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ORIGINAL REPORT

Combined Resistance and Aerobic Exercise Program Reverses Muscle Loss in Men Undergoing Androgen Suppression Therapy for Prostate Cancer Without Bone Metastases: A Randomized Controlled Trial

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Clinical Trials repository link available on JCO.org.

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A B S T R A C T

Purpose
Androgen suppression therapy (AST) results in musculoskeletal toxicity that reduces physical function and quality of life. This study examined the impact of a combined resistance and aerobic exercise program as a countermeasure to these AST-related toxicities.

Patients and Methods
Between 2007 and 2008, 57 patients with prostate cancer undergoing AST (commenced > 2 months prior) were randomly assigned to a program of resistance and aerobic exercise (n = 29) or usual care (n = 28) for 12 weeks. Primary end points were whole body and regional lean mass. Secondary end points were muscle strength and function, cardiorespiratory capacity, blood biomarkers, and quality of life.

Results
Analysis of covariance was used to compare outcomes for groups at 12 weeks adjusted for baseline values and potential confounders. Patients undergoing exercise showed an increase in lean mass compared with usual care (total body, $P = .047$; upper limb, $P < .001$; lower limb, $P = .019$) and similarly better muscle strength ($P < .01$), 6-meter walk time ($P = .024$), and 6-meter backward walk time ($P = .039$). Exercise also improved several aspects of quality of life including general health ($P = .022$) and reduced fatigue ($P = .021$) and decreased levels of C-reactive protein ($P = .008$). There were no adverse events during the testing or exercise intervention program.

Conclusion
A relatively brief exposure to exercise significantly improved muscle mass, strength, physical function, and balance in hypogonadal men compared with normal care. The exercise regimen was well tolerated and could be recommended for patients undergoing AST as an effective countermeasure to these common treatment-related adverse effects.

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INTRODUCTION

There has been a substantial increase in the use of temporary androgen suppression treatment (AST) as an adjuvant management of prostate cancer.[1] However, AST leads a number of well established toxicity-related musculoskeletal deficits (eg, skeletal muscle loss, and strength), osteoporosis and skeletal fractures that can substantially reduce quality of life, physical function, and independence.[2-6] Moreover, recent work suggests an increased incidence of cardiovascular and metabolic morbidity associated with temporary AST.[7-10] These treatment-related toxicities may be compounded by delay or failure of testosterone to recover in some men after cessation of AST, hence AST-related complications may not be temporary.[11,12]

Currently, there is no established treatment to reverse the array of adverse effects associated with AST. Physical exercise has been suggested as a key lifestyle intervention due to its potential to limit and even reverse such toxicities,[13,14] but evidence is limited to only a few studies.[15-17] Nonetheless, physical exercise is acknowledged as an essential lifestyle contributor that can significantly reverse the age-related loss of muscle mass (sarcopenia)[18] and reduce cardiovascular and metabolic disease, however, efficacy for patients receiving AST has not been established.[14] We previously found that a 20-week resistance exercise program significantly improved the musculoskeletal function of men treated with AST in an uncontrolled pilot study[19] without elevating levels of testosterone or prostate-specific antigen (PSA).[20] Others have reported that resistance and aerobic exercise as individual exercise modes have reduced fatigue and improved quality of life in patients undergoing AST or radiation therapy.[16,21] In this report, we extend these findings by comparing the effects of a combined resistance and low volume aerobic exercise program versus usual care in patients with hypogonadal prostate cancer. We hypothesized that a 12-week combined resistance and low volume aerobic exercise regimen would result in an array of benefits in men on AST including improvements in muscle mass, strength, and physical function, and enhanced cardiorespiratory capacity and health status without compromising levels of testosterone or PSA.

PATIENTS AND METHODS

Settings and Participants

Ninety-seven patients with prostate cancer were screened for participation from July 2007 to September 2008 at Sir Charles Gairdner Hospital (Perth, Western Australia) and their progress through the study is shown in Figure 1. Inclusion criteria included histologically documented prostate cancer, minimum prior exposure to AST longer than 2 months, without PSA evidence of disease activity, and anticipated to remain hypogonadal for the subsequent 6 months. Exclusion criteria included bone metastatic disease, musculoskeletal, cardiovascular, or neurological disorders that could inhibit them from exercising, inability to walk 400 meters or undertake upper and lower limb exercise, and resistance training in the previous 3 months. All participants obtained medical clearance from their physician and completed a health history questionnaire. The study was approved by the University Human Research Ethics Committee and all participants provided written informed consent.

Study Design and Procedures

This was a two-armed prospective randomized controlled trial. Potential participants were identified by their treating oncologist and referred to the study coordinator to confirm eligibility, describe the study, and obtain informed consent. Study patients underwent a familiarization session that included correct exercise technique followed by baseline testing comprising physical and functional tests, a whole body dual energy x-ray absorptiometry scan, questionnaires, and blood testing.

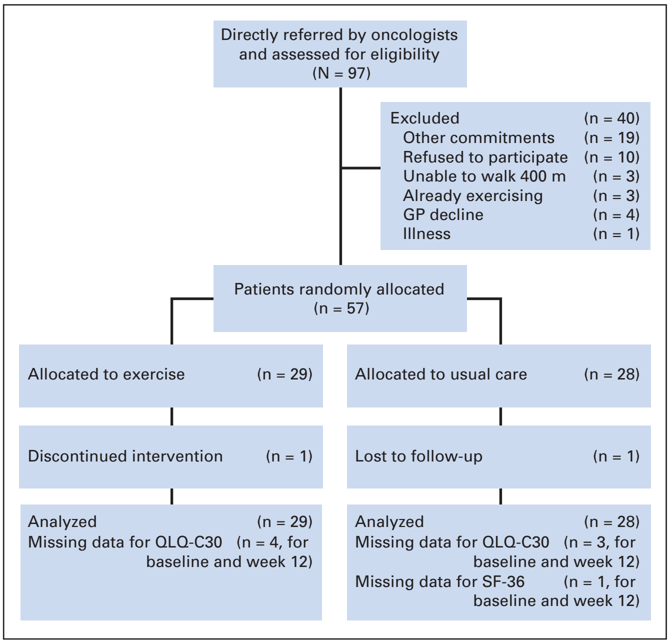

Fig 1. CONSORT diagram. GP, general practitioner; QLQ-C30, European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire C30; SF-36, Short Form-36.

Random Assignment

After completion of the baseline assessment, participants were randomly assigned to the two arms: exercise (EX) or usual care controls (CO) in a ratio of 1:1 using a computer random assignment program. The allocation sequence was concealed from the project coordinator and exercise physiologist involved in assigning participants to groups. Control participants could undergo the training after the assessment period had been completed.

Exercise Training Program

Participants undertook combined progressive resistance and aerobic training twice a week for 12 weeks. The resistance exercises included the chest press, seated row, shoulder press, triceps extension, leg press, leg extension and leg curl, with abdominal crunches also performed. Sessions commenced and concluded with general flexibility exercises. The resistance exercise program was designed to progress from 12- to 6-repetition maximum (RM) for two to four sets per exercise.[13,15] The aerobic component of the training program included 15 to 20 minutes of cardiovascular exercises (cycling and walking/jogging) at 65% to 80% maximum heart rate and perceived exertion at 11 to 13 (6 to 20 point, Borg scale). Sessions were conducted in small groups of one to five participants under direct supervision of an exercise physiologist. During the course of the study, participants were encouraged to maintain customary activity and dietary patterns and the Mini Nutritional Assessment instrument was used to monitor nutritional status.[22] Training was confined to two sites.

Primary and Secondary Study End Points

Study outcomes were assessed at baseline (where all participants were at least 2 months on AST) and after the 12-week intervention. Whole body and regional lean mass, fat mass, and percent fat were assessed by DXA (Hologic Discovery A, Waltham, MA).[23,24] Dynamic muscle strength was determined for the chest press, seated row, leg extension, and leg press using the maximal weight lifted one time (1-RM).[25] Muscle endurance was measured using the maximal number of repetitions performed at 70% of 1-RM for the chest press and leg press exercises using baseline as well as final 1-RM values.[26] Functional performance was assessed by repeated chair rise to standing (5 times)[25,26] and the 6-meter usual and fast walk using electronic timing gates,[18] and cardiovascular capacity by the 400-meter walk.[26-29] Tests were performed in triplicate (except 400-meter walk) with recovery time between trials.[26] Balance was assessed by the sensory organization test using the Neurocom Smart Balance Master (Neurocom International Inc, Clackamas, OR)[19] and dynamic balance by the 6-meter backwards walk.[18,25] Falls self-efficacy was determined using the Activities-Specific Balance Confidence scale,[30] the Short Form-36 (SF-36) was used to assess general quality of life status,[31] and the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire (QLQ) C30 to assess cancer specific quality of life status.[5] Blood samples were obtained early in the morning for fasting specimens. Testosterone, PSA, insulin, glucose, C-reactive protein (CRP), and lipid profile levels were measured commercially by an accredited Australian National Association of Testing Authorities Laboratory (Pathwest Diagnostics, Perth, Western Australia).

Statistical Analyses and Sample Size Calculation

To achieve 80% power at an α level of .05 (two tailed), 25 participants per group would be required to detect a mean difference in change for whole body lean mass of 1 kg (standard deviation of 1.25 kg) at the end of the 12-week intervention. This was based on a number of reports showing marked reductions in muscle loss in patients with prostate cancer undergoing AST.[6,32,33] Based on our previous experience with exercise trials, we anticipated an attrition rate of up to 10%. As a result, to adequately ensure that we had sufficient participant numbers at the end of the intervention, 57 participants were recruited and randomly assigned to EX (n = 29) and CO (n = 28).

Data were analyzed using the SPSS version 15 (SPSS Inc, Chicago, IL) statistical software package. Normality of the distribution for outcome measures was tested using the Kolmogorov-Smirnof test. Analyses included standard descriptive statistics, independent *t*-tests, χ^2, and analysis of covariance adjusted for baseline values, AST time, use of antiandrogen, number of medications, and education. To determine if general health changes were mediated by changes in lean mass and functioning, correlations were explored between self-reported general health and objective measures of lean mass and muscle strength. An intention-to-treat approach was used for all analyses including missing data in all analyses by imputing change across time to be zero. However, one participant dropped-out after baseline testing and did not return the SF-36 questionnaire and there was no QLQ-30 data for seven participants as the instrument was included in the assessment battery after these participants entered the study. All tests were two tailed and an α level of .050 was required for significance.

RESULTS

Patients Characteristics

Patient characteristics are presented in Table 1. There were no significant differences between groups at baseline. One participant from the EX group withdrew after 2 weeks training as he did not enjoy the program and one loss to follow-up occurred in the CO group. The EX group completed a mean of 23 ± 4 (standard deviation) of the 24 exercise sessions (94%).

Soft Tissue Composition

Change to the soft tissue end points across the 12-week assessment period differed significantly between the groups, with gains in the EX group (Table 2). The adjusted mean difference at 12 weeks for total body lean mass was approximately 0.8 kg ($P = .047$) reflecting differences between groups for upper limb ($P < .001$), lower limb ($P = .019$), and appendicular skeletal muscle ($P = .003$). In contrast, changes observed for whole body fat, trunk fat, % fat mass, and whole body weight were not significant.

Dynamic Muscle Strength and Endurance

Change to muscle strength and endurance also differed significantly between the groups (Table 3) for all muscle strength tests with EX improving their muscle performance. The adjusted mean difference in strength between groups ranged from 31 kg for the leg press

Table 1. Baseline Characteristics of Exercise and Usual Care Control Groups

	Exercise (n = 29)		Control (n = 28)		
Variable	Mean	SD	Mean	SD	*P*
Age, years	69.5	7.3	70.1	7.3	.749
Height, cm	171.7	6.1	172.0	7.7	.837
Total weight, kg	80.7	10.3	83.2	14.4	.461
BMI, kg/m^2	27.4	3.2	28.0	3.8	.523
No. of medications	2.3	2.2	3.2	1.4	.100
No. of comorbidities*	1.0	1.3	1.0	1.1	.922
Self-rated health†	2.7	0.6	2.6	0.9	.204
MNA, max score 30‡	27.6	1.6	27.4	3.0	.743
Postsecondary education	15		20		.127
%	51.7		71.4		
Married	26		22		.251
%	89.7		78.6		
Employed full time	4		2		.413
%	13.8		7.1		
Current smoker	3		3		.964
%	10.3	10.7			
Cancer stage grouping					
Localized	27		25		.601
%	93.1		89.3		
Presence of nodal metastases	2		3		
%	6.9		10.7		
Presence of bone metastases	0		0		
%	0		0		
Gleason score	7.2	1.6	7.5	1.0	.297
AST time, months	18.2	38.5	10.1	26.8	.360
LHRHa + antiandrogen	6		11		.125
%	20.7		39.3		
Previous AST	5		4		.760
%	17.2		14.3		
Previous radiation	11		11		.916
%	37.9		39.3		
Current radiation	8		6		.
%	27.6		21.4		.589

Abbreviations: BMI, body mass index; MNA, Mini Nutritional Assessment; AST, androgen suppression therapy; LHRHa, luteinizing hormone–releasing hormone agonists.
*Cardiovascular disease, hypertension, diabetes, osteoporosis, and dyslipidemia.
†Self-rated health: 1 = excellent; 2 = very good; 3 = good; 4 = fair; 5 = poor.
‡MNA: malnourished, < 17; undernourishment, 17 to 23.5; well nourished, > 23.5.

Table 2. Total and Regional Body Composition Absolute Values and Change Over 12 Weeks Exercise Training

	Baseline				12 Weeks				Adjusted Group Difference in Mean Change Over 12 Weeks		
	Exercise		Control		Exercise		Control				
Measure	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	95% CI	P*
Lean mass, kg											
Total body	56.1	6.7	57.8	8.3	56.8	6.8	57.8	8.7	0.76	0.01 to 1.5	.047
Upper limb	6.3	0.9	6.5	0.9	6.5	0.9	6.4	1.0	0.26	0.11 to 0.42	< .001
Lower limb	17.2	2.5	18.0	3.1	17.4	2.5	17.9	3.6	0.54	0.09 to 1.0	.019
ASM	23.5	3.4	24.6	4.0	24.0	3.4	24.4	4.6	0.80	0.29 to 1.3	.003
Fat mass, kg											
Total body	22.5	5.6	23.2	7.2	22.3	6.9	23.5	6.9	−0.01	−0.82 to 0.79	.964
Trunk	12.2	3.3	12.4	4.2	11.9	3.5	12.2	4.0	0.03	−0.56 to 0.57	.991
Body fat, %	27.5	4.5	27.3	4.8	27.2	4.4	27.5	4.7	−0.34	−1.0 to 0.41	.366
Whole body mass, kg											
Total body weight	80.7	10.3	83.2	14.4	81.4	10.7	83.2	14.4	0.76	−0.32 to 1.8	.163

Abbreviations: SD, standard deviation; ASM, appendicular skeletal muscle.
*Between group change by analysis of covariance (adjusted for baseline, androgen suppression treatment time, use of antiandrogen, number of medications, and education).

($P < .001$) to 3 kg for the chest press ($P = .018$). Similarly, muscle endurance was significantly enhanced ($P < .001$) for the chest press and leg press using the pretest 70% of 1-RM.

Cardiorespiratory Fitness and Physical Performance and Balance

The EX group showed a borderline improvement ($P = .080$) in the 400-meter walk performance at 12 weeks with an adjusted mean group difference of 7 seconds.

Change to performance and balance after 12 weeks also differed significantly between the groups (Table 4) with improved performance in the EX group for the 6-meter usual walk ($P = .024$) and a trend for the chair rise test ($P = .074$). Balance assessed by the 6-meter backward walk was also significantly different between EX and CO after the intervention ($P = .039$) with a borderline difference for balance confidence by the Activities-Specific Balance Confidence scale favoring EX compared with CO ($P = .061$).

Blood Biomarkers

At 12 weeks, CRP differed (Table 5), decreasing in the EX group and increasing in CO ($P = .008$). Differences were not observed for PSA, testosterone, glucose, insulin, lipids, nor homocysteine.

Quality of Life and Adverse Events

Quality of life assessed by the SF-36 (Table 6) showed better change scores for general health ($P = .022$), vitality ($P = .019$), and the physical health composite scores ($P = .020$) for the EX group. Change in general health was associated with change in whole body lean mass ($r = .385$; $P = .039$) and approached significance for change in average muscle strength ($r = .249$; $P = .064$).

Table 3. Muscle Strength and Endurance Absolute Values and Change Over 12 Weeks Exercise Training

	Baseline				12 Weeks				Adjusted Group Difference in Mean Change Over 12 Weeks		
	Exercise		Control		Exercise		Control				
Measure	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	95% CI	P*
Muscle strength, one repetition maximal, kg											
Chest press	34.6	11.2	34.7	13.6	38.4	11.3	35.2	12.1	2.8	0.50 to 5.1	.018
Seated row	40.1	7.6	39.2	8.0	45.8	8.8	40.0	8.9	5.1	3.3 to 7.0	< .001
Leg press	98.4	43.0	102.6	54.1	134.6	52.8	109.6	53.3	30.8	20.1 to 41.6	< .001
Leg extension	38.1	14.9	40.0	15.7	50.1	15.4	41.6	16.9	11.5	7.2 to 15.8	< .001
Muscle endurance											
Chest press											
At baseline test 70% of 1-RM (rep)	10.9	3.9	11.9	4.1	16.0	5.2	11.3	4.2	5.2	3.0 to 7.5	< .001
At post-test 70% of 1-RM (rep)	10.9	3.9	11.9	4.1	11.7	5.1	10.3	3.3	2.5	0.11 to 4.9	.041
Leg press											
At baseline test 70% of 1-RM (rep)	17.8	7.3	16.8	6.4	30.0	8.8	19.5	9.2	10.8	7.1 to 14.6	< .001
At post-test 70% of 1-RM (rep)	17.8	7.3	16.8	6.4	21.5	8.4	17.3	8.3	3.4	−0.96 to 7.8	.124

Abbreviations: SD, standard deviation; 1-RM, one repetition maximal; rep, number of repetitions.
*Between group change by analysis of covariance (adjusted for baseline, androgen suppression therapy time, use of antiandrogen, number of medications, and education).

Table 4. Functional Performance and Balance Absolute Values and Change Over 12 Weeks Exercise Training

Measure	Baseline				12 Weeks				Adjusted Group Difference in Mean Change Over 12 Weeks		
	Exercise		Control		Exercise		Control				
	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	95% CI	P*
Functional performance											
Walk, meters											
400	269.4	32.1	273.9	33.9	257.4	37.0	269.5	33.8	−7.0	−15.0 to 0.88	.080
6, usual	4.7	0.5	4.8	0.6	4.4	0.4	4.7	0.7	−0.31	−0.59 to −0.04	.024
6, fast	3.6	0.4	3.6	0.6	3.3	0.5	3.5	0.5	−0.12	−0.30 to 0.06	.187
Chair rise(s)	13.3	2.6	13.4	2.6	12.1	2.2	13.2	3.5	−1.0	−2.1 to 0.10	.074
Stair climb(s)	5.2	1.0	5.3	1.2	5.0	1.0	5.2	1.2	−0.09	−0.33 to 0.14	.420
Balance											
6-m backward walk(s)	22.2	10.5	23.7	14.6	17.4	7.0	22.6	19.6	−4.1	−8.1 to −0.21	.039
SOT, 0-100	74.4	7.1	74.0	8.6	76.8	5.8	75.0	8.4	1.5	−0.71 to 3.7	.178
ABC, 0-160	143.3	18.9	143.3	21.7	144.8	25.2	135.2	28.4	8.7	−0.40 to 17.8	.061

Abbreviations: SD, standard deviation; SOT, sensory organization test; ABC, Activities-Specific Balance Confidence scale.
*Between group change by analysis of covariance (adjusted for baseline, androgen suppression therapy time, use of antiandrogen, number of medications, and education).

Assessments using the QLQ-C30 (Appendix Table A1, online only) identified better change scores for EX in role ($P < .001$), cognitive ($P = .007$), fatigue ($P = .021$), nausea ($P = .025$), and dyspnea ($P = .017$), and a borderline difference for physical ($P = .062$), emotional ($P = .098$), pain ($P = .092$), and insomnia ($P = .055$).

There were no adverse events during testing or the exercise intervention.

DISCUSSION

To our knowledge, this is the first randomized controlled study to evaluate the combined effects of a resistance and low volume aerobic exercise program against usual care in patients with hypogonadal prostate cancer on musculoskeletal-related adverse effects arising from AST. There were four important findings: total body and regional lean mass significantly increased in the EX group compared with CO, all muscle strength tests, functional performance and balance assessments significantly improved in the EX group compared with the CO group, several aspects of quality of life including general health and reduced fatigue were significantly enhanced in EX in comparison with the CO group, and the program was well tolerated and there were no adverse events.

Loss of lean mass after the first year of AST has been extensively documented.[6,32] We previously reported a reduction of 1.4 kg in total body lean mass after 36 weeks of AST.[6] Longer term studies report continued loss of lean mass after 2 years of interrupted AST.[34] In contrast, our combined resistance/aerobic program reversed total body and regional lean mass loss compared to usual care (approximately 1 kg net difference between groups). In our previous pilot exercise study (n = 10) improvements in whole body lean mass was not significant, however, quadriceps muscle thickness as determined by ultrasound increased after 20 weeks of resistance training.[19] The

Table 5. Blood Markers Absolute Values and Change Over 12 Weeks Exercise Training

Measure	Baseline				12 Weeks				Adjusted Group Difference in Mean Change Over 12 Weeks		
	Exercise		Control		Exercise		Control				
	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	95% CI	P*
Testosterone, nmol/L	1.4	2.3	1.0	0.8	2.1	2.9	1.0	0.6	0.63	−0.21 to 1.4	.139
PSA, μg/L	0.6	0.9	2.1	4.3	0.9	2.3	0.7	2.1	0.18	−0.73 to 1.1	.690
Total cholesterol, mmol/L	5.2	1.2	5.0	0.9	5.3	1.1	4.9	1.0	0.09	−0.39 to 0.58	.711
Triglycerides, mmol/L	1.7	0.7	1.5	0.7	1.8	0.7	1.7	1.1	0.01	−0.40 to 0.46	.951
Cholesterol, mmol/L											
LDL	3.1	1.1	3.1	0.8	3.1	1.0	2.9	0.8	0.03	−0.39 to 0.45	.884
HDL	1.2	0.3	1.3	0.3	1.2	0.3	1.2	0.3	0.01	−0.13 to 0.16	.818
Insulin, mU/L	9.4	7.2	10.0	5.7	10.2	7.4	10.9	7.1	1.4	−2.2 to 5.1	.435
Glucose, mmol/L	6.2	1.1	6.0	0.8	6.0	0.7	6.2	1.2	−0.24	−0.68 to 0.19	.267
CRP, mg/L	2.7	3.2	2.3	2.6	1.8	1.1	4.5	6.9	−3.5	−6.2 to −0.97	.008
Homocysteine, umol/L	11.7	4.5	12.1	4.0	11.2	4.0	12.4	7.6	−0.81	−3.8 to 2.2	.597

Abbreviations: SD, standard deviation; PSA, prostate-specific antigen; LDL, low density lipoprotein; HDL, high density lipoprotein; CRP, C-reactive protein.
*Between group change by analysis of covariance (adjusted for baseline, androgen suppression therapy time, use of antiandrogen, number of medications, and education).

Table 6. SF-36 Profile Values and Change Over 12 Weeks Exercise Training

	Baseline				12 Weeks				Adjusted Group Difference in Mean Change Over 12 Weeks		
	Exercise		Control		Exercise		Control				
Measure	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	95% CI	*P**
Physical functioning	81.7	14.8	74.0	28.9	82.9	17.3	77.5	18.7	3.8	−6.1 to 13.8	.441
Role physical	82.6	28.9	79.7	26.9	85.5	24.6	77.3	35.2	10.8	−4.2 to 26.0	.154
Bodily pain	79.7	26.4	73.5	29.0	79.8	21.6	71.4	21.6	9.2	−2.4 to 20.9	.119
General health	66.0	23.1	67.3	23.1	71.4	17.5	60.2	26.7	12.9	1.9 to 23.9	.022
Vitality	59.6	20.8	55.0	21.5	62.4	20.4	50.7	22.6	13.1	2.6 to 24.1	.019
Social functioning	84.9	20.6	81.9	19.4	87.0	18.4	83.3	23.5	6.8	−4.2 to 18.0	.223
Role emotional	79.3	30.0	67.9	40.8	72.4	39.9	77.7	40.2	−6.6	−26.0 to 12.7	.491
Mental health	76.8	16.9	73.9	19.4	77.9	18.1	73.2	17.9	6.3	−3.6 to 16.3	.207
Physical health composite	47.8	7.1	46.9	10.2	49.2	7.9	44.8	9.5	5.0	0.81 to 9.2	.020
Mental health composite	50.8	8.1	48.6	10.9	50.2	10.4	49.2	11.4	1.2	−3.9 to 6.4	.639

Abbreviations: SF-36, Short Form-36; SD, standard deviation.
*Between group change by analysis of covariance (adjusted for baseline, AST time, use of antiandrogen, number of medications, and education).

increase observed in this study is comparable to those in healthy men undertaking similar exercise protocols.[35] AST can negatively affect muscle strength and function.[3,36] Our program resulted in a significant improvement in upper and lower body muscle strength compared with usual care. These findings are consistent with previous studies examining resistance training as an individual exercise mode.[16,19,21] Muscle endurance was also improved, which may lead to tasks becoming more easily accomplished and with less fatigue. Hence, we believe that the attenuation/reversal of AST-induced muscle loss that followed our exercise intervention is clinically meaningful. Moreover, it is possible that exercise initiated at the onset of AST may provide important benefits by attenuating the initial loss of muscle and its associated adverse effects.

Our 12-week exercise program improved functional performance (eg, gait speed) and balance measures compared to usual care. These changes in functional performance and balance are similar to those achieved in our pilot study of patients on AST undertaking resistance training[19] and comparable to previous studies in healthy older men undertaking resistance training alone. Moreover, these changes are clinically important as AST is associated with reduced functional performance, poor dynamic balance and reduction in bone density, resulting in an increased risk for falls and fractures in men on AST.[4,37]

Aerobic walking capacity as measured by the 400-meter walk has been shown to be a strong predictor of mortality, cardiovascular disease, and mobility limitations in older adults.[27-29] We have previously reported that cardiorespiratory fitness is reduced in patients treated with AST compared to healthy age-matched controls not on AST.[3] The combined effects of resistance and aerobic exercise lead to a borderline improvement in the 400-meter walk compared to usual care. These findings are in agreement with those from a recent exercise trial by Segal and colleagues[21] which indicated improvements in aerobic capacity after either resistance or aerobic training in men with prostate cancer where approximately 60% of patients were on AST. We believe that the trend for an apparent 7 seconds difference, although minor, would at least provide a greater safety margin before thresholds for disability are encountered, hence it may potentially be clinically meaningful (especially for men in poorer condition than those in this study).

PSA did not change during the study indicating that combined resistance and aerobic exercise can safely be undertaken in patients with prostate cancer on AST, and is consistent with other studies examining the individual effects of resistance or aerobic training after AST and radiation therapy.[16,19,21] There was little if any change in any other blood biomarkers except for CRP where there was a difference between groups at week 12 with values decreasing in EX and increasing in those undergoing usual care. This is an important finding, as low-grade systemic inflammation in older persons is associated with a number of chronic conditions, as well as poorer physical performance and mortality.[38,39]

In addition, change to perceived general health, the commonly employed global scale of the SF-36, was significantly better in the EX group compared with CO, and the magnitude of the difference was clinically important ($>$ 10 points).[40] While it was not possible to identify which components of the exercise program are responsible for this outcome, we did note that change in lean mass was associated with change in general health. Segal et al[21] also reported that resistance or aerobic exercise as a sole training mode improved quality of life compared to usual care in men undergoing radiation therapy for prostate cancer. Further, we also found significant differences between the groups favoring EX for several components of the QLQ-C30 including reduction in fatigue, nausea, and dyspnea, and improvements in role and cognitive functioning. These findings indicate that physical performance and musculoskeletal benefits in this patient group may translate into improved well-being.

Our study has several limitations and strengths which are worthy of comment. The short-term nature of the training program may have limited our ability to observe changes in the participants' metabolic profile or maximal achievable gains in the various primary and secondary outcomes. In addition, given the number of comparisons made, it is possible that a few chance findings may have occurred.

Nevertheless, we have shown improvements in an array of musculoskeletal-related factors with as little as 12 weeks training undertaken twice weekly in different training locations which could be easily replicated on a larger scale. Our study included a comprehensive battery of measures for body composition, muscle strength, direct measures of functional performance, and the assessment of blood biomarkers. Further, based on recommendations from the American

College of Sports Medicine[41] to incorporate both resistance and aerobic exercise to enhance cardiovascular and musculoskeletal function in healthy older adults, this is the first study to use this approach in older patients with prostate cancer on AST. Moreover, combined with the stretching/flexibility exercises undertaken as part of the warm-up and cool-down process, a comprehensive multimodal exercise program has been delivered and well tolerated by this patient group. However, it is probable that the volume of aerobic exercise undertaken was insufficient to produce marked changes in blood lipids, glucose control, and body fat given the current recommendation of 5 sessions per week for health maintenance[42] and greater than 250 minutes per week for substantial fat loss.[43] Lastly, four large and even clinically meaningful differences in the quality of life subscales at baseline may limit the interpretation of the quality of life data. However, groups were not different at baseline for physical, behavioral, clinical, and demographic variables and analysis of covariance was used to compare outcomes adjusted for baseline values and potential confounders.

In summary, to our knowledge, this is the first randomized controlled study to examine the effects of combined resistance and low volume aerobic training in patients with hypogonadal prostate cancer in reversing musculoskeletal and metabolic related toxicities. A broad range of objective improvement to lean mass, muscle strength, physical function, and balance resulted from a relatively brief exposure to exercise. These changes were accompanied with improvement to patient perceived well-being. The training regimen was well tolerated in this patient group and could be recommended for patients undergoing AST as an effective countermeasure for treatment-related adverse effects to the musculoskeletal system and to improve well-being. Future studies should test the combined effects of resistance and aerobic exercises against resistance or aerobic exercise alone.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Although all authors completed the disclosure declaration, the following author(s) indicated a financial or other interest that is relevant to the subject matter under consideration in this article. Certain relationships marked with a "U" are those for which no compensation was received; those relationships marked with a "C" were compensated. For a detailed description of the disclosure categories, or for more information about ASCO's conflict of interest policy, please refer to the Author Disclosure Declaration and the Disclosures of Potential Conflicts of Interest section in Information for Contributors.

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