ORIGINAL RESEARCH

Responsiveness to Resistance-Based Multimodal Exercise Among Men With Prostate Cancer Receiving Androgen Deprivation Therapy

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ABSTRACT

Background: Androgen deprivation therapy (ADT) in the management of prostate cancer (PCa) results in an array of adverse effects, and exercise is one strategy to counter treatment-related musculoskeletal toxicities. This study assessed the prevalence of exercise responsiveness in men with PCa undergoing ADT in terms of body composition, muscle strength, and physical function. **Methods:** Prospective analyses were performed in 152 men (aged 43–90 years) with PCa receiving ADT who were engaged in resistance exercise combined with aerobic or impact training for 3 to 6 months. Whole-body lean mass and fat mass (FM), trunk FM, and appendicular skeletal muscle were assessed with dual x-ray absorptiometry; upper and lower body muscle strength were assessed with the one-repetition maximum; and physical function was assessed with a battery of tests (6-m usual, fast, and backward walk; 400-m walk; repeated chair rise; stair climb). **Results:** Significant improvements were seen ($P<.01$) in lean mass (0.4±1.4 kg [range, −2.8 to +4.1 kg]), appendicular skeletal muscle (0.2±0.8 kg [range, −1.9 to +1.9 kg]), and all measures of muscle strength (chest press, 2.9±5.8 kg [range, −12.5 to +37.5 kg]; leg press, 29.2±27.6 kg [range, −50.0 to +140.0 kg]) and physical function (from −0.1±0.5 s [range, +1.3 to −2.1 s] for the 6-m walk; to −8.6±15.2 s [range, +25.2 to −69.7 s] for the 400-m walk). An increase in FM was also noted (0.6±1.8 kg [range, −3.6 to +7.3 kg]; $P<.01$). A total of 21 men did not exhibit a favorable response in at least one body composition component, 10 did not experience improved muscle strength, and 2 did not have improved physical function. However, all patients responded in at least one of the areas, and 120 (79%) favorably responded in all 3 areas. **Conclusions:** Despite considerable heterogeneity, most men with PCa receiving ADT responded to resistance-based multimodal exercise, and therefore our findings indicate that this form of exercise can be confidently prescribed to produce beneficial effects during active treatment.

J Natl Compr Canc Netw 2019;17(10):1211–1220
doi: 10.6004/jnccn.2019.7311

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Background

Androgen deprivation therapy (ADT) is used extensively in the management of localized and advanced prostate cancer (PCa).[1] Although effective in delaying disease progression and enhancing survival,[1,2] ADT is associated with an array of adverse effects, including reduced muscle[3] and bone mass,[4] an increase in body fat,[4] and reduced muscle strength and physical function,[5] leading to an increased risk of comorbidities that compromise functioning and quality of life.[6,7]

One strategy to combat a number of these treatment-related toxicities is exercise; specifically, resistance exercise as a sole training mode or as part of a multimodal exercise program. We and others have demonstrated the efficacy of exercise programs containing a resistance-based component for improving muscle mass and strength,[8–10] bone mass,[11] and physical function,[9] and reducing adverse effects such as fatigue[12] and sexual health[13] in men with PCa receiving ADT. Although study conclusions are that exercise is an effective countermeasure to the adverse effects of ADT on body composition, strength, and function, it is clear that considerable interindividual variation exists given the measures of variability provided, such as the standard deviation, and therefore some men may not derive a favorable response. In contrast, exercise interventions to mitigate the effects of ADT on whole-body and trunk fat mass (FM) have been less successful,[10,14] although, given the variation in response as indicated by measures of variability, some men would respond favorably.

In recommending and prescribing exercise for patients, the referring clinician and the exercise professional administering the program must be confident that the desired beneficial effect will be achieved, and patients need to have an appreciation of the likelihood of a favorable response. This raises some questions. Do all patients who are prescribed and undertake exercise achieve the outcomes of interest ("responders"), and if not, what percentage is likely to not achieve the objectives ("nonresponders"), and is this nonresponse related to factors such as age, body size, training duration, session attendance, or whether they were already receiving or had just commenced an ADT regimen? To address these questions, our study assessed the prevalence of exercise responsiveness among men with PCa receiving ADT in terms of body composition, muscle strength, and physical function.

Methods

Patients

This study examined 152 men with a histologic diagnosis of PCa and treated with ADT from 4 randomized exercise trials[10–12,15] performed at the Exercise Medicine Research Institute at Edith Cowan University in Perth, Australia. Participants had complete data available on all outcome measures, and were assigned to exercise arms in 3 of the trials[10,12,15] and the immediate exercise arm in the fourth trial[11]; 99 patients were receiving established ADT regimens that specified a minimum exposure of 2 months,[10,12] and 53 were commencing ADT.[11,15] A total of 52 men engaged in exercise training for 3 months,[10,15] and 100 men engaged in exercise training for 6 months.[11,12] Exclusion criteria included established metastatic disease; participation in structured exercise in the previous 3 months; inability to walk 400 m; acute illness; or any musculoskeletal, cardiovascular, or neurologic disorder that could inhibit participants or put them at risk from exercising as determined by their physician. The studies were approved by the Human Research Ethics Committee of Edith Cowan University, and all patients provided written informed consent.

Exercise Interventions

Exercise training was undertaken 2[10,12,15] or 3 times[11] per week for approximately 60 minutes per session, conducted in small groups of up to 10 participants, and supervised. Two exercise trials used a combined resistance and aerobic exercise program[10,15]; one trial had 2 exercise arms that used either combined resistance and aerobic exercise or combined resistance and impact-loading exercise[12]; and one trial used combined resistance, aerobic, and impact-loading exercise.[11] Detailed descriptions of the exercise programs and their progression have been published elsewhere.[10–12,15] Briefly, resistance exercise comprised training for the major upper and lower body muscle groups, with patients performing 2 to 4 sets of each exercise at an intensity of 6 to 12 repetition maximum (ie, the heaviest weight that can be lifted 6–12 times). Aerobic exercise consisted of various modes and included walking or jogging on a treadmill and cycling or rowing on a stationary ergometer at an intensity of 60% to 85% of estimated maximum heart rate for 15 to 40 minutes. Impact-loading exercise consisted of a series of bounding, hopping, skipping, leaping, and drop jumping activities. All sessions commenced with a warmup comprising low-level aerobic activities and concluded with a cooldown of stretching activities.

Body Composition

Whole-body lean mass (LM) and FM, trunk FM (TrFM), and appendicular skeletal muscle (ASM) were derived from a whole-body dual x-ray absorptiometry scan (Hologic Discovery A; Hologic, Inc.). ASM was calculated as the sum of upper limb and lower limb bone-free LM.[16]

Muscle Strength and Physical Function

Dynamic muscle strength for the upper and lower body was determined using the 1-repetition maximum[17] for the chest press and leg press exercises, respectively. Physical function was assessed using a battery of tests[9,10,18] that included usual and fast 6-m walk (as measures of gait speed); 6-m backward tandem walk (as a measure of dynamic balance); 400-m walk (as a measure of cardiorespiratory fitness and walking endurance); stair climb (as a measure of lower body muscle power); and repeated chair rise, which measures the time needed to rise from a chair 5 times (as a measure of lower body function).

Other Measures

Demographic and clinical data were collected through self-report and medical records, respectively. Height and weight were assessed using a stadiometer and electronic scales, respectively, with body mass index (BMI; kg/m^2) calculated. Testosterone and prostate-specific antigen were measured at a commercial laboratory (PathWest Laboratory Medicine).

Statistical Analyses

Data were analyzed using SPSS Statistics, version 24 (IBM Corp). Normality of the distribution was assessed using the Kolmogorov-Smirnov test. Descriptive statistics included the mean and standard deviation and the minimum and maximum values. Pre- and post-training changes were determined using either paired t tests or the Wilcoxon signed rank test, as appropriate. Between-group differences for 3 versus 6 months were determined using independent t tests or the Mann-Whitney U test. Comparisons between responders and nonresponders regarding age, BMI, commencing versus receiving established ADT regimens, duration of exercise, and exercise attendance (with good attendance categorized as ≥70% of sessions) were performed using independent t tests or the Mann-Whitney U and chi-square tests. A responder was defined as experiencing improvement and a nonresponder as experiencing no improvement in the outcome measure of interest.[19–22] Tests were 2-tailed, and to adjust for the number of comparisons, statistical significance was set at $\alpha=0.01$.

Results

Demographic and clinical characteristics of the study population are shown in Table 1. Participants were aged 43 to 90 years, had a BMI of 19.1 to 38.9 kg/m², and were predominantly married, nonsmokers, and no longer employed. Body composition, muscle strength, and physical function values before training are shown in Table 2.

After 3 to 6 months of exercise training, significant increases ($P<.01$) were seen in LM (0.4±1.4 kg), ASM (0.2±0.8 kg), and FM (0.6±1.8 kg) (Table 3). However, the response was heterogeneous with a wide variation, with minimum and maximum values of −2.8 to +4.1 kg, −1.9 to +1.9 kg, and −3.6 to +7.3 kg for LM, ASM, and FM, respectively. No significant change in TrFM was seen ($P=.346$); however, the variation was wide (−2.8 kg to +4.7 kg). Similarly, a significant increase ($P<.001$) occurred in chest press and leg press strength that equated to gains of 9.5%±18.2% and 30.4%±34.9%, respectively, with a wide variation in response. All physical function measures improved ($P<.01$), with time to perform the task reduced. The largest absolute change was for the 400-m walk (−8.6±15.2 s; range, +25.2 to −69.7 s), and the largest relative change was for the chair rise test (−7.3%±11.4%; range, +27.6% to −40.7%).

Changes by duration of training and ADT status are shown for body composition in Table 4 and for muscle strength and physical function in Table 5. Overall, for duration of training, the only significant difference was in FM ($P<.001$), with an increase of 0.9±1.9 kg in the 6-month group compared with −0.1±1.3 kg in the 3-month group. There was no significant difference in training duration among those receiving established ADT regimens; however, in those commencing ADT, there was a significant difference in FM ($P=.002$), with an increase of 1.3±1.8 kg in the 6-month group compared with −0.2±1.3 kg in the 3-month group.

Figures 1–3 show the absolute change in body composition; muscle strength, chair rise, and stair climb performance; and physical function (ie, walking tasks), respectively, for each individual. The number of patients who showed an increase in LM or ASM greatly exceeded the number who showed decline (112 responders vs 40 nonresponders), whereas slightly more individuals showed increased rather than reduced FM or TrFM (78 nonresponders vs 74 responders), with a larger magnitude of change. Most men showed improvement in chest press (101 responders

Table 1. Participant Characteristics

Characteristic	3-Month Exercise Analysis (n=52)	6-Month Exercise Analysis (n=100)	All (N=152)
Age, mean (SD), y	69.1 (7.2)	68.7 (8.1)	68.8 (7.7)
Height, mean (SD), cm	172.1 (6.1)	172.9 (6.0)	172.6 (6.1)
Weight, mean (SD), kg	83.0 (11.6)	82.7 (14.0)	82.8 (13.2)
BMI, mean (SD), kg/m²	28.0 (3.7)	27.5 (3.7)	27.7 (3.7)
Gleason score, mean (SD)	7.2 (1.2)	7.7 (0.9)	7.5 (1.1)
ADT duration, median (IQR), mo	2.0 (0.0–5.0)	2.0 (0.0–3.0)	2.0 (0.0–3.0)
Married, n (%)[a]	44 (84.6)	79 (80.6)	123 (82.0)
Currently employed, n (%)[a]	12 (23.1)	34 (34.7)	46 (30.7)
Tertiary education, n (%)	17 (32.7)	43 (43.0)	60 (39.5)
Current smoker, n (%)[a]	2 (3.8)	5 (5.1)	7 (4.6)
Number of medications, median (IQR)	3.0 (1.3–5.0)	3.0 (2.0–4.0)	3.0 (2.0–4.0)
PSA level, median (IQR), ng/mL	1.1 (0.05–3.8)	0.6 (0.05–2.4)	0.6 (0.05–3.0)
Testosterone level, median (IQR), nmol/L	1.3 (0.8–4.7)	0.9 (0.0–2.6)	1.0 (0.0–3.8)
Prostatectomy, n (%)[a]	16 (40.0)	34 (34.3)	50 (36.0)
Radiation, n (%)[a]	11 (39.3)	68 (68.0)	79 (61.7)
Number of comorbidities, median (IQR)[b]	1.0 (0.0–2.0)	0.0 (0.0–1.0)	1.0 (0.0–2.0)

Abbreviations: ADT, androgen deprivation therapy; BMI, body mass index; PSA, prostate-specific antigen; IQR, interquartile range.
[a]Missing values: married, n=2; currently employed, n=2; current smoker, n=1; prostatectomy, n=13; radiation, n=24.
[b]Cardiovascular disease, hypertension, dyslipidemia, diabetes.

Table 2. Baseline Values of Body Composition, Muscle Strength, and Physical Function

	Mean (SD)	Minimum	Maximum
Body composition, kg			
Lean mass	56.8 (7.8)	35.8	76.8
Fat mass	23.5 (7.1)	9.7	49.9
Trunk fat mass	12.7 (4.5)	3.7	29.0
ASM	24.3 (3.7)	13.5	34.1
Muscle strength, kg			
Chest press	39.7 (12.3)	10.0	70.0
Leg press	125.3 (50.2)	20.0	330.0
Physical function, s			
6-m usual walk	4.6 (0.8)	3.2	7.8
6-m fast walk	3.4 (0.5)	2.3	5.7
6-m backward walk	17.4 (7.7)	5.8	69.3
400-m walk	256.6 (38.2)	191.0	470.7
Chair rise	12.0 (2.4)	8.0	20.1
Stair climb	4.9 (1.2)	3.0	10.4

Abbreviation: ASM, appendicular skeletal muscle.

vs 51 nonresponders) and leg press (127 responders vs 25 nonresponders) strength, with modest changes for nonresponders. More patients improved in the various physical function tasks than had no change or declined (6-m usual walk, 84 vs 68 patients; 6-m fast walk, 89 vs 63 patients; 6-m backwards walk, 108 vs 44 patients; 400-m walk, 109 vs 43 patients; chair rise, 120 vs 32 patients; stair climb, 83 vs 69 patients), with a greater magnitude of change.

Overall, 20 patients (13%) did not have a favorable response in at least one body composition component; 9 (6%) did not improve in a measure of muscle strength; 1 (<1%) did not improve in body composition and strength; and 2 (1%) did not improve in any measure of physical function. For body composition, nonresponders tended to be older ($P=.023$) and engaged in exercise training for 6 months ($P=.010$), with no difference in BMI ($P=.283$), exercise attendance ($P=.885$), or commencing versus receiving established ADT regimens ($P=.408$). Similarly, there was no difference in age ($P=.940$), BMI ($P=.905$), exercise attendance ($P=.216$), or commencing versus receiving established ADT regimens ($P=.738$) between responders and nonresponders regarding muscle strength, although they tended to have trained for 6 months ($P=.095$). The 2 men who did not respond in physical function were commencing ADT, underwent 6 months of training with good attendance, and had BMIs of 22.4 and 29.8 kg/m^2 and were aged 79 and 68 years, respectively. Consequently, all patients responded in at least one measure of body composition, muscle strength, and physical function, and 79% had a positive response in some component of all 3 assessment areas.

Table 3. Absolute and Relative Changes After 3 to 6 Months of Training

	Absolute			Relative (%)		
	Mean (SD)	Minimum	Maximum	Mean (SD)	Minimum	Maximum
Body composition, kg						
Lean mass	0.4 (1.4)[a]	−2.8	+4.1	0.7 (2.5)	−5.1	+9.0
Fat mass	0.6 (1.8)[a,b]	−3.6	+7.3	3.1 (8.5)	−19.3	+28.9
Trunk fat mass	0.1 (1.2)	−2.8	+4.7	1.4 (10.3)	−27.4	+39.5
ASM	0.2 (0.8)[c]	−1.9	+1.9	1.1 (3.2)	−5.7	+12.1
Muscle strength, kg						
Chest press	2.9 (5.8)[b,c]	−12.5	+37.5	9.5 (18.2)	−21.7	+125.0
Leg press	29.2 (27.6)[b,c]	−50.0	+140.0	30.4 (34.9)	−25.0	+211.2
Physical function,[d] s						
6-m usual walk	−0.1 (0.5)[a,b]	+1.3	−2.1	−2.3 (11.0)	+32.6	−46.0
6-m fast walk	−0.2 (0.4)[c]	+1.2	−1.6	−3.9 (10.9)	+42.2	−39.0
6-m backward walk	−2.0 (4.7)[b,c]	+9.5	−26.4	−6.5 (25.5)	+88.6	−52.4
400-m walk	−8.6 (15.2)[b,c]	+25.2	−69.7	−3.2 (5.5)	+10.4	−19.1
Chair rise	−1.0 (1.6)[b,c]	+4.7	−6.4	−7.3 (11.4)	+27.6	−40.7
Stair climb	−0.1 (0.5)[a,b]	+2.2	−2.0	−1.9 (9.5)	+35.0	−25.7

Abbreviation: ASM, appendicular skeletal muscle.
[a]Significant change, $P<.01$.
[b]Wilcoxon signed rank test.
[c]Significant change, $P<.001$.
[d]Reduced time indicates improved performance from baseline to posttest.

Table 4. Absolute Change in Body Composition by Training Duration and ADT Status

	3 Months[a]			6 Months[b]		
	Mean (SD)	Minimum	Maximum	Mean (SD)	Minimum	Maximum
Lean mass, kg						
All	0.3 (1.1)	−1.6	+2.5	0.4 (1.5)	−2.8	+4.1
Established	0.7 (1.0)	−1.6	+2.5	0.6 (1.6)	−2.8	+4.1
Commencing	−0.1 (0.9)	−1.5	+2.0	0.0 (1.4)	−2.8	+3.2
Fat mass, kg						
All	−0.1 (1.3)	−3.6	+2.9	0.9 (1.9)	−3.0	+7.3
Established	0.0 (1.3)	−2.6	+2.9	0.8 (2.0)	−3.0	+7.3
Commencing	−0.2 (1.3)	−3.6	+1.9	1.3 (1.8)	−2.1	+4.2
Trunk fat mass, kg						
All	−0.2 (0.9)	−2.8	+1.8	0.2 (1.2)	−2.2	+4.6
Established	−0.1 (0.8)	−1.5	+1.8	0.2 (1.2)	−2.2	+4.6
Commencing	−0.3 (1.1)	−2.8	+1.5	0.4 (1.3)	−2.1	+2.5
ASM, kg						
All	0.2 (0.5)	−0.7	+1.6	0.3 (0.8)	−1.9	+1.9
Established	0.4 (0.6)	−0.6	+1.6	0.4 (0.8)	−1.4	+1.8
Commencing	0.0 (0.4)	−0.7	+1.0	0.0 (0.8)	−1.9	+1.9

Abbreviations: ADT, androgen deprivation therapy; ASM, appendicular skeletal muscle.
[a]All: n=52; established: n=28; commencing: n=24.
[b]All: n=100; established: n=71; commencing: n=29.

Discussion

This study examined exercise responsiveness among men with PCa receiving ADT in terms of body composition, muscle strength, and physical function (which are all adversely affected by ADT) to determine whether all patients prescribed and undertaking exercise achieve outcome objectives, and if not, what percentage are likely to be nonresponders. After either 3 or 6 months of supervised resistance-based multimodal exercise, 79% had a favorable response in at least one parameter of all 3 areas of body composition, muscle strength, and physical function, with the remainder responding in varying degrees in at least one of the areas. Therefore, despite ADT, our findings show that this form of targeted exercise can be confidently prescribed and undertaken to derive beneficial effects in most men during active treatment.

Despite group improvements in all outcome measures except FM and TrFM, considerable interindividual variability was seen. However, responders far outnumbered nonresponders in each of the other individual components or parameters, and the magnitude of change in responders was greater than in nonresponders, ranging in relative terms from −5.1% to + 9.0% for LM and up to −25.0% to +211.2% for leg press strength. Increases in muscle strength were substantial for most participants, especially for the leg press, and are of clinical importance, given the association between muscle strength and mortality from all causes and cancer in men.[23] In exercise trials, a wide variation in response is not unusual. For instance, Kohrt et al[24] reported that after 9 to 12 months of aerobic exercise–based training in older men and women, maximal aerobic power increased by 24%, with a range of 0% to 58%, whereas Bouchard et al,[25] in the HERITAGE Family Study, reported a range of 0% to 100% increase after 20 weeks of training. Similarly, Hubal et al[26] found considerable heterogeneity in muscle strength and size after 12 weeks of resistance training in men and women aged 18 to 40 years, with changes in strength of 0% to 250% and in muscle area of −2% to +59%. However, nonresponsiveness in one outcome or measure does not preclude responsiveness and adaptation in another, as evident in our results, and given the systemic nature of exercise affecting multiple organ systems, numerous unmeasured or undetermined benefits would result.[27]

Both muscle strength/physical function and LM are likely important in the setting of ADT for PCa, although the level of importance of each component will depend on the patient's needs and physiologic and functional requirements. For example, in those with advanced disease, preserving physical function by improving muscle strength and maintaining activities of daily living could be viewed as a clinically meaningfully outcome. Similarly, for those experiencing substantial loss of LM and at risk for developing sarcopenia and metabolic

Table 5. Absolute Changes in Muscle Strength and Physical Function by Training Duration and ADT Status

	3 Months[a]			6 Months[b]		
	Mean (SD)	Minimum	Maximum	Mean (SD)	Minimum	Maximum
Chest press, kg						
All	3.6 (4.6)	−5.0	+22.5	2.5 (6.3)	−12.5	+37.5
Established	3.9 (3.7)	−3.8	+10.0	3.2 (6.7)	−12.5	+37.5
Commencing	3.3 (5.6)	−5.0	+22.5	0.7 (5.0)	−7.5	+15.0
Leg press, kg						
All	33.5 (24.9)	−20.0	+100.0	27.0 (28.8)	−50.0	+140.0
Established	37.5 (20.6)	+10.0	+90.0	28.8 (28.7)	−50.0	+140.0
Commencing	28.9 (28.8)	−20.0	+100.0	22.5 (29.1)	−40.0	+80.0
6-m usual walk,[c] s						
All	−0.2 (0.4)	+0.9	−1.1	−0.1 (0.6)	+1.3	−2.1
Established	−0.4 (0.4)	+0.3	−1.1	−0.2 (0.6)	+1.3	−2.1
Commencing	0.0 (0.4)	+0.9	−0.9	0.1 (0.3)	+1.0	−0.4
6-m fast walk,[c] s						
All	−0.2 (0.3)	+0.5	−1.3	−0.1 (0.4)	+1.2	−1.6
Established	−0.3 (0.4)	+0.5	−1.3	−0.2 (0.5)	+1.2	−1.6
Commencing	0.0 (0.2)	+0.4	−0.6	−0.1 (0.2)	+0.3	−0.6
6-m backward walk,[c] s						
All	−2.3 (5.2)	+7.2	−26.4	−1.8 (4.4)	+9.5	−12.9
Established	−5.0 (5.3)	+0.3	−26.4	−2.6 (4.4)	+9.5	−12.9
Commencing	0.8 (3.0)	+7.2	−5.3	0.4 (3.6)	+9.1	−7.8
400-m walk,[c] s						
All	−9.2 (13.0)	+20.0	−34.6	−8.3 (16.3)	+25.2	−69.7
Established	−12.5 (14.1)	+17.7	−34.6	−10.2 (17.7)	+22.9	−69.7
Commencing	−5.4 (10.6)	+20.0	−31.2	−3.6 (11.2)	+25.2	−28.3
Chair rise,[c] s						
All	−1.1 (1.3)	+2.5	−4.9	−0.9 (1.7)	+4.7	−6.4
Established	−1.2 (1.6)	+2.5	−4.9	−1.0 (1.9)	+4.7	−6.4
Commencing	−1.0 (0.9)	+1.1	−3.1	−0.6 (1.0)	+1.7	−2.9
Stair climb,[c] s						
All	−0.1 (0.4)	+0.5	−1.4	−0.1 (0.6)	+2.2	−2.0
Established	−0.2 (0.4)	+0.5	−1.1	−0.1 (0.7)	+2.2	−2.0
Commencing	−0.1 (0.4)	+0.5	−1.4	−0.2 (0.4)	+0.3	−1.9

Abbreviation: ADT, androgen deprivation therapy.
[a]All: n=52; established: n=28; commencing: n=24.
[b]All: n=100; established: n=71; commencing: n=29.
[c]Reduced time indicates improved performance.

complications, preservation of LM will be critical. Conversely, in the older frail patient, enhancement in both parameters of lower limb muscle strength and LM may be required. As a result, individualization and the patient's clinical requirements will dictate the level of importance of the exercise response and required prescription to induce these adaptations.

For FM, the effects of exercise, if any, are modest when group values are analyzed in men receiving ADT, with no significant change generally reported,[9,10,14] although this in itself is beneficial, given that FM increases with ADT[4] and persists after treatment cessation.[28] FM (and TrFM) increased in just more than half of the men in this analysis, with the magnitude of increase greater than in those who experienced a reduction. However, nearly half of the participants did respond favorably, with reductions in whole-body FM (n=28 with a reduction >1 kg) and TrFM (n=25 with a

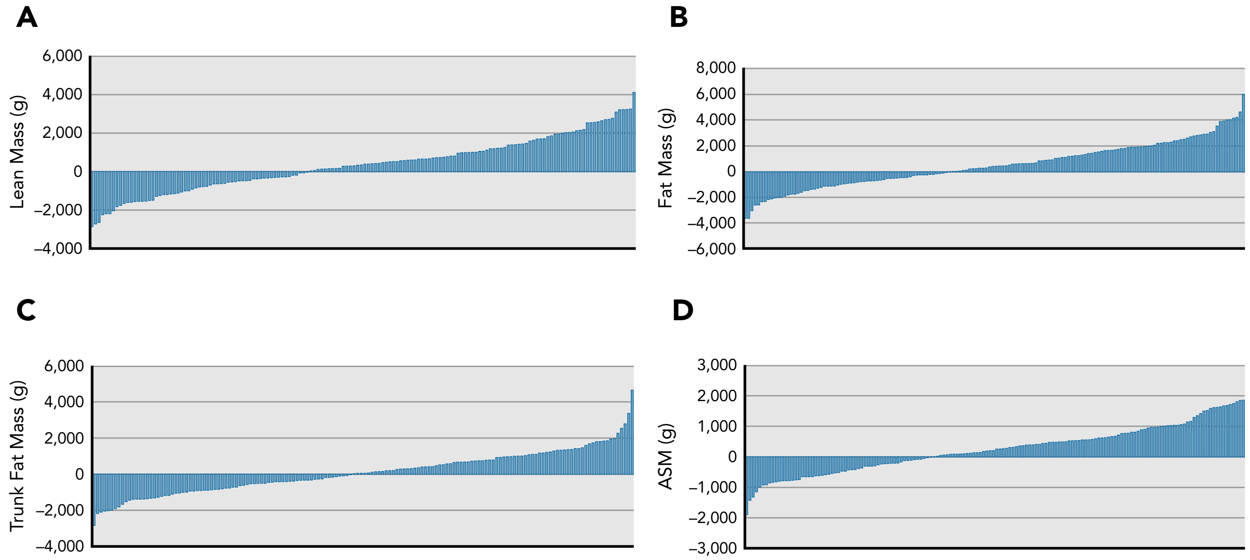

Figure 1. Absolute change in body composition for each individual: (A) lean mass, (B) fat mass, (C) trunk fat mass, and (D) appendicular skeletal muscle (ASM).

reduction >1 kg), and therefore the programs were successful for these patients and in some cases would be meaningful, given the magnitude of fat reduction. In a similar fashion, maximum oxygen consumption was directly assessed in a subgroup of men participating in one of the included trials,[12] showing considerable variation in response (range, −8.8 to +8.5 mL/kg/min) such that a favorable response was observed in nearly half of the participants; therefore, for this outcome, as with FM and TrFM, a beneficial effect may be achieved for some men.

Importantly, every participant in the present study responded in at least one of the areas, with most showing favorable responses in body composition, strength, and physical function. Among nonresponders, no clear pattern was seen across the 3 outcome areas with regard to

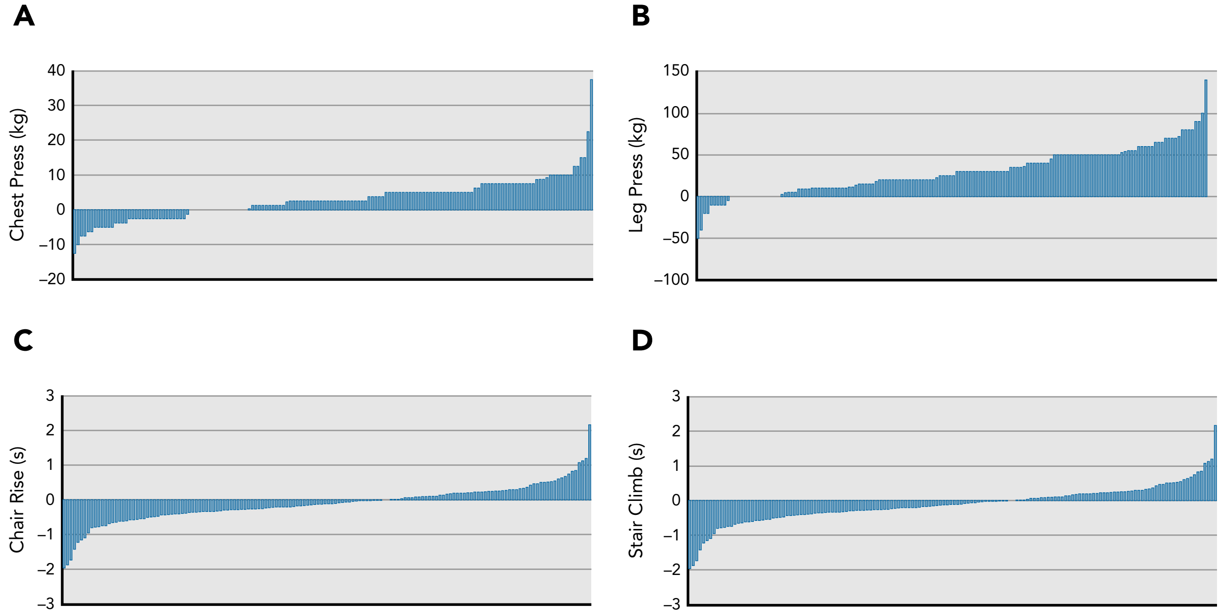

Figure 2. Absolute change in muscle strength, chair rise, and stair climb for each individual: (A) chest press, (B) leg press, (C) chair rise, and (D) stair climb. Reduced time for the chair rise and stair climb indicates improved performance.

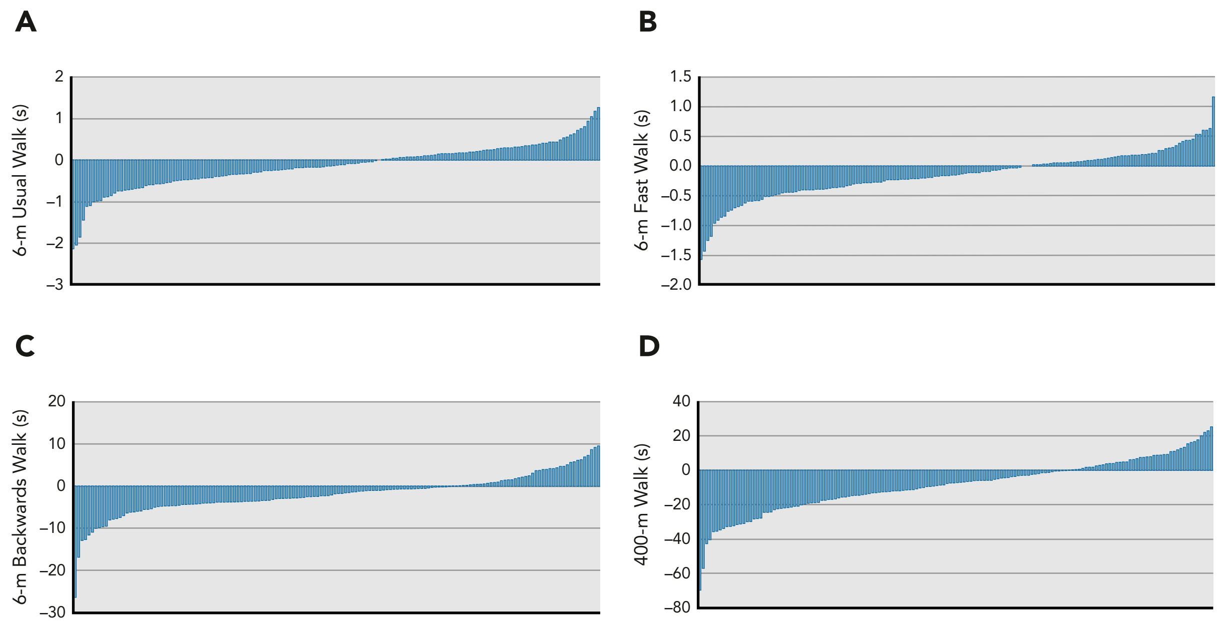

Figure 3. Absolute change in physical function for each individual: (A) 6-m usual walk, (B) 6-m fast walk, (C) 6-m backwards walk, and (D) 400-m walk. Reduced time for the walking tasks indicates improved performance.

age, BMI, commencing versus receiving established ADT, or exercise attendance, although they were more likely to have engaged in exercise training for 6 months. It is not readily apparent what would account for this, because there was little difference in any baseline characteristic between those who trained for 3 versus 6 months. In any event, for nonresponders, given the dose–response nature of exercise on health-related outcomes,[29,30] it may be that a higher exercise stimulus or dose would have resulted in a favorable response. For instance, Montero and Lundby[31] recently showed that among healthy adults, all initially classed as nonresponders in cardiorespiratory fitness after 6 weeks of endurance training became responders after a successive 6-week training period that included additional weekly sessions. Similarly, Bonafiglia et al[32] showed that the incidence of nonresponse in cardiorespiratory fitness parameters among men and women was reduced when the training stimulus was altered. Consequently, although multiple factors, both genetic and nongenetic, influence an individual's trainability,[27] increased training time, volume, or intensity may be required in low-sensitivity individuals for a beneficial effect to occur. In addition, adjuvant therapies may be required to optimize the efficacy of exercise in these individuals, including nutritional strategies, such as protein supplementation and its timing in relation to exercise,[33] and pharmacologic strategies.[34,35] For instance, we recently determined that evidence supporting dietary interventions to mitigate adverse effects of ADT remains limited,[36] and proposed a role for creatine supplementation to enhance exercise training adaptations in patients with cancer, including those with PCa receiving ADT.[37]

Given the applied prescription of the 4 trials included in our analyses, the resistance-based multimodal exercise program can be replicated in real-world practice. Protocols used in our trials followed initial recommendations from the American College of Sports Medicine,[38] the American Cancer Society,[39] and Exercise and Sports Science Australia,[40] and were further expanded, prioritizing specificity of exercise prescription (eg, impact training to preserve bone loss). As a result, there would be opportunities for such exercise protocols to be incorporated into existing programs in the United States, such as LiveStrong at the YMCA, and globally. For example, from an Australian national program perspective, we have used similar prescriptions with positive results in a national community exercise program for men undergoing ADT for PCa.[41] Moreover, it is never too late to introduce exercise; however, commencing exercise with the initiation of ADT may prevent the development of treatment-related toxicities.[11]

Strengths of this study include the reporting of data from 4 independent randomized controlled trials, with assessment of multiple body composition components using whole-body dual x-ray absorptiometry, and of physical function using a comprehensive battery of tests capturing different aspects of performance as well as upper and lower body dynamic muscle strength. As a result, we were able to assess the true utility of the exercise programs for improving physical functioning, which may have been missed had only 1 or 2 performance measures been assessed. In addition, the number of patients who underwent supervised training was relatively large, with complete data available for all outcome measures. We defined a responder as experiencing improvement and a nonresponder as experiencing no improvement in the outcome measure of interest.[19–22] Although it may be argued that requiring a certain level of improvement is desirable to identify an individual as a responder, it should be noted that these men were undergoing ADT, and therefore in the absence of appropriate exercise, they would likely experience a loss of muscle mass and strength, a decline in physical function, and a gain in FM due to testosterone withdrawal.[4] As a result, in this patient group, no change or minimal adverse change could be viewed as a beneficial outcome. Consequently, we believe that our definitions of responder and nonresponder are appropriate in this patient group.

Conclusions

In this group of men with PCa receiving ADT, most had a favorable response to supervised, resistance-based, multimodal exercise with regard to body composition, muscle strength, and physical function. Clinicians can be confident in referring a patient for exercise assessment and prescription, as can exercise physiologists and physical therapists designing and supervising the exercise programs, that most men with PCa receiving ADT will benefit from exercise with improved body composition and a higher level of strength and physical functioning.

Submitted October 4, 2018; accepted for publication April 12, 2019.

Author contributions: *Study concept and design:* All authors. *Data acquisition:* All authors. *Data analysis:* Taaffe. *Manuscript preparation:* All authors. *Manuscript approval:* All authors.

Disclosures: The authors have not received any financial consideration from any person or organization to support the preparation, analysis, results, or discussion of this article.

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