Six-Week Improvements in Muscle Mass and Strength During Androgen Therapy in Older Men

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Background. The purpose of our study was to assess the early effects of a potent anabolic androgen on muscle mass and strength, lower extremity power, and functional performance in older men.

Methods. Thirty-two men 72 ± 6 years of age were randomized to receive oxandrolone (10 mg twice daily) or matching placebo in a 2:1 manner for 12 weeks. Total and appendicular lean body mass (LBM) were assessed by dual-energy x-ray absorptiometry (DEXA). Lower extremity muscle volume was determined by magnetic resonance imaging to validate DEXA changes.

Results. Total LBM increased by 2.7 ± 1.6 kg after 6 weeks with oxandrolone ($p < .001$), which was greater ($p < .001$) than the decline in LBM (-0.5 ± 0.9 kg) with placebo. Appendicular LBM increased by 1.2 ± 0.9 kg after just 6 weeks with oxandrolone ($p < .001$), which was greater ($p < .001$) than the decline in LBM (-0.4 ± 0.5 kg) with placebo. These changes were >90% of the gains in total and appendicular LBM (3.0 ± 1.5 kg and 1.3 ± 0.9 kg, respectively) after 12 weeks. Total thigh and hamstring muscle volume increased by 111 ± 29 mm^3 ($p = .001$) and 75 ± 18 mm^3 ($p = .001$), respectively, after 12 weeks. Maximal strength increased for the leg press $6.3 \pm 5.6\%$ ($p = .003$), leg curl $6.7 \pm 8.6\%$ ($p = .01$), chest press $6.9 \pm 6.5\%$ ($p = .001$), and latissimus pull-down $4.8 \pm 6.3\%$ ($p = .009$) with oxandrolone after 6 weeks; these increases were different than those with placebo ($p < .001$) and were 93%, 96%, 74%, and 94% of the respective gains at week 12. There were no improvements in functional measures.

Conclusion. Treatment with a potent anabolic androgen may produce significant increases in muscle mass and strength after only 6 weeks in healthy older men. However, such treatment did not improve leg muscle power or walking speed.

ADVANCING age is associated with a progressive loss of muscle mass (sarcopenia), skeletal muscle strength, and physical function (1–3). Sarcopenia increases the risk for frailty, falls, fractures, dependency, and depression (4,5). The contribution of age-associated hormonal alterations to these adverse health consequences is unclear. Both cross-sectional (6,7) and longitudinal (8,9) studies have shown that serum total and free concentrations of testosterone, an important regulator of net myofibrillar protein anabolic balance, decline with advancing age in men. Evidence, albeit limited, suggests that bioavailable testosterone levels correlate with skeletal muscle mass and muscle strength in different ethnic populations (10,11), but the relationship between gonadal hormone status and age-associated alterations in body composition, skeletal muscle strength, and physical function in older persons remains uncertain.

Testosterone treatment in hypogonadal young men increases lean tissue (12–14) and muscle strength (12,13). In the largest studies, in which relatively hypogonadal older men received testosterone replacement for 1 and 3 years, respectively, lean body mass (LBM) was only modestly increased (1.0 and 1.9 kg, respectively), and there were no improvements in skeletal muscle strength. Furthermore, smaller studies conducted for shorter periods of time in similar aged men showed comparably modest changes in body composition (i.e., increases in total LBM of <2 kg) and no consistent improvements in strength of the major muscle groups (15–19). Whereas, in one study of relatively hypogonadal men older than 60 years, testosterone treatment produced significant increases in upper and lower body maximal voluntary strength, but doses of testosterone were largely supraphysiologic (20). Different doses of testosterone (200 mg biweekly vs 5 mg/day), variable duration of treatment (3 months to 3 years), different delivery strategies for testosterone (intramuscular vs transdermal), different methods to assess body composition (bioelectrical impedance analysis, dual-energy x-ray absorptiometry [DEXA], magnetic resonance imaging [MRI], hydrostatic weighing), and variable methods to measure muscle strength (handheld dynamometers, isokinetic dynamometers, or weight machines) likely contributed to the lack of consistent findings in the aforementioned studies of older men.

We previously reported that 12 weeks of treatment with oxandrolone, a potent anabolic androgen, significantly increased LBM and muscle strength in older men. These gains were almost entirely lost 12 weeks after discontinuing treatment (21), suggesting that prolonged therapy with an anabolic androgen would be necessary to sustain these benefits. However, the long-term safety of androgen supplementation for the prostate and heart has not been established. We, therefore, sought to determine if benefits could be achieved earlier than the 3–4 months, a common duration of treatment in many androgen supplementation studies (22). We speculated that if short-term benefits could be achieved, other potentially safer treatments such as resistance exercise could then be implemented to sustain or

even augment the early changes achieved with androgen treatment. We believe that this is the first study to report significant improvements in muscle mass and strength in both the upper and lower extremities as early as 6 weeks after treatment was initiated.

METHODS

Study Design

This was a single center, investigator initiated, double blind, placebo-controlled investigation to determine the 6-week effects of a potent, convenient to administer anabolic androgen, oxandrolone (Oxandrin; Savient Pharmaceuticals, Inc., East Brunswick, NJ). 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 in 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 60–87 (mean 72 ± 6) years of age were recruited from the Los Angeles communities surrounding the University of Southern California Health Sciences Campus. To be eligible, men had to have a body mass index (BMI) ≤ 35 kg/m^2 and have no untreated endocrine abnormalities (e.g., diabetes, hypothyroidism), active inflammatory conditions, uncontrolled hypertension, or active cardiac problems. Blood tests for eligibility included a prostate specific antigen (PSA) ≤ 4.1 µg/L and hematocrit $\leq 50\%$. Men doing or planning to initiate vigorous exercise were excluded, but regular walking programs were allowed. Further details of the study population have been described previously (23).

Study Interventions

Eligible participants were randomized in a 2:1 manner to receive either oxandrolone (Oxandrin) at a dose of 20 mg/day (10 mg twice daily) or matching placebo for 12 weeks. Twenty milligrams was chosen because this is the FDA-approved dose for treatment of weight loss or inability to maintain normal body weight. 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 study weeks 6 and 12. Additionally, liver function tests were obtained at study weeks 3 and 9. We did not measure testosterone levels at study week 6 or 12 because semisynthetic androgens, including oxandrolone, cross-react in testosterone assays.

Body Composition by DEXA

Whole-body DEXA scans (Hologic QDR-4500, version 7.2 software; Waltham, MA) were performed at baseline and study weeks 6 and 12 to quantify LBM and fat mass. One blinded, experienced technician (CF) performed and analyzed the scans. The coefficient of variation for repeated measures was <1% for lean and fat mass.

Muscle Volume

Volume of the dominant thigh muscles was assessed using proton MRI at baseline and week 12. ^{1}H-MRI was performed using a 1.5 Tesla GE Signa-LX scanner (Philips ACS II; Shelton, CT) with the body coil used as both transmitter and receiver. Nine axial images of the thigh were acquired after obtaining a T1-weighted coronal scout image (T1-weighted TR/TE 300/TE) that was used to identify the exact anatomical 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.

Pixels associated with intramuscular fat, bone, and major arteries, veins, and nerves were subtracted from the image by using specialized software (SliceOmatic version 4.2; TomoVision, Montreal, Canada) previously validated (24). Because each pixel reflects a given density, regions of muscle tissue are segregated from other regions of tissue using the SliceOmatic Morpho mode of analysis. This segregation allows the tissue compartments (muscle, subcutaneous fat, intermuscular fat) to be segmentalized based on signal amplitude by highlighting small regions of similar density pixels to determine muscle cross-sectional area (CSA). The thigh musculature was calculated after highlighting the respective tissue regions with different colors. Thigh muscle volume was then automatically calculated using the SliceOmatic Morpho mode following analysis of serial slices for CSA. The same investigator (AFV) blinded to treatment located the region of interest, set the threshold value, and performed the image analyses. The coefficient of variation for repeated measures of total thigh CSA was <1%.

Evaluation of Muscle Strength

Maximal voluntary muscle strength was assessed using the one-repetition maximum (1-RM) method (25) at baseline and weeks 6 and 12. The 1-RM was defined as the greatest resistance that could be moved through a defined range of motion using proper technique. Prior to strength testing, participants warmed up on a cycle ergometer or by walking for 5 minutes. Maximum voluntary strength was determined for the bilateral leg press, leg flexion, latissimus (lat) pull-down, and chest press exercises on Keiser A-300 pneumatic equipment (Keiser Corp., Fresno, CA). The leg press and chest press machines displayed units of measure in Newtons only. The Newton measurement of force cannot accurately be converted to kilograms; 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 week prior to initiating study therapy. 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 exercise technician was blinded to the participants' treatment.

Evaluation of Muscle Power and Function

Unilateral leg extension power (Watts) was determined using the Bassey Power Rig (University of Nottingham, Nottingham, U.K.) and has been described elsewhere (26). Leg extension power measured with the Bassey Power Rig has been highly correlated with lower extremity physical function in older adults (27). Additionally, lower extremity power was assessed using the Margaria stair-climb test (28). Lastly, lower extremity muscular endurance was determined by having the participants walk and/or jog as quickly as possible for 400 meters (29).

Statistical Considerations

The details of power calculation based on the primary outcome, total LBM by DEXA scanning, have been described elsewhere (21). Data were presented in the tables and text as the mean $\pm$ 1 standard deviation (*SD*). For the outcome variables of interest in this study, a two (oxandrolone vs placebo group) by three (baseline, week 6, and week 12) repeated-measures analysis of variance was used to compare mean differences within participants and between groups. Greenhouse–Geisser adjustment was used to justify the assumption of sphericity. When a significant Group $\times$ Time interaction was found, the changes from baseline to week 6 and the changes from baseline to week 12 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. All statistical testing was performed with a two-sided 5% level of significance (0.83% for each post hoc *t* test) using Statistical Analysis System version 8.0 (SAS Institute, Inc., Cary, NC).

RESULTS

Participants

Thirty-two participants, 20 receiving oxandrolone and 12 receiving placebo, completed the study and were included in this analysis (21). Although the mean age was similar between groups (Table 1), the distribution in age resulted in unequal variance with a range of 60–87 years in the oxandrolone group and 67–78 years in the placebo group. On the basis of tablet count, these participants were adherent to their assigned treatment (94 $\pm$ 7.4% of all pills prescribed were ingested with no difference between the groups). Baseline characteristics for laboratory values, body composition, and maximum skeletal muscle strength and power were similar in the two study groups (Table 1). In particular, baseline total testosterone was 369 $\pm$ 147 ng/dL and 357 $\pm$ 153 ng/dL in the groups receiving oxandrolone and placebo, respectively. Albumin tended to be lower in the oxandrolone treatment group but the difference did not reach significance ($p = .07$). Additionally, baseline energy, protein, carbohydrate, and fat intakes were similar between the two groups (23).

Repeated-Measures Analysis of Variance

A significant Group $\times$ Time interaction was found for total LBM ($p < .001$), appendicular LBM ($p < .001$), chest

Table 1. Baseline Characteristics of the Study Population

Characteristic	Oxandrolone ($N = 20$)	Placebo ($N = 12$)	p Value*
Age, y	72.8 $\pm$ 6.9	71.5 $\pm$ 3.2	.49[†]
Laboratory values			
Hemoglobin g/dL	15.1 $\pm$ 0.9	15.1 $\pm$ 0.5	.76
Creatinine, mg/dL	1.5 $\pm$ 1.3	1.2 $\pm$ 0.4	.34
Albumin, g/dL	4.0 $\pm$ 0.2	4.2 $\pm$ 0.2	.07
ALT, U/L	38 $\pm$ 7	38 $\pm$ 4	.83
Ultrasensitive CRP, mg/L	1.4 $\pm$ 1.0	2.3 $\pm$ 2.7	.21
Thyroid stimulating hormone, U/L	1.86 $\pm$ 1.31	1.97 $\pm$ 0.63	.79
Total testosterone, ng/dL	369 $\pm$ 147	357 $\pm$ 153	.83
Luteinizing hormone, U/L	8.3 $\pm$ 7.1	6.5 $\pm$ 6.7	.51
PSA, ng/ml	2.4 $\pm$ 1.1	1.3 $\pm$ 0.8	.009
Total cholesterol, mg/dL	187 $\pm$ 30	186 $\pm$ 34	.91
HDL cholesterol, mg/dL	40 $\pm$ 10	45 $\pm$ 11	.18
LDL cholesterol, mg/dL	126 $\pm$ 28	123 $\pm$ 31	.75
Body composition			
Weight, kg	81.3 $\pm$ 13.3	84.8 $\pm$ 8.9	.43
BMI, kg/m^2	27.5 $\pm$ 3.5	29.1 $\pm$ 2.9	.20
Total lean body mass, kg	56.5 $\pm$ 5.6	58.3 $\pm$ 5.9	.39
Appendicular lean body mass, kg	25.0 $\pm$ 2.8	24.5 $\pm$ 2.4	.54
Total thigh muscle volume, mm^3	1394 $\pm$ 168	1496 $\pm$ 215	.17
Maximum muscle strength and power			
Chest press, Newtons	212 $\pm$ 41	215 $\pm$ 44	.82
Latissimus pull-down, kg	54 $\pm$ 9	55 $\pm$ 10	.78
Leg press, Newtons	1245 $\pm$ 132	1250 $\pm$ 213	.95
Leg curl, kg	70 $\pm$ 9	28 $\pm$ 13	.42
Bassey leg power, Watts	180 $\pm$ 40	212 $\pm$ 65	.10

Note: Values are means $\pm$ 1 standard deviation.

*p value obtained by independent *t* test.

[†]Unequal variance.

ALT = alanine aminotransferase; CRP = C-reactive protein; BMI = body mass index; PSA = prostate-specific antigen; high-density lipoprotein; LDL = low-density lipoprotein.

press ($p = .001$), lat pull-down, leg press, leg curl, and leg extension power ($p < .02$ for each). Therefore, post hoc tests were performed for each outcome variable of interest (Table 2).

Changes in Body Composition

Lean body mass.—Total LBM increased significantly ($p < .001$) in the oxandrolone group (2.7 $\pm$ 1.6 kg) after 6 weeks; this increase was greater ($p < .001$) than the small decline in LBM (−0.5 $\pm$ 0.9 kg) in the placebo group (Table 2; Figure 1A). By study week 12, total LBM in the oxandrolone group increased only an additional 10% to 3.0 $\pm$ 1.5 kg; this change was significantly different than baseline ($p < .001$) and different than the 12-week change (0.1 $\pm$ 1.5 kg) in the placebo group (Table 2; Figure 1A) (21). Similar to total LBM, 90% of the gains in appendicular LBM were achieved by study week 6. Appendicular LBM increased significantly ($p < .001$) in the oxandrolone group (1.2 $\pm$ 0.9 kg) after 6 weeks of therapy; this increase was greater ($p < .001$) than the small decline in LBM (−0.4 $\pm$ 0.5) in the placebo group (Table 2; Figure 1B). By study week 12, appendicular LBM in the oxandrolone group increased only 9% to 1.3 $\pm$ 0.9 kg, which was significantly different from baseline ($p < .001$); this increase was greater

Table 2. Absolute Change in Body Composition, Muscle Strength, and Power

Variable	Oxandrolone ($N = 20$)	Placebo ($N = 12$)	p Value*
Total lean body mass, kg			
Change at week 6	$2.7 \pm 1.6^\dagger$	-0.5 ± 0.9	$<.001$
Change at week 12	$3.0 \pm 1.5^\dagger$	0.1 ± 1.5	$<.001$
Appendicular lean body mass, kg			
Change at week 6	$1.2 \pm 0.9^\dagger$	-0.4 ± 0.5	$<.001$
Change at week 12	$1.3 \pm 0.9^\dagger$	-0.9 ± 0.5	$<.001$
Total thigh muscle volume, mm^3			
Change at week 6	NT	NT	NT
Change at week 12	$111 \pm 29^\dagger$	-47 ± 48	$.006$
Chest press, Newtons			
Change at week 6	$13 \pm 13^\dagger$	-2 ± 14	$.006$
Change at week 12	$19 \pm 14^\dagger$	-2 ± 12	$<.001$
Latissimus pull-down, kg			
Change at week 6	$2.6 \pm 3.9^\dagger$	-0.8 ± 2.6	$.006$
Change at week 12	$2.6 \pm 4.9^\dagger$	-1.5 ± 2.9	$.006$
Leg press, Newtons			
Change at week 6	$75 \pm 63^\dagger$	5 ± 45	$.001$
Change at week 12	$81 \pm 78^\dagger$	1 ± 65	$.005$
Leg curl, kg			
Change at week 6	$4.3 \pm 5.3^\dagger$	-0.4 ± 2.7	$.003$
Change at week 12	$4.8 \pm 5.7^\dagger$	0.2 ± 3.1	$.007$
Bassey leg extension power, Watts			
Change at week 6	3 ± 24	-13 ± 14	$.23$
Change at week 12	10 ± 27	-13 ± 12	$.12$

Note: *Significant difference between groups by independent t test.

†Significant within-group change compared to baseline $p < .05$ by paired t test.

NT = not tested.

Figure 1. Absolute change in total lean mass (**A**) and appendicular lean mass (**B**) by dual-energy x-ray absorptiometry. Filled bars represent change from baseline to study week 6; open bars represent change from baseline to study week 12. The whiskers are one standard error. *Significant ($p < .001$) within-group difference from baseline. †Significant ($p < .001$) difference in the change between study groups.

($p < .001$) than the 12-week change (-0.9 ± 0.5 kg) in the placebo group.

Thigh muscle volume.—Total thigh muscle volume in the oxandrolone group increased significantly (111 ± 29 mm^3; $p = .001$) from baseline to study week 12; this increase was greater ($p = .006$) than the change (-47 ± 48 mm^3) in the placebo group (Table 2, Figure 2). Similarly, in the oxandrolone group, hamstring muscle volume increased significantly (75 ± 18 mm^3; $p = .001$) from baseline to study week 12. This increase was greater ($p = .009$) than the change (1 ± 13 mm^3) in the placebo group (Figure 2). Quadriceps muscle volume did not significantly change in either the oxandrolone or placebo group ($p > .05$ for both).

Changes in Maximal Voluntary Strength

After 6 and 12 weeks, the absolute (Table 2) and relative (Figure 3A and B) increases in maximal voluntary muscle strength were greater for participants receiving oxandrolone. These increases were significantly different from the placebo group for chest press, lat pull-down, leg press, and leg curl exercises and for the assessment of leg extension power (Table 2). The increases in strength by study week 6 were greater than 90% of the gains achieved by study week 12 with the exception of the chest press
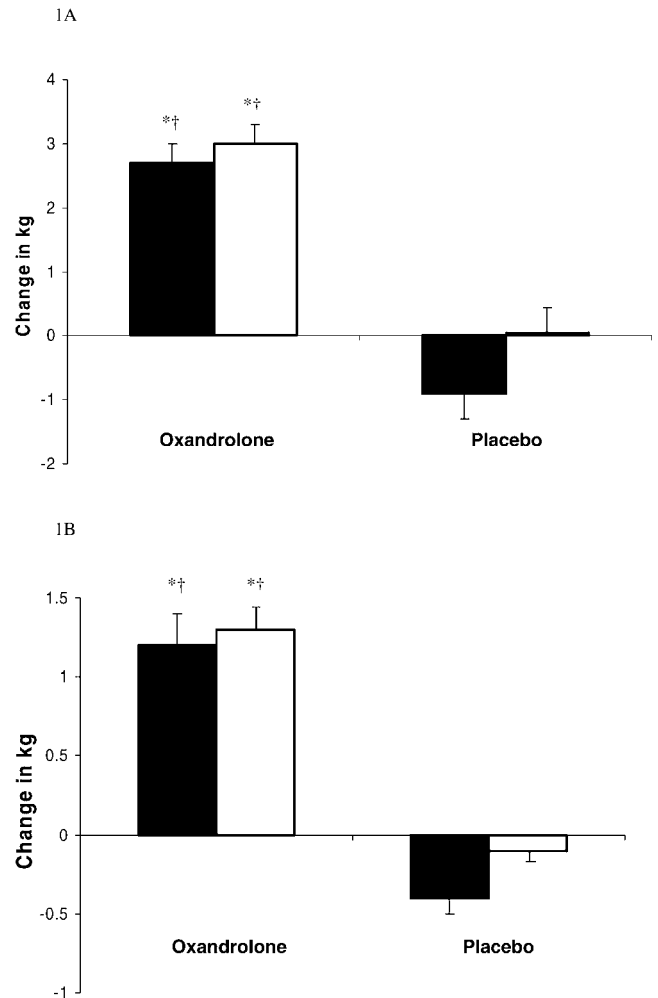
exercise that reached approximately 75% of the gains in strength achieved by study week 12. For the leg press at study week 6, the relative strength increased by $6.3 \pm 5.6\%$ ($p = .003$), for leg curl by $6.7 \pm 8.6\%$ ($p = .01$), for chest press by $6.9 \pm 6.5\%$ ($p = .001$), and for lat pull-down by $4.8 \pm 6.3\%$ ($p = .009$) in the group receiving oxandrolone. By study week 12, the relative strength for leg press increased by $6.8 \pm 6.4\%$ ($p = .005$), for leg curl by $7.0 \pm 7.8\%$ ($p = .012$), for chest press by $9.3 \pm 6.7\%$ ($p < .001$), and for lat pull-down by $5.1 \pm 9.1\%$ ($p = .013$) in the group receiving oxandrolone (Figure 3A and B). Thus, the increases in maximum voluntary strength at study week 6 were 93%, 96%, 74%, and 94% of the respective gains for leg press, leg curl, chest press, and lat pull-down at study week 12.

Lower Extremity Muscle Function

Leg extension power assessed using the Bassey Power Rig did not significantly improve (3 ± 24 and -13 ± 14
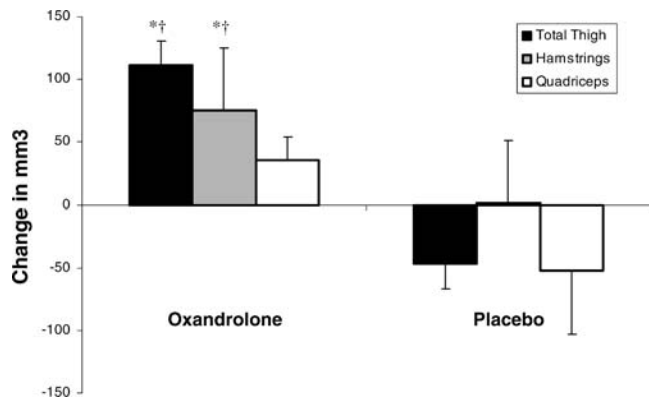
Figure 2. Absolute change in muscle volume by magnetic resonance imaging for the total thigh (black bars), hamstrings (gray bars), and quadriceps (white bars) muscle groups. The whiskers are one standard error. *Significant ($p = .001$) within-group difference from baseline. †Significant ($p = .006$) difference in the change between study groups.

Watts) by study week 6 in either the oxandrolone or placebo group, respectively (Table 2). Furthermore, by study week 12 the increases (10 ± 27 Watts) in leg extension power in the group receiving oxandrolone was not different from the loss (-13 ± 12 Watts) in the placebo group. Lower extremity power determined by the Margaria stair-climb test and the 400 meter walk and/or jog test did not demonstrate significant improvements ($p > .05$) nor was there a significant difference between groups (data not shown).

Safety Evaluation

There were no serious adverse events that could be attributed to oxandrolone. However, one serious adverse event occurred during the study when a participant randomized to oxandrolone developed hypotension after his primary doctor modified the patient's antihypertensive medications at the participant's request (21); this participant resumed study therapy without further problems. Although serum albumin and alkaline phosphatase levels decreased more with oxandrolone than with placebo, there was no change in ultrasensitive C-reactive protein levels at week 12, suggesting that inflammation was not more common in the oxandrolone group. There were minimal increments in the liver transaminase levels that reached statistical significance, but alanine aminotransferase was only increased beyond the normal range in two participants where it reached 71 and 99 U/L (≤ 1.5 times the upper limit of normal) (21). Both participants were asymptomatic without liver enlargement, and the alanine aminotransferase returned to normal in both shortly after study therapy was discontinued.

Total cholesterol and triglyceride levels did not change by study week 12 in either group. However, at study week 6, low-density lipoprotein (LDL) cholesterol increased (31 ± 41 mg/dL; $p = .02$) and by study week 12 was 23 ± 37 mg/dL greater ($p = .06$) than were baseline values in the oxandrolone group but returned to baseline values 12 weeks after study therapy was discontinued (23). For high-density lipoprotein (HDL) cholesterol, levels decreased (20 ± 7 mg/dL; $p < .001$) at study week 6 and by study week 12, remained
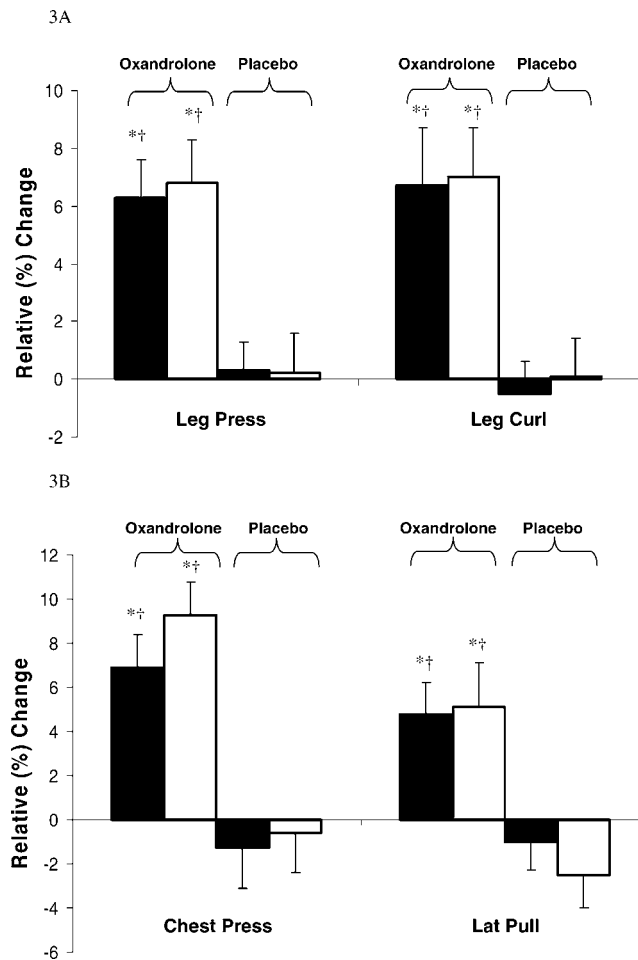

Figure 3. Relative (%) change in lower (**A**) and upper (**B**) extremity voluntary maximum muscle strength. Filled bars represent change from baseline to study week 6; open bars represent change from baseline to study week 12. The whiskers are one standard error. *Significant ($p < .001$) within-group difference from baseline. †Significant ($p < .001$) difference in the change between study groups.

decreased (19 ± 8 mg/dL, $p < .001$) in the oxandrolone group. The effects of oxandrolone on HDL cholesterol were not sustained, and 3 months following treatment there was a rebound to levels greater than baseline (23).

Hematocrit levels did not increase in either group. The PSA measures did not change significantly by study week 6; however, by study week 12 there was a small (-0.6 ± 0.9 ng/ml) but significant ($p = .03$) decrease in the PSA in the oxandrolone group.

DISCUSSION

Testosterone replacement therapy in older men, even when given for more than a year, has resulted in only modest increases in total lean tissue of 1–2 kg (22), and the increases in muscle strength have been modest at best and inconsistent (15,16,30,31). Whereas, treatment with oxandrolone, a potent oral androgen, produced a robust 3-kg increase in total LBM along with significant increases in appendicular LBM, muscle volume, and maximal voluntary strength of the major

muscle groups of the upper and lower body after just 12 weeks of treatment. The only other study in which comparable changes in lean tissue and consistent improvements in the major muscle groups were achieved used largely supraphysiologic doses of testosterone for 6 months (20). Likewise, the FDA-approved dose of oxandrolone (20 mg/day dose) appeared to be supraphysiologic because endogenous production of luteinizing hormone was suppressed. Thus, the magnitude of accretion in myofibrillar protein and benefits for skeletal muscle strength may be related to dose or potency of the anabolic androgen used for treatment.

The most important finding of this study was that greater than 90% of the gains in total LBM, appendicular lean tissue, and skeletal muscle strength were achieved by study week 6. Indeed, total LBM increased by 2.7 ± 1.6 kg at study week 6 and only increased an additional 0.3 ± 0.1 kg by study week 12. Appendicular LBM by DEXA, an indirect measure of muscle mass, increased by 1.2 ± 0.9 kg at study week 6, which was greater than 90% of the gain at study week 12, namely 1.3 ± 0.9 kg. Similarly, the increases in maximum voluntary strength at study week 6 were 93%, 96%, 74%, and 94% of the respective gains for leg press, leg curl, chest press, and lat pull-down at study week 12. These increases in maximal voluntary strength of the upper and lower body appendicular muscles suggest that functionally important improvements may be attained with a relatively short course of therapy using a potent androgen. These observations are consistent with the findings of Bhasin and colleagues, who showed that changes in body composition and skeletal muscle strength are proportional to the dose of testosterone administered for 20 weeks to younger men (12).

We believe that the significant improvements in maximal skeletal muscle strength corroborate our findings of increased total and appendicular LBM by DEXA scanning and that these findings are not merely the result of hydration from the androgen treatment (21). Furthermore, our findings of increased thigh muscle volume determined by serial MRI CSA slices support the contention that increases in muscle mass with androgen supplementation are responsible for the gains in strength because CSA is proportional to muscle strength (32) and we have previously shown that increases in muscle CSA are proportional to increases in strength (33). Of note, there were greater absolute changes in hamstrings compared to quadriceps muscle volume probably due to the quadriceps muscle compartment being larger and more likely recruited during normal physical activity. The fact that the quadriceps muscle group is more often used for habitual daily activities may explain why this muscle group did not respond as well to the oxandrolone treatment. It is possible that smaller muscle groups, such as the hamstrings, which are not recruited as often for typical patterns of movement or activity, have a lower threshold for stimulus and respond better to androgen therapy.

Increases in LBM in older men at risk for sarcopenia and frailty is of limited value unless meaningful improvements in skeletal muscle strength, power, and physical function can be demonstrated. We tested muscle strength for various upper and lower body muscle groups as well as leg extension power, stair-climb power, and time to walk and/or jog 400 meters. Although the majority of strength gains were achieved by study week 6, the modest yet statistically significant 7% average improvement in relative strength for lower extremity muscle groups did not translate into improvements in lower extremity leg extension power, stair-climb power, or the ability to walk and/or jog 400 meters, which has been associated with changes in physical function (26,27). The most likely explanation for the absence of improvements in measures of lower extremity performance may have related to the functional status of the population tested. Our participants were healthy, active, ambulatory community-dwelling older men. It is possible that similar treatment of sedentary, frail individuals may have resulted in substantive improvement in physical function but this is largely speculation. In addition, our study was not powered to show changes in physical function.

That more than 90% of the gains in muscle mass and strength were achieved in just 6 weeks could be beneficial to individuals with physical limitations, frailty, or catabolic illness and associated muscle wasting because the long-term safety of androgen supplementation for cardiovascular and prostatic health is unknown. In addition, short-term treatment with potent anabolic androgens may "jumpstart" the anabolic process for improving muscle mass and skeletal muscle strength until these individuals are capable of engaging in resistance exercises, a potent stimulus for myofibrillar muscle protein synthesis and proven means to significantly increase muscle quality (33,34) and physical function even in nonagenarians (35).

There are several limitations of this study. First, oxandrolone unlike testosterone is 5-alpha reduced and non-aromatizable, and blood levels for this drug are not available in clinical laboratories. This makes it difficult to determine dose–response effects or compare timing and magnitude of outcomes measured in our study to other trials using testosterone or testosterone conjugates. Second, it is unclear whether treatment for longer than 12 weeks would have resulted in further gains in LBM and skeletal muscle strength that would have clinical or functional significance as there appears to be a threshold for androgen effects as there are limited benefits of treatment with testosterone when therapy is prolonged beyond 3 months (15,31). Third, whether the effects of treatment in a more impaired population of frail individuals or those with underlying catabolic disease would be similar is unknown. Lastly, there are additional challenges of conducting clinical trials in older adults, such as impaired nutritional status, catabolic effects of various comorbidities, and the physical limitations associated with frailty that complicate studying hormone replacement therapy.

Lastly, the safety and efficacy of long-term androgen therapy has yet to be established in older persons. Because 17-alkylated androgens, such as oxandrolone, reduce HDL cholesterol and may elevate LDL cholesterol as occurred in this study, oxandrolone should not be used for otherwise healthy persons with increased risk of cardiovascular disease. However, it is possible that short-term treatment may minimize the cardiovascular and prostatic disease risks that could occur with long-term androgen therapy until definitive safety studies have been completed as advised by the Institutes of Medicine (36). Furthermore, when life expectancy is short, as may occur in older persons with

advanced cancer, severe obstructive lung disease, or cardiac cachexia, risk–benefit considerations may be different and a brief course of treatment with a potent anabolic androgen may produce significant increases in muscle mass, also an important source of amino acids for synthesis of white blood cells and proteins to combat infection and cancer cells (37). Thus, the observation that as little as 6 weeks of treatment with a potent androgen improves muscle mass serves to justify further studies in older populations.

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