritional status, including total daily intake of energy, protein, carbohydrate, and fat, was not different within or
between groups over the 24-wk course of the study (P > 0.19 by ANOVA for each; data not shown). Additionally, on entry into the study, subjects were instructed to maintain their habitual physical activity and not to engage in a new exercise routine during the course of the study. On the basis of self-report at each study evaluation, subjects did not alter their physical activity levels.

Safety Evaluation

One serious adverse event occurred during the study. A subject randomized to oxandrolone developed hypotension (systolic blood pressure < 90 mmHg) when his primary doctor modified the patient’s antihypertensive medications at the subject’s request. His systolic blood pressure had been in the 140- to 155-mmHg range before, and during the study and he desired tighter control. Study therapy was suspended for 3 wk while his antihypertensive medications were adjusted; study therapy was then resumed without problem.

There were no new symptoms or physical findings that could be ascribed to oxandrolone. After 12 wk, there were only modest changes in blood chemistry (Table 3). In the oxandrolone group, serum albumin and alkaline phosphatase levels decreased more than with placebo. The decline in albumin could have reflected the new onset of subclinical inflammation, but there was no change in ultrasensitive CRP levels at week 12 (Table 3) or week 24. There were minimal increments in the liver transaminase levels that reached statistical significance, but ALT was only increased beyond the normal range in two subjects in whom it reached 71 and 99 U/l (upper limit of normal). Both subjects were asymptomatic without liver enlargement, and the ALT returned to normal in both at the week 24 evaluation. Finally, there was a small but significant decrease in PSA in the oxandrolone group.

As described in METHODS, we only measured serum testosterone levels at baseline and week 24. Oxandrolone and placebo groups had similar baseline (P = 0.28; Table 1) and week 24 testosterone levels (358 ± 119 ng/dl in the oxandrolone group and 421 ± 196 ng/dl; P = 0.26). There was a trend toward a greater decline in LH levels with oxandrolone, suggesting that oxandrolone treatment may have suppressed the hypothalamic-pituitary-gonadal axis.

DISCUSSION

These findings demonstrated that a relatively brief course of treatment with a potent anabolic androgen in men over 60 yr of age increased LBM as well as upper and lower body maximal strength. The increase in leg press did not reach statistical significance, but increase in leg extension and lat pull-down between study groups at week 12 with Bonferroni adjustment, P < 0.001. Approaching significant increase from baseline for leg flexion and lat pull-down between study groups at week 12 with Bonferroni adjustment, P < 0.001.

Table 3. Change in safety measures after 12 wk of study therapy

<table>
<thead>
<tr>
<th>Measure</th>
<th>Oxandrolone</th>
<th>Placebo</th>
<th>P Value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hematocrit %</td>
<td>-2.9 ± 2.2</td>
<td>-2.9 ± 1.5</td>
<td>0.95</td>
</tr>
<tr>
<td>BUN, mg/dl</td>
<td>-1.0 ± 3.6</td>
<td>2.0 ± 4.8</td>
<td>0.06</td>
</tr>
<tr>
<td>Albumin, g/dl</td>
<td>-0.6 ± 0.2</td>
<td>-0.3 ± 0.2</td>
<td>0.003</td>
</tr>
<tr>
<td>ALT, U/l</td>
<td>15 ± 18</td>
<td>-1 ± 5</td>
<td>0.001</td>
</tr>
<tr>
<td>AST, U/l</td>
<td>8 ± 8</td>
<td>-1 ± 4</td>
<td>0.001</td>
</tr>
<tr>
<td>Alkaline phosphatase, U/l</td>
<td>-24 ± 13</td>
<td>-7 ± 12</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Total serum bilirubin, mg/dl</td>
<td>0 ± 0</td>
<td>0 ± 0</td>
<td>0.93</td>
</tr>
<tr>
<td>Ultrasensitive CRP, mg/l</td>
<td>0.1 ± 1.9</td>
<td>1.0 ± 2.6</td>
<td>0.23</td>
</tr>
<tr>
<td>PSA, ng/ml</td>
<td>-0.6 ± 0.9</td>
<td>0.1 ± 0.5</td>
<td>0.004</td>
</tr>
<tr>
<td>Luteinizing hormone, U/l</td>
<td>-3.3 ± 6.6</td>
<td>-0.7 ± 2.2</td>
<td>0.13</td>
</tr>
<tr>
<td>Total cholesterol, mg/dl</td>
<td>2 ± 38</td>
<td>-5 ± 22</td>
<td>0.60</td>
</tr>
</tbody>
</table>

Values are means ± SD. BUN, blood urea nitrogen; AST, aspartate aminotransferase. *P value obtained by independent t-test.

Table 2. Maximal voluntary skeletal muscle strength

<table>
<thead>
<tr>
<th>Measure</th>
<th>Week 0</th>
<th>Week 12</th>
<th>Week 24</th>
<th>P vs. 12</th>
<th>P vs. 24</th>
</tr>
</thead>
<tbody>
<tr>
<td>Leg press, N</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Oxandrolone</td>
<td>1,245 ± 132</td>
<td>1,357 ± 189</td>
<td>1,266 ± 191</td>
<td>&lt;0.001*</td>
<td>0.81</td>
</tr>
<tr>
<td>Placebo</td>
<td>1,250 ± 213</td>
<td>1,250 ± 210</td>
<td>1,246 ± 242</td>
<td>0.98</td>
<td>0.30</td>
</tr>
<tr>
<td>Leg flexion, kg</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Oxandrolone</td>
<td>69.6 ± 9.1</td>
<td>74.4 ± 10.6</td>
<td>70.5 ± 8.8</td>
<td>0.002*</td>
<td>0.58</td>
</tr>
<tr>
<td>Placebo</td>
<td>66.5 ± 12.5</td>
<td>68.1 ± 13.2</td>
<td>67.4 ± 12.9</td>
<td>0.86</td>
<td>0.67</td>
</tr>
<tr>
<td>Chest press, N</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Oxandrolone</td>
<td>212 ± 41</td>
<td>233 ± 40†</td>
<td>214.0 ± 40.5</td>
<td>&lt;0.001*</td>
<td>0.89</td>
</tr>
<tr>
<td>Placebo</td>
<td>216 ± 44</td>
<td>213 ± 49‡</td>
<td>198 ± 43</td>
<td>0.69</td>
<td>0.43</td>
</tr>
<tr>
<td>Latissimus pull-down, kg</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Oxandrolone</td>
<td>52.8 ± 9.9</td>
<td>55.5 ± 11.0</td>
<td>52.4 ± 10.3</td>
<td>0.02</td>
<td>0.48</td>
</tr>
<tr>
<td>Placebo</td>
<td>54.0 ± 8.5</td>
<td>56.6 ± 8.9</td>
<td>53.7 ± 8.7</td>
<td>0.10</td>
<td>0.57</td>
</tr>
</tbody>
</table>

Values are means ± SD. *P value significant at P < 0.05 with Bonferroni adjustment for within-group paired t-test. †P value significant at P < 0.05 with Bonferroni adjustment for between-group comparison on the change from baseline to week 12.

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voluntary strength more than placebo. The increase of 3.0 ± 1.5 kg in LBM in this study is approximately twofold greater than the increase in LBM reported by other investigators using testosterone supplementation in older men (6, 21, 46, 51). The only other study of androgen therapy to achieve comparable increases in LBM (4.2 ± 0.6 kg) used a dose of testosterone enanate adjusted to produce nadir levels in the upper normal range, suggesting that dosing was “supraphysiological” because nadir levels were tested 2 wk after a prior intramuscular dose (11). Moreover, subjects were treated for 24 wk compared with 12 wk in our study. These observations suggest that the formulation and potency of the androgen, dose, and duration of therapy may affect the changes in lean tissue achieved, which is in keeping with a recent dose ranging study of testosterone in younger men (5).

The significant increases in both upper and lower body maximal voluntary strength in subjects receiving oxandrolone are noteworthy. In the few studies assessing the effects of androgen supplementation in older men, muscle strength was not tested (51) or was evaluated with either handgrip (31, 44) or isokinetic dynamometry (46, 52), which may measure different mechanistic aspects of strength [reviewed in Storer et al. (47)]. Therefore, these evaluations may not be representative of true changes in maximal strength for larger muscle groups important for optimal physical function in older persons. Moreover, only one study demonstrated substantial increases in 1-RM strength in both upper body and lower body muscle groups, although neuromuscular learning may have contributed to the gains in strength with testosterone because multiple baseline trials of maximal strength were not assessed (11). However, older adults typically produce their best performance (highest force production) on the second or third 1-RM trial (12, 40). Thus, studies to assess the affects of anabolic interventions on maximal voluntary strength should test strength on at least two separate occasions before study therapy is initiated.

The increases in muscle strength and CSA in the oxandrolone group suggest that a major portion of the anabolic androgen-induced increase in LBM was due to increases in muscle protein mass, because strength is closely related to muscle size (27). Oxandrolone and testosterone exert their actions by enhancing the rate of mixed muscle (11, 52) and myofibrillar protein synthesis (7), and by reducing the rate of muscle protein breakdown (43). However, our $^{2}$H$_{2}$O dilution measurements indicated a disproportionate increase in TBW (∼2.9 kg) compared with the increase in DEXA-derived LBM (3 kg). If the entire increase in DEXA-derived LBM were protein, we would have anticipated only ∼2.3-kg increase in TBW. Also, the rapid loss of LBM (∼2.5 kg) after oxandrolone was discontinued suggests that tissue fluid was a component of the oxandrolone-induced increase in LBM. Future studies should measure muscle amino acid balance after androgen administration in elderly men at risk for physical frailty.

To our knowledge, this is the first study to determine the durability of the effects achieved with androgen therapy after the treatment was discontinued. We speculated that at least some portion of the gains in LBM and strength would be sustained 12 wk after treatment with oxandrolone. However, the fact that gains in both LBM and strength were largely lost within 12 wk after treatment was discontinued suggests that prolonged therapy with an anabolic androgen will be necessary to maintain and enhance increases in LBM and muscle strength. Other anabolic strategies with potentially better safety profiles such as resistance training, a potent stimulus for skeletal muscle protein synthesis in older persons (56), or specific androgen receptor modulators should be investigated for sustaining gains in muscle mass and strength during the aging process.

Another important and unique finding of this study was the oxandrolone-induced decrease in total and trunk fat that was largely sustained 12 wk after oxandrolone was stopped. In younger hypogonadal men, testosterone decreased total body and abdominal fat mass (4, 20, 54). However, it is not clear whether androgen therapy affects adipose tissue in eugonadal men. Bhasin et al. (4) reported no change in fat mass with replacement doses of 125 mg testosterone weekly over 4 mo in eugonadal, healthy men, although much higher supraphysiological doses reduced adipose tissue. Marin et al. (24) reported that low-dose androgen therapy reduced abdominal fat in middle-aged men with central obesity. However, the effects occurred primarily in subjects with low testosterone levels, which is consistent with observations that intra-abdominal fat is inversely correlated with free testosterone levels (42). Only five of our subjects had baseline total testosterone levels <270 ng/dl (lower limit of normal in our laboratory), but levels for the entire group were generally less than those of younger men. Whether the relative hypogonadism (compared with younger men) of our participants or the potency or structure of the synthetic androgen, oxandrolone, was primarily responsible for the reductions in whole body and trunk fat is uncertain.

These results do provide clarification as to whether metabolism of testosterone by aromatase to estradiol (∼40%) is largely responsible for changes in fat mass when men are treated with testosterone (18). The fact that adipocytes contain estradiol receptors and the observation that estrogen receptor knockout mice have increased adipose tissue have suggested that estrogen is important in downregulating fat mass (8). However, oxandrolone is not aromatized to estrogen, suggesting that the favorable declines in adipose tissue observed in the present study were due to direct and specific actions of oxandrolone.

The discordant effects of oxandrolone on lean tissue and fat mass 12 wk after study therapy was discontinued were puzzling. According to 3-day food diaries and self-report of exercise activity, subjects did not change their dietary or habitual activity during the study. Thus the durability of the effects of oxandrolone on adipose but not lean tissue likely reflect the biological differences in these tissues and/or the effects of other concurrent regulators of metabolism. In a population prone to obesity, it is remarkable that 80% of the reduction in total and central fat mass after a relatively short period of androgen therapy (12 wk) were sustained for at least 3 mo after treatment was discontinued. The reductions in fat mass observed in obese middle-aged men have been associated with decreases in visceral adipose tissue, improvements in insulin sensitivity, and declines in cholesterol, triglycerides, and diastolic blood pressure (24, 25). These effects are consistent with the known effects of androgens to decrease lipoprotein lipase and upregulate β-adrenergic receptors on adipocytes, which would inhibit the accumulation of lipid and enhance the efflux of lipid from these cells in response to catecholamines (26, 38, 55). Further studies will be necessary...
to assess whether the reductions in fat mass observed in our older men would be associated with beneficial measures of metabolism and health in an aging population.

A limitation of this study is that we assessed a 17-methylated androgen and not generic testosterone. Thus we cannot extrapolate our findings to a dose of testosterone. Although we did not demonstrate short-term adverse clinical effects with oxandrolone, evaluation of anabolic androgens, including testosterone, as potential treatments for sarcopenia, must be investigated in sufficiently powered studies of long-term treatment to demonstrate their safety for prostate and cardiovascular health.

In conclusion, substantial gains in LBM and muscle size were achieved safely with a relatively short course of therapy with an anabolic androgen in 60- to 87-yr-old men. Moreover, these changes were associated with significant gains in maximal voluntary strength in the large upper and lower body muscle groups, which are important for normal physical function in older persons. However, the benefits were lost within 12 wk after oxandrolone was discontinued, suggesting that prolonged androgen treatment would be needed to maintain these anabolic benefits. Thus the long-term safety and efficacy of androgen therapy in older men need to be established. In addition, whole body and trunk fat mass decreased significantly during therapy, and the effects were largely sustained after treatment was discontinued. Whether the reduction in central adiposity with androgen therapy has tangible health benefits is uncertain. These observations, therefore, raise several important questions that must be addressed before androgen therapy is widely prescribed as long-term therapy for sarcopenia in older individuals.

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ANDROGEN SUPPLEMENTATION AND DURABILITY OF EFFECTS


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