Oxandrolone Augmentation of Resistance Training in Older Women: A Randomized Trial

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ABSTRACT

MAVROS, Y., E. O'NEILL, M. CONNERTY, J. F. BEAN, K. BROE, D. P. KIEL, D. MACLEAN, A. TAYLOR, R. A. FIELDING, and M. A. FIATARONE SINGH. Oxandrolone Augmentation of Resistance Training in Older Women: A Randomized Trial. *Med. Sci. Sports Exerc.*, Vol. 47, No. 11, pp. 2257–2267, 2015. **Introduction**: Sarcopenia is disproportionately present in older women with disability, and optimum treatment is not clear. We conducted a double-blind, randomized, placebo-controlled trial to determine whether oxandrolone administration in elderly women improves body composition or physical function beyond that which occurs in response to progressive resistance training (PRT). **Methods**: Twenty-nine sedentary women (age 74.9 ± 6.8 yr; 5.9 ± 2.8 medications per day) were randomized to receive high-intensity PRT (three times a week for 12 wk) combined with either oxandrolone (10 $mg \cdot d^{-1}$) or an identical placebo. Peak strength was assessed for leg press, chest press, triceps, knee extension, and knee flexion. Power was assessed for leg press and chest press. Physical function measures included static and dynamic balance, chair rise, stair climb, gait speed, and 6-min walk test. Body composition was assessed using dual energy x-ray absorptiometry. **Results**: Oxandrolone treatment augmented increases in lean tissue for the whole body (2.6 kg; 95% confidence interval (CI), 1.0–4.2 kg; $P = 0.003$), arms (0.3 kg; 95% CI, 0.1–0.5 kg; $P = 0.001$), legs (0.8 kg; 95% CI, 0.1–1.4 kg; $P = 0.018$), and trunk (1.4 kg; 95% CI, 0.4–2.3 kg; $P = 0.004$). Oxandrolone also augmented loss of fat tissue of the whole body (−1 kg; 95% CI, −1.6 to −0.4; $P = 0.002$), arms (−0.2 kg; 95% CI, −0.5 to −0.02 kg; $P = 0.032$), legs (−0.4 kg; 95% CI, −0.6 to −0.1; $P = 0.009$), and tended to reduce trunk fat (−0.4 kg; 95% CI, −0.9 to 0.04; $P = 0.07$). Improvements in muscle strength and power, chair stand, and dynamic balance were all significant over time ($P < 0.05$) but not different between groups ($P > 0.05$). **Conclusions**: Oxandrolone improves body composition adaptations to PRT in older women over 12 wk without augmenting muscle function or functional performance beyond that of PRT alone. **Key Words:** SARCOPENIA, FRAILTY, OXANDROLONE, RESISTANCE TRAINING

Sarcopenia (reduction in muscle mass and strength with aging) is estimated to affect 45% of women over 80 yr of age (4). The direct health care costs attributed to sarcopenia in the United States in 2000 were estimated at $18.5 billion, with $7.7 billion attributable to women (14). Sarcopenia has been associated with mobility limitations, disability, and metabolic disturbances, particularly when compounded with visceral obesity (14,21,36). In women, the sex steroid estrogen exerts anabolic effects on the skeletal muscle through upregulation of the nuclear receptors estrogen receptors α and β (ERα and ERβ), along with its interaction with the anabolic hormone insulin-like growth factor 1 (41). Thus, the natural decline in estrogen after menopause can be partly attributed to the onset of sarcopenia and frailty (18,20,24). Progressive resistance training (PRT) has been shown to be an effective intervention to counteract these changes, with benefits including increased skeletal muscle mass, reductions in adipose tissue, and improvements in mobility, physical function, and metabolic profile (7,16,31). Another approach to anabolic enhancement is the use of the anabolic androgenic steroids (AAS) (7). However, despite the known positive effects of AAS on body composition and strength, limited data are available on the effects of AAS in older women (26).

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Oxandrolone (trade name Anavar or Oxandrin) is an AAS with an anabolic-to-androgenic ratio of 10:1, making it a more feasible therapy (particularly in women) than other AAS or testosterone itself (25). Currently, oxandrolone is the only Food and Drug Administration-approved AAS used clinically to preserve lean tissue in catabolic conditions (25). Previously, PRT combined with oxandrolone has been examined in men and women with HIV-related weight loss, with improvements in lean tissue and strength in men (38) and increases in body weight and quality of life in women (27). To our knowledge, investigations into the combined effects of oxandrolone and PRT within older adults, or specifically older women, have not been performed. Therefore, the purpose of this clinical trial was to study the effects of 12 wk of PRT in combination with 10 $mg \cdot d^{-1}$ of oxandrolone or placebo in older women with mild frailty. We hypothesized that PRT plus oxandrolone would show significantly greater increases in lean tissue and reduction in adipose tissue as measured using dual energy x-ray absorptiometry (DXA) compared with PRT plus placebo. Furthermore, we hypothesized that PRT plus oxandrolone would result in increases in physical function, peak muscle strength (one-repetition maximum (1RM)), as well as muscle peak power and endurance compared with participants receiving PRT plus placebo.

METHODS

Participants and study design. Twenty-nine functionally limited older women were recruited for this randomized, double-blind, placebo-controlled trial. Participants were randomized to receive PRT with either 10 $mg \cdot d^{-1}$ of oxandrolone (PRT + Ox) or identical placebo (PRT + Pl) (manufactured for BTG Pharmaceuticals by G.D. Searle & Co., Chicago, IL) for 12 wk. Randomization was performed by Pfizer central office, and randomization sequence was kept offsite. Randomization occurred at the completion of the entire baseline assessment via e-mail to pharmacy staff who prepared study medications for each participant, distributed by research staff identified as "B" or "C" only. Baseline and follow-up assessments at 12 wk were conducted over two separate days by the same assessors who were blinded to study medication. A written informed consent was obtained from all participants. The study was approved by the Clinical Investigation Committee, Hebrew Rehabilitation Center for Aged (protocol 00–011) on August 7, 2000.

Sample size. The study was powered on the adaptive response of muscle as determined by muscle fiber cross-sectional area; however, at the time of publication, these data were not available. Sample size estimates were based on Fiatarone Singh et al. (10) who showed that the combination of nutrition and PRT increased Type II fiber diameter by 21.6% compared with resistance training alone. It was estimated that with an alpha of 0.05 and a power of 0.8, a sample size of 32 (16 in each group) was required to detect a significant change in Type II fiber area in participants receiving oxandrolone compared with those receiving placebo.

Eligibility criteria. Women were eligible for the study if they were community dwelling, between the ages of 65 and 90 yr inclusive, and had evidence of a frail or prefrail condition by demonstration of one of the following: gait speed between 0.5 and 0.9 $m \cdot s^{-1}$, chair rise time >12 s, one or more limitations in Nagi's instrumental activities of daily living (23), self-reported limitation of the physical component section of the Short Form 36 Health Survey (SF-36) categories B through J inclusive, a loss of 10 lb (5 kg) or more in the 5 yr preceding screening, a body mass index (BMI) < 24 $kg \cdot m^{-2}$, one fall within the previous 6 months, or two or more falls within the previous 2 yr. In addition, participants generally were in good health or had clinically stable chronic disease, no acute illness precluding participation in a resistance training program, able to ambulate at least 50 m independently, had a BMI between 18 and 36 $kg \cdot m^{-2}$, and a mini mental state examination (MMSE) score >24 (11). Additional inclusion/exclusion criteria can be found in the supplementary material (see Document, Supplemental Digital Content 1, Supplementary methods, http://links.lww.com/MSS/A540).

Laboratory data. Venous blood was sampled, and HDL, LDL, and liver function tests (LFT) were analyzed at a commercial pathology laboratory. Tests were repeated at 4 wk for safety. If aspartate aminotransferase (AST) or alanine aminotransferase (ALT) concentrations increased three times the normal level, the study physician was notified and the supplement was withheld permanently without change to the PRT intervention.

Muscle strength and power. Testing was performed on Keiser pneumatic resistance machines (Keiser Sports Health Equipment, Ltd., Fresno, CA). Participants' 1RM was determined on the leg press (LP), knee extension (KE), knee flexion (KF), triceps pushdown (TP), and chest press (CP). At baseline, the strength testing and the 6-min walk test (6MWT) were repeated during a second visit, with the best result achieved used in analyses. Power testing was performed on the LP and CP, following adequate rest. For power testing, resistances equivalent to 20%, 30%, and up to 100% of the best 1RM at baseline were calculated. Participants were instructed to lift each resistance as quickly as possible, and the power for each repetition was recorded. Peak power was determined as the highest power achieved. The same process was repeated at 12 wk, with the resistances set to the newly determined 1RM. Maximal strength and power testing are safe, valid, and highly relevant outcomes in mobility-limited older adults (9,30).

Anthropometric data collection. Anthropometric data were measured in triplicate to the nearest 0.1 cm or 0.1 kg where appropriate. Height and weight were measured, and BMI was calculated. Waist circumference was measured at the midpoint between the iliac crest and the lowest rib (1). Hip circumference was measured at the largest girth of the buttocks. Waist-to-hip ratio was calculated.

Body composition. Whole body and regional body composition was measured using DXA (Hologic DelphiW, software package QDR 11.1; Hologic, Bedford, MA) following

the manufacturer's standard protocol. One blinded experienced technician performed and analyzed the scans. Scan quality was reviewed by an International Society of Clinical Densitometry-certified investigator blinded to group assignment.

Physical function. Physical function was assessed using the 6-min walk test, one-leg stance, forward and backward tandem walk over 6 m (20 ft), habitual and maximal gait speed measured over 2 m (Ultra-timer Raymar, Oxfordshire, United Kingdom), chair rise time, and stair climb power. Further information on these tests can be found in the supplementary material (see Document, Supplemental Digital Content 1, Supplementary methods, http://links.lww.com/MSS/A540).

Physical activity and dietary intake. Habitual physical activity was quantified using the Physical Activity Scale for the Elderly (PASE) (39,40) and excluded study resistance training. Dietary intake over past 4 months was assessed using the Block Food Frequency Questionnaire (5).

Quality of life and depression. Health-related quality of life was determined by the Short Form 36 Health Survey questionnaire (SF36, version 1). Depression was assessed using the Center for Epidemiological Studies of Depression Short Form (CES-D 10) (2).

Oxandrolone/placebo supplementation. Participants were instructed to take 2 × 2.5 mg tablets twice per day (10 mg) for 12 wk. The oxandrolone dosage of 10 $mg \cdot d^{-1}$ is consistent with previously reported trials in women with HIV-related weight loss (27). Both oxandrolone and the placebo were identical in appearance, packaging, taste, and texture to ensure blinding of participants and investigators to group allocation and were dispensed by the pharmacy of the Hebrew Rehabilitation Center. Compliance to supplementation was measured by self-report and the returning of empty packaging by the participants.

PRT intervention. Participants in both groups received identical PRT and were instructed by the same experienced trainer who was blinded to the participants' group allocation. Participants exercised 3 $d \cdot wk^{-1}$ on Keiser pneumatic resistance equipment at a minimum of 80% of their previously determined 1RM. Sessions lasted approximately 45 min. Participants performed three sets of eight repetitions on the LP, KE, KF, TP, plantarflexion, and CP. 1RM testing was carried out every 2 wk to ensure participants were progressed appropriately. Resistance was adjusted accordingly if participants developed musculoskeletal complaints that could be exacerbated with PRT; however, no significant reduction in training load occurred.

Statistical methods. All data were inspected for normality before use in parametric statistics. Baseline comparisons and comparisons of group compliance to the exercise and pharmacological intervention were performed using one-way ANOVA. Sequential linear mixed-effects models with repeated measures and an unstructured covariance matrix were used to determine the effects of group assignment over time for all dependent variables using an intention-to-treat analytic strategy without regard to adherence or dropout. The comparison of percent training intensity over time between groups was analyzed using an autoregressive one [AR(1)] covariance structure due to having six repeated measures. Groups were compared at baseline to identify potential confounders, but no relevant group differences were identified. Linear regression models were constructed between changes in indices of body composition, muscle strength and power, as well as physical performance. Primary data analysis was performed without any covariates. Linear mixed models were then adjusted for PASE scores because this was found to be associated with indices of strength and physical function; however, no effect was found, except in the case of trunk fat mass. All data are presented from unadjusted models as mean ± SD or median (interquartile range), as appropriate. Mean differences for time and group–time effects from linear mixed-effects models are presented as β (95% confidence intervals). A P value < 0.05 indicated statistical significance, as all analyses were specified *a priori*. SPSS version 21.0 (IBM Corp., Armonk, NY) was used for data analysis.

RESULTS

Participant flow through the study is shown in Figure 1. Among the 29 participants recruited, three participants dropped out of the study. One participant in the oxandrolone group dropped out at week 11 because of diverticulitis. Two participants from the placebo group also dropped out; one developed a pulmonary embolism, whereas another participant was withdrawn at week 5 due to discovery of a preexisting abnormal computed tomography results with question of malignancy. Baseline characteristics are shown in Table 1. The women were all community dwelling, with mild functional impairment, preserved cognitive function, and good quality of life on average. Depressive symptoms were prevalent, however, with 27.6% of the cohort classified as having at least mild depression from the CES-D 10 questionnaire. Participants randomized to PRT + Ox had significantly lower CP 1RM ($P = 0.03$) and tended to have reduced triceps 1RM ($P = 0.083$) and reduced peak power on the CP ($P = 0.09$). No other differences were observed between groups for any variables ($P > 0.05$).

Adherence to interventions. Participants randomized to PRT + Ox had a significantly greater medication compliance than those randomized to PRT + Pl (94.2% ± 7.0% vs 81.2% ± 22.3%; $P = 0.049$). Overall compliance to the exercise intervention was similar ($P = 0.35$) between participants receiving oxandrolone (88.9% ± 8.2%) or placebo (84.9% ± 13.3%). Notably, the average training load of all exercises relative to the most recently determined 1RM was close to the intended 80% intensity, also similar between groups across the intervention (see Figure, Supplemental Digital Content 2, Average training intensity throughout the study, http://links.lww.com/MSS/A541) ($P = 0.23$).

Body composition. Results are presented in Table 2. Compared with participants receiving PRT + Pl, participants receiving PRT + Ox had significantly greater increases in whole body lean tissue ($P = 0.003$) as well as trunk

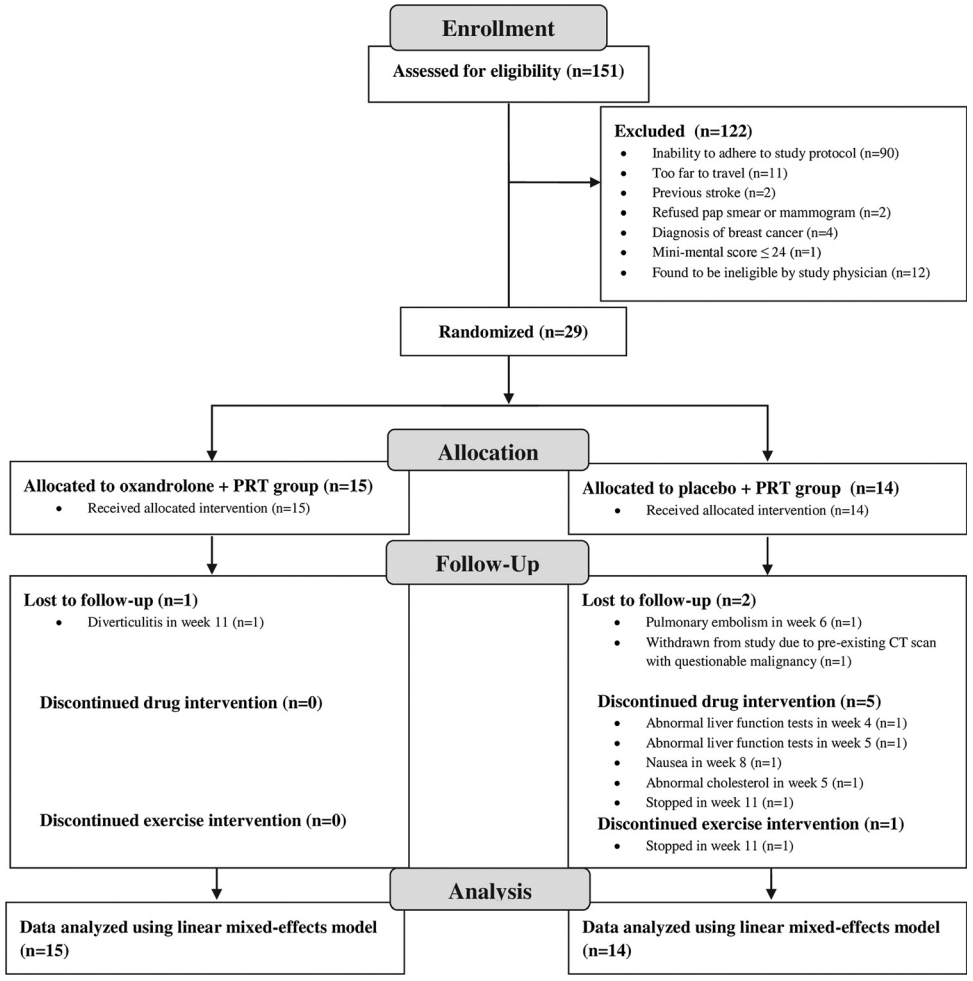

FIGURE 1—CONSORT flow diagram. This diagram shows the flow of participants through the study. Linear mixed-effects models with repeated measures were used to determine the group effects over time. This allows for all participants to be included in the model without imputation for missing data. Thus, despite three participants being lost to follow-up and not having data at 12 wk, all participants were entered into the model.

($P = 0.004$), arm ($P = 0.001$), and leg ($P = 0.018$) lean tissues (Fig. 2). Furthermore, participants receiving PRT + Ox had significant reductions in whole body fat mass ($P = 0.002$), percent body fat ($P < 0.0001$), arm fat ($P = 0.03$), and leg fat ($P = 0.009$) compared with those receiving PRT + Pl. Trunk fat tended to reduce ($P = 0.07$) in participants receiving PRT + Ox compared to participants receiving PRT + Pl, and this was attenuated after adjusting for PASE scores ($P = 0.11$) (Fig. 3). No other differences between groups over time were observed for any other body composition parameter ($P > 0.05$).

Muscle strength and power. Data are presented in Table 2. LP, CP, triceps, KE and KF peak strength improved in all participants ($P < 0.0001$), irrespective of group assignment (Fig. 4A–E) ($P > 0.05$). LP peak power increased similarly in both groups ($P < 0.001$). Peak power on the CP significantly increased in participants receiving PRT + Ox ($P = 0.046$) compared to participants receiving PRT + Pl. Because CP 1RM was significantly lower in participants receiving PRT + Ox at baseline, a mixed-effects model for peak CP power was constructed with CP 1RM entered as a covariate. In this model, the significant increase in CP power in PRT + OX was attenuated and no longer significant ($P = 0.13$).

Physical performance tests. Data are presented in Table 2. One-leg stance, backward tandem walk, and chair rise time significantly improved in all participants regardless of group assignment ($P < 0.05$). No group–time interaction was observed for any physical performance measure ($P > 0.05$).

Nutrition and physical activity. Data are presented in Table 2. No changes in habitual physical activity, total daily energy intake, or daily protein intake were observed ($P > 0.05$).

Quality of life and depression. Data are presented in Table 2. No effect was observed for change in depressive symptoms via CES-D 10 ($P = 0.22$). No changes in any of the SF-36 subscales were found ($P > 0.05$).

Associations with physical function outcomes. Increases in stair climb power were associated with increases in KE 1RM ($r = 0.45$, $P = 0.03$) and increases in leg lean tissue ($r = 0.67$, $P < 0.001$). Improvements in forward tandem walk were associated with increases in LP 1RM ($r = -0.61$, $P = 0.002$), KF 1RM ($r = -0.49$, $P = 0.02$), and KE

TABLE 1. Baseline characteristics.

	Total (n = 29)	Placebo (n = 14)	Oxandrolone (n = 15)	P Value
Age (yr)	74.9 ± 6.8	73.3 ± 6.2	76.5 ± 7.2	0.21
Ethnicity (% Caucasian)	100%	100%	100%	—
Nagi instrumental ADL (0–15)	1.9 ± 1.8	1.4 ± 1.8	2.3 ± 1.7	0.17
MMSE (0–30)	30 (0)	30 (0)	30 (0.75)	0.99
SF-36 version 1 (0–100)				
General health	70.4 ± 10.6	73.9 ± 9.0	67.1 ± 11.2	0.09
Physical function	80.2 ± 19.8	86.1 ± 17.1	74.8 ± 21.1	0.13
Role physical	100 (25)	100 (0)	100 (50)	0.21
Bodily pain	75.3 ± 20.1	71.1 ± 21.4	79.1 ± 18.8	0.29
Vitality	70 (25)	75 (15)	70 (32.5)	0.71
Social function	100 (3)	100 (0)	100 (25)	0.42
Role emotional	100 (0)	100 (0)	100 (33.3)	0.20
Mental health	83.0 ± 11.3	85.1 ± 9.2	81.1 ± 13.0	0.34
Medications (n per day)	5.9 ± 2.8	5.1 ± 2.6	6.5 ± 2.9	0.19
CES-D 10 (0–30)	8.83 ± 3.20	8.43 ± 2.98	9.20 ± 3.45	0.53
Depression (%)	27.6	14.3	40	0.12

Normally distributed data are presented as mean ± SD. Nonnormally distributed data are presented as median (interquartile range). Normally distributed continuous data were analysed using one-way ANOVA. Nonnormally distributed data were analyzed using Kolmogorov–Smirnov test. Nominal data were analyzed using a chi-square test.
For CES-D 10, higher scores indicate more depressive symptoms and scores ≥ 10 classified as depression. For ADL, higher scores indicate more functional impairment.
ADL, activities of daily living.

1RM (r = −0.47, P = 0.02) as well as increases in trunk lean tissue (r = −0.43, P = 0.04) and tended to be associated with increases in CP 1RM (r = −0.39, P = 0.07). Improvements in backward tandem walk were associated with increases in LP 1RM (r = −0.52, P = 0.02) and reductions in total calorie intake (r = 0.47, P = 0.03) and total protein intake (r = 0.51, P = 0.02).

Associations with changes in physical activity levels. Increases in PASE scores were associated with increases in LP 1RM (r = 0.40, P = 0.04) and KF 1RM (r = 0.44, P = 0.03), stair power (r = 0.43, P = 0.04), and habitual gait speed (r = 0.42, P = 0.04) and reductions in trunk fat (r = 0.41, P = 0.04), while they also tended to be associated with increases in KE 1RM (r = 0.38, P = 0.06), improvements in chair rise (r = 0.37, P = 0.08), and reductions in whole body fat (r = 0.36, P = 0.07) and percent body fat (r = 0.36, 0.07).

Laboratory data. Compared with participants receiving placebo, participants receiving oxandrolone had a significant reduction in HDL (P = 0.02), with no change in LDL (P = 0.80). Participants receiving oxandrolone also had a significant increase in ALT (P = 0.02) and tended to increase AST (P = 0.08), although none of the elevations in enzymes reached the safety threshold established by the investigators of a threefold or greater rise in LFT.

Adverse events. Overall, the total number of adverse events was not different between groups (P = 0.29) (see Table, Supplemental Digital Content 3, Adverse events, http://links.lww.com/MSS/A542). Adverse events related to exercise were predominantly minor musculoskeletal complaints requiring adjustments to training load intensity and did not occur differentially between groups (P = 0.42). Only one participant reported androgenic side effects associated with oxandrolone (growth of pubic and facial hair). Participants taking oxandrolone had significantly higher incidence of HDL cholesterol falling below normal limits (P < 0.01), with no difference observed for rises in LDL above normal limits (P = 0.78) (see Table, Supplemental Digital Content 4, Incidence of abnormal liver function test results, http://links.lww.com/MSS/A543). Participants receiving oxandrolone had significantly greater incidence of ALT rising above normal limits (40% of participants receiving oxandrolone vs 7% of participants receiving placebo; P = 0.04), whereas the incidence for AST rising above normal limits tended to be higher (20% of participants receiving oxandrolone vs 0% of participants receiving placebo; P = 0.08) (see Table, Supplemental Digital Content 4, Incidence of abnormal liver function test results, http://links.lww.com/MSS/A543). No participants discontinued oxandrolone administration. Four participants discontinued placebo by instruction of investigators because of abnormal LFT (weeks 4 and 5), increased LDL cholesterol (week 5), and nausea (week 8). One further participant in the placebo group discontinued supplementation on her own, as well as her exercise, in week 11. All other adverse events (see Table, Supplemental Digital Content 3, Adverse events, http://links.lww.com/MSS/A542) were unrelated to either intervention, as adjudicated by the safety monitoring board.

DISCUSSION

As hypothesized, 12 wk of PRT in combination with 10 mg·d^{-1} of oxandrolone in older women with mild frailty resulted in significantly greater benefits for body composition, with increases in whole body (2.6 kg) and appendicular lean tissue (1.1 kg) and reductions in whole body (−1 kg) and appendicular fat mass (−0.6 kg) when compared with those in participants receiving PRT and a placebo. However, despite these potentially clinically meaningful changes in body composition, improvements in muscle strength and power as well as functional mobility (dynamic balance and chair rise time) were no greater in participants receiving oxandrolone compared with those in participants receiving placebo after 12 wk of PRT. Data on oxandrolone administration in combination with exercise are minimal, with three studies previously performed in men (12,38) and women (27) with HIV-associated wasting and two others performed in children with severe burns (28,29). This is only the second study investigating the effects of oxandrolone and *any* exercise intervention in women and is the first with a robust randomized controlled trial design, with the only previous study performed in women with HIV comparing two dosages of oxandrolone (10 mg·d^{-1} vs 20 mg·d^{-1}) (27).

Regardless of group assignment, all participants showed an average increase in body weight of 1.0 kg. The cessation of weight loss and, perhaps more importantly, an increase in weight gain are purported to have beneficial effects in older adults with frailty, making them more tolerable to the stress of illness, hospitalization, and immobility (3). The addition of oxandrolone was not found to enhance weight gain compared with PRT alone; however, the study may be underpowered to show an effect on body weight, with participants

TABLE 2. Changes in participant characteristics.

Variable	Baseline	12 Wk	β (95% CI), T	*P T*	β (95% CI), G × T	*P*, G × T
Weight (kg)						
Placebo	66.2 ± 13.0	66.7 ± 12.2	1.0 (0.2 to 1.8)	0.013	1.0 (−0.5 to 2.6)	0.19
Oxandrolone	68.6 ± 16.0	70.2 ± 17.2				
BMI ($kg \cdot m^{-2}$)						
Placebo	25.3 ± 4.6	26.0 ± 4.7	0.4 (0.1 to 0.7)	0.02	0.4 (−0.2 to 1.0)	0.22
Oxandrolone	27.2 ± 4.8	27.8 ± 5.4				
Waist circumference (cm)						
Placebo	83.1 ± 9.8	84.1 ± 8.9	0.1 (−1.6 to 1.9)	0.878	1.3 (−2.2 to 4.8)	0.47
Oxandrolone	86.8 ± 16.6	87.6 ± 15.6				
Hip circumference (cm)						
Placebo	102.5 ± 10.2	103.1 ± 9.9	−0.6 (−1.4 to 0.1)	0.106	0.2 (−1.3 to 1.8)	0.76
Oxandrolone	106.6 ± 12.6	106.1 ± 12.4				
Waist/hip (ratio)						
Placebo	0.81 ± 0.06	0.82 ± 0.06	0.01 (−0.01 to 0.02)	0.509	0.01 (−0.03 to 0.04)	0.65
Oxandrolone	0.81 ± 0.1	0.82 ± 0.07				
Bone mineral density ($g \cdot cm^{-2}$)						
Placebo	0.95 ± 0.15	0.97 ± 0.19	0.00 (−0.01 to 0.01)	0.501	−0.01 (−0.55 to 0.59)	0.59
Oxandrolone	1.02 ± 0.11	1.02 ± 0.11				
Both arms lean (kg)						
Placebo	3.9 ± 0.6	4.0 ± 0.5	0.2 (0.1 to 0.3)	<0.0001	0.3 (0.1 to 0.5)	0.001
Oxandrolone	3.9 ± 0.7	4.4 ± 0.7				
Both legs lean (kg)						
Placebo	12.8 ± 1.8	13.0 ± 2.1	0.5 (0.2 to 0.8)	0.003	0.8 (0.1 to 1.4)	0.018
Oxandrolone	12.8 ± 2.6	13.8 ± 2.5				
Trunk lean (kg)						
Placebo	20.4 ± 2.2	20.4 ± 2.0	0.5 (−2.7 to 0.9)	0.054	1.4 (0.4 to 2.3)	0.004
Oxandrolone	21.3 ± 3.3	22.6 ± 3.7				
Whole body lean (kg)						
Placebo	40.6 ± 4.6	41.0 ± 4.7	1.3 (0.5 to 2.1)	0.003	2.6 (1.0 to 4.2)	0.003
Oxandrolone	41.5 ± 6.7	44.3 ± 6.8				
Both arms fat (kg)						
Placebo	3.0 ± 1.2	3.1 ± 1.1	−0.2 (−0.3 to −0.1)	0.004	−0.2 (−0.5 to −0.02)	0.032
Oxandrolone	3.2 ± 1.7	2.9 ± 1.8				
Both legs fat (kg)						
Placebo	9.7 ± 3.4	10.2 ± 3.1	−0.1 (−0.3 to 0.002)	0.054	−0.4 (−0.6 to −0.1)	0.009
Oxandrolone	9.6 ± 3.8	9.4 ± 3.9				
Trunk fat (kg)						
Placebo	11.7 ± 4.7	11.7 ± 4.4	−0.3 (−0.5 to −0.05)	0.021	−0.4 (−0.9 to 0.04)	0.07 *
Oxandrolone	12.8 ± 5.9	12.2 ± 6.4				
Whole body fat (kg)						
Placebo	25.2 ± 8.8	25.7 ± 8.1	−0.6 (−0.9 to −0.3)	0.001	−1.0 (−1.6 to −0.4)	0.002
Oxandrolone	26.3 ± 10.9	25.3 ± 11.6				
Whole body percent fat (%)						
Placebo	37.2 ± 6.7	37.8 ± 5.6	−1.3 (−1.8 to −0.7)	<0.0001	−2.5 (−3.6 to −1.4)	<0.0001
Oxandrolone	37.3 ± 8.1	34.7 ± 8.3				
HDL ($mg \cdot dL^{-1}$)						
Placebo	58.3 ± 13.0	57.1 ± 16.9	−20.5 (−30.6 to −10.3)	0.006	−18.5 (−33.9 to −3.2)	0.02
Oxandrolone	59.8 ± 11.5	38.8 ± 23.8				
LDL ($mg \cdot dL^{-1}$)						
Placebo	132.9 ± 35.3	132.0 ± 39.9	5.9 (−9.8 to 21.7)	0.44	2.9 (−20.9 to 26.7)	0.80
Oxandrolone	127.3 ± 25.1	131.2 ± 47.2				
AST ($U \cdot dL^{-1}$)						
Placebo	22.6 ± 9.3	21.8 ± 7.6	5.9 (1.2 to 10.7)	0.02	6.1 (−0.7 to 12.9)	0.08
Oxandrolone	22.6 ± 3.8	27.2 ± 8.9				
ALT ($U \cdot dL^{-1}$)						
Placebo	18.2 ± 6.1	19.8 ± 8.2	12.5 (6.6 to 18.4)	<0.0001	10.9 (2.4 to 19.4)	0.02
Oxandrolone	18.9 ± 5.1	30.8 ± 14.9				
KF 1RM (N·m)						
Placebo	319.0 ± 57.1	352.1 ± 40.7	44.9 (29.6 to 60.2)	<0.0001	19.0 (−11.6 to 49.6)	0.21
Oxandrolone	294.4 ± 61.8	348.9 ± 38.9				
KE 1RM (N·m)						
Placebo	275.7 ± 62.4	345.0 ± 36.3	80.1 (59.1 to 101.1)	<0.0001	21.2 (−20.7 to 63.2)	0.31
Oxandrolone	244.9 ± 64.4	338.2 ± 47.8				
Triceps 1RM (N)						
Placebo	509.6 ± 93.0	640.0 ± 144.5	113.7 (82.4 to 145.0)	<0.0001	−11.1 (−73.6 to 51.5)	0.72
Oxandrolone	446.8 ± 94.8	564.5 ± 107.1				
CP 1RM (N)						
Placebo	103.4 ± 21.1	130.2 ± 28.7	26.7 (19.5 to 33.9)	<0.0001	2.1 (−12.3 to 16.5)	0.76
Oxandrolone	87.7 ± 16.4 **	116.3 ± 24.4				
LP 1RM (N)						
Placebo	384.1 ± 94.0	487.7 ± 97.8	105.2 (77.6 to 132.8)	<0.0001	−4.8 (−60.0 to 50.4)	0.86
Oxandrolone	374.9 ± 87.7	487.0 ± 83.9				

(continued on next page)

TABLE 2. *(Continued)*

Variable	Baseline	12 Wk	β (95% CI), T	*P T*	β (95% CI), G × T	*P*, G × T
CP peak power (W)						
Placebo	114.1 ± 41.4	120.2 ± 49.7	13.8 (2.9 to 24.8)	0.015	22.3 (0.5 to 44.1)	0.046
Oxandrolone	90.2 ± 30.8	115.1 ± 38.9				
LP peak power (W)						
Placebo	303.8 ± 120.7	346.1 ± 115.5	53.3 (26.0 to 80.5)	<0.0001	16.0 (−38.5 to 70.5)	0.55
Oxandrolone	262.7 ± 119.6	321.3 ± 124.1				
Habitual gait speed ($m \cdot s^{-1}$)						
Placebo	1.14 ± 0.21	1.18 ± 0.18	0.06 (−0.02 to 0.13)	0.12	0.01 (−0.14 to 0.16)	0.89
Oxandrolone	1.01 ± 0.20	1.04 ± 0.27				
Maximal gait speed ($m \cdot s^{-1}$)						
Placebo	1.57 ± 0.20	1.60 ± 0.24	0.01 (−0.11 to 0.13)	0.842	0.01 (−0.22 to 0.25)	0.91
Oxandrolone	1.49 ± 0.20	1.48 ± 0.50				
Chair rise time (s)						
Placebo	14.9 ± 3.2	12.7 ± 3.0	−1.91 (−3.2 to −0.6)	0.005	0.37 (−2.2 to 2.9)	0.77
Oxandrolone	15.9 ± 3.9	14.0 ± 4.7				
One-leg stand (s)						
Placebo	8.1 ± 5.7	12.6 ± 6.9	3.3 (1.7 to 4.8)	<0.0001	−2.6 (−5.8 to 0.6)	0.10
Oxandrolone	5.4 ± 4.9	6.9 ± 5.2				
Tandem walk forward (s)						
Placebo	24.7 (16.2)	24.9 (12.5)	N/A	0.136	N/A	0.66
Oxandrolone	31.0 (17.5)	23.5 (18.6)				
Tandem walk backward (s)						
Placebo	35.5 (13.5)	32.1 (23.4)	N/A	0.02	N/A	0.70
Oxandrolone	36.0 (11.7)	30.7 (20.0)				
Stair climbing power (W)						
Placebo	251.8 ± 78.2	254.2 ± 74.4	−2.5 (−24.9 to 19.8)	0.82	8.0 (−36.81 to 52.8)	0.71
Oxandrolone	229.0 ± 82.8	221.0 ± 110.2				
6-min walk distance (m)						
Placebo	477.2 ± 73.4	473.2 ± 96.7	−7.7 (−38.9 to 18.5)	0.55	9.6 (−42.7 to 61.9)	0.71
Oxandrolone	440.5 ± 235.2	429.6 ± 91.9				
PASE						
Placebo	109.0 ± 47.1	88.2 ± 39.9	−11.3 (−31.0 to 8.4)	0.25	19.1 (−20.3 to 585)	0.33
Oxandrolone	90.4 ± 67.4	88.7 ± 59.7				
Energy intake ($kcal \cdot d^{-1}$)						
Placebo	1502 ± 817	1662 ± 582	34 (−129 to 198)	0.67	−199 (−526 to 128)	0.22
Oxandrolone	1570 ± 492	1504 ± 373				
Protein intake ($g \cdot kg^{-1} \cdot d^{-1}$)						
Placebo	1.0 ± 0.5	1.0 ± 0.3	−0.1 (−0.2 to 0.1)	0.31	−0.1 (−0.3 to 0.1)	0.47
Oxandrolone	1.1 ± 0.6	1.0 ± 0.5				
CES-D 10						
Placebo	8.4 ± 3.0	8.9 ± 2.2	−0.2 (−1.5 to 1.1)	0.75	−1.6 (−4.3 to 1.1)	0.223
Oxandrolone	9.2 ± 3.4	8.2 ± 2.4				

Normally distributed data are presented as mean ± SD, and nonnormally distributed data are presented as median (interquartile range). Nonnormally distributed data were log-transformed before use in linear mixed-effects models. Mean differences are presented as β (95% CI). Adjusting models for PASE scores had no significant effect on the data, except in the case of trunk fat. For ADL, higher scores indicate more functional impairment. For CES-D 10, higher scores indicate more depressive symptoms and scores ≥ 11 classified as depression. Adjusting for PASE scores had no effect on the results.

*The group–time association for trunk fat was attenuated after adjusting for PASE scores ($P = 0.11$).

**CP 1RM values were significantly different at baseline between groups ($P = 0.03$).

ADL, activities of daily living; G × T, group × time; and T, time.

receiving oxandrolone showing an increase of 1.5 kg compared with 0.4 kg in those receiving placebo. Previously, women with HIV-related wasting receiving either 10 or 20 $mg \cdot d^{-1}$ of oxandrolone in combination with PRT and a dietary supplement showed much larger increases in body weight of 7 lb (3.1 kg) (27). Notably, our participants reported no change in total energy or protein intake during the course of the intervention, suggesting that weight gain might be further enhanced with the addition of dietary modifications. Appropriately powered studies are required to determine whether oxandrolone therapy in addition to PRT and/or dietary modifications has greater efficacy than either intervention alone in facilitating weight gain in frail elders and whether there are any associated long-term benefits.

Participants receiving oxandrolone gained an additional 2.6 kg of lean tissue compared with those receiving a placebo (Fig. 2A–D). Oxandrolone has known anabolic effects, and administration of 15 $mg \cdot d^{-1}$ of oxandrolone for 2 wk has been shown to increase fractional protein synthesis in older women and men (35). Further support for the use of oxandrolone in combination with PRT can be found in men with AIDS-related muscle wasting who received 8 wk of PRT and testosterone with or without oxandrolone. In this trial, participants randomized to receive oxandrolone gained an extra 3.1 kg of lean tissue compared with participants receiving a placebo (38). In addition to increases in lean tissue, participants receiving oxandrolone also showed 1-kg greater reductions in body fat (Fig. 3A–D). This is consistent with the known effects of AAS in decreasing lipoprotein lipase and upregulating the β-adrenergic receptors in adipocytes, with the net effect of increasing lipid breakdown and efflux from adipocytes (19). In agreement with our data, older men receiving 20 $mg \cdot d^{-1}$ of oxandrolone for 12 wk showed reductions of total body fat of 1.9 kg (33). Conversely, the combination of oxandrolone and PRT failed to reduce total body fat in men with AIDS-associated muscle

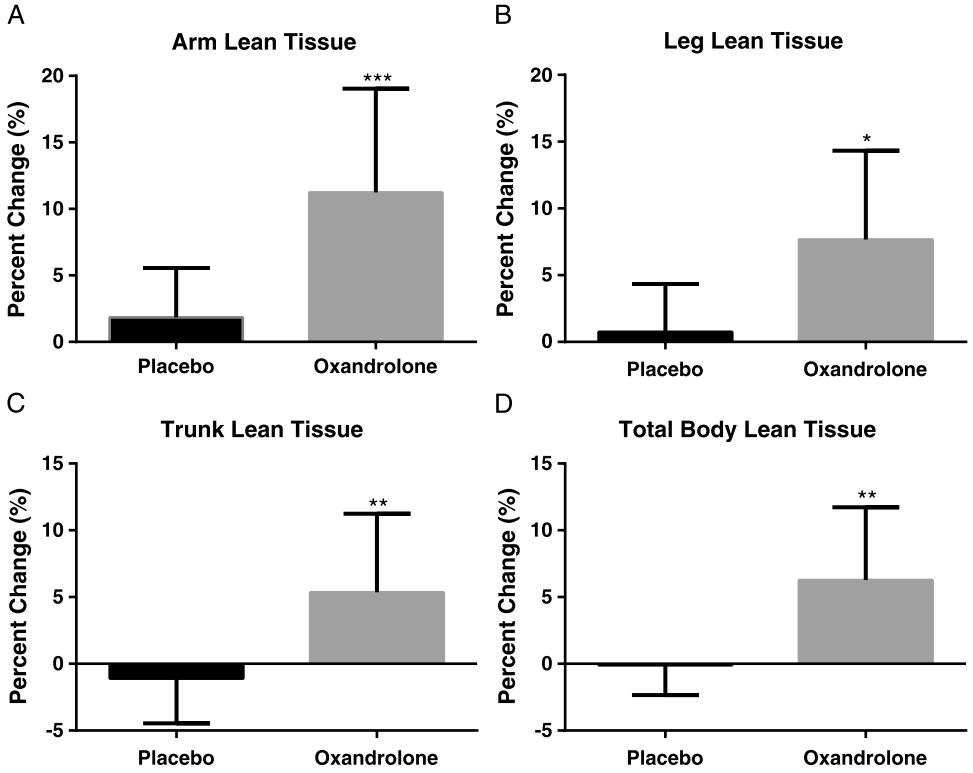

FIGURE 2—Percent changes in lean tissue. Data are presented as mean percent change (%) ± SD. Participants receiving the placebo are denoted by the *black bars*, whereas participants receiving oxandrolone are denoted by the *gray bars*. *$P \leq 0.05$, **$P \leq 0.01$, and ***$P \leq 0.001$.

wasting (38). However, the shorter duration of the therapy (8 vs 12 wk) and the presence of a catabolic disease and antiretroviral therapy promoting central adipose tissue gain may have affected the efficacy of oxandrolone therapy to further reduce whole body fat in that cohort. Interestingly, our results show that trunk fat only tended to decrease in participants receiving oxandrolone, with no changes in waist or hip circumference or waist-to-hip ratio. Previously, a 9-month trial of caloric restriction in combination with either nandrolone decanoate (similar AAS analog to oxandrolone), spironolactone, or placebo in obese older women found that women receiving nandrolone had preferential loss of subcutaneous fat, with a significant gain in visceral fat mass (assessed using gold standard computed tomography) (17). It has been suggested that androgen therapy above the physiological window can increase visceral adiposity and cardiovascular risk (6). Thus, the potential adverse effects on visceral adiposity and cardiometabolic risk that may accompany oxandrolone administration must be considered.

Despite favorable changes in body composition in those receiving oxandrolone, there was little to no additional benefit in muscle performance measures, with all participants showing similar improvements in muscle strength (Fig. 4A–E) and power. Although participants receiving oxandrolone had greater improvement in CP peak power, their baseline CP 1RM was significantly lower and adjusting for their peak strength attenuated the increase in peak power. Similarly, women receiving oxandrolone plus PRT showed similar improvements in dynamic balance and chair rise time to those achieved by PRT alone. Our results suggest that despite increases in lean tissue in the arms and legs, there was no direct translation to an improvement in strength otherwise attained with strength training alone. This is consistent with our regression analyses that show that improvements in stair climb power, chair rise time, forward tandem walk, and habitual gait speed were associated with increases in leg strength, with no association found with increases in leg lean tissue (with the exception of stair climb power). Furthermore, no association was observed between increases in leg lean tissue and increases in leg strength or power. Our results indicate that improvements in strength, as opposed to gains in lean tissue alone, should be the main focus of interventions aimed at reducing frailty and mobility limitations in older women (8,34).

Previous investigations of the effects of AAS administration on strength, functional performance, and quality of life are inconclusive (32,33,42). Muscle strength is multifactorial, with muscle mass being only one variable that can influence strength. Other factors such as neural drive (recruitment), fiber type composition, motor unit innervations/denervation, and fat and collagen infiltration of skeletal muscle, among others, are all factors that can contribute to muscle function (22). After 12 wk of resistance training initiation, improvements in strength are largely attributable to neurogenic factors rather than changes in muscle mass itself (13). Thus, it is likely that this potent effect of PRT was largely responsible for the functional benefits observed in

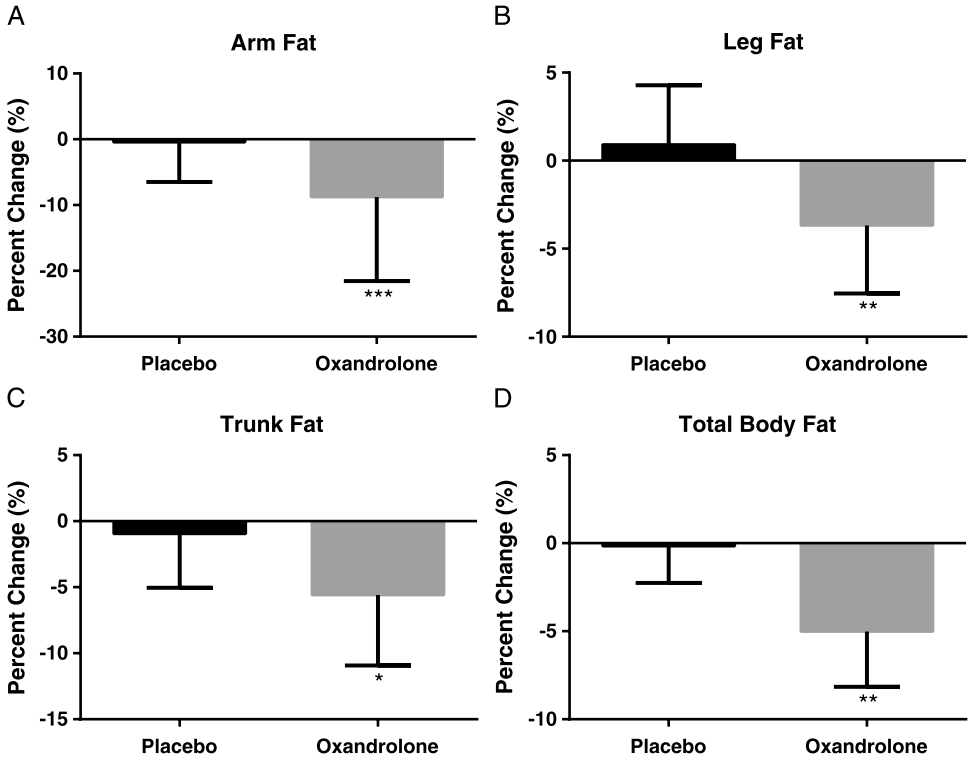

FIGURE 3—Percent changes in fat tissue. Data are presented as mean percent change (%) ± SD. Participants receiving the placebo are denoted by the *black bars*, whereas participants receiving oxandrolone are denoted by the *gray bars*. *$P \leq 0.05$, **$P \leq 0.01$, and ***$P \leq 0.001$.

this 12-wk study. Future trials over 6–12 months could perhaps identify the contributions of changes in body composition with anabolic hormone administration to long-term functional performance.

Oxandrolone, like other AAS, has the potential to cause hepatotoxic effects, with unfavorable alterations to HDL and LDL cholesterol as well as increases in ALT and AST among the two most common (25). Consistent with this, administration of oxandrolone was associated with reducing HDL cholesterol below normal range and increasing ALT, with a trend to increasing AST above normal limits (Table 2; See Table, Supplemental Digital Content 4, Incidence of abnormal liver function test results, http://links.lww.com/MSS/A543). These hepatotoxic/metabolic effects, as well as the other

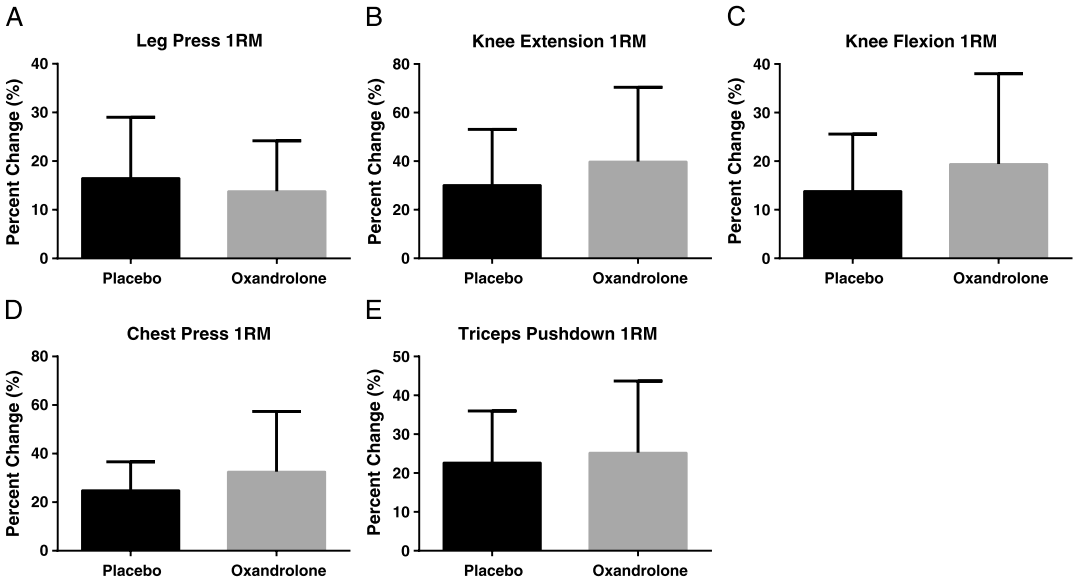

FIGURE 4—Percent changes in strength. Data are presented as mean percent change (%) ± SD. Participants receiving the placebo are denoted by the *black bars*, whereas participants receiving oxandrolone are denoted by the *gray bars*. No differences were observed between groups for changes in strength ($P > 0.05$).

possible side effects of oxandrolone, must be considered before therapeutic administration, especially as there are limited data on the long-term effects of oxandrolone administration (>12 wk). Importantly, however, no participants receiving oxandrolone were required to stop their therapy because of elevations of laboratory values, no clinical evidence of hepatoxicity was present in any individual (Fig. 1), and no other serious adverse events were reported (see Table, Supplemental Digital Content 3, Adverse events, http://links.lww.com/MSS/A542).

There are some limitations to this study. Without the use of a no-treatment control group and one receiving oxandrolone only, it is impossible to determine whether oxandrolone alone could increase muscle strength or functional performance in this particular cohort of older frail women. Oxandrolone administration has been shown to elicit gains in strength (33), and thus, appropriately designed studies are warranted to investigate whether administration of oxandrolone alone is sufficient to increase muscle strength in older frail women. In addition, a disproportionate increase in total body water compared with DXA-derived increase in lean tissue has been noted with oxandrolone administration (33), and this could affect DXA-derived lean tissue estimates (37). Furthermore, DXA is unable to quantify visceral versus subcutaneous abdominal fat, and thus, image analysis techniques such as computed tomography scanning or magnetic resonance imaging would be needed to determine specific oxandrolone-induced changes in these compartments relative to PRT, which has been associated with reductions in visceral fat (15). As noted earlier, there is evidence that androgen therapy may actually *increase* visceral fat (6,17), which, in addition to the decreases in HDL cholesterol we and others (25) have noted, would constitute an overall unfavorable change in metabolic profile despite lean tissue gains.

In conclusion, 12 wk of PRT in combination with 10 $mg \cdot d^{-1}$ of oxandrolone significantly improved body composition in older women with early signs of frailty. Specifically, gains in lean tissue and reductions in fat mass were observed after oxandrolone administration compared with a placebo. Despite these improvements in body composition, there was no additive benefit to strength, power, or functional outcomes, with similar robust improvements observed in women from both groups undertaking high-intensity PRT.

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The results of the present study do not constitute endorsement by the American College of Sports Medicine.

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