THE EFFECTS OF ACCENTUATED ECCENTRIC RESISTANCE TRAINING ON MUSCLE MASS AND STRENGTH IN PROSTATE CANCER PATIENTS UNDERGOING ANDROGEN-DEPRIVATION THERAPY

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Abstract

Background: Androgen deprivation therapy (ADT) leads to several adverse effects including loss of muscle mass and strength in prostate cancer patients. Previous investigations have implemented resistance training as a method of increasing muscle mass and strength, however, testosterone suppression during ADT may blunt these adaptations. Accentuated eccentric exercise training could induce improvements in muscle mass and strength through anabolic pathways that are less dependent on testosterone. Thus, the purpose of this study is to examine the feasibility, adherence, muscle thickness and strength, and body composition outcomes resulting from accentuated eccentric resistance training (AERT).

Methods/Design: The study will be a single-armed, exploratory trial of 14 prostate cancer patients currently undergoing ADT in the city of Perth (Australia). Primary endpoints will consist of muscle strength, function, thickness, and body composition, while secondary endpoints will include a panel of metabolic, hormonal, and cancer-related blood markers, protocol adherence, safety and patient-reported outcomes in relation to prostate cancer. These outcomes will be tested before and after 36 sessions of AERT in combination with whey protein supplementation after each training session.

Discussion: This will be the first study to examine the feasibility, tolerance, body composition, and strength outcomes of AERT in prostate cancer patients undergoing ADT. Determining if higher loading of the eccentric phase is well-tolerated by the patients, and if there are significant increases in muscle mass and function, could lead to clinically meaningful benefits. The results from this study will form the basis for future randomized controlled trials and prescription of AERT protocols in prostate cancer patients undergoing ADT, in order to alleviate disease burden, counteract the adverse side-effects of the disease and ADT, and enhance quality of life.

Introduction

In the developed world, prostate cancer is the most common cancer diagnosis in men [1]. A commonly used treatment for prostate cancer is androgen-deprivation therapy (ADT), which is administered to almost one in two prostate cancer patients in the United States [2]. While evidence exists that ADT is effective at slowing tumor progression and improving survival, its use is associated with numerous side effects [3–5]. For example, studies have reported that ADT results in decreases in lean body mass and increases in fat mass [6–12], decreases in muscle function and strength [13] and decreases in bone mineral density [8,12,14]. These adverse effects can increase the risk of falling, osteoporosis, and bone fractures [3–5] as well as compromise physical function and quality of life [15]. Further, accumulating evidence suggests low muscle mass is associated with poorer prognosis for cancer patients, greater chemotherapy toxicities and reduced overall survival [16]. Effective therapies are needed to prevent ADT-induced muscle loss and provide optimal hypertrophy.

To examine if muscle mass and function can be increased while undergoing ADT, previous investigations have used resistance training interventions in prostate cancer patients [17,18]. It is well known that the anabolic effect of exercise in muscle is partially mediated via the interaction of the androgen receptors with testosterone, leading to the upregulation of several transcripts specific to muscle and increases in insulin-like growth factor 1 (IGF-1) levels [19,20]. ADT decreases serum testosterone levels to <5% of the normal values [5], and suppression of testosterone has been shown to impair resistance training-induced muscle strength and mass outcomes [21]. Nevertheless, improved outcomes for muscle strength and endurance, and increased muscle thickness and preservation of lean mass have been reported after 12 –20 weeks of resistance training in prostate cancer patients undergoing ADT [17,18]. Several mechanisms exist that increase muscle mass in response to exercise that are not mediated by testosterone [22], and it is therefore important to examine which modalities and

dosages (e.g. intensity, volume) of exercise are most effective at increasing muscle mass and function while undergoing ADT.

Conventional resistance training includes concentric and eccentric muscle actions, and the same absolute load is used for both phases of each repetition [23]. Due to previous investigations demonstrating that long-term training with eccentric muscle actions is effective at stimulating muscle hypertrophy [24,25], some studies have utilized accentuated eccentric resistance training (AERT) by loading the eccentric phase with greater force than the concentric; either manually or by using specialized equipment. AERT has been shown to induce greater type II muscle fiber cross-sectional area [23], lean mass [26], and muscle strength [23,27] compared to conventional resistance training. The underlying mechanisms of eccentric training-induced outcomes are still not fully understood. Greater insulin growth factor-1 mRNA increases in human [28] and rat muscle [29], and greater myostatin mRNA decreases in rat muscle [29], were observed after eccentric exercise when compared with equivalent concentric training, despite both concentric and eccentric exercise shown to elicit similar serum testosterone level increases [30]. These findings suggest that eccentric exercise training may trigger anabolic pathways that are less dependent on testosterone, compared to conventional concentric training. However, no studies have compared the effects of AERT on muscle mass and strength outcomes in prostate cancer patients undergoing ADT.

It is not known if the combination of eccentric and concentric muscle actions is more effective in increasing muscle mass and strength than eccentric muscle actions alone. For example, previous investigations that used submaximal, eccentric-only modalities such as eccentric cycling found increases in muscle cross-sectional area, strength, power, six-minute walk distance, and a decrease in the time to descend stairs [31]. Concentric exercise is more metabolically- and cardiovascularly-demanding than mechanical work-matched eccentric exercise on a cycle ergometer [32]. It could be that AERT could achieve similar or greater

increases in muscle mass and strength outcomes than conventional resistance training, but with lower required effort. Moreover, whey protein, a leucine-enriched essential amino acid supplement, has been shown to be effective in increasing the exercise-induced protein synthesis when used in combination with exercise, by increasing post-exercise serum IGF-1 concentrations [33]. It is therefore important to investigate and compare the strength and muscle mass outcomes after an AERT and whey protein supplementation protocol in prostate cancer patients undergoing ADT.

Given the above, the purpose of this study will be to examine the (1) muscle damage, soreness, and inflammation responses after the first session; (2) inflammation, immune, cancer-specific, metabolic, and hormonal blood marker changes; (3) muscle function and lean mass outcomes; and (4) feasibility and tolerance in prostate cancer patients undergoing ADT following 36 sessions of AERT with whey protein supplementation. The outcomes of this trial will be used to improve clinical knowledge pertaining to exercise prescription for prostate cancer patients, and explore the use of resistance exercise to enhance the quality of life, and attenuate the adverse effects of disease and ADT on muscle mass and strength.

Methods

This will be a single-arm, exploratory trial. Primary endpoints will consist of muscle strength, function, thickness, and body composition, while secondary endpoints will include a panel of metabolic, inflammatory, immune, hormonal, and cancer-related blood biomarkers, protocol adherence, safety and patient-reported outcomes in relation to prostate cancer. All participants will be asked to maintain their existing physical activity and dietary patterns over the intervention period.

Participants

A total of 14 men with prostate cancer undergoing ADT will take part in the study. Exclusion criteria will include absence of histologically documented prostate cancer; having undergone chemotherapy within the previous 6 months; not receiving ADT in the previous 3 months; not scheduled to receive ADT for the subsequent 4 months; any metastatic disease; any musculoskeletal, cardiovascular, or neurological disorder that could inhibit them from exercising; inability or unwillingness to undertake upper- and lower-limb exercise training; unwillingness or inability (lactose intolerance) to consume whey protein supplementation after each exercise session; and having performed resistance training in the previous 6 months. All participants will obtain physician clearance and provide written informed consent prior to partaking in the study.

Study design

The study design is shown in Figure 1. All exercise and testing sessions will take place at Edith Cowan University (Joondalup, Australia). When the participants report to the laboratory for the first time, anthropometric measures, questionnaires, an ultrasound test, peripheral Quantitative Computed Tomography (pQCT) and dual-energy X-ray absorptiometry (DEXA) scans for body composition will be conducted. In the same visit, the first familiarization session will be conducted, during which a muscle strength test, and a pre-conditioning exercise session will be conducted. The participants will then return to the laboratory 7 days after for a second familiarization session involving strength and muscle function testing and another pre-conditioning exercise session.

Seven days after the second familiarization session, they will visit the laboratory and a blood sample and muscle soreness test will be conducted before, immediately after, 24, and 48 h after the first exercise training session to ensure the participant is eligible and safe to exercise.

After the participant has been deemed to be safe to exercise by the investigator, in conjunction with their medical specialist, they will be assigned 35 further sessions of AERT with whey protein supplementation.

After the 12th and 24th training sessions, all participants will perform a muscle strength test to further adjust the prescribed intensity of their exercise program. The post-training measures will take place at least 4 days after the last exercise session. In the post-training testing session, anthropometric measurements, questionnaires, pQCT, DEXA, and an ultrasound scan will be conducted, followed by strength and the muscle function tests.

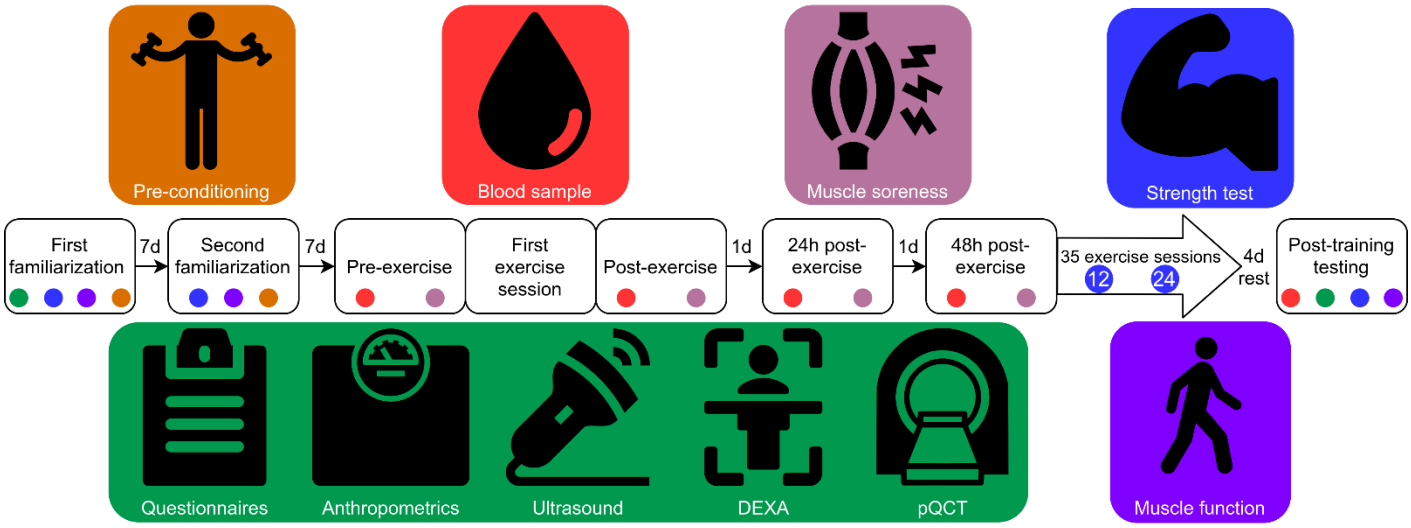

Figure 1. The study design. The different tests are indicated in each session by their respective colors.

Primary endpoints

Muscle strength

To ensure the safety of the participants from muscle damage that is induced by unaccustomed maximal eccentric muscle actions [34–36], muscle strength testing will consist of concentric-only isokinetic movements using servomotor-driven resistance training equipment (BioCircuit, TechnoGym, Italy). The servomotor-driven resistance training equipment allows the execution

of isokinetic contractions. This contraction mode makes it possible to estimate the force generated by the person during movement at a constant speed. The participants will perform a single isokinetic concentric muscle action and the software will calculate the participant's concentric repetition maximum (1RM). The test will be performed for all the exercises that will be performed during the exercise intervention (abdominal crunch, seated row, chest press, lat pulldown, shoulder press, and leg press). The calculated 1RM (in kilos) of the participant will be displayed on a screen and will be recorded by the investigator. The 1RM will be used both as a muscle strength test and for exercise load prescription purposes.

Muscle function

Stair descent test

The stair descent test has been used as a mobility assessment task with cancer patients in previous studies, to assess the eccentric capacity of the lower limbs, which, if compromised, can lead to a greater number of stair falls [31]. Participants will be asked to descend one flight of stairs under close or contact supervision as quickly and safely as possible [37]. Time will be recorded electronically to the nearest 0.01 s from a verbal 'go' signal to final foot placement on a standard flight of 10 stairs, and the average of three trials will be used for subsequent analysis.

Sit-to-stand test

As a measurement of functional performance relevant to activities of daily living, previous studies have used the 5-repetitions sit-to-stand test in prostate cancer patients [38]. The participants will be asked to sit and stand from a standard hard-backed chair (with a seat height of 40 cm), and the total time for the successful execution of 5 repetitions will be recorded. They will be seated, instructed to look straight forward, and to rise after the "1, 2, 3, go" command

as fast as possible with their arms folded across their chest [39]. The participants will have to make contact with the chair when sitting and to fully extend their knees and hips in the standing position for the repetition to be counted as successful by the investigator.

Sensory organization test

To assess postural stability the participants will undergo a sensory organization test (NeuroCom Smart Balance Master, Natus Medical, USA). The participants will stand on the NeuroCom force plate without socks or any footwear and with a security belt attached (to prevent falls). According to the manufacturer's protocol and previous studies [18], subjects will undertake three 20 s trials for each of the following conditions: 1) eyes open, fixed support surface and surround (visual, vestibular, and somatosensory input); 2) eyes closed, fixed support surface and surround (absent of visual input); 3) eyes open, fixed support surface, and sway-referenced surround (visual input imprecise); 4) eyes open, fixed surround, and sway-referenced support surface (somatosensory inputs imprecise); 5) eyes closed, fixed surround, and sway-referenced support surface (somatosensory inputs imprecise and absent of visual input); and 6) eyes open, sway-referenced support surface and surround (imprecise somatosensory and visual inputs). The equilibrium score will be reported as a value between 0 and 100, with 0 indicating a large sway and loss of balance and 100 indicating perfect stability.

Body composition

Participants will be asked to come to the laboratory in a rested, fasted, and euhydrated state at the same time in the morning, wearing the same clothing for each DEXA whole body assessment (Horizon A, Hologic Inc., USA). Using in-built computer software (Version 12.4; QDR for Windows, Hologic, USA) lean and fat tissue mass of the total body, arms, trunk, and lower limbs will be calculated. An additional segmental analysis of the lean and fat tissue mass

of the thighs of each participant will be performed following the method of Hart et al. [40], and the average values of the two thighs will be used for further analyses.

Ultrasonography

Ultrasound images of the vastus lateralis and intermedius will be taken to measure muscle thickness and echo intensity using a real-time B-mode ultrasound apparatus (Aloka SSD-alpha10, Aloka Co., Japan). The ultrasound settings including focus, contrast and gain will be kept the same between measurements. An ultrasound probe (60 mm, linear array) will be placed on a marked site at the middle point between the lateral epicondyle and greater trochanter of the right leg, while the participant is lying on a massage table. Three transverse images of each muscle will be obtained and then transferred to a computer for the assessment of muscle thickness (in mm), and mean echo intensity of a greyscale histogram (0: black, 256: white) using image analysis software (ImageJ, National Institute of Health, USA). The average value of the three images will be used for statistical analysis.

peripheral Quantitative Computed Tomography (pQCT)

Using previously reported methods [41], the right thigh of the participants will be scanned to quantify muscle cross-sectional area using pQCT (XCT-3000, Stratec, Pzochienheim, Germany). The participants will be asked to sit on a height-adjustable chair with their left lower limb fully extended through the acrylic cylinder and central gantry of the pQCT machine and secured to the foothold attachment. A pQCT slice will then be taken at the middle point between the lateral epicondyle and greater trochanter of the femur. Total muscle density, and muscle area will be calculated using the manufacturer's computer software.

Anthropometry

Stature will be recorded to the nearest 0.1 cm using a wall-mounted stadiometer (Model 222, Seca, Germany), with body mass recorded to the nearest 0.1 kg using an electronic scale (AE Adams CPW Plus-200, Adam Equipment, USA).

Secondary endpoints

Blood analytes

Fasted serum samples (20 ml per visit) will be collected before, immediately after, 24, and 48 h after the first exercise session, as well as 5 days after the last exercise session. Serum will be separated and stored in secure -80° C biomedical freezers at Edith Cowan University, prior to batch analyses at the completion of the trial.

The blood samples immediately before and up to 48 h after the first session will be used to monitor markers associated with immune function and muscle damage, including interleukin-6 (IL-6), tumor necrosis factor-α (TNF-α), and creatine kinase (CK). Muscle anabolism will be investigated through markers including serum insulin growth factor-1 (IGF-1), growth hormone (GH), and dehydroepiandrosterone (DHEA). Markers will be analyzed as per our previous study by Galvao et al. [42], which showed them to be affected by acute exercise in prostate cancer patients.

The blood samples collected immediately before the first session as well 5 days after the last training session will be further analyzed for serum levels of free testosterone, blood lipid profile (LDL, HLD, tryglycerides, cholesterol), fructosamine and PSA, to assess metabolic, hormonal, and cancer-related health status. These analyses will be carried out by a local pathology laboratory.

Feasibility and adherence

The feasibility of the exercise intervention will be assessed and reported based on the recruitment (the ratio of people recruited to people who gave permission to be contacted), completion (the ratio of participants who finished the intervention to participants recruited), adherence to the sessions (the ratio of the total number of training sessions attended to the number scheduled), and dose compliance (sets × repetition × weight(kg), described in detail in 'Exercise dosage' below) [43]. The number of weeks the participants took to complete their intervention will be calculated as the mean completion time [43]. Exercise protocol safety will be assessed by recording the incidence and severity of any adverse events throughout the on-trial period for all participants.

Exercise safety

All adverse events will be graded according to the National Cancer Institute's Common Terminology Criteria for Adverse Events (V.4.0) and will be assessed at every visit. Adverse events type, severity, attribution (disease-related or exercise-related), expectedness and timing will be recorded on case report forms. Serious adverse events include events that may be life-threatening, require and/or prolong inpatient hospitalization, result in persistent or significant disability or incapacity, or result in death. Adverse events expected on-trial include musculoskeletal injury, joint pain, and falls. All participants will require medical clearance following adverse events prior to recommencing exercise or testing.

Exercise dosage

Recently published guidelines on resistance training dose and adherence have recommended the detailed reporting of the total training volume (sets × repetition × weight(kg)) as adherence to the protocol [44]. Due to the different loading weight in the eccentric and concentric phases

of each repetition in the AERT protocol, the total training volume performed for the concentric load (total number of repetitions × concentric weight(kg)) will be reported separately to the eccentric load (total number of repetitions × eccentric weight(kg)) and compared to the initially prescribed doses (ratio of total actual to total prescribed cumulative dose) and expressed as a percentage (dose compliance).

Patient-reported outcomes

Perception of fatigue will be measured using the Functional Assessment of Chronic Illness Therapy – Fatigue, Version 4 (FACIT-F) questionnaire where higher scores indicate lower fatigue. The FACIT-F scale has been previously used to investigate patient-reported outcomes among cancer patients [43], and consists of a 13-item, one-dimensional measure of fatigue with each item answered on a five-point scale from 0 to 52 [45]. A score of ≤34 will be used to classify 'clinically significant fatigue' [43,45], and a change of >4 to identify those with a minimal clinically important difference [43,46].

The Functional Assessment of Cancer Therapy – Prostate, Version 4 (FACT-P) questionnaire will be used to assess reduced health-related quality of life (HRQL), based on previous studies of exercise interventions with cancer patients [43,47]. The FACT-P questionnaire consists of a 39-item instrument with a 12-item subscale specific to prostate cancer concerns, and 27 questions in four other domains: physical well-being (7), social/family well-being (7), emotional well-being (6), and functional well-being (7) [48]. Each item will be answered on a five-point scale from 0 (worst possible HRQL) to 144 (best possible HRQL) [43,47]. A clinically significant change in FACT-P score will be represented by a difference of ≤12 as feeling worse, and ≥6 to rate feeling better [43,47].

Muscle soreness

Muscle soreness will be quantified using a 100 mm visual analog scale (VAS), in which 0 indicates no pain, and 100 represents the worst pain imaginable [34]. The participants will be asked to mark the level of perceived soreness on the VAS while performing three repetitions for each exercise without any added resistance.

Exercise intervention

Norris et al. [17] reported that resistance training performed 3 × week^{-1} displayed a trend for more favorable outcomes in lower body strength than 2 × week^{-1} in prostate cancer patients. Thus, the participants will undergo 36 sessions of an AERT protocol planned for 3 × week^{-1} for approximately 12 weeks.

Details of the resistance training protocol are shown in Table 1. The participants will perform circuits of 6 exercises (in their order of execution: abdominal crunch, seated row, chest press, lat pulldown, shoulder press, and leg press) using servomotor-driven resistance exercise machines (BioCircuit, TechnoGym, Italy). Before each training session, the participants will warm up by performing a circuit of 6 repetitions in each machine using ~50% of their prescribed resistance for the session.

The intensity of the concentric phase will be 40–80% of 1RM, while the eccentric phase will be 125% of the concentric load. Both the intensity and number of repetitions will vary during the trial. As shown in Table 1, the repetitions will be split into 3 circuits. The time the participant takes to walk from one exercise station to another and assume the correct position will be used as an active rest period between exercises.

The resistance training sessions will be at least 48 h apart for each participant to allow for adequate recovery. All sessions will be conducted in small groups of one to five participants under direct supervision to ensure safety and appropriate exercise technique.

Table 1: The resistance training protocol. The total volume is calculated based on a hypothetical 100 kg 1RM for total volume calculation.

Session	Repetitions	Concentric load (% 1RM)	Eccentric load (% 1RM)	Total volume (kg)
1 - 4	32	40%	50%	2880
5 - 8	29	50%	62.5%	3262.5
9 - 14	24	60%	75%	3240
15 - 20	27	60%	75%	3645
21-25	21	70%	87.5%	3307.5
26 - 30	24	70%	87.5%	3780
31 – 33	19	80%	100%	3420
34 - 36	21	80%	100%	3780

1RM: Repetition maximum

Pre-conditioning

It has been shown that preconditioning the muscles with eccentric muscle actions at 10% or 20% of the 1RM attenuates the muscle damage responses following maximal intensity eccentric exercise [36]. Therefore, to minimize the muscle damage and soreness responses for the safety of the participants, two preconditioning exercise sessions will be given during the familiarization sessions and will involve the same exercises that will be performed during the exercise intervention. The first pre-conditioning session will take place 14 days before the first training session, during which the participants will perform 1 circuit of 10 repetitions at 10% of their prescribed workload for both phases. The second pre-conditioning session will take place 7 days before the first training session, during which the participants will perform 2 circuits of 10 repetitions at 20% of their prescribed workload for both phases.

Protein supplementation

Protein and amino acid metabolism has been found to be altered in cancer patients, with men on ADT, in particular, experiencing a 30 – 50% decrease in resting muscle protein synthesis levels [49]. As a macronutrient, increased protein intake has been identified as a key nutrient to consume in order to improve skeletal muscle growth. Specifically, whey protein supplementation is a widespread dietary strategy in the field of oncology, with the potential to modulate IGF-1 concentrations [33], and has been effective at increasing resting muscle protein synthesis in prostate cancer patients undergoing ADT with no differences compared to an aged-matched healthy group. Therefore, to reduce the attenuating effects of ADT on muscle protein synthesis, and to ensure all participants have adequate protein intake, a serving of 30 g of whey protein concentrate (Bulk Nutrients, Australia), containing 22.3 g of protein, 1.9 g of fat, and 2.8 g of carbohydrates, will be dissolved in 300 ml of water and given to the participants at the end of each exercise session. The participants will be asked to consume the drink in front of the investigator prior to leaving the facility. All participants will be informed about the allergens of the product (milk, soy, soybean, whey) prior to participation in the study.

Statistical analysis

Sample size estimation

No previous studies have examined the effects of AERT on muscle mass changes of prostate cancer patients undergoing ADT. However, Hansen et al. [50] examined the effects of high-intensity eccentric-only exercise on a cycle ergometer for 12 weeks ($3 \times week^{-1}$) on prostate cancer patients undergoing ADT, and found increases in isometric knee extension strength (pre-training: 323.0 ± 94.9, post-training: 385.9 ± 125.8). Using these reported values, and assuming a correlation between measures of at least r = 0.8, a power level of 0.8, an alpha level

of 0.05 and a one-tailed design, it was calculated that total of at least 11 participants are required. To account for a possible 25% attrition, 14 participants in total will be recruited.

Data analysis

A linear mixed-effects model will be used with participant ID as the random-effects factor. The assumption of normality and homoscedasticity of the residuals will be verified by visual quantile-quantile plot inspection of the plots and a Shapiro-Wilk test. In the case of a significant interaction effect, pairwise comparisons will be performed between conditions and timepoints, with a Holm's p value adjustment. The criterion significance level will be set to $P \leq 0.05$. All statistical testing will be performed using R (R Core Team) using the package lmerTest [51]. Data will be presented as means (95% confidence intervals).

Discussion

This will be the first study to examine the feasibility and tolerance to AERT for prostate cancer patients undergoing ADT and examine changes in body composition, muscle strength, function, and thickness outcomes. The hypertrophic and strength benefits of eccentric exercise on muscle have been reported in previous studies [24,25]. However, the muscle damage phenomena after a single unaccustomed bout of high-intensity eccentric exercise is a concern for exercise training adherence and safety [52]. Nevertheless, previous investigations have successfully implemented high-intensity eccentric-only cycling exercise in prostate cancer patients and reported increases in muscle strength [31,50]. Moreover, it has been shown that repeating the same eccentric exercise produces smaller changes in muscle strength and swelling, and attenuates DOMS significantly when compared with the initial bout [34]. Examining if higher loading of the eccentric phase, performed in a gradually progressing exercise training protocol, is well-tolerated by the patients, and effective at increasing muscle

mass and strength, could lead to clinically meaningful benefits in terms of effective muscle function and mass improvements, and counteract the negative effects of ADT. The results from this study will form the basis for future larger trials and prescription of AERT protocols in prostate cancer patients undergoing ADT, in order to counteract the adverse effects of the disease and ADT, and enhance quality of life and potentially survival.

Conflict of interest

The authors declare that they have no conflicts of interest. No funding was received for this work.

Author contributions

RUN and GM developed the study concept and protocols, drafted the manuscript, and initiated the project. DAG, EG, KN, SZ and DRT assisted in further development of the protocol. GM and JSK will implement the protocol. GM, and RUN will oversee collection of the data. All authors contributed and approved the final manuscript.

References

[1] Jemal A, Bray F, Center MM, Ferlay J, Ward E, Forman D. Global cancer statistics. CA Cancer J Clin 2011;61:69–90. https://doi.org/10.3322/caac.20107.
[2] Gilbert SM, Kuo Y-F, Shahinian VB. Prevalent and incident use of androgen deprivation therapy among men with prostate cancer in the United States. Urol Oncol 2011;29:647–53. https://doi.org/10.1016/j.urolonc.2009.09.004.
[3] Isbarn H, Boccon-Gibod L, Carroll PR, Montorsi F, Schulman C, Smith MR, et al. Androgen deprivation therapy for the treatment of prostate cancer: consider both benefits and risks. Eur Urol 2009;55:62–75. https://doi.org/10.1016/j.eururo.2008.10.008.
[4] Uhlman MA, Moul JW, Tang P, Stackhouse DA, Sun L. Risk stratification in the hormonal treatment of patients with prostate cancer. Ther Adv Med Oncol 2009;1:79–94. https://doi.org/10.1177/1758834009340164.
[5] Grossmann M, Zajac JD. Management of side effects of androgen deprivation therapy. Endocrinol Metab Clin North Am 2011;40:655–71, x. https://doi.org/10.1016/j.ecl.2011.05.004.

[6] Smith MR, Finkelstein JS, McGovern FJ, Zietman AL, Fallon MA, Schoenfeld DA, et al. Changes in body composition during androgen deprivation therapy for prostate cancer. J Clin Endocrinol Metab 2002;87:599–603. https://doi.org/2016092613293800312.
[7] Smith MR. Changes in fat and lean body mass during androgen-deprivation therapy for prostate cancer. Urology 2004;63:742–5. https://doi.org/10.1016/j.urology.2003.10.063.
[8] Greenspan SL, Coates P, Sereika SM, Nelson JB, Trump DL, Resnick NM. Bone loss after initiation of androgen deprivation therapy in patients with prostate cancer. J Clin Endocrinol Metab 2005;90:6410–7. https://doi.org/2016092613245600574.
[9] Smith MR. Androgen deprivation therapy for prostate cancer: new concepts and concerns. Curr Opin Endocrinol Diabetes Obes 2007;14:247–54. https://doi.org/10.1097/MED.0b013e32814db88c.
[10] Galvão DA, Spry NA, Taaffe DR, Newton RU, Stanley J, Shannon T, et al. Changes in muscle, fat and bone mass after 36 weeks of maximal androgen blockade for prostate cancer. BJU Int 2008;102:44–7. https://doi.org/10.1111/j.1464-410X.2008.07539.x.
[11] Smith MR, Lee H, McGovern F, Fallon MA, Goode M, Zietman AL, et al. Metabolic changes during gonadotropin-releasing hormone agonist therapy for prostate cancer: differences from the classic metabolic syndrome. Cancer 2008;112:2188–94. https://doi.org/10.1002/cncr.23440.
[12] Grossmann M, Hamilton EJ, Gilfillan C, Bolton D, Joon DL, Zajac JD. Bone and metabolic health in patients with non-metastatic prostate cancer who are receiving androgen deprivation therapy. Med J Aust 2011;194:301–6.
[13] Galvão DA, Taaffe DR, Spry N, Joseph D, Turner D, Newton RU. Reduced muscle strength and functional performance in men with prostate cancer undergoing androgen suppression: a comprehensive cross-sectional investigation. Prostate Cancer Prostatic Dis 2009;12:198–203. https://doi.org/10.1038/pcan.2008.51.
[14] Taylor LG, Canfield SE, Du XL. Review of major adverse effects of androgen-deprivation therapy in men with prostate cancer. Cancer 2009;115:2388–99. https://doi.org/10.1002/cncr.24283.
[15] Casey RG, Corcoran NM, Larry Goldenberg S. Quality of life issues in men undergoing androgen deprivation therapy: a review. Asian J Androl 2012;14:226–31. https://doi.org/10.1038/aja.2011.108.
[16] Pin F, Couch ME, Bonetto A. Preservation of muscle mass as a strategy to reduce the toxic effects of cancer chemotherapy on body composition. Curr Opin Support Palliat Care 2018;12:420–6. https://doi.org/10.1097/SPC.0000000000000382.
[17] Norris MK, Bell GJ, North S, Courneya KS. Effects of resistance training frequency on physical functioning and quality of life in prostate cancer survivors: a pilot randomized controlled trial. Prostate Cancer Prostatic Dis 2015;18:281–7. https://doi.org/10.1038/pcan.2015.28.
[18] Galvão DA, Nosaka K, Taaffe DR, Spry N, Kristjanson LJ, McGuigan MR, et al. Resistance training and reduction of treatment side effects in prostate cancer patients. Med Sci Sports Exerc 2006;38:2045–52. https://doi.org/10.1249/01.mss.0000233803.48691.8b.
[19] Rossetti ML, Steiner JL, Gordon BS. Androgen-mediated regulation of skeletal muscle protein balance. Mol Cell Endocrinol 2017;447:35–44. https://doi.org/10.1016/j.mce.2017.02.031.
[20] Sheffield-Moore M. Androgens and the control of skeletal muscle protein synthesis. Ann Med 2000;32:181–6. https://doi.org/10.3109/07853890008998825.
[21] Kvorning T, Andersen M, Brixen K, Madsen K. Suppression of endogenous testosterone production attenuates the response to strength training: a randomized, placebo-controlled, and blinded intervention study. Am J Physiol Endocrinol Metab 2006;291:E1325-1332. https://doi.org/10.1152/ajpendo.00143.2006.

[22] Joanisse S, Lim C, McKendry J, Mcleod JC, Stokes T, Phillips SM. Recent advances in understanding resistance exercise training-induced skeletal muscle hypertrophy in humans. F1000Research 2020;9:141. https://doi.org/10.12688/f1000research.21588.1.
[23] Friedmann-Bette B, Bauer T, Kinscherf R, Vorwald S, Klute K, Bischoff D, et al. Effects of strength training with eccentric overload on muscle adaptation in male athletes. Eur J Appl Physiol 2010;108:821–36. https://doi.org/10.1007/s00421-009-1292-2.
[24] Hather BM, Tesch PA, Buchanan P, Dudley GA. Influence of eccentric actions on skeletal muscle adaptations to resistance training. Acta Physiol Scand 1991;143:177–85. https://doi.org/10.1111/j.1748-1716.1991.tb09219.x.
[25] Hortobágyi T, Dempsey L, Fraser D, Zheng D, Hamilton G, Lambert J, et al. Changes in muscle strength, muscle fibre size and myofibrillar gene expression after immobilization and retraining in humans. J Physiol 2000;524:293–304. https://doi.org/10.1111/j.1469-7793.2000.00293.x.
[26] English KL, Loehr JA, Lee SMC, Smith SM. Early-phase musculoskeletal adaptations to different levels of eccentric resistance after 8 weeks of lower body training. Eur J Appl Physiol 2014;114:2263–80. https://doi.org/10.1007/s00421-014-2951-5.
[27] Walker S, Blazevich AJ, Haff GG, Tufano JJ, Newton RU, Häkkinen K. Greater strength gains after training with accentuated eccentric than traditional isoinertial loads in already strength-trained men. Front Physiol 2016;7. https://doi.org/10.3389/fphys.2016.00149.
[28] Bamman MM, Shipp JR, Jiang J, Gower BA, Hunter GR, Goodman A, et al. Mechanical load increases muscle IGF-I and androgen receptor mRNA concentrations in humans. Am J Physiol Endocrinol Metab 2001;280:E383-390. https://doi.org/10.1152/ajpendo.2001.280.3.E383.
[29] Heinemeier KM, Olesen JL, Schjerling P, Haddad F, Langberg H, Baldwin KM, et al. Short-term strength training and the expression of myostatin and IGF-I isoforms in rat muscle and tendon: differential effects of specific contraction types. J Appl Physiol 2007;102:573–81. https://doi.org/10.1152/japplphysiol.00866.2006.
[30] Durand RJ, Castracane VD, Hollander DB, Tryniecki JL, Bamman MM, O'Neal S, et al. Hormonal responses from concentric and eccentric muscle contractions. Med Sci Sports Exerc 2003;35:937–43. https://doi.org/10.1249/01.MSS.0000069522.38141.0B.
[31] LaStayo PC, Marcus RL, Dibble LE, Smith SB, Beck SL. Eccentric exercise versus usual-care with older cancer survivors: the impact on muscle and mobility--an exploratory pilot study. BMC Geriatr 2011;11:5. https://doi.org/10.1186/1471-2318-11-5.
[32] Flück M, Bosshard R, Lungarella M. Cardiovascular and muscular consequences of work-matched interval-type of concentric and eccentric pedaling exercise on a soft robot. Front Physiol 2017;8. https://doi.org/10.3389/fphys.2017.00640.
[33] Teixeira FJ, Santos HO, Howell SL, Pimentel GD. Whey protein in cancer therapy: A narrative review. Pharmacol Res 2019;144:245–56. https://doi.org/10.1016/j.phrs.2019.04.019.
[34] Nosaka K, Clarkson PM. Muscle damage following repeated bouts of high force eccentric exercise. Med Sci Sports Exerc 1995;27:1263–9. https://doi.org/10.1249/00005768-199509000-00005.
[35] Nosaka K, Newton M. Difference in the magnitude of muscle damage between maximal and submaximal eccentric loading. J Strength Cond Res 2002;16:202–8. https://doi.org/10.1519/00124278-200205000-00006.
[36] Chen TC-C, Chen H-L, Pearce AJ, Nosaka K. Attenuation of eccentric exercise-induced muscle damage by preconditioning exercises. Med Sci Sports Exerc 2012;44:2090–8. https://doi.org/10.1249/MSS.0b013e31825f69f3.

[37] Van Belle S, Paridaens R, Evers G, Kerger J, Bron D, Foubert J, et al. Comparison of proposed diagnostic criteria with FACT-F and VAS for cancer-related fatigue: proposal for use as a screening tool. Support Care Cancer 2005;13:246–54. https://doi.org/10.1007/s00520-004-0734-y.
[38] Galvão DA, Taaffe DR, Spry N, Joseph D, Newton RU. Acute versus chronic exposure to androgen suppression for prostate cancer: impact on the exercise response. J Urol 2011;186:1291–7. https://doi.org/10.1016/j.juro.2011.05.055.
[39] Millor N, Lecumberri P, Gómez M, Martínez-Ramírez A, Izquierdo M. An evaluation of the 30-s chair stand test in older adults: frailty detection based on kinematic parameters from a single inertial unit. J NeuroEngineering Rehabil 2013;10:86. https://doi.org/10.1186/1743-0003-10-86.
[40] Hart NH, Nimphius S, Spiteri T, Cochrane JL, Newton RU. Segmental musculoskeletal examinations using dual-energy x-ray absorptiometry (DXA): positioning and analysis considerations. J Sports Sci Med 2015;14:620–6.
[41] Hart NH, Newton RU, Spry NA, Taaffe DR, Chambers SK, Feeney KT, et al. Can exercise suppress tumour growth in advanced prostate cancer patients with sclerotic bone metastases? A randomised, controlled study protocol examining feasibility, safety and efficacy. BMJ Open 2017;7:e014458. https://doi.org/10.1136/bmjopen-2016-014458.
[42] Galvão DA, Nosaka K, Taaffe DR, Peake J, Spry N, Suzuki K, et al. Endocrine and immune responses to resistance training in prostate cancer patients. Prostate Cancer Prostatic Dis 2008;11:160–5. https://doi.org/10.1038/sj.pcan.4500991.
[43] Lavigne C, Twomey R, Lau H, Francis G, Culos-Reed SN, Millet GY. Feasibility of eccentric overloading and neuromuscular electrical stimulation to improve muscle strength and muscle mass after treatment for head and neck cancer. SportRxiv; 2019. https://doi.org/10.31236/osf.io/jqzt9.
[44] Fairman CM, Nilsen TS, Newton RU, Taaffe DR, Spry N, Joseph D, et al. Reporting of resistance training dose, adherence, and tolerance in exercise oncology. Med Sci Sports Exerc 2020;52:315–22. https://doi.org/10.1249/MSS.0000000000002127.
[45] Yellen SB, Cella DF, Webster K, Blendowski C, Kaplan E. Measuring fatigue and other anemia-related symptoms with the Functional Assessment of Cancer Therapy (FACT) measurement system. J Pain Symptom Manage 1997;13:63–74. https://doi.org/10.1016/s0885-3924(96)00274-6.
[46] Elting LS, Keefe DM, Sonis ST, Garden AS, Spijkervet FKL, Barasch A, et al. Patient-reported measurements of oral mucositis in head and neck cancer patients treated with radiotherapy with or without chemotherapy: demonstration of increased frequency, severity, resistance to palliation, and impact on quality of life. Cancer 2008;113:2704–13. https://doi.org/10.1002/cncr.23898.
[47] Lavigne C, Lau H, Francis G, Culos-Reed SN, Millet GY, Twomey R. Neuromuscular function and fatigability in people diagnosed with head and neck cancer before versus after treatment. SportRxiv; 2019.
[48] Chu D, Popovic M, Chow E, Cella D, Beaumont JL, Lam H, et al. Development, characteristics and validity of the EORTC QLQ-PR25 and the FACT-P for assessment of quality of life in prostate cancer patients. J Comp Eff Res 2014;3:523–31. https://doi.org/10.2217/cer.14.41.
[49] Hanson ED, Nelson AR, West DWD, Violet JA, O'Keefe L, Phillips SM, et al. Attenuation of resting but not load-mediated protein synthesis in prostate cancer patients on androgen deprivation. J Clin Endocrinol Metab 2017;102:1076–83. https://doi.org/20170130230000.

[50] Hansen PA, Dechet CB, Porucznik CA, LaStayo PC. Comparing eccentric resistance exercise in prostate cancer survivors on and off hormone therapy: a pilot study. PM&R 2009;1:1019–24. https://doi.org/10.1016/j.pmrj.2009.09.016.
[51] Kuznetsova A, Brockhoff PB, Christensen RHB. lmerTest package: tests in linear mixed effects models. J Stat Softw 2017;82. https://doi.org/10.18637/jss.v082.i13.
[52] LaStayo P, Marcus R, Dibble L, Frajacomo F, Lindstedt S. Eccentric exercise in rehabilitation: safety, feasibility, and application. J Appl Physiol 2014;116:1426–34. https://doi.org/10.1152/japplphysiol.00008.2013.