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REVIEW

Exercise can prevent and even reverse adverse effects of androgen suppression treatment in men with prostate cancer

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Side effects accompanying androgen deprivation therapy (ADT), including sarcopenia, loss of bone mass and reduction in muscle strength, can compromise physical function, particularly in older patients. Exercise, specifically resistance training, may be an effective and cost-efficient strategy to limit or even reverse some of these adverse effects during and following therapy. In this review, we discuss common morphological and physiological ADT-related side effects or 'Androgen Deprivation and Sarcopenia-Related Disorders' and the existing clinical trials incorporating physical exercise in prostate cancer patients receiving active therapy. Further, training concepts and guidelines are provided for prescribing resistance exercise programs for this population.
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Introduction

Worldwide prostate cancer is the second most common cancer in men representing 19% of cancers among men in developed countries.[1] With the aging of the population in developed and developing countries, the incidence of all cancers, which are normally higher in those aged >65 years, is predicted to substantially rise, particularly for colon and prostate cancer, which are well established aging-related cancers.[2] Advancing age increases not only the vulnerability to cancer but also the risk for other comorbid conditions (for example, cardiovascular disease, diabetes, osteoporosis, arthritis and sarcopenia)[3] that can compromise physical function and independent living and ultimately result in death.

The introduction of the prostate-specific antigen (PSA) blood test into routine clinical practice in Australia and the USA in the 1990s has led to earlier diagnosis of disease.[4,5] Men are often minimally symptomatic or completely asymptomatic and can be expected to survive substantially longer than their historical counterparts.[5,6] Full characterization of toxicity is now seen to be an important priority for research.[6–8] For example, sarcopenia, which is the age-related loss of muscle mass and strength, can be largely exacerbated in this cancer group owing to the catabolic side effects of some forms of treatment such as androgen deprivation therapy (ADT).[9]

In the non-cancer older population, resistance exercise has been endorsed as a potent countermeasure to sarcopenia and its implementation in clinical and home settings are relatively simple and inexpensive.[10] Additionally, this exercise mode has reliably shown to induce other health benefits by promoting increases in the ability to perform daily tasks and increased physical reserve capacity.[11] Recently, the role of structured exercise as a possible adjuvant therapy during cancer treatment has gained recognition, with most intervention trials incorporating cardiovascular activities.[9,12] Research into the effects of resistance exercise in prostate cancer patients and survivors are limited with only two studies reported.[13,14] Although research in this area is still emerging, preliminary findings indicate the beneficial effect of resistance exercise on the musculoskeletal system, reducing levels of fatigue and enhancing quality of life among cancer patients and survivors.[9,12,15]

In this review, we discuss (1) common ADT treatment-related side effects relevant to the musculoskeletal system, chronic disease and functional ability; (2) the beneficial effects derived from existing resistance exercise trials in this patient group and (3) guidelines for implementing this exercise mode as a potential treatment strategy.

Treatment of prostate cancer

Prostate cancer is the most frequent cancer in older men (those 65 years and older) with 80% of cases occurring in this age group. ADT is a widely employed means of treating this cancer, and is achieved by either surgical

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castration or more commonly by administering LHRHa (luteinizing hormone-releasing hormone agonist) and/or antiandrogen medications that block the androgen receptors.[16] Traditionally, ADT has been administrated in the latter stage of prostate cancer (for example presence of metastases).[17] However, owing to earlier detection of prostate cancer through better screening (for example PSA), patients are undertaking ADT in the early stages of the disease and therefore being exposed to this therapy for longer periods of time.[18] Additionally, ADT is now used as adjuvant therapy to radical prostatectomy and radiotherapy.[16] Although very effective,[16] concerns related to the detrimental effects of ADT on muscle, fat and bone mass have arisen as it can exacerbate the risk of sarcopenia, osteoporosis and obesity, and therefore induce other health related complications. This array of side effects related to ADT affecting the musculoskeletal system and physiological function or 'Androgen Deprivation and Sarcopenia-Related Disorders' is presented in Table 1. ADT has also been shown to contribute to emotional disturbances, fatigue and memory difficulties, with these cognitive ADT-related disorders referred to as 'Androgen Deprivation Syndrome'[18] (Table 1).

Side effects from ADT

Androgen deprivation and sarcopenia-related disorders

Body composition. Several studies have documented marked alterations in body composition in men receiving ADT for prostate cancer. Smith *et al.*[19] reported a 9.4% increase in whole body fat and a 2.7% reduction in whole body lean mass assessed by dual energy X-ray absorptiometry (DXA) following 48 weeks of ADT. Recently, Greenspan *et al.*[20] observed comparable changes in whole body fat (10.4%) and lean mass (−3.5%) during the initial 12 months of ADT. Cross-sectional studies comparing ADT- versus non-ADT-treated prostate cancer patients and healthy matched individuals have also indicated lower whole-body lean mass, higher percent and whole body fat mass in ADT-treated men.[21,22] Importantly, reduction of lean mass following ADT can reduce musculoskeletal fitness, compromising muscle strength, physical function and physical reserve capacity[9] (Figure 1). Such changes have implications in terms of reducing the age at which the individual falls below the functional capacity threshold, requiring a shift away from independent living and a reduced quality of life. Moreover, the increase in fat mass during ADT can lead to increased levels of total cholesterol and triglycerides[19,23] and consequently the possible development of cardiovascular complications.[24]

Bone mass and skeletal fracture. Apart from a decline in muscle mass and strength, ADT-treated men suffer a reduction in bone mass, and consequently bone strength, that contributes to an increased incidence of fracture and associated disability.[25,26] The ADT-related bone losses are significant and exceed those of women experiencing early menopause.[27] Recently, Greenspan *et al.*[20] indicated that men with prostate cancer initiating ADT have a 5- to 10-fold loss of bone mineral density (g/cm^2) compared to healthy controls or men with prostate cancer not on ADT. Importantly, following ADT, there is a significant dose–response relation between fracture risk and the number of LHRHa doses administrated.[25] The reduced structural bone strength is compounded by the reduction in muscle

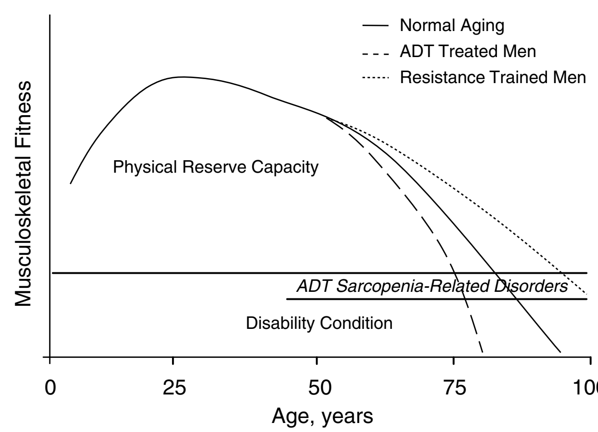

Figure 1 Theoretical model of musculoskeletal fitness reduction during aging and ADT. Potential role of resistance exercise providing an increase in musculoskeletal fitness and physical reserve capacity in ADT-treated men. ADT, androgen deprivation therapy.

Table 1 Side effects from androgen deprivation therapy

Reference	
	Androgen deprivation and sarcopenia-related disorders
Smith *et al.*,[19] Greenspan *et al.*,[20] Chen *et al.*,[21] Basaria *et al.*[22]	Decrease whole-body lean mass
Smith *et al.*,[19] Greenspan *et al.*,[20] Chen *et al.*,[21] Basaria *et al.*[22]	Increase whole-body fat mass
Greenspan *et al.*,[20] Chen *et al.*,[21] Shahinian *et al.*[25]	Decrease bone mass
Shahinian *et al.*,[25] Smith *et al.*[26]	Increase fracture risk
Basaria *et al.*[22]	Decrease muscle strength
Basaria *et al.*[29]	Increase insulin resistance
Smith *et al.*[19,23]	Negative lipoprotein profile
	Androgen deprivation syndrome
Shahinian *et al.*[18]	Increase depression
Shahinian *et al.*[18]	Decrease cognitive function
Shahinian *et al.*,[18] Spry *et al.*[31]	Increase fatigue
	Other side effects from androgen deprivation
Spry *et al.*[31]	Decrease health-related quality of life
Spry *et al.*[31]	Hot flashes
Spry *et al.*[31]	Decrease libido

strength and power, which has been related to increased falls incidence[28] resulting in two separate side effects of ADT combining to greatly increase fractures due to falls.

Insulin resistance and lipoprotein profile. Recently, Basaria *et al.*[29] suggested that men with prostate cancer undergoing long-term ADT can develop insulin resistance and hyperglycemia and these metabolic alterations are independent of age and body mass index. In this cross-sectional study,[29] ADT-treated men had significantly higher fasting levels of glucose, insulin and leptin when compared to healthy aged-matched controls and prostate cancer patients not on ADT. Moreover, significant negative correlations were reported between total and free testosterone levels with fasting glucose, insulin and leptin. Further, data from the same research group also indicated that long-term ADT-induced hypogonadal men have higher fasting levels of total cholesterol, low-density lipoprotein cholesterol and non-high-density lipoprotein cholesterol than non-ADT prostate cancer men and aged-matched controls.[23] Other studies[19] have also indicated the long-term negative alterations in lipoprotein profile in men treated with ADT with increases in serum total cholesterol (9%) and triglycerides (26.5%) following 48 weeks of therapy.

Androgen deprivation syndrome and quality of life

Quality of life, depression and cognitive function. Testosterone suppression for prostate cancer has been shown to negatively affect health-related quality of life. As such, reduced physical function and general health have also been reported in men on ADT- compared to non-ADT-treated men and healthy matched controls.[30] For example, Spry *et al.*[31] reported results from a large longitudinal, multicenter study examining the dynamic change in quality of life and testosterone in men initiating an intermittent maximal androgen blockade program. ADT lead to a significant reduction in health-related quality of life during the initial 9 months of therapy with substantial changes occurring by 3 months. Further, during the recovery phase (off-ADT), improvements in quality of life occurred in a more gradual manner and were of smaller magnitude than the changes observed during the ADT phase.

Bioavailable testosterone has been positively associated with cognitive function in older men.[32] Further, the hypogonadal condition has been associated with an increased incidence of depressive illness.[33] Despite the limited number of controlled studies examining the effects of testosterone suppression on depressive and cognitive function during ADT, a recent large population-based study reported an increased incidence of depressive and cognitive disorders in ADT-treated men, although the effects were diminished after adjustment for potential confounders.[18]

Exercise interventions in prostate cancer patients

Resistance exercise

A summary of the exercise interventions examining the effect of resistance or cardiovascular training in cancer patients undergoing treatment is shown in Table 2. To date, only two studies have examined the effects of resistance training in prostate cancer patients receiving ADT.[13,14] Segal *et al.*[13] studied 155 men in a multisite trial with localized and non-localized prostate cancer undertaking or scheduled to receive different forms of ADT for at least a 12-week exercise training period. Using a randomized controlled design, patients were assigned to either whole body resistance training, which incorporated three upper and four lower body exercises ($n = 82$) or a non-exercise control group ($n = 73$). Training intensity was set at 60–70% of one repetition maximum (1-RM; the maximal weight that can be lifted once only) for two sets of 12 repetitions three times per week. Progression was incorporated by increasing load (~2.5 kg) when subjects were able to pass the 12-repetition mark. The exercise group experienced improved symptoms of fatigue and health-related quality of life compared to the non-exercise group. Moreover, submaximal muscle strength increased by 42 and 32% for the chest press and leg press, respectively. The observed changes for fatigue and quality of life are extremely relevant given that they are negatively affected during ADT.[31,34] Importantly, information from this study provides support that even a low volume training program at a moderate intensity undertaken for a relatively short time period can confer substantial benefits to this group of cancer patients on therapy.

Recently, we examined the effects of a longer (20-week) progressive resistance exercise intervention in a group of men receiving ADT for prostate cancer.[14] Training intensity, volume and frequency were set at 12- to 6-RM using two to four sets for 10–12 exercises undertaken twice weekly. This study aimed to extend the work of Segal *et al.*[13] by examining the physical, functional, morphological and physiological outcomes of the intervention. Dramatic improvements in muscle strength (chest press, 40.5%; seated row, 41.9%; leg press, 96.3%) and muscle endurance (chest press, 114.9%; leg press, 167.1%) resulted as well as improvements in a number of physical performance measurements including the 6-m usual walk, 6-m backwards walk, chair rise, stair climbing, 400-m walk and balance ranging from 7 to 27%. Despite the suppression of testosterone, changes in muscle strength were comparable to the effects of resistance exercise interventions in healthy older adults not on ADT.[35] Further, changes in muscle endurance and functional capacity indicated that ADT-treated men may carry out functional daily activities with less fatigue following resistance exercise regimes and could partially explain the reduced levels of fatigue in resistance trained men reported by Segal *et al.*[13] The results also indicated that muscle thickness increased at the quadriceps site and whole-body lean mass by DXA was preserved with no change in fat mass. Considering that detrimental alterations in body composition are well established side effects from ADT, these results provide support for the role of resistance exercise to preserve body habitus and enhance physical function in prostate cancer patients undergoing therapy.

Cardiovascular exercise

Although a number of studies have utilized cardiovascular exercise programs in other cancer groups,[9,12] only

Table 2 Experimental design exercise studies in prostate cancer patients undergoing therapy

Study	*Study design/duration*	*n/age*	*Therapy mode/time*	*Exercise program*	*Intensity/volume/frequency*	*Outcome measures*
Segal *et al.*[13]	Randomized controlled trial (multi-site) 12 weeks	*n* = 155 (68 years)	Receiving or scheduled to receive ADT for at least 12 weeks	Resistance training (clinic-based)	12-RM, 2 sets 8 exercises 3 × week	↓Fatigue* ↑Quality of life* ↑Muscle fitness* ↔Body composition* ↔Testosterone* ↔PSA*
Windsor *et al.*[36]	Randomized controlled trial (single-site) 4 weeks	*n* = 66 (69 years)	External beam radiotherapy 50 grays in 20 fractions over 4 weeks	Cardiovascular walking (home-based)	60–70% MHR 30 min 3 × week	↔Fatigue*, ↑Fatigue‡ ↑Walking distance*
Galvão *et al.*[14]	Non-randomized controlled trial (single-site) 20 weeks	*n* = 10 (70 years)	Minimum 8 weeks on ADT prior to entering the study and scheduled to receive ADT for at least 20 weeks	Resistance training (clinic-based)	12- to 6-RM, 2–4 sets 10–12 exercises 2 × week	↑Muscle strength ↑Muscle endurance ↑Functional performance ↔Body composition ↑↔ Muscle thickness ↑Balance ↔Hemoglobin ↔Testosterone ↔PSA ↔GH

↔, no change; ↑, increase; ↓, decrease; ADT, androgen deprivation therapy; PSA, prostate-specific antigen; GH, growth hormone; MHR, maximum heart rate; *, exercise intervention group; ‡control group.

Windsor *et al.*[36] have examined the effects of a cardiovascular training mode incorporating a home-based walking program, at least 3 days of each week at 60–70% maximum heart rate, in prostate cancer patients initiating a 4-week external beam radiotherapy program. In this randomized controlled trial, 66 patients were assigned to standard care (control) or an exercise group. While fatigue levels for the control group increased following the radiotherapy regimen, there was no change in the exercise group who also experienced a significant increase in walking endurance of 13%. This study indicates that beneficial effects can be derived from even a modest short-term unsupervised, home-based exercise program.

Exercise studies and effects on testosterone and PSA

PSA is the most commonly used serum marker for prostate cancer disease from both diagnostic and disease progression perspectives.[37] Segal *et al.*[13] in their 12-week resistance exercise intervention found that PSA remains unchanged following training. We also observed no systematic changes in PSA in men with prostate cancer on ADT undergoing 20 weeks exercise and using a higher intensity exercise protocol.[14] These results combined, although preliminary, indicate that this exercise mode can be safely undertaken by prostate cancer patients without compromising basal levels of PSA. Further, testosterone castration via ADT has also been shown to remain at suppressed levels following resistance training indicating that this exercise mode is unlikely to alter the therapy purpose of reduced androgen levels.[13,14] Additionally, we have also observed (data not shown) that testosterone remains suppressed even immediately following an acute bout of high intensity resistance exercise. This is important given that several studies have demonstrated considerable elevation of testosterone in older men as a result of an acute bout of resistance training.[38,39] These findings collectively suggest that non-androgen-mediated mechanisms, such as neurological adaptations to training, and possible acute exercise-induced elevations in other muscle growth mediators, such as hGH and IGF-1, are likely responsible for the observed changes in muscle function and hence physical performance following resistance training.

Possible role of exercise during on- and off-treatment phases

The biological rationale that prolonged ADT may facilitate progression from androgen dependence to androgen independence has lead to the adoption of intermittent regimens of ADT to reduce this risk and also diminish ADT-related side effects.[40] To date, only small non-randomized trials on intermittent therapy have been reported, while two large clinical trials are currently in progress.[40] Importantly, improvements in quality of life during off-treatment phases have been observed,[31,41] while the effects of intermittent regimens of therapy on Androgen Deprivation and Sarcopenia-Related Disorders remains to be determined. Nevertheless, the possible role of introducing a program of resistance exercise during on- and off-ADT therapy to improve and maintain physical function, particular during off-ADT phases to enhance physical reserve capacity when undergoing periods of testosterone suppression is a potentially important strategy that should be considered in future clinical trials.

Guidelines for resistance exercise prescription

Designing a resistance-training regimen involves the manipulation of a range of variables, such as the number of sets and repetitions, intensity of training (load lifted), duration of rest between sets and exercises, frequency of training and repetition velocity. Each of these training variables have been previously identified[10] and are listed in Table 3. Importantly, most of these training variables have been examined in healthy older adults and favorable responses in muscle strength and physical performance result from a range of training programs, including those using moderate exercise intensity, frequencies and volume of work.[11,42,43] However, it is also well known that acute and chronic manipulation of these variables results in distinct adaptations of the neuromuscular and skeletal systems. Practical examples of structured resistance programs based on previous studies[13,14] undertaken with ADT-treated men are shown in Table 4. Particularly for this cancer group experiencing a reduction in lean mass and physical function, the exercise goal is to progressively overload the muscles, so that increases in muscle strength and physical capacity can be achieved. As in the older non-cancer population, exercises should be dynamic in nature using both concentric (lifting and pushing/pulling phase) and eccentric (controlled lowering/returning phase) muscle contractions.[10] Major functional lower body muscle groups, such as knee flexors and extensors, hip extensors, dorsiflexors and plantarflexors, should be targeted to maintain or enhance functional mobility and balance and therefore decrease the risk of falls and fractures. Suggested guidelines[9] for resistance exercise programs in cancer patients are shown in Table 5.

A vast array of equipment is available, so that resistance can be applied to the target muscle groups in a safe manner for the user. Most use the gravitational weight force but there are also a number of machines that use elastic, surface friction, hydraulic, aerodynamic drag or pneumatic resistance. Further, free weights or dumbbells and barbells can also be used, although some exercises will require a training partner or trainer to provide assistance during the activity. Body weight, elastic bands specifically designed for exercise and home made resistance devices can be particularly effective for implementing an inexpensive, home-based resistance training program.

In addition, clinicians could inform patients that exercise does not aggravate the cancer, even low amounts are better than nothing and more activity may provide additional benefits. In cases of significant

Table 3 Resistance training program variables

Training components	*Description*
Repetition	One completed movement of exercise
Set	Series of repetitions performed without stopping (for example eight repetitions/set)
Intensity	Amount of weight lifted that can be determined by the percentage of 1-RM or a specific number of RM
RM	The maximal number of repetitions that can be performed at a given exercise intensity (for example 8-RM)
1-RM	The maximal weight that can be lifted once with acceptable form
Velocity	Repetition movement speed (for example 2–3 s concentric and 2–3 s eccentric)
Rest between sets	Recovery period undertaken between sets for a particular exercise (for example 1–2 min)
Frequency	Days per week
Duration	Length of an individual session (for example 40 min)

Abbreviation: RM, repetitions maximum.

Table 4 Resistance exercise by specific region from studies undertaken with prostate cancer patients

Study	*Upper body*	*Lower body*	*Trunk*
Segal *et al.*[13]	Chest press, lat pull down, shoulder press biceps curl, triceps extension	Leg extension, leg curl, calf raises	Modified curl-ups
Galvão *et al.*[14]	Chest press, lat pull down, seated row, shoulder press, biceps curl, triceps extension	Leg extension, leg curl, squat, leg press	Abdominal crunch, back extension

Table 5 Guidelines for resistance exercise in cancer patients

Exercise modality	*Intensity*	*Frequency*	*Volume/dosage*
Anabolic/resistance exercises	50–80% 1-RM 6–12-RM	1–3 × per week	1–4 sets per muscle group

Abbreviation: RM, repetition maximum.

comorbidity, a referral to an exercise clinic would be appropriate given that unsupervised or inappropriate supervision may lead to injury. Consequently, the clinician needs to locate appropriate health professionals, such as exercise physiologists, trained to deal with individuals with chronic and complex conditions and refer their patients (see below). Suggesting that patients undertake resistance exercise in small groups will facilitate adherence and compliance, and also reduce the financial cost to the patient. In addition, varying components of the program from time to time will assist with motivation. However, it is important for both the specialist and the general practitioner to provide a consistent message regarding exercise and physical activity, and to monitor the patient's progress.

It should be recognized that progressive resistance training can result in some minor delayed onset muscle soreness during the initial phases of training or when training components are modified (e.g. resistance and/or number of sets increased) but should quickly resolve and patients can be informed that this may occur. Warm-up and cool-down activities of stretching and low-intensity level activities such as walking/cycling should be incorporated into each training session to prepare the individual for exercise and to return the individual to their resting level before leaving the training facility.

Although it is possible for the practicing oncologist to develop a small-scale exercise facility for patients, it may be more efficient to refer patients to clinical exercise physiologists or to exercise centers with qualified staff in this field. The American College of Sports Medicine (ACSM – www.acsm.org) provides registered professionals with University qualifications in exercise science or related area. Similarly, other countries, such as Australia and United Kingdom possess organizations (Australian Association for Exercise and Sports Science, AAESS – www.aaess.com.au/ – British Association of Sport and Exercise Sciences, BASES – www.bases.org.uk/) that provide registered exercise professionals with University qualifications who are able to conduct exercise training with this patient population.

Implications for oncologists and future directions

Although lifestyle modifications (predominantly diet, but also physical activity in general, smoking and alcohol cessation) and agents such as calcium/vitamin D for bone health have been indicated as potential sources available to counter or partially counter the side effects of ADT,[17] none are likely to provide the magnitude of effects that are observed with resistance exercise. Although considerably more work is required in the area of exercise and prostate cancer recovery, preliminary results indicate that resistance exercises can be an important adjuvant therapy to counteract the catabolic side effects from ADT in older men with prostate cancer. Larger randomized controlled trials are required to confirm and expand current findings, as are studies to investigate the role of progressive resistance training before ADT as well as those incorporating this training mode during radiation therapy to combat treatment-related side effects.

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