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Original research

Creatine supplementation does not add to resistance training effects in prostate cancer patients under androgen deprivation therapy: A double-blind randomized trial

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ABSTRACT

Objectives: Androgen deprivation therapy (ADT) leads to loss of lean mass (LM) and reduced strength and physical function. Resistance exercise alone can counteract these changes; however, it is unknown if the addition of creatine supplementation can further protect against these ADT-induced toxicities. We compared the effects of creatine supplementation with resistance exercise versus resistance exercise alone in patients with prostate cancer undergoing ADT on LM, muscle strength, and physical function.
Design: A 12-week randomized trial.
Methods: Men with prostate cancer receiving ADT ($n = 30$) were randomized to either resistance exercise + placebo (PLA) or resistance exercise + creatine (SUPP), with both groups undertaking supervised exercise 3 days per week. Outcomes included whole body and appendicular LM and fat mass (FM) assessed by dual-energy X-ray absorptiometry, as well as muscle strength (chest press, seated low, leg press), and physical function (timed up-and-go, chair rise, 400-m walk) assessed at baseline and following the intervention.
Results: Patients were aged 59–84 years with a BMI of 28.6 $kg \cdot m^{-2}$. PLA completed a mean of 30 sessions (83 %) and SUPP a mean of 33 sessions (92 %). Despite similar within-group improvements ($p < 0.05$) in whole-body LM (PLA + 0.6 kg, SUPP + 1.3 kg), appendicular LM (PLA + 0.5 kg, SUPP + 0.6 kg), muscle strength (PLA + 8.8–49.3 kg, SUPP + 9.4–40.4 kg) and physical function, there were no between group differences ($p = 0.078$–0.951). No adverse events were reported due to creatine supplementation or resistance exercise.
Conclusions: A short-term program of resistance exercise alone results in meaningful improvements in LM, muscle strength and physical function, with no additional effects of creatine supplementation.

Practical implications

- In untrained men with prostate cancer undergoing androgen deprivation therapy, resistance exercise improves lean mass, muscle strength and physical function, with no additional effects of creatine supplementation.
- Increases in fat mass during androgen deprivation therapy for prostate cancer appear to be mitigated with resistance training and creatine supplementation.

1. Introduction

Androgen deprivation therapy (ADT) is foundational in the treatment of prostate cancer,[1] and is used across the disease trajectory as

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monotherapy as well as in combination with other systemic therapies as doublet and triplet therapy.[2] However, ADT is accompanied by several deleterious side effects impacting musculoskeletal health with reductions in lean mass (LM), gains in fat mass (FM) and declines in physical function extensively reported.[3,4] Collectively, these changes increase the risk of functional decline and development of comorbidities.[5] Recently, we have reported a significant relationship between lower LM and reduced overall survival in men with prostate cancer[6] highlighting the importance of preserving or increasing LM during and following ADT.

In previous randomized controlled trials, men with prostate cancer on ADT undertaking resistance exercise have shown to improve quality of life,[7] reduce fatigue,[8] increase LM,[9] and increase types I and II muscle fiber size and capillarization.[10] In addition, resistance exercise undertaken at the onset of ADT prevents the decline in LM expected in the initial 6–12 months of treatment.[11] Nonetheless, LM changes observed following various resistance exercise regimes in men on ADT can be modest and vary substantially.[12] As such, additional strategies that can further improve the LM response to exercise in patients undertaking ADT should be further investigated.

We have previously described the potential therapeutic effects of creatine supplementation in combination with resistance exercise on LM and muscle function in cancer patients,[13] however, the impact of this strategy in men on ADT is yet to be examined. In brief, creatine is a naturally occurring nitrogen containing compound synthesized in the body that plays a critical role in energy provision during exercise.[13,14] Creatine supplementation has been demonstrated to consistently yield superior improvements in LM, muscle strength and physical function outcomes relative to resistance exercise alone in older adults.[15] These adaptations may vary as a result of baseline levels of intramuscular creatine, and dietary habits (whereby individuals with a vegan/vegetarian diet may benefit more from supplementation).[16] Nevertheless, given the accelerated decline of lean mass, strength and physical function that is commonly observed with ADT in prostate cancer,[3,17,18] there is a clear and strong rationale for the investigation of therapeutic strategies to offset these declines. Further, the reliable improvements in body composition and functional outcomes experienced in individuals supplementing with creatine and resistance training, compared to resistance training alone,[19–21] highlight the potential that creatine supplementation could have synergistic effects with resistance training to augment adaptations in body composition and functional outcomes in this patient population.[13]

In this manuscript, we report the first double-blind, placebo-controlled randomized trial examining the effects of creatine supplementation with resistance exercise versus resistance exercise alone on LM, muscle strength and physical function outcomes in patients with prostate cancer receiving ADT. Our hypothesis was that the addition of creatine supplementation to resistance exercise would lead to greater improvements in these outcomes compared to resistance exercise alone.

2. Methods

Fifty-five men with prostate cancer on ADT were referred to the study and 30 were randomized. Patients were eligible if they were: 1) currently receiving ADT for prostate cancer, 2) no presence of bone metastases, 3) not being treated for any other cancer, 4) not receiving medications known to alter body composition (i.e., corticosteroids, metformin, etc.), 5) not participating in regular resistance training (≥2 days per week for 6 months or longer), and 6) not taken creatine supplementation in the past 6 months. The primary method of recruitment was through referrals from each patient's treating specialist. Details of the trial, including intended goals, risks, and benefits were discussed with patients individually and those who were interested consented to have their information forwarded to a member of the research team. Interested patients were telephoned to screen for, and verify, eligibility. Eligible patients were invited to participate and schedule a visit with the study team for baseline assessments. All participants were required to receive physician clearance and provide written informed consent prior to engaging in any study activities.

2.1. Study design

This was a 12-week, double-blind, randomized, placebo-controlled trial from July 2019 to January 2022 in Western Australia. Following completion of baseline assessments, patients were stratified according to time on ADT (≤6 and >6 months) and age (≤65 and >65 years), and randomly assigned in a ratio of 1:1 to either resistance exercise plus placebo (PLA, n = 15) or resistance exercise plus creatine supplementation (SUPP, n = 15) using a computer-generated random assignment by a member of the research team with no contact with participants. Patients and all other study members were blinded to group allocation. Testing occurred at the Exercise Medicine Research Institute, Edith Cowan University in Perth, Western Australia, and exercise was undertaken in three exercise clinics located across the metropolitan area. The study was approved by the Human Research Ethics Committee at Edith Cowan University (HREC ID: 22243) and the protocol was prospectively registered at anzctr.org.au (ACTRN12619000099123). Based on the initial sample size calculation to achieve 80 % power,[22] we initially planned to recruit fifty-six men for the study; however, the study experienced significant delays due to COVID-19 and consequently the study closed with a final sample of 30 men randomized to PLA and SUPP.

2.2. Exercise program

Patients were asked to complete 36 resistance exercise sessions, performed 3 times per week for 12 weeks. All sessions were supervised by accredited exercise physiologists with extensive experience in exercise oncology. The program included 8 exercises targeting large muscle groups of the body (leg press, deadlift, step up, chest press, push-ups, shoulder press, lat pulldown, and seated row). The initial loading was equivalent to ~65 % 1RM (3 sets of 12 repetitions), progressing toward ~80 % 1RM (4 sets of 8 repetitions). The initial loading for week one was determined during the 2-week familiarization period, where the exercise physiologists worked with patients to find a training load sufficient to reach the target repetition range, with approximately 2 repetitions in reserve. Loading was progressed throughout the program whereby if a patient was able to complete 2 additional reps on the *last* set of an exercise for 2 consecutive sessions, the weight for an exercise was increased (~5–10 % for upper body and ~10–15 % for lower body). In cases where this progression structure was not possible, decisions on progression schema and load were left to the discretion of the attending exercise physiologist. Further, the exercise physiologist monitored each patient to autoregulate training load where variations in their fatigue, recovery, energy, and physical capacity were used to adjust each training session. Specific details of the program are outlined in the protocol paper.[22]

2.3. Supplement and placebo protocol

Patients in the SUPP group received 20 g/day of creatine monohydrate for 5 days, beginning on day 4 of the familiarization and testing phase (immediately after randomization, approximately 7 days prior to first training session), divided into four equal doses throughout the day. Participants then received 5 g/day thereafter, for the remainder of the 12-week intervention. This dosing protocol has been previously demonstrated to be safe and efficacious in older adults.[15,23] Patients in the PLA group followed the same dosing protocol but with dextrose, a type of sugar that is commonly used as a placebo.[23,24] Patients were asked to dissolve the supplements in 200–300 mL of juice (orange or apple) to mask the solubility of Cr and taste of dextrose.

2.4. Study outcomes

Prior to the intervention, all patients underwent a 2-week familiarization/testing period, where they completed baseline testing, began supplementation, and received instruction on safe and appropriate exercise technique. Specifically, body composition was measured on Day 1, followed by 2 days of instruction on correct exercise technique on Day 2 and Day 3, before performing baseline muscle strength and physical function testing on Day 4. Information related to participant demographics and cancer-related information (treatment history, time on treatment, stage of cancer) were obtained via questionnaires prior to baseline testing.

2.4.1. Primary outcome

2.4.1.1. Lean mass. Whole body LM (kg) and appendicular LM (ALM, kg, lower and upper limb bone-free LM) was assessed using dual-energy X-ray absorptiometry (DXA; Horizon A, Hologic Inc., Massachusetts, USA).[9] Patients were asked to avoid strenuous exercise for 24 h prior to testing and to avoid the consumption of food and water 4 h and 1 h prior to testing, respectively.

2.4.2. Secondary outcomes

2.4.2.1. Fat mass. Whole body and trunk FM (kg), and body fat percentage were obtained from the DXA scan.

2.4.2.2. Muscle strength and physical function. One-repetition maximum (1RM) testing was used to assess upper and lower body strength using the chest press, seated row, and leg press exercises.[9] Physical function was assessed using the 400-meter walk test, timed up-and-go and repeated chair rise.[9]

2.4.3. Additional measures and adverse effects

A wall-mounted stadiometer (Model 222, Seca, Hamburg, DE), and calibrated electronic scale (AE Adams CPW Plus-200, Adam Equipment, Connecticut, USA) were used to assess height and weight, respectively. Self-reported physical activity was assessed by the Leisure Score Index of the Godin Leisure-Time Exercise Questionnaire.[25] To examine any potential side effects of supplementation in this population, fasted blood samples were collected and analyzed commercially by an accredited National Association of Testing Authorities laboratory (Australian Clinical Labs, Perth, Australia) for creatinine and Glomerular Filtration Rate (eGFR) at baseline and follow-up. Additionally, participants completed a modified questionnaire related to gastrointestinal distress (nausea, bloating, upset stomach, etc.) from supplementation.[26] Specifically, patients were asked to rate the presence and severity of symptoms. Severity was rated as either "mild", "moderate", or "severe". To monitor dietary intake 3-day food records were obtained pre- and post-intervention and analyzed using FoodWorks 10 (Version 2, Australia).

2.5. Statistical analysis

Our initial sample size was based on an estimated mean difference in change between the two groups for LM of 1.4 kg at the end of the 12-week intervention.[19] To achieve 80 % power at an alpha level of $p < 0.05$ (two-tailed), 25 participants per group were required to detect this difference.[22] Due to logistics and COVID-19, the study closed with a final sample of 30 men (~60 % of our intended sample) randomized 1:1 to PLA and SUPP. Statistical analysis was conducted using IBM SPSS (Version 29, Armonk, New York). The Shapiro–Wilk test was used to assess the normality of the distribution. Baseline characteristics were compared using independent *t*-tests or the Mann–Whitney *U* test, as appropriate, for continuous data and Chi-square for categorical data. Outcome measures were assessed using analysis of covariance (ANCOVA) adjusted for baseline values and the Godin LSI. For creatinine, eGFR, and dietary intake values were only adjusted for baseline. An intention-to treat approach was used for all analyses with imputation of missing values using expectation maximization. Data not normally distributed were log transformed (ln) for analysis. In addition, within-group differences were assessed using either paired *t*-tests or the Wilcoxon Signed Rank test, as appropriate. All tests were two-tailed and an alpha level of 0.05 was required for significance.

3. Results

Participant flow through the study is provided in the CONSORT diagram (Fig. 1). Common reasons for exclusion from the trial were time constraints, lack of interest, or ineligible due to treatment status, presence of bone metastases, or current activity levels. Baseline characteristics of patients are presented in Table 1. Patients were aged 59–84 years, most were married and not currently employed, with a BMI of 28.6 $kg \cdot m^{-2}$. There were no significant differences between groups at baseline apart from marital status and the Godin LSI. In addition, there were no significant differences between groups for baseline dietary intake, including energy ($p = 0.831$), protein ($p = 0.457$), fat ($p = 0.694$), or carbohydrates ($p = 0.805$). Of the 36 planned exercise sessions, PLA completed a mean of 30 sessions (83 %) and SUPP a mean of 33 sessions (92 %).

3.1. Lean mass

There was no difference between groups across the 12 weeks for LM ($p = 0.623$) with an adjusted difference of 0.3 kg (95 % CI, −0.7–1.3) (Table 2). However, both groups significantly improved LM across the 12-week period (PLA 0.6 kg, 95 % CI 0.1–1.1, $p = 0.030$; SUPP 1.3 kg, 95 % CI 0.6–2.1, $p = 0.001$). Similarly, there was no difference between groups for ALM ($p = 0.723$), however, both groups improved in a comparable fashion (PLA 0.5 kg, 95 % CI 0.2–0.8, $p = 0.009$; SUPP 0.6 kg, 95 % CI 0.1–1.0, $p = 0.015$).

3.2. Fat mass

There was no difference between groups following the 12-week intervention for FM ($p = 0.207$), % body fat ($p = 0.233$), or trunk FM ($p = 0.335$) (Table 2). However, PLA increased FM (1.3 kg, 95 % 0.7–2.0, $p < 0.001$), % body fat (0.8 %, 95 % 0.3–1.3, $p = 0.002$), and trunk FM (0.7 kg, 95 % 0.4–1.0, $p < 0.001$). In contrast, there was no significant change for SUPP for FM (0.4 kg, 95 % −0.9–1.8, $p = 0.069$), % body fat (0.0 %, 95 % −0.9–0.8, $p = 0.912$), and trunk FM (0.2 kg, 95 % −0.6–1.0, $p = 0.112$).

3.3. Muscle strength and physical function

Change in muscle strength and physical function did not differ between groups ($p = 0.078$–0.929) over the intervention (Table 3). However, both groups significantly improved in muscle strength across the 12-week period (PLA 8.8 kg–49.3 kg, $p < 0.001$; SUPP 9.4 kg–40.4 kg, $p < 0.001$). For physical function, PLA improved in the timed up and go (−0.8 s, $p = 0.012$) and 400-m walk (−12.5 s, $p = 0.002$), while SUPP improved in the chair rise (−2.1 s, $p = 0.009$), the timed up and go (−0.8 s, $p = 0.005$), and 400-m walk (−33.3 s, $p = 0.002$).

3.3.1. Adverse events and other measures

From pre- to post-intervention, there was no significant change between groups for energy ($p = 0.250$), protein ($p = 0.864$) or fat ($p = 0.214$), however, carbohydrate intake was lower ($p = 0.028$) in SUPP with an adjusted difference of −32.6 g (95 % CI, −61.5 to −3.7) (Supplementary Table). Following 12 weeks of creatine supplementation, serum creatinine levels were significantly higher ($p = 0.004$) in SUPP compared to PLA with an adjusted difference of 6.3 μmol/L (95 % CI, 2.2–10.5), however, levels remained within the normal range.[27] eGFR

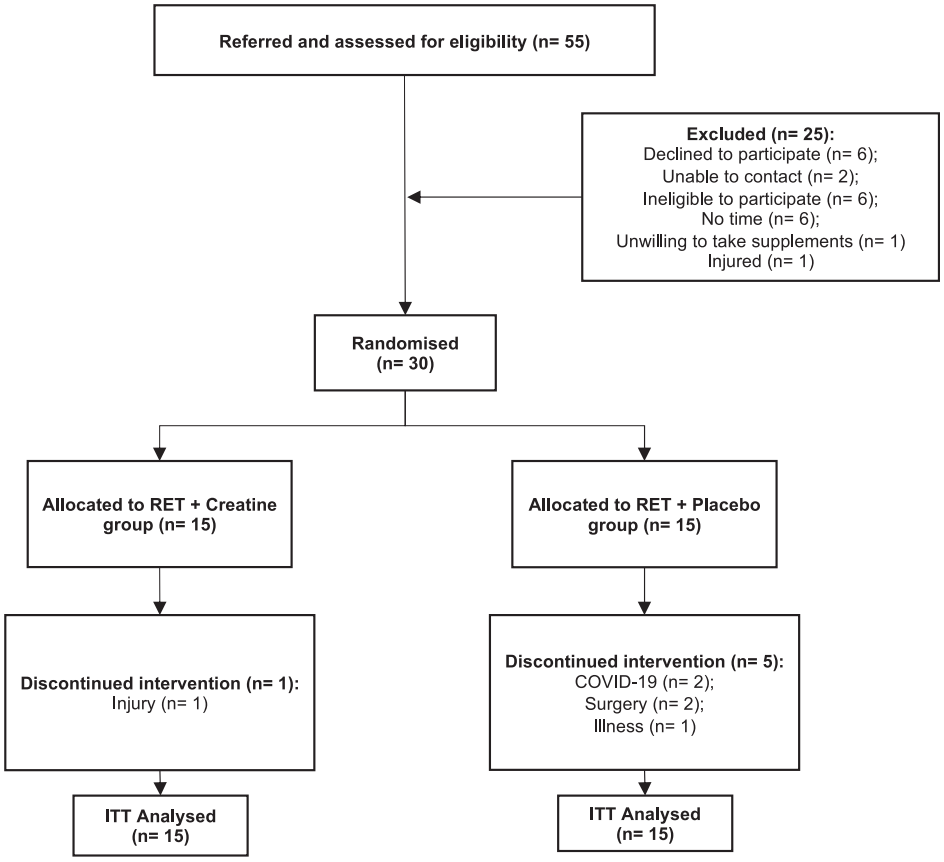

Fig. 1. CONSORT diagram.

significantly decreased ($p = 0.011$) following 12 weeks in SUPP compared to PLA with an adjusted difference of −4.8 mL/min/1.73 m^2 (95 % CI, −8.3 to −1.2), however, values remained within the normal range.[28] Non-hematologic adverse events were not significantly different between groups. Further, individuals in each group reported an absence of most gastrointestinal adverse events (i.e. nausea, vomiting, abdominal pain, constipation, etc.). Individuals in each group reported mild diarrhea (PLA: n = 2; SUPP: n = 2) at baseline which did not change at post-test (PLA: n = 3; SUPP; n = 2).

Table 1
Participant characteristics.

	Placebo (n = 15)	Creatine (n = 15)	p value
Age, yr	70.9 ± 6.4	70.5 ± 7.7	0.878
Height, cm	170.5 ± 6.5	170.5 ± 7.5	0.990
Weight, kg, mdn (IQR)	85.7 (72.7–94.1)	75.5 (72.2–90.3)	0.419
BMI, kg/m^2, mdn (IQR)	28.3 (25.3–31.8)	27.4 (26.4–29.2)	0.520
Body fat (%)	33.4 ± 7.3	32.7 ± 5.2	0.767
Married, N (%)	10 (66.7)	15 (100.0)	0.014
Currently employed, N (%)	4 (26.7)	4 (26.7)	1.000
Tertiary education, N (%)	5 (33.7)	5 (33.7)	1.000
Current smoker, N (%)	0 (0.0)	1 (6.7)	0.309
Godin LSI[a]	13.9 ± 11.4	33.9 ± 23.5	0.008
Dietary intake			
Energy (kJ)	8899 ± 2506	8593 ± 2746	0.831
Protein (g/kg)	1.2 ± 0.4	1.1 ± 0.3	0.457
Fat (g)	81.7 (71.0–90.9)	79.8 (50.5–106.7)	0.694
Carbohydrate (g)	200.6 ± 50.7	206.9 ± 79.6	0.805
Creatinine, μmol/L	79.0 (71.0–87.0)	78.0 (69.0–89.0)	0.983
eGFR, mL/min/1.73 m^2	86.0 (80.0–90.0)	85.0 (71.0–90.0)	0.899
Medications number, mdn (IQR)	4.0 (2.0–5.0)	3.0 (2.0–6.0)	0.870
Comorbidities number, mdn (IQR)[b]	1.0 (1.0–2.0)	1.0 (0.0–2.0)	0.520
Time on ADT, months, mdn (IQR)	3.0 (1.0–9.0)	3.0 (1.0–11.0)	0.403
Previous treatments, N (%)			
Prostatectomy	3 (20.0)	5 (33.3)	0.409
Radiation	12 (80.0)	10 (66.7)	0.409
Chemotherapy	1 (6.7)	2 (13.3)	0.543

Values are the mean ± SD unless stated otherwise; mdn, median; IQR, inter-quartile range; eGFR, Glomerular Filtration Rate.

[a] LSI, Leisure Score Index with a moderate-to strenuous LSI ≥24 classed as active and ≤23 classed as insufficiently active.

[b] Cardiovascular disease, hypertension, diabetes, and dyslipidemia.

4. Discussion

This study compared the effects of resistance exercise with creatine supplementation versus resistance exercise alone in patients with prostate cancer receiving ADT. We found that participation in resistance exercise led to improvements in whole body and appendicular LM as well as improvements in upper and lower body muscle strength, and physical function, with no additional benefits observed in those who received creatine supplementation. In addition, increase in FM appeared to be mitigated in the SUPP group. Lastly, our findings also support the safety and feasibility of supplementation with creatine in patients with prostate cancer, with no adverse events related to supplementation.

Reduction of LM during ADT has been extensively documented.[3,17] Resistance exercise has been shown to counteract these changes, however, contrary to our hypothesis, the addition of creatine supplementation to resistance exercise did not lead to greater improvements in LM compared to resistance exercise alone following a 12-week program. The lack of significant additional whole body and ALM increases for the SUPP group is in contrast with trials in apparently healthy older adults. For example, results of a recent meta-analysis were that supplementing resistance exercise with creatine resulted in ~1.4 kg greater increase in LM compared to resistance exercise alone.[29] The mean change of 0.6 kg in LM in the PLA group is consistent to what is typically expected in similar interventions in patients with prostate cancer on ADT.[9,30] Increases in types I and II muscle fiber size and

Table 2
Baseline and post exercise change in body composition.

	Baseline		12 weeks		Adjusted group difference[a]		
	Placebo	Creatine	Placebo	Creatine	Mean	95 % CI	p value[b]
Lean mass[c] (kg)	53.2 ± 6.7	52.7 ± 8.0	53.8 ± 6.6	54.0 ± 8.3	0.3	(−0.7, 1.3)	0.623
ALM[c] (kg)	22.1 ± 3.0	22.6 ± 3.8	22.6 ± 3.0	23.2 ± 3.8	−0.1	(−0.7, 0.5)	0.723
Fat mass[c] (kg)	29.2 ± 11.0	27.4 ± 8.9	30.6 ± 10.9	27.8 ± 7.2	−1.0	(−2.6, 0.5)	0.207
Body fat (%)	33.4 ± 7.3	32.7 ± 5.2	34.2 ± 7.1	32.7 ± 5.2	−0.6	(−1.7, 0.4)	0.233
Trunk fat mass[c] (kg)	15.5 ± 6.4	13.7 ± 4.5	16.2 ± 6.5	13.9 ± 3.7	−0.5	(−1.5, 0.5)	0.335

Values are the mean ± SD; ALM, appendicular lean mass.
[a] Adjusted group difference, Creatine − Placebo.
[b] Between group change by ANCOVA (adjusted for baseline and Godin LSI).
[c] p value based on log transformed data.

capillarization[10] and quadriceps muscle cross-sectional area by computed tomography scan[30] are likely the mechanism observed for increased LM. It could also be that resistance exercise alone represents such a large stimulus in previously untrained individuals, that supplementation is unlikely to result in sufficiently large differences between groups to detect a change. This is consistent with other interventions in prostate cancer, where nutritional or protein supplementation combined with resistance exercise did not augment adaptations in LM compared to resistance exercise alone.[30] Nevertheless, it has recently been suggested that in light of challenges to accruing muscle mass in cancer patients exacerbated by the low anabolic environment of ADT, even retention of LM may very well be considered a positive outcome.[5,31]

Improvements in upper and lower body strength, with no additional improvements from creatine supplementation, were also observed in our patients with prostate cancer undertaking ADT and participating in resistance exercise. We have previously reported increases in upper and lower body muscle strength with continuing gains over 20 weeks of resistance exercise.[31] As above, we posit that the initial response to a resistance exercise intervention may yield such large improvements in strength, that supplementation with creatine may be unlikely to confer additional benefits. Nevertheless, given the short time frame employed in this study, future research should investigate longer periods of exercise/supplementation to determine the long-term impact of creatine supplementation on exercise adaptations. Alternatively, creatine supplementation could be commenced after 4–6 months of the initial exercise intervention period following early musculoskeletal adaptions.

Significant improvement in the 400-meter walk test with a time reduction to complete the task of ~12 and ~33 s for PLA and SUPP was found, respectively. These are larger changes than what we reported previously (e.g. ~7 s) in patients on ADT[9] and similar to those who have completed ADT (e.g. ~19 s)[32] and likely provide a safety margin before thresholds of disability are encountered[9] as walking capacity has been shown to be a strong predictor of mortality in older adults.[33] There were also significant improvements in chair rise and timed up and go performance. These tests are commonly employed in older adults and clinical populations, primarily as an indicator of functional status and/or risk of falls, disability, and mortality. For example, a cutoff of ~13.5 s is commonly referenced as an indicator of high risk of falls for timed up and go.[34] Participants in our trial completed the timed up and go in 9.7 s (PLA) and 8.0 s (SUPP), respectively. Further, ≥15 s for the 5 times sit-stand is regularly referenced cutoff scores to identify individuals at risk of falls.[35] Participants in our trial had an average of 13.7 s (PLA) and 13.1 s (SUPP), respectively, at baseline. Therefore, it may very well be that individuals who participated in our trial had higher functional status to begin with, and these tests exhibited a "ceiling effect", limiting the ability to detect any further improvements.

It is well established that ADT leads to increases in FM[3,18] and has been associated with increased metabolic and cardiovascular complications.[36] It has been reported that adults undertaking resistance exercise and creatine supplementation reduced FM by ~0.5 kg more than those undertaking resistance exercise alone.[37] In the current study, there was an increase in FM in PLA (1.4 kg) with no significant change in SUPP and no significant differences between groups. However, it could be argued that the adjusted between group differences (~1.0 kg) could be clinically relevant. We have previously shown that low dose aerobic plus resistance exercise alone had little impact on FM in patients on ADT,[9] however, higher doses of exercise such as 300 min per week (including resistance exercise) in combination caloric restriction have led to positive impact in FM reduction of −2.8 kg.[38] It may be that higher exercise volume in combination with caloric restriction is the best combination to impact FM during ADT.

Importantly, there were no significant differences between the groups at baseline regarding energy and macronutrient intake. There were also no differences between groups in energy and macronutrient intake from baseline to 12-week follow-up, with the exception of carbohydrates (where the SUPP group experienced a significant reduction in carbohydrate consumption). Importantly, there was no significant difference in protein intake between the groups based on pre- and post-intervention measures. Consequently, it is unlikely that dietary intake or modifications to diet across the study influenced our results.

Table 3
Baseline and post exercise change in muscle strength and physical function.

	Baseline		12 weeks		Adjusted group difference[a]		
	Placebo	Creatine	Placebo	Creatine	Mean	95 % CI	p value[b]
Muscle strength (kg)							
Chest press	37.9 ± 15.7	37.7 ± 14.8	46.7 ± 14.5	47.1 ± 16.1	−0.2	(−3.9, 3.6)	0.929
Leg press[c]	101.6 ± 53.2	108.0 ± 46.3	150.9 ± 74.1	148.4 ± 67.0	−17.9	(−40.4, 4.6)	0.078
Seated row[c]	62.5 ± 19.0	64.4 ± 16.3	72.6 ± 14.9	75.9 ± 17.3	0.6	(−4.5, 5.6)	0.951
Physical function (s)							
Chair rise[c]	13.7 ± 6.9	13.1 ± 7.2	13.6 ± 7.3	11.0 ± 2.4	−1.8	(−4.7, 1.1)	0.601
Timed up-and-go[c]	9.7 ± 5.7	8.0 ± 3.0	8.9 ± 6.7	7.2 ± 2.2	0.1	(−1.6, 1.8)	0.526
400-m walk[c]	304.2 ± 112.7	299.5 ± 131.4	291.6 ± 109.7	266.2 ± 60.2	−18.0	(−49.7, 13.7)	0.332

Values are the mean ± SD.
[a] Adjusted group difference, Creatine − Placebo.
[b] Between group change by ANCOVA (adjusted for baseline and Godin LSI).
[c] p value based on log transformed data.

Limitations of this trial include a relatively short intervention period (12 weeks) and lack of generalizability to patients with prostate cancer who may be unable to attend supervised exercise sessions (i.e., due to physical limitations, or extensive comorbidities). Further, our reduced sample size limited our ability to detect significant changes between groups. A larger sample size would provide a more robust analysis and potentially reveal trends that could be explored in future research. Additionally, the use of an intention-to-treat analysis rather than a per-protocol analysis could introduce variability in the results.[39] While intention-to-treat analysis preserves the initial random assignment of participants and helps avoid bias, it may dilute the observed effects if participants do not fully adhere to the intervention protocol.[40] A per-protocol analysis might provide further insights into the efficacy of creatine supplementation among participants who strictly followed the training and supplementation regimen.

Another limitation of this study is the reliance on self-reported dietary intake, which is susceptible to biases such as underreporting or overreporting of food consumption, potentially leading to inaccuracies in assessing the actual dietary habits and nutrient intake of participants.[41] These values may not accurately reflect the participants' true energy consumption, potentially impacting the study's findings regarding dietary intake and its effects. Future studies should consider employing more objective measures of dietary intake, such as doubly labeled water or direct observation, to enhance data accuracy. Lastly, our assessment of blood markers was limited to creatinine and eGlomular Filtration Rate as we did not measure markers of inflammation or immune response to exercise, hence these parameters could be investigated in future studies. Nevertheless, this study is the first to investigate the impact of creatine supplementation with resistance exercise in patients with prostate cancer on ADT with LM assessed by DXA and objective measures of muscle strength and physical function.

5. Conclusions

In summary, resistance exercise results in meaningful improvements in LM, muscle strength and physical function, in patients with prostate cancer on ADT with no additional improvements for creatine supplementation. However, it may well be that creatine supplementation may facilitate resistance exercise benefits after the initial period of adaptation (past 12 weeks intervention) and future trials could consider examining such a strategy to augment the effects of resistance exercise.

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CRediT authorship contribution statement

CMF, KLK, RUN, NHH, DRT, RC, CIT, and DAG developed the study concept and protocols and initiated the project. CMF, KLK, RUN, DRT, and DAG drafted the manuscript. RC and CIT provided access to patients. CMF, KLK, RUN, DRT, and DAG implemented the protocol and oversaw collection of the data. All authors contributed and approved the final manuscript.

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Confirmation of ethical compliance

All participants were required to receive physician clearance and provide written informed consent prior to engaging in any study activities. The study was approved by the Human Research Ethics Committee at Edith Cowan University (HREC ID: 22243) and the protocol was prospectively registered at anzctr.org.au (ACTRN12619000099123). All methods were performed in accordance with the Declaration of Helsinki.

Declaration of interest statement

Daniel A. Galvão had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. All authors had no conflict of interest, including relevant financial interests, activities, relationships, and affiliations to declare relating to this manuscript. The sponsors did not participate in the design or conduct of the study; collection, management, analysis, and interpretation of the data; or in the preparation, review, or approval of the manuscript.

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