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Androgen therapy improves muscle mass and strength but not muscle quality: results from two studies

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Schroeder, E. Todd, Michael Terk, and Fred R. Sattler. Androgen therapy improves muscle mass and strength but not muscle quality: results from two studies. *Am J Physiol Endocrinol Metab* 285: E16–E24, 2003. First published March 11, 2003; 10.1152/ajpendo.00032.2003.—The relationship of strength to muscle area was used to assess change in muscle quality after anabolic interventions. *Study 1*: asymptomatic human immunodeficiency virus-positive men (39 ± 9 yr) were randomized to nandrolone (600 mg/wk) ± resistance training (RT). *Study 2*: older healthy men (72 ± 5 yr) were randomized to oxandrolone (20 mg/day) or placebo. Maximum voluntary strength was determined by the 1-repetition maximum (1-RM) method for leg press, flexion and extension, and cross-sectional area of leg muscles by MRI. From *study week 0* to *study week 12*, muscle quality was unchanged with nandrolone, oxandrolone, or oxandrolone placebo, respectively, for total thigh muscles (1.23 ± 0.012 vs. 1.27 ± 0.29 kg/cm^2; 9.0 ± 1.1 vs. 8.9 ± 1.2 N/cm^2; 8.9 ± 1.2 vs. 8.9 ± 1.9 N/cm^2) and hamstrings (0.41 ± 0.08 vs. 0.43 ± 0.07 kg/cm^2; 0.90 ± 0.14 vs. 0.95 ± 0.016 N/cm^2; 0.94 ± 0.23 vs. 0.93 ± 0.21 N/cm^2). Lower-extremity 1-RM strength increased several times greater with RT+nandrolone (51–63% increases) than with nandrolone alone (4.7–16%), despite similar increases in muscle area; therefore, muscle quality increased from 1.13 ± 0.17 to 1.51 ± 0.18 kg/cm^2 (+36 ± 19%; $P < 0.001$) for total thigh muscle, 0.37 ± 0.10 to 0.53 ± 0.08 kg/cm^2 (+49 ± 39%; $P < 0.001$) for hamstrings, and 0.73 ± 0.19 to 1.07 ± 0.16 kg/cm^2 (+55 ± 36%; $P < 0.001$) for quadriceps. Thus androgen therapy alone did not improve muscle quality, but the addition of RT to nandrolone produced substantive improvements.

nandrolone decanoate; oxandrolone; resistance training; magnetic resonance imaging

IN POPULATIONS PRONE TO MUSCLE WASTING, such as those with human immunodeficiency virus (HIV) infection or who are aging, different anabolic strategies have been investigated to augment total lean tissue and skeletal muscle mass. These anabolic interventions have included androgen therapies (testosterone and semisynthetic derivatives of testosterone) (2, 17) and resistance training (4, 18, 33). There is compelling evidence that both types of interventions increase myofibrillar protein synthesis (10, 20, 39, 45, 47). Because maximum voluntary strength is proportional to skeletal muscle mass (26), it is not surprising that these strategies also augment skeletal muscle strength (4, 11, 14, 18). Moreover, recent data suggest that treatment with testosterone increases lean tissues and maximum voluntary strength in a dose-related manner in healthy volunteers (5), suggesting that the gains in strength may be directly proportional to change in skeletal muscle mass with this form of anabolic stimulus. However, with resistance training, there are theoretical reasons to expect that the relative gains in strength may be greater than the gains in muscle mass, possibly due to neuromuscular adaptations (19, 29, 32) or other factors (36).

Muscle quality is a quantitative concept to assess the relationship of skeletal muscle strength to muscle mass. Muscle quality is determined by calculating the ratio of skeletal muscle strength per unit of skeletal muscle (44, 46). Maximum voluntary strength is frequently measured using the one-repetition maximum (1-RM) method (12). Skeletal muscle mass may be quantified by determining cross-sectional area of muscle groups by using imaging procedures such as magnetic resonance imaging (MRI) (22, 28) or computed tomography (13, 21), of appendicular lean tissue by dual-energy X-ray absorptiometry (DEXA) (15, 25), or of muscle fiber area by histological staining of muscle tissue (35). As such, muscle quality may be used to determine whether increases in strength are proportional to increases in muscle mass (i.e., no change in muscle quality) or whether increases in strength are of greater magnitude than the relative increases in muscle mass (namely, improvements in muscle quality).

Improvements in muscle quality suggest that the muscle is capable of developing greater force relative to the size of the muscle. Enhancements in muscle quality indicate that there are factors contributing to the augmentation in strength that are beyond the gross increases in muscle size. Understanding the mechanisms whereby muscle quality is improved will be important in determining the most efficient anabolic interventions to improve physical function. In fact, an expert panel meeting at the National Institutes of Aging Workshop (Sarcopenia and Physical Performance in Old Age) in 1996 concluded that comprehensive eval-

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uations of age-related changes in muscle quality should be a top priority (9). Therefore, enhancing muscle quality should be of particular importance in populations (e.g., older persons or those with disabilities) in which the loss of muscle mass may result in decrements of physical function, frailty, risk of falls and bone fractures, and immobility and risk for pulmonary embolism, loss of independence, and thus declining overall health.

To better understand the influence of androgen therapy on muscle quality, we analyzed the data from two of our previous investigations, hypothesizing that resistance training will improve muscle quality, whereas androgen therapy alone will proportionally increase muscle size and strength with no change in muscle quality. From these studies, we previously reported that supplemental therapy with different semisynthetic testosterone derivatives (androgens) significantly augmented total and appendicular lean body tissue in two very different populations, namely, men infected with HIV (23, 33) and older individuals at risk for loss of skeletal muscle mass, which is referred to as sarcopenia (37). In each case, there were also significant increases in maximum voluntary strength. Therefore, the purpose of this investigation was to report the similar effects of these different androgens on muscle quality and to contrast those outcomes with the potential for improvements in muscle quality that may be achieved with resistance training.

METHODS

The data reported here are results from two studies, each using different androgens (nandrolone decanoate or oxandrolone) (33). Although the target populations differed (namely, HIV-positive men and healthy men >60 yr of age), the goals in both studies were to increase appendicular lean tissue and voluntary muscle strength. These studies were based on our hypotheses that supplemental androgen therapy would increase skeletal muscle mass and strength during chronic catabolic illness and aging, even in the absence of overt hypogonadism. Methods have been reported previously for the nandrolone study (33) and will be described only briefly. Approvals for these studies were obtained from the Institutional Review Board of the Los Angeles County-University of Southern California Medical Center. All subjects provided written informed consent.

Study 1: Nandrolone vs. Nandrolone plus Resistance Training in HIV-Positive Men

In this study, subjects were recruited from the greater Los Angeles area and were required to be asymptomatic, weight stable for the previous 6 mo (no weight change >5%), and to have plasma HIV RNA levels at screening of <30,000 copies/mm^3. Thirty HIV-seropositive men ≥18 yr of age with CD4 lymphocyte counts between 50 and 400/mm^3 were enrolled in the study.

The study was an open-label, prospective, controlled investigation in which all study subjects received nandrolone decanoate (Deca Durabolin; Organon, West Orange, NJ) by weekly intramuscular injections. The first dose was 200 mg, and the second dose was 400 mg to acclimate the subjects to the study therapy. The dose was 600 mg for *weeks 3–12*.

Strength training intervention. Study subjects were randomly assigned to receive 12 wk of progressive resistance training (PRT) or no exercise while receiving treatment with nandrolone. The PRT was performed with free weights and machines (ParaBody). The PRT included exercises for both the upper and lower body. Lower-body exercises were performed three times per week and included the leg press, leg extension, leg flexion, and calf raise. Subjects completed three sets of eight repetitions at 80% of the 1-RM, with the final set performed to failure. If a subject successfully accomplished 10 or more repetitions in the final set, the weight was increased 5% for the subsequent training session. Two-minute rest periods were allowed between sets. To ensure that the training intensity was maintained at 80% of the 1-RM, the subject's 1-RM strength was reassessed every 2 wk.

Study 2: Placebo Controlled Study of Oxandrolone in Older Men

The oxandrolone study was a double-blind study that randomized older men 60–85 yr of age to either the licensed dose of oral oxandrolone (Oxandrin; BTG, Iselin, NJ) at 20 mg/day or matching placebo in a 2:1 manner for 12 wk. To be eligible for this study, subjects had to have a body mass index ≤35 kg/m^2, blood pressure <180/95 mmHg, prostate-specific antigen (PSA) <4.1 ng/ml, serum hematocrit ≤50%, alanine aminotransferase less than three times the upper limit of normal, and serum creatinine <2 mg/dl. Subjects with untreated endocrine abnormalities (e.g., diabetes, hypothyroidism), active inflammatory conditions, or cardiac problems in the preceding 3 mo (heart failure, myocardial infarction, or angina) were excluded. An incremental treadmill exercise test with 12-lead electrocardiographic and blood pressure monitoring was administered before resistance exercise testing to identify exercise-induced ischemia, abnormalities in cardiac rhythm, or abnormal blood pressure responses.

Common Testing Procedures for Both Studies

Muscle strength evaluation. Muscle strength was assessed using the 1-RM method (12) at baseline and *study week 12* in the two studies. Before strength testing, subjects warmed up on a cycle ergometer or by walking for 5 min. The 1-RM was defined as the greatest resistance that could be overcome through a defined range of motion using proper technique. In the nandrolone study, 1-RM strength was determined for all PRT exercises including the bilateral leg press, leg extension, and prone leg flexion exercises, as well as upper-body exercises using free weights. In the oxandrolone study, lower-extremity 1-RM strength (in newtons or pounds) was determined for the bilateral leg press and leg flexion exercises on Keiser A-300 pneumatic equipment (Keiser, Fresno, CA) twice within 1 wk before initiating study therapy to accommodate familiarization and learning of the testing procedures. The greatest 1-RM measured for each exercise during the two testing sessions was used as the baseline value for maximal voluntary muscle strength.

Muscle cross-sectional area. In the nandrolone study, cross-sectional area (CSA) of the right thigh muscles was assessed by MRI with a 1.5-T scanner (Philips ACS II, Shelton, CT) at baseline and *study week 12*. Imaging was performed by using sequence gradient echo recall scans to determine thigh muscle areas. Seven serial slices were obtained, with one at the juncture of the middle and proximal third of the femur and three adjacent slices both proximal and distal to that position. The following parameters were used to acquire images: time to repeat (TR) = 823 ms; time to echo (TE) = 19 ms; flip angle = 35°; field of view (FOV) = 20

cm; matrix size = 256 × 205; and a 6-mm slice thickness with a 1.5-mm gap. In the oxandrolone study, change in muscle CSA was assessed from images obtained using a 1.5-T GE Signa-LX MRI scanner, with the body coil serving as both transmitter and receiver. Nine axial images of the thigh were obtained after a T1-weighted coronal scout image using T1-weighted TR/TE 300/TE. The slice thickness was 7.5 mm with a 1.5-mm gap. The FOV was 24 × 24 cm with a 254 × 128 matrix. One signal average was used.

To determine CSA (cm^2) of thigh muscles in the two studies, the juncture of the proximal and middle thirds of the femur was chosen for analysis, because greater relative increases in CSA of the proximal quadriceps have been reported after anabolic interventions (30). Areas of intramuscular fat, bone, and major arteries, veins, and nerves were subtracted (using either 4.4 Gyroview, version 2.1–2, Philips Medical Systems, for the nandrolone study or Scion Image, version Beta 4.0.2, Scion, for the oxandrolone study) before calculation of muscle areas by setting threshold values on the basis of signal amplitude. This allowed adipose tissue to be differentiated from other more dense tissue. Once the threshold values were established, lean tissue (muscle, nerve, and blood vessels) and fat displayed signal strength above and below the threshold, respectively. Area of the femur, nerve tissue, and blood vessels were removed manually by digitizing the circumference of those areas and deleting with the software. After isolation of the total thigh muscle CSA, quadriceps CSA and hamstrings CSA were calculated by manually dividing the thigh into two compartments through the facial plane. The same blinded investigator (E. T. Schroeder) performed the analyses, and a <1% coefficient of variation for repeated measures was determined for total thigh CSA by reanalyzing 13 subjects (pre and post) in each study on three separate occasions.

Muscle quality. Muscle quality for the lower extremity was calculated by dividing maximal voluntary strength (in either kg or N) for the leg press, leg flexion, and leg extension exercises by the CSA in square centimeters for the total thigh, hamstrings, and quadriceps muscle groups, respectively. Muscle quality was defined in this manner to match most closely the CSA of the involved muscles that would primarily be responsible for the specific movement (exercise). Only the nandrolone study included all three lower-extremity tests of strength and therefore has three different muscle quality calculations. The oxandrolone study included tests of strength for the leg press and leg flexion exercises and therefore has two muscle quality calculations.

DEXA. Whole body DEXA scans (Hologic QDR-4500, version 7.2 software, Waltham, MA) were performed at baseline and *study week 12* to assess lean tissue and fat mass. One experienced technician (blinded to subject identification and date of exam) performed and analyzed the scans. The coefficients of variation in study subjects for repeated measures of lean tissue and fat were <1% as determined by reanalyzing all scans (pre and post) in each study on two separate occasions.

Statistical considerations. Both studies were adequately powered to demonstrate significant differences between the study interventions in total lean body mass (LBM) by DEXA and maximum voluntary skeletal muscle strength (33, 37). All statistical comparisons were made with respect to each individual study, with no comparisons made between studies. Results were analyzed using the Statistical Package for Social Sciences (SPSS) version 10.0 software (SPSS, Chicago, IL). Baseline characteristics and change from baseline to *study week 12* were compared between groups for each respective study (nandrolone to nandrolone plus PRT, oxandrolone to placebo) by utilizing independent *t*-tests. Within-group changes were evaluated using paired *t*-tests. A bidirectional α-level of significance was set at $P < 0.05$ for all measures.

RESULTS

In the nandrolone study, 5 of the 30 subjects missed their scheduled appointments for MRI, and because of limited access they were not rescheduled; two additional subjects could not undergo MRI due to claustrophobia. However, these seven subjects completed all of the strength testing and training sessions and were in no way different at baseline from the subjects undergoing paired MRI testing. Moreover, as shown in Fig. 1, the relative change in lower-extremity strength of the 30 subjects was of similar magnitude to the change in strength for the subset of 23 subjects (Fig. 2) who completed both MRI and strength measurements at

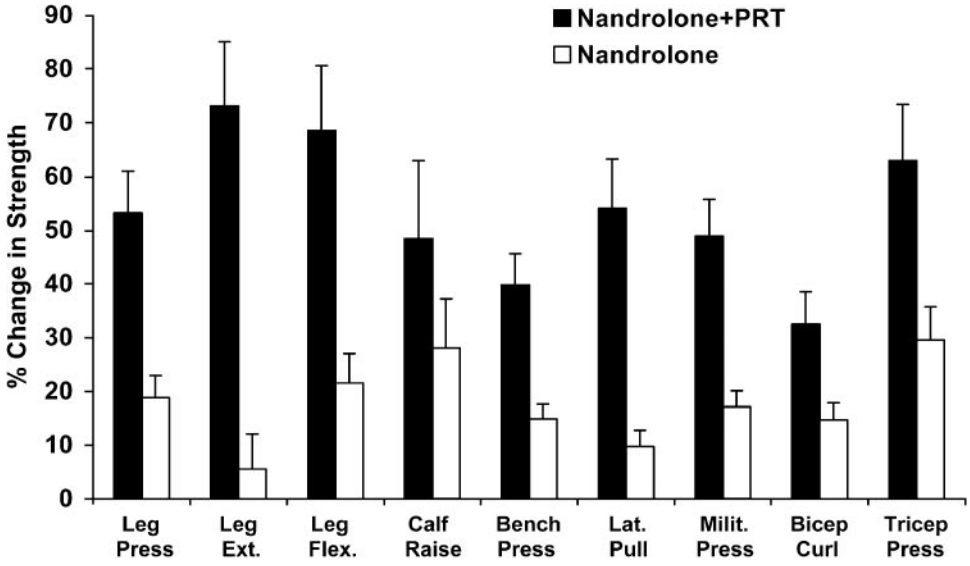

Fig. 1. Relative (%) change from baseline to *study week 12* in one-repetition maximum (1-RM) strength for the nandrolone-only (open bars; $n = 15$) and nandrolone plus progressive resistance training (PRT; solid bars; $n = 15$) groups. Within-group increases for 1-RM strength were significantly different (each $P < 0.001$) from baseline for both interventions, except for leg extension in the nandrolone-only group ($P = 0.38$). Increases in strength for the nandrolone plus PRT group were significantly greater ($P < 0.001$ for each comparison) than changes in the nandrolone-only group. Values are means ± SE.

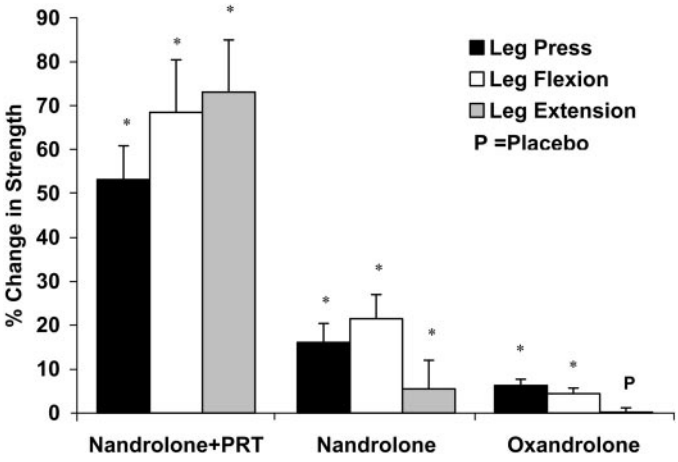

Fig. 2. Relative (%) change from baseline to *study week 12* in 1-RM strength for the leg press (solid bars), leg flexion (open bars), and leg extension (gray bars) exercises. P represents the placebo group (cross-hatched bars) for the oxandrolone study. Values are means ± SE. *Significant ($P \leq 0.035$) increase from baseline.

baseline and *study week 12* for determining muscle quality.

In the oxandrolone study, 3 of the 33 subjects could not complete all of the strength measurements at *week 12*. Therefore, 30 subjects in the oxandrolone study completed the MRI and strength measurements necessary to calculate muscle quality at both baseline and *study week 12*. Table 1 shows the baseline characteristics for subjects in the nandrolone and oxandrolone studies. There were no differences between the randomized intervention groups within either study ($P > 0.05$) for all comparisons.

In both studies, there were no new or worsening urinary symptoms, change in PSA for the older men, increases in blood pressure, occurrence of edema, onset of cardiorespiratory symptoms, or change in blood urea nitrogen (data not shown).

Changes in Body Composition

In the two studies, the primary outcome was change in LBM. In both studies, the groups receiving androgen therapy demonstrated significant changes in total LBM over 12 wk. In the nandrolone study, LBM increased by 3.9 ± 2.3 kg in the group randomized to receive only nandrolone ($P < 0.001$) and by 5.2 ± 5.7 kg in the group randomized to nandrolone plus PRT ($P < 0.001$). Moreover, the change in LBM with PRT was greater than without PRT ($P = 0.03$). In the oxandrolone study, total LBM increased by 3.0 ± 1.5 kg for subjects randomized to oxandrolone ($P < 0.001$) and by 0.1 ± 1.5 kg in the group randomized to placebo ($P = 0.63$), which was significantly different from the change in the oxandrolone group ($P < 0.001$).

Changes in Maximal Voluntary Muscle Strength

In the nandrolone study, maximal voluntary muscle strength by 1-RM increased significantly with both interventions (nandrolone alone and nandrolone plus PRT) after 12 wk for all strength tests, with the exception of the leg extension exercise in the nandrolone-only group, which showed no improvement ($P = 0.38$; Table 2 and Fig. 1). Increases in strength for various upper- and lower-body muscle groups ranged from 10.3 to 31.0% in the nandrolone-only group; however, improvements ranged from 14.4 to 53.0% in the nandrolone plus PRT group ($P < 0.006$ for all comparisons between groups). The gains in strength were not only significantly greater ($P < 0.005$) with PRT, but for many of the strength tests, the improvements were several orders of magnitude greater for the PRT group, as shown in Fig. 1. Figure 2 illustrates the proportionally greater increases in lower-extremity strength in the nandrolone plus PRT group compared with the groups that received androgen only in both studies.

Table 1. *Baseline characteristics of study groups*

	Nandrolone		Oxandrolone	
Dose of Androgen:	600 mg/wk	600 mg/wk + PRT	Placebo	20 mg/day
Treatment Duration:	12 wk	12 wk	12 wk	12 wk
No. of subjects	12	11	9	21
Age, yr	38 ± 9	39 ± 8	71.5 ± 3.2	73.3 ± 7.2
Weight, kg	73.3 ± 6.5	70.9 ± 11.1	86.6 ± 9.3	83.5 ± 12.9
BMI, kg/m^2	24.9 ± 2.2	23.9 ± 2.4	29.1 ± 2.9	27.3 ± 3.6
Laboratory tests				
Hemoglobin, g/dl	14.8 ± 1.3	14.3 ± 1.5	14.6 ± 0.7	14.6 ± 1.1
Creatinine, mg/dl	1.0 ± 0.2	1.0 ± 0.2	1.2 ± 0.4	1.2 ± 0.2
Albumin, g/dl	4.5 ± 0.4	4.6 ± 0.4	4.2 ± 0.2	4.0 ± 0.2
ALT, U/l	30 ± 15	42 ± 29	38 ± 4	38 ± 7
PSA, ng/dl	NT	NT	1.3 ± 0.8	2.4 ± 1.1*
Body composition				
Total LBM, kg	58.7 ± 4.5	54.0 ± 7.3	58.3 ± 5.9	56.5 ± 5.6
Extremity LBM, kg	23.7 ± 3.4	22.7 ± 3.5	25.0 ± 2.8	24.5 ± 2.4
Fat mass, kg	13.2 ± 3.3	12.6 ± 5.0	23.7 ± 4.4	23.5 ± 7.7
%Fat	17.6 ± 3.3	17.9 ± 4.9	27.9 ± 3.4	27.8 ± 5.6

Values are means ± SD. PRT, progressive resistance training; BMI, body mass index; ALT, alanine aminotransferase; PSA, prostate-specific antigen; LBM, lean body mass; NT, not tested. Body composition variables were measured by dual-energy X-ray absorptiometry (DEXA). *Significantly different from placebo ($P < 0.01$).

Table 2. *Changes in muscle strength, cross-sectional area, and muscle quality in the nandrolone study*

	Nandrolone (n = 12)		Nandrolone + PRT (n = 11)	
	Baseline	*Week 12*	Baseline	*Week 12*
Muscle strength, kg				
Leg press	162.4 ± 23.2†	188.2 ± 23.0*	135.6 ± 25.0	204.9 ± 36.1*
Leg extension	62.6 ± 4.7	66.2 ± 5.1	48.2 ± 4.0‡	76.7 ± 3.9*
Leg flexion	26.0 ± 1.6	31.0 ± 1.6*	23.0 ± 1.7	35.9 ± 1.8*†
CSA, cm^2				
Total thigh	132.9 ± 16.8	148 ± 20.2*	120.0 ± 13.8	135.1 ± 14.7*
Quadriceps	68.7 ± 9.1	75.8 ± 9.8*	62.3 ± 7.7	69.5 ± 7.3*
Hamstrings	63.7 ± 9.2	72.2 ± 11.9*	57.4 ± 7.5	65.5 ± 8.3*
Muscle quality, kg/cm^2				
Total thigh	1.23 ± 0.12	1.27 ± 0.29	1.13 ± 0.17	1.51 ± 0.18*
Quadriceps	0.93 ± 0.24	0.88 ± 0.25	0.73 ± 0.16‡	1.07 ± 0.16*†
Hamstrings	0.41 ± 0.08	0.43 ± 0.07	0.37 ± 0.10	0.53 ± 0.58*†

Values are means ± SD. Changes in muscle strength were assessed by one-repetition maximum (1-RM) method. CSA, cross-sectional area. *Significantly different from baseline, $P < 0.001$; †significantly different from nandrolone-only group at *week 12*, $P < 0.001$; ‡significantly different from nandrolone-only group at baseline, $P < 0.05$.

In the oxandrolone study, maximal voluntary muscle strength increased significantly ($P \leq 0.003$) in the group receiving androgen for the leg press (6.3 ± 6.6%) and the leg flexion (6.3 ±8.3%) exercises after 12 wk of study therapy (Fig. 2). These changes in strength were significantly different ($P \leq 0.035$) from the absence of change in the placebo group (Table 3).

Changes in Muscle CSA

The absolute increase in muscle CSA was significant ($P < 0.001$) in both studies (Tables 2 and 3) for subjects receiving androgen. In the nandrolone study, the relative within-group increase in muscle CSA of the total thigh was 11.6 ± 5.6 and 12.7 ± 1.5% ($P < 0.001$ for each comparison), and these increases were of similar magnitude ($P = 0.61$) in the nandrolone and nandrolone plus PRT groups, respectively (Fig. 3). The lack of difference in muscle CSA between these two groups contrasts remarkably with the appreciably greater gains in maximal voluntary strength in the group undergoing PRT.

Similarly, after 12 wk of study therapy with oxandrolone, the relative increase in muscle CSA of the total thigh was 8.7 ± 6.5% ($P < 0.001$; Fig. 3), which was significantly different ($P = 0.004$) from the absence of change (1.1 ± 5.4%) within the group randomized to placebo ($P = 0.57$; Table 3).

Changes in Muscle Quality

Muscle quality did not significantly improve in the nandrolone-only group or for study subjects receiving oxandrolone or placebo ($P > 0.20$; Table 3 and Fig. 4). Muscle quality improved significantly ($P < 0.001$) for leg press strength relative to total thigh muscle CSA (35.6 ± 19.5%), leg extension strength relative to quadriceps muscle CSA (55.1 ± 36.4%), and leg flexion strength relative to hamstrings muscle CSA (48.5 ± 38.8%) only in the nandrolone plus PRT group (Fig. 4).

DISCUSSION

We and others have used muscle quality to assess the relationship of the force-generating capacity of muscle contraction against resistance per unit of muscle on the basis of high-resolution imaging procedures (8, 44, 46). Muscle force is often determined by assessing maximal voluntary strength for a particular movement, because it is difficult to isolate individual muscle groups for strength assessment. Moreover, maximal voluntary strength represents changes in agonistic,

Table 3. *Changes in muscle strength, cross-sectional area, and muscle quality in the oxandrolone study*

	Placebo (n = 9)		Oxandrolone (n = 21)	
	Baseline	*Week 12*	Baseline	*Week 12*
Muscle strength				
Leg press, N	1,250 ± 213	1,250 ± 210	1,225 ± 156	1,332 ± 218*
Leg flexion, kg	66.5 ± 12.5	68.1 ± 13.2	68.2 ± 11.1	72.6 ± 13.2†
CSA, cm^2				
Total thigh	140.4 ± 18.8	141.6 ± 20.5	138.0 ± 14.1	149.8 ± 15.7*
Quadriceps	69.7 ± 11.7	68.3 ± 12.5	68.3 ± 8.3	73.1 ± 7.9*
Hamstrings	70.7 ± 10.0	73.3 ± 9.3	69.6 ± 7.4	76.8 ± 9.9*
Muscle quality, kg/cm^2				
Total thigh	8.9 ± 1.2	8.9 ± 1.9	9.0 ± 1.1	8.9 ± 1.2
Hamstrings	0.94 ± 0.23	0.93 ± 0.21	0.90 ± 0.14	0.95 ± 0.16

Values are means ± SD. Significantly different from baseline, *$P < 0.001$; significantly different from placebo, †$P < 0.005$.

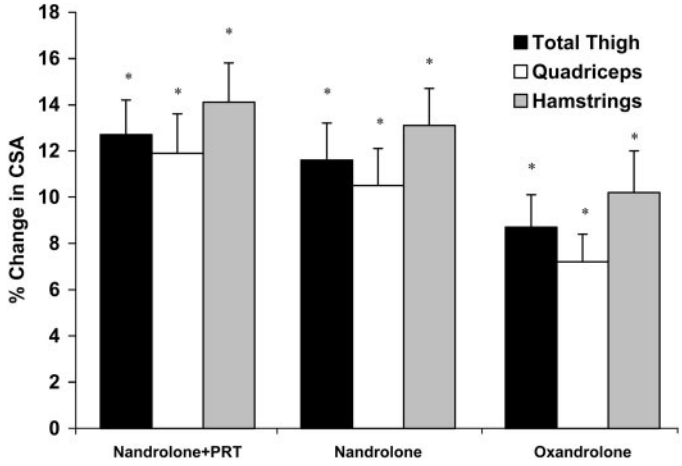

Fig. 3. Relative (%) change from baseline to *study week 12* in cross-sectional area (CSA) assessed by MRI for the total thigh muscle (solid bars), quadriceps muscle (open bars), and hamstrings muscle (gray bars). Values are means ± SE. *Significant ($P < 0.001$) increase from baseline.

synergistic, and antagonistic muscle groups as well as in neuronal effects that may result from study interventions. In contrast, muscle specific tension is a more exact construct that measures the maximal force that can be generated by a single muscle fiber in ex vivo experiments (43). Regardless, assessing muscle quality provides a convenient and important clinical means to determine the magnitude of change in maximal voluntary muscle strength relative to the change in gross muscle size or mass.

Our pilot studies tested two very different androgens, namely, a parenteral androgen (nandrolone decanoate) with direct systemic effects and an oral androgen (oxandrolone) that undergoes first-pass effects in the liver. Moreover, the populations differed greatly in that nandrolone was tested in middle-aged men with chronic catabolic illness due to HIV, whereas oxandrolone was tested in relatively healthy older men who by age alone have lost muscle mass, albeit the mechanisms for sarcopenia in the latter population probably vary from individual to individual. It is also likely that the eating habits and levels of activity and exercise differed in the study populations. Thus there are a number of reasons that the two populations might respond differently to androgen therapy. Notwithstanding these limitations, the most important observation of these two pilot studies was that supplemental androgen therapy did not improve muscle quality despite statistically significant increases in maximal voluntary muscle strength and CSA of large muscle groups of the leg in both projects.

The absence of improvements in muscle quality after therapy with either nandrolone or oxandrolone alone provides important information for determining the optimal anabolic intervention for enhancing physical function. It is well established that supplemental therapy with androgens can increase myofibrillar protein synthesis (10, 39, 45), contributing to increased muscle mass and strength in men with hypogonadism (3, 6) and during illness (4, 18, 33). In our studies, supplemental androgen alone significantly increased muscle mass and strength, as reported by others (10, 18, 38, 41, 42), but the increments were of modest magnitude despite pharmacological dosing with both agents. However, initial treatment with an androgen may be a means to quickly and effectively enhance muscle size and strength in persons with illness or sarcopenia resulting in significantly impaired physical function. For example, a short course of androgen therapy in persons too weak or frail (e.g., those who are older or those with HIV or cancer) to initially participate in resistance training might be suitable for augmenting muscle mass and strength, with the goal of transitioning to a safer and more efficient anabolic strategy (i.e., resistance training) that would enhance muscle quality. Also, for some individuals with frailty, resistance training may be too taxing, and some may not have the motivation, access, or other resources to participate.

However, even a short course of androgen therapy has potential limitations. Although testosterone and 17-beta esterified parenteral androgens (e.g., nandrolone) have only modest effects on blood lipids that are largely limited to changes in HDL cholesterol (34, 40), the 17-alkylated derivatives (e.g., oxandrolone) used for oral therapy also increase total and LDL cholesterol (1, 16). Moreover, the long-term safety of any androgen for prostate health (namely, risks for obstructive uropathy and cancer) in older men has not been demonstrated. Thus available androgens are not ideally suited for prolonged therapy. With these uncertainties about safety, the demonstration that androgens do not increase muscle quality provides additional impetus to study other anabolic stimuli. Selective androgen receptor modulators that spare effects on the prostate but have preferential anabolic properties are thus potentially more attractive than available androgens as therapeutic agents for age-related sarcopenia. The effects of these new agents on muscle quality will have to be determined.

By contrast to the effects of androgen therapy alone, the addition of PRT to nandrolone resulted in remark-

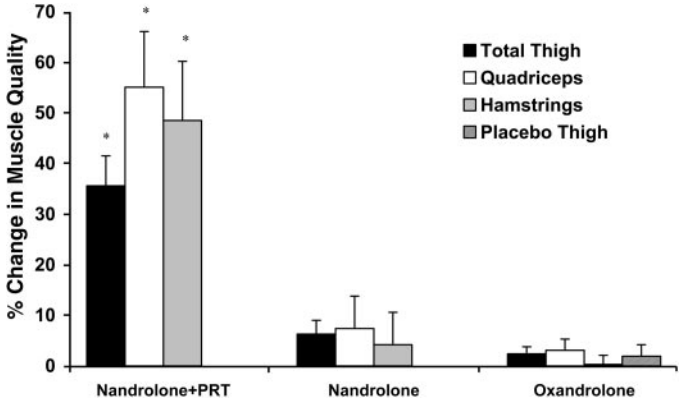

Fig. 4. Relative (%) change from baseline to *study week 12* in muscle quality (MQ, strength in kg/CSA in cm^2) for total thigh MQ (solid bars), quadriceps MQ (open bars), hamstrings MQ (gray bars), and the oxandrolone placebo group (cross-hatched bar). Values are means ± SE. *Significant ($P < 0.001$) increase from baseline.

able 36–55% improvements in muscle quality, suggesting that muscle strength increased to a greater magnitude relative to the increases in muscle CSA. These improvements in muscle quality were similar to or greater than those reported previously, of 14–32%, in persons participating in studies using resistance training as the sole anabolic intervention (44, 46). Moreover, enhancements in muscle quality have been reported to occur after resistance training in both young (7, 8, 19, 46) and older men (19, 44, 46), indicating that resistance training is highly efficient in augmenting strength beyond the gains expected from improvements in muscle mass per se and that the effects are not limited by aging. Therefore, if the goal is to maximize voluntary muscle strength, and by inference to improve physical function in subjects who are frail, resistance training compared with androgen therapy appears to produce significantly greater affects on strength relative to the change in muscle CSA. However, it remains to be determined whether the potential for improvement in muscle quality with the same training stimulus is similar in younger and older persons.

Previous investigations of resistance training (11, 14, 44, 46) reported similar (5–15%) increases in thigh muscle CSA compared with the 11–14% increases demonstrated in our nandrolone study. Surprisingly, our study group that received only nandrolone had very similar increases in muscle CSA compared with the group that received nandrolone in combination with PRT. Therefore, it appears that these two anabolic stimuli may affect muscle tissue by different mechanisms, because the group receiving PRT demonstrated considerably greater increases in strength. One possible mechanism would be enhanced myofibrillar packing (31). If greater muscle fiber contractile proteins occupy a given area, theoretically the muscle could produce more force per unit of muscle. In fact, greater packing of myofilaments may occur with fiber hypertrophy in pennated muscle due to increased packing of contractile elements along the muscle tendon (24, 30). It is also possible that PRT, unlike androgens, enhances neuronal mechanisms (19, 29, 32). Neuromuscular adaptations may result from increased motor unit recruitment and firing frequency, increased activation of synergistic muscles, or inhibition of the antagonist muscles. Such adaptations with resistance training may result in substantial increases in strength with minimal increases in muscle CSA (32). A third possibility may be the increase in proportion or CSA of type II muscle fibers compared with type I fibers that may occur with resistance training (27), since type II fibers are capable of generating greater force.

Thus, as an anabolic intervention, PRT has a number of potential advantages over androgen supplementation. First, the results of our study and those of other investigators indicate that PRT is a highly efficient means to increase skeletal muscle strength in certain populations. Second, the long-term safety of androgen supplementation in nonhypogonadal men has not been demonstrated in randomized controlled studies, making these agents undesirable for long-term therapy. Therefore, understanding how PRT increases muscle quality will be important in designing treatment strategies for prevention and treatment of muscle wasting and sarcopenia.

There were several limitations related to our studies. First, we did not include a resistance training-only intervention in the nandrolone study. The addition of a resistance training arm would have provided information about the potential of this intervention per se to augment muscle quality in HIV-positive men. However, other studies showing significant increases in muscle quality with PRT alone (7, 8, 19, 44, 46) support our contentions about the value of PRT in improving muscle quality. Second, it is possible that subclinical increases in extracellular water with androgen supplementation occurred despite the absence of overt change in mean blood pressure, occurrence of edema, decreases in blood urea nitrogen, and the like. Artificially increasing muscle CSA could have obscured small but true increases in muscle quality that might have resulted from the androgens. We doubt that excess hydration greatly affected measures of muscle quality on the basis of lack of clinical evidence of increased volume status and the consistent findings of no change in muscle quality in either study despite significant gains in voluntary strength, which suggests that true hypertrophic effects with increases in CSA occurred in the muscles imaged by MRI. However, to refute this concern more definitively, future studies will need to assess changes in extracellular water by use of methods such as sodium bromide isotope dilution. Third, muscle quality of the upper extremity, also expected to be an important measure relative to physical function, may not directly parallel change in the lower extremities. Because we did not assess CSA of the upper arm by MRI, studies are needed to determine the effects of androgens and PRT on muscle quality of the upper-extremity muscle groups. Indeed, we have previously reported twofold greater increases in muscle mass of the upper vs. lower extremities in subjects receiving nandrolone with and without rigorous PRT for both upper- and lower-extremity muscle groups (23). Finally, similar investigations need to be conducted in women.

In summary, androgen therapy only modestly increased maximum voluntary strength and skeletal muscle mass and did not improve muscle quality in young men with chronic HIV infection or in relatively healthy older men. Of importance, the addition of PRT to nandrolone in the HIV population improved muscle quality of the lower extremity by as much as 55%. We believe that this is the first report of the effects of androgens on muscle quality in any population. Furthermore, PRT was responsible for substantial increases in maximal voluntary muscle strength (without greater increases in CSA) that were several orders of magnitude greater than in those subjects receiving only androgen supplementation. The mechanisms whereby muscle quality is enhanced remain unknown

but may be the result of muscle architectural changes (including myofibrillar packing), neuromuscular adaptations, alteration in the number or size of type II fibers, or a combination of factors. The optimal intervention and application for enhancing muscle quality in populations in which the loss of muscle mass may result in decrements of physical function, frailty, risk of falls and bone fractures, immobility, and risk for pulmonary embolism and loss of independence need further investigation.

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