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REVIEW

Muscle function, physical performance and body composition changes in men with prostate cancer undergoing androgen deprivation therapy

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Prostate cancer (PCa) is the most common visceral malignancy in men with androgen deprivation therapy (ADT) the preferred therapy to suppress testosterone production and hence tumor growth. Despite its effectiveness in lowering testosterone, ADT is associated with side effects including loss of muscle mass, diminished muscle strength, decrements in physical performance, earlier fatigue and declining quality of life. This review reports a survey of the literature with a focus on changes in muscle strength, physical function and body composition, due to short-term and long-term ADT. Studies in these areas are sparse, especially well-controlled, prospective randomized trials. Cross-sectional and longitudinal data (up to 2 years) for men with PCa treated with ADT as well as patients with PCa not receiving ADT and age-matched healthy men are presented when available. Based on limited longitudinal data, the adverse effects of ADT on muscle function, physical performance and body composition occur shortly after the onset of ADT and tend to persist and worsen over time. Exercise training is a safe and effective intervention for mitigating these changes and initial guidelines for exercise program design for men with PCa have been published by the American College of Sports Medicine. Disparities in study duration, types of studies and other patient-specific variables such as time since diagnosis, cancer stage and comorbidities may all affect an understanding of the influence of ADT on health, physical performance and mortality.
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Keywords: androgen deprivation therapy; androgen suppression; exercise prescription; exercise training; functional assessment; lean body mass; older men; prostate cancer

INTRODUCTION

Prostate cancer (PCa) is the most common visceral malignancy in men.[1] Since the tumor is initially testosterone dependent, androgen deprivation therapy (ADT) is the preferred modality to suppress testosterone production in men with this disease. ADT has been extensively studied with surgical and chemical castration achieved *via* bilateral orchiectomy, use of a gonadotropin hormone-releasing hormone (GnRH) agonist or anti-androgens. Annually, about 500 000 men in the United States are treated with GnRH agonists.[2] Though their effectiveness in lowering serum testosterone to castrate levels is well established, side effects are common.

Testosterone and its metabolites are essential for the maintenance of muscle mass and bone mineral content. Body composition changes in men undergoing ADT place them at increased risk not only for diminished physical capacity, but also for coronary artery disease, type II diabetes and the metabolic syndrome,[3] though a recent meta-analysis suggests no increase in cardiovascular mortality.[4] In addition, ADT-associated decreases in muscle and bone mass are thought to be associated with increased fracture risk, diminished muscle strength, decrements in physical performance, earlier fatigue and declining quality of life (**Figure 1**).

This narrative review focuses on changes in muscle strength, physical function and body composition. The effects of ADT on bone are discussed elsewhere in this issue. Cross-sectional and longitudinal data (up to 2 years) for men with PCa treated with ADT as well as patients with PCa not receiving ADT and age-matched healthy men (HC) are presented. For the purpose of this review, treatment durations of less than 6 months will be termed short-term ADT (ST-ADT) while treatment durations $\geqslant$6 months will be considered long-term treatment (LT-ADT). In addition, we examine the efficacy of exercise training interventions and briefly offer current recommendations for exercise intervention for possible mitigation of the adverse consequences of ADT.

APPROACH TO LITERATURE REVIEW

The key words 'PCa, androgen deprivation therapy, ADT, androgen suppression, muscle strength, physical function, body composition exercise and exercise training', were used in PubMed and Google Scholar searches. Studies included in this review were complete articles in peer-reviewed journals, and delimited to those studies in men with PCa undergoing or about to start ADT. Studies were included only if they reported measures of muscle strength or endurance, physical function or body composition either in randomized controlled trial (RCT), cross-sectional reports or studies with repeated measures over at least 3 months. Interventions during the study other than ADT or exercise training were excluded as were studies that did not clearly

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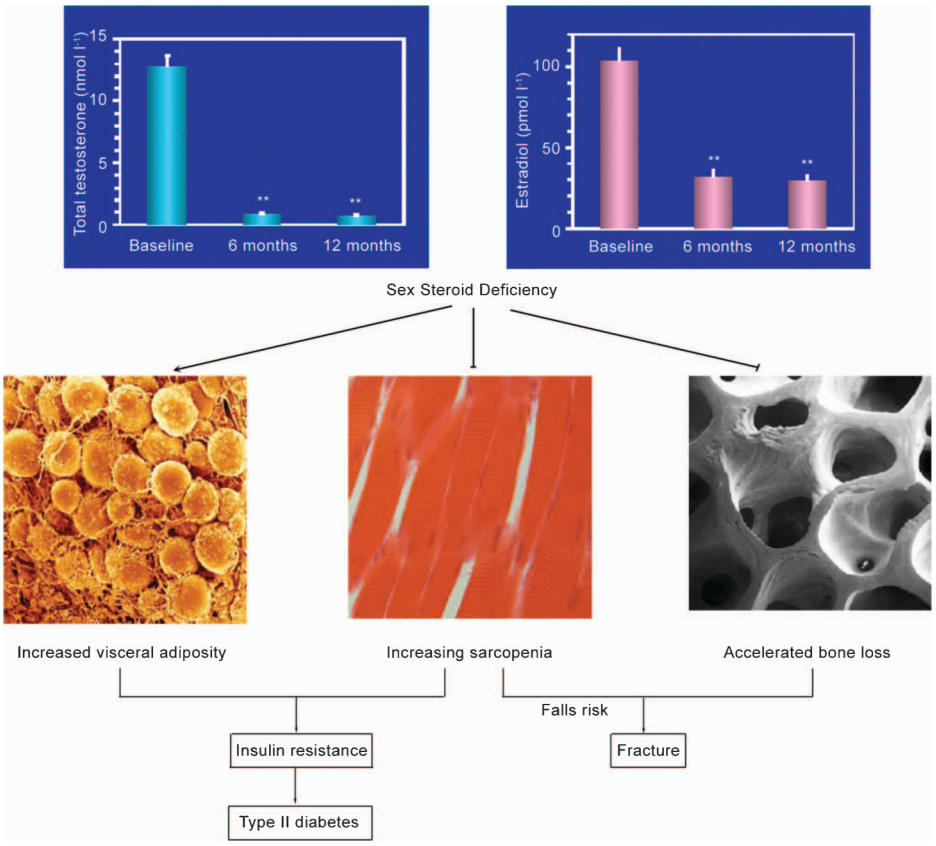

Figure 1 Consequences of androgen deprivation therapy (Courtesy of Mathis Grossmann, MD, University of Melbourne).

delineate PCa patients from patients with other cancers. Only English language papers were included.

MUSCLE FUNCTION CHANGES WITH ADT

Taken together, epidemiology and clinical trials data provide strong evidence of reduced muscle mass and strength in the presence of low testosterone levels occurring naturally or arrived at *via* artificial means. Both frank[5] and 'late-onset'[6–9] hypogonadism are associated with loss of lean body mass and muscle strength, increased fat mass and impaired physical function.[5–9] In epidemiological studies of older men, lower endogenous bioavailable testosterone concentrations are associated with less lean body mass and lower levels of both upper and lower extremity skeletal muscle strength;[6] decrements in self-reported and objective measures of physical function have also been reported though less conclusively. Larger longitudinal studies conducted in the United States[10,11] and the Netherlands[12] have concluded that low levels of circulating testosterone are associated with impaired mobility and low muscle strength in aging men.

Clinical trials investigating the durability of exogenous testosterone effects reinforce these observations, and suggest that the effects of perturbations in circulating testosterone are localized in time and can be reversed. For instance, in a recent 12-month trial with 274 intermediate-frail and frail older men, lean body mass and leg muscle strength increased after 6-month treatment with 25–75 mg day^{-1} testosterone gel, but returned to baseline 6 months after withdrawal from treatment.[13] The differing changes in lean mass and strength between groups appeared to be the direct influence of changing testosterone levels and not secondary treatment-related factors. A similar pattern of on-treatment gains and subsequent losses in muscle mass and strength were reported in a 24-week study of the durability of effects of 12 weeks' administration of oxandrolone on lean body mass, fat mass and several measures of muscle strength.[14] In a manner mirroring these observations, administration of ADT is associated with loss of lean mass (see complete review below), contributing directly to loss of muscle strength. Aside from muscle mass, however, there are additional potential mediators of ADT influence on diminished muscle strength; androgen suppression has also been found to decrease androgen receptor concentration, decrease conduction of end-plate potentials at the myoneural junction and inhibit muscle protein synthesis by increasing insulin-like growth factor-binding factors thereby reducing local insulin-like growth factor-1.[15] The relative contributions of these factors to overall loss in strength are at this point unknown.

Reports on muscle function or its change over time in men receiving ADT are few and have typically focused on strength measured with handgrip dynamometry. Declining grip strength or its absolute value[16] has been shown to be associated with a number of important clinical outcomes. A 2008 systematic review[17] reported that low grip strength was consistently associated with greater probability of premature mortality, earlier onset of disability and increased risk of complications or prolonged length of stay after hospitalization or surgery. Decreased functional status,[18] increased prevalence of poor self-reported physical functioning[19] and loss of independence in activities of daily living[20,21] have also been associated with low grip strength.

Several studies that have examined the effects of ADT on various measures of muscle performance are presented in **Table 1**. Most of these studies are cross-sectional with some studies including comparison groups comprised of men with PCa not initially treated with androgen suppression (PCa-0) and/or healthy age-matched men. One

longitudinal study is included, but only baseline data are presented since no follow-up numerical data were provided.[22]

Grip strength

Soyupek *et al.*[23] measured the effects of ADT on handgrip strength in 20 men with PCa treated for 35 months with an LH–RH agonist and in 20 age-matched HC (**Table 1**). Handgrip strength in men on ADT was 28% lower than in the control group. Both total and free testosterone were shown to be moderately correlated (r=616, P<0.001 and r=0.569, P<0.001, respectively) with handgrip strength. Conversely, other studies comparing men on LT-ADT with HC[24] or men with PCa about to begin androgen suppression with PCa-0 and HC[22] have shown no differences between groups in baseline handgrip strength (**Table 1**). In a study of 59 patients with PCa, higher levels of fatigue were not associated with objective measures of dominant hand grip strength, grip strength endurance or recovery from gripping exercise.[25] Three months of ADT in this study resulted in a statistically significant decline in 3-min grip strength endurance, but grip strength and recovery from repeated fatiguing grip strength efforts did not change. Alibhai *et al.*[22] showed no difference in baseline grip strength between men PCa-0 groups and HC, but a significant decline after 3 months of ADT in 87 men with PCa assigned to this group compared with no change in their PCa-0 and HC groups. After 12 months, subjects receiving ADT experienced a total fall of 5% in grip strength; men in the PCa-0 and HC groups remained stable over this period.

Dynamic strength measures

Measurement of muscle strength, power and endurance by means other than grip strength may be more well associated with greater muscle group specificity with implications for performance and

Table 1 Summary of baseline values in studies examining measures of muscle strength and endurance in men with prostate cancer treated with androgen deprivation therapy of different durations compared with control groups with and without prostate cancer

Performance measure	*Type of study*	*Time on ADT (month) at baseline*	N	*Age (y)*	*Value*	*References*
Grip strength (kg)	P-Long	0	87	70	40	Alibhai *et al.*,[22] 2010
		PCa-0	86	70	42	
		HC	86	68	41	
Right hand	CS	34.8	20	74	28[a]	Soyupek *et al.*,[23] 2008
		HC	20	73	39[a]	
Left hand	CS	21.6	57	73	35	Joly *et al.*,[24] 2006
Right hand					39	
Left hand		HC	51	72	35	
Right hand					37	
Dominant hand	CS	0	59	69	37	Stone *et al.*,[25] 2000
Chest press 1-RM (kg)	RCT	18.2	29	70	34.6	Galvao *et al.*,[92] 2010
		10.1	28	70	34.7	
	CS	37	10	70	39.9	Galvao *et al.*,[37] 2006
	CS	>2	48	70	32.4[a]	Galvao *et al.*,[66] 2009
		HC	70	70	37.5[a]	
Bench press 1-RM (kg)	CS	45	20	70	21.6[a]	Basaria *et al.*,[26] 2002
		PCa-0	18	66	36.1[a]	
		HC	20	69	27.7	
Leg press 1-RM (kg)	RCT	18.2	29	70	98.4	Galvao *et al.*,[92] 2010
		10.1	28	70	102.6	
	CS	37	10	70	81.3	Galvao *et al.*,[37] 2006
	CS	>2	48	70	91.0	Galvao *et al.*,[66] 2009
		HC	70	70	86.8	
	CS	45	20	70	86.2	Basaria *et al.*,[26] 2002
		PCa-0	18	66	118.4	
		HC	20	69	110.2	
Leg extension 1-RM (kg)	RCT	18.2	29	70	38.1	Galvao *et al.*,[92] 2010
		10.1	28	70	40.0	
	CS	>2	48	70	36.3[a]	Galvao *et al.*,[66] 2009
		HC	70	70	44.9[a]	
Chest press end (reps to failure, 70% 1-RM)	RCT	18.2	29	70	10.9	Galvao *et al.*,[92] 2010
		10.1	28	70	11.9	
	CS	37	10	70	9.0	Galvao *et al.*,[37] 2006
	CS	>2	48	70	11.6	Galvao *et al.*,[66] 2009
		HC	70	70	11.4	
Reps to failure fixed resistance 20 kg	RCT	12.8	155	68	32.2	Segal *et al.*,[117] 2003
Leg press end (reps to failure, 70% 1-RM)	RCT	18.2	29	70	17.8	Galvao *et al.*,[92] 2010
		10.1	28	70	16.8	
	CS	37	10	70	20.3	Galvao *et al.*,[37] 2006
	CS	>2	48	70	18.0	Galvao *et al.*,[66] 2009
		HC	70	70	17.7	
Reps to failure fixed resistance 40 kg	RCT	12.8	155	68	37.4	Segal *et al.*,[117] 2003

Abbreviations: CS, cross-sectional; END, endurance; HC, healthy control; PCa-0, patients with PCa but not using ADT; P-Long, prospective-longitudinal; RCT, randomized controlled triall; RM, repetitions maximum.

[a] Identical symbols represent significant differences between groups within a study.

impact on physical function. However, it is difficult to equate performance between cross-sectional studies unless test procedures, and particularly test equipment, movement pattern and muscle action are equivalent. When longitudinal data are presented using similar test procedures, use of percent change may allow reasonable comparisons of groups between studies. However, data presented here are largely cross-sectional with no commonality in test equipment. Consequently, caution is advised in comparing scores between studies even if the test exercise is the same.

In a well controlled cross-sectional study, Basaria *et al.*[26] measured the effects of ADT on upper and lower body strength assessed by a one repetition maximum (1-RM) protocol with machine weights for the bench press and leg press exercises. Twenty men undergoing ADT for at least 12 months were compared with a PCa-0 group and an HC group all matched for age (**Table 1**). Men receiving ADT had 40% less upper body strength than the non-ADT group ($P<0.05$) and 22% less strength than the healthy controls. Although not significant, the ADT group had 27% and 22% less lower body strength than PCa-0 or HC, respectively. Somewhat surprisingly, men with PCa not receiving ADT (PCa-0) had non-significant 7% greater upper and 23% lower extremity strength than the healthy controls. The time since PCa diagnosis was not reported. Overall, these data suggest that lower levels of absolute muscular strength were associated with androgen suppression and not with PCa *per se*. However, apart from one other study,[27] no baseline differences in 1-RM strength have been noted between men treated with ADT and HC groups (**Table 2**). No study has demonstrated differences in muscle endurance.

Very few studies have examined the specific impact of ADT on muscular performance. Handgrip strength appears to yield similar baseline values in men undergoing ST-ADT, LT-ADT, men with PCa receiving no ADT, and in age-matched HC. A single exception found a significant 28% decrement in right grip strength in men with LT-ADT exposure with an average 35-month ADT exposure compared to HC.[23] One study showed no change in grip strength after 3 months of ADT[25] and one study demonstrated a 5% loss of grip strength over 12 months of ADT exposure compared with no change in controls.[28] Logically, handgrip strength might be a reasonable predictor of upper body strength. Grip strength has been shown to correlate well with other muscle strength tests[29] such as knee extension strength or diaphragmatic strength; it should not be used as surrogate for muscle function of lower extremities when evaluating physical performance.[30] Despite its previously published associations with a number of important outcomes, grip strength cannot replace evaluation of assessment of activities of daily living, lower extremity strength or walking speed in fragile populations, such as the elderly or in patients with diseases that might affect physical performance. Measures of dynamic muscle strength using muscle groups, type of muscle action and movement patterns similar to activities of daily living, may be more logical choices for strength assessments and their relation to physical performance.

Well-designed, longitudinal studies including PCa-0 and age-matched healthy control groups with sample sizes large enough to confirm adequate statistical power are needed. Of added importance is the need to establish whether loss of muscle strength *per se* is mechanistically related to decrements in lean body mass, physical function and survival in men treated with ADT.

PHYSICAL PERFORMANCE ALTERATIONS WITH ADT

Measures of physical function reported in studies of ADT include subjective self-reports, as well as objective measures of physical function. Commonly used objective assessments include the short physical performance battery (SPPB),[31–35] walk tests with targeted walk distances of 4–400 m[24,28,34–37] or target durations such as the 6-min walk test (6-MWT).[38] In addition, repetitive chair stands,[34,35] the timed up-and-go (TUG),[22,24,39] and stair climb tests[37] have also been used to characterize physical performance in men undergoing ADT. Acquiring these data should provide insight into whether PCa *per se* or use of ADT in its treatment results in differential decrements in physical performance or whether interventions to mitigate these outcomes are effective. This report focuses on the objective measures of physical function.

Only a small number of studies have examined physical function in men undergoing ADT. **Figure 2** displays annualized proportionate changes in a number of physical function outcomes in two longitudinal studies of at least one year duration. **Table 2** summarizes baseline data from several longitudinal and cross-sectional studies. These are described below.

SPPB

Lower-extremity physical function assessed by the SPPB has been in widespread use since its development over 15 years ago.[31] Strong associations have been found between SPPB performance in older persons and measures of self reported disability,[31] functional measures such as the 6-MWT[27] and 400-m walk time,[40,41] and is a strong and consistent predictor of progressive disability, hospitalization, poor clinical outcomes after hospitalization, nursing home admission and mortality.[31,42–48] Criteria for small and substantial meaningful change scores have been established.[49,50]

Baseline SPPB scores in men with PCa suggest normally functioning individuals (scores greater than 9 out of 12 possible), but with a tendency for men with longer ADT exposure to have slightly lower scores compared with control groups. Notably, one cross-sectional study reported an SPPB score of 7.9 in men averaging 36 months of ADT.[32] In this study, 56% of subjects had abnormal (<9 points) SPPB scores. Another cross-sectional study reported baseline SPPB scores in men with surgical or chemical castration of 31 months duration that were significantly lower than in men who had only 4 months treatment and in men with PCa who had not been treated, although the latter group tended to be younger than the other groups.[34] One prospective study[35] reported a 1.02 point change in SPPB score over 24 months in men who had been treated with a GnRH agonist alone or in combination with an antiandrogen for an average of 25 months. This >1 point difference from baseline is suggestive of a substantial meaningful change.[49,50] Men who had an average of 4 months of ADT at baseline as well as men with PCa not receiving ADT or HC changed by 0.42 and 0.17 points in SPPB, respectively, over the 24-month study period. Neither baseline values nor changes after 24 months were significantly different between groups.

Walk tests

Walking is a fundamental activity of daily living, that has been reported as a clinical indicator of well-being, reflective of health and functional status, and associated with mobility-related fatigue and survival among older adults.[51–58] Walking speed of 1 m s^{-1} is an important threshold for predicting an individual's physical function, ability to live independently, global health decline, rates of hospitalizations and mortality.[52,59] Walk tests of fixed distances of 4–400 m as well as the 6-MWT have been frequently used to assess functional capacity in patient groups.[38,60–65] In their prospective, 24-month trial, Levy *et al.*[35] examined changes in the 4-m walk time in men

Table 2 Summary of baseline values in studies examining objective measures of physical function in men with prostate cancer treated with androgen deprivation therapy of different durations compared with control groups with and without prostate cancer

Performance measure	*Type of study*	*Time on ADT (month) at baseline*	N	*Age (y)*	*Values*	*References*
SPPB (0–12)	P-Long	3.8	12	74	10.3	Levy *et al.*,[35] 2008
		24.6	23	71	9.5	
		PCa-0 or HC	13	67	10.3	
	CS	3.7	13	73	10.4[a]	Clay *et al.*,[34] 2007
		30.7	42	74	9.6[a,b]	
		PCa-0	25	65	10.4[b]	
		HC	20	69	10.3	
	P-Long	36	50	78	7.9	Bylow *et al.*,[32] 2008
	Case–control	⩾6	63	72	10	Bylow *et al.*,[33] 2011
		PCa-0	71	71	10.3	
6-MWT, m ($m\ s^{-1}$)	P-Long	0	87	70	471 (1.3)	Alibhai *et al.*,[22] 2010
		PCa-0	86	70	483 (1.3)	
		HC	86	68	483 (1.3)	
	CS	>6	56	68	669 (1.9)	Culos-Reed *et al.*,[36] 2010
	CS	21.6	57	73	466 (1.3)	Joly *et al.*,[24] 2006
		HC	51	72	470 (1.3)	
400-m walk, s ($m\ s^{-1}$)	RCT	18.2	29	70	269.4	Galvao *et al.*,[92] 2010
		10.1	28	70	273.9	
	CS	37	10	70	283 (1.41)	Galvao *et al.*,[37] 2006
	CS	>2	48	70	274[b]	Galvao *et al.*,[66] 2009
		HC	70	70	256[b]	
4-m walk, s ($m\ s^{-1}$)	P-Long	3.8	12	74	1.02	Levy *et al.*,[35] 2008
		24.6	23	71	1.04	
		PCa-0 or HC	13	67	1.07	
	CS	3.7	13	73	1.04	Clay *et al.*,[34] 2007
		30.7	42	74	0.99[b]	
		PCa-0	25	65	1.06	
		HC	20	69	1.17[b]	
6-m usual walk, s ($m\ s^{-1}$)	RCT	18.2	29	70	4.7 (1.3)	Galvao *et al.*,[92] 2010
		10.1	28	70	4.8 (1.3)	
	CS	37	10	70	5.0 (1.2)	Galvao *et al.*,[37] 2006
	CS	>2	48	70	4.8[b] (1.3)	Galvao *et al.*,[66] 2009
		HC	70	70	4.5[b] (1.3)	
6-m fast walk, s ($m\ s^{-1}$)	RCT	18.2	29	70	3.6 (1.7)	Galvao *et al.*,[92] 2010
		10.1	28	70	3.6 (1.7)	
	CS		10	70	3.7 (1.62)	Galvao *et al.*,[37] 2006
	CS	>2	48	70	3.7[b] (1.6)	Galvao *et al.*,[66] 2009
		HC	70	70	3.5[b] (1.7)	
6-m backward walk, s ($m\ s^{-1}$)	RCT	18.2	29	70	22.2 (0.3)	Galvao *et al.*,[92] 2010
		10.1	28	70	23.7 (0.3)	
	CS	37	10	70	23.5 (0.26)	Galvao *et al.*,[37] 2006
	CS	>2	48	70	23.8[b] (0.3)	Galvao *et al.*,[66] 2009
		HC	70	70	19.9[b] (0.3)	
5× chair rise, s	P-Long	3.8	12	74	13.5[b]	Levy *et al.*,[35] 2008
		24.6	23	71	16.2[b]	
		PCa-0 or HC	13	67	14.0	
	RCT	18.2	29	70	13.3	Galvao *et al.*,[92] 2010
		10.1	28	70	13.4	
	CS	3.7	13	73	13.2	Clay *et al.*,[34] 2007
		30.7	42	74	15.2	
		PCa-0	25	65	13.7	
		HC	20	69	14.5	

To be continued

Table 2 (Continued) Summary of baseline values in studies examining objective measures of physical function in men with prostate cancer treated with androgen deprivation therapy of different durations compared with control groups with and without prostate cancer

Performance measure	*Type of study*	*Time on ADT (month) at baseline*	N	*Age (y)*	*Values*	*References*
	CS	37	10	70	15.4	Galvao *et al.*,[37] 2006[37]
	CS	>2	48	70	13.5[b]	Galvao *et al.*,[66] 2009
		HC	70	70	12.0[b]	
TUG, s	P-Long	0	87	70	6.9	Alibhai *et al.*,[22] 2010
		PCa-0	86	70	6.8	
		HC	86	68	6.5	
	CS	21.6	57	73	6.0	Joly *et al.*,[24] 2006
		HC	51	72	6.0	
13-step stair climb, s	RCT	18.2	29	70	5.2 (326 W)	Galvao *et al.*,[92] 2010
		10.1	28	70	5.3 (340 W)	
	CS	37	10	70	7.0 (248 W)	Galvao *et al.*,[37] 2006

Abbreviations: 5× chair rise is the time (s) to perform five complete stands from an armless chair; CS, cross-sectional; HC, healthy control; 6-MWT, 6-min walk test expressed in meters walked and (gait speed, m s^{-1}). The 400-, 4- and 6-m walk tests are in expressed in seconds and (m s^{-1}); PCa-0, patients with PCa but not using ADT; P-Long, prospective-longitudinal; RCT, randomized controlled trial; SPPB, Short Physical Performance Battery scored on a 0–12 point scale; TUG, timed up-and-go expressed in seconds.

[a,b] Identical symbols represent significant differences between groups within a study.

undergoing ST-ADT or LT-ADT. Performance on these tests was contrasted with a control group comprised of men who had PCa but without surgical or chemical castration (PCa-0) or healthy, age-matched men.[35] There were no differences in gait speed between groups at baseline, but LT-ADT subjects had significant decrements in gait speed from 1.04 to 0.79 m s^{-1} which was significantly different from the change observed in the control subjects. No difference was observed between LT-ADT and ST-ADT walk speeds despite a 0.24-s decrease in speed. The >0.2 s decline in gait speed over the 24-month study period for these subjects is substantial[50] and portends increased morbidity and mortality.[52,56,58]

Also evaluating 4-m walk time in a cross-sectional study, Clay *et al.*[34] revealed significant differences in speed over the 4-m course between men receiving LT-ADT and healthy controls; no differences were seen among ST-ADT, men with PCa but without ADT or healthy controls. However, the 0.99 m s^{-1} walk speed in the LT-ADT group suggests greater risk for mobility limitation.[52,58]

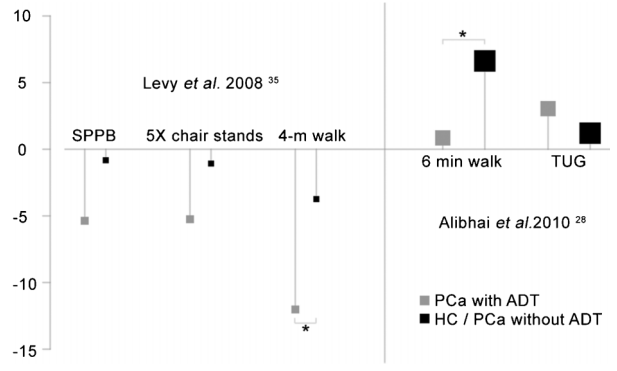

Figure 2 Annualized proportionate change in physical function outcomes in two longitudinal studies of at least 1-year duration, by treatment arm (ADT or control). Points are displayed with magnification proportionate to the square root of group sample size. Statistically significant differences between ADT (grey; PCa treated with ADT) and control (black; healthy control or PCa without ADT) are denoted with a star (*). ADT, androgen deprivation therapy; HC, healthy men; PCa, prostate cancer; SPPB, short physical performance battery; TUG, timed up-and-go test.

One group has used the 6-m walk distance at both usual and fast speeds as well as a backward 6-m walk to assess dynamic balance in men undergoing ADT.[37,66] In an earlier study, Galvao *et al.*[37] assessed 10 men who had averaged 37 months of ADT (half had averaged 5 months on treatment) before and after 20 weeks of progressive, high-intensity resistance exercise training (see exercise training in ADT, below). Walk speeds for usual pace and fast pace were 1.2 and 1.6 m s^{-1}, respectively. Speed for the backwards walk was 0.26 m s^{-1}. The study design did not include control groups but for comparison, published reference values for healthy men in their 70s reported usual and fast walk speeds averaging (s.d.) 1.33 (0.20) and 2.08 (0.36) m s^{-1}, respectively. Six meter backward walk speeds of 0.36 to 0.27 m s^{-1} have been reported in healthy men and women of similar age.[67] Encouragingly, Galvao *et al.*[37] reported improved usual pace, fast paced, and backward 6-m walk by 14%, 5.5% and 22.3%, respectively. The improvement in usual pace walk speed from 1.2 to 1.4 m s^{-1} exceeds the 0.1 m s^{-1} improvement criteria for substantial meaningful change.[49,50] Subsequently, in a larger, cross-sectional evaluation, Galvao *et al.*[37] demonstrated significant differences between men receiving ADT and age matched healthy men (**Table 2**).[66]

The 6-MWT is an assessment of physical function used widely in several fragile populations[62,64,68–73] as the ability to walk for a distance is a quick and inexpensive measure of physical function, and an important component of independence and quality of life. Reference values[68,74–76] and criteria for meaningful change are published.[50,77–80] The significant associations have been demonstrated between 6-min walk distance and lower extremity physical function,[27,81] lower extremity strength and power[27] and survival.[61,72] **Table 2** displays results from studies using this functional measure.

Three studies have examined 6-MWT scores in studies of men using ADT.[22,24,36] Culos-Reed *et al.*[36] reported that men on ADT for >6 months averaged 669 m in 6 min, a gait speed of 1.9 m s^{-1}. These were baseline data prior to the onset of a 16-week controlled exercise training intervention. The training program did not result in significant improvements in either group, but the 25 and 20 additional meters walked in the two groups, respectively, suggest a small, meaningful change.[50] The ability of subjects in this cohort to improve the 6-MWT may have been limited by a

ceiling effect due to their exceptional baseline performance that is at least equal to that in HC of the same age: 525 m or about 1.5 m s^{-1}.[74] Another cross-sectional study reported 6-MWT performance in men who averaged 22 months of ADT that was nearly identical to an age-matched HC group, both groups averaging about 470 m (1.3 m s^{-1}).[24] Similarly, in a 12-month study of men about to begin ADT, men with PCa who would serve as non-ADT controls, and HC, baseline values for the 6-MWT were not significantly different, averaging about 480 m.[22] Notably, while both control groups in this study improved over the 12-month observation period, patients treated with ADT remained stable. Differences in walk performance between HC and patients on ADT, although not statistically significant, were seen after just 3 months on treatment.

The 400-m walk test is somewhat analogous to the 6-MWT but uses a target distance rather than time. Walking speed over 400 m has been shown to be significantly faster than that for the 6-MWT.[82] Test–retest reliability has been established[83] and significant associations have been reported between 400-m walk time and aerobic capacity, lower extremity strength and power,[40,84] mobility limitation[85] as well as mortality prognosis in older persons.[86–89] Minimally significant change for the 400-m walk test has been estimated at 20–30 s, while 50–60 s was suggested as criteria for substantial change.[49]

Prior to their 20-week progressive, resistance exercise training study in long-term users of ADT, Galvao *et al.*[37] reported a mean 400-m walk time of 283 s (1.4 m s^{-1}). This compares favorably with a mean walk speed of 1.34 m s^{-1} over 400 m for a group of 20 (four women) healthy subjects at 73 years of age.[82] Also, the walk speed reported by Galvao *et al.*[37] was similar to those observed in two cross-sectional studies of men receiving ADT who were measured with the 6-MWT.[22,24] The effectiveness of the exercise training was seen in a significant 30 s (7.4%) improvement which exceeds the 20 s criteria reported by Kwon *et al.*[49] for a minimally significant change.

Additional measures to assess physical function in men with ADT have included time for five chair stands, TUG and stair climbs. These are relevant assessments of everyday activities and reasonable choices for examining the consequences of ADT on muscle function and physical performance. Data from studies using these measures of are summarized in **Table 2**.

One study noted significantly slower chair stand times in LT-ADT versus ST-ADT but not between either of these groups and PCa-0 or controls.[35] In a cross-sectional study, men with at least 2 months ADT exposure were significantly slower in completing five chair stands than healthy controls.[66] Several other studies have not been able to detect differences in chair stand time between using and not using ADT.

TUG and a 13-step stair climbing task

A meta-analysis of 21 studies showed that time for TUG in healthy older adults progressively increased with age averaging 8.1 s among 60–69 year olds, 9.2 s among 70–79 year olds and 11.3 s among 80–99 year olds.[90] Two studies that assessed TUG in men receiving ADT and their control groups (**Table 2**) revealed times that were actually 23%–35% faster than reported of healthy age-matched individuals in the meta-analysis.

The stair climb test has been used infrequently as a measure of physical function in men undergoing ADT, but has the advantage of not being as susceptible to ceiling effects as other functional tests.[91] To our knowledge, only one small uncontrolled study[37] and one RCT[92] of men exposed to LT-ADT have used this physical performance measure in ADT (**Table 2**). In the RCT, time for climbing 13 steps at baseline was not different between men assigned to exercise (18 months ADT use) or men with 10-month ADT exposure assigned to control. Twelve weeks of exercise training improved time by 4% and 2%, respectively, but the difference was not significant. Conversely, in their uncontrolled study, this same group demonstrated a significant 10% improvement in time to ascend the 13 steps after 20 weeks of resistance training.[37] For comparison, we have estimated stair climb power in this study by using reported values for step rise, number of steps, an estimate of body weight and time to climb the 13 steps. At baseline, powers so calculated were 251 and 326–340 W for the two groups in the RCT. Recently, we reported that baseline 12-step stair climbing power averaged 322 W[93] in 165 older men (mean age: 74 years) with mobility limitation. Although stair climb data in older men with PCa receiving ADT are limited, data from the studies noted above and in **Table 3** suggest a 22% deficit when compared with men of approximately the same age with mobility limitation.

When documenting the effects of ADT on physical function, future studies should consider ceiling effects in physical function tests. While the ideal test is one in which performance on the test is linearly related to the participant's ability, many tests reach a ceiling when performance cannot be improved once a particular ability is achieved.[94] In this case, more physically demanding, yet realistic assessments might be considered. For example, performing 50-m walk test or climbing a flight of 12 steps while carrying a load was better able to discriminate performances among older, HC and older men with mobility limitations.[93,94]

BODY COMPOSITION

Body composition is defined as the proportion of different tissue masses in the body. Its analysis can be very detailed and include water compartments, and elemental components of the body; however, the most common approach used to study the effect of ADT on body composition in studies of effects are measurements of fat mass (often expressed as percent body fat), lean mass (% LBM) and bone density. These tissue masses are generally reported for the whole body, although regional measures of body composition such as appendicular skeletal muscle mass (ASM)[95] and ASM index (ASM Ht^{-2})[96] have also been reported. Not strictly a measure of body composition, body mass and body mass index (BMI), are common indicators in studies on the effects of ADT on body weight. BMI was the focus of one study in over 450 men with ADT[97] and body mass alone is commonly reported and was the subject of one 3-year study with the natural history of change in body mass with ADT.[98]

The summary of published data reported here focuses on BMI, % LBM and % Fat, as affected by androgen suppression. Except where noted all body composition variables were measured with dual energy X-ray absorptiometry (DEXA).

Body mass

Kim *et al.*[98] reported change in body mass from a study of 132 men aged 66 years identified from the Shared Equal Access Regional Cancer Hospital database who started and continued ADT for up to 3 years after radical prostatectomy. Weight change was defined as the difference in body weight 6 months before starting ADT and between 6 and 18 months after starting ADT. Seventy percent of men in the study gained weight in the first year, while 26% lost weight with an overall mean (s.d.) change of 2.2 (4.1) kg. In the men who gained weight, gain averaged 4.2 (2.9) kg; weight losers lost a mean of 2.4 (2.4) kg. Among the men with body weight recorded in the year before and in the second year after starting ADT (64% of total sample), there was no

significant weight change in the year prior to ADT or in the second year on therapy. However, the average weight while on ADT was 2.1 kg higher than pre-ADT weight and was thus similar to the entire cohort. Overall, these data support previously published smaller data[99,100] indicating the majority of weight change occurs within the first year of starting ADT, although neither was actually measured.

BMI

The effects of short- and long-term exposure to ADT on BMI are summarized in **Table 3A** and in **Figure 3** along with comparisons of generally age-matched men with PCa and HC. The majority of these studies suggest no differences in BMI for men receiving ADT, PCa-0 or HC and that men in these studies are generally overweight with BMI averaging about 28.2 kg m^{-2}. Only two[26,101] of the 23 studies included in **Table 3** found statistically significant differences between groups with men receiving LT-ADT and healthy, age-matched controls. Beehler *et al.*[97] assessed the association between ADT and changes in BMI with multilevel modeling in 473 cases of men with PCa drawn from the tumor registry at the Buffalo Veterans Administration Comprehensive Cancer Center. Neither surgery, radiation treatment nor ADT was associated with significant change in BMI over time. However, there was a linear relationship between the number of GnRH agonists dose and decreasing BMI over time especially among men who were younger at PCa diagnosis; younger survivors had a significant 33% greater rate of change than men averaging 68 years and 100% greater rate of change than men aged 77 years. A recent systematic review reported data from eight longitudinal studies (208 total patients) on the effects of ADT on body composition and BMI.[102] The right panel of **Figure 3** displays these data as an annualized percent change in BMI in studies with at least 1-year exposure.[102] **Figure 3** also presents longitudinal relationships between length of ADT exposure and BMI (left panel). Subjects newly receiving ADT show the most rapid changes, but overall changes are modest, reflecting the combined effect of ADT on lean mass (increases) and fat mass (decreases), and BMI's limited utility as a proxy for measures of body composition.

LBM

Table 3B presents baseline values for % LBM from longitudinal[35,95,96,99,103–107] and cross-sectional studies.[1,34,37,101,108–110] In addition, two longitudinal studies include data for baseline and 6-month[96] and 9-month[95] values for LBM reported in kg. Prospective, longitudinal studies investigating effects of ADT on lean body mass that are included in **Table 3B**[99,103,104,107,111,112] were summarized in a recent systematic review that included 261 patients in aggregate and observation periods of 3–24 months.[102] Changes in lean mass in these studies ranged between −1.4% and −3.86%, the latter reported in a 24-month study, one of the longest studies of ADT effects on body composition in the literature. The mean change (95% CI) in percent lean mass was −2.82% (−3.64%−2.01%). The right panel of **Figure 4** displays annualized differences in percent change from studies with at least 1-year exposure.[102] The mean annualized change was −2.0%. These changes typically occurred without significant changes in BMI.

The left side of **Figure 4** displays qualitative changes from baseline in LBM in seven studies conducted over 3–24 months. LBM is seen to fall in all groups especially for men just beginning ADT. The average change from baseline to end of study, regardless of study length, was −1.5% LBM for patients receiving ADT compared with a 0.2% LBM change for HC. A 10-year longitudinal study of change in body composition in healthy older (61±8 year) men found a 1.9% decrease in LBM per decade in the 53 male participants,[113] a 10-fold difference when compared with the annualized change in % LBM for men using ADT shown in the right panel of **Figure 4**.

Overall, theses data show a consistent trend of decreasing lean body mass with increasing ADT exposure consequent to the effects of androgen suppression. Whether this loss of lean mass affects muscle performance (strength, power or muscle fatigability) or physical function in men treated with ADT is yet to be demonstrated, though epidemiologic evidence suggests a potent association between skeletal muscle mass, mobility and physical ability.[114] Changes in LBM occur early in the course of ADT suggesting that countermeasures be instituted to minimize the predicable loss of LBM with strategies implemented ideally prior to the onset of ADT.

Relative body fat (% Fat)

Androgen deprivation increases accumulation of fat mass, especially subcutaneous fat, and increases risk of obesity.[104,115] Relative body fat (% Fat) values from cross-sectional and longitudinal studies in men receiving ADT are given in **Table 3C** and summarized in **Figure 5**. The right panel of **Figure 5** illustrates the annualized percent change in fat mass reported in four prospective, longitudinal studies with at least 1-year exposure to ADT. These studies, reviewed in a recent meta-analysis,[102] included patients in a wide range of PCa stages with treatment durations of 3–12 months. All studies showed statistically significant increases in fat mass with an average annualized change of 11.1%. The left panel of **Figure 5** illustrates rates of increase in % Fat from the longitudinal studies summarized in **Table 3C**. Taken together, these data provide clear indications of the effect of ADT on relative body fat at various points in time in exposure to therapy. Relative to men with PCa, healthy, age-matched men, in general, have lower % Fat values at baseline and show only modest increases over 2 years. Unfortunately, the comparative data for HC of similar age presented here are from only two studies. A 10-year study of longitudinal changes in body composition showed that fat mass (underwater weighing) increased 0.7% per year in 53 men averaging 61 years of age.[113] This annual increase in fat mass is 16 times lower than the average 11.1% annualized percent change in fat mass for men undergoing androgen suppression therapy illustrated in **Figure 5**. As with changes in LBM, increases in fat mass with ADT occur as early as within 3 months of starting treatment.

CHANGES WITH EXERCISE TRAINING

The adverse effects of ADT-induced low serum testosterone on body composition and strength are well appreciated and seen as contributors to loss of physical functional and increased levels of fatigue[25,32,34,35,66] with fatigue itself interfering with functional ability and physical activity.[116] Fatigue or lack of energy is a highly prevalent side effect of ADT and has been shown to be severe in 14 percent of men after only 3 months of androgen suppression.[25] A number of RCT in men with PCa receiving androgen suppression have shown the value of well-designed exercise training programs. These studies have demonstrated significant improvements in muscle performance,[37,92,117] physical function[37,92,118,119] and body composition[37,120] that occurred after as little as 12 weeks of training. **Table 4** summarizes the efficacy of exercise training from five RCT, two uncontrolled trials and one small non-randomized pilot study in men undergoing androgen suppression therapy.

Three randomized trials using supervised RT,[117] RT or AT,[120] and RT plus AT[92] for 12–24 weeks have shown significant benefits in

Table 3 Summary of baseline values in studies examining measures of body composition in men with prostate cancer treated with androgen deprivation therapy of different durations compared with control groups with and without prostate cancer

Type of study	*Time on ADT (month) at baseline*	N	*Age (y)*	*Baseline values*	*References*
Table 3A Body mass index (kg m^{-2})					
P-Long	3.8	12	74	28.7	Levy *et al.*,[35] 2008
	24.6	23	71	29.6	
	PCa-0 or HC	13	67	28.7	
P-Long	3.0	43	71	28.4	van Londen *et al.*,[105] 2008
	30.7	67	71	29.1	
	PCa-0	81	67	28.3	
	HC	53	63	27.6	
P-Long	0	32	66	26.9	Smith *et al.*,[104] 2002
P-Long	0	79	71	28.4	Smith *et al.*,[129] 2004
P-Long	0	35	75	25.9	Berruti *et al.*,[106] 2002
	11.6	50	73	25.3	Denti *et al.*,[130] 1996
	HC	58	74	24.4	
P-Long	0	10	74	25.2	Tayek *et al.*,[131] 1990
P-Long	PCa-0	18	67	24.7	Nowicki *et al.*,[132] 2001
P-Long	0	25	68	29.1	Smith *et al.*,[107] 2006
P-Long	0-12	26	65	27.1	Smith *et al.*,[100] 2008
P-Long	0	62	69	25.4	Stone *et al.*,[25] 2000
RCT	18.2	29	70	27.4	Galvao *et al.*,[92] 2010
	10.1	28	70	28.0	
RCT	3 (median)	120	72	28.8	Ryan *et al.*,[133] 2007
CS	3.7	13	73	28.3	Clay *et al.*,[34] 2007
	30.7	42	74	28.1	
	PCa-0	25	65	28.0	
	HC	20	69	27.6	
CS	>12	20	74	26.6	Soyupek *et al.*,[23] 2008
	HC	20	73	25.9	
CS	45	20	70	29.6[a]	Basaria *et al.*,[26] 2002
	PCa-0	18	66	27.6	
	HC	20	69	24.7[b]	
CS	<6	24	74	28.6	Dacal *et al.*,[109] 2006
	⩾6	29	73	27.4	
	PCa-0	23	64	28.5	
	HC	20	64	26.9	
CS	12-60	62	74	27.4[a]	Chen *et al.*,[101] 2002
	HC	47	73	25.8[a]	
CS	>6	30	72	26.8	Boxer *et al.*,[96] 2005
	HC	25	75	26.1	
CS	PCa-0	11	69	28.4	Maturo *et al.*,[110] 2003
	HC	11	70	27.6	
CS	>6	63	68	28.7	Culos-Reed *et al.*,[36] 2010
CS	41	19	72[a]	28.0	Stoch *et al.*,[1] 2001
	PCa-0	41	70[b]	26.6	
	HC	197	66[a,b]	27.9	
CS	PCa-0	155	68	28.8	Segal *et al.*,[117] 2003
CS	37	10	70	28.0	Galvao *et al.*,[37] 2006
Table 3B Percent Lean body mass					
P-Long	3.8	12	74	70.9	Levy *et al.*,[35] 2008
	24.6	23	71	65.6	
	PCa-0 or HC	13	67	72.3	
P-Long		65[a]	66	69.7	Lee *et al.*,[99] 2005
P-Long	3.0	43	71	69.9	van Londen *et al.*,[105] 2008
	30.7	67	71	65.9	
	PCa-0	81	67	70.3	
	HC	53	63	71.6	
P-Long	0	32	66	70.3	Smith *et al.*,[104] 2002
P-Long	PCa	79	71	68.7	Smith *et al.*,[103] 2004
P-Long	0	72	74	55.8 kg	Galvao *et al.*,[95] 2008
P-Long	0	35	75	68.5	Berruti *et al.*,[106] 2002

To be continued

Table 3 (Continued) Summary of baseline values in studies examining measures of body composition in men with prostate cancer treated with androgen deprivation therapy of different durations compared with control groups with and without prostate cancer

Type of study	*Time on ADT (month) at baseline*	N	*Age (y)*	*Baseline values*	*References*
P-Long	0	25	68	68.1	Smith *et al.*,[107] 2006
RCT	18.2	29	70	69.5	Galvao *et al.*,[92] 2010
	10.1	28	70	69.5	
CS	3.7	13	73	71.1[c]	Clay *et al.*,[34] 2007
	30.7	42	74	66.7[a–c]	
	PCa-0	25	65	71.1[a]	
	HC	20	69	71.2[a]	
CS	<6	24	74	68.1	Dacal *et al.*,[109] 2006
	⩾6	29	73	66.8	
		P<0.01 for ADT groups *vs.* no ADT groups			
	PCa-0	23	64	70.7	
	HC	20	64	72.2	
CS	12-60	62	74	64.2	Chen *et al.*,[101] 2005
	HC	47	73	70.6	
CS	>6	30	72	53.3	Boxer *et al.*,[96] 2005
	HC	25	75	54.3	
CS	PCa-0	11	69	65.1[a]	Maturo *et al.*,[110] 2003
	HC	11	70	67.3[a]	
CS	41	19	72[a]	71.0	Stoch *et al.*,[1] 2001
	PCa-0	41	70[a]	75.0	
	HC	197	66[a,b]	NA	
Appendicular skeletal muscle mass (kg)					
P-Long	0	72	74	23.4	Galvao *et al.*,[95] 2008
Appendicular skeletal muscle mass index (ASM Ht^{-2})					
CS	>6	30	72	7.5	Boxer *et al.*,[96] 2005
	HC	25	75	7.5	
Table 3C Percent relative body fat					
P-Long	3.8	12	74	26.5	Levy *et al.*,[35] 2008
	24.6	23	71	31.6	
	PCa-0 or HC	13	67	24.7	
P-Long	35	65[d]	66	27.1	Lee *et al.*,[99] 2005
P-Long	0	26	65	25.1	Smith *et al.*,[112] 2004
P-Long	0	25	68	28.7	Smith *et al.*,[107] 2006
P-Long	0	79	71	28.0	Smith *et al.*,[103] 2004
P-Long	3.0	43	71	27.1	van Londen *et al.*,[105] 2008
	30.7	67	71	31.4	
	0	81	67	26.7	
	HC	53	63	25.1	
P-Long	0	32	66	26.4	Smith *et al.*,[104] 2002
P-Long	0	72	74	25.8	Galvao *et al.*,[95] 2008
P-Long	0	35	75	24.7	Berruti *et al.*,[106] 2002
P-Long	>6	30	72	29.8[a]	Boxer *et al.*,[96] 2005
	HC	25	75	26.6[a]	
RCT	18.2	29	70	27.5	Galvao *et al.*,[92] 2010
	10.1	28	70	27.3	
CS	3.7	13	73	26.2[c]	Clay *et al.*,[34] 2007
	30.7	42	74	30.5[a–c]	
	PCa-0	25	65	25.9[a]	
	HC	20	69	25.6[b]	
CS	45	20	70	32.2[a,b]	Basaria *et al.*,[26] 2002
	PCa-0	18	66	26.2[a]	
	HC	20	69	22.4[b]	
CS	<6	24	74	29.0	Dacal *et al.*,[109] 2006
	⩾6	29	73	30.2	
		P<0.01 for ADT groups *vs.* no ADT groups			
	PCa-0	23	64	26.3	
	HC	20	64	24.6	
CS	12-60	62	74	30.2[a]	Chen *et al.*,[101] 2002

To be continued

Table 3 (Continued) Summary of baseline values in studies examining measures of body composition in men with prostate cancer treated with androgen deprivation therapy of different durations compared with control groups with and without prostate cancer

Type of study	*Time on ADT (month) at baseline*	N	*Age (y)*	*Baseline values*	*References*
	HC	47	73	25.7[a]	
CS	PCa-0	11	69	29.5	Maturo *et al.*,[110] 2003
	HC	11	70	29.6	
CS	41	19	72[a]	29	Stoch *et al.*,[1] 2001
	PCa-0	41	70[b]	25	
	HC	197	66[a,b]	NA	
CS	37	10	70	30.7	Galvao *et al.*,[37] 2006

Abbreviations: ASM, appendicular skeletal muscle mass; ASM Ht^{-2}, appendicular skeletal muscle mass index, ASM divided by height squared; CS, cross-sectional; HC, healthy control; PCa-0, patients with PCa but not using ADT; P-Long, prospective-longitudinal; RCT, randomized controlled trial.
[a–c] Identical symbols represent significant differences between groups within a study.
[d] 35% of the 65 subjects had received GnRH agonist treatment for 35 months before entry into study. The remainder began ADT and continued treatment over the 12-month study duration.

avoiding or reversing some of the changes associated with ADT. In one study, 155 men beginning ADT were randomly assigned to 12 weeks of thrice weekly resistance exercise training or no exercise.[117] The exercising group had significantly improved upper and lower extremity muscle endurance, and less fatigue and better quality of life scores, but the change between groups for anthropometric and body composition measures were not different. Galvao *et al.*[92] recently reported a 12-week RCT that evaluated the combined effects of RT and AT on comprehensive measures of muscle function, physical performance and body composition in men receiving ADT. After only

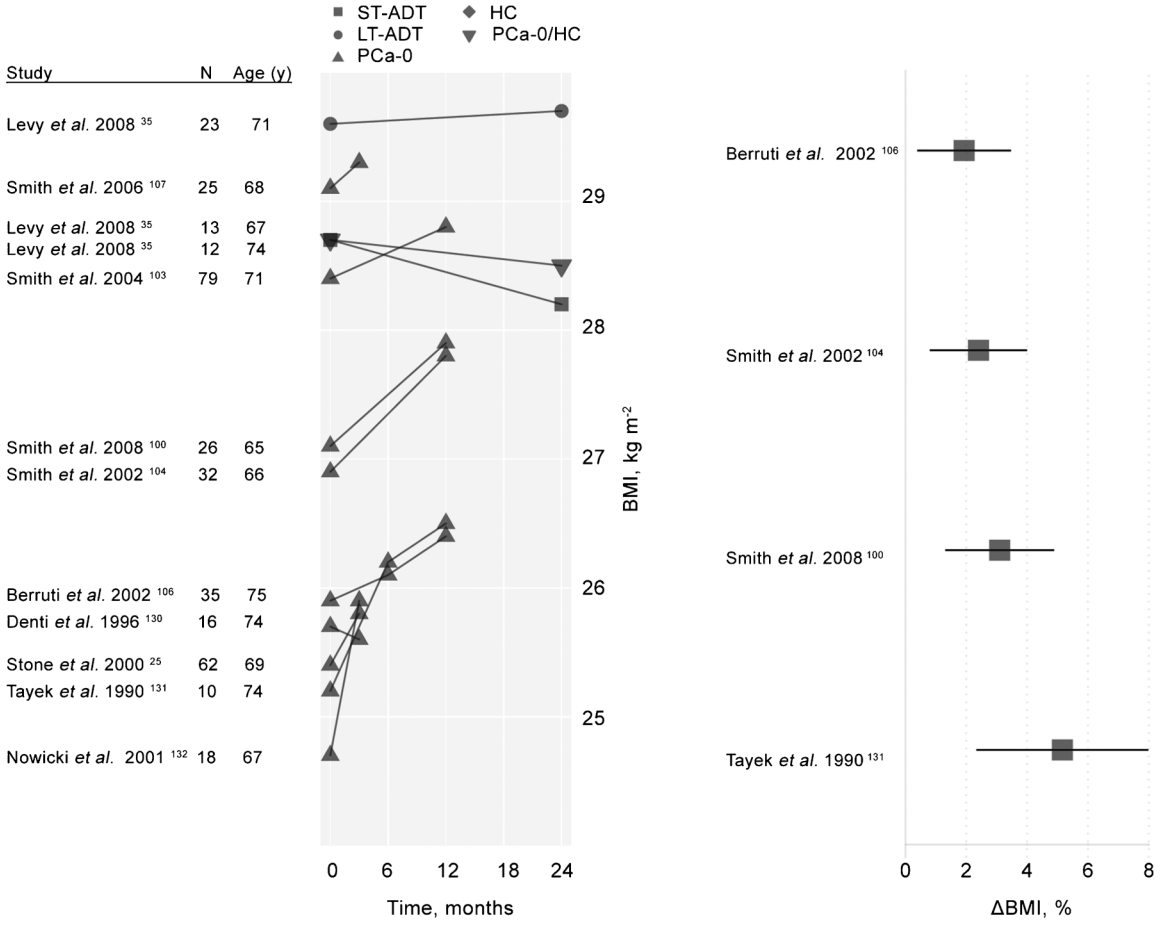

Figure 3 Left: Longitudinal changes in BMI among men enrolled in ADT studies. Untreated, healthy control participants are denoted as HC. A single mixed control group of healthy men and men with PCa not treated with ADT (HC/PCa-0) is also displayed. The remaining participants (all with PCa diagnoses and treated with ADT in the studies displayed) are classified according to their history of treatment with ADT prior to the current study. These groups include subjects with short-term (less than 6 months) previous exposure to ADT (ST-ADT groups), longer-term (six months or longer) previous exposure to ADT (LT-ADT groups) and subjects with no prior history of ADT exposure (PCa-0). Right: Annualized percent change in BMI among subjects treated with ADT in studies of at least 1-year duration reporting BMI change values, adapted from Haseen *et al.*[102] ADT, androgen deprivation therapy; BMI, body mass index; HC, healthy men; PCa, prostate cancer.

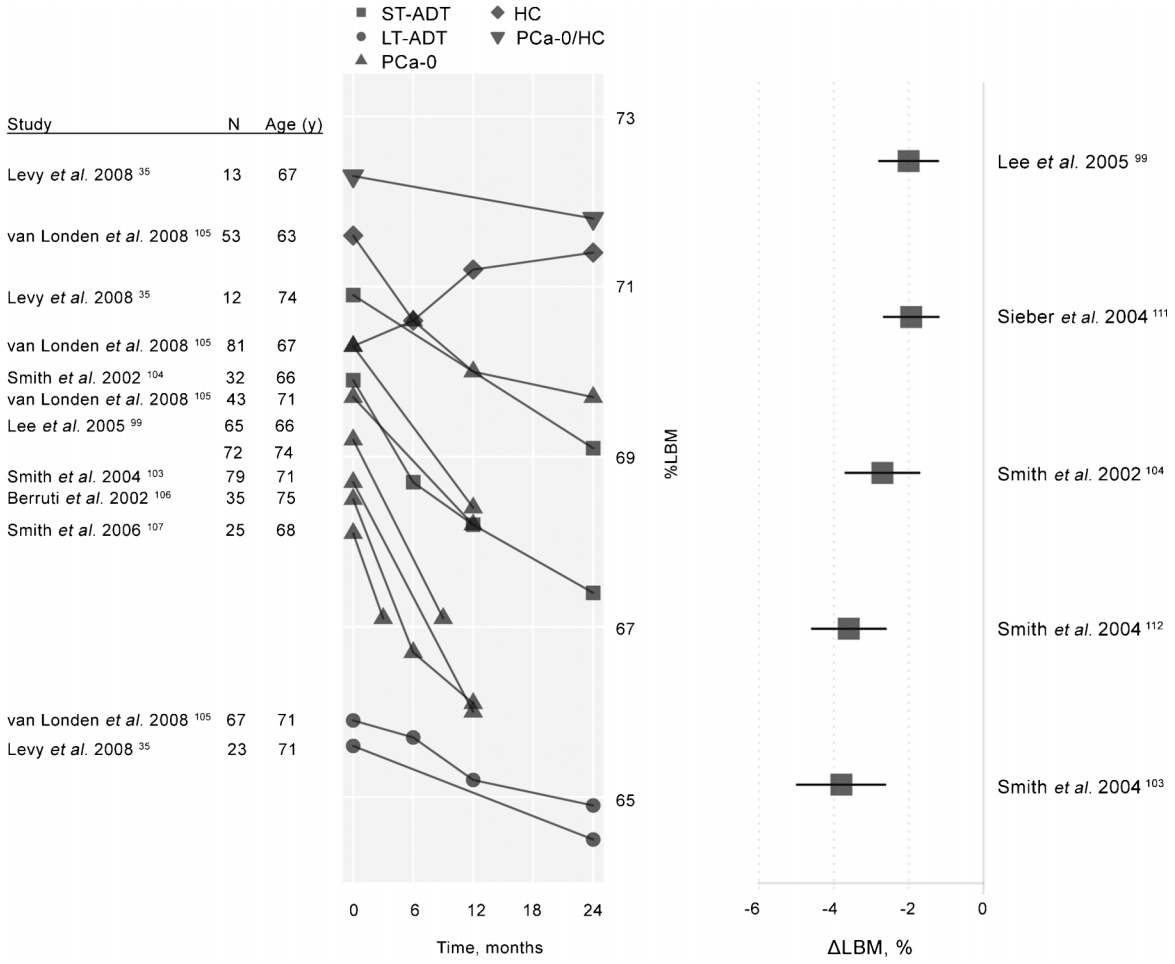

Figure 4 Left: Longitudinal changes in percent LBM among men enrolled in ADT studies. Untreated, healthy control participants are denoted as HC. A single mixed control group of healthy men and men with PCa not treated with ADT (HC/PCa-0) is also displayed. The remaining participants (all with PCa diagnoses and treated with ADT in the studies displayed) are classified according to their history of treatment with ADT prior to the current study. These groups include subjects with short-term (less than 6 months) previous exposure to ADT (ST-ADT groups), longer-term (6 months or longer) previous exposure to ADT (LT-ADT groups), and subjects with no prior history of ADT exposure (PCa-0). Right: Annualized percent change in percent lean body mass among subjects treated with ADT in studies of at least 1-year duration reporting LBM change values, adapted from Haseen *et al.*[102] ADT, androgen deprivation therapy; HC, healthy men; LBM, lean body mass; PCa, prostate cancer.

12 weeks of training, exercising subjects showed significantly greater changes from baseline than controls for several measures of upper and lower body muscle strength and endurance, 6-m usual gait speed and the 6-m backward walk. Changes between groups for the 400-m and fast 6-m walks, chair rises and stair climb were not significantly different. For measures of body composition, only the 0.8 kg mean difference for LBM change was significantly different between groups. Improvements were also noted for quality of life, and reduced fatigue. There were no adverse events due to assessments or training. In a prior uncontrolled trial of men undergoing ADT, Galvao *et al.*[37] demonstrated substantial improvements in muscle strength, muscle endurance and several measures of physical function after 20 weeks of high intensity RT (**Table 4**). Although body composition did not change, neither did it deteriorate. The positive outcomes from these comprehensive studies are encouraging.

Home-based exercise interventions using walking, light resistance exercise or cognitive-behavioral approach to increase physical activity have produced mixed results in improving muscle performance, physical function and body composition in men receiving ADT (**Table 2**).[36,118,119] One uncontrolled 12-week study requiring 3–5 day week^{-1} walking and light resistance exercise plus biweekly group sessions showed statistically significant changes in 6-MWT (+12%) and BMI (+1%) in men undergoing ADT.[118] The 63-m improvement in 6-MWT is clinically meaningful.[50] In a later study by the same group, 6-MWT distance increased by 25 m in the home exercise group and 29 m in the controls. However, initial 6-MWT distances were 650–700 m for these groups, respectively, suggesting relatively high functioning individuals[74] and a possible ceiling effect. One RCT evaluated the effectiveness of a 6-month group-based lifestyle physical activity program (Project Active[121]) in men who had undergone 33 months of continuous ADT.[119] An educational support group controlling for group and facilitator support provided in the lifestyle program, and a standard care group were included. After 6 and 12 months of the program, no differences were observed between groups for physical activity, self-reported physical functioning (SF-36), 6-min walk distance or measures of body composition. It is possible that the participant's physical activity was of sufficient intensity to prevent declines in physical function and body composition, but not adequate to show the levels of improvement seen in studies utilizing formalized and more rigorous exercise training. Currently, the

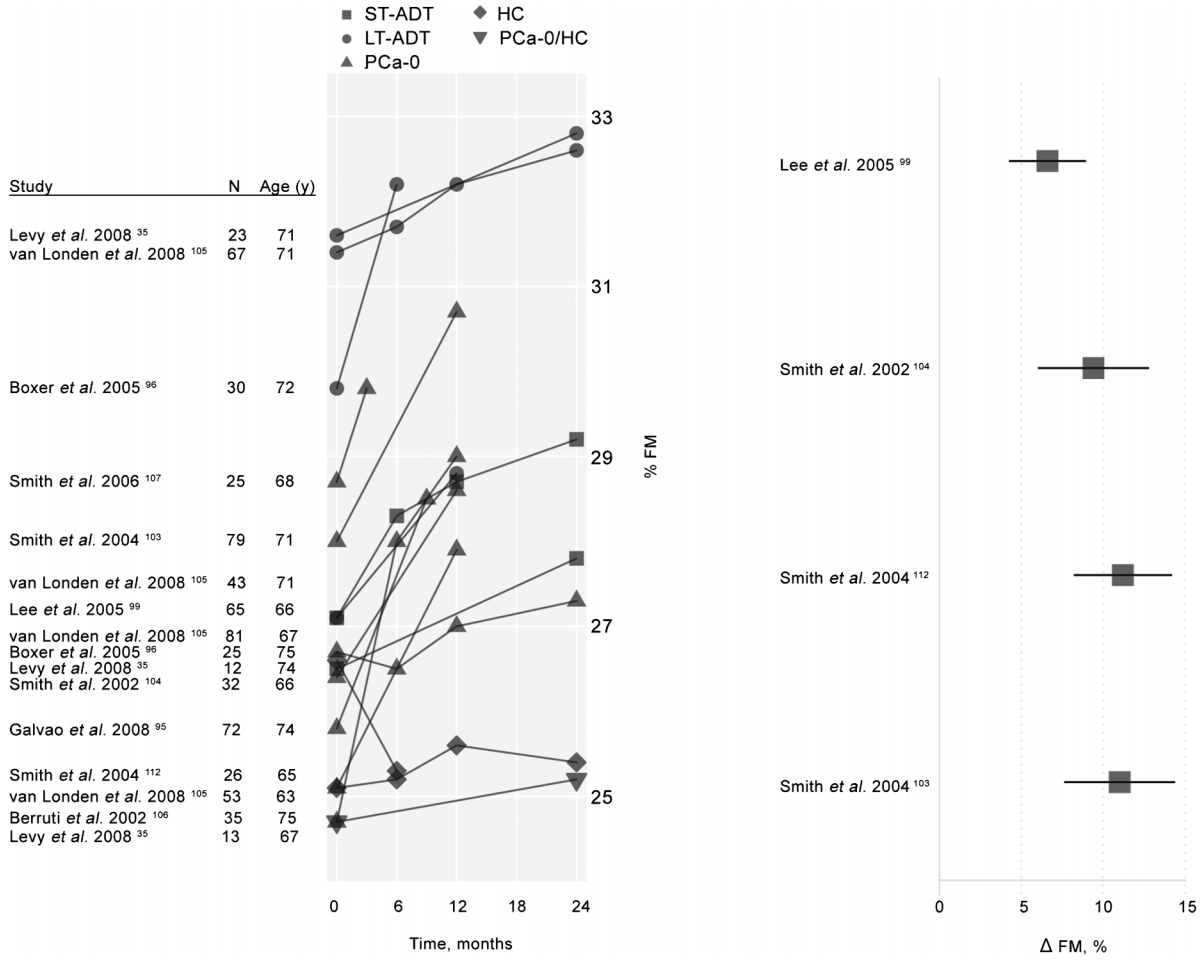

Figure 5 Left: Longitudinal changes in percent FM among men enrolled in ADT studies. Untreated, healthy control participants are denoted as HC. A single mixed control group of healthy men and men with PCa never treated with ADT (HC/PCa-0) is also displayed. The remaining participants (all with PCa diagnoses and treated with ADT in the studies displayed) are classified according to their history of treatment with ADT prior to the current study. These groups include subjects with short-term (less than 6 months) previous exposure to ADT (ST-ADT groups), longer-term (six months or longer) previous exposure to ADT (LT-ADT groups) and subjects with no prior history of ADT exposure (PCa-0). Right: Annualized percent change in percent FM among subjects treated with ADT in studies of at least 1-year duration reporting fat mass change values, adapted from Haseen *et al.*[102] ADT, androgen deprivation therapy; FM, fat mass; HC, healthy men; LBM, lean body mass; PCa, prostate cancer.

dose of physical activity or exercise in men with PCa, especially those undergoing ADT, is unknown. However, the lack of decline in physical function and body composition variables noted above[119] suggest that lifestyle guidelines that focus on increasing physical activity might be considered as a minimal dose.

The specific side effects of ADT (e.g., fatigue, muscle atrophy, weight gain, declining physical functional ability), suggest the value of combined resistance and aerobic activities. Largely, supervised exercise training appears to be more effective, but well-designed and monitored home-based physical activity programs may provide fitness benefits while being offered as a more cost-effective option.[118] There are no studies to date which have directly compared home versus supervised exercise training in men receiving androgen suppression. However, with the growing use of telehealth approaches,[122,123] home-based exercise training may prove to be a viable solution.

A recent American College of Sports Medicine (ACSM) Expert Panel has provided a consensus statement on exercise guidelines and the safety of exercise for cancer survivors[124] organized according to NHLBI classifications of evidence-based research.[125] Based on the 12 interventional studies reviewed by the expert panel specifically for men with PCa undergoing ADT and/or radiotherapy, evidence in favor of exercise training safety, improvements in aerobic capacity due to AT and/or RT, improved muscle strength due to RT and improved fatigue was judged to be definitive ('Category A' assessment). Improvements in at least one variable associated with body composition, physical function and improved measures of quality of life were rated reasonably strong but not overwhelming ('Category B' assessment).

A systematic review of exercise training in men undergoing androgen suppression provided clear support for the ACSM Expert Panel's findings in reducing the adverse effects of ADT on body composition, muscle performance and physical function.[126] As suggested in the ACSM Expert Panel report,[124] evidence for change in body composition due to exercise interventions was not as strong perhaps due to the considerable loss of LBM and increased fat mass occurring with ADT.[96] Maintenance of LBM and fat mass might therefore be important objectives of an exercise intervention.[96,124,126]

The ACSM Expert Panel advised that exercise prescription recommendations for both AT and RT for men with PCa should follow the 2008 Physical Activity Guidelines for Americans.[127] While there were

Table 4 Summary of studies examining longitudinal changes in measures of muscle strength, physical performance, and body composition in men with prostate cancer treated with androgen deprivation therapy

Study	*Study design/ Duration*	*Duration of ADT (month)*	N	*Age (y)*	*Intensity duration/ volume, frequency*	*Groups*	*Outcome variables*	*% change from baseline*	P *between groups*
Segal *et al.*,[117] 2003	RCT 12 weeks	12	82	68	Eight exercises 12-RM, two sets, 3 days week^{-1}	RT supervised	CP end (rep)	41%*	0.009
							LP end (rep)	32%*	<0.001
		13	73	68		Control	CP end (rep)	−8%	
							LP end (rep)	−4%	
Carmack Taylor *et al.*,[119] 2006	RCT 26 weeks	32.7	35	69	Lifestyle physical activity, moderate intensity. Most day week^{-1}	Physical activity	6-MWT	3%	Not significant
							BMI	−0.3%	
							Waist circumference	0.2%	
			44			Education	6-MWT	4%	
							BMI	3%	
							Waist circumference	0.8%	
			34			Usual care	6-MWT	4%	
							BMI	0%	
							Waist circumference	0.3%	
Galvao *et al.*,[37] 2006	UC 20 weeks	⩾2	10	70	10–12 exercises 12-6 RM. 2–4 sets 2 days week^{-1}	RT supervised	1-RM (kg)[a]	79%*	
							Muscle end (rep)[b]	129%*	
							5× chair rise (s)	−27%*	
							6-m walk usual (s)	−14%*	
							6-m walk fast (s)	−6%	
							6-m backward (s)	−22%*	
							400-m walk (m s^{-1})	−7%*	
							Stair climb (s)	−10%*	
							Lean mass (kg)	−0.4%	
							Fat mass (kg)	−0.0%	
							% Fat	0.3%	
Culos-Reed *et al.*,[118] 2007	UC 12 weeks	Not given	31	67	Intensity, duration, volume not reported 3–5 days week^{-1}	Home-based walking, light RT plus biweekly group sessions	6-MWT (ft)	11%*	
							BMI	1%*	
Hansen *et al.*,[135] 2009	Controlled pilot 12 weeks	Not given	5	66	Progressive RPE 7–13 5–20 min 3 days week^{-1}	Eccentric AT supervised	Iso-KE, right	19%*	Not significant
							Iso-KE, left	8%	
							6-MWT	9%*	
							TUG	14%	
							Thigh muscle volume, right	2%	
							Thigh muscle volume, left	0.9%	
		PCa-0	5	67			Iso-KE, right	15%	
							Iso-KE, left	-1%	
							6-MWT	5%	
							TUG	13%	
							Thigh muscle volume, right	2%	
							Thigh muscle volume, left	3%*	
Galvao *et al.*,[92] 2010	RCT 12 weeks	18.2	29	70	10–12 exercises 2–4 sets, 12-6 RM Walk/cycle 15–20 min 65%–80% HR_{max} 11–13 RPE 2 days week^{-1}	RT and AT supervised	1-RM (kg)[c]	30%	0.018
							Muscle end (rep)[b]	60%	<0.001
							5× chair rise (s)	−9%	0.074
							Stair climb	−4%	0.420
							6-m walk usual (s)	−6%	0.024
							6-m walk fast	−8%	0.187
							6-m walk backward	−22%	0.039
							400-m walk (m s^{-1})	−4%	0.080
							LBM	1%	0.047
							FM	−0.9%	0.964
							% Fat	−1%	0.366

To be continued

Table 4 (Continued) Summary of studies examining longitudinal changes in measures of muscle strength, physical performance, and body composition in men with prostate cancer treated with androgen deprivation therapy

Study	*Study design/ Duration*	*Duration of ADT (month)*	N	*Age (y)*	*Intensity duration/ volume, frequency*	*Groups*	*Outcome variables*	*% change from baseline*	P *between groups*
		10.1	28	70		Control	1-RM (kg)[c]	5%	
							Muscle end (rep)[b]	7%	
							5× chair rise (s)	−2%	
							6-m walk usual (s)	−2%	
							6-m walk fast	−2%	
							6-m walk backward	−5%	
							400-m walk (m s^{-1})	−2%	
							LBM	0%	
							FM	1%	
							% Fat	0.7%	
Culos-Reed *et al.*,[36] (2010)	RCT 16 weeks	⩾9	53	67	Intensity, duration, volume not reported 3–5 day $week^{-1}$	Home-based RT+walking	6-MWT (m)	4%	0.926
							BMI	−0.8%	0.225
							Waist circumference	−0.5%	0.044
			57	68		Control	6-MWT (m)	4%	
							BMI	3%	
							Waist circumference	2%	

Abbreviations: CP, chest press; CP end, repetitions to failure using fixed 20 kg resistance; Iso-KE, isokinetic knee extension; LP, leg press; LP end, repetitions to failure using fixed 40 kg resistance; Muscle end, muscle endurance, repetitions to failure, using 70% baseline 1-RM; *P*, difference in change from baseline between groups; RM, repetition maximum; 1-RM, maximum amount of weight that can be lifted once; 6-RM, maximum of weight than be lifted six times only.
BMI, waist circumference or sum of four skinfolds; RCT, randomized controlled trial; TUG, timed up-and-go expressed in seconds; FM, fat mass; LBM, lean body mass.
[a] Muscle strength by 1-RM—values are mean changes for chest press and leg press exercises.
[b] Muscle endurance—mean of changes in chest press and leg press exercise.
[c] Muscle strength by 1-RM—mean of changes for chest press, leg press and leg extension exercise.
* $P<0.05$.

Table 5 Metrics and equipment used to assess muscle function, physical performance and body composition in men with prostate cancer treated with androgen deprivation therapy

Measure	*Equipment*
Muscle strength	
1-RM or 3-RM	Plate loaded, selectorized or pneumatic weight machines; free weights. Exercises for major muscle groups of upper and lower extremity, e.g., chest/bench press and leg press or leg extension
Grip strength	
Sum both hands	Hand grip dynamometer
Repetitions to failure—70%–80% 1-RM or 3-RM	Plate loaded, selectorized or pneumatic weight machines; free weights. Exercises for major muscle groups of upper and lower extremity, e.g., chest/bench press and leg press or leg extension
Grip endurance	Hand grip dynamometer
Repetitions to failure at 50%–70% maximal force OR time to failure while sustaining 50%–50% max force	
SPPB	4-m measured course, armless chair, stopwatch
4-, 6-, 400-m, 6-min walk tests	Accurately measured course, stopwatch or timing system. For 400-m and 6-MWT, at least 20-m per lap
Chair stands	Armless chair and stopwatch
Timed up-and-go	Armless chair, stopwatch or timing system
Stair climb	Staircase and timing system
Body mass	Calibrated scale
BMI	Calibrated scale and stadiometer
Lean mass and fat mass	DEXA[a]
Skeletal muscle mass	DEXA[a]
Appendicular skeletal mass	DEXA[a]
Skin fold thickness	Skinfold calipers
Waist circumference	Tape measure
Appendicular skeletal mass index (ASM Ht^{-2})	DEXA[a] and stadiometer
Visceral fat area	DEXA[a]

[a] DEXA is the preferred instrument for assessing body composition. If unavailable, BIA may offer a reliable index of change but has greater error in assessing absolute values.

no PCa-specific contraindications for beginning or stopping an exercise program, the panel advised awareness of fracture risk in men with PCa treated with ADT and to use general ACSM guidelines for stopping exercise.[128]

It is clear that appropriately and judiciously applied exercise training in men with PCa receiving ADT is a valuable adjunct for mitigating many of the adverse events associated with ADT. The field is in need of additional well controlled randomized trials investigating dose–response relationships and the longer-term sustainability of not only benefits derived from exercise training but also continuation of the training itself.

LIMITATIONS TO THIS REVIEW

We have not implemented a formal meta-analysis or systematic review, but rather a broad literature search. Among the studies examined, disparities in study duration, design and population are tremendous and resist easy summary. These may dramatically affect our understanding of the influence of ADT on men's health and physical capacity. In addition, though some studies have explicitly examined the influence of PCa itself on these outcomes, differentiating the effects of cancer itself from that of its treatment is fraught with difficulty.

The study of the adverse effects of ADT on the outcomes reported is rapidly growing. Larger, randomized controlled trials are needed to better understand these and other adverse effects and thereby develop interventions that will successfully mitigate the negative outcomes of ADT.

SUMMARY AND RECOMMENDATIONS

1. Clinicians should obtain baseline values for muscle performance, physical function and body composition in men with PCa beginning ADT or as soon as reasonable during the course of treatment if previous data are not available. Examples of possible assessments and instruments are summarized in **Table 5**.
2. Assessment tools should have demonstrated validity and precision[94] with consideration of possible ceiling effects, especially in tests of physical function.
3. Hand grip strength correlates well with other muscle strength tests,[29] but caution is advised when considering its use as a surrogate for muscle function of lower extremities when evaluating physical performance.[30] Measures of dynamic muscle strength using muscle groups, type of muscle action and movement patterns similar to activities of daily living, may be more logical choices for strength assessments and their relation to body composition and physical performance.[26,37,92]
4. Performance-based measures of physical function can provide objective assessments of an individual's physical performance. Walking tests and chair stands are easily administered in the clinician's office.
5. Men who are receiving ADT for PCa should be encouraged to avoid physical inactivity. With consideration of individual disease and treatment adverse effects, the ACSM Expert Panel[124] advised implementation of the age-appropriate 2008 Physical Activity Guidelines for Americans[127] with a goal of accumulating 150-min activity per week. Guidance from knowledgeable and experienced fitness professionals with training in working with cancer patients may facilitate positive outcomes. A certification program for fitness trainers working with cancer patients is offered by the ACSM (http://certification.acsm.org/acsm-cancer-exercise-trainer).
6. As appropriate, resistance exercise training should be emphasized for its beneficial effects on LMB, muscle strength and physical function.
7. Use of telehealth services and physiological sensing systems including triaxial accelerometers and heart rate monitors could be considered aids in improving compliance and program efficacy.
8. Expert groups should continue to evaluate and recommend methods of exercise training of appropriate type, intensity, duration and frequency for men with PCa, especially those receiving ADT.[124]
9. For the researcher, long-term efficacy outcomes from exercise interventions should include measures of morbidity and mortality.

COMPETING FINANCIAL INTERESTS

All authors declare that there are no competing financial interests.

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