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Radiotherapy before or during androgen-deprivation therapy does not blunt the exercise-induced body composition protective effects in prostate cancer patients: a secondary analysis of two randomized controlled trials

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Abstract

Background: Androgen deprivation therapy (ADT) contributes to lean mass loss and adiposity increases in prostate cancer patients. Radiotherapy during ADT might act synergistically and further worsen body composition. Previous investigations have shown that resistance training is an effective method of preserving body composition during ADT, however, most have not accounted for direct or indirect effects of other therapies, such as radiotherapy. Therefore, the purpose of this study was to examine training adaptations of the tissue composition in patients receiving radiation therapy (RT) prior or during ADT.

Methods: Analyses were performed by combining data from two previous trials for a total of 131 prostate cancer patients who underwent a combination of resistance and aerobic exercise training (N=70, age: 68.9±6.6y, RT-before: 11%, RT-during: 14%) or usual care (N=61, age: 67.5±7.9y, RT-before: 16%, RT-during: 20%) for 3 months upon ADT onset. Whole-body lean mass (LM), fat percentage and appendicular LM were determined by dual energy x-ray absorptiometry, and lower-leg muscle area and density by peripheral computed tomography at baseline (onset of ADT) and at 3 months post-intervention. Covariates included RT prior and during the intervention, demographic characteristics, physical symptoms, and chronic conditions.

Results: Radiotherapy before or during the intervention did not affect body composition. Only the usual care group experienced a significant decrease in whole-body LM (-994±150g, P<0.001) and appendicular LM (-126±19g, P<0.001), and an increase in whole-body fat percentage (1%±0.1%, P<0.001). There was no change in lower-leg muscle area or density in either group.

Conclusion: We suggest that radiation prior to and during ADT does not interfere with the beneficial effects of exercise training on body composition in men with prostate cancer.

Keywords: muscle mass, hypertrophy, atrophy, adiposity, resistance exercise

Highlights

1. Androgen-deprivation therapy (ADT) reduces lean mass and increases adiposity.
2. There was no additive effect of radiotherapy prior or during ADT on body composition.
3. Exercise training at onset of ADT counteracted the ADT-induced loss of lean mass.
4. Similarly, exercise therapy counteracted the ADT-induced increase in fat percentage.

Introduction

In the developed world, prostate cancer is the second most frequent cancer diagnosis in men (Sung et al., 2021), with a lifetime risk of about 1 in 8 (and up to 1 in 4 in black men), increased risk for those aged over 55 years, and three- quarters of cases occurring in men aged over 65 years (Al-Youzbaki et al., 2020; Lloyd et al., 2015; Quinn and Babb, 2002). 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 (Gilbert et al., 2011), that operates as a chemical castration by decreasing serum testosterone levels to <5% of the normal values (Grossmann and Zajac, 2011). While evidence exists that ADT is effective at slowing tumor progression and improving survival, its use is associated with numerous side effects (Grossmann and Zajac, 2011; Isbarn et al., 2009; Uhlman et al., 2009). For example, it has been reported that ADT results in a decrease in lean body mass, an increase in fat mass, worsening of metabolic profile, and acceleration of aging-induced frailty, (Bylow et al., 2007; Galvão et al., 2008; Greenspan et al., 2005; Grossmann et al., 2011; Smith, 2007, 2004; Smith et al., 2008, 2002) which can increase the risk of falling, osteoporosis, and bone fractures (Grossmann and Zajac, 2011; Isbarn et al., 2009; Uhlman et al., 2009) as well as compromising physical function and quality of life (Casey et al., 2012). ADT might therefore act as a model of accelerated aging, as these negative effects are similar to that typically observed in aging, the severity of which has been directly associated with the aging-induced decline in testosterone levels (Chin et al., 2012; Hyde et al., 2010; Vermeulen et al., 1999). Further, a strong relationship between reduction of appendicular muscle mass and worsening disability is being increasingly demonstrated (Fantin et al., 2007), while a low muscle mass has been associated with poorer prognosis for cancer patients, greater chemotherapy toxicities and reduced overall survival (Pin et al., 2018). As a result, there is a need for effective therapies to prevent ADT-induced muscle loss and fat mass increase.

In addition to ADT, more than 40% of prostate cancer patients aged 65 and older receive radiotherapy (RT) as their primary treatment, (Skolarus et al., 2014). It has been shown that radiation causes muscle atrophy and fibrosis (Kim et al., 2015; Nichol et al., 2003; Paulino, 2004; van Leeuwen-Segarceanu et al., 2012; Zhang et al., 2015), which is of considerable concern as decreased skeletal muscle mass is a significant predictor of non-cancer mortality in men undergoing radiotherapy for prostate cancer (McDonald et al., 2016). Apart from a localized tissue effect, fatigue is a severe symptom of RT affecting up to 80% of patients, (Hickok et al., 2005; Jereczek-Fossa et al., 2002) which may not only discourage daily movement and ambulation but could also reduce willingness to participate in the exercise protocols (adherence), or participate but with reduced intensity or volume (dosage). Specifically in prostate cancer, it has been reported that RT-related fatigue is primarily due to neuromuscular origin, rather than psychological and it has been shown to affect other muscles, rather than being localized to the administration site (Beard et al., 1997; Monga et al., 1997). Based on these findings, it is clear when investigating the effects of ADT on body composition changes in prostate cancer patients, RT administered either before or during intervention must also be taken into consideration.

Exercise training, such as resistance and/or aerobic training, has been shown to be safe and effective in counteracting the adverse effects of ADT such as reduced muscle mass, strength, and physical function (Galvão et al., 2010, 2006; Segal et al., 2003). For example, Galvão et al. (2010), demonstrated that resistance exercise during ADT had a beneficial effect on body composition compared to usual care after 3 months of intervention. However, it is not known if radiation undertaken prior to or during ADT would alter the exercise responses in men with prostate cancer. It is therefore difficult to draw conclusions regarding the effectiveness of exercise protocols, if there was treatment imbalance in the exercise and usual care groups which could have influenced body composition changes.

Given the above, decline of body composition is a common occurrence in men with prostate cancer undergoing ADT, with a potential additive effect of RT . Therefore, the purpose of this study was to examine adaptations in body composition over the course of exercise therapy in patients receiving radiation therapy (RT) prior to or during ADT. We hypothesized that RT would have a significant contributing effect in the decline of body composition, which would be counteracted by exercise intervention.

Materials and Methods

Participants

This study is a secondary analysis of 131 men with a histologic diagnosis of prostate cancer initiating ADT pooled from 2 randomized exercise trials (Cormie et al., 2015; Taaffe et al., 2019), performed at the Exercise Medicine Research Institute at Edith Cowan University in Perth, Australia. These datasets were combined to provide sufficient statistical power to complete analysis of the impact of radiation prior to and during ADT. Participant characteristics are presented in detail in Table 1. All participants had completed a written informed consent and medical questionnaire approved by the institution's human research ethics committee before participating in their respective studies, which included approval for future re-use of their data.

Inclusion criteria consisted of beginning treatment for prostate cancer involving ADT and intending to remain on ADT for at least 3 months, no regular exercise (structured aerobic or resistance training of more than 2 sessions per week) in the past 3 months, and having obtained medical clearance from their physician. Exclusion criteria consisted of having previously received ADT, acute illness, or having musculoskeletal, cardiovascular and/or neurological disorders that could inhibit the participant from exercising (as determined by the patient's physician).

The included participants had complete data available on all outcome measures and were assigned to one of two groups upon ADT initiation: an exercise group (N = 70) or a usual care group (N = 61). The project coordinator and exercise physiologists involved in assigning participants to groups were blinded to the allocation sequence. Participants randomized to the usual care group received no intervention during the study period, but were offered the exercise program after completion of the intervention period. All participants maintained standard medical care for the treatment of prostate cancer and had been instructed to maintain their customary activity and dietary patterns throughout the intervention period.

Body composition

Whole-body lean mass and fat percentage were assessed by dual energy X-ray absorptiometry (DXA) (Hologic Discovery A, USA), with the participant lying in a supine position. 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 were calculated. Appendicular lean mass was calculated as the sum of upper- and lower-limb bone free lean mass (Heymsfield et al., 1990).

Lower-leg muscle area and density

Muscle density (mg/cm^3) and area (mm^2) of the lower leg was determined by peripheral quantitative computer tomography (pQCT) (XCT3000, Stratec, Germany) at the 66% tibia site, while the participant was sitting 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. Total muscle density, and muscle area were calculated using the manufacturer's computer software.

Demographic and anthropometric measures

Clinical and demographic data were collected through medical and self-report records, respectively. Height and weight were assessed using a stadiometer and electronic scales, respectively. Fatigue was assessed using the Functional Assessment of Chronic Illness Therapy-Fatigue (FACIT-Fatigue) questionnaire (higher scores indicate less fatigue) (Yellen et al., 1997).

Exercise training

The usual-care group did not receive any exercise training. The exercise intervention involved 2 (Cormie et al., 2015) or 3 (Taaffe et al., 2019) clinic-based sessions per week for 3 months in one of 6 exercise clinics across Perth and regional Western Australia. The clinic-based sessions consisted of a combination of aerobic and resistance exercise that were ~60 min in duration, and one study included additional impact loading in each session (Taaffe et al., 2019). A warm-up was conducted before the exercise sessions and consisted of low-level aerobic activities and concluded with a cooldown of stretching exercises. In Taaffe et al. (2019), aerobic and resistance exercise frequency was weekly alternated so as two aerobic and one resistance exercise sessions were performed in one week, and one aerobic and two resistance exercise sessions were performed in the subsequent week. All clinic-based sessions were conducted in small groups of 8 – 10 participants and were supervised by accredited exercise physiologists. In addition to the clinic exercise sessions, the participants were encouraged to undertake weekly home-based training twice a week, that consisted of aerobic exercises such as walking or cycling in order to accumulate 150 mins/week of aerobic activity (Cormie et al., 2015), while the other study supplemented the home-based training with a modified version of the impact-loading program consisting of leaping, hopping, and drop jumping (Taaffe et al., 2019).

Aerobic exercise sessions were composed of various modes and included walking/jogging on a treadmill and cycling or rowing on a stationary ergometer at an intensity of 60 – 85% of age-predicted maximum heart rate for 25 – 40 min, with heart rate monitored using chest straps and heart rate watches (Polar Electra Oy, Finland). Resistance training consisted of upper- and lower-body exercises for the major muscle groups and included leg extension, leg press, leg curl, seated row, lat pulldown, chest press, and bicep curls. The intensity was set at 6 – 12 repetition maximum (RM; the maximal weight lifted 6 – 12 times) using 2 – 4 sets per exercise. To ensure the progressive nature of the program, the participants were encouraged to work past the specific prescribed weight and the resistance was increased by a 5 – 10% increment for the next set/session if the participant exceeded the target. Exercise was prescribed as 2 – 3 sets for the initial weeks of the intervention and increased to 3 – 4 sets depending on patient tolerance. Resistance training load was periodised across the week for moderate and high load sessions with repetitions ranging between 6 – 12 per set, adjusted depending on patient tolerance The impact loading component of the sessions that was included in one of the studies progressively increased in intensity and volume, and was composed of 2-4 rotations of bounding (15 - 30 cm hurdles, 10 times), leaping (10 times), skipping (30 s), hopping (10 times), and drop jump exercises (15 - 20 cm, 10 times), resulting in peak ground reaction forces of 3.4 – 5.2 × body weight (Taaffe et al., 2019).

Statistical analysis

A linear mixed-effects model was used with participant ID as the random-effects factor, while fixed-effects factors consisted of demographic and physical characteristics (age, baseline body fat percentage, which study they took part in), physical symptoms and conditions (hypertension, high cholesterol, cardiovascular disease, diabetes, osteoporosis),

and prostate cancer-specific treatments before and during intervention (prostatectomy, radiotherapy). The assumption of normality and homoscedasticity of the residuals was 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 were performed between conditions and timepoints, with a Holm's p value adjustment. The criterion significance level was set to $P \leq 0.05$. All statistical testing was performed using R 4.0.3 (R Core Team) using the package lmerTest 3.1-3 (Kuznetsova et al., 2017). Data are presented as means (95% confidence intervals).

Results

Demographic and clinical characteristics of the study population are shown in Table 1. Participants were aged 46 to 84 years, had a BMI of 18.8 to 38.9 kg/m^2, and were predominantly married, non-smokers, and no longer employed. Regarding cancer therapy prevalence, 23% of the participants in the exercise and 31% in the usual care had undergone prostatectomy before baseline, while 13% and 16% had undergone RT before, and 14% and 20% during the intervention, for the exercise and usual care groups, respectively. The typical RT duration was 7 – 8 weeks. In the exercise group, attendance (number of sessions attended / number of sessions prescribed) was 98.1 ± 26.2% for those that underwent RT during the intervention, and 91.3 ± 24.6% for those that did not.

Raw values for the outcome measures and reported fatigue are shown in Table 2, and the results of the linear mixed-effects model are shown in Table 3. There was a significant group × time interaction for whole-body lean mass (Table 3, P = 0.002), with the usual care group showing a significant change at the 3-month timepoint by -1.7 ± 2% [-994 g (-1383 – -604), P < 0.001], while the -0.6 ± 2.2% [-345 g (19 – 709), P = 0.536] change in the exercise group was not significant (Figure 1). Training frequency (2 vs 3·week^{-1}) or additional impact

loading did not influence the 3-month change in whole-body lean mass (P = 0.505). No baseline physical characteristics, chronic conditions, or RT (either before or during ADT) influenced the 3-month change in whole-body lean mass.

Similarly, there was a significant group × time interaction for appendicular lean mass (Table 3, P < 0.001), with the usual care group showing a significant change at the 3-month timepoint by -2.2 ± 2.4% [-126 g (-176 – -75 g), P < 0.001], while the -0.5 ± 2.6% [-34 g (-83 – 14), P = 0.266] change in the exercise group was not significant (Figure 1). Training frequency or additional impact loading did not influence the 3-month change in appendicular lean mass (P = 0.708). Advanced age was associated with a greater decrease in appendicular lean mass by -23.3 g [(-44.6 – -2.00), P = 0.032] per year of age. Other baseline physical characteristics, chronic conditions, or RT (either before or during ADT) did not influence the 3-month change in appendicular lean mass.

There was also a significant group × time interaction for whole-body fat percentage (Table 3, P < 0.001), with the usual care group showing a significant change at the 3-month timepoint by 1% (0.5 – 1.3%, P < 0.001), while the 0.2% (-0.2 – 0.5%, P = 0.767) change in the exercise group was not significant (Figure 1). Training frequency or additional impact loading did not influence the 3-month change in whole-body fat percentage (P = 0.587). No baseline physical characteristics, chronic conditions, or RT (either before or during ADT) influenced the 3-month change in whole-body fat percentage.

Lower leg muscle area did not change significantly over the intervention period for either group (Table 3). Training frequency or additional impact loading did not influence the 3-month change in lower-leg muscle area (P = 0.644). Higher baseline body fat percentage was associated with decreased muscle area by 43.9 mm^2 (2.6 – 85.3 mm^2, P = 0.037) Other baseline physical characteristics, health conditions, or RT (either before or during ADT) did not influence the 3-month change in lower-leg muscle area. Similarly, lower leg muscle

density did not change significantly over the intervention period for any of the groups (Table 3, and Figure 1). However, as shown in Table 3, advanced age was associated with a greater decrease in muscle density by -0.1 mg/cm^3 (-0.2 – 0 mg/cm^3, P = 0.005), whereas higher baseline body fat percentage was associated with decreased muscle density by -0.2 mg/cm^3 (-0.4 – -0.1 mg/cm^3, P < 0.001). Training frequency or additional impact loading did not influence the 3-month change in lower-leg muscle density (P = 0.641). Other baseline physical characteristics, chronic conditions, or RT (either before or during ADT) did not influence the 3-month change in lower-leg muscle density.

Discussion

This study was undertaken to examine if the effects of exercise training on body composition would differ in patients receiving radiation prior to or during ADT in men with prostate cancer. Contrary to our hypothesis, we report that radiation timing (prior to or during ADT) did not exert a significant effect on body composition. However, only patients in the usual-care group experienced a significant loss of whole-body and appendicular lean mass, with concurrent increases in fat percentage, while the implemented exercise programs counteracted deterioration of body composition.

There is compelling evidence that ADT has detrimental effects on body composition such as decreases in lean mass, and increases in adiposity (Galvão et al., 2008; Greenspan et al., 2005; Grossmann et al., 2011; Smith, 2007, 2004; Smith et al., 2008, 2002), that mimic the typically observed decline of testosterone levels with aging, effectively accelerating the aging process toward structural and functional deterioration culminating in frailty. In addition, RT causes muscle atrophy and fibrosis (Kim et al., 2015; Nichol et al., 2003; Paulino, 2004; van Leeuwen-Segarceanu et al., 2012; Zhang et al., 2015) and neuromuscular fatigue in prostate cancer patients (Beard et al., 1997; Monga et al., 1997). Moreover, a

reverse relationship also exists, as lower skeletal muscle mass can also exacerbate RT-induced toxicity (Matsuo et al., 2018; Panje et al., 2019; van Rijn-Dekker et al., 2020), therefore rendering the loss of muscle mass not only important for the health and physical function of the patient, but also critical for their survival. In addition, up to 80% of patients experience fatigue (Hickok et al., 2005; Jereczek-Fossa et al., 2002), which may further discourage physical activity and compromise exercise adherence and thus indirectly contribute to muscle atrophy. Based on our findings, there was no effect of timing of RT on any of the examined endpoints, suggesting that ADT may play a much more substantial role in compromising body composition than RT, and therefore the smaller effect of RT on the endpoints did not reach significance. Nevertheless, even though ADT was associated with a worsening of body composition at 3 months post-initiation, the implemented exercise interventions counteracted the decrease in whole body and appendicular lean mass, as well as the increase in fat mass. This is clinically relevant, as it denotes that exercise helps to preserve body composition during ADT even when the patient is undergoing RT.

In the present study, advanced age was associated with a worsening in appendicular lean mass and muscle density. More specifically, advanced age was associated with decreased appendicular lean mass by -23.3 g per year of age, and muscle density by -0.1 mg/cm^3 per year of age. Worsening of both appendicular lean mass, and muscle density have been independently associated with increased likelihood of falls and mortality (Scott et al., 2019). Three- quarters of prostate cancer cases occur in men aged over 65 years, (Quinn and Babb, 2002) therefore, exercise training in prostate cancer patients can help counteract not only the body composition decline during ADT, but also the decline induced by aging.

Apart from body composition preservation, in some studies there were even increases in lean mass despite the patients having no testosterone-mediated anabolic pathway (Dawson et al., 2018; Galvão et al., 2010, 2006; Hansen et al., 2009; Hanson et al., 2013; Newton et

al., 2019; Nilsen et al., 2016; Wall et al., 2017). In the present study, we only found a preservation of body composition, without an improvement compared to baseline, and while this is significant both for health and survival, future research should attempt to identify training protocols that further increase muscle mass. It has been shown that a strength training frequency of 2 times a week in previously untrained healthy men combined with endurance training 2 times a week leads to muscle hypertrophy to the same degree as in strength training only (Häkkinen et al., 2003). Whether this occurs similarly in patients who are castrate, needs further research. We have previously reported that prostate cancer patients undergoing ADT where all participants received the identical resistance training intervention, those that completed an additional 20 – 30 min aerobic exercise component each session were compromised with lower increases in appendicular lean mass (Newton et al., 2019). Interestingly, most of the aforementioned studies in which muscle mass or thickness increases were observed, only resistance training was implemented (Galvão et al., 2006; Hansen et al., 2009; Hanson et al., 2013; Newton et al., 2019; Nilsen et al., 2016), while one study included protein supplementation to enhance the exercise-induced protein synthesis (Dawson et al., 2018). Therefore, future research and clinical practice should focus on resistance training when the aim is to increase muscle mass in prostate cancer patients undergoing ADT. Additionally, as ADT is a long-term treatment, a 3-month resistance exercise protocol implemented in a clinic is likely to only provide short-term amelioration of disease and treatment related issues. It is therefore important to implement strategies to support patients to continue resistance exercise outside of a clinical setting. For ease of access and affordability the preferred setting is likely in the patient's home, local park or exercise facility with ongoing monitoring and supervision by qualified exercise professionals, increasingly through the use of telehealth to provide motivation for the patient, and ensure a safe and effective exercise program for the long term (Newton et al., 2020).

Moreover, the type of resistance training must also be taken into consideration. Conventional resistance training includes concentric and eccentric muscle actions, and the same absolute load is used for both phases of each repetition (Friedmann-Bette et al., 2010). However, a study which successfully elicited increases in muscle mass in prostate cancer patients on and off ADT utilized high-force eccentric-only training, with the ADT group not experiencing a blunted exercise response (Hansen et al., 2009). Greater insulin growth factor-1 mRNA increases in human (Bamman et al., 2001), and rat muscle (Heinemeier et al., 2007), and greater myostatin mRNA decreases in rat muscle (Heinemeier et al., 2007), have been observed after eccentric exercise when compared with equivalent concentric training, despite both concentric and eccentric exercise shown to elicit similar serum testosterone level increases (Durand et al., 2003). These findings suggest that eccentric exercise training may trigger anabolic pathways that are less dependent on testosterone, compared to conventional concentric training. Therefore, apart from implementing resistance training to counteract worsening of body composition upon ADT or RT onset, researchers should consider attention to the type of resistance training implemented.

No significant group × time interactions, were observed for lower-leg muscle area and density. One possible reason is that lower-leg muscles are composed to a greater extent of type I myofibers, compared to, for example, knee extensor muscles (Edgerton et al., 1975; Houmard et al., 1998), and it has been shown that type I myofibers are more resistant to both atrophy and hypertrophy, when compared to type II myofibers (Boonyarom and Inui, 2006). Therefore, even though there were opposing trends in the two groups for both lower-leg muscle area and density (Table 3), the 3-month intervention might have been too short to observe significant changes in these variables, and the lower leg was not specifically targeted. Fat percentage appeared to affect muscle density, possibly because muscle density is indicative of 'muscle quality' and a lower muscle density reflects greater intramuscular

fibrosis and fat content. Therefore, future investigations should explore the assessment of tissue composition through tomography in muscles that are more responsive to exercise, such as the knee extensors, especially when the protocols are less than 3 months in duration. Tissue composition assessment through tomography might be an assessment method more sensitive to the effects of aging.

One potential limitation of the current study is the lack of information regarding the dosage of exercise (performed divided by prescribed volume) to further examine if higher adherence to the initial prescribed protocol is proportionately associated with better body composition outcomes, over simply group (exercise vs usual care) allocation. The difference between attendance for those that underwent RT during the intervention (98.1 ± 26.2%), and for those that did not (91.3 ± 24.6%) was not significant suggesting addition of RT did not compromise patient capacity to exercise, however this is highly speculative and requires further research specifically examining prescribed versus exercise dosage received as per our paper (Fairman et al., 2020). In addition, very few (3%) of the participants underwent chemotherapy prior to baseline, and none underwent brachytherapy before or during the intervention, and as such these therapies were not included as covariates in the analysis. Moreover, the pQCT scans were conducted in the lower-leg, and were not specific to major muscle groups, that could have larger responses to exercise. Future studies should explore the use of pQCT to assess tissue composition in the thigh or arm muscles. Nevertheless, despite the above limitations, this study performed a secondary analysis on two randomized controlled clinical trials, in a unique population, where the timing of ADT onset was taken into consideration, and multiple participant characteristics that could have affected body composition changes were investigated.

Conclusions

Here we show that radiation timing (prior or during ADT) did not exert a significant effect on body composition. ADT reduced whole-body lean mass, and increased fat percentage within only a 3-month period after onset, but exercise training using a combination of aerobic and resistance training, with or without impact loading, performed either 2 or 3 times per week, has a significant body composition preservation effect in men initiating ADT for prostate cancer. Therefore, exercise training appears to be a critically important adjunct modality for cancer patients, regardless of the received therapy.

Declaration of interest

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

Author contributions

- Conception or design of the work: RUN, DRT, NS, DJ, DAG
- Data collection: RUN, DRT, DAG
- Data analysis and interpretation: RUN, GM, DRT, DAG
- Drafting the article: RUN, GM, MSF, WJK, KH, DRT, NS, DJ, DAG
- Critical revision of the article: RUN, GM, MSF, WJK, KH, DRT, NS, DJ, DAG
- Final approval of the version to be published: RUN, GM, MSF, WJK, KH, DRT, NS, DJ, DAG

Clinical trial registry

Can exercise ameliorate treatment toxicity during the initial phase of testosterone deprivation in prostate cancer patients? Is this more effective than delayed rehabilitation? ACTRN12612000097842.

Lucrin immediate exercise pilot trial – The effect of an exercise intervention on quality of life in prostate cancer patients commencing Lucrin treatment; ACTRN12610000691044; https://www.anzctr.org.au/Trial/Registration/TrialReview.aspx?id=335822

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Tables

Table 1

Table 1: Participant characteristics per group. Values are presented as mean ± standard deviation.

Variables	Exercise (N = 70)	Usual care (N = 61)
Age (y ± SD)	68.9 ± 6.6	67.5 ± 7.9
Height (cm ± SD)	173.0 ± 6.8	172.3 ± 6.5
Body mass (kg ± SD)	83.8 ± 15.5	85.3 ± 12.5
Married (N (%))	52 (74%)	45 (74%)
Currently unemployed (N (%))	51 (73%)	34 (56%)
Current smoker (N (%))	17 (24%)	12 (20%)
Hypertension (N (%))	40 (57%)	38 (62%)
Hypercholesterolemia (N (%))	32 (46%)	31 (51%)
Cardiovascular disease (N (%))	16 (23%)	11 (18%)
Type 2 diabetes (N (%))	13 (19%)	14 (23%)
Osteoporosis (N (%))	2 (3%)	2 (3%)
Time since diagnosis (weeks ± SD)	111 ± 180	144 ± 374
Prostatectomy (before, N (%))	16 (23%)	19 (31%)
Radiotherapy (before, N (%))	9 (13%)	10 (16%)
Chemotherapy (before, N (%))	0 (0%)	2 (3%)
Brachytherapy (before, N (%))	0 (0%)	0 (0%)
Prostatectomy (during, N (%))	0 (0%)	0 (0%)
Radiotherapy (during, N (%))	10 (14%)	12 (20%)
Chemotherapy (during, N (%))	0 (0%)	0 (0%)
Brachytherapy (during, N (%))	0 (0%)	0 (0%)

Table 2

Table 2: Mean values for the outcome measures and reported fatigue per group with and without radiotherapy (during the intervention). Values are presented as mean ± standard deviation.

Variables	Timepoint	Exercise		Usual care	
		With RT	Without RT	With RT	Without RT
Whole-body lean mass (g ± SD)	Pre	58,597 ± 9,655	55,536 ± 8,023	57,193 ±5,803	56,374 ± 7,388
	Post	57,727 ± 9,329	55,256 ± 7,724	56,1[illegible]3 ± 5,717	55,371 ± 7,027
Appendicular lean mass (g ± SD)	Pre	6,275 ± 1,142	5,884 ± 924	6,12[illegible] ±698	5,975 ± 823
	Post	6,172 ± 1,039	5,955 ± 1220	5,9[illegible]9 ± 660	5,827 ± 781
Fat percent (% ± SD)	Pre	30.0 ± 3.2	29.1 ± 5.4	28.3 ± 4.7	31.3 ± 4.6
	Post	30.4 ± 2.4	29.3 ± 5.0	29.3 ± 4.7	32.3 ± 4.4
Muscle area (mm^2 ± SD)	Pre	7,961 ± 1,327	7,37[illegible] ± 1,613	7,707 ± 790	7,613 ± 1,230
	Post	7,730 ± 1,124	7,386 ± 1,278	7,498 ± 891	7,365 ± 1,531
Muscle density (mg/cm^3 ± SD)	Pre	72.4 ± 3.2	73.0 ± 3.7	73.3 ± 3.8	72.6 ± 2.9
	Post	72.3 ± 2.7	73.0 ± 3.4	74.1 ± 3.7	71.8 ± 3.1
Fatigue (score ± SD)	Pre	14.6 ± 4.9	10.9 ± 5.4	12.3 ± 4.5	12.7 ± 9.1
	Post	14.5 ± 9.2	10.9 ± 5.7	12.3 ± 6.4	12.7 ± 8.5

Table 3

Table 3: Linear mixed-effects model for the response variables before and after 3 months of ADT onset (Timepoint) with exercise or with usual care.

Predictors	Whole-body lean mass (g)	Appendicular lean mass (g)	Fat percent (%)	Muscle area (mm^2)	Muscle density (mg/cm^3)
Group (Usual care)	-265 (-2806 – 2276)	44.6 (-250.7 – 339.9)	1.18 (-0.49 – 2.86)	-90.9 (-510.0 – 328.3)	-0.14 (-1.23 – 0.94)
Timepoint (3 months)	-345 (-619 – -71)*	-34.4 (-70.5 – 1.7)	0.17 (-0.10 – 0.43)	-31.0 (-104.0 – 43.0)	-0.09 (-0.53 – 0.34)
Group × Timepoint (Usual care, 3-months)	-649 (-1050 – -247)**	-91.4 (-143.6 – -38.6)***	0.75 (0.36 – 1.14)***	-59.2 (-168.2 – 49.7)	-0.46 (-1.10 – 0.19)
Allocated study	1008 (-1954 – 3970)	66.4 (-281.6 – 414.4)	0.16 (-1.78 – 2.11)	-116.3 (-609.2 – 376.7)	0.33 (-0.88 – 1.53)
Age	-151 (-334 – 31)	-23.3 (-44.6 – -2.00)*	-0.06 (-0.13 – 0.06)	-28.1 (-58.1 – 1.8)	-0.11 (-0.19 – -0.03)**
Baseline body fat %	276 (13 – 538)	12.7 (-18.1 – 43.5)		43.9 (2.6 – 85.3)	-0.24 (-0.35 – -0.14)***
Hypertension	-654 (-3338 – 2031)	28.4 (-280.6 – 337.4)	-1.62 (-3.38 – 0.13)	-15.9 (-449.9 – 418.1)	0.52 (-0.57 – 1.61)
Cholesterol	-1711 (-4405 – 983)	-222.6 (-532.9 – 87.7)	-0.09 (-1.88 – 1.71)	-307.0 (-753.4 – 139.3)	0.50 (-0.60 – 1.60)
Cardiovascular disease	1501 (-1686 – 4688)	185.5 (-183.9 – 554.8)	-0.18 (-2.33 – 1.96)	186.9 (-349.7 – 723.5)	-0.64 (-2.00 – 0.72)
Diabetes	-2774 (-6204 – 657)	-94.4 (-499.2 – 311.1)	-0.87 (-3.14 – 1.40)	109.9 (-473.9 – 693.6)	-0.30 (-1.72 – 1.12)
Osteoporosis	2087 (-5574 – 9748)	24.5 (-857.8 – 906.8)	2.87 (-2.19 – 7.92)	-418.0 (-1636.9 – 800.8)	2.36 (-0.70 – 5.42)
Prostatectomy (before)	1238 (-1994 – 4470)	198.6 (-179.1 – 576.4)	0.03 (-2.12 – 2.18)	186.7 (-343.5 – 717.0)	-1.01 (-2.34 – 0.32)
Radiotherapy (before)	369 (-3410 – 4147)	179.4 (-279.3 – 638.6)	-0.85 (-3.34 – 1.64)	-49.2 (-669.1 – 570.7)	-0.67 (-2.25 – 0.91)
Radiotherapy (during)	-2040 (-5805 – 1725)	200.7 (-643.0 – 241.6)	1.52 (-0.96 – 4.00)	-282.5 (-907.6 – 342.7)	0.62 (-0.95 – 2.19)
Model R^2	0.989	0.985	0.975	0.968	0.859

Data presented as estimates (95% confidence interval) in the unit of the response variable. *: $P \leq 0.05$; **: $P \leq 0.01$; ***: $P \leq 0.001$.

Figure captions

Figure 1: Changes in A: whole-body body lean mass (g), B: appendicular lean mass (g), C: whole-body fat percent (%), and D: lower-leg muscle density (mg/cm^3) 3 months after ADT onset with exercise (left) or with usual care (right). Violin plots (grey-shaded area) indicate sample spread. Boxplots indicate median (black line), bottom and top indicate first and third quartiles respectively, and whiskers indicate ± 1.5IQR.