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Urologic Oncology: Seminars and Original Investigations 000 (2018) 1–9

UROLOGIC ONCOLOGY

Seminars Article

Exercise medicine for the management of androgen deprivation therapy-related side effects in prostate cancer

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Abstract

Androgen deprivation therapy (ADT) is associated with considerable adverse side effects which compromise the health and wellbeing of many men with prostate cancer. Exercise has been identified as a therapy to help manage ADT-related treatment toxicities. This paper systematically reviews the scientific literature investigating the impact of exercise on men receiving ADT and discusses strategies to effectively implement exercise in clinical practice. The findings of this review demonstrate that exercise has therapeutic benefit for the management of ADT-related side effects. Significant positive effects following exercise were observed for aerobic fitness, muscular strength, physical function, body composition, fatigue, sexual wellbeing, mental wellbeing, social function, comorbid disease risk factors, and quality of life. Emerging evidence suggests exercise may also play a role in managing bone loss, cognitive decline, and urinary problems, and may be delivered without exacerbating bone pain. Exercise did not negatively influence ADT treatment efficacy and led to few adverse events of minor severity, rendering it a safe intervention for men receiving ADT. To maximize the therapeutic effect of exercise, men with prostate cancer should participate in moderate-to-high intensity aerobic, resistance and impact exercise which is prescribed and supervised by a qualified exercise physiologist and delivered at a convenient location in a prostate cancer specific group-based environment. The level of evidence now available supports the view that the prescription of exercise medicine should be part of routine prostate cancer care.

Keywords: Aerobic exercise; Resistance exercise; Urology

Introduction

Based on worldwide data, every 30 seconds a man is diagnosed with prostate cancer [1]. Many of these men will be treated with androgen deprivation therapy (ADT), a mainstay treatment for locally advanced and advanced prostate cancer [2,3]. ADT effectively slows prostate cancer progression but is associated with adverse effects caused by severe hypogonadism. These effects impact cardiovascular, musculoskeletal and metabolic function and compromise patients' physical, mental and sexual wellbeing. Exercise has been identified as a therapy to help manage ADT-related treatment toxicities [4–8]. This paper systematically reviews the scientific literature investigating the impact of exercise on men receiving ADT providing an overview of the current level of evidence. Evidence-based strategies to effectively implement exercise in clinical practice and engage men with prostate cancer in exercise are discussed.

Exercise for the management of ADT-related side effects

A systematic search of the literature was conducted to evaluate the efficacy of exercise for the management of adverse effects secondary to ADT (search strategy detailed in Supplementary Table 1). These data demonstrate that exercise ameliorates a range of ADT-related side effects leading to improvements in physical and mental health and wellbeing and enhanced quality of life in men with prostate cancer (Table 1) [5–52].

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https://doi.org/10.1016/j.urolonc.2018.10.008
1078-1439/

Table 1
Summary of the common ADT-related side effects positively influenced by exercise [5–52]. Supplementary Table 2 includes the citation list for each outcome detailed across all levels of evidence.

Outcomes	Exercise Modality[a]	Level of Evidence[b]				
Aerobic Fitness		MA	SR	RCT	OB	QUAL
Muscular Strength		MA	SR	RCT	OB	QUAL
Body Composition		MA[c]	SR	RCT	OB	QUAL
Fatigue/Energy		MA	SR	RCT	OB	QUAL
Quality of Life		MA	SR	RCT	OB	QUAL
Physical Function			SR	RCT	OB	QUAL
Social Functioning			SR	RCT		QUAL
Psychological Distress				RCT	OB	QUAL
Bone Health				RCT[d]	OB	
Co-Morbid Disease Risk Factors				RCT[e]	OB[e]	
Sexual Wellbeing				RCT		QUAL
Bone Pain				RCT[f]		
Urinary Problems				RCT[g]		
Cognitive Decline				RCT[g]		

 - Aerobic exercise (e.g. walking, running, cycling, swimming, rowing)
 - Resistance exercise (e.g. repetitively lifting weights using free weights, weight machines or resistance bands)
 - Impact exercise (e.g. jumping, skipping, hopping, bounding)
MA - Meta-analyses
SR - Systematic reviews
RCT - Randomised controlled trials
OB - Observational studies (incl. controlled trials, non-controlled trials, cross-sectional studies, case reports)
QUAL - Qualitative studies

[a] Exercise modality involved in the interventions; presented in the order of importance for eliciting therapeutic effect
[b] Evidence is based on studies with significant results
[c] Effect observed for body mass index and total body mass
[d] Effect observed for selected bones sites only; no significant effect observed for other bone sites examined
[e] Risk factors examined include cholesterol, c-reactive protein, flow-mediated dilatation, Sex hormone-binding globulin, triglycerides, glucose, blood pressure, insulin sensitivity
[f] Evidence from only one trial reporting no significant exacerbation of bone pain (i.e. not alleviation of pain)
[g] Evidence from only one trial reporting beneficial effect during and after radiation

Physical health

Functional capacity

Exercise counteracts the detrimental changes to aerobic fitness [10,11,17,20,23,26,27,32,42,45,49], muscular strength [10,17,20,23,24,26,37,40,41,44,45,51], and physical function [10,17,20,23,24,26,40] associated with ADT. While it is not surprising that exercise improves physical capacity, these findings establish that men undergoing ADT can exercise at a dosage sufficient enough to overcome changes caused by severe hypogonadism.

Fatigue

Exercise has established efficacy for counteracting the cancer-related fatigue experienced by men on ADT

[10,11,20,24,32,44,45,48]. Notably, patients experiencing higher severity of fatigue receive a more pronounced benefit (i.e. reduction in fatigue) following an exercise intervention [48]. Thus, while men experiencing fatigue may be reluctant to exercise, it is a therapy that will provide meaningful benefit (arguably the best management strategy currently available [53]).

Body composition

The unfavourable changes to body composition associated with ADT can also be mitigated through exercise [17,20,24,27,40,42,43,45,49,50]. Loss of lean muscle mass has been significantly attenuated across most interventions involving a structured and progressive resistance exercise program (e.g. lifting weights). Only few trials have observed exercise to positively influence the increase in fat mass observed during ADT. Gains in fat mass during the initial 3-month phase of ADT were prevented with the concurrent prescription of moderate-high intensity aerobic (e.g. walking, cycling) and resistance exercise three times per week [20]. For men on longer-term ADT, reductions in fat mass have only been observed when exercise is coupled with dietary intervention [42]. The potential of exercise to attenuate the loss of bone mass has been explored in few trials to date.

Bone

Mitigation of declines in bone mineral density have been reported following exercise interventions at some but not all bone sites examined [13,52]. Observational data extend these findings, reporting that increased participation in exercise is associated with superior bone mineral density [39]. Further research is required to elucidate the impact of exercise on bone health in men undergoing ADT and how to appropriately prescribe exercise to preserve bone mass during ADT (e.g. [54]).

Cardiometabolic outcomes

A range of risk factors associated with cardiovascular and metabolic comorbid diseases have been investigated following exercise intervention trials. A number of these trials report that exercise favourably modulates C-reactive protein, cholesterol, triglycerides, glucose, and insulin sensitivity [20,23,24,27,45]. While extensive data involving nonprostate cancer populations demonstrates exercise protects against the development of these diseases, it is currently unclear if exercise reduces the risk of cardiovascular and metabolic disease events in men undergoing ADT.

Other outcomes

Exercise has been proposed as a strategy to manage declines in libido and potency associated with ADT [55]. Emerging evidence indicates that exercise helps to maintain sexual activity and libido and attenuate the declines in sexual function during ADT [18,20,32]. Reports from men with prostate cancer support these findings, suggesting that exercise counteracts the emasculating effects of ADT and helps enhance sexual wellbeing by reinforcing masculine self-esteem [28,35]. The impact of exercise on managing bone pain in men with metastatic disease is currently unclear. To date, only a pilot randomised control trial (RCT) reported no exacerbation of pain throughout a 3-month supervised resistance exercise intervention in which the exercise prescription was tailored to the location of the bone lesions [17]. Emerging evidence suggests that exercise may contribute to reducing the severity of urinary problems experienced by men on ADT undergoing radiotherapy [32] but further research is required.

Collectively, these data support the view that exercise is an important management strategy to ameliorate negative changes to physical function, fatigue, and body composition following ADT. Additional research is required to clarify the impact of exercise across other ADT-related side effects.

Mental health

There is a strong theoretical rationale for the potential of exercise to counteract detrimental changes to mental health and wellbeing experienced by men undergoing ADT [56]. However, to date there are no RCTs specifically designed to examine the impact of exercise on the psychological side effects of ADT. Current evidence arises from trials evaluating changes in mental wellbeing as secondary endpoints. Significant improvements in mental wellbeing and/or reductions in psychological distress have been reported in three RCTs [20,23,32]. These results are supported by qualitative data in which men describe considerable improvements in mood and overall mental wellbeing following exercise interventions [12,19,28,35]. Specifically, these data revealed that men perceive structured, group-based exercise as beneficial for improving feelings of depression, reducing anxiety and fear of disease progression, providing emotional and social support as well as eliciting a sense of camaraderie [12,19,28,35]. Data from observational studies further extend these findings, reporting that men who participate in higher volumes of exercise experience lower rates and severity of depression and anxiety [15,16]. Exercise, when delivered in a supervised, prostate cancer specific group based setting, has also been reported to improve social functioning in men undergoing ADT [20,23]. Furthermore, early evidence involving self-reported appraisal of cognitive function suggest the possibility that exercise may help reduce cognitive impairments experienced by men on ADT [32]. Thus, exercise shows promise as a management strategy to counteract the declines in mental wellbeing experienced by men undergoing ADT. However, insufficient evidence is currently available to determine the efficacy of exercise as a therapy to alleviate depression,

anxiety and cognitive impairment experienced by men undergoing ADT.

Quality of life

Significant improvements in health-related and prostate cancer-specific quality of life have been observed in a series of RCTs [11,23,24,32,44,45] and reported in previous systematic reviews [6,14,31,34,38]. Observational reports consistently demonstrate superior quality of life among men undergoing ADT who are involved in greater levels of exercise [15,16,30,36]. Qualitative analyses confirm that men's appraisal of their quality of life is enhanced following exercise interventions [12,19,35]. Given the breadth of benefits conferred by exercise for men on ADT these observations are not surprising. However, RCTs involving exercise interventions during ADT have also reported no change in quality of life questionnaires [10,45]. It is possible that the quality of the exercise prescription and/or the delivery of the intervention (e.g. supervised vs. un-supervised exercise) modulates the magnitude of the observed effect. There is a consistent trend throughout the literature for more pronounced improvements in quality of life arising from higher quality RCTs which involve exercise prescriptions that are in line with evidence-based guidelines (i.e. at least 150 minutes of moderate intensity or 75 minutes of vigorous intensity aerobic exercise and 2 to 3 sessions of resistance exercise per week) [57–61]. Therefore, exercise interventions that are appropriately prescribed and monitored contribute to attenuating the negative changes to quality of life experienced by men undergoing ADT.

Potential impact of exercise on prostate cancer progression

Provocative data arising from epidemiological studies suggest the benefits of exercise may also extend to slowing prostate cancer progression [62]. These data, which involve observations of over 9,600 men with prostate cancer, suggests a trend for reduced risk of prostate cancer-specific mortality, prostate cancer recurrence and all-cause mortality in patients who have superior exercise behaviours [62–66]. The observed magnitude of effect is notable, with hazard ratios ranging between 0.83–0.42 for prostate cancer-specific mortality, 0.94–0.43 for prostate cancer recurrence and 0.80–0.38 for all-cause mortality [62–66]. Secondary analyses reveal a dose-response relationship with regards to the quality of exercise performed [63,64]. Specifically, a greater risk reduction was observed in patients who were involved with higher intensity exercise (i.e. faster speed of walking; $\geq$3.0mph) compared to those conducting the same amount of exercise at a lower intensity (i.e. slower speed of walking; $<$3.0mph) [63,64]. While these data are limited by their observational nature, several pre-clinical trials support their findings. Exercise was observed to inhibit the progression and growth of prostate cancer tumours in mouse models, likely in a dose dependent manner [67–69]. Furthermore, acute exercise serum was reported to have an inhibitory effect on prostate cancer cell growth [70]. The mechanisms driving the observed protective effect of exercise are yet to be elucidated [71,72]. However, these data imply that the potential benefits of exercise may extend beyond the prevention and management of ADT-related side effects. Large randomized controlled trials in the human setting are necessary to elucidate the impact of exercise on prostate cancer progression and investigate the underlying mechanisms. The INTERVAL-GAP4 trial has been recently initiated to evaluate whether exercise influences overall survival in patients with metastatic castrate-resistant prostate cancer [73].

Safety of exercise for men on ADT

The potential harms of exercise must be weighed against the observed benefits of prescribing exercise concurrent to ADT. The most pressing question to evaluate is whether exercise influences the treatment efficacy of ADT. To date, eight RCTs have examined prostate specific antigen levels (PSA) [10,11,20,23,24,45,49,74] and six RCTs measured serum testosterone [10,20,23,24,45,49] following exercise interventions in men receiving ADT. Across all trials no differences were observed in PSA or testosterone levels between exercise and usual care groups [10,20,24,25,30,45,74]. Four single-group studies also reported no change over time in PSA or testosterone levels in men receiving ADT involved in exercise interventions [22,25,30,75]. Thus, the evidence to date indicates that exercise does not interfere with ADT treatment efficiency. A second pertinent question to examine when exploring potential harms is does exercise cause adverse events? Across the 22 RCTs conducted to date involving approximately 1,750 men on ADT [10,11,20,23,24,26,27,32,37,40–45,48,49,51,52,74,76–78], few adverse events were reported, most of which were relatively minor in severity. One serious adverse event related to the exercise intervention was reported by Segal and colleagues [45]. The participant experienced a myocardial infarction during their third exercise training session; the patient was resuscitated and made a full recovery but did not return to the exercise intervention [45]. Other adverse events reported to be related to exercise interventions included joint pain (e.g. back, knee), muscle pain/stiffness and aggravation of pre-existing injuries (e.g. rotator cuff strain, back pain) [23,26,32,40,42,74]. The nature and severity of reported adverse events are common to any person participating in exercise. These data provide support for the safety of exercise in men on ADT. However, these trials were conducted in well-controlled environments (predominantly acute or tertiary settings) and may not be generalizable to all settings in which men undergoing ADT participate in exercise. Thus, the available

evidence indicates that exercise may be considered safe for men on ADT when it is appropriately prescribed and monitored.

Implementing exercise as part of routine prostate cancer care

There is a strong argument for all men undergoing ADT to participate in exercise given the level of evidence supporting the therapeutic benefit of exercise and acceptable levels of potential harm [61]. However, the vast majority of men with prostate cancer do not exercise regularly with only ~12% reported to exercise at sufficient levels to prompt significant health benefits [79]. Clearly effective strategies are required to implement exercise into routine prostate cancer care and engage men in exercise. Importantly, consistent results throughout the literature demonstrate that participation in higher quality exercise leads to more pronounced benefits to patients physical health, mental health, and quality of life. This raises two questions key to realising the therapeutic potential of exercise: (1) what is the appropriate exercise prescription for men undergoing ADT?; and (2) how do you get men on ADT to follow this exercise prescription?

To maximise the benefits of exercise, men on ADT should be performing moderate-to-high intensity aerobic, resistance, and impact exercise in line with the details provided in Table 2 (informed by [5–52]). Drawing on a growing body of literature and learnings from clinical practice there are a series of key components to effectively engage men in regular, high-quality exercise. First, prostate cancer specialists should actually prescribe exercise; that is designate exercise as a component of their patients prostate cancer care [61]. Eighty percent of men with prostate cancer report that their clinicians' advice to exercise influenced their exercise behaviour [80]. However, a recommendation to exercise is not sufficient to realise a significant therapeutic effect [23], hence a referral to an exercise physiologist should accompany the prescription of exercise medicine [61]. To optimise benefits, this referral should ideally be to an exercise physiologist with specialised expertise in working with men with prostate cancer [19,61]. Such a specialist can appropriately tailor evidence-based prescriptions to each individual, minimise the risk of harm using effective screening and monitoring techniques, and maximise patient engagement through prostate cancer-specific strategies. Exercising under the supervision of an exercise physiologist as part of a structured program is an important factor to attaining a therapeutic effect. Extensive research involving cancer patients and other populations have consistently reported significantly superior benefits for supervised interventions compared to unsupervised interventions [81,82]. While most research trials involve at least 3 months of supervision, it is currently unclear what length of supervision is required to facilitate long-term continuation of exercise and sustained health benefits. The location of the exercise program is a significant factor influencing men's compliance with the exercise prescription. Approximately 80% of men with prostate cancer report a convenient location influenced their exercise behaviour [80] and the location of exercise facilities has been reported to be among the most prominent predictors of adherence to interventions [83]. Another important factor evident in the literature is the delivery of exercise in a prostate cancer-specific group setting [19,28,56,84]. Exercising with a group of other men undergoing ADT provides patients with the opportunity to access peer support in a manner which articulates with men's preferences (e.g. action-oriented, stoic, nonhealth care setting) [19,28,56,84]. Furthermore, men report the camaraderie and social connections developed in that environment enhance enjoyment and positively influenced adherence [19,28,56,84].

Therefore, the keys to getting men to exercise in line with evidence-based recommendations are: (1) prescribe exercise as part of the prostate cancer treatment plan; (2) refer to an exercise physiologist with experience in prostate cancer; (3) perform exercise at a convenient location; and (4) deliver exercise within a prostate cancer-specific group environment.

Conclusions

The findings of this review demonstrate that exercise has therapeutic benefit for the management of ADT-related side effects. Significant positive effects following exercise were observed for aerobic fitness, muscular strength, physical function, body composition, fatigue, sexual wellbeing, mental wellbeing, social function, comorbid disease risk factors, and quality of life. Emerging evidence suggests exercise may also play a role in managing bone loss, cognitive decline, and urinary problems, and may be delivered without exacerbating bone pain. Exercise did not negatively influence ADT treatment efficacy and led to few adverse events of minor severity, rendering it a safe intervention for men receiving ADT. Further research is required to elucidate the precise mechanisms underlying the beneficial effects of exercise for men undergoing ADT and any prostate cancer biomarkers that may be influenced by exercise. To maximize the therapeutic effect, men with prostate cancer should participate in moderate-to-high intensity aerobic, resistance and impact exercise which is prescribed and supervised by a qualified exercise physiologist and delivered at a convenient location in a prostate cancer-specific group-based environment. The level of evidence now available supports the view that the prescription of exercise medicine should be part of routine prostate cancer care [62].

Table 2
Summary of the exercise prescription required to maximize the therapeutic effect for men on ADT (informed by [5–17, 20–52]).

Exercise modality	Aerobic exercise		Resistance exercise		Impact exercise	
Example exercises	Walking, running, cycling, swimming, rowing		Repetitively lifting weights using free weights, weight machines or resistance bands; body weight exercises		Marching, skipping, jumping, hopping, bounding, leaping, drop jumps	
Prescription to maximize therapeutic effect	Frequency:	≥ 5 d/wk	Frequency:	2–3 d/wk	Frequency:	≥ 3 d/wk
	Intensity:	Moderate-to-vigorous (55%–75% of predicted HR maximum or RPE of 12–17 i.e. "somewhat hard to very hard")	Intensity:	Moderate-to-vigorous (70%–85% of 1-RM or RPE of 12–17 i.e. "somewhat hard to very hard")	Intensity:	Moderate-to-vigorous (RPE of 12–17 i.e. "somewhat hard to very hard")
	Time:	≥ 20–30 min/session	Time:	~30–45 min/session	Time:	~15–20 min/session
	Type:	Continuous and/or interval exercise	Type:	Multijoint exercises targeting major muscle groups	Type:	Weight bearing exercise involving high loading
	Volume:	150 min/week of moderate-intensity or 75 min/week of vigorous-intensity exercise	Volume:	6–10 exercises; 2–4 sets of 8–15 repetitions; 2–3 min rest between sets and exercises	Volume:	2–4 exercises; 2–3 sets of 10–20 repetitions; 2–3 min rest between sets and exercises
	Progression:	Gradually increase intensity, duration, and/or frequency	Progression:	Gradually increase intensity (e.g. weight); progress to 4 sets of each exercise	Progression:	Gradually increase intensity (e.g. height of jumps); progress to 50–100 jumps per session
Primary contraindications[a]	- Uncontrolled hypertension - Recent myocardial infarction - Acute congestive heart failure - Unstable angina		- Bone metastases with severe pain and/or uncontrolled progression - Uncontrolled cardiovascular issues (e.g. hypertension, angina etc.)		- Bone metastases - Osteoporosis (at risk of fracture) - Joint pain - Impaired balance	

RPE scale = the Borg Rated Perceived Exertion Scale ranging from 6 to 20 (6 = no exertion; 20 = maximal exertion).
1-RM = One-repetition maximum (maximum amount of force that can be generated in one maximal contraction).
[a] Only a selection of the primary contraindications indicated here; all absolute and relative contraindications to exercise need to be considered.

Funding

This work was not supported by any sources of funding.

Disclosure Statement

The authors declare that they have no conflicts of interest.

Acknowledgment

The authors acknowledge the contribution of Mr Mark Trevaskis in providing expert input as a clinical exercise physiologist with specialist expertise in prostate cancer.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.urolonc.2018.10.008.

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