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Metabolic effects of nandrolone decanoate and resistance training in men with HIV

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Sattler, Fred R., E. Todd Schroeder, Michael P. Dube, S. Victoria Jaque, Carmen Martinez, Patricia J. Blanche, Stanley Azen, and Ronald M. Krauss. Metabolic effects of nandrolone decanoate and resistance training in men with HIV. *Am J Physiol Endocrinol Metab* 283: E1214–E1222, 2002. First published August 27, 2002; 10.1152/ajpendo.00189. 2002.—Thirty human immunodeficiency virus (HIV)-infected men were randomized to a high dose of nandrolone decanoate weekly (*group 1*) or nandrolone plus resistance training (*group 2*) for 12 wk. For the two groups, nandrolone had no significant effects on total cholesterol, LDL cholesterol, LDL phenotype, or fasting triglycerides, although triglycerides decreased by 66 ± 124 mg/dl for the entire population ($P = 0.01$). *Group 2* subjects had a favorable increase of 5.2 ± 7.7Å in LDL particle size ($P = 0.03$), whereas there was no change in *group 1*. Lipoprotein(a) decreased by 7.3 ± 6.8 mg/dl for *group 1* ($P = 0.002$) and by 6.9 ± 8.1 for *group 2* ($P = 0.013$). However, HDL cholesterol decreased by 8.7 ± 7.4 mg/dl for *group 1* ($P < 0.001$) and by 10.6 ± 5.9 for *group 2* ($P < 0.001$). Percentages of HDL_{2b} (9.7–12 nm) and HDL_{2a} (8.8–9.7 nm) subfractions decreased similarly for the two groups, whereas HDL_{3a} (8.2–8.8 nm) and HDL_{3b} (7.8–8.2 nm) increased in the groups during study therapy ($P \leq 0.02$ for all comparisons). There was no evidence of a decreased insulin sensitivity in either group, whereas fasting glucose, fasting insulin, and homeostasis model assessment improved in *group 2* ($P < 0.05$). These metabolic effects were favorable (other than for HDL), but changes were generally transient (except for HDL in *group 2*), with measurements returning to baseline 2 mo after the interventions were completed.

anabolic steroids; lipoprotein(a); androgen therapy; insulin resistance; high-density lipoprotein cholesterol; low-density lipoprotein cholesterol; serum triglycerides

THE PRINCIPAL USE of supplemental testosterone therapy is to restore eugonadal hormone levels in men with primary or secondary hypogonadism. However, treatment with androgens, including semisynthetic derivatives of testosterone, also has positive anabolic effects in subjects with cachexia due to severe burns (16), renal failure (32), chronic lung disease (51), cancer (13), and alcoholic hepatitis (44). Androgens also promote synthesis of myofibrillar proteins (53, 59) and are attractive therapies for sarcopenia in older individuals with frailty (19, 56). Thus it is likely that androgens will be further tested for a broad range of medical conditions.

Androgens can also influence lipid and carbohydrate metabolism in both men and women. These effects include reductions in plasma triglycerides (30), HDL cholesterol (7, 21, 55), and lipoprotein(a) [Lp(a)] (41), with variable effects on insulin sensitivity (17, 43). Evidence suggest that the 17-alkylated derivatives may affect lipids and insulin sensitivity more than 17β-esterified analogs (see review in Refs. 23 and 24). However, doses of the different androgens evaluated have varied, baseline measurements were not described in some reports, persistence of metabolic effects after discontinuation of these agents has been described infrequently, and in studies involving athletes, subjects often received multiple anabolic agents. Thus there is incomplete understanding of the extent to which supplemental androgens affect lipid metabolism and insulin sensitivity and their risks for cardiovascular disease and diabetes when used for purposes other than treatment of hypogonadism.

Androgens have been evaluated as therapies to improve weight, muscle mass, and strength for patients with human immunodeficiency virus (HIV) (9, 26, 50). Studies are also underway to determine whether therapy with testosterone will reduce visceral adipose tissue in this population, as reported in HIV-negative middle-aged men with abdominal obesity (43). In this context, a lipodystrophy syndrome (peripheral fat wasting and/or central fat accumulation) with abnormalities in lipid metabolism and evidence of insulin resistance may occur in 30–80% of persons with HIV (12, 29, 57). Thus understanding the effects of specific androgens on serum lipids and insulin sensitivity in subjects with HIV will be important in minimizing the risks for cardiovascular disease during therapy with these agents.

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Nandrolone decanoate is a 17β-esterified derivative of testosterone, which on the basis of its molecular structure is not expected to have profound adverse effects on important components of metabolism. We hypothesized and previously reported that high doses of nandrolone for 12 wk would significantly increase muscle mass and strength in HIV weight-stable men and that these effects were augmented with progressive resistance training (PRT) (31, 50, 52). A secondary objective was to assess safety, which included comprehensive measures of lipid and carbohydrate metabolism. We now describe the effects of the study interventions on plasma lipoprotein components related to cardiovascular disease (CVD), including HDL subfractions, LDL peak particle size and phenotype, and Lp(a) as well as indirect measures of insulin sensitivity. Our results differed from those described in other populations receiving nandrolone (24, 28, 41), and, unlike reports with other androgens, we evaluated the persistence of metabolic effects several months after study interventions were discontinued. Because patients with HIV are predisposed to metabolic dysregulation, which may increase their risk for accelerated atherogenesis and diabetes, understanding the effects of specific androgens on lipid and carbohydrate metabolism will be important when these agents are prescribed for treatment of weight loss or central obesity in this population.

SUBJECTS AND METHODS

Study Design and Test Population

This was an open-label, proof-of-concept study to assess whether pharmacological doses of an androgen not aromatized to estrogen, and with or without resistance training, could increase skeletal muscle mass and voluntary muscle strength in men with chronic HIV infection. Subjects were recruited through local advertisements. To be eligible, subjects had to be HIV-seropositive men ≥18 yr of age with CD4 lymphocyte counts between 50 and 400/mm^3, have had no prior weight loss >5% or weight variation >3% recorded in medical records in the prior 6 mo, and have a body mass index of 20–27.5 kg/m^2. Subjects were required to have HIV plasma RNA levels at screening of <30,000 copies/mm^3 and a dietary energy intake >0.8 of basal energy expenditure in the week before enrollment.

Subjects were excluded from participation if they had an active opportunistic infection, malignancy, chronic viral hepatitis, or diarrhea in the prior month. They could not have participated in weight training or vigorous exercise in the preceding 28 days, have any prostate abnormalities, evidence of organic heart disease, or a history of deep venous thrombosis. Subjects could not have used anabolic therapies (e.g., growth hormone, testosterone, or synthetic steroids) or appetite stimulants in the preceding 6 mo. All subjects signed informed consent documents approved by the Institutional Review Board of the Los Angeles County University of Southern California (USC) Medical Center.

Study Interventions

Nandrolone. All subjects received nandrolone decanoate (Deca Durabolin; Organon, West Orange, NJ) by weekly intramuscular injection for 16 wk. Subjects were randomized to nandrolone alone or nandrolone plus progressive resistance training (PRT). The first dose of nandrolone was 200 mg, the second dose was 400 mg, and for *weeks 2–12* the dose was 600 mg. Doses were reduced during *weeks 13–16* (400 mg, 200 mg, 100 mg, and 50 mg, respectively) to withdraw patients from pharmacological dosing.

Exercise training regimen. Subjects received periodized PRT under direct supervision by an exercise physiologist (E. T. Schroeder) in the Exercise Laboratory at USC three times per week for 12 wk (50). Upper body exercises included bench press, lat pull downs, military press, biceps curl, and triceps extension. Lower body exercises included leg press, calf raises, leg curl, and leg extension. After warm-up, subjects performed three sets of eight repetitions at 80% of the 1-repetition maximum (1-RM), with the final set performed to failure. The 1-RM was assessed every 2 wk for all exercises to adjust the training load to maintain intensities at 80% of the 1-RM.

Subjects assigned to nandrolone only were interviewed each week about their activities to ensure that they were not initiating or participating in any resistance training activities. Subjects receiving only nandrolone were offered instructions on PRT at the completion of the 12 wk of study therapy.

Measurements

Lean mass and fat mass. Whole body and regional measures of body composition were determined by dual-energy X-ray absorptiometry (DEXA; Hologic QDR 1500W scanner, version 7.1 software; Waltham, MA). Scans were performed at baseline and at the end of *study weeks 6* and *12* but not *study week 24*. The same experienced technician who was blinded to study assignment analyzed all scans in accordance with the manufacturer's guidelines. Scans were analyzed in real time without knowledge of prior or subsequent results. The coefficient of variation was <1.0%.

Fasting blood specimens. Subjects were instructed not to eat or drink any beverage other than water after 8:00 PM of the night before and until blood was collected the next day. Blood was collected between 10:00 AM and 12:00 noon on the next day before exercise testing. Plasma (Na_2EDTA) was separated and stored at −80°C for later testing. Subjects were then allowed to eat before their exercise testing and training sessions.

Bioimmunochemical measurements. Fasting specimens were analyzed for total cholesterol, triglycerides, HDL cholesterol, and glucose by use of enzyme end-point reagent kits and an Express 550 autoanalyzer (Ciba-Corning Diagnostics, Oberlin, OH). LDL cholesterol was calculated from the Friedewald equation (20). Measurements and measurement error were within limits set by the Centers for Disease Control and Prevention Lipid Standardization Program (www.cdc.gov/nceh/dls/cv.htm; Berkeley Laboratory ID no. LSP-142). The coefficients of variation for total cholesterol, triglycerides, and HDL cholesterol were 1.74, 2.22, and 3.18%, respectively.

Lp(a) concentration in plasma was measured by "sandwich"-style ELISA by use of purified goat anti-human Lp(a) polyclonal antibodies with and without conjugation to horseradish peroxidase and detection reagent *o*-phenylenediamine. Standardization was linked to reference plasma obtained from Northwest Lipid Research Center and to commercially available calibration standards. Samples were analyzed in triplicate. The coefficient of variation was within ±10%.

Insulin concentration in fasting plasma was measured by radioimmunoassay with a commercial kit (catalog no. 07–

160102, ICN, Costa Mesa, CA). Radioactivity in the test product was measured by gamma counter (model 5002 Cobra, Packard Instruments), and sample concentrations were calculated from a standard curve (standard material included with each kit). Kit controls, as well as in-house controls, were used to monitor assay performance, which was within ±10% coefficient of variation.

Peak LDL particle diameter and LDL subclass analysis by gradient gel electrophoresis. Measurement of LDL peak particle size was performed on whole plasma by use of nondenaturing 2–14% polyacrylamide gradient gel electrophoresis (GGE) and standardized conditions (46). After electrophoresis, lipoproteins were lipid stained with Oil Red O, and calibration standards were stained with Coomassie R-250. Gels were analyzed using computer-automated densitometry, and calculation of peak particle sizes was based on the migration of reference standards of known particle size. The coefficient of variation for LDL measurements was within ±1%. LDL subclass phenotype analysis was performed as described previously (6).

HDL particle size and subpopulation distribution. HDL peak particle sizes and subpopulation area distribution were analyzed using nondenaturing 4–30% GGE. Before electrophoresis, plasma was incubated for 30 min at 28°C with fluorescent lipophyllic reagent, DiIC18 (Molecular Probes, Eugene, OR) in the presence of 1 mM diethyl *p*-nitrophenyl phosphate (DENP, Sigma-Aldrich, St. Louis, MO). After centrifugation at 4°C for 10 min at 10,000 rpm to remove excess reagent, samples were mixed with 40% sucrose (1:4, sucrose/sample) and pipetted to wells of a gel sample comb. After electrophoresis, gels were analyzed by scanning densitometry of the fluorescent signal (560 nm emission filter) with a model FX Molecular Imager and Quantity One Software (Bio-Rad Instruments, Hercules, CA). Gel images were analyzed with modified NIH Image (version 1.61/PPC)-based software. Lipoprotein controls included on each gel were measured for peak particle sizes and area distribution within HDL subclasses, and coefficient of variation was consistently within ±10% or better.

Insulin resistance. Several indirect tests of insulin resistance, such as fasting insulin, homeostasis model assessment (HOMA-IR), and quantitative insulin sensitivity check index (QUICKI), have been utilized and correlated with insulin sensitivity by the hyperinsulinemic euglycemic clamp (33, 37, 39). 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 $1/[\log (I_f) + \log (G_f)]$ (33).

Indirect calorimetry for resting energy expenditure. To assess resting energy expenditure (REE), indirect calorimetry was performed using a ventilated hood and dedicated metabolic cart (Delta Track, Sensor Medics, Anaheim CA). Before testing, CO_2 and O_2 gas analyzers were calibrated at existing temperature and atmospheric pressure. After subjects rested quietly at bed rest for 30 min, rates of oxygen consumption and carbon dioxide production were measured at 1-min intervals. The final thirty 1-min intervals of a 45-min test period were measured and recorded to calculate the 24-h REE.

Nutritional assessment. Subjects recorded dietary intake on three consecutive days, including two weekdays and one weekend day in the week before baseline, *study week 12*, and *study week 24*. Subjects were counseled that the days should be chosen to include usual activities and typical eating patterns. A licensed nutritionist (C. Martinez) 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 habit during the course of the study.

Statistical Considerations

The sample size for the original study was based on the hypothesis that nandrolone would cause a significant increase in total lean body mass (LBM) by DEXA and that nandrolone plus PRT would induce a greater than 3.0 kg increase in total LBM than treatment with nandrolone alone. With 15 subjects per group, the statistical power (1-β) was >0.80. All analyses utilized the Statistical Package for Social Sciences (SPSS, Chicago, IL), version 10.0.

To test the hypothesis of no group differences for each variable (e.g., macronutrients, lipids, and measures of glucose metabolism) at baseline and at 12 and 24 wk, we utilized two-sample *t*-tests. If data were not normally distributed, we utilized the Wilcoxon rank sum test. To test the hypothesis of no treatment effect at 12 and 24 wk within each group (total study population and for each treatment group), we compared the change from baseline for each variable with paired *t*-tests. We also contrasted changes from 12 to 24 wk with the same procedure. Finally, to test the hypothesis of no difference in treatment effect between the two randomized groups at 12 and 24 wk, we utilized the two-sample *t*-test. The χ^2 test was used to compare ethnic and racial characteristics and the change in LDL phenotype for the study groups. A bidirectional α-level of significance was set at 0.05 for all measures.

RESULTS

Subject Characteristics

Thirty-three men were enrolled, and 15 subjects per group completed their randomized study therapy. Two subjects did not return for their *week 24* evaluations. Thus final analyses included 28 subjects, unless otherwise indicated. Age, ethnicity, total serum testosterone, caloric and macronutrient intake, REE, and body composition were similar in the two treatment groups at baseline (Table 1). Measures of body composition indicated that study subjects were neither malnourished nor obese. Antiretroviral therapies, CD4 lymphocyte counts, HIV RNA levels, blood counts, and chemistries for subjects in each of the groups were also comparable at baseline (data not shown) (50). None of the study subjects changed their antiretroviral therapy during the study, and none showed evidence of lipodystrophy. Only three subjects in the nandrolone-only group requested instructions in PRT after the 12-wk intervention, and only two in the PRT group continued training during the second 12-wk period.

Changes in Body Composition

As reported previously (50), subjects randomized to nandrolone without resistance training had a 3.9 ± 2.3 kg increase in LBM ($P < 0.001$) by *study week 12*, whereas the group who also received resistance training had a 5.2 ± 5.7 kg increase in LBM ($P < 0.001$). The difference in change in LBM between the groups was significant ($P = 0.03$). There were no changes in body fat in the nandrolone-only group. However, the combination group showed a significant decline in total body

Table 1. *Baseline characteristics of study patients*

Clinical Features and Blood Tests	Nandrolone-Only Group	Nandrolone + PRT Group	*P* Value*
Age, yr	37 ± 8.2	39 ± 7.9	0.59
Ethnicity			0.86
Hispanics	8(53%)	9(60%)	
Nonhispanic Caucasians	5(33%)	2(13%)	
Nonhispanic blacks	2(13%)	2(13%)	
Asian Pacific islanders	0(0%)	2(13%)	
Total testosterone, (μg/ml)	647 ± 199	573 ± 156	0.27
Total caloric intake, $KJ \cdot kg^{-1} \cdot day^{-1}$	182 ± 39.7	167 ± 44.8	0.16
Protein intake, $g \cdot kg^{-1} \cdot day^{-1}$	1.77 ± 0.38	1.82 ± 0.53	0.69
Carbohydrate intake, $g \cdot kg^{-1} \cdot day^{-1}$	5.62 ± 1.3	4.79 ± 1.7	0.12
Fat intake, $g \cdot kg^{-1} \cdot day^{-1}$	1.62 ± 0.40	1.57 ± 0.47	0.29
REE/FFM, $J \cdot kg^{-1} \cdot 24\ h^{-1}$	128 ± 19.6	132 ± 17.1	0.62
Body mass index, kg/m^2	24.9 ± 2.2	23.9 ± 2.4	0.26
Total lean body mass, kg	57.1 ± 5.5	55.3 ± 7.1	0.43
Truncal fat, kg	6.3 ± 1.5	6.3 ± 2.8	0.99
%Body fat	18.6 ± 3.7	18.1 ± 5.0	0.77

Values are means ± SD of 15 subjects per group. PRT, progressive exercise training; REE, resting energy expenditure; FFM, fat free mass measured by dual-energy X-ray absorptiometry. *Two-sample *t*-tests for continuous variables; χ^2 tests for categorical variables.

adiposity (−1.2 ± 1.3 kg, $P = 0.003$), trunk fat (−0.6 ± 0.9 kg, $P = 0.02$), and appendicular fat (−0.6 ± 0.8 kg, $P = 0.016$) during study treatment.

Dietary Intake and REE

Total caloric intake corrected for body weight ($kJ \cdot kg^{-1} \cdot day^{-1}$) did not change from baseline to *weeks 12* or *24* ($P > 0.10$ for each comparison). The amount and proportion of protein and carbohydrate intake remained constant during the course of therapy. However, total fat intake for the entire study population decreased from 1.59 ± 0.43 $g \cdot kg^{-1} \cdot day^{-1}$ at baseline to 1.42 ± 0.37 $g \cdot kg^{-1} \cdot day^{-1}$ at *study week 12* ($P = 0.04$), although values at *week 24* (1.44 ± 0.50 $g \cdot kg^{-1} \cdot day^{-1}$) were similar to those at baseline ($P = 0.24$). There were no within-group differences in fat intake during the course of the study. REE corrected for fat-free mass (FFM) did not change from baseline to *study week 12* (130 ± 18.0 vs. 131 ± 15.0 kJ/kg FFM, respectively, $P = 0.75$).

Total/LDL Cholesterol Concentrations, LDL Peak Particle Size, and LDL Subclass Phenotype

There were no changes ($P \geq 0.15$ for all comparisons) in total (198 ±42, 191 ±45, 208 ±60 mg/dl) or calculated LDL concentrations (117 ±30, 128 ±37, 128 ±36 mg/dl) from baseline to *week 12* or *week 24* for the entire study population (Table 2). Similarly, there were no changes in either total or LDL cholesterol for the individual groups ($P \geq 0.24$ for all comparisons; data not shown). However, in *group 2* (nandrolone plus PRT), mean LDL particle size significantly increased ($P = 0.03$) by *study week 12*, but it returned to the baseline value by *study week 24* (Table 2). There was no change in the proportion of subjects with LDL subclass phenotype A (predominantly large), AB (intermediate), and B (predominantly small) after 12 wk of study therapy ($P > 0.10$ for all categorical comparisons; data not shown).

Lp(a) Concentrations

In both groups, there were sizable and significant decreases in the concentrations of Lp(a) by *study week 12*, but concentrations returned to values similar to baseline by *study week 24* (Table 2).

Fasting Serum Triglycerides

For the entire study population, there was a significant decrease in fasting triglycerides at *study week 12* (Table 2). There was large variability in results for the two groups; thus the differences did not reach statistical significance in either group. Values were similar to baseline at *study week 24*.

Total HDL Cholesterol, Peak Particle Size, and HDL Subfraction Concentrations

Total HDL cholesterol (HDL-C) decreased significantly after 12 wk of study intervention (Table 3). The absolute magnitude of the decrease was similar with the study interventions (P = NS). At *study week 24*, namely 8 wk after nandrolone was discontinued and 12 wk after completion of PRT, there was an increase of similar magnitude in both groups compared with *study week 12*. The mean HDL-C in *group 1* was not significantly different from baseline, but in *group 2*, levels remained statistically below baseline at *week 24* ($P < 0.012$).

There were also changes in HDL particle size distribution in the two study groups, with no differences between groups. Diameter of the major HDL peak decreased significantly at *week 12* and then returned toward baseline at *week 24*. The percentage of the larger HDL subfractions, HDL_{2b} and HDL_{2a}, also decreased significantly in both groups by *study week 12* but returned to levels similar to baseline at *week 24*. In contrast, the percentage of the smaller subfractions, HDL_{3a} and HDL_{3b}, significantly increased similarly in both groups after 12 wk and returned to baseline by

Table 2. *Measurement of plasma lipids and lipoproteins*

	Baseline (n = 28)	*Week 12* (n = 28)	*Week 24* (n = 28)	P Value* 0 vs. 12	P Value* 0 vs. 24
Fasting triglycerides, mg/dl					
Total nandrolone population	228 ± 138†	163 ± 78	299 ± 293	0.01	0.29
Nandrolone only	213 ± 144	173 ± 90	307 ± 335	0.12	0.41
Nandrolone + PRT	245 ± 136	151 ± 65	289 ± 249	0.07	0.54
P value†	0.56	0.47	0.88		
Total cholesterol, mg/dl					
Total nandrolone population	198 ± 42†	191 ± 45	208 ± 60	0.25	0.23
Nandrolone only	200 ± 41	192 ± 42	204 ± 47	0.24	0.76
Nandrolone + PRT	196 ± 45	192 ± 49	213 ± 75	0.63	0.24
P value†	0.81	0.98	0.71		
LDL cholesterol, mg/dl					
Total nandrolone population	117 ± 30	128 ± 37	128 ± 46	0.15	0.24
Nandrolone only	115 ± 25	129 ± 30	121 ± 54	0.54	0.90
Nandrolone + PRT	120 ± 36	136 ± 47	138 ± 54	0.20	0.15
P value†	0.72	0.66	0.43		
LDL peak particle size, Å					
Total nandrolone population	257.4 ± 9.3	260.9 ± 7.9	256.0 ± 7.9	0.09	0.53
Nandrolone only	258.8 ± 12	260.9 ± 8.8	256.5 ± 9.7	0.54	0.45
Nandrolone + PRT	255.7 ± 5.2	260.9 ± 7.2	255.4 ± 9.2	0.03	0.97
P value†	0.39	0.99	0.75		
Lp(a), mg/dl					
Total nandrolone population	15.9 ± 18.3	8.8 ± 12.1	15.2 ± 18.8‡	<0.001	0.19
Nandrolone only	15.6 ± 19.0	8.4 ± 13.1	12.6 ± 16.6	0.002	0.12
Nandrolone + PRT	16.2 ± 18.3	9.3 ± 11.5	18.7 ± 22.0	0.01	0.98
P value†	0.94	0.85	0.44		

Values are means ± SD for 14 subjects per group at each time point. Lp(a), lipoprotein(a). *Difference in outcomes between indicated time points by paired t-tests. †Difference in outcomes between nandrolone alone and nandrolone + PRT groups by 2-sample t-tests. ‡Only 26 specimens were available for testing at this time point.

week 24. There was no change during the study in the percentage of HDL_{3c}, the smallest of the HDL particles.

Relationships of Lipid Changes

There was a correlation between change in LDL peak particle diameter with both fasting triglycerides ($r = -0.59$, $P = 0.001$) and HDL cholesterol ($r = 0.51$, $P = 0.005$) after 12 wk of study intervention for the entire study population, with similar relationships in both study groups. However, there was no relationship between change in HDL cholesterol and fasting triglycerides in the total population ($r = 0.19$, $P = 0.34$) or in either of the two treatment groups during the 12-wk study period.

For diet, in the group that received PRT, the decrease in fat intake at *week 12* was associated with the decrease in triglycerides at this time point ($r = -0.59$, $P = 0.035$). However, all other changes in lipids could not be associated with change in dietary fat.

Carbohydrate Metabolism

There was a significant decrease in fasting plasma glucose levels at *study week 12*, due primarily to a decrease in *group 2* (Table 4). Likewise, fasting insulin was significantly decreased in study *group 2*. A decrease in HOMA-IR for the entire study population was nearly significant at *study week 12* and was significant for the group assigned to PRT. Of importance, the effect was sustained at *study week 24*. For QUICKI, both the entire study population and *group 2* showed significant improvements by *week 12*, but the effects were not sustained at *week 24* for this calculation of insulin resistance.

DISCUSSION

The dose of nandrolone decanoate evaluated in this proof-of-concept study is of similar magnitude to the high doses of parenteral androgens used by body builders, is in the range of popular regimens to treat autoimmune deficiency syndrome, or AIDS wasting syndrome (e.g., 400 mg of testosterone enanthate plus 400 mg of nandrolone), and may be similar to the supraphysiological doses of testosterone (600 mg weekly) shown to be safe for 20 wk (10). The importance of our findings relates to the effects of pharmacological doses of this 17β-esterified androgen with and without resistance exercise on lipid and carbohydrate metabolism in subjects with HIV who are prone to metabolic dysregulation. Moreover, we believe that this is the first study to assess the evolution of metabolic outcomes 2 mo after completion of a course of treatment with this anabolic steroid.

The effects of anabolic steroids on total and LDL cholesterol have been variable, with some studies showing significant increases and others relatively little change, although dose, duration of therapy, and type of agent have varied (23). In our study, pharmacological dosing did not result in deleterious effects on total or LDL cholesterol. To the contrary, there was a favorable shift of LDL particle size from 255.7 ± 5.2 to 260.9 ± 72 Å ($P = 0.03$) for the group receiving resis-

Table 3. *Measurements of HDL cholesterol*

	Baseline (n = 28)	*Week 12* (n = 28)	*Week 24* (n = 26)	P Value*	
				0 vs. 12	0 vs. 24
HDL cholesterol, mg/dl					
Total nandrolone population	35.9 ± 7.6	26.3 ± 5.8	31.3 ± 8.0	<0.001	0.02
Nandrolone only	35.4 ± 7.6	26.7 ± 6.2	32.4 ± 7.8	<0.001	0.31
Nandrolone + PRT	36.5 ± 7.9	25.8 ± 5.4	29.9 ± 8.5	<0.001	0.01
P value†	0.72	0.71	0.75		
HDL peak particle diameter, Å					
Total nandrolone population	91.2 ± 7.7	86.7 ± 5.7	88.9 ± 6.9	0.003	0.08
Nandrolone only	90.9 ± 8.7	87.4 ± 7.5	90.1 ± 9.1	0.043	0.42
Nandrolone + PRT	91.6 ± 6.5	85.9 ± 2.5	87.5 ± 3.3	0.045	0.13
P value†	0.81	0.51	0.36		
HDL subfractions					
% 2b Total nandrolone population	25.8 ± 3.6	22.8 ± 4.1	24.8 ± 4.4	<0.001	0.11
Nandrolone only	26.1 ± 4.0	23.1 ± 5.1	24.9 ± 5.7	0.008	0.19
Nandrolone + PRT	25.5 ± 3.3	22.3 ± 2.7	24.7 ± 2.6	0.01	0.41
P value†	0.70	0.62	0.90		
% 2a Total nandrolone population	27.2 ± 2.7	26.1 ± 3.0	26.8 ± 3.5	<0.001	0.34
Nandrolone only	26.8 ± 2.5	25.8 ± 2.3	27.1 ± 2.6	0.02	0.73
Nandrolone + PRT	27.7 ± 3.1	26.4 ± 3.7	26.5 ± 4.4	0.008	0.08
P value†	0.37	0.60	0.71		
% 3a Total nandrolone population	27.2 ± 2.9	29.3 ± 3.5	27.9 ± 3.6	<0.001	0.14
Nandrolone only	27.0 ± 3.3	28.8 ± 4.2	27.7 ± 4.5	0.02	0.26
Nandrolone + PRT	27.5 ± 2.5	29.8 ± 2.6	28.2 ± 2.2	0.01	0.36
P value†	0.64	0.44	0.71		
% 3b Total Nandrolone population	13.0 ± 2.2	14.7 ± 2.7	13.8 ± 2.7	<0.001	0.03
Nandrolone only	13.0 ± 1.8	14.6 ± 2.1	13.5 ± 2.7	<0.001	0.28
Nandrolone + PRT	13.0 ± 2.7	14.9 ± 3.3	14.1 ± 2.8	0.002	0.04
P value†	0.92	0.82	0.57		
% 3c Total nandrolone population	6.8 ± 2.6	7.2 ± 2.8	6.7 ± 3.1	0.11	0.78
Nandrolone only	7.1 ± 2.7	7.7 ± 2.8	6.8 ± 3.3	0.16	0.58
Nandrolone + PRT	6.3 ± 2.4	6.6 ± 2.9	6.5 ± 3.0	0.41	0.76
P value†	0.41	0.30	0.79		

Values are means ± SD. *Difference in outcomes between indicated time points by paired t-tests; †Difference in outcomes between nandrolone alone and nandrolone + PRT groups by 2-sample t-tests.

tance training. This short-term change would be predictive of a reduced CVD risk (4, 22, 38), but the effects were not sustained at *week 24*. Furthermore, there was no increase in the proportion of subjects with phenotype B (characterized by a predominance of small LDL particles <255 Å), a documented risk factor for cardiovascular morbidity (4).

There was a significant decrease in fasting triglycerides, a lipid that independently predicts cardiac events (3, 5), from 228 ± 138 to 163 ± 78 mg/dl (P = 0.01) for the entire study population. These effects appeared to be largely due to improvements in the resistance training group. However, triglycerides returned to baseline values at *study week 24*. In other populations, serum triglycerides are inversely related to LDL particle size (18, 27). In our subjects, decreases in triglycerides were associated with a favorable increase in LDL particle size (r = −0.59, P = 0.001).

Levels of plasma Lp(a) are highly correlated with measures of atherosclerosis and may act synergistically with LDL in the pathogenesis of atherogenesis (15, 36, 42). However, none of the lipid-lowering agents, other than nicotinic acid, affect levels of Lp(a). Hormone replacement in women can lower Lp(a), and those with elevated pretreatment levels of Lp(a) have had fewer subsequent coronary events (54). Because use of protease inhibitors is reported to increase Lp(a) (35, 48), it is noteworthy that our subjects had an almost 50% reduction in Lp(a). Whether short-term improvements in Lp(a) in our male subjects and, as reported for other anabolic steroids in women (1, 14), have any CVD protective effects is uncertain.

In keeping with the known effects of testosterone and other androgenic derivatives to reduce HDL cholesterol through induction of hepatic lipase (21, 58) and evidence that the hepatic lipase gene is closely linked with HDL cholesterol levels (2, 25), total HDL decreased modestly (9.6 ± 6.7 mg/dl) by *study week 12* for the entire population. Levels increased significantly by *week 24* but were still below baseline for the group assigned to resistance training. Further follow-up is not available to ascertain whether levels eventually returned to pretreatment values in this group.

Low levels of the larger, less dense HDL_2 subfractions have been associated with LDL phenotype B and other risk factors for CVD (11, 34) and may bear a closer relationship to CVD than total HDL (8). However, it is not certain whether the transient reductions in HDL_2, as well as total HDL, that are induced by nandrolone carry the same risk as has been observed in cross-sectional studies. There were also significant increases in the smaller, more dense subfractions HDL_{3a} and HDL_{3b} during study therapy, but the significance of changes in this subfraction for risk of CVD remains

Table 4. *Measurements of glucose and insulin metabolism*

	Baseline (n = 28)	Week 12 (n = 28)	Week 24 (n = 28)	P Value*	
				0 vs. 12	12 vs. 24
Fasting glucose, mg/dl					
Total nandrolone population	85.2 ± 16.0[b]	75.4 ± 8.2	79.4 ± 16.1	0.005	0.30
Nandrolone only	80.4 ± 14.8	75.2 ± 7.5	78.8 ± 17.8	0.17	0.46
Nandrolone + PRT	90.8 ± 16.1	75.7 ± 9.3	80.1 ± 14.6	0.02	0.49
P value†	0.10	0.89	0.85		
Fasting insulin (μU/mL)					
Total nandrolone population	17.7 ± 30.6	8.3 ± 5.3	9.9 ± 7.4	0.15	0.46
Nandrolone only	15.7 ± 39.0	8.5 ± 5.3	10.4 ± 8.5	0.61	0.57
Nandrolone + PRT	20.0 ± 18.0	8.0 ± 5.5	9.2 ± 6.0	0.049	0.66
P value†	0.72	0.81	0.72		
HOMA-IR					
Total nandrolone population	4.4 ± 8.5	1.6 ± 1.1	2.1 ± 2.1	0.06	0.93
Nandrolone only	4.0 ± 10.8	1.6 ± 1.0	2.3 ± 2.6	0.77	0.96
Nandrolone + PRT	4.9 ± 5.0	1.6 ± 1.3	1.8 ± 1.0‡	0.045	0.87
P value†	0.65	0.88	0.98		
QUICKI					
Total nandrolone population	0.504 ± 0.032	0.521 ± 0.015	0.515 ± 0.026	0.02	0.26
Nandrolone only	0.514 ± 0.034	0.521 ± 0.012	0.517 ± 0.027	0.42	0.68
Nandrolone + PRT	0.494 ± 0.028	0.521 ± 0.018	0.512 ± 0.163	0.03	0.22
P value†	0.12	0.86	0.57		

Values are means ± SD. Homeostasis model assessment (HOMA-IR) is calculated as $[(I_f) \times (G_f)]/22.5$, where I_f is fasting insulin level (μU/ml) and G_f is the fasting glucose level (mmol/l). Quantitative insulin sensitivity check index (QUICKI) is calculated as $1/[\log (I_f) + \log (G_f)]$. *Difference in outcomes between indicated time points by paired t-tests; †difference in outcomes between nandrolone alone and nandrolone plus PRT groups by 2-sample t-test; ‡*week 24* value by paired t-test was significantly different from baseline value ($P = 0.04$).

unknown (8, 45). It is likely that these changes were direct effects of study therapy, because there were no correlations ($P > 0.10$) between the small but statistically significant reductions in dietary fat observed for the entire study population during the treatment interventions and the reductions in HDL levels and HDL_2 subsets (60).

There is concern that androgen excess may worsen carbohydrate metabolism. Moreover, insulin resistance has been linked to LDL phenotype B and low levels of HDL cholesterol (40, 49), possibly through linkage to a locus near the LDL and insulin receptor genes on chromosome 19p (47). In our subjects, there was no evidence of worsening carbohydrate metabolism as measured by fasting glucose, fasting insulin, HOMA-IR, and QUICKI, which suggests that the decreases in HDL cholesterol during study therapy were not due to worsening insulin sensitivity. Moreover, fasting glucose and QUICKI for the entire population actually improved significantly during study therapy (Table 4). Because fasting insulin, HOMA-IR, and QUICKI improved significantly during study therapy in the exercise group, it is possible that any overall benefits in carbohydrate metabolism were largely due to PRT per se or greater changes in appendicular body composition (either an increase in skeletal muscle mass and/or reduction in intramyocellular lipid) for the group receiving PRT.

Several limitations of the study design need to be considered, including the absence of a nonintervention control group. However, the data suggest that the adverse effects on HDL-C and improvements in Lp(a) were largely due to the nandrolone, because changes were generally reversible shortly after nandrolone was discontinued. The reversibility of these effects also argues against the acute decreases in HDL as being primarily due to HIV infection per se. The short-term improvements in serum triglyceride and carbohydrate metabolism appeared to be related primarily to PRT, but an exercise-only group would have strengthened this contention, because the small decrease in dietary fat in this group may have contributed to the improvement in their triglycerides. Moreover, it is unlikely that PRT would have negatively affected HDL cholesterol, and it may be a safer strategy. Regardless, these outcomes may not be generalizable to other parenteral androgens with different anabolic potency or to use of these agents at different doses and for different lengths of therapy. Additionally, oral androgens, which are 17-alkylated and have high first-pass effects in the liver, might have even greater effects on hepatic lipase and HDL concentrations (21, 58). Finally, the effects of nandrolone might be different in subjects with established lipodystrophy or dysregulation of lipid and carbohydrate metabolism, and the effects may differ in women.

Although our study population lacked evidence of lipodystrophy, the study provides important insights into the potential for adverse effects when pharmacological doses of 17β-esterified androgens with or without exercise are administered to persons receiving highly active antiretroviral therapy. Although reductions in total HDL and HDL_2 concentrations appeared readily reversible, the short-term effects of declines in HDL for subjects with a cumulative number of other CVD risk factors are uncertain. Thus great care should be taken in prescribing androgens to HIV-positive subjects, and the duration of therapy should be relatively

brief to minimize the potential for adverse metabolic outcomes. However, treatment with nandrolone per se resulted in lower levels of Lp(a), and concomitant resistance exercise appeared to improve LDL particle size, fasting triglycerides, and indirect measures of insulin sensitivity. We are uncertain whether these short-term changes have any cardioprotective effects. Additional research is necessary to clarify these issues and further define the benefits and risks of androgen therapy in HIV subjects at risk for metabolic complications.

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