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Time on androgen deprivation therapy and adaptations to exercise: secondary analysis from a 12-month randomized controlled trial in men with prostate cancer

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Objectives

To explore if duration of previous exposure to androgen deprivation therapy (ADT) in men with prostate cancer (PCa) undertaking a year-long exercise programme moderates the exercise response with regard to body composition and muscle performance, and also to explore the moderator effects of baseline testosterone, time since ADT, and baseline value of the outcome.

Patients and Methods

In a multicentre randomized controlled trial, 100 men who had previously undergone either 6 months (short-term) or 18 months (long-term) of ADT in combination with radiotherapy, as part of the TROG 03.04 RADAR trial, were randomized to 6 months supervised exercise, followed by a 6-month home-based maintenance programme, or to printed physical activity educational material for 12 months across 13 university-affiliated exercise clinics in Australia and New Zealand. The participants were long-term survivors of PCa with a mean age of 71.7 ± 6.4 years, and were assessed for lower extremity performance (repeated chair rise), with a subset of men (n = 57) undergoing additional measures for upper and lower body muscle strength and body composition (lean mass, fat mass, appendicular skeletal muscle [ASM]) by dual X-ray absorptiometry. Data were analysed using generalized estimating equations.

Results

Time on ADT significantly moderated the exercise effects on chair rise ($\beta_{interaction}$ = −1.3 s, 95% confidence interval [CI] −2.6 to 0.0), whole-body lean mass ($\beta_{interaction}$ = 1194 g, 95% CI 234 to 2153) and ASM mass ($\beta_{interaction}$ = 562 g, 95% CI 49 to 1075), and approached significance for fat mass ($\beta_{interaction}$ = −1107 g, 95% CI −2346 to 132), with greater benefits for men previously on long-term ADT. At 6 months, the intervention effects on chair rise time −1.5 s (95% CI −2.5 to −0.5), whole-body lean mass 824 g (95% CI 8 to 1640), ASM mass 709 g (95% CI 260 to 1158), and fat mass −1377 g (95% CI −2156 to −598) were significant for men previously on long-term ADT, but not for men on short-term ADT. At 12 months, the intervention effects for men on long-term ADT remained significant for the chair rise, with improved performance (−2.0 s, 95% CI −3.0 to −1.0) and increased ASM (537 g, 95% CI 153 to 921). Time on ADT did not moderate the exercise effects on muscle strength, nor did time since ADT cessation moderate any intervention effects. Similarly, testosterone and baseline values of the outcome had negligible moderator effects.

Conclusions

Men with PCa previously treated long-term with ADT respond more favourably to exercise in terms of lower body muscle performance and body composition (lean and fat mass, and ASM) than those with short-term ADT exposure.

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As a result, men who were formerly on long-term androgen suppression regimens should be especially prescribed exercise medicine interventions to alleviate residual treatment-related adverse effects.

Keywords

androgen deprivation therapy, exercise, #PCSM, #Prostate cancer

Introduction

Androgen deprivation therapy (ADT), in conjunction with radiotherapy (RT) or prostatectomy or as a stand-alone treatment, is widely used in men with prostate cancer (PCa) to delay disease progression and enhance survival [1,2]; however, it is also associated with an array of adverse effects including a reduction in muscle mass, bone mass and physical performance, an increase in fat mass, sexual dysfunction and fatigue, and altered metabolic profile and cognition [3–7]. Moreover, many men will be on ADT for extended periods of time and will survive for many years after the cessation of treatment. We [8–10] and others [11,12] have shown the beneficial effect of physical exercise as a countermeasure to these treatment-related toxicities in men currently undergoing androgen suppression, resulting in an overall enhancement in physical function and quality of life. Likewise, we also undertook a year-long exercise trial in long-term survivors of PCa previously treated with adjuvant ADT and RT for either 6 or 18 months [13]. Those undertaking supervised resistance and aerobic exercise experienced significant improvements in cardiorespiratory fitness, muscle strength, appendicular skeletal muscle (ASM), and physical function compared with those supplied with printed educational material on physical activity. However, given the magnitude of acute and longer-term changes in muscle and fat mass [4,14,15], as well as muscle strength and objective and self-reported physical function with androgen suppression [16,17], that is, pronounced changes in the initial stages that persist or worsen while therapy is continued, it is possible that the exercise response may differ based on the duration of previous exposure to ADT.

Survival rates in men with PCa have improved dramatically over the past 40 years, with current relative 5-year relative survival rates of 90% in the UK [18], 95% in Australia [19] and 99% in the USA [20], although this is influenced by disease stage at diagnosis. As a result, men with PCa are living longer after active treatment including the use of ADT. In prescribing or referring men with PCa including long-term survivors to exercise medicine [21], it is imperative for the clinician and exercise specialist to know what factors may moderate the response to exercise (e.g. time on ADT) so that appropriate patients/survivors and specific outcomes (e.g. reversal of muscle loss and muscle function) can be targeted. Accordingly, we extended our findings on exercise in long-term survivors of PCa [13] to explore if time on ADT prior to undertaking a year-long exercise programme moderates (i.e. influences) the response to exercise. Given the deleterious effects of androgen suppression on body composition and physical function and the anabolic nature of exercise, we evaluated the exercise response on body composition and muscle performance in those with previous short-term exposure (6 months) vs long-term exposure (18 months). In addition, we examined the moderator effect of baseline testosterone, time since ADT, and baseline value of the outcome.

Materials and Methods

Recruitment and Study Procedures

In the present study, we used data from men who participated in the Trans-Tasman Radiation Oncology Group (TROG) 03.04 Randomised Androgen Deprivation And Radiotherapy (RADAR) trial [22,23], and were subsequently enrolled into a multicentre randomized controlled trial (Perth, WA; Newcastle, New South Wales, Australia; and Wellington, New Zealand) that evaluated the effects of a yearlong resistance and aerobic exercise programme compared to a control group in which participants received physical activity advice supported with printed material. The detailed procedures and main effects of this randomized controlled trial have been described previously [13]. Briefly, 347 out of 843 men (41.2%) from the RADAR cohort responded to the letter of invitation from their oncologist and were screened for eligibility. The men were eligible if they: were previously treated with ADT and RT; were insufficiently active within the past 6 months (not meeting 150 min of aerobic and two resistance training sessions per week); were able to walk 400 m; and had obtained medical clearance from their physician. Exclusion criteria were bone metastases, acute illness, or any musculoskeletal, cardiovascular or neurological disorder that could inhibit or put them at risk when exercising.

After completion of the baseline assessment, 100 men were randomly assigned to the exercise or control group in a ratio of 1:1 by a computer random assignment programme, with the allocation sequence using the minimization technique, and stratified according to treatment centre, age (<69, 69–74 and >74 years), original RADAR study arm (6 months ADT

and RT; 6 months ADT and RT and 18 months of bisphosphonate; 18 months ADT and RT; and 18 months ADT and RT and 18 months of bisphosphonate) current level of testosterone (<3, 3–8, >8 nmol/L), whether disease relapse occurred, and waist circumference (<120 cm). A total of 51 men had previously undertaken 6 months ADT (exercise, $n = 22$; control, $n = 29$) and 49 men had received ADT for 18 months (exercise, $n = 28$; control, $n = 21$). The main reasons why men were excluded from the study were: not interested/no further response ($n = 85$); travel constraints or proximity to exercise sites ($n = 43$); illness or existing medical conditions ($n = 41$); other commitments/time constraints ($n = 28$); and already meeting exercise oncology guidelines ($n = 21$) [13]. The study was approved by the Human Research Ethics Committee and all participants provided written informed consent. (Clinical Trial Registry number: ACTRN12609000729224.)

Exercise Programme

A detailed description of the exercise programme is provided elsewhere [13]. Briefly, men in the exercise group undertook combined progressive resistance and aerobic exercise twice a week for 6 months in small groups under direct supervision of an exercise physiologist, with sessions lastly approximately 1 h. Twice per week was the chosen intervention frequency to facilitate recruitment and adherence to the programme, based on our previous experience in undertaking exercise trials in men with PCa [8,9], and complied with current exercise and cancer guidelines for resistance training from the American College of Sports Medicine [24] and Exercise and Sports Science Australia [25]. The resistance exercises included chest press, seated row, shoulder press, triceps extension, leg press, leg extension, leg curl, and abdominal crunches, with loading progressing from 12- to 6-repetition maximum (RM) for two to four sets per exercise. Aerobic exercises (cycling, walking or jogging) were included for 20–30 min at 70–85% of maximum heart rate and perceived exertion at 11–13 on the Borg Rating of Perceived Exertion Scale (6–20 points). In addition, participants were instructed to complete two aerobic exercise sessions per week at home. The exercise programme was identical across the various training sites. During months 7–12, the exercise group received a home-based exercise programme supported by a booklet with detailed information on resistance, aerobic and flexibility exercises that replicated the supervised sessions.

The control group received a pedometer and a modified educational booklet with the general recommendation to perform 150 min per week of moderate intensity physical activity for the 12 months. During the course of the study, participants of both groups were encouraged to maintain their customary dietary patterns.

Outcome and Moderator Assessments

A moderator is a variable that affects the direction and/or strength of the relation between an independent variable and a dependent or outcome variable [26] and, in the case of a clinical trial, identifies which patients or subgroup of patients will benefit from the intervention [27]. The moderating effect of time on ADT (6 vs 18 months) was based on randomization in the RADAR study [22]. Outcomes were assessed at baseline, 6 months and 12 months. For all participants, lower extremity performance was assessed using the repeated chair rise test, in which the men were timed to rise to a standing position five times, as fast as possible, without using their hands for support. Participants from the Western Australian site ($n = 57$), who were assessed in the Exercise Medicine Research Institute at Edith Cowan University which has extensive assessment and testing infrastructure, undertook additional measurements of muscle strength and body composition. Dynamic muscle strength was determined for the chest press and leg press using the 1-RM method [28]. Whole-body lean and fat mass were assessed using dual-energy X-ray absorptiometry (Hologic Discovery A, Waltham, MA, USA), with ASM mass derived from the sum of upper limb and lower limb lean mass [29]. Total testosterone was assessed by an accredited laboratory.

Other Measures

Demographic and clinical data were collected by self-report and medical records, respectively. Height and weight were assessed using a stadiometer and electronic scales, respectively, with body mass index calculated from weight in kg divided by height in m^2. Physical activity was assessed using the Leisure Score Index of the Godin Leisure-Time Exercise Questionnaire [30] and nutritional status was assessed using the Mini Nutritional Assessment (MNA) [31].

Statistical Analyses

The sample size estimate in this report was based on projected changes in cardiorespiratory fitness for the RADAR exercise trial [13] and not for the moderator effect of ADT time which was a secondary analysis from the trial. Data were analysed using IBM SPSS version 24 (IBM Corp., Armonk, NY, USA). Between-group differences in baseline characteristics were assessed using independent *t*-tests for continuous data and the chi-squared test for categorical data, and a group × time repeated measures ANOVA for change over time (baseline, 6 and 12 months) for measures such as the MNA and testosterone. An intention-to-treat approach was used for all exercise trial analyses. In line with our previous work [13,32], analyses were conducted after a likelihood imputation of missing values (expected maximization). Although the main effects on the outcomes have been published previously [13],

we included these analyses to facilitate the interpretation of the moderator effects. Generalized estimating equation analyses with an exchangeable correlation structure were applied to simultaneously evaluate the exercise intervention effects on the outcomes at 6 and 12 months. We added intervention, time and their interaction as independent variables into the regression model, adjusting for the baseline value of the outcome [33]. Regression coefficients (β) and 95% CIs are presented, indicating the between-group differences in the outcome variable, expressed in their unit of measurement.

Potential moderating effects of ADT time, baseline testosterone, time since ADT cessation, and baseline value of the outcome were examined by adding the moderator and its interaction term with the intervention as independent variables within the generalized estimating equation models, separately for each potential moderator. Regression coefficients of the interaction term ($\beta_{interaction}$) and 95% CIs indicate the difference in intervention effects between moderator subgroups. Related to the small sample size, stratified analyses for each subgroup were conducted in case the *P* value of the interaction term was ≤0.10.

Results

Demographic and clinical characteristics of the 100 participants have been published previously [13,32]. In brief, participants' mean (SD) age was 71.7 (6.4) years, and their mean (SD) height was 170.6 (8.4) cm, weight was 85.2 (12.2) kg, Gleason score was 7.6 (0.9), and number of comorbidites was 1.5 (1.4). The characteristics of the 57 participants from the Western Australian site who undertook all assessments in this analysis and form the vast majority of the results are shown in Table 1. Of these 57 participants, 29 had previously undertaken short-term ADT (exercise, *n* = 12; control, *n* = 17) and 28 had been on long-term ADT (exercise, *n* = 16; control, *n* = 12). The mean (SD) age of these 57 participants was 72.6 (6.9) years, and they had a mean interval since ADT of 40.6 (15.9) months. There was no difference in any baseline characteristic between the exercise and the control group or between those previously on short-term and long-term ADT for either the full cohort of 100 participants or for the 57 participants from the Western Australia site (Table S1). Further, there was no difference between short-term and long-term ADT users for any of the outcome measures at baseline. Exercise attendance was 77% and 73% for the full cohort and for the participants from the Western Australia site, respectively.

For the full cohort of 100 men, there was no change in nutritional status between the two groups as determined by the MNA (group × time interaction *P* = 0.279) although there was for the Western Australia site (interaction *P* = 0.015); however, in follow-up tests the change was only an increase of 1 point in the control group from 27.6 to 28.6 (*P* = 0.021). For either the full cohort or those from the Western Australia site there was no change in the MNA when analysed by duration of ADT (interaction *P* = 0.342 and 0.234, respectively). In addition, there was no change in testosterone levels over the 12-month period for either the exercise or control groups (*n* = 100, interaction *P* = 0.233; *n* = 57, interaction *P* = 0.251), or when analysed as short- and long-term ADT groups (*n* = 100, interaction *P* = 0.303; *n* = 57, interaction *P* = 0.807).

Table 1 Demographic and clinical characteristics of participants from the Western Australia site (*n* = 57).

	Exercise (*n* = 28)	Control (*n* = 29)	*P*
Age, years	73.0 (5.2)	72.2 (8.4)	0.679
Height, cm	172.0 (6.1)	170.5 (6.7)	0.374
Weight, kg	87.8 (12.2)	84.4 (10.6)	0.282
BMI, kg/m^2	29.7 (4.4)	29.1 (3.3)	0.539
Tertiary education, *n* (%)	9 (33)	6 (22)	0.362
Currently employed, *n* (%)	3 (11)	7 (24)	0.104
Married, *n* (%)	21 (75)	20 (74)	0.937
Current smoker, *n* (%)	0 (0)	0 (0)	
ADT duration, *n* (%)			
6 months	12 (43)	17 (59)	0.234
18 months	16 (57)	12 (41)	
T stage, *n* (%)			
T2	12 (43)	15 (52)	0.619
T3	16 (57)	14 (48)	
Gleason score *n* (%) >7	15 (54)	11 (48)	0.374
Time since ADT, months	38.0 (17.7)	43.1 (13.9)	0.229
Testosterone, nmol/L	12.8 (8.5)	14.3 (7.2)	0.448
≥8 nmol/L	20 (71)	23 (82)	0.342
MNA*	28.3 (2.2)	27.6 (2.0)	0.247
Godin LSI†	24.3 (18.9)	21.8 (19.9)	0.638
Number of comorbidities‡	1.6 (1.4)	1.5 (1.6)	0.751

BMI, body mass index; ADT, androgen deprivation therapy; LSI, Leisure Score Index; MNA, Mini Nutritional Assessment; Values are the mean (SD) unless stated otherwise. **Malnourished <17, undernourished 17–23.5, well-nourished >23.5.* *†Moderate-to strenuous LSI ≥ 24 classed as active and LSI ≤ 23 classed as insufficiently active.* *‡Cardiovascular disease, hypertension, diabetes, osteoporosis, and dyslipidemia.*

Compared with the control group, the exercise intervention significantly reduced chair rise time and improved chest press strength at 6 and 12 months, and improved leg press and ASM at 6 months (Table 2). For chair rise time, the between-group difference was −1.0 s (95% CI −1.7 to −0.2), favouring the exercise group (net reduction in time to perform the task) at 6 months, and −1.4 s (95% CI −2.1 to −0.6) at 12 months. For chest press strength the between-group difference favouring the exercisers at 6 and 12 months was 3.1 kg (95% CI 1.1 to 5.0) and 4.2 kg (95% CI 1.0 to 7.3), respectively. In a similar fashion, the between-group difference for leg press strength was 13.5 kg (95% CI 0.2 to 26.7) and for ASM 463 g (95% CI 108 to 818) at 6 months, while at 12 months leg press strength and ASM approached significance at 15.8 kg (95% CI −1.8 to 33.3) and 238 g (95% CI −47 to 534), respectively. No significant overall intervention effects were found for total body lean and fat mass.

Table 2 Descriptive characteristics of the outcomes at baseline, 6 months and 12 months for the exercise and control group, and the intervention effects at 6 and 12 months.

	Exercise			Control			Intervention effect	
	Baseline Mean (SD)	6 months Mean (SD)	12 months Mean (SD)	Baseline Mean (SD)	6 months Mean (SD)	12 months Mean (SD)	6 months β (95% CI)	12 months β (95% CI)
Chair rise*, s	12.9 (3.5)	12.0 (4.4)	11.5 (3.4)	11.7 (2.0)	11.8 (2.3)	11.8 (2.4)	−1.0 (−1.7 to −0.2)‡	−1.4 (−2.1 to −0.6)‡
Chest press†, kg	37.9 (8.8)	40.4 (9.6)	39.5 (11.1)	38.7 (10.6)	38.1 (10.1)	36.1 (11.7)	3.1 (1.1 to 5.0)‡	4.2 (1.0 to 7.3)‡
Leg press†, kg	134.8 (38.0)	158.5 (36.1)	157.2 (36.0)	134.9 (52.9)	144.5 (51.4)	140.9 (53.0)	13.5 (0.2 to 26.7)‡	15.8 (−1.8 to 33.3)§
Whole-body lean mass†, g	60078 (6335)	60196 (6138)	60205 (5951)	59076 (6699)	58965 (6418)	58937 (6342)	291 (−256 to 838)	328 (−272 to 927)
Whole-body fat mass†, g	24292 (8816)	23657 (9028)	24276 (8782)	22917 (5272)	22653 (5047)	22818 (4441)	−322 (−1017 to 373)	131 (−497 to 759)
ASM†, g	26203 (3005)	26483 (2939)	26345 (2736)	25852 (3249)	25693 (3143)	25780 (3105)	463 (108 to 818)‡	238 (−47 to 534)§

ASM, appendicular skeletal muscle. **n* = 98, †*n* = 57. ‡$P \leq 0.05$. §$0.05 < P \leq 0.10$.

Time on ADT significantly moderated the exercise intervention effects on chair rise ($\beta_{interaction}$ = −1.3s, 95% CI = −2.6 to 0.0), whole-body lean mass ($\beta_{interaction}$ = 1194 g, 95% CI 234 to 2153) and ASM mass ($\beta_{interaction}$ = 562 g, 95% CI 49 to 1075), and approached significance for fat mass ($\beta_{interaction}$ = −1107 g, 95% CI −2346 to 132), with larger benefits for men on previous long-term ADT (Table 3). At 6 months, the net intervention effects on chair rise time −1.5 s (95% CI −2.5 to −0.5), whole-body lean mass 824 g (95% CI 8 to 1640), ASM mass 709 g (95% CI 260 to 1158), and fat mass −1377 g (95% CI −2156 to −598) were significant for men previously on long-term ADT, but not for men on short-term ADT. That is, previous long-term users had a reduced time to rise repeatedly from a chair (~12.2%), increased their lean mass (~1.4%) and ASM mass (~2.7%), and had a reduction in fat mass (~5.8%) compared with controls. At 12 months, intervention effects for men on long-term ADT remained significant for the chair rise with improved performance (−2.0 s, 95% CI −3.0 to −1.0) and increased ASM (537 g, 95% CI 153 to 921), equivalent to ~16.3% and ~2.1% compared with controls. Time on ADT did not influence the exercise effect on muscle strength.

Men with higher baseline testosterone levels had larger reductions in chair rise time ($\beta_{interaction}$ = −0.1s, 95% CI −0.2 to 0.0 [Table 4]), such that for every nmol/L higher testosterone level the reduction in chair rise time was 0.1 s. Baseline whole-body fat mass moderated the intervention effects on whole-body fat mass ($\beta_{interaction}$ = 0.14 g, 95% CI 0.00; 0.27), such that intervention-induced reductions in whole-body fat mass were smaller in men with higher fat mass at baseline. No other significant moderator effects were found for baseline testosterone, time since ADT cessation, and baseline outcome values.

Discussion

The exploratory study produced two important findings: (1) time on ADT moderated the exercise effect on body composition with increases in whole-body lean mass at 6 months and appendicular lean mass at 6 and 12 months, and reduced fat mass at 6 months, in men who had previously undergone long-term ADT (18 months) but not for those who had undergone short-term ADT (6 months), and (2) previous ADT duration modified the effect on lower extremity performance with an improvement in chair rise time in former long-term ADT users at 6 and 12 months. These results suggest that men previously treated with long-term ADT respond more favourably to exercise medicine interventions to counteract deficits in lower extremity performance and detrimental changes in lean and fat mass. This is a key message for inclusion in PCa survivorship care plans.

A reduction in lean mass and increase in fat mass are well-known adverse effects of ADT [4,7,14,15] and may not be

Table 3 Moderating effect of androgen deprivation therapy time (short-term, 6 months vs long-term, 18 months), and subsequent stratified analysis in case of significant moderation.

	Moderating effect of ADT time		Intervention effects for short-term ADT		Intervention effects for long-term ADT	
	β (95% CI)	*P*	6 months β (95% CI)	12 months β (95% CI)	6 months β (95% CI)	12 months β (95% CI)
Chair rise*, s	−1.3 (−2.6 to 0.0)	0.05	−0.3 (−1.4 to 0.8)	−0.7 (−1.9 to 0.5)	−1.5 (−2.5 to −0.5)‡	−2.0 (−3.0 to −1.0)‡
Chest press†, kg	0.4 (−4.8 to 5.5)	0.89	–	–	–	–
Leg press†, kg	6.0 (−11.6 to 34.5)	0.68	–	–	–	–
Whole-body lean mass†, g	1194 (234 to 2153)	0.02	−309 (−935 to 316)	−362 (−1055 to 331)	824 (8 to 1640)‡	903 (−28 to 1835)§
Whole-body fat mass†, g	−1107 (−2346 to 132)	0.08	752 (−239 to 1742)	389 (−587 to 1366)	−1377 (−2156 to −598)‡	−13 (−946 to 921)
ASM†, g	562 (49 to 1075)	0.04	192 (−264 to 648)	−93 (−483 to 296)	709 (260 to 1158)‡	537 (153 to 921)‡

*ADT, androgen deprivation therapy; ASM, appendicular skeletal muscle. *n = 98. †n = 57. ‡P ≤ 0.05, §0.05 < P ≤ 0.10.*

Table 4 Moderating effects of baseline testosterone, time since androgen deprivation therapy, and baseline value of the outcome.

	Baseline testosterone, nmol/L		Time since ADT, months		Baseline outcome value	
	β (95% CI)	*P*	β (95% CI)	*P*	β (95% CI)	*P*
Chair rise (s)*	−0.1 (−0.2 to −0.0)	0.03	0.0 (−0.0 to 0.1)	0.11	0.2 (−0.2 to 0.5)	0.32
Chest Press (kg)†	0.2 (−0.1 to 0.5)	0.23	−0.0 (−0.2 to 0.2)	0.70	0.1 (−0.1 to 0.3)	0.23
Leg press (kg)†	−0.6 (−2.4 to 1.2)	0.50	−0.0 (−0.8 to 0.8)	0.97	0.2 (−0.5 to 0.2)	0.31
Whole-body Lean mass (g)†	60 (−18 to 137)	0.13	−12 (−45 to 21)	0.49	0.0 (−0.1 to 0.1)	0.95
Whole-body Fat mass (g)†	−60 (−142 to 21)	0.15	18 (−17 to 52)	0.32	0.1 (0.0 to 0.3)	0.04
ASM (g)†	17 (−−42 to 76)	0.58	−12 (−30 to 6)	0.21	−0.0 (−0.1 to 0.1)	0.97

*ADT, androgen deprivation therapy; ASM, appendicular skeletal muscle. *n = 98. †n = 57. Results are unadjusted.*

reversed after treatment cessation [34]. For instance, van Londen et al. [14] reported declines in lean mass of ~0.9 kg and an increase in fat mass of ~1.5 kg after 12 months in men on acute ADT, when changes in body composition are more pronounced, with smaller but still significant gains in fat mass and loss in lean mass in those on chronic ADT. Similarly, in men initiating ADT, we have previously reported a loss in lean mass of 1.4 kg and an increase in fat mass of 2.3 kg after 9 months [4]. Exercise in these men, specifically resistance exercise, is a strategy to counter the marked catabolic effects on skeletal muscle [7,9] and when short- and long-term former ADT users are combined there was a significant increase of ~0.5 kg in ASM at 6 months (supervised portion of the 12-month programme) [13]; however, this effect was influenced by ADT time with a substantial exercise effect on lean mass only in former long-term ADT users of ~0.8 kg at 6 months and ~0.9 kg at 12 months with a significant increase in ASM of 0.7 kg and 0.5 kg at 6 and 12 months, respectively, with no change in former short-term ADT users. Although most men in the study had recovered testosterone by commencement of the intervention, some remained with low levels (<8 nmol/L) [35]; however, testosterone levels did not influence the intervention effects on lean mass, nor did time since ADT cessation or baseline values. The exercise effect appears to be clearly more marked in previous long-term ADT users, with substantial gains in lean mass and ASM, and they may benefit the most when embarking on a resistance and aerobic exercise programme. Moreover, these changes partially offset the adverse effects in lean mass that result from ADT and are likely to be clinically meaningful for the patient and assist in the prevention of sarcopenia.

Our previous work in men currently undergoing ADT indicates that there is a negligible effect of exercise, either resistance exercise alone [8] or resistance combined with aerobic exercise [9], on fat mass. Similarly, in the present study, when short- and long-term former ADT users were combined, the intervention had no effect on fat mass; however, at 6 months there was a moderating effect of ADT time, with a substantial reduction of −1.4 kg in long-term users (equivalent to ~6% net reduction in fat mass). This change substantially reverses gains in fat mass observed with ADT which, apart from being statistically significant, may be considered to be clinically meaningful. We previously noted an effect of ADT time in men undergoing a 12-week resistance and aerobic exercise programme, where there was an adjusted group difference between current short- (<6 months) and long-term (>6 months) ADT users of ~0.9 kg, where the short-term group had a significant within-group increase of ~0.6 kg and the long-term ADT users a significant within-group decrease of −0.4 kg [36]. Taken together, the present study and our previous work [36] indicates that duration of treatment, in both current and

former users of ADT, may influence the effects on the body fat response to exercise and should be considered when discussing the benefits of exercise to patients, given the increased metabolic risk factors associated with ADT [6].

As expected, the intervention had a significant effect on lower extremity performance and upper and lower body muscle strength; however, although there was no moderating effect on muscle strength, there was a moderating effect on chair rise time, with a substantial improvement in performance (decreased time) at 6 and 12 months in those with previous exposure to long-term androgen suppression. This effect on chair rise performance was not influenced by chair rise baseline values. Repeated chair rise performance is not only a measure of muscle strength and power but also balance and coordination [37,38]. Moreover, in older people, lower extremity function is associated with functional limitations and subsequent mobility disability [39], as well as mortality [40]. Former long-term users of ADT, therefore, appear to gain the most benefit from exercise on lower extremity performance which may provide a greater safety margin for prevention of mobility-related disability. The values observed after 6 and 12 months in the long-term ADT group are in alignment with a previously reported minimally important clinical difference of ~1.7 s in older patients with chronic obstructive pulmonary disease [41] and, as such, we would consider the change in our patients to not only be statistically significant but also clinically important.

It is not readily apparent why former long-term ADT users would have a better response to exercise compared with short-term users. There were no differences at baseline between the short- and longer-term ADT users for any clinical/demographic characteristic, including testosterone levels. Moreover, there was no difference at baseline in the outcome variables of muscle performance and body composition. As a result, the moderating effect of ADT time was not attributable to the long-term group having lower initial values and hence more room for improvement (increased responsiveness to exercise) based on the 'law of initial values' [42]. There was also no significant difference in the number of training sessions attended between the short-term and long-term group. Regarding testosterone levels, although testosterone recovery after cessation of treatment is dependent on duration of ADT [43], given the length of time since cessation of treatment in the present study, most men had recovered testosterone levels to within the normal or borderline range, and baseline testosterone was not a moderator of muscle strength or body composition. In addition, there was no change in testosterone levels over the 12-month period. In any event, if there was a difference in testosterone recovery with it being delayed in the long-term group then this would favour the short-term ADT group and not the long-term group.

It is possible that differences in nutritional status over the course of the intervention could have influenced the results, augmenting the response to exercise; however, there was no change in nutritional status over the course of the exercise trial in either the short-term or long-term group, nor was there a significant change in physical activity as determined by the Godin LSI. It is possible, however, that more sensitive measures of nutrition such as serial 4-day or 7-day dietary records and physical activity using accelerometers may have detected differences between the groups that could partially explain the results found. Lastly, possible differential effects based on duration of ADT use on skeletal muscle androgen receptors [44,45] and endocrinological factors, such as IGF-1 [46] may be implicated in the divergent responsiveness to exercise. Alternatively, it may be that former long-term ADT users had more deficits than shorter-term users that are not detected by the measurement techniques employed, and which respond more to an exercise stimulus. This would suggest that there are unrecognized longer-term consequences of hormone suppression than currently appreciated.

The present study has several strengths and limitations that are worthy of comment. Firstly, only patients at the Western Australia site underwent the muscle strength and body composition assessment, and this may have limited our ability to detect a moderating effect of ADT time for muscle strength; however, the moderating effect for muscle strength was negligible and unlikely to be of any clinical importance. Secondly, men undertaking exercise had, on average, undergone ADT >3 years previously; however, time since ADT cessation within the group did not moderate any intervention effects. Thirdly, our study sample was relatively small and the results should therefore be confirmed in future studies. Lastly, the participants were volunteers for an exercise trial and met specific inclusion criteria, and therefore may not be representative of all men previously treated with ADT.

The strengths of the study were that we evaluated a well-characterized cohort of older men previously treated with ADT from the TROG 03.04 RADAR trial [13,22], who were long-term PCa survivors. Both upper and lower body strength were assessed by the 1-RM test in addition to lower extremity performance and, in using dual X-ray absorptiometry, we were able not only to assess whole-body lean mass and fat mass but also to evaluate ASM mass. Lastly, the men participated in a year-long exercise trial that comprised a supervised and then a home-based component which enhances the translatability in the clinical/community setting.

In conclusion, men previously treated long-term with ADT responded more favourably to a resistance and aerobic exercise programme in terms of lower extremity performance and body composition than those with previous short-term ADT exposure. As a result, although all men currently or previously on ADT should be undertaking exercise, men who

were formerly on long-term androgen suppression regimens should be especially prescribed exercise medicine interventions to alleviate residual treatment-related adverse effects due to their enhanced exercise response. Exercise guidelines are available for patients with cancer from a number of major international organizations [24,25,47] and, in general, recommend that patients avoid inactivity and accumulate 150 min of moderate-intensity or 75 min of vigorous-intensity aerobic activity, or an equivalent combination, and undertake at least two resistance or strength training sessions per week, similar to the intervention prescribed in the present study. Detailed exercise recommendations (including rationale and programming considerations) for men with PCa that are applicable to those with localized or advanced disease including men with bone metastases have recently been published [48] and provide an excellent platform for prescribing exercise medicine in this population.

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Conflict of Interest

None declared.

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Abbreviations: ADT, androgen deprivation therapy; ASM, appendicular skeletal muscle; MNA, Mini Nutritional Assessment; PCa, prostate cancer; RM, repetition maximum; RT, radiotherapy.

Supporting Information

Additional Supporting Information may be found in the online version of this article:

Table S1. Demographic and clinical characteristics of exercise and control groups by short-term and long-term ADT status (n = 57).