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Effects of Androgen Therapy on Adipose Tissue and Metabolism in Older Men

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We investigated the effects of oxandrolone on regional fat compartments and markers of metabolism. Thirty-two 60- to 87-yr-old men (body mass index, 28.1 ± 3.4 kg/m^2) were randomized to oxandrolone (20 mg/d; n = 20) or matching placebo (n = 12) treatment for 12 wk. Oxandrolone reduced total (−1.8 ± 1.0 kg; $P < 0.001$), trunk (−1.2 ± 0.6 kg; $P < 0.001$), and appendicular (−0.6 ± 0.6 kg; $P < 0.001$) fat, as determined by dual energy x-ray absorptiometry. The changes in total and trunk fat were greater ($P < 0.001$) than the changes with placebo. By magnetic resonance imaging, visceral adipose tissue decreased (−20.9 ± 12 cm^2; $P < 0.001$), abdominal sc adipose tissue (SAT) declined (−10.7 ± 12.1 cm^2; $P = 0.043$), the ratio VAT/SAT declined from 0.57 ± 0.23 to 0.49 ± 0.19 ($P = 0.002$), and proximal and distal thigh SC fat declined [−8.3 ± 6.7 cm^2 ($P < 0.001$) and −2.2 ± 3.0 kg ($P = 0.004$), respectively]. Changes in proximal and distal thigh SC fat with oxandrolone were different than with placebo ($P = 0.018$ and $P = 0.059$). A marker of insulin sensitivity (quantitative insulin sensitivity check index) improved with oxandrolone by 0.0041 ± 0.0071 ($P = 0.018$) at study wk 12. Changes in total fat, abdominal SAT, and proximal extremity SC fat were correlated with changes in fasting insulin from baseline to study wk 12 ($r \geq 0.45$; $P < 0.05$). Losses of total fat and SAT were greater in men with baseline testosterone of 10.4 nmol/liter or less (≤ 300 ng/dl) than in those with higher levels [−2.5 ± 1.1 *vs.* −1.5 ± 0.8 kg ($P = 0.036$) and −24.1 ± 14.3 *vs.* −2.9 ± 21.3 cm^2 ($P = 0.03$), respectively]. Twelve weeks after discontinuing oxandrolone, 83% of the reductions in total, trunk, and extremity fat by dual energy x-ray absorptiometry scanning were sustained ($P < 0.02$). Androgen therapy, therefore, produced significant and durable reductions in regional abdominal and peripheral adipose tissue that were associated with improvements in estimates of insulin sensitivity. However, high-density lipoprotein cholesterol decreased by −0.49 ± 0.21 mmol/liter and directly measured low-density lipoprotein cholesterol increased by 0.57 ± 0.67 mmol/liter and non-high-density lipoprotein cholesterol increased by 0.54 ± 0.97 mmol/liter ($P < 0.03$ for each) during treatment with oxandrolone; these changes were largely reversible. Thus, therapy with an androgen that does not adversely affect lipids may be beneficial for some components of the metabolic syndrome in overweight older men with low testosterone levels. (*J Clin Endocrinol Metab* 89: 4863–4872, 2004)

ADVANCING AGE IS associated with increasing risks for a number of serious medical disorders, including coronary artery disease, stroke, peripheral vascular complications, and diabetes mellitus. Impaired mobility, accumulation of central adiposity, and loss of muscle mass (sarcopenia) contribute to these risks, as do frailty, spontaneous and fall-related bone fractures, and loss of independence. With advancing age, increases in central adiposity, especially visceral adipose tissue (VAT), are associated with increased risk for hypertension, insulin resistance, abnormalities in serum lipids, and impaired fibrinolysis characteristic of the metabolic syndrome (1), also known as the insulin resistance syndrome. This constellation of abnormalities predisposes these older individuals to accelerated atherosclerosis and type 2 diabetes.

Abbreviations: BMI, Body mass index; CSA, cross-sectional area; CV, coefficient of variation; DEXA, dual energy x-ray absorptiometry; HDL, high-density lipoprotein; HOMA-IR, homeostasis model assessment for insulin resistance; IMCL, intramyocellular lipid; IMF, intermuscular fat; LBM, lean body mass; LDL, low-density lipoprotein; Lp(a), lipoprotein a; MRI, magnetic resonance imaging; QUICKI, quantitative insulin sensitivity check index; SAT, sc adipose tissue; VAT, visceral adipose tissue.

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Cross-sectional (2, 3) and longitudinal (4, 5) studies indicate that total and free levels of serum testosterone decline with advancing age in men. In healthy men, abdominal VAT quantified by computed tomography has been inversely associated with testosterone levels (6), and both natural and experimentally induced hypogonadism are associated with significant increases in fat mass (7, 8). Moreover, in middle-aged men with abdominal obesity and low levels of testosterone, replacement doses of androgen have resulted in significant decreases in VAT, increased lipid turnover in adipocytes, improvements in insulin sensitivity, and declines in blood pressure (9, 10). These observations are consistent with studies in hypogonadal young men, which showed that treatment with testosterone decreases fat mass (11–13).

However, the relationship between gonadal hormone status and age-associated increases in adipose tissue and the metabolic disorders frequently associated with central obesity in older individuals is less certain. Moreover, obesity is associated with decreases in SHBG, which may confound assessment of the relationship of change in testosterone levels and change in fat mass. The effects of testosterone on fat mass have been variable as testosterone treatment in older men have either shown no change (14–16) or only modest reductions in fat (17–19). The variability in the effects of

testosterone treatment in older men may be related to the different formulations of testosterone (im *vs.* transdermal delivery), dose (200 mg biweekly *vs.* 5 mg/d), baseline testosterone status, magnitude of change in testosterone levels in response to therapy, duration of treatment (weeks *vs.* years), and different methods used to assess body composition [*e.g.* magnetic resonance imaging (MRI), computed tomography scanning, dual energy x-ray absorptiometry (DEXA) scanning, hydrostatic weighing, or bioelectrical impedance analysis].

Based on the studies in younger men with low levels of testosterone and central obesity, we hypothesized that androgen therapy in older men would significantly decrease regional abdominal fat mass (visceral and sc fat stores) and appendicular (sc and intermuscular) adipose tissue as well as improve markers of the metabolic syndrome. To test this hypothesis, we conducted a substudy of a placebo-controlled investigation designed to evaluate the effects of treatment with a potent anabolic androgen for 3 months on lean body tissue, skeletal muscle mass, maximum voluntary muscle strength, and physical function (20). The study was unique in that it assessed the durability of effects 3 months after study therapy was discontinued. We, herein, describe the results of the substudy to test our hypothesis that androgen therapy would have beneficial effects on central and peripheral adipose tissue and that these changes would favorably affect systemic markers of the metabolic syndrome.

Subjects and Methods

Study design

This was an investigator-initiated, double-blind, placebo-controlled study with the primary objective to determine the magnitude and durability of effects of a potent, anabolic androgen, oxandrolone (Oxandrin) on measures of total and regional lean tissue, musculoskeletal muscle mass, and voluntary maximum muscle strength (20). This report describes the substudy to investigate the effects of these interventions on regional fat mass and markers of metabolism. The protocol and informed consent were approved and annually reviewed by the institutional review board of the Los Angeles County-University of Southern California Medical Center. Each study subject provided written informed consent before enrollment. The body composition and metabolic components of the study were performed at the University of Southern California General Clinical Research Center.

Study population

Men at least 60 yr of age were recruited from the surrounding communities of southern California. To be eligible, subjects had to have a body mass index (BMI) of 35 kg/m^2 or less and have no untreated endocrine abnormalities (*e.g.* diabetes or hypothyroidism), active inflammatory conditions, uncontrolled hypertension, or cardiac problems in the prior 3 months. Blood tests for eligibility included a prostate-specific antigen level of 4.1 μg/liter or less and a hematocrit of 50% or less. Subjects performing or planning to initiate vigorous exercise were excluded, but casual walking was allowed.

Study interventions

To provide subjects with increased opportunity to receive active study therapy, we used a 2:1 randomization schedule. Eligible participants were randomized to receive either the approved oral dose (10 mg twice daily) of oxandrolone (Oxandrin, Savient Pharmaceuticals, Inc., East Brunswick, NJ) or matching placebo for 12 wk. The dose of oxandrolone is the FDA-approved dose for treatment of weight loss or inability to maintain normal body weight. Adherence to study therapy was monitored by tablet counts at each study visit. Subjects were reevaluated 12 wk after completing the study therapy (*i.e.* at study wk 24) to assess the durability of effects.

Nutritional assessment

Subjects were instructed to record dietary intake on 3 consecutive days, including 2 weekdays and 1 weekend day during the week before baseline as well as at study wk 12 and 24. Subjects were counseled that the days should be chosen to include usual activities and typical eating patterns. A licensed nutritionist (C.M.) reviewed 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.

Body composition by DEXA

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

Body composition by MRI

Cross-sectional area (CSA) of VAT and sc abdominal (SAT) fat were assessed using proton MRI (^{1}H-MRI) at baseline and study wk 12 (but not wk 24). ^{1}H-MRI was performed using a 1.5 Tesla GE Signa-LX scanner with the body coil used as both transmitter and receiver. Single proximal and distal thigh slices were acquired after obtaining a T1-weighted coronal scout image (T1-weighted TR/TE 300/TE) that was used to demarcate the proximal and distal thigh by bisecting the femur into three segments. The mid of seven slices proximal and seven slices distal with a slice thickness of 7.5 mm and a 1.5-mm gap was analyzed for comparison. The junction of the proximal and middle third of the femur served as the proximal thigh, and the junction of the middle third and distal femur served as the distal thigh. The field of view was 24 $\times$ 24 cm with a 254 $\times$ 128-pixel matrix. One signal average was used.

Subcutaneous and visceral adipose CSA were measured by analyzing a single slice at the junction of the fourth and fifth lumbar vertebrae using specialized software (SliceOmatic version 4.2, TomoVision, Montréal, Canada). Because each pixel reflects a given density, regions of adipose tissue are segregated from other regions of tissue using the SliceOmatic Morpho mode of analysis. This allows the tissue compartments [sc fat, muscle, intermuscular fat (IMF), *etc.*] to be segmentalized based on signal amplitude by highlighting small regions of similar density pixels to determine adipose CSA. Subcutaneous and visceral adipose CSA were calculated after highlighting the respective adipose tissue regions with different colors. Similarly, CSA of thigh sc fat and IMF were calculated after highlighting the respective pixels with different colors. IMF was defined as high intensity pixels located between and within the thigh muscles, excluding the femur.

MRI scans were not performed at study wk 24. The same technician (M.O.), blinded to treatment, located the regions of interest and performed all image analyses. The CV for repeated measures of sc and visceral adipose CSA was less than 2%.

Serum lipid and lipoprotein concentrations

Blood was collected after a 14-h overnight fast at baseline, study wk 12, and study wk 24 for plasma lipid determinations. Plasma was analyzed for total cholesterol, high-density lipoprotein (HDL) cholesterol, and triglycerides using the Ortho/Vitros DTII system (Ortho Diagnostics, Rochester, NY) in the University of Southern California General Clinical Research Center core laboratory. Plasma lipid concentrations in baseline, wk 12, and wk 24 samples for each subject were run in the same assay to eliminate the effects of interassay variation. The CVs for the three lipids were less than 4.5%, less than 4.4%, and less than 3.0%, respectively.

Low-density lipoprotein (LDL) cholesterol was measured directly with an enzymatic assay using photometric detection (Cobas Integra 400 System, Roche, Indianapolis, IN). The sensitivity of the assay was de-

fined as the change in the analytical response (ΔA) per unit change in analyte concentration at a path length of 1 cm. The sensitivity was 0.18 ΔA/mmol/liter LDL cholesterol. The precision of the assay was evaluated on the Integra 700 using two human serum pools and following the guidelines of the National Committee for Clinical Laboratory Standards manual EP5-T2. The level 1 CV was 1.9%, and the level 2 CV was 2.1%. Lipoprotein a [Lp(a)] was determined using an immunoassay, Macra Lp(a) (Wampole, Trinity Biotech, Jamestown, NY). The sensitivity of the test was 0.03 μmol/liter, and the CV was less than 10%.

Fasting blood sugar

Blood was collected after a 14-h overnight fast in prechilled heparinized tubes. Plasma was removed and frozen within 10 min of collection. Glucose was measured by the glucose oxidase method (model 2300 STAT PLUS glucose analyzer, YSI, Inc., Yellow Springs, OH) with a CV of 2.5%.

Hormone concentrations

The serum testosterone concentration was measured by the Los Angeles County-University of Southern California Medical Center Clinical Diagnostic Laboratory (endocrinology section) using Coat-A-Count (Diagnostic Products Corp., Los Angeles, CA). This competitive RIA uses a solid phase polyclonal antibody. The CV for total testosterone was 7.7% or less. The LH concentration (international units per milliliter) was measured using a microparticle enzyme immunoassay (AxSYM, Abbott Diagnostics, Chicago, IL). The CV for LH was 4.9% or less.

Insulin was measured by RIA (Linco Research, Inc., St. Charles, MO), which had less than 0.2% cross-reactivity with proinsulin and a CV of 3.2%. Glucose and insulin concentrations from baseline, 12-wk, and 24-wk tests for each subject were measured in the same assay to eliminate the effects of interassay variation.

Estimates of insulin resistance

The homeostasis model assessment for insulin resistance (HOMA-IR) and quantitative insulin sensitivity check index (QUICKI) were used to estimate insulin resistance. These estimates correlate with insulin sensitivity measured using the hyperinsulinemic euglycemic clamp (21, 22). HOMA-IR was calculated as $[(I_f) \times (G_f)]/22.5$, where (I_f) is the fasting insulin level (microunits per milliliter) and (G_f) is the fasting glucose level (millimoles per liter). QUICKI was calculated as $1/[\log (I_f) + \log (G_f)]$ (21).

Safety monitoring

To assess the safety of the study therapy, blood was collected every 3 wk during treatment. Safety tests included complete blood counts, comprehensive chemistries with tests of renal and hepatic functions, and prostate-specific antigen. These tests were repeated at study wk 24.

Statistical considerations

The study was conservatively powered at 80% to detect a difference in means between the oxandrolone and placebo groups of 1.36 times the common SD, using a two-sample *t* test with a Bonferroni-adjusted $P = 0.01$, with 20 in oxandrolone group and 10 in placebo group (20). The power calculation was based on the primary outcome, total LBM by DEXA scanning. As such, the sample size was selected to detect a mean difference of 2 kg, assuming the common SD is 1.5 kg. For the substudy, this sample size would provide a power of at least 85% to show a 1.0-kg difference in the change in trunk fat between the groups by DEXA scanning assuming a common SD of 0.8 kg and a 25-cm^2 difference in the change in abdominal VAT by MRI assuming a common SD of change of 20 cm^2.

For the main outcome variables, a two (oxandrolone and placebo group) by three (baseline, wk 12, and wk 24) repeated measure ANOVA was used to statistically compare mean differences within subjects and between groups. Greenhouse-Geisser adjustment was used to justify the assumption of sphericity. When a significant group by time interaction was found, the changes from baseline to wk 12 and the changes from baseline to wk 24 between and within groups were compared by independent *t* tests and paired *t* tests, respectively. All *post hoc* tests were performed with Bonferroni adjustment for six possible comparisons. Baseline characteristics and the changes in safety evaluation from baseline to wk 12 were compared between oxandrolone and placebo group using an independent *t* test.

The change in fat measured from baseline to wk 12 by DEXA and MRI was also compared between low testosterone (≤10.4 nmol/liter; ≤300 ng/dl) and normal testosterone (>10.4 nmol/liter; >300 ng/dl) using both independent *t* tests and Wilcoxon rank-sum tests. The significant between-strata differences observed in independent *t* tests were also demonstrated in Wilcoxon rank-sum tests. Based on the distribution of data, the associations between the change in body fat from baseline to study wk 12 compared with baseline characteristics were tested with Spearman's correlation coefficients. Associations between the change in fat and changes in metabolic markers from baseline to study wk 12 were tested with Pearson's correlation coefficients.

All statistical testing was performed with a two-sided 5% level of significance (0.83% for each *post hoc t* test) using Statistical Analysis System version 8.0 (SAS Institute, Inc., Cary, NC). Statistical analyses are presented in the tables and text as the mean ± 1 SD.

Results

Subjects (Table 1)

Thirty-two subjects were randomized to receive either oxandrolone (n = 20) or placebo (n = 12). As reported previously (20), the baseline characteristics of the two treatment groups were similar, including indirect measures of body composition (weight and BMI), markers of inflammation (albumin and C-reactive protein), and thyroid and hypothalamic-pituitary-gonadal functions (Table 1). Two subjects (one assigned to each group) did not return for the wk 24 evaluation; thus, there were 19 subjects in the oxandrolone group and 11 in the placebo group at the last evaluation.

BMI

The average BMI of the total population of 32 subjects was 28.1 ± 3.4 kg/m^2. Of these, 20 subjects had a BMI in the overweight range of 25–29.9 kg/m^2, and seven others had a BMI of 30 kg/m^2 or more, indicating obesity. Thus, 27 (84%) of 32 subjects were either overweight or obese.

TABLE 1. Baseline characteristics of the study population

	Oxandrolone	Placebo	*P* value[a]
n	20	12	
Age (yr)	72.8 ± 6.9	71.5 ± 3.2	0.49
Weight (kg)	81.3 ± 13.3	84.8 ± 8.9	0.43
BMI (kg/m^2)	27.5 ± 3.5	29.1 ± 2.9	0.20
Hemoglobin (mmol/liter)	2.3 ± 0.1	2.3 ± .1	0.76
Creatinine (mmol/liter)	0.13 ± 0.16	0.12 ± 0.04	0.34
Albumin (μmol/liter)	606 ± 30	636 ± 30	0.07
ALT (U/liter)	38 ± 7.0	38 ± 4.4	0.83
Ultrasensitive CRP (μg/liter)	1.4 ± 1.00	2.3 ± 2.7	0.21
TSH (U/liter)	1.86 ± 1.31	1.97 ± 0.63	0.79
Total testosterone (nmol/liter)	12.8 ± 5.1	12.4 ± 5.3	0.83
LH (U/liter)	8.3 ± 7.1	6.5 ± 6.7	0.51

Values are the mean ± 1 SD. ALT, Alanine aminotransferase; CRP, C-reactive protein. For conventional metric units, divide hemoglobin by 0.1550 for g/dl, creatinine by 0.8840 for mg/dl, albumin by 151.5 for g/dl, and total testosterone by 0.0345 for ng/dl.

[a] *P* value was obtained by independent *t* test.

Nutrition and exercise (Table 2)

During the course of the study, there were no significant changes in total caloric or macronutrient intake when analyzed by ANOVA with week as the repeated measure for study group using Greenhouse-Geisser adjustment (Table 2). Additionally, upon entry into the study, subjects were instructed to maintain their habitual physical activity and not to engage in a new exercise program during the course of the study. Based on self-report at each study evaluation, subjects did not alter their physical activity levels.

Body composition (Table 3 and Figs. 1 and 2)

Changes in fat mass by DEXA scanning. There was a significant ($P = 0.03$) group by time (baseline, study wk 12, and study wk 24) interaction for total fat mass. At study wk 12, oxandrolone reduced whole body fat mass (-1.8 ± 1.0 kg; $P < 0.001$) and trunk fat mass (-1.2 ± 0.6 kg; $P < 0.001$), whereas placebo did not [whole body, -0.2 ± 1.0 kg ($P = 0.58$); trunk, 0.0 ± 0.7 kg ($P = 0.87$); Table 3]. The decreases in whole body and trunk fat mass were greater in the oxandrolone group than the changes in the placebo group ($P < 0.001$). Seven

TABLE 2. Measures of dietary intake

	Oxandrolone			Placebo		
	Wk 0	Wk 12	Wk 24	Wk 0	Wk 12	Wk 24
Total calories (kcal/kg·d)	25.9 ± 6.3	25.3 ± 7.2	26.2 ± 8.3	25.2 ± 4.6	23.0 ± 2.6	22.6 ± 4.9
% Protein	19 ± 5.4	20 ± 5.8	20 ± 7	18 ± 1	19 ± 2	18 ± 4
% Carbohydrate	47 ± 9.9	46 ± 11	47 ± 12	50 ± 12	47 ± 12	48 ± 16
% Total fat	34 ± 11.8	34 ± 13	32 ± 12	32 ± 8	33 ± 8	33 ± 10
% Saturated fat	11 ± 3.6	11 ± 4.3	10 ± 4	11 ± 3	12 ± 6	10 ± 3

P values for each dietary parameter using two-way ANOVA with week as repeated measure for treatment group × week with Greenhouse-Geisser adjustment were all greater than 0.20.

TABLE 3. Measures of regional abdominal and appendicular adipose tissue

	Wk 0	Wk 12	Wk 24	*P* value	
				0 *vs.* 12	0 *vs.* 24
DEXA					
Total fat (kg)					
Oxandrolone	23.5 ± 7.7	21.7 ± 7.4[a]	22.0 ± 7.3	<0.001	0.001
Placebo	23.7 ± 4.4	23.5 ± 4.3	22.9 ± 5.6	0.58	0.29
Trunk fat (kg)					
Oxandrolone	13.7 ± 4.2	12.4 ± 4.1[a]	12.7 ± 4.1	<0.001	0.001
Placebo	13.2 ± 2.4	13.2 ± 2.4	12.6 ± 3.4	0.87	0.17
Appendicular fat (kg; 4 extremities)					
Oxandrolone	8.9 ± 3.6	8.3 ± 3.5[b]	8.2 ± 3.5	<0.001	0.014
Placebo	9.5 ± 2.2	9.3 ± 2.2	9.3 ± 2.5	0.22	0.70
MRI					
VAT (cm^2)					
Oxandrolone (n = 20)	136.2 ± 53.3	115.3 ± 51.8		<0.001	
Placebo (n = 11)	157.6 ± 47.5	146.9 ± 53.9		0.30	
SAT (cm^2)					
Oxandrolone	255.1 ± 92.7	244.4 ± 93.7		0.04	
Placebo	260.8 ± 63.6	260.7 ± 60.4		0.98	
VAT/SAT abdominal ratio					
Oxandrolone	0.57 ± 0.23	0.49 ± 0.19		0.002	
Placebo	0.62 ± 0.19	0.58 ± 0.21		0.18	
MRI					
Proximal sc thigh fat (cm^2)					
Oxandrolone	98.3 ± 41.7	90.0 ± 38.7[c]		<0.001	
Placebo	104.9 ± 25.4	104.1 ± 27.5		0.79	
Distal sc thigh fat (cm^2)					
Oxandrolone	41.8 ± 18.3	39.6 ± 16.4[d]		0.004	
Placebo	47.5 ± 11.3	51.5 ± 17.9		0.36	
Proximal IMF (cm^2)					
Oxandrolone	25.6 ± 6.2	24.5 ± 5.2		0.43	
Placebo	29.5 ± 8.6	27.4 ± 9.9		0.32	
Distal IMF (cm^2)					
Oxandrolone	32.5 ± 20.5	26.1 ± 6.6		0.22	
Placebo	26.7 ± 9.4	26.8 ± 8.8		0.98	

P values are shown for between-group comparison of the change from study wk 0 (baseline) to study wk 12.
[a] $P < 0.001$.
[b] $P = 0.08$.
[c] $P = 0.018$.
[d] $P = 0.059$.

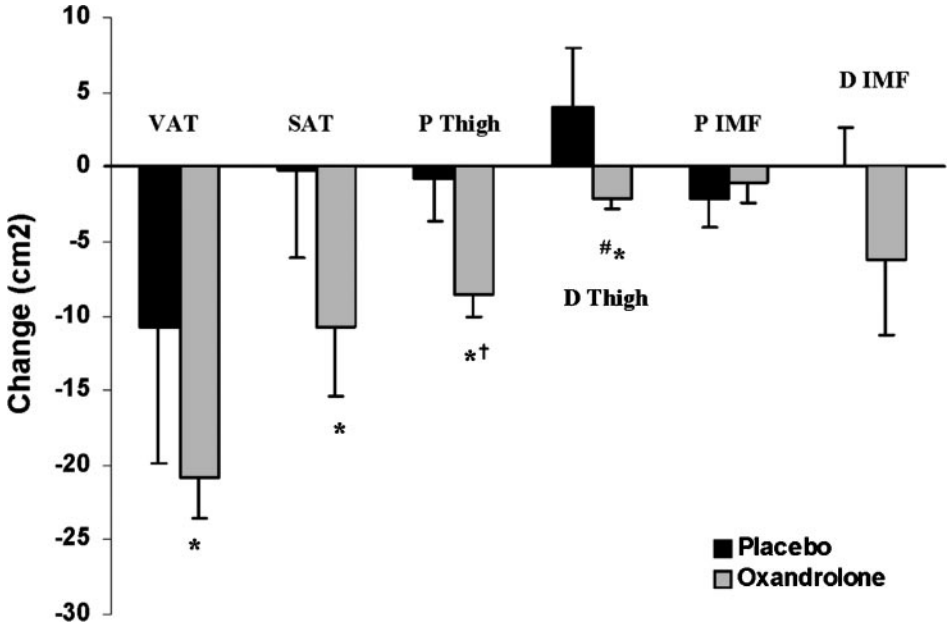

FIG. 1. Absolute change in fat mass, determined by MRI, between baseline and study wk 12 for VAT, SAT of the abdomen, and SAT of the proximal and distal thigh (P Thigh and D Thigh, respectively) and the IMF of the proximal and distal thigh (P IMF and D IMF, respectively). The whiskers are 1 SE. *, Significant ($P < 0.001$) within-group difference from baseline; †, significant ($P = 0.018$) difference in the change between study groups; #, near-significant difference ($P = 0.059$) in the change for the study groups.

subjects with baseline testosterone levels of 10.4 nmol/liter or less lost a total of −2.5 ± 1.1 kg, whereas the 13 subjects with baseline testosterone levels greater than 10.4 nmol/liter lost only −1.5 ± 0.8 kg during treatment with oxandrolone ($P = 0.036$, by Wilcoxon rank-sum test). Moreover, the change in trunk fat at wk 12 was correlated ($r = 0.5$; $P = 0.02$) with baseline testosterone. At study wk 12, there was also a significant ($P < 0.001$) decrease in total appendicular fat (−0.6 ± 0.6 kg), but this difference was not statistically different ($P = 0.08$) from the decrease in appendicular fat (−0.2 ± 0.6; $P = 0.22$) in the group receiving placebo.

Twelve weeks after discontinuing study treatment (wk 24), whole body, trunk, and appendicular fat, determined by DEXA scanning, were still less than baseline [−1.5 ± 1.7 kg ($P = 0.001$), −1.0 ± 1.1 kg ($P = 0.001$), and −0.5 ± 0.8 ($P = 0.014$), respectively] for the group receiving oxandrolone. However, differences were not statistically different ($P > 0.10$) from the small changes in total, trunk, and appendicular fat (−0.6 ± 1.6, −0.5 ± 1.2, and −0.5 ± 0.8 kg, respectively) in the placebo group.

Change in fat by MRI scanning. At study wk 12, VAT significantly ($P < 0.001$) declined by −20.9 ± 12 cm^2, whereas the change in the placebo group (−10.7 ± 32 cm^2) was not significant ($P = 0.30$; Table 3 and Fig. 1). The difference in change between the groups was not significant ($P = 0.22$). Similarly, abdominal SAT declined significantly ($P = 0.043$) by −10.7 ± 12.1 cm^2 with oxandrolone, but only −0.2 ± 20.4 with placebo ($P = 0.98$); the difference in change between the groups was not significant ($P = 0.20$). The improvement in abdominal SAT with oxandrolone was greater ($P = 0.03$) in subjects with baseline testosterone levels of 10.4 nmol/liter or less compared with those with levels greater than 10.4 nmol/liter (−24.1 ± 14.3 *vs.* −2.9 ± 21.3 cm^2, respectively). Finally, the VAT/SAT ratio declined significantly ($P = 0.002$) from 0.57 ± 0.23 to 0.49 ± 0.19 after 12 wk in the oxandrolone group. However, the change from 0.62 ± 0.19 to 0.58 ± 0.21 in the placebo group was not significant ($P = 0.18$), nor was the difference in change between the groups ($P = 0.11$).

The group receiving oxandrolone also experienced significant ($P < 0.001$) decreases of −8.3 ± 6.7 cm^2 in proximal sc thigh fat, whereas the change in the placebo group of −0.8 ± 9.8 cm^2 was not significant ($P = 0.79$), but the difference in the changes in these two groups was significant ($P = 0.018$). The changes in distal sc thigh fat were smaller, but significant ($P = 0.004$), with oxandrolone (−2.2 ± 3.0 cm^2); this difference was not quite significantly different ($P = 0.059$) from the nonsignificant change ($P = 0.36$) in the placebo group of 4.0 ± 13.8 cm^2. The changes in proximal thigh IMF of −1.1 ± 5.9 cm^2 and −2.1 ± 6.8 cm^2 in the oxandrolone and placebo groups, respectively, were not significant ($P = 0.43$ and $P = 0.32$). Similarly, the changes in distal thigh IMF of −6.4 ± 22.5 and 0.1 ± 8.9 cm^2 in the oxandrolone and placebo groups, respectively, were not significant ($P = 0.22$ and $P = 0.98$). These small changes in IMF were not different between the groups ($P > 0.40$).

Glucose metabolism and estimates of insulin resistance (Table 4)

There were no significant group by study week interactions (two-way ANOVA with Greenhouse-Geisser adjustment) for fasting blood sugar ($P = 0.26$), fasting insulin ($P = 0.41$), HOMA-IR ($P = 0.53$), or QUICKI ($P = 0.10$). Similarly, there were no significant within-group changes ($P > 0.05$) for HOMA-IR. However, there was a significant ($P = 0.018$) increase in QUICKI (0.0041 ± 0.0071) at study wk 12 for the oxandrolone group (Table 4). The increase in QUICKI (from wk 0 to wk 12) was greater in the oxandrolone group than in the placebo group ($P = 0.045$).

Lipid metabolism (Table 4)

There were no significant group by study week interactions (two-way ANOVA with Greenhouse-Geisser adjust-

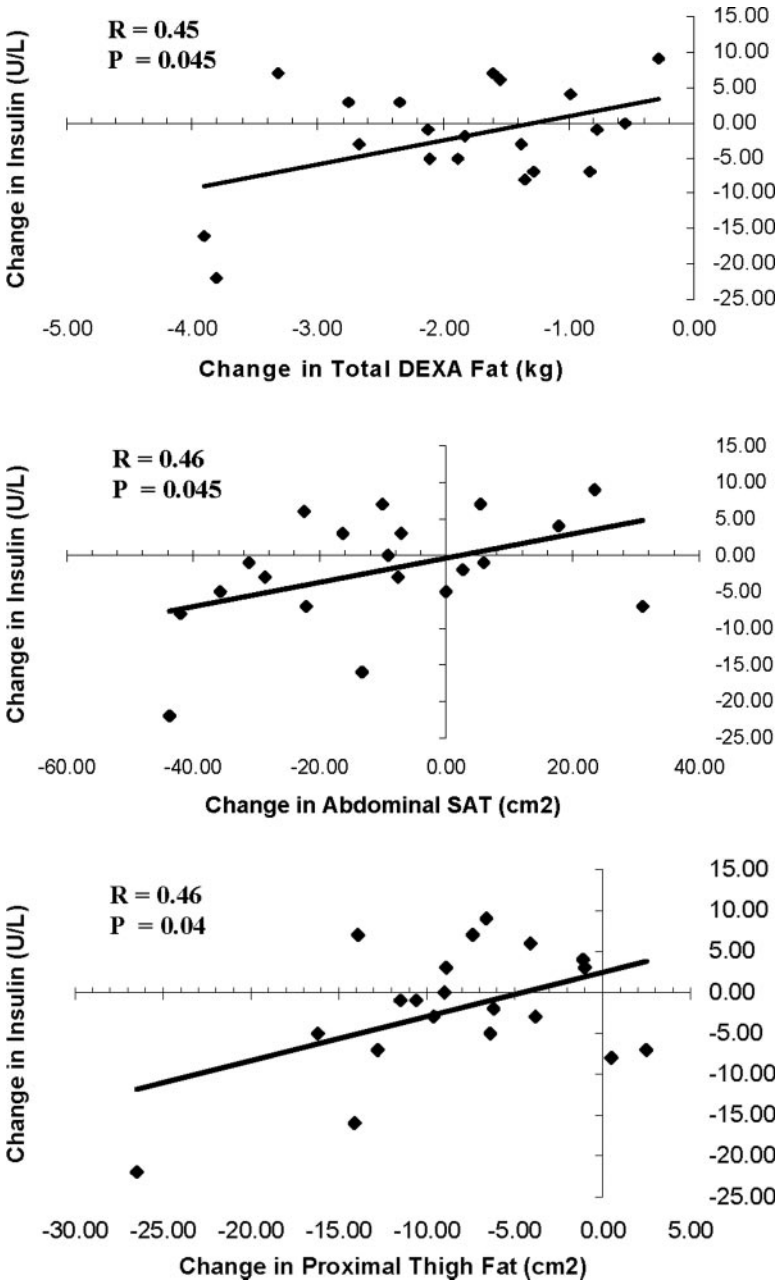

FIG. 2. Change in fasting insulin related (Pearson correlation coefficients) to change in total fat determined by DEXA (*top panel*), change in abdominal SAT determined by MRI (*middle panel*), and change in proximal sc thigh fat determined by MRI (*lower panel*) from baseline to study wk 12 for subjects receiving oxandrolone (n = 20).

ment) for total cholesterol ($P = 0.75$), LDL cholesterol ($P = 0.06$), non-HDL cholesterol ($P = 0.20$), or fasting triglycerides ($P = 0.058$). There were significant group by study week interactions for HDL cholesterol ($P < 0.001$) and Lp(a) ($P = 0.006$). At study wk 12, HDL cholesterol decreased (-0.49 ± 0.21 mmol/liter) significantly ($P < 0.001$) in the oxandrolone group. HDL cholesterol decreased modestly with placebo (-0.07 ± 0.12 mmol/liter) at wk 12; thus, the difference in change between the two groups was significant ($P < 0.001$). The effects of oxandrolone on HDL cholesterol were not sustained, and there was a rebound to levels greater than baseline at study wk 24 (Table 4).

At study wk 12, directly measured LDL cholesterol increased by 0.57 ± 0.67 mmol/liter in the oxandrolone group ($P = 0.001$) and remained greater than baseline at study wk 24 (0.41 ± 0.57 mmol/liter; $P = 0.004$). The increase in LDL chcholesterol from study wk 0 to wk 12 was greater in the oxandrolone group than in the placebo group ($P = 0.008$). Non-HDL cholesterol increased significantly ($P = 0.022$) during treatment with oxandrolone by 0.54 ± 0.97 mmol/liter, which was significantly different ($P = 0.03$) than the small nonsignificant decrease in non-HDL cholesterol with placebo (-0.06 ± 0.47 mmol/liter) at study wk 12. The increase in non-HDL cholesterol of 0.39 ± 0.70 mmol/liter at wk 24 in the oxandrolone group remained significant ($P = 0.02$), but the change was not different ($P = 0.45$) from the nonsignificant change with placebo ($P = 0.52$).

At study wk 12, Lp(a) declined by 252 ± 283 μmol/liter in the oxandrolone group ($P = 0.001$), whereas there was a small increase of 16 ± 56 μmol/liter in the placebo group

TABLE 4. Change in metabolic markers

	Wk 0	Wk 12	Wk 24	*P* value	
				0–12 wk	0–24 wk
Fasting blood sugar (mmol/liter)					
Oxandrolone	5.3 ± 0.7	4.8 ± 2.1	5.9 ± 3.2	0.39	0.39
Placebo	6.5 ± 3.5	6.1 ± 2.9	6.1 ± 2.7	0.08	0.14
Fasting insulin (μU/ml)					
Oxandrolone	20.3 ± 10.7	18.2 ± 9.0	19.4 ± 8.4	0.25	0.66
Placebo	17.0 ± 6.1	18.4 ± 6.8	19.4 ± 8.3	0.22	0.12
HOMA-IR					
Oxandrolone	4.67 ± 2.42	3.99 ± 2.99	5.14 ± 3.70	0.17	0.48
Placebo	5.26 ± 4.30	5.22 ± 3.98	5.52 ± 4.22	0.93	0.43
QUICKI					
Oxandrolone	0.134 ± 0.008	0.139 ± 0.009[a]	0.134 ± 0.008	0.018	0.54
Placebo	0.135 ± 0.011	0.134 ± 0.010	0.134 ± 0.010	0.60	0.29
Total cholesterol (mmol/liter)					
Oxandrolone	4.8 ± 0.8	4.9 ± 1.1	5.4 ± 1.1	0.85	0.005
Placebo	4.8 ± 0.9	4.7 ± 0.8	5.0 ± 0.8	0.46	0.26
Fasting triglycerides (mmol/liter)					
Oxandrolone	1.1 ± 0.5	1.0 ± 0.4[b]	1.3 ± 0.5	0.12	0.11
Placebo	1.0 ± 0.6	1.2 ± 0.9	1.1 ± 0.5	0.22	0.77
HDL cholesterol (mmol/liter)					
Oxandrolone	1.0 ± 0.3	0.5 ± 0.2[a]	1.2 ± 0.4	<0.001	0.009
Placebo	1.2 ± 0.3	1.1 ± 0.3	1.3 ± 0.3	0.08	0.005
LDL cholesterol direct (mmol/liter)					
Oxandrolone	2.9 ± 0.6	3.4 ± 0.9[a]	3.3 ± 0.8	0.001	0.004
Placebo	2.8 ± 0.6	2.7 ± 0.5	2.8 ± 0.5	0.67	0.66
Non-HDL cholesterol (mmol/liter)					
Oxandrolone	3.8 ± 0.7	4.3 ± 1.0[a]	4.2 ± 1.0	0.02	0.02
Placebo	3.7 ± 0.8	3.6 ± 0.6	3.7 ± 0.7	0.68	0.52
Lp(a) (μmol/liter)					
Oxandrolone	0.36 ± 0.40	0.05 ± 0.02[a]	0.14 ± 0.46	0.001	0.10
Placebo	0.31 ± 0.25	0.33 ± 0.25	0.29 ± 0.21	0.35	0.46
Ultrasensitive CRP (μg/liter)					
Oxandrolone	2.3 ± 2.7	2.3 ± 2.9	1.9 ± 1.8	0.90	0.24
Placebo	1.5 ± 1.0	2.6 ± 2.9	1.5 ± 0.7	0.20	0.83

For conventional metric units divide: fasting blood sugar by 0.05551 for mg/dl; total, LDL, HDL, and non-HDL cholesterol by 0.02586 for mg/dl; fasting triglycerides by 0.01129 for mg/dl; and LP(a) by 0.0357 for mg/dl. CRP, C-reactive protein.

[a] Change from study wk 0 to 12 was significantly different from placebo group, $P < 0.05$.

[b] Change from study wk 0 to 12 differed from placebo group, $P = 0.053$.

($P = 0.35$). The decrease in Lp(a) from study wk 0 to wk 12 was greater in the oxandrolone group than in the placebo group ($P < 0.001$).

Associations of hormone levels and changes in fat (Fig. 2)

Three different estimates of insulin sensitivity, namely, fasting insulin, HOMA-IR, and QUICKI at baseline, were related (Spearman correlation coefficients of −0.53, −0.49, and 0.49, respectively) to change in total fat determined by DEXA scanning from baseline to study wk 12 ($P = 0.016$, 0.03, and 0.03, respectively) for the group receiving oxandrolone. Similarly, these baseline markers of insulin sensitivity were related (r = −0.45, −0.49, and 0.49, respectively) to the change in trunk fat determined by DEXA during the 12 wk of study therapy ($P = 0.048$, 0.03, and 0.03, respectively). Importantly, the change in fasting insulin was correlated (Pearson correlation coefficients) with the change in total fat determined by DEXA (r = 0.45; $P = 0.045$), as was the change in abdominal SAT and proximal thigh sc fat by MRI and fasting insulin (r = 0.46; $P = 0.045$ and r = 0.46; $P = 0.04$, respectively) from baseline to study wk 12 in the oxandrolone group (Fig. 2). The small changes in estimates of insulin sensitivity were not related to the small, nonsignificant changes in various total or regional measures of body fat with placebo ($P > 0.05$).

Safety evaluation

During the study there were no new symptoms or physical findings that could be ascribed to oxandrolone (20). In addition, there were no significant changes or differences in prostate symptoms, prostate-specific antigen levels, or hematocrit during therapy with oxandrolone and placebo (20).

Discussion

The findings of this study indicate that treatment with an anabolic androgen may produce substantial reductions in central and appendicular fat mass in older, largely overweight or obese men at risk for the metabolic syndrome. To our knowledge, this is the first study of androgen therapy in an aging population to quantify regional changes in sc and deep adipose tissue using both DEXA scanning and MRI. Although worsening of the atherogenic lipid profile with oxandrolone would preclude prolonged use of this agent in older subjects at risk for cardiovascular complications, the study provides important new information about the poten-

tial effects of androgen therapy in older subjects with increased fat stores.

Three prior studies of testosterone therapy in older men reported reductions of total fat by up to 3.0 kg (18, 19, 23). In the largest of these studies, involving 108 subjects treated for 3 yr, there was no reduction in trunk fat determined by DEXA scanning (23). In our study, DEXA scanning showed significant decreases in central fat during treatment with oxandrolone. Moreover, by MRI there were significant reductions in both abdominal VAT and SAT with oxandrolone. These effects on abdominal fat are consistent with the known effects of androgens to decrease lipoprotein lipase and up-regulate β-adrenergic receptors on adipocytes to inhibit the accumulation of lipid and enhance the efflux of lipid from these cells in response to catecholamines (10, 24, 25). Importantly, the amount of VAT has been directly correlated with insulin resistance (26, 27) and various markers of atherosclerosis (28, 29), and abdominal SAT has been positively correlated to the acute insulin response (27). In our study VAT decreased more than abdominal SAT with oxandrolone treatment, as reflected by the significant between-group decrease in the VAT/SAT ratio, which is consistent with the larger reductions in VAT than SAT during diet-induced weight loss (30). These improvements in abdominal fat would be expected to result in favorable effects on risks for cardiovascular complications in older subjects.

DEXA scanning also revealed significant reductions in appendicular (extremity) fat. Similarly, MRI of the dominant leg showed significant reductions in sc fat in both the proximal and the distal thigh. Although several studies have suggested that sc extremity fat is directly related to insulin resistance (31, 32), others suggest that intramyocellular lipid (IMCL) is the most important peripheral site of fat relative to insulin sensitivity (33, 34). However, accurately determining IMCL requires proton or carbon MR spectroscopy, which to date has not been performed in older subjects treated with androgens. Because evidence suggests that IMF may also be correlated with insulin sensitivity in type 2 diabetes (32), we examined IMF at the distal and the proximal thigh using MRI. Oxandrolone had no appreciable effect on IMF, but the lack of change may have been due to the small volume of IMF in the cross-sectional area at only two landmarks of the thigh and may require measurement of the entire thigh muscle volume.

To our knowledge, this is also the first study to determine the durability of effects achieved with androgen therapy after treatment was discontinued. Unlike the effects on LBM and skeletal muscle strength, which generally returned to baseline (20), the reductions in both central and peripheral fat mass were largely (>80%) sustained 3 months after treatment with oxandrolone was discontinued. Our nutritionists carefully assessed dietary intake with 3-d food diaries and self-report of exercise activity during the 24 wk of the study. Because there were no significant changes in consumption of daily total calories or specific macronutrients, and habitual activity did not change, this suggests that the observed alterations in body composition and metabolic markers were related to the effects of the androgen treatment. We speculate that the durability of the effects of oxandrolone on adipose tissue, but not lean mass, may reflect biological differences in these tissues, such as density or saturation of ligands on androgen receptors, differences in regulation of androgen-responsive corepressors or coactivators, or the effects of other concurrent regulators of metabolism, such as glucocorticoid activity, that might be affected by androgen therapy.

Although testosterone therapy decreases fat mass in young hypogonadal men (35, 36), Bhasin *et al.* (37) reported no change in VAT or abdominal SAT by MRI even with supraphysiological doses of testosterone (300 and 600 mg weekly) over 4 months in healthy, lean, young men, raising the question of whether supplemental androgen has the potential to reduce abdominal fat in eugonadal lean men. In obese, middle-aged men, androgen therapy has been associated with decreases in VAT, improvements in insulin sensitivity, and declines in cholesterol, triglycerides, and diastolic blood pressure, but the effects were largely limited to men with low pretreatment testosterone levels (10, 38).

In our study 84% of the subjects were either overweight or obese, and the loss of total body fat was significantly greater in subjects with baseline testosterone levels of 10.4 nmol/liter or less ($\leq$300 ng/dl) compared with those with higher levels (-2.5 ± 1.1 *vs.* -1.5 ± 0.8 kg, respectively; $P = 0.036$). Similarly, decreases in abdominal SAT were significantly greater in subjects with baseline levels of testosterone of 10.4 nmol/liter or less (-24.1 ± 14.3 *vs.* -2.9 ± 21.3 cm^2; $P = 0.03$). Thus, in older overweight or obese men with hypogonadal or age-related low normal levels of testosterone, central adipose tissue may be more sensitive to the lipolytic actions of androgen than in eugonadal, lean, younger subjects.

Androgens appear to directly affect pleuripotent stems cells by promoting the commitment of mesenchymal precursor cells to the myogenic lineage while down-regulating adipogenic differentiation and the transformation of preadipocytes into mature fat cells (39). The durability of the reductions in the metabolically active abdominal VAT and SAT tissues observed in our study is consistent with the hypothesis that subjects had a decrease in total adipocytes (40), because the simple loss of lipid induced by lipolysis during androgen therapy would be expected to reaccumulate under conditions of constant diet and exercise once treatment is discontinued.

The masses of central (abdominal VAT and SAT) and appendicular (sc, IMF, and IMCL) adipose tissue have been related to insulin resistance and dyslipidemia (41, 42). In castrated rats, pharmacological doses of androgen produce insulin resistance, as assessed with the euglycemic clamp (43), whereas treatment with physiological doses of androgen improves insulin sensitivity using the hyperinsulinemic euglycemic clamp in middle-aged men with abdominal obesity and low normal testosterone levels (9, 10). We, therefore, determined whether changes in central and peripheral fat would affect markers related to enhanced risk for diabetes and cardiovascular complications during treatment with a potent androgen. There were no significant changes in fasting glucose, insulin, or HOMA-IR.

However, QUICKI improved significantly after 12 wk of oxandrolone therapy, and the changes were significantly different from those occurring with placebo. Moreover, the changes in total fat determined by DEXA as well as in abdominal SAT and proximal thigh sc fat determined by MRI

were correlated with the change in fasting insulin from baseline to study wk 12. Together, these results suggest that the improvements in adipose tissue stores with androgen therapy have the potential to favorably affect insulin-carbohydrate metabolism in older men who are overweight or obese as they do in younger men with low testosterone levels and central obesity.

Free fatty acids entering the portal circulation from VAT are hypothesized to be important in the pathogenesis of dyslipidemia as well as the development of hepatic insulin resistance (44, 45). Despite significant reductions in VAT in our subjects, HDL and LDL cholesterol concentrations worsened during the 12 wk of therapy with oxandrolone. These changes are in keeping with the known effects of 17-alkylated steroids to reduce HDL cholesterol, presumably through induction of hepatic lipase (46), and evidence that the hepatic lipase gene is closely linked with HDL cholesterol levels (47). The effects of anabolic androgens on LDL cholesterol have been variable, with some studies showing increases, others relatively little change, and one study even showed improvements in LDL particle morphology (48), although dose, duration of therapy, and type of agent varied (reviewed in Ref. 49). Regardless, reductions in intraabdominal fat could not overcome the direct adverse effects of oxandrolone on lipid metabolism. Thus, 17-methyl-substituted androgens would not be suitable for therapy in older men with relatively low testosterone levels and abdominal obesity.

As demonstrated with other androgens (48, 50, 51), there were sizable reductions in plasma Lp(a) with oxandrolone, a potentially beneficial effect because elevation of Lp(a) has been highly correlated with measures of atherosclerosis (52, 53). However, it is uncertain whether improvements in Lp(a) have lipid protective effects, although decreasing Lp(a) with hormone replacement therapy in women with elevated pretreatment levels of Lp(a) resulted in less subsequent coronary heart disease events (54).

There were several limitations of this study. Because we assessed the effects of a 17-alkylated androgen, changes in fat mass and metabolic markers cannot be extrapolated to a dose of testosterone. Although the favorable reductions in total and trunk fat masses by DEXA and sc extremity fat determined by MRI after treatment were significantly greater in the oxandrolone group than in the placebo group, the between-group changes in appendicular fat determined by DEXA ($P = 0.08$) and in abdominal VAT and SAT fat as measured by MRI were not significant ($P = 0.22$ and $P = 0.20$, respectively). However, the significant within-group changes in appendicular fat determined by DEXA and abdominal fat determined by MRI were consistent with the significant between-group changes in extremity sc fat with MRI and changes in trunk fat with DEXA, respectively. In addition, the fact that the changes in abdominal SAT determined by MRI correlated with improvements in fasting insulin during treatment provides additional biological plausibility to the observed within-group-only changes in abdominal fat determined by MRI in the oxandrolone group. Finally, evidence that oxandrolone improved one static estimate of insulin sensitivity (QUICKI) should be interpreted cautiously and confirmed with dynamic tests of insulin sensitivity (*e.g.* hyperinsulinemic euglycemic clamp or frequently sampled iv glucose tolerance test).

We were unable to demonstrate short-term adverse clinical effects with oxandrolone, other than the expected changes in atherogenic lipids. However, the use of any anabolic androgen, including testosterone, as a potential treatment for increased adipose tissue or sarcopenia in older subjects must be investigated in sufficiently powered, long-term treatment studies to demonstrate the safety of these agents for prostate and cardiovascular health, even though a body of data already exists suggesting that replacement doses of testosterone should be safe in an aging population (reviewed in Ref. 55). The results of our study provide new information about the biological effects of androgen therapy on regional fat mass that could favorably affect measures of metabolism and cardiovascular health in an aging population. Moreover, the observation that these changes were largely sustained for 3 months after treatment was discontinued should be explored to determine the mechanisms by which androgens may cause fat loss in older individuals.

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