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Effects of an oral androgen on muscle and metabolism in older, community-dwelling men

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Schroeder, E. Todd, Atam Singh, Shalender Bhasin, Thomas W. Storer, Colleen Azen, Tina Davidson, Carmen Martinez, Indrani Sinha-Hikim, S. Victoria Jaque, Michael Terk, and Fred R. Sattler. Effects of an oral androgen on muscle and metabolism in older, community-dwelling men. *Am J Physiol Endocrinol Metab* 284: E120–E128, 2003. First published September 24, 2002; 10.1152/ajpendo.00363.2002.—To determine whether oxymetholone increases lean body mass (LBM) and skeletal muscle strength in older persons, 31 men 65–80 yr of age were randomized to placebo (*group 1*) or 50 mg (*group 2*) or 100 mg (*group 3*) daily for 12 wk. For the three groups, total LBM increased by 0.0 ± 0.6, 3.3 ± 1.2 ($P < 0.001$), and 4.2 ± 2.4 kg ($P < 0.001$), respectively. Trunk fat decreased by 0.2 ± 0.4, 1.7 ± 1.0 ($P = 0.018$), and 2.2 ± 0.9 kg ($P = 0.005$) in *groups 1, 2,* and *3*, respectively. Relative increases in 1-repetition maximum (1-RM) strength for biaxial chest press of 8.2 ± 9.2 and 13.9 ± 8.1% in the two active treatment groups were significantly different from the change (−0.8 ± 4.3%) for the placebo group ($P < 0.03$). For lat pull-down, 1-RM changed by −0.6 ± 8.3, 8.8 ± 15.1, and 18.4 ± 21.0% for the groups, respectively (1-way ANOVA, $P = 0.019$). The pattern of changes among the groups for LBM and upper-body strength suggested that changes might be related to dose. Alanine aminotransferase increased by 72 ± 67 U/l in *group 3* ($P < 0.001$), and HDL-cholesterol decreased by −19 ± 9 and −23 ± 18 mg/dl in *groups 2* and *3*, respectively ($P = 0.04$ and $P = 0.008$). Thus oxymetholone improved LBM and maximal voluntary muscle strength and decreased fat mass in older men.

oxymetholone; androgen therapy; older men; sarcopenia; lean body mass

AGING IN HUMANS IS CHARACTERIZED by a number of anatomic and physiological changes, including the progressive loss of muscle mass (sarcopenia), which contributes to the sequential loss of voluntary skeletal muscle strength and physical function (1, 3, 12, 17, 22). When severe, these outcomes may result in disability, dependency, and depression (39, 41). At the same time, aging is associated with increased fat mass, particularly central adiposity, which increases the risk for insulin resistance, hypertension, dyslipidemia, impaired fibrinolysis, and the occurrence of gallstones (42). Cross-sectional (2, 35, 52) and longitudinal (20, 36) studies are in agreement that total and free testosterone concentrations decline with advancing age in men, although a causal relationship between levels of testosterone and changes in body composition, skeletal muscle strength, and metabolism has not been well established during aging. However, serum bioavailable testosterone concentrations have been shown to correlate with skeletal muscle mass and muscle strength in both African-Americans and Caucasians (4, 40). Results from another study suggest that free testosterone levels are also closely related to muscle mass in women during chronic illness (19).

Although a number of studies are in agreement that testosterone supplementation in healthy, young, hypogonadal men increases fat-free mass (6, 9, 24, 49, 56, 57), muscle size (6), and strength (6, 57), the effects of testosterone supplementation on muscle mass and performance have been less clear in older men (26, 37, 46, 50, 52, 53). Although several studies have reported increases in fat-free mass following testosterone replacement in older men with low or low normal testosterone concentrations (25, 50, 52), one study did not find any change in fat-free mass (46). Supporting the increase in fat-free mass is evidence suggesting that androgen supplementation increases synthesis of myofibrillar proteins in older persons (13, 55). However, the effects of testosterone supplementation on muscle strength in this population have been inconsistent (46, 50). On the basis of this background, we hypothesized that a course of androgen supplementation would increase muscle mass and maximum voluntary strength in older men at risk for sarcopenia. We also hypothesized that this intervention would decrease central adiposity (32, 33) and that changes in muscle mass, strength, and adipose tissue would be dose related on the basis of our recent studies in younger men (7).

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To test these hypotheses, we conducted a double-blind, placebo-controlled, proof-of-concept study by use of a convenient-to-administer potent oral androgen. The results indicated that muscle and adipose tissue in older individuals are responsive to supplemental androgen therapy and that adaptations in lean body mass (LBM) may change in a dose-related manner.

METHODS

Study Population

Men 65–80 yr of age were recruited from the Los Angeles communities surrounding the University of Southern California Health Sciences Campus and Charles Drew University of Medicine and Science. To be eligible for the study, subjects had to have a body mass index (BMI) <36 kg/m^2, blood pressure <160/95 mmHg, prostate-specific antigen (PSA) <4.1 ng/ml, serum hematocrit <50%, alanine aminotransferase (ALT) less than three times the upper limit of normal (ULN), 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. The institutional review boards of the Los Angeles County-USC Medical Center and Charles Drew University approved this study. All subjects provided written, informed consent.

Safety Monitoring

Complete blood counts, comprehensive chemistries with tests of renal and hepatic function, and prostatic specific antigen were measured at baseline and during *treatment weeks 6* and *12*. Liver test panels were also obtained at *weeks 3* and *9* in addition to the aforementioned time points.

Intervention

The study was a two-center, investigator-initiated, dose-ranging, double-blind, placebo-controlled trial. Subjects were randomized to receive oral doses of placebo, 50 mg of oxymetholone, or 100 mg of oxymetholone daily for 12 wk. To achieve blinding, the subjects received two placebo tablets, one placebo plus one 50-mg oxymetholone tablet, or two 50-mg oxymetholone tablets. Adherence was monitored by pill counting at each study visit.

Dual-Energy X-Ray Absorptiometry

Whole body dual-energy X-ray absorptiometry (DEXA) scans [Hologic QDR-4500, version 7.2 software (Waltham, MA) at both institutions] were performed at baseline and *study week 12* to assess lean tissue and fat mass. Two experienced technicians performed and analyzed the scans, one at each of the respective test sites. The coefficients of variation (CV) in study subjects for repeated measures of lean tissue and fat were <1%.

Regional Measures of Body Composition

Regional body composition was determined at only one of the centers. Change in appendicular (extremity) LBM and in trunk fat were assessed by DEXA. Change in muscle cross-sectional area (CSA) was assessed by magnetic resonance imaging (MRI). The MRI scans were performed using a 1.5-Tesla GE Signa-LX 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 field of view was 24 × 24 cm with a 254 × 128 matrix. One signal average was used.

To determine muscle CSA, the juncture of the proximal and middle thirds of the femur was chosen for analysis, as greater relative increases in CSA of the proximal quadriceps have been reported following resistance training (38). Areas of intramuscular fat, bone, connective tissue, and blood vessels were subtracted (4.4 Gyroview, version 2.1–2, Philips Medical Systems) before calculation of muscle areas. Setting threshold values based on signal amplitude allowed the various tissues to be segmentalized. Once the threshold values were established, lean tissue (muscle, connective tissue, and blood vessels) and fat displayed signal strength above and below the threshold, respectively. Area of the femur was removed manually by digitizing the circumference of the bone and deleting this area with the software. The same blinded investigator (E. T. Schroeder) performed the analyses, and the CV for repeated measures was <1%.

Muscle Strength Evaluation

Before strength testing, subjects warmed up on a cycle ergometer or by walking for 5 min. Strength was determined for the bilateral leg press, seated biaxial chest press, and lat pull-down exercises. Subjects performed five repetitions of the test exercises at 50 and 75% of their projected maximal strength on Keiser A-300 pneumatic equipment (at both test centers) or on lat pull-down machines. The lat pull-down machines used at the two sites had different pulley systems. Therefore, changes in strength were reported as relative (%) change. Maximum voluntary muscle strength was determined by the one-repetition maximum (1-RM) method (14), defined as the greatest resistance that could be overcome through the range of motion using proper technique. The 1-RM was determined for all exercises 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. The 1-RM for these exercises was assessed again during *study week 12*.

Nutritional Assessment

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

Measurement of Fasting Serum Lipids

Blood was collected after a 14-h overnight fast at baseline and during *study week 12* for plasma lipids. Plasma was analyzed for total cholesterol, HDL-cholesterol, and triglycerides by means of the Ortho/Vitros DTII system (Ortho Diagnostics, Rochester, NY) in the University of Southern

California General Clinical Research Center Core Laboratory (58). Plasma lipid concentrations in baseline and *week 12* samples for each subject were run in the same assay to eliminate the effects of interassay variation. The CVs for the three lipids were <4.5, <4.4, and <3.0%, respectively. LDL-cholesterol was calculated using the Friedewald equation (15).

Measurement of Fasting Blood Sugar and Insulin

Blood was collected after a 14-h overnight fast in pre-chilled heparinized tubes. Plasma was removed and frozen within 10 min of collection. Glucose was measured by the glucose oxidase method (YSI model 2300 STAT PLUS glucose analyzer, YSI, Yellow Springs, OH) with a CV of 2.5%. Insulin was measured by radioimmunoassay (Linco Research, St. Charles, MO), which had <0.2% cross-reactivity with proinsulin and a CV of 3.2%. Glucose and insulin concentrations from baseline and 12-wk tests for each subject were measured in the same assay to eliminate the effects of interassay variation.

To assess for insulin resistance, fasting insulin, the homeostasis model assessment of insulin resistance (HOMA-IR), and quantitative insulin sensitivity check index (QUICKI) were calculated, since these measures have been correlated with insulin sensitivity by the hyperinsulinemic euglycemic clamp (23, 28, 29). HOMA-IR is calculated as $[(I_f) \times (G_f)]/22.5$, where (I_f) is the fasting insulin level (μU/ml) and (G_f) is the fasting glucose level (mmol/l). QUICKI is calculated as $1/[\log (I_f) + \log (G_f)]$ (23).

Measurements of Testosterone

Total testosterone concentrations were measured by RIA, using iodinated testosterone as tracer (5, 7) (no. 07–189102; ICN Biomedical, Costa Mesa, CA). This assay has a sensitivity of 0.44 ng/dl and intra- and interassay CVs of 9.1 and 7.5%, respectively. Free testosterone levels were measured by equilibrium dialysis (47, 48). Two hundred microliters of serum were placed in the inner dialysis chamber and dialyzed against 2,400 μl of dialysis buffer that approximates protein-free human serum. Dialysis was performed overnight for 16 h at 37°C. The free testosterone concentration in the dialysate was measured by RIA with the use of ^{125}I-labeled testosterone. The sensitivity of the free testosterone assay was 0.6 ρg/ml, and the intra- and interassay CVs were 4.2 and 12.3%, respectively. We did not test for total and free testosterone levels at the end of the 12-wk treatment period, because semisynthetic androgens including oxymetholone cross-react in these assays for testosterone. Serum luteinizing hormone (LH) and sex hormone-binding globulin (SHBG) concentrations were measured by immunofluorometric assays (5, 7).

Statistical Considerations

On the basis of variance of body composition in different ethnic and racial populations (27) and the standard deviation (SD) of change in response to an anabolic agent used in one of our previous studies (44), we hypothesized that a 3.0-kg increase in total LBM with oxymetholone compared with placebo would be associated with an SD of change between 2.0 and 2.5 kg. We conservatively estimated that the common SDs could be in the order of 2.5–3.0. With a sample size of 20–24 in the combined oxymetholone group and 10–12 subjects in the placebo group, the statistical power (1-β) was 0.80 to 0.90 to detect differences at the $P < 0.05$ level when the average change in total LBM by DEXA between the active treatment group and placebo was ≥3 kg.

Data were entered into Excel spreadsheets, and 100% of the entries were quality checked. Results were analyzed using the Statistical Package for Social Sciences (SPSS) version 10.0 software (SPSS, Chicago, IL). Baseline characteristics and change from baseline at *study week 12* were compared among the groups by one-way analysis of variance (ANOVA). Bonferroni post hoc pairwise comparisons were made in the case of significant *F*-scores. Within-group changes were evaluated using paired *t*-tests. Variables whose distributions differed significantly from normal were analyzed using the nonparametric Kruskal-Wallis test. χ^2 Tests were used for categorical variables. A bidirectional α-level of significance was set at $P = 0.05$ for all measures. Summary statistics are reported in the tables and text as means ± 1 SD.

RESULTS

Subjects

Thirty-three subjects were enrolled and randomized to the three treatment arms. One subject elected not to participate after providing informed consent but received no study therapy. A second subject missed a majority of doses during the last 6 wk of study therapy and was not included in the analysis; all other subjects were adherent (97 ± 5.9%) based on pill counts. The remaining 31 men completed all phases of the study. The three study groups were not significantly different in their baseline characteristics, including age, weight, BMI, blood counts, chemistries, PSA, total and free testosterone, and fasting serum lipids (Table 1). The total daily energy, protein and macronutrient intake also did not differ significantly among the three treatment groups. Although BMI appeared greater in the 50-mg group, there was no relation by Spearman correlation analyses (*P* values of 0.22–0.90) between baseline BMI and changes in body composition or strength during the study (data not shown).

Body Composition Changes

Lean body mass. After 12 wk of treatment, total body weight changed little (−0.2 ± 1.1, 0.9 ± 2.0, and 1.5 ± 2.5 kg) in the placebo, 50 mg/day, and 100 mg/day groups, respectively, without significant within- or between-group changes. Total LBM increased significantly ($P < 0.001$) within the 50 mg/day and 100 mg/day groups (3.3 ± 1.2 and 4.2 ± 2.4 kg, respectively), and these increases in LBM in the two oxymetholone groups were each significantly ($P < 0.001$) different from the change (0.0 ± 0.6 kg) in the placebo group (Fig. 1).

Fat mass. Although there was no change in total fat mass in the group that received placebo for 12 wk (0.0 ± 1.0 kg), total fat mass decreased significantly ($P < 0.001$) in the 50 mg/day and 100 mg/day ($P \leq 0.001$) groups (−2.6 ± 1.2 and −2.5 ± 1.6 kg, respectively; Fig. 1). The absolute changes in trunk fat for the placebo, 50 mg/day, and 100 mg/day groups (0.2 ± 0.4, −1.7 ± 1.0, and −2.2 ± 0.9 kg, respectively) were significantly different from baseline only in the two oxymetholone treatment groups ($P = 0.018$ and $P = 0.005$). These changes in trunk and total fat mass were

Table 1. *Baseline characteristics of the study population*

	Placebo	50 mg/day	100 mg/day	*P* Value*
n	11	11	9	
Ethnicity				0.45
Non-Hispanic whites	9	9	9	
Hispanics	2	1	0	
African-Americans	0	1	0	
Age, yr	73 ± 4	71 ± 4	70 ± 4	0.25
Weight, kg	77.4 ± 9.2	86.1 ± 9.9	80.8 ± 10.8	0.14
BMI, kg/m^2	25.5 ± 2.4	28.1 ± 3.9	26.6 ± 2.9	0.18
Caloric intake, kcal/kg	28.9 ± 8.0	28.7 ± 8.0	26.7 ± 6.6	0.79
Intake of protein, g/kg	1.2 ± 0.3	1.2 ± 0.4	1.0 ± 0.3	0.37
Intake of carbohydrate, g/kg	3.7 ± 1.3	3.6 ± 1.1	3.5 ± 0.8	0.90
Hemoglobin, g/dl	14.7 ± 1.3	14.5 ± 0.8	14.9 ± 1.6	0.81
Creatinine, mg/dl	0.9 ± 0.2	1.0 ± 0.2	1.0 ± 0.2	0.63
Albumin, g/dl	4.0 ± 0.3	4.2 ± 0.3	4.2 ± 0.2	0.49
ALT, U/l	29 ± 10	30 ± 12	38 ± 12	0.22
PSA, ng/ml	1.8 ± 1.4	1.8 ± 0.9	1.9 ± 0.9	0.99
Total testosterone, μg/dl	382 ± 86	382 ± 79	360 ± 141	0.86
Free testosterone, pg/ml	24.9 ± 7.5	26.2 ± 5.2	22.6 ± 6.4	0.48
Luteinizing hormone, U/l	5.5 ± 4.7	8.4 ± 4.4	8.7 ± 13.7	0.65
Total cholesterol, mg/dl	176 ± 31	189 ± 22	177 ± 28	0.46
LDL-cholesterol, mg/dl	117 ± 25	130 ± 19	114 ± 24	0.26
HDL-cholesterol, mg/dl	38 ± 8	34 ± 10	42 ± 20	0.38
Triglycerides, mg/dl	103 ± 56	128 ± 45	105 ± 96	0.64
Fasting blood sugar, mg/dl	108 ± 28	92 ± 9	100 ± 17	0.20

Values for the 3 study groups are means ± SD; *n* = no. of subjects. BMI, body mass index; ALT, alanine aminotransferase; PSA, prostate-specific antigen. *One-way ANOVA across the three groups.

similar in the two active treatment groups ($P = 0.91$ and $P = 0.99$), indicating an absence of a dose-related response to the change in fat mass.

Appendicular body composition. The change in lower extremity lean tissue (primarily muscle) by DEXA was not significant for the three groups (0.1 ± 0.5, −0.2 ± 3.0, 1.0 ± 1.3 kg) after 12 wk of treatment ($P = 0.54$ by one-way ANOVA). However, upper-extremity LBM increased significantly and similarly in the 50 mg/day (0.7 ± 0.4 kg, $P = 0.017$) and 100 mg/day (0.7 ± 0.2 kg, $P = 0.002$; Fig. 2) groups. These changes were significantly different ($P = 0.005$) from those observed in the placebo group (0.0 ± 0.2 kg).

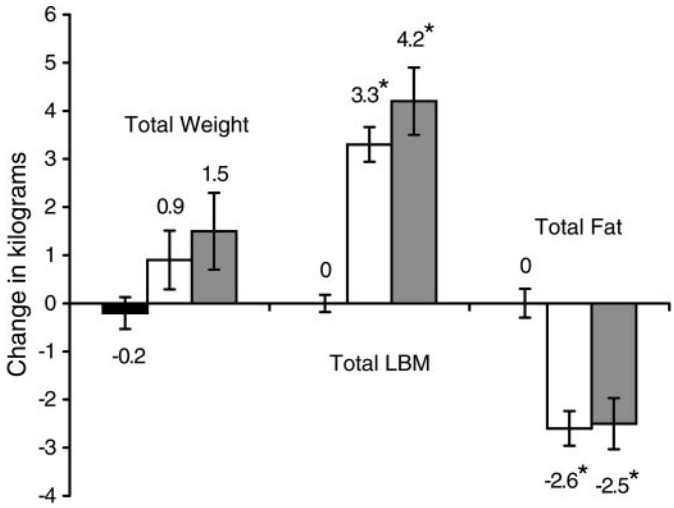

Fig. 1. Changes in body composition are shown for the groups receiving placebo (filled bars), 50 mg of oxymetholone per day (open bars), and 100 mg per day (gray bars). Numbers above the bars represent the mean absolute changes and the error bars are ± 1 SE. For total lean body mass (LBM) and total fat, differences among the 3 groups were significant ($P < 0.0001$, one-way ANOVA). *Significant differences from placebo, $P \leq 0.001$.

The MRI assessment of the proximal total thigh musculature showed a near-significant increase (24.5 ± 31.0 cm^2, $P = 0.056$ by one-way ANOVA) in CSA for the 100 mg/day group compared with the placebo and 50 mg/day groups, for which there were no appreciable changes (−0.8 ± 6.1cm^2, −1.6 ± 4.1 cm^2, respectively; Fig. 2). Most of the putative change in leg muscle CSA was due to change in the posterior thigh muscles (−0.6 ± 3.2, −0.2 ± 2.8, 16.1 ± 19.5 cm^2; $P = 0.052$ by one-way ANOVA).

Changes in Maximal Voluntary Strength

Chest press 1-RM strength increased significantly by 8.2 ± 9.2% ($P = 0.04$) in the 50 mg/day group and by 13.9 ± 8.1% ($P = 0.002$) in the 100 mg/day group (Fig. 3), resulting in a significant ($P = 0.001$) difference among the groups. Both the 50 mg/day and the 100 mg/day groups demonstrated significant increases compared with the placebo group (−0.8 ± 4.3%). Although the change was greater in the 100 mg/day group than in the 50 mg/day group, the difference was not statistically significant between these two groups. Similarly, the relative change in maximal lat pull-down strength differed significantly ($P = 0.034$) among the groups, due primarily to change in the 100 mg/day group (Fig. 3). In fact, lat pull-down strength increased significantly 18.4 ± 21.0% ($P = 0.024$) in the 100 mg/day group, whereas the 50 mg/day and placebo groups showed a nonsignificant 8.8 ± 15.1% increase

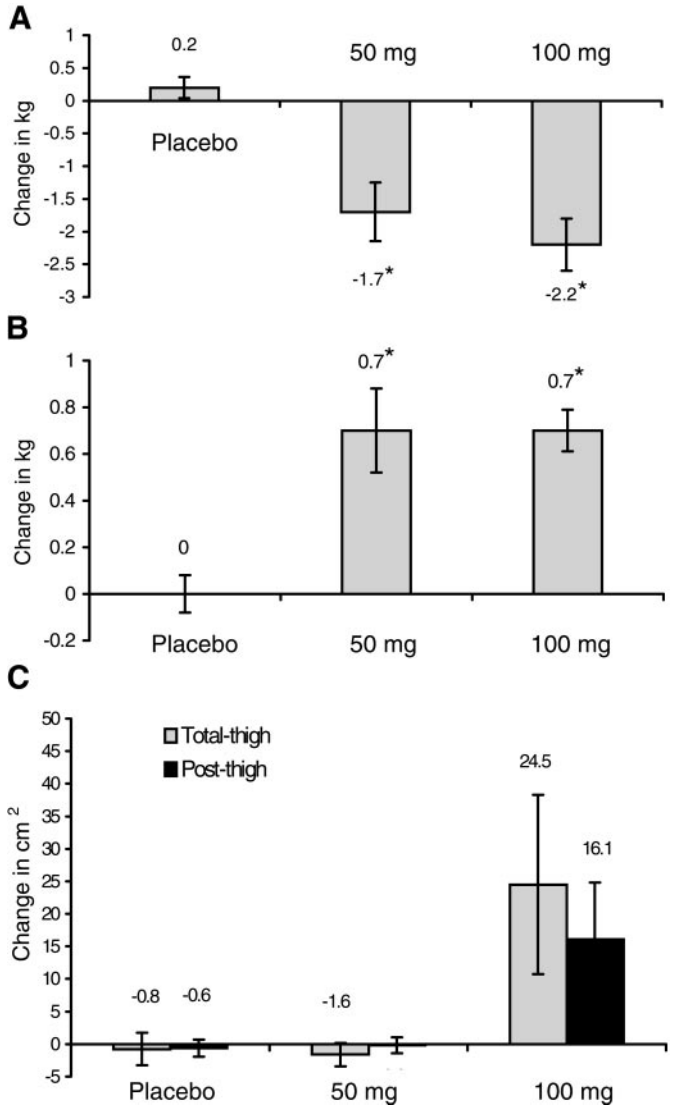

Fig. 2. Changes in regional composition (n = 16) are shown for the placebo, 50 mg/day, and 100 mg/day groups. *A*: nos. above bars represent mean absolute changes for trunk fat by dual-energy X-ray absorptiometry (DEXA). *B*: bars represent mean absolute changes (kg) for upper-extremity LBM (right arm plus left arm) by DEXA. *C*: muscle cross-sectional area of total proximal (gray bars) and posterior (filled bars) thigh muscles by magnetic resonance imaging. Error bars are ± 1 SE. *Significant difference from placebo, $P \leq 0.005$. See text for other statistical analyses.

($P = 0.15$) and −0.6 ± 8.3 decrease ($P = 0.42$), respectively.

Furthermore, there was a high correlation between change in upper extremity LBM with chest press and lat pull-down ($r = 0.88$ and $r = 0.75$, $P < 0.001$ and $P = 0.001$, respectively).

The percent increase in leg press strength was not significant in any of the three treatment groups (3.9–12.0%). However, there was a trend for change among the groups ($P = 0.09$ by one-way ANOVA); and the absolute increase of 174 ± 272 N in the 100 mg/day group from baseline to *week 12* (Fig. 3) did not quite reach significance ($P = 0.07$ by paired t-test).

Changes in Hormone Levels

Serum LH decreased by 6.0 ± 4.1 and 5.6 ± 9.7 U/l in 50 mg/day and 100 mg/day treatment groups, respectively, which were both significantly different from the changes observed in the placebo group (Table 2). Likewise, serum SHBG concentrations decreased by −54.9 ± 25.8 and −45 ± 16.2 nmol/l in the 50- and 100-mg treatment groups, and these changes were significantly different from baseline ($P < 0.001$). Fasting insulin concentrations and derived indexes of insulin sensitivity using either the HOMA-IR model or the QUICKI method did not change significantly within treatment groups, nor were there differences between these groups (Table 2).

Safety Evaluation

Table 2 shows that a significantly greater increase in mean ALT and aspartate aminotransferase (AST) occurred in the group that received the 100-mg dose of oxymetholone than in the other two groups. However, the ALT did not exceed 1.5 times the ULN except in two subjects (1.6 and 3.1 × ULN) in this group. Subjects who developed elevated ALT and AST remained asymptomatic and did not develop hepatomegaly, and their bilirubin and alkaline phosphatase levels remained normal. The subject with the highest increase in ALT admitted to drinking three to four glasses of wine per day during the period shortly before the tests were drawn. He was advised to discontinue alcohol, and his liver tests 1 wk later were normal. A small but statistically significant decrease in serum albumin occurred in the two oxymetholone treatment groups.

Changes in total cholesterol, LDL-cholesterol, and fasting triglycerides with study therapy did not differ among the three groups (Table 2). In addition, there were no significant within-group changes for these three lipids ($P > 0.05$ for each). However, decreases in plasma HDL-cholesterol concentrations (−19 ± 9 and

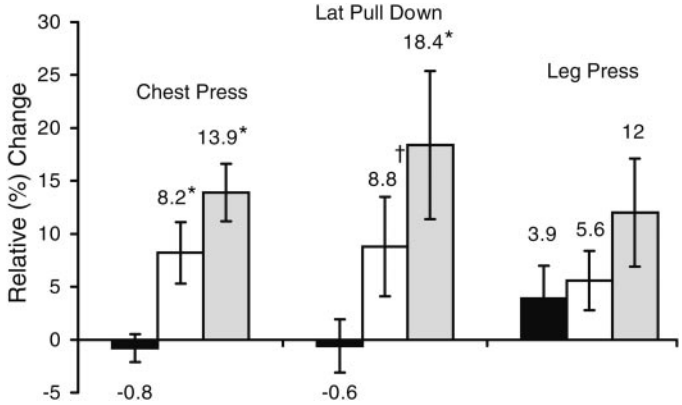

Fig. 3. Relative (%) changes in strength are shown for the groups receiving placebo (filled bars), 50 mg/day oxymetholone (open bars), and 100 mg/day oxymetholone (gray bars). Nos. above bars represent relative change (%) from baseline to *week 12* for the 1-repetition maximum tests of strength. Error bars represent ± 1 SE from the mean. *Significant difference from placebo, $P < 0.05$; †significant difference from placebo by Wilcoxon test, $P < 0.02$. See text for additional statistical analyses.

Table 2. *Change in safety measures after 12 wk of study therapy*

	Placebo	50 mg/day	100 mg/day	*P* Value[a]
Hematocrit, %	−1.2 ± 2.0	−2.1 ± 2.1	0.2 ± 2.7	0.10
BUN, mg/dl	0.5 ± 2.5	−0.6 ± 3.1	0.4 ± 2.9	0.65
Albumin, g/dl	−0.3 ± 0.2	−0.7 ± 0.3[b]	−0.8 ± 0.3[b]	0.001
ALT, U/l	0 ± 2	21 ± 15	72 ± 67[a]	0.001
AST, U/l	1 ± 2	14 ± 6	38 ± 29[c]	<0.0001
Alkaline phosphatase, U/l	−10 ± 6	−25 ± 8[b]	−12 ± 14	0.004
Total serum bilirubin, mg/dl	0.0 ± 0.1	0.0 ± 0.4	0.3 ± 0.8	0.30
PSA, ng/ml	−0.2 ± 0.5	−0.3 ± 0.5	−0.2 ± 0.8	0.96
Luteinizing hormone, U/l	1.0 ± 2.0	−6.0 ± 4.1[b]	−5.6 ± 9.7[d]	0.02
SHBG, nmol/l	1.3 ± 26.0	−54.9 ± 25.8[c]	−45.0 ± 16.2[c]	<0.001
Total cholesterol, mg/dl	−14 ± 17	8 ± 57	17 ± 39	0.22
LDL-cholesterol, mg/dl	4 ± 28	41 ± 57	13 ± 31	0.11
HDL-cholesterol, mg/dl	−4 ± 11	−19 ± 9[b]	−23 ± 18[b]	0.005
Triglycerides, mg/dl	−20 ± 39	−12 ± 50	1 ± 33	0.54
Fasting insulin, mU/dl	−1.7 ± 4.7	−2.9 ± 4.6	−2.9 ± 8.2	0.87
HOMA-IR[e]	−0.01 ± 0.02	−0.01 ± 0.01	−0.01 ± 0.02	0.84
QUICKI[f]	0.2 ± 0.3	0.0 ± 0.2	0.0 ± 0.4	0.30

Values are means ± SD. BUN, blood urea nitrogen; AST, aspartate aminotransferase; SHBG, sex hormone-binding globulin. [a]One-way ANOVA across the 3 groups; [b]Bonferroni-adjusted, $P < 0.05$ for comparison to placebo (independent *t*-test, $P < 0.03$). [c]Bonferroni adjusted, $P < 0.001$ for comparison to placebo (independent *t*-test, $P < 0.0005$). [d]Bonferrroni adjusted, $P < 0.025$ for comparison to placebo (Kruskal-Wallis test, $P < 0.02$). [e]Homeostasis model assessment of insulin resistance. (HOMA-IR) is calculated as $[(I_f) \times (G_f)]/22.5$, where (I_f) is the fasting insulin level (μU/ml) and (G_f) is the fasting glucose level (mmol/l). [f]Quantitative insulin sensitivity check index. (QUICKI) is calculated as $1/[\log (I_f) + \log (G_f)]$, where (I_f) is the fasting insulin level (μU/ml) and (G_f) is the fasting glucose level (mmol/l).

−23 ± 18 mg/dl) were significantly greater ($P = 0.05$) than for placebo (−4.4 ± 11.3 mg/dl). There was no difference in the change in HDL between the two groups who received oxymetholone.

Changes in hematocrit and PSA did not differ among the three treatment groups (Table 2). All subjects had digital rectal examinations before and at the completion of study therapy, and none showed important change in their prostate glands (e.g., new nodules or unusual firmness).

DISCUSSION

The results of our study demonstrate that treatment with oxymetholone for 12 wk significantly augmented total LBM and maximum voluntary strength in older men, a segment of the population that is at risk for sarcopenia (4, 17, 18, 35). Indeed, with 50 and 100 mg/day of oxymetholone, total LBM increased by 3.3 ± 1.2 and 4.2 ± 2.4 kg, respectively. These effects are of a magnitude similar to that achieved with 125 and 300 mg of testosterone enanthate (2.9 ± 0.8 and 5.5 ± 0.7 kg, respectively) when administered by intramuscular injection weekly for 20 wk to young healthy men (7). Although the anabolic potency and pharmacokinetics of testosterone enanthate and oxymetholone likely differ, our results suggest that important enhancements in lean tissue can be achieved with androgen administration in older persons as in younger men.

Although it is possible that increases in LBM as measured by DEXA were related to water retention caused by the androgen therapy, the sizeable gains in muscle strength as measured by the 1-RM method in the 50 and 100 mg/day groups (8.2–18.4%) suggest that the increases in LBM were likely due to accretion of myofibrillar protein as well as total LBM, since strength is closely related to muscle size (34). Moreover, members of our group have reported that changes in appendicular LBM by DEXA are quantitatively related to changes in skeletal muscle strength in response to anabolic stimuli (45). Indeed, in the present study, we were able to corroborate this relationship by demonstrating that the significant increases in upper-body lean tissue by appendicular DEXA scanning were highly correlated with changes in upper-body strength as assessed by chest press and lat pull-down. Furthermore, changes in maximal voluntary muscle strength for the upper-body exercises showed a dose-related response.

In contrast, there were nonsignificant gains across the three treatment groups for lower extremity strength (3.9–12.0%), consistent with the lack of a significant increase in lower-extremity LBM by DEXA scanning. However, there was a near-significant difference ($P = 0.052$) between the groups for change in CSA of the thigh muscles by MRI, suggesting that study therapy may have positively affected lower-extremity muscle. It is possible that strength tests of multiple, large-muscle groups such as those used with the leg press exercise are less sensitive to modest change in muscle mass, and the study may not have had sufficient power to detect small but significant gains in the lower extremities. We speculate that the large leg muscles are routinely used more frequently for load bearing (e.g., walking, rising from a chair) compared with upper-extremity muscles in older adults. Small but significant gains in lower-body strength and muscle mass may be less demonstrable than for muscles of the upper body, which may be used less for high-volume work and more prone to sarcopenia in older persons. Additionally, muscles of the upper extremities, compared with muscles of the lower extremities, have greater proportions of fast-twitch, type II fibers

(31, 43), which may be preferentially lost with aging (30). Furthermore, a longitudinal study in older men showed that type I fibers were lost primarily in the vastus lateralis of the leg (17), leading us to speculate that there might be greater loss in type II fibers in the arms with aging. Thus the response to anabolic stimuli may be more readily demonstrable in the upper extremities of this population.

There were also significant but similar within-group decreases in total body fat of 2.6 ± 1.2 and 2.5 ± 1.6 kg in the 50 and 100 mg/day groups, respectively. Of importance, a major portion of the improvement in adiposity involved decrements in trunk fat (1.7 ± 1.0 and 2.2 ± 0.9 kg in the two respective active treatment groups). A significant reduction in trunk fat could be expected to favorably affect risk factors for cardiovascular disease (32, 33). Although we would expect the reduction in abdominal fat to be reflected by improved insulin sensitivity, our indirect measures (HOMA-IR and QUICKI) may not have been sensitive enough. It is also possible that there were too few subjects in each group to detect small but meaningful changes.

There are theoretical reasons to have concern that androgen excess may result in or be associated with insulin resistance, although this relationship has been substantiated only in women with polycystic ovary syndrome (10, 11). We did not directly measure insulin sensitivity by either the hyperinsulinemic euglycemic clamp or frequently sampled intravenous glucose tolerance tests. However, indirect measures of insulin sensitivity (fasting insulin, HOMA-IR, QUICKI) did not show evidence of insulin resistance.

Liver transaminases (AST and ALT) increased only in the 100 mg/day treatment group. However, these changes were modest, and subjects remained asymptomatic and had no hepatic enlargement or evidence of cholestasis. There were no changes in total or LDL-cholesterol or fasting triglycerides, but HDL-cholesterol decreased significantly in the two oxymetholone groups (−19 ± 9 and −23 ± 18 mg/dl). Androgen effects on plasma lipids depend on the dose, route of administration, and type of androgen used (aromatizable or not). Thus nonaromatizable, orally administered androgens such as oxymetholone are expected to produce greater reductions in plasma HDL cholesterol than aromatizable testosterone (16, 54). Hematocrit did not increase significantly in the study groups, but this lack of change may have been related to phlebotomy for the collection of multiple specimens.

Observations that eunuchs do not develop cancer of the prostate (59) and that androgen ablation is an effective therapy for treatment of prostatic carcinoma (51) have led to concern that supplemental androgen therapy could increase the risk for enlargement of the prostate or even unmask carcinoma (52). In our study, there was no change in the texture of the prostate gland by digital examination or increase in serum PSA with treatment. This observation is consistent with the findings of Snyder et al. (50), who did not find significant differences in PSA levels after 3 yr between placebo and testosterone-treated older men with initially low or low normal testosterone levels.

Oxymetholone administration was associated with decreases in serum LH and SHBG concentrations. Therefore, at the doses of oxymetholone that are used for anabolic applications, this compound has significant androgenic activity at the hypothalamic-pituitary level. Unsubstantiated claims notwithstanding, it remains to be seen whether the androgenic and anabolic properties of androgens can be dissociated (8, 60).

Several limitations may have influenced the findings of this study. First, the small sample size of fewer than a dozen subjects per group may have limited the ability to detect small but important changes in variables such as lower-extremity LBM and CSA of thigh musculature. Similarly, it is possible that the differences observed for changes in total LBM and strength might have been significant between the treatment groups with larger sample sizes. The latter would have provided further support for our supposition of a dose-dependent response with oxymetholone. Second, our population represented older adult men, whom we characterized as being at risk for age-related sarcopenia on the basis of reports showing loss of muscle mass and strength with aging (4, 17, 18, 35). However, subjects were not recruited for weight loss, frailty, or overt hypogonadism per se, since we have shown that younger men with normal testosterone concentrations can achieve appreciable increases in muscle mass and strength after androgen supplementation (5, 7, 44). Furthermore, there is evidence that myofibrillar protein synthesis in older persons may be significantly augmented to levels comparable to those achieved in younger persons in response to a potent anabolic stimulus (21). Finally, because oxymetholone is a 17-methyl-substituted analog resulting in a high first-pass effect in the liver, additional safety data in older subjects should be obtained before this agent is used for treatment of sarcopenia. Regardless, the important observation from this study is that measures of muscle mass and maximal voluntary strength can be significantly improved in older persons with supplemental androgen therapy.

In summary, results of this study indicate that, in older men, supplementation with a brief course of androgen therapy can significantly increase lean tissue and maximal voluntary skeletal muscle strength. These translational findings are consistent with earlier studies showing that androgens increase synthesis of myofibrillar proteins and further document the plasticity of muscle in older people. The results also suggest that these changes were quantitatively related to the dose of oxymetholone. Of importance, there were also significant decreases in trunk fat in the active treatment groups consistent with findings in middle-aged men with abdominal obesity and relative hypogonadism. The study leaves a number of issues unresolved, including the optimal formulation of androgen for supplementation in this age group, the benefits and risks of longer periods of therapy, the durability of outcomes associated with intermittent therapy, the question of

whether measures of visceral adipose tissue and markers of atherosclerosis are improved, and the question of whether similar beneficial effects can be achieved in older women.

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