Effect of Exercise on Serum Androgens in Postmenopausal Women: A 12-Month Randomized Clinical Trial

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Abstract

Postmenopausal women with elevated circulating androgen concentrations have an increased risk of developing breast cancer, yet interventions to reduce androgen levels have not been identified. We examined the effects of a 12-month moderate intensity exercise intervention on serum androgens. The study was a randomized clinical trial in 173 sedentary, overweight (body mass index $\geq$ 24.0 kg/m^2, body fat > 33%), postmenopausal women, ages 50 to 75 years, not using hormone therapy and living in the Seattle, WA area. The exercise intervention included facility-based and home-based exercise (45 minutes, 5 days per week of moderate intensity sports/recreational exercise). A total of 170 (98.3%) women completed the study, with exercisers averaging 171 minutes per week of exercise. Women in the exercise and control groups experienced similar, nonsignificant declines in most androgens. Among women who lost >2% body fat, testosterone and free testosterone concentrations fell by 10.1% and 12.2% between baseline and 12 months in exercisers compared with a decrease of 1.6% and 8.0% in controls (P = 0.02 and 0.03 compared with exercisers, respectively). Concentrations of testosterone and free testosterone among exercisers who lost between 0.5% and 2% body fat declined by 4.7% and 10.4%. In controls who lost this amount of body fat, concentrations of testosterone and free testosterone declined by only 2.8% and 4.3% (P = 0.03 and 0.01 compared with exercisers, respectively). In summary, given similar levels of body fat loss, women randomized to a 12-month exercise intervention had greater declines in testosterone and free testosterone compared with controls. The association between exercise and breast cancer risk may be partly explained by the effects of exercise on these hormones. (Cancer Epidemiol Biomarkers Prev 2004; 13(7):1099–105)

Introduction

Despite considerable efforts, few modifiable risk factors for breast cancer have been identified (1). Postmenopausal women who engage in regular ($\geq$3 hours per week) physical activity have a reduced risk for breast cancer compared with inactive women (2, 3). Sedentary behavior is modifiable, although the effect of increasing physical activity on breast cancer biomarkers is unknown.

Overweight, obese, and sedentary postmenopausal women have elevated concentrations of circulating total and free androgens (4-6), and one report suggests that this association may be due to increased amounts of 17β-hydroxysteroid dehydrogenase in subcutaneous and intraabdominal fat (7). A combined analysis of nested case-control studies within nine cohort studies, which included data from 663 breast cancer cases and 1765 women without breast cancer, found that postmenopausal women with serum hormone concentrations in the top quintile for testosterone, androstenedione, dehydroepiandrosterone (DHEA), and DHEA sulfate (DHEA-S) were approximately twice as likely to develop breast cancer compared with women with serum hormones in the bottom quintile (8). In the same analysis, a doubling of androgen concentration resulted in a 20% to 40% increase in risk for breast cancer. When estradiol and testosterone were included in the same model, the effect of doubling of testosterone on breast cancer risk was greater than that of estradiol (relative risks 1.32 and 1.18, respectively), and similar results were observed for androstenedione when combined in a model with estradiol. These androgens may increase cell proliferation by being converted to estradiol and estrone in the circulation or target tissue (9). In addition, androgens may affect breast cancer risk by directly stimulating the growth and division of breast cells (8). While not proven, a reasonable hypothesis is that reduction of circulating androgen concentrations would lower breast cancer risk.

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We conducted a randomized clinical trial to examine the effect of a 12-month moderate intensity exercise intervention on circulating concentrations of serum testosterone, free testosterone, androstenedione, DHEA, and DHEA-S among sedentary, overweight/obese postmenopausal women not taking hormone therapy. We reported previously that this program significantly decreases body fat in postmenopausal women (10) and hypothesized that it would therefore lower serum androgens because of the observed associations between increased adiposity and increased androgens (4-6). In secondary analyses planned before initiation of the study, we assessed the effect of exercise on serum androgens by change in adiposity and, among exercisers, by adherence to the intervention.

Methods

The study was a randomized clinical trial comparing the effect of a 12-month moderate intensity aerobic exercise intervention versus stretching control program on circulating androgens measured at baseline (prerandomization) and at 3 and 12 months (11). All study procedures, including a written informed consent, were reviewed and approved by the Fred Hutchinson Cancer Research Center Institutional Review Board.

Participants. Participants were ages 50 to 79 years, from the greater Seattle area, sedentary [<60 minutes per week of moderate or vigorous intensity recreational activity and a maximal oxygen consumption ($VO_{2\ max}$) > 25.0 mL/kg/min], with a body mass index (BMI) $\geq$ 25.0 kg/m^2 (or a BMI between 24.0 and 25.0 kg/m^2 if percentage body fat measured by bioelectrical impedance was >33.0%), not taking menopausal hormone therapy in any form during the past 6 months, without serious comorbidities including diabetes, and nonsmokers. We defined ''postmenopausal'' as having no menstrual periods for the previous 12 months and, for women ages 50 to 54 years, a serum follicle stimulating hormone > 30 mIU/mL.

We recruited women through a combination of mass mailings and media placements (12). After extensive screening (Fig. 1), we randomly assigned 173 women to an exercise intervention (n = 87) or a control group (n = 86) stratified by BMI (<27.5 versus $\geq$27.5 kg/m^2). Randomization was performed by random number generation, and group assignment was placed in a sealed envelope, which was opened by the study coordinator at the time of randomization.

Exercise Intervention. The exercise prescription consisted of at least 45 minutes of moderate intensity exercise, 5 days per week for 12 months. Participants were required to attend three supervised sessions per week at a study facility (University of Washington or a commercial gym) during months 1 to 3 and to exercise 2 days per week at home. During months 4 to 12, they were required to attend at least one session per week at a study facility

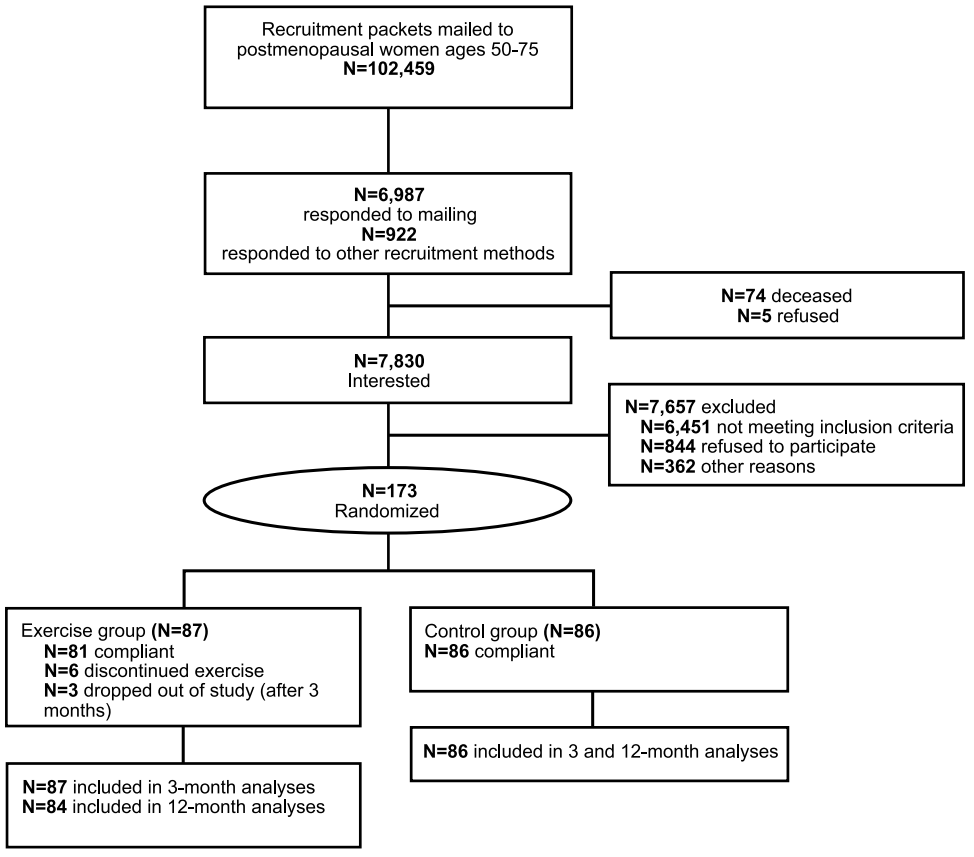

Figure 1. Participant recruitment, screening, randomization, and retention.

Table 1. Baseline characteristics* of randomized participants

	Exercisers	Controls
n	87	86
Age (y), mean ± SD	60.7 ± 6.7	60.6 ± 6.8
BMI (kg/m^2), mean ± SD	30.4 ± 4.1	30.5 ± 3.7
Percentage body fat (dual energy X-ray absorptiometry), mean ± SD	47.4 ± 4.8	47.3 ± 4.6
$VO_{2\ max}$ (mL/kg/min), mean ± SD	20.0 ± 3.5	20.4 ± 3.0
Alcohol (g/d), mean ± SD	4.03 ± 8.4	4.62 ± 7.2
Total calories (kcal/d), mean ± SD	1635 ± 792.2	1722 ± 671.8
Full-time employment, *n* (%)	25 (29)	25 (29)
Education, *n* (%)		
High school graduate	10 (12)	9 (10)
Some college	36 (41)	35 (41)
College graduate	5 (6)	10 (12)
Graduate degree	36 (41)	32 (37)
Ethnicity, *n* (%)		
Non-Hispanic White	74 (86)	75 (87)
African American	4 (5)	3 (4)
Asian/Pacific Islander	6 (7)	3 (4)
Hispanic/Latino	0 (0)	2 (2)
American Indian	0 (0)	2 (2)
Other	2 (2)	1 (1)
Family history of breast cancer, *n* (%)		
None	59 (68)	58 (67)
First degree	14 (16)	16 (19)
Second degree	13 (15)	11 (13)
Ever used hormone therapy, *n* (%)	35 (48)	38 (52)
History of hysterectomy, *n* (%)	13 (14.9)	18 (20.9)

*There were no statistically significant differences at baseline between intervention and control participants for these variables.

and to exercise 4 days per week at home or at the facility. The training program started at 40% of observed maximal heart rate for 16 minutes per session and gradually increased to 60% to 75% of maximal heart rate for 45 minutes per session by week 8. Participants wore Polar heart rate monitors during exercise sessions and primarily engaged in treadmill and outdoor walking and stationary bicycling (10).

Women randomized to the control group attended weekly 45-minute stretching sessions and were asked not to change other exercise habits during the study. Exercisers and control participants were asked to maintain their usual diet.

We used two measures of exercise adherence. We assessed baseline and 12-month $VO_{2\ max}$ in all participants using a maximal graded treadmill test, with heart rate and oxygen uptake monitored by an automated metabolic cart (Medgraphics, St. Paul, MN; ref. 10). In addition, exercise intervention participants kept daily activity logs of all sports or recreational activities of $\geq$3 metabolic equivalent level, where 1 metabolic equivalent is equal to the oxygen cost at rest (1 kcal/kg/h; ref. 13). For each exercise session, participants recorded the type of exercise performed, peak heart rate, rating of perceived exertion (on a scale of 6 to 20), and duration of exercise.

Baseline, 3-Month, and 12-Month Follow-up Measures. At baseline and at 3 and 12 months, we collected demographic information, medical history, health habits, medication use, reproductive and body weight history, past 3 months total energy intake via a 120-item self-administered food frequency questionnaire (14), and past 3 months frequency, duration, and intensity of physical activity with a self-administered adaptation of the Minnesota Physical Activity Questionnaire (15). Baseline, 3-month, and 12-month weight and height (to the nearest 0.1 kg and 0.1 cm, respectively) were obtained using a balance beam scale and wall-mounted stadiometer. Waist (standing, smallest circumference between abdomen and chest) and hip (standing, largest circumference between waist and thigh) circumferences were measured in a standardized manner to the nearest 0.1 cm using an anthropometric fiberglass tape measure.

We assessed total body fat and percentage body fat using a dual energy X-ray absorptiometry whole body scanner (Hologic QDR 1500, Hologic Inc., Waltham, MA) and intraabdominal and subcutaneous fat using computed tomography (model CT 9800 scanner, General Electric, Waukesha, WI) at baseline and 12 months. The computed tomographic scan was performed at the umbilicus (L4-L5 space; at 125 kV and with a slice thickness of 8 mm). A technician who was blinded to group assignment measured the subcutaneous and intraabdominal fat areas using a computerized image analysis that identifies and measures each of the areas of interest by tracing lines around them and computing the circumscribed areas (16). Coefficients of variation for repeat measurement of the computed tomographic images of subcutaneous and intraabdominal fat were 1.2% and 1.5%, respectively. At baseline and at 3 and 12 months, participants provided a 12-hour fasting 50 mL sample of blood. Blood was processed within 1 hour of collection, and serum was aliquoted into 1.8 mL tubes and stored at −70°C.

Hormone Assays. Laboratory assays were performed at the Reproductive Endocrine Research Laboratory, University of Southern California (Frank Z. Stanczyk, Director). Samples were placed into batches such that, within each batch, all samples from a participant were included, the number of exercise and control participants was approximately equal, the randomization dates of participants were similar, and the sample order was random. Two specimens of a quality control pooled sample and a 10% random sample of repeat prerandomization blood draws were placed in each batch. Laboratory personnel were blinded to sample identity.

Testosterone, androstenedione, and DHEA were quantified by sensitive and specific RIAs following organic solvent extraction and Celite column partition chromatography (17, 18). Chromatographic separation of the steroids was achieved by use of different concentrations of toluene in isooctane. Sex hormone binding globulin (measured for calculating free testosterone) was quantified via an immunometric assay using the Immulite Analyzer (Diagnostic Products Corporation, Los Angeles, CA). Free testosterone was calculated using the measured testosterone and sex hormone binding globulin concentrations and an assumed constant for albumin (19-21). DHEA-S was quantified via a competitive immunometric assay using the Immulite Analyzer (Diagnostic Products Corporation). The intraassay, interassay, and within-person coefficients of variation for assays were as follows: testosterone 8.4%, 12.2%, and 12.2%; androstenedione 7.4%, 9.8%, and 25.6%; DHEA 6.1%, 11.6%, and 28.9%;

DHEA-S 9.5%, 10.9%, and 46.6%; and sex hormone binding globulin 6.7%, 10.0%, and 21.1%.

Statistical Analyses. We first assessed the baseline associations between androgens and several measures of adiposity including percentage body fat, BMI, waist circumference, and intraabdominal and subcutaneous abdominal fat, with Spearman correlation coefficients. We computed the change in geometric means of hormone end points (testosterone, free testosterone, androstenedione, DHEA, and DHEA-S) from baseline to 3 and 12 months stratified by intervention group. The primary trial analysis assessed the intervention effect based on assigned treatment at the time of randomization regardless of adherence or compliance status (intent-to-treat). The analysis considered log-transformed hormone measures at baseline and at 3 and 12 months as repeated measures and assessed the intervention effects using a generalized estimating equation modification of linear regression models (22). For secondary analyses, we assessed the effect modification by change in body fat and, among exercisers only, by minutes exercised per week and change in $VO_{2\ max}$. We classified change in body fat into the following categories: any gain in percentage body fat of ≥0.5%, percentage body fat changed by <0.5%, and two equal-sized categories of loss in percentage body fat. We also assessed whether factors that are potentially related to hormone concentrations might have changed differentially between exercisers and controls, including alcohol use, caloric intake, and use of certain medications such as thyroid medications that could theoretically affect sex hormone concentrations. All statistical tests were two sided. Statistical analyses were performed using SAS software (version 8.2, SAS Institute Inc., Cary, NC).

Results

Study Participants. Hormone measurements were available for all women at 3 months and for 170 women at 12 months. At baseline, the intervention and control groups were similar with regard to demographic characteristics, body composition, mean daily caloric intake, fitness levels, and hormone concentrations (Tables 1 and 2). Participants, on average, were 61 years old, obese, highly educated, and with a low level of fitness. Less than one third of the participants worked full time; 86% were non-Hispanic White, 4% were African American, and 6% were Asian American.

Participant Retention and Exercise Adherence. On average, the exercisers participated in moderate intensity sports/recreational activity on 4.0 days per week for a total of 171 minutes per week (versus goal 225 minutes per week). Six (8%) exercisers ''dropped out'' of the exercise intervention (e.g., stopped exercising) after 3 months. However, three provided 12-month blood and are included in the analyses. Exercise adherence was significantly higher during months 1 to 3 of the intervention than during months 4 to 12 (10). Six (7%) of the women in the control group reported an increase ≥225 minutes per week of moderate vigorous sports/recreational activity from baseline to 12 months. On average, $VO_{2\ max}$ increased from baseline to 12 months by 12.7% in exercisers and by 0.8% in controls ($P < 0.0001$).

Baseline Associations between Adiposity and Serum Hormones. There was a statistically significant correlation between baseline percentage body fat and free testosterone ($r = 0.20$, $P = 0.0007$); correlations between other androgens and percentage body fat were small and not statistically significant. DHEA was statistically significantly, but negatively, correlated with amount of intraabdominal fat ($r = -0.16$, $P = 0.03$).

Intervention Effects. Women in the exercise and control groups experienced similar, nonsignificant declines in testosterone, androstenedione, DHEA, and DHEA-S from baseline to 3 and 12 months such that the comparison of change over time between exercisers and controls was not statistically significant (Table 2). Exercisers experienced a 6.5% decline in free testosterone

Table 2. Hormone concentrations [Geometric Mean (95% Confidence Interval)] at baseline and at 3 and 12 months in exercise intervention and control participants

	Baseline	3 Months	P*	12 Months	P†
Androstenedione (pg/mL)					
Exercisers	533 (494-575)	480 (439-525)	0.15	480 (447-516)	0.89
Controls	585 (541-633)	566 (524-611)		525 (489-564)	
DHEA (ng/mL)					
Exercisers	2.19 (1.93-2.49)	2.00 (1.73-2.30)	0.21	1.93 (1.68-2.20)	0.47
Controls	2.46 (2.22-2.72)	2.39 (2.15-2.65)		2.24 (2.03-2.47)	
DHEA-S (μg/dL)					
Exercisers	53.0 (45.5-61.8)	49.0 (41.9-57.3)	0.50	47.8 (41.2-55.5)	0.57
Controls	63.1 (54.8-72.7)	58.5 (50.6-67.6)		58.5 (50.9-67.2)	
Testosterone (pg/mL)					
Exercisers	211 (196-228)	207 (191-224)	0.95	208 (190-227)	0.94
Controls	223 (204-243)	218 (201-238)		218 (199-239)	
Free testosterone (pg/mL)					
Exercisers	4.6 (4.2-4.9)	4.3 (4.0-4.7)	0.28	4.3 (3.9-4.7)	0.42
Controls	4.7 (4.3-5.2)	4.6 (4.3-5.1)		4.6 (4.2-5.0)	

*Difference in hormone change from baseline to 3 months in exercisers versus controls resulting from repeated-measures analysis.
†Difference in hormone change from baseline to 12 months in exercisers versus controls resulting from repeated-measures analysis.

Table 3. Hormone concentrations [Geometric Mean (95% Confidence Interval)] at baseline and at 3 and 12 months in exercise intervention and control participants by change in percentage body fat

	Exercisers			Controls		
	Baseline	3 Months	12 Months	Baseline	3 Months	12 Months
Androstenedione (pg/mL)						
Gained percentage body fat	498 (432-573)	505 (433-590)	473 (410-546)	601 (513-704)	562 (479-659)	538 (461-628)
No change in percentage body fat	526 (459-603)	443 (345-570)	551 (437-694)	574 (473-696)	527 (455-611)	502 (434-582)
Lost 0.5-2% body fat	526 (460-602)	489 (405-591)	470 (424-521)	595 (527-672)	608 (530-697)	526 (467-592)
Lost >2% body fat	558 (472-661)	463 (398-540)	463 (398-539)	557 (471-659)	554 (462-664)	506 (441-580)
DHEA (ng/mL)						
Gained percentage body fat	1.59 (1.12-2.26)	1.63 (1.13-2.34)	1.46 (1.00-2.14)	2.53 (2.08-3.09)	2.50 (2.04-3.07)	2.26 (1.89-2.72)
No change in percentage body fat	2.16 (1.75-2.67)	1.84 (1.28-2.66)	2.31 (1.63-3.29)	2.54 (2.07-3.11)	2.29 (1.89-2.77)	2.27 (1.90-2.73)
Lost 0.5-2% body fat	2.26 (1.80-2.84)	2.15 (1.62-2.85)	1.99 (1.60-2.49)	2.55 (2.14-3.04)	2.50 (2.18-2.88)	2.33 (1.97-2.75)
Lost >2% body fat	2.51 (2.02-3.12)	2.18 (1.77-2.67)	2.01 (1.63-2.50)	1.83 (1.44-2.33)	1.81 (1.27-2.57)	1.68 (1.32-2.15)
DHEA-S (g/dL)						
Gained percentage body fat	41.9 (29.5-59.5)	42.7 (31.8-57.4)	37.3 (25.9-53.7)	69.4 (53.2-90.4)	63.5 (48.3-83.6)	63.0 (48.7-81.6)
No change in percentage body fat	52.1 (37.6-72.2)	47.3 (29.9-74.8)	52.4 (35.0-78.7)	63.3 (48.1-83.1)	54.5 (40.4-73.6)	58.0 (43.6-77.2)
Lost 0.5-2% body fat	52.3 (39.3-69.6)	48.1 (35.2-65.7)	50.2 (40.2-62.6)	64.3 (52.1-79.2)	63.2 (50.2-77.0)	58.1 (46.3-72.8)
Lost >2% body fat	62.5 (46.3-84.3)	55.4 (42.4-72.3)	48.9 (36.3-66.0)	42.9 (26.6-69.3)	43.4 (26.4-71.4)	44.3 (28.8-68.2)
Testosterone (pg/mL)						
Gained percentage body fat	215 (184-260)	233 (191-284)	237 (187-300)	236 (198-281)	217 (182-257)	223 (184-269)
No change in percentage body fat	224 (179-281)	227 (189-273)	234 (194-281)	210 (170-260)	214 (173-265)	213 (168-271)
Lost 0.5-2% body fat	213 (187-243)	210 (187-236; $P = 0.024$)*	200 (175-229; $P = 0.027$)†	215 (190-242)	215 (195-237)	209 (190-230)
Lost >2% body fat	199 (173-230)	179 (154-207; $P = 0.005$)*	183 (156-213; $P = 0.023$)†	248 (196-315)	244 (193-308)	239 (192-298)
Free testosterone (pg/mL)						
Gained percentage body fat	4.8 (4.1-5.7)	5.1 (4.2-6.2)	5.2 (4.2-6.5)	4.8 (3.9-5.8)	4.5 (3.7-5.4)	4.5 (3.7-5.5)
No change in percentage body fat	4.6 (3.6-6.0)	4.4 (3.5-5.6; $P = 0.065$)*	4.8 (3.9-5.9)	4.6 (3.8-5.7)	4.7 (3.7-5.8)	4.7 (3.7-5.9)
Lost 0.5-2% body fat	4.8 (4.2-5.5)	4.6 (4.0-5.2; $P = 0.033$)*	4.3 (3.7-4.9; $P = 0.010$)†	4.6 (4.1-5.1)	4.6 (4.2-5.0)	4.4 (4.0-5.0)
Lost >2% body fat	4.1 (3.6-4.7)	3.6 (3.1-4.1; $P = 0.010$)*	3.6 (3.1-4.2; $P = 0.031$)†	5.4 (4.5-6.6)	5.3 (4.3-6.5)	5.0 (4.1-6.0)

NOTE: The numbers of exercisers who gained, no change, lost 0.5% to 2.0% body fat, and lost >2% body fat were 16, 12, 29, and 26, respectively; the numbers of controls who gained, no change, lost 0.5% to 2.0% body fat, and lost >2% body fat were 27, 20, 25, and 11, respectively.

*P value for hormone change from baseline to 3 months in exercisers versus controls within level of percentage body fat change compared with those that gained percentage body fat. P values not presented were >0.05.

†P value for hormone change from baseline to 12 months in exercisers versus controls within level of percentage body fat change compared with those that gained percentage body fat. P values not presented were >0.05.

from baseline to 3 and 12 months compared with a 2.1% decline in controls ($P = 0.28$ and 0.42, respectively).

At 3 and 12 months, androgen concentrations decreased to a greater extent among exercisers who lost at least 0.5% body fat versus exercisers who did not lose body fat (Table 3). Among women who lost between 0.5% and 2% body fat, exercisers' testosterone declined by 1.5% and 4.7%, respectively, at 3 and 12 months, while, in controls, it did not change at 3 months and declined by only 2.8% at 12 months ($P = 0.02$ and 0.03 compared with exercisers, respectively). Among those who lost >2% body fat, exercisers' testosterone declined by 10.1% and 8.0%, respectively, at 3 and 12 months, while, in controls, it declined by only 1.6% and 3.6% ($P = 0.005$ and 0.02 compared with exercisers, respectively). Among women who lost between 0.5% and 2% body fat, exercisers' 12-month free testosterone declined by 10.4%, while, in controls, it declined by only 4.3% ($P = 0.03$ and 0.01, respectively). Among those who lost >2% body fat, exercisers' 12-month free testosterone declined by 12.2%, while, in controls, it declined by only 8.0% ($P = 0.01$ and 0.03, respectively). Although not statistically significant, exercisers versus controls who lost >2% body fat had greater 12-month changes in androstenedione (−17.1% versus −9.2%, respectively), DHEA (−20.0% versus −8.2%, respectively), and DHEA-S (−21.8% versus 3.3%, respectively). Similar results were observed according to change in BMI and waist and hip

Table 4. Hormone levels [Geometric Mean (95% Confidence Interval)] at baseline and 12 months in exercise intervention participants by change in fitness ($VO_{2\ max}$)

	Exercisers		
	Baseline	12 Months	P*
Androstenedione (pg/mL)			
Decrease or stable $VO_{2\ max}$†	500 (413-604)	418 (370-472)	
1-10% increase in $VO_{2\ max}$‡	578 (494-676)	542 (459-640)	0.37
>10% increase in $VO_{2\ max}$§	520 (464-582)	477 (428-531)	0.39
DHEA (ng/mL)			
Decrease or stable $VO_{2\ max}$	1.54 (1.07-2.23)	1.27 (0.88-1.83)	
1-10% increase in $VO_{2\ max}$	2.54 (1.97-3.26)	2.29 (1.68-3.12)	0.45
>10% increase in $VO_{2\ max}$	2.26 (1.90-2.69)	2.08 (1.75-2.47)	0.22
DHEA-S (μg/dL)			
Decrease or stable $VO_{2\ max}$	41.3 (26.6-64.1)	33.7 (22.1-51.2)	
1-10% increase in $VO_{2\ max}$	61.1 (43.5-85.9)	60.3 (45.7-79.6)	0.13
>10% increase in $VO_{2\ max}$	56.5 (45.4-70.3)	49.2 (39.9-60.6)	0.39
Testosterone (pg/mL)			
Decrease or stable $VO_{2\ max}$	177 (151-207)	167 (143-194)	
1-10% increase in $VO_{2\ max}$	244 (213-280)	252 (211-302)	0.18
>10% increase in $VO_{2\ max}$	205 (181-232)	197 (173-223)	0.71
Free testosterone (pg/mL)			
Decrease or stable $VO_{2\ max}$	3.9 (3.3-4.6)	3.6 (3.0-4.2)	
1-10% increase in $VO_{2\ max}$	5.1 (4.3-6.0)	5.0 (4.0-6.2)	0.35
>10% increase in $VO_{2\ max}$	4.5 (4.0-5.0)	4.1 (3.6-4.6)	0.95

*P value for difference in hormone change from baseline between $VO_{2\ max}$ groups (referent is decrease or stable $VO_{2\ max}$ group).
†n = 14.
‡n = 20.
§n = 41.

circumferences (data not shown). Changes in intra-abdominal and subcutaneous fat, on the other hand, did not modify the intervention versus control changes in any of the hormones (data not shown).

The change in hormone concentrations from baseline to 12 months among exercisers was not consistently related to change in $VO_{2\ max}$ (Table 4). Similarly, there was no clear evidence of an increase in exercise effect on hormone concentration with increasing minutes per week of exercise (data not shown).

Discussion

The results of this randomized clinical trial suggest that exercise can lower levels of circulating testosterone and free testosterone in a subset of previously sedentary, overweight postmenopausal women. The study had excellent retention and adherence, which decreases the chance of biased results and increases study power. We noted that concentrations of most androgens decreased over the 12-month period in both exercisers and controls, which may reflect the physiology of androgens as women age (23). Nevertheless, we noted that, among women who lost body fat, testosterone and free testosterone decreased to a greater degree in exercisers compared with controls; these results were statistically significant. Thus, the data indicate that loss of body fat in conjunction with moderate intensity exercise causes greater reductions in androgen levels than loss of body fat alone and that the exercise need not be of a vigorous intensity.

The larger testosterone decrease in exercisers over controls was limited to women who lost body fat. Increased adiposity is associated with elevated concentrations of testosterone perhaps because fat tissue contains the enzyme 17β-hydroxysteroid dehydrogenase, which catalyzes the conversion of androstenedione to testosterone (7). Abdominal subcutaneous and intraabdominal fat contain higher amounts of 17β-hydroxysteroid dehydrogenase than aromatase (24). Women who reduce body fat through exercise, particularly abdominal fat, might therefore reduce the amount of enzyme available and thereby reduce production of testosterone.

The exercisers lost only an average of only 1.4 kg of total body fat over the 12-month study (10), so we were not able to assess the effect of large amounts of body fat loss on hormones. We tested only one exercise intervention; thus, we cannot speculate on the effects of different types, intensities, and durations of exercise on circulating sex hormones. We did not test the effect of dietary change, so we cannot address the overall issue of energy balance and serum hormone effects.

Women who change exercise behaviors might also change other behaviors. However, we observed no differences between exercisers and controls with respect to changes in factors that could affect hormone levels. Daily median alcohol intake increased by 0.1 g in exercisers and 0 g in controls. Mean energy intake decreased in exercisers and controls by 15 and 114 kcal per day, respectively (P = 0.34). Medication use did not change differently in exercisers versus controls.

One potential adverse effect of lowering androgens in postmenopausal women might be a decrease in bone

density (25). Whole body bone density from dual energy X-ray absorptiometry scans in our study, however, showed no decrease in bone density in exercisers from baseline to 12 months ($P = 0.20$), and the changes in bone density did not differ between exercisers and controls ($P = 0.60$).

While we speculate that lowering testosterone and free testosterone concentrations with exercise may reduce risk of breast cancer, there could be adverse effects of lowering testosterone including decrease in sexual function, decrease in muscle mass and function, and increased frailty with aging (23, 26, 27).

The exercise intervention in this study was specifically designed to be acceptable and achievable by postmenopausal, previously sedentary women and may be a useful regimen for reducing risk of breast cancer.

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