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The clinical relevance of adiposity when assessing muscle health in men treated with androgen deprivation for prostate cancer

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Abstract

Background Androgen deprivation therapy (ADT) for prostate cancer (PCa) may prospectively decrease absolute lean mass (LM) and increase absolute fat mass (FM). Given that estimates of LM by dual-energy X-ray absorptiometry may be overestimated in obese people, this study examined the influence of adiposity on muscle health in men treated with ADT for PCa.

Methods This cross-sectional study examined the influence of adiposity on total and appendicular LM (ALM), muscle cross-sectional (CSA), and muscle strength in 70 men treated with ADT [mean (standard deviation) age, 71 (6) years] for PCa compared with age-matched PCa (n = 52) and healthy controls (n = 70). Total body LM, FM and ALM, and 66% tibia and radius muscle CSA were quantified by dual-energy X-ray absorptiometry and peripheral quantitative computed tomography, respectively. ALM was further divided by height (m^2) or body mass index, with muscle CSA expressed as a per cent of total limb CSA. Upper and lower body and back (three-repetition maximum and dynamometry) muscle strength were expressed per kilogram of body weight.

Results On average, ADT-treated men had 4.4–6.4 kg greater FM compared with controls ($P \leq 0.014$) and there were no differences in total body or ALM. Total body per cent LM and ALM_{BMI} were 3.8–5.4% ($P \leq 0.001$) and 7.8–9.4% ($P \leq 0.001$) lower, respectively, in ADT-treated men compared with both controls. Percentage muscle CSA at both sites and muscle strength (except leg) were 3.0–6.0% ($P \leq 0.031$) and 15–17% ($P \leq 0.010$) lower, respectively, in ADT-treated men compared with both controls.

Conclusions The findings from this study indicate muscle mass, size, and strength are compromised in men treated with ADT after accounting for their increased adiposity or body size.

Keywords Sarcopenia; Atrophy; Prostatic neoplasms; Body composition; Adipose tissue

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Introduction

Prostate cancer (PCa) is the most commonly diagnosed male cancer both worldwide and in Australia.[1,2] Besides the notable contribution to male cancer-related deaths,[1] the diagnosis and treatment of PCa may predispose men to a range of adverse health outcomes. One specific treatment, androgen deprivation therapy (ADT), is often accompanied by deleterious effects on lean mass, fat mass, and muscle strength.[3,4] This is of clinical relevance given that these changes increase

the risk of cardiometabolic diseases, osteoporosis, falls, fractures, mobility limitations, and mortality.[5–8] When compared with healthy-hormonal and non-hormonal PCa-matched controls, men treated with ADT have consistently been shown to have increased fat mass.[9,10] However, similar comparisons of lean mass and muscle strength have yielded mixed results that may be related to the inclusion of different comparison groups. For instance, absolute total body lean mass was shown to be approximately 3.8 kg lower in 67 men treated with ADT (mean age, 71 years) when compared with both healthy and PCa controls, respectively.[10] However, controls were on average 4–8 years younger, which may have confounded these results. In another study that compared 20 ADT-treated men (mean age, 70 years) with age-matched healthy (n = 18) and PCa controls (n = 20), no significant differences were detected between groups for absolute total body lean mass.[11] Similar conflicting findings have been reported for muscle strength. For instance, when compared with age-matched healthy controls, men treated with ADT had similar[12] or 29% lower[13] handgrip muscle strength. Another cross-sectional study of 20 ADT-treated men (mean age, 70 years) demonstrated that they had approximately half the upper body muscle strength (bench press one-repetition maximum) compared with 18 age-matched PCa controls, but similar leg muscle strength (leg press one-repetition maximum).[11] One factor that could contribute to the heterogeneity in the results for lean mass and muscle strength between men treated with and without ADT and healthy controls is a difference in fat (adiposity).

Previous research has shown that increased adiposity (fat mass) is often associated with increased lean mass and muscle strength in men aged greater than 55 years, which may be explained by additional muscle contractile work required during normal locomotion and activities of daily living associated with excess fat.[14,15] Currently, there are several methods to adjust lean mass for adiposity (body size), including appendicular lean mass (ALM) divided by height (m) squared (ALMI) or body mass index (BMI) (ALM_{BMI})[16,17] and total body lean mass expressed as a percentage of total body weight.[18] Increased adiposity has been associated with greater muscle strength in healthy older men,[14] and thus, muscle strength is often normalized to body weight (e.g. expressed as strength per kilogram of body weight). To date, these adiposity-based adjustments have received limited attention in men treated with ADT. One cross-sectional study observed that 30 ADT-treated men (mean age, 72 years) and 25 age-matched non-ADT hypogonadal controls had similar ALMI (mean, both 7.5 kg/m^2); however, no comparison was made to eugonadal men.[19] Conversely, neither ALM_{BMI} nor body weight-adjusted muscle strength has been examined in this clinical population group. Therefore, the aim of this study was to compare absolute and adiposity-adjusted measures of total body and regional lean mass and muscle strength in men treated with ADT to appropriately selected age-matched PCa and healthy controls.

Methods

Participants

This was a pre-planned cross-sectional study, performed parallel to the baseline of a randomized controlled trial,[20] where comparisons were made between 70 men treated with ADT for PCa, 52 men treated with non-hormonal therapies (i.e. surgery, radiotherapy, or active surveillance) for PCa (PCa controls), and 70 men not diagnosed with PCa (healthy controls). Eligible participants were men aged 50–85 years. Participants were excluded if they did not have the ability to complete surveys in the English language, had any disorder known to affect bone, calcium, or vitamin D metabolism (other than hypogonadism), were currently receiving pharmacological intervention known to affect bone metabolism (other than ADT), had supplemented with protein, calcium (>600 mg/day), or vitamin D (>1000 IU/day) in the past three months, had undertaken progressive resistance training (>one session/week) or regular weight-bearing impact exercise (>150 min/week) in the past three months, were current smokers, had a weight greater than 159 kg, or had any absolute contraindications to exercise testing (e.g. musculoskeletal, cardiovascular, or neurological) according to the American College of Sports Medicine guidelines.[21] Specific to men treated with ADT, treatment must have been pharmacological (surgical orchiectomy excluded) and administered for greater than 12 weeks at enrolment.

Men treated with ADT were recruited via clinician referral from Alfred Health (Melbourne, Australia), Peter MacCallum Cancer Centre (Victoria, Australia), and private urology practices (Victoria, Australia), as well as from PCa support groups (Victoria, Australia) and advertisements in state/local newspapers. PCa and healthy controls were recruited from PCa support groups and advertisements in state/local newspapers. The study was approved by the human research ethics committees at Deakin University (HREC 2013-184), Alfred Health (Project No: 4515/15), and Peter MacCallum Cancer Centre (Project No: 17/118). All participants gave their informed written consent prior to participation. This study was conducted in accordance with the 1964 Declaration of Helsinki and its later amendments.

Measurements

Lean and fat mass

Total and regional lean and fat mass (kg) and total body per cent lean and fat mass (%) were assessed by dual-energy X-ray absorptiometry (DXA) and analysed using software

version 12.30.008 (Lunar iDXA, GE Lunar Corp., Madison, USA). Participants were assigned an individual study identifier code, which allowed for blinded assessment of all DXA scans. ALM was calculated as arm lean mass (kg) plus leg lean mass (kg). ALMI was calculated as ALM (kg) divided by height (m) squared. ALM adjusted for BMI (ALM_{BMI}) was calculated as ALM (kg) divided by BMI (kg/m^2). Percentage ALM was calculated as ALM divided by total weight multiplied by 100.

Muscle and limb cross-sectional area

Muscle and limb cross-sectional area (CSA) of the forearm (66% radius) and lower leg (66% tibia) was assessed by peripheral quantitative computed tomography (pQCT; XCT 3000, Stratec Medizintechnik GmbH, Pforzheim, Germany). After performing a scout view of the distal radius and tibia, scans were performed at the 4% and 66% regions of the radius and tibia. Slice thickness was 1 mm, and voxel size was set at 0.5 mm with a scanning speed of 20 mm/s. ImageJ version 1.52 (http://rsb.info.nih.gov/ij/) and the BoneJ plugin (version 1.4.2; http://bonej.org) soft tissue analysis was used to analyse all pQCT images.[22] Muscle CSA (cm^2) was calculated by subtracting fat CSA and bone CSA from total CSA. Thresholds of 40 and 690 mg/cm^3 hydroxyapatite density were used for the estimation of fat and bone CSA, respectively. Individual study identifier codes allowed for the blinded assessment of all pQCT scans. Per cent muscle CSA was calculated as muscle CSA (cm^2) divided by total limb CSA (cm^2).

Muscle strength

Maximal muscle (grip) strength was assessed using a digital hand-held dynamometer (Jamar Plus Digital, Lafayette Instrument Company, Lafayette, IN, USA).[23] The participant was seated with their foreman resting on the arm of chair whilst maintaining a 90° angle at the elbow. Participants were asked to squeeze the dynamometer maximally. Six trials were completed (three with each hand alternating) with the single highest score recorded.

Muscle strength was obtained for the upper body (Chest press, Powerline Smith Machine PSM144X, Body-Solid Inc., Forest Park, IL, USA), lower body (Leg press, Omni Leg Press S-31-OPD, Synergy Fitness, Yatala, Australia), and back (Seated row, Adjustable Tower Pulley System F3ATFS, Nautilus, Independence, VA, USA) using a three-repetition maximum (3-RM) protocol.[21] The 3-RM protocol assessed the maximum weight that could be lifted for three repetitions whilst maintaining correct form and technique. Prior to completing the 3-RM testing, participants completed a 5 min aerobic warm-up. Thereafter, each participant performed a warm-up set of 8–10 repetitions with a light load. The participant then completed 6–8 repetitions at a heavier weight. The load was increased incrementally until only three repetitions could be completed. A 2 min recovery period was provided between each set. Muscle strength per kilogram body weight was calculated as muscle strength (kg) divided by weight (kg).

Medical history, demographics, and lifestyle

A lifestyle and medical questionnaire was used to obtain age and ethnicity, past and current co-morbidities, use of prescription medication, and PCa details and treatment. The Community Healthy Activities Model Program for Seniors physical activity questionnaire was used to assess participation in a comprehensive list of low, moderate, and vigorous physical activities.[24] Participants documented the frequency and duration of their participation in a 'typical week' of the preceding 4 weeks with the result expressed as the total habitual physical activity (kJ/day). Diet was assessed using a 24 h food recall. Dietary analysis was performed using Australia-specific dietary analysis software (FoodWorks, Xyris software, Highgate Hills, Australia).

Statistical analysis

Based on previous research, this study was powered (≥80%, $P < 0.05$, two tailed) to detect the following between-group differences between men treated with ADT and healthy controls (hypothesized to demonstrate the largest differences between groups): total body lean mass (mean ± standard deviation; −4.0 kg ± 5.6 kg),[25] total body per cent fat mass (5.4% ± 6.4%),[25] and handgrip strength (−11.2 kg ± 5.9 kg).[13] All analyses were performed using SPSS 25.0 (IBM Corp, Chicago, USA). Initially, all data were screened for outliers and descriptive statistics were computed to compare the three groups on known confounding variables of the outcomes of interest. Equality of variances and normality of distribution of all data were assessed using Levene's test and Shapiro–Wilk's test, respectively (no data violated these assumptions). Between-group comparisons were assessed by analyses of variance or χ^2 tests. Continuous data were reported as mean ± standard deviation, whereas categorical variables were reported as frequency and percentage, unless stated otherwise. $P < 0.05$ (two tailed) was adopted as significant for all statistical tests.

Results

Participant characteristics

Participant characteristics are shown in Table 1. For men treated with ADT, the mean (range) treatment duration was 25 (3–166) months. On average, men treated with ADT had a 7.9% greater BMI than PCa controls ($P = 0.012$), but not healthy controls. There was a between-group difference for obesity (BMI ≥ 30 kg/m^2), with the highest proportion in ADT-treated men (29%) compared with PCa (17%) and

Table 1 Participant characteristics of men with prostate cancer (PCa) treated with androgen deprivation therapy (ADT), PCa controls, and healthy controls

	Men treated with ADT	PCa controls	Healthy controls	*P* value
n	70	52	70	—
Age (years)	71 ± 6	69 ± 6	69 ± 7	0.073
Height (cm)	175.1 ± 6.4	176.1 ± 7.2	176.0 ± 6.5	0.726
Weight (kg)	88.5 ± 17.1	82.4 ± 13.5	85.1 ± 14.7	0.073
Body mass index (kg/m^2)	28.8 ± 5.0	26.6 ± 4.0	27.5 ± 3.1	**0.013**
Obese, *n* (%)	20 (29.0)	9 (17.3)	15 (21.4)	**0.002**
Ethnicity, *n* (%)				
Caucasian	68 (97.1)	51 (98.1)	66 (94.3)	0.382
Asian	1 (1.4)	1 (1.9)	4 (5.7)	
African	1 (1.4)	0 (0.0)	0 (0.0)	
Co-morbidities, *n* (%)*	62 (88.6)	42 (80.8)	61 (87.1)	0.441
If yes, total (*n*)	3 ± 1	2 ± 1	2 ± 1	0.372
Prescription medication, *n* (%)	55 (78.6)	34 (65.4)	45 (64.3)	0.132
If yes, total (*n*)	3 ± 2	3 ± 2	3 ± 2	0.201
Physical activity (kJ/day)	2634 ± 1706	3199 ± 1960	3016 ± 1698	0.192
Diet				
Energy (kJ/day)	8666 ± 2579	8316 ± 2151	8571 ± 2354	0.727
Protein (g/day)	93 ± 31	103 ± 34	99 ± 31	0.239
Protein (g/kg/day)	1.07 ± 0.36	1.28 ± 0.43	1.18 ± 0.38	**0.017**
Protein (% of energy/day)	19 ± 5	21 ± 6	20 ± 4	**0.021**
Carbohydrate (g/day)	214 ± 87	203 ± 67	218 ± 66	0.508
Carbohydrate (% of energy/day)	40 ± 10	40 ± 10	42 ± 8	0.477
Fat (g/day)	77 ± 34	76 ± 32	73 ± 29	0.683
Fat (% of energy/day)	33 ± 10	33 ± 11	31 ± 7	0.234
Saturated fat (g/day)	28 ± 13	26 ± 12	29 ± 13	0.472
Saturated fat (% of energy/day)	12 ± 4	11 ± 4	12 ± 4	0.390
Time since PCa diagnosis (mo)[a]	69 ± 70	71 ± 58	—	0.889
Stage of PCa, n (%)[a]				
Localized/removed	20 (28.6)	44 (84.6)	—	**<0.001**
Advanced	45 (64.3)	6 (11.1)	—	
Unknown	5 (7.1)	2 (3.7)	—	
Duration of ADT (months)	25 ± 36	—	—	—
Previous prostatectomy, *n* (%)[a]	34 (48.6)	36 (69.2)	—	**0.022**
Previous radiotherapy, *n* (%)[a]	48 (68.6)	12 (23.1)	—	**<0.001**
Previous chemotherapy, *n* (%)[a]	11 (15.7)	0 (0.0)	—	**0.003**
Active surveillance, *n* (%)	—	8 (15.4)	—	—

Data are mean ± standard deviation and number (percentage). Bold = statistical significance.
*Co-morbidities included asthma/respiratory problems, chronic bronchitis, muscle/ligament problems, back pain, angina/stroke/heart condition, diabetes, hypertension, and hypercholesteromaemia.
[a]Men treated with ADT vs. PCa controls only.

healthy controls (21%). ADT-treated men reported a 9.8% lower dietary protein intake per kilogram of body weight compared with PCa controls ($P = 0.014$), but not healthy controls. When compared with PCa controls only, men treated with ADT were more likely to have been diagnosed with advanced PCa and previously undergone radiotherapy or chemotherapy, but less likely to have had a prostatectomy. No other significant differences were observed between groups for other demographic, diet, physical activity, or medical treatment outcomes (Table 1).

Lean and fat mass

There were no significant differences between the groups for absolute total body, appendicular, or leg lean mass nor ALMI, but ADT-treated men had 9.2% lower absolute arm lean mass compared with healthy controls ($P = 0.007$), but not PCa controls (Table 2). Men treated with ADT also had 4.4–6.4 kg ($P \leq 0.014$) and 3.8–5.4% ($P \leq 0.002$) greater total body fat mass compared with both controls. When adjusted for BMI, ADT-treated men had 9.4% and 7.8% lower ALM_{BMI} compared with PCa ($P < 0.001$) and healthy controls ($P = 0.002$), respectively. Additionally, when compared with PCa and healthy controls, men treated with ADT had 5.4% ($P < 0.001$) and 3.8% ($P = 0.001$) lower total body per cent lean mass, respectively.

Muscle cross-sectional area

Forearm muscle CSA was lower in ADT-treated men when compared with healthy controls (8.4%; $P = 0.003$), but no significant differences were observed between groups for lower leg muscle CSA (Table 2). However, when expressed as a per cent of total limb CSA, ADT-treated men had 5.2–6.0% ($P < 0.001$) lower forearm and 3.0–3.7% ($P \leq 0.031$) lower leg muscle CSA compared with both controls.

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Table 2 Mean total body and regional lean mass, muscle cross-sectional area, and total body fat mass in men with prostate cancer (PCa) treated with androgen deprivation therapy (ADT), PCa controls and healthy controls, and the mean difference between the three groups

	Unadjusted mean ± standard derivation				Unadjusted mean difference (95% confidence interval)		
	Men treated with ADT	PCa controls	Healthy controls	*P* value	Men treated with ADT vs. PCa controls	Men treated with ADT vs. healthy controls	PCa controls vs. healthy controls
Lean mass							
Total body (kg)	53.8 ± 6.5	54.8 ± 6.3	55.5 ± 6.4	0.263	−1.0 (−3.9, 1.8)	−1.8 (−4.4, 0.8)	−0.7 (−3.6, 2.1)
Total body (%)	62.2 ± 6.7	67.5 ± 6.0	65.9 ± 5.1	**<0.001**	**−5.4 (−8.0, −2.7)*****	**−3.8 (−6.2, −1.3)****	1.6 (−1.0, 4.2)
Arm (kg)	6.2 ± 1.1	6.7 ± 0.9	6.8 ± 1.0	**0.006**	−0.4 (−0.9, 0.0)	**−0.5 (−0.9, −0.1)****	−0.1 (−0.6, 0.3)
Leg (kg)	18.5 ± 2.6	18.6 ± 2.7	19.1 ± 2.6	0.362	−0.1 (−1.3, 1.1)	−0.6 (−1.7, 0.5)	−0.5 (−1.7, 0.7)
Appendicular (kg)	24.7 ± 3.5	25.3 ± 3.5	25.9 ± 3.5	0.164	−0.5 (−2.1, 1.0)	−1.1 (−2.6, 0.3)	−0.6 (−2.2, 0.9)
ALMI (kg/m^2)	8.07 ± 0.95	8.13 ± 0.86	8.36 ± 0.78	0.119	−0.07 (−0.45, 0.32)	−0.29 (−0.65, 0.06)	−0.23 (−0.61, 0.16)
ALM_{BMI}	0.875 ± 0.117	0.961 ± 0.128	0.946 ± 0.117	**<0.001**	**−0.086 (−0.139, −0.032)*****	**−0.071 (−0.120, −0.022)****	0.015 (−0.038, 0.068)
Muscle cross-sectional area							
Forearm (cm^2)	38.8 ± 5.8	41.3 ± 5.2	42.2 ± 6.0	**0.003**	−2.5 (−5.2, 0.1)	**−3.5 (−5.9, −1.0)****	−0.9 (−3.6, 1.8)
Forearm (%)	67.5 ± 6.1	73.5 ± 4.5	72.7 ± 4.8	**<0.001**	**−6.0 (−8.4, −3.5)*****	**−5.2 (−7.4, −2.9)*****	0.8 (−1.7, 3.3)
Lower leg (cm^2)	75.4 ± 11.7	73.5 ± 9.2	76.4 ± 12.1	0.403	1.8 (−3.3, 7.0)	−1.0 (−5.7, 3.7)	−2.9 (−8.0, 2.3)
Lower leg (%)	73.5 ± 6.8	76.4 ± 6.8	77.2 ± 6.3	**0.004**	**−3.0 (−6.0, −0.1)***	**−3.7 (−6.5, −1.0)****	−0.8 (−3.9, 2.4)
Fat mass							
Total body (kg)	30.5 ± 10.9	24.1 ± 8.6	26.1 ± 7.5	**<0.001**	**6.4 (2.4, 10.5)****	**4.4 (0.7, 8.2)***	−2.0 (−6.0, 2.0)
Total body (%)	35.3 ± 7.1	29.8 ± 6.4	31.5 ± 5.4	**<0.001**	**5.4 (2.6, 8.3)*****	**3.8 (1.2, 6.4)****	−1.7 (−4.5, 1.1)

Data are unadjusted mean ± standard deviation and unadjusted mean difference (95% confidence interval). ALM, appendicular lean mass; ALM_{BMI}, appendicular lean mass adjusted for body mass index; ALMI, appendicular lean mass index. Bold = statistical significance.
*$P < 0.05$.
**$P < 0.01$.
***$P < 0.001$.

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Muscle strength

Absolute handgrip muscle strength was 9.5–13% ($P \leq 0.016$) lower in ADT-treated men compared with both controls, whereas back (seated row) muscle strength was only lower in men treated with ADT compared with healthy controls (14%, $P = 0.001$; Table 3). ADT-treated men had similar absolute leg (leg press) and chest (chest press) muscle strength compared with both controls. However, when muscle strength was expressed per kilogram of body weight and compared with both controls, men treated with ADT had lower handgrip (15–17%; $P < 0.001$), chest (15%; $P \leq 0.009$), and back muscle strength (15–16%; $P < 0.001$). Body weight-adjusted leg muscle strength was also 15% lower ($P = 0.010$) in ADT-treated men compared with healthy controls, but not PCa controls.

Discussion

The main findings from this study were that absolute total body and ALM were not different between men with PCa treated with and without ADT and healthy controls, but after adjusting for greater adiposity in men treated with ADT, they were found to have 3.8–5.4% and 7.8–9.4% lower per cent total body lean mass and ALM_{BMI}, respectively. Similarly, there were limited differences in absolute appendicular muscle CSA and muscle strength, but after accounting for differences in adiposity or body size, men treated with ADT had 3.0–6.0% and 15–17% lower per cent muscle CSA and body weight-adjusted muscle strength, respectively. Collectively, these findings suggest that it is important to account for adiposity when examining muscle health in men treated ADT for PCa.

Several previous cross-sectional studies have shown total body fat mass to be greater in men treated with ADT when compared with non-treated PCa men (mean difference, 3.9 kg)[10] and healthy controls (mean difference, 5.7–5.8 kg).[9,10] Consistent with these findings, we found that men treated with ADT had greater total body fat mass compared with PCa controls (6.4 kg) and healthy controls (4.4 kg). Similarly, total body per cent fat mass has been reported to be 3.9–6.0%[10,11,26,27] and 2.9–9.8%[9–11,26–28] greater in ADT-treated men when compared with PCa and healthy controls, respectively. Interestingly, in a sample of 1129 healthy older men (mean age, 74 years), Koster *et al.*[14] observed that leg lean mass was 1.3 kg greater per standard deviation increment (7.0 kg) of total body fat mass, suggesting that men with greater adiposity have increased lean mass.[14] Consistent with these findings, there is evidence from one cross-sectional study that showed obese older men (mean BMI, 31.9 kg/m^2; mean age, 66 years) had 18%, 26%, and 14% higher absolute lean mass in the trunk, android, and gynoid

Table 3 Mean muscle strength outcomes in men with prostate cancer (PCa) treated with androgen deprivation therapy (ADT), PCa controls and healthy controls, and the mean differences between the three groups

	Unadjusted mean ± standard derivation				Unadjusted mean difference (95% confidence interval)		
	Men treated with ADT	PCa controls	Healthy controls	*P* value	Men treated with ADT vs. PCa controls	Men treated with ADT vs. healthy controls	PCa controls vs. healthy controls
Muscle strength							
Handgrip (kg)	37.9 ± 6.5	41.7 ± 6.7	43.3 ± 8.0	**<0.001**	**−3.8 (−7.0, −0.5)***	**−5.4 (−8.4, −2.4)*****	−1.6 (−4.8, 1.6)
Handgrip/weight (kg/kg)	0.44 ± 0.11	0.52 ± 0.10	0.51 ± 0.09	**<0.001**	**−0.08 (−0.12, −0.03)*****	**−0.07 (−0.12, −0.03)*****	0.002 (−0.04, 0.47)
Chest (kg)	38.2 ± 10.3	40.2 ± 6.6	42.6 ± 11.2	0.073	−2.1 (−7.1, 3.0)	−4.4 (−9.0, 0.2)	−2.4 (−7.4, 2.7)
Chest/weight (kg/kg)	0.44 ± 0.11	0.51 ± 0.11	0.51 ± 0.12	**0.002**	**−0.07 (−0.13, −0.01)****	**−0.07 (−0.12, −0.01)****	0.004 (−0.06, 0.06)
Leg (kg)	139.7 ± 46.9	143.4 ± 42.0	160.2 ± 49.5	**0.049**	−3.8 (−26.8, 19.3)	−20.6 (−41.5, 0.4)	−16.8 (−40.2, 6.6)
Leg/weight (kg/kg)	1.61 ± 0.49	1.80 ± 0.48	1.88 ± 0.51	**0.010**	−0.19 (−0.44, 0.05)	**−0.28 (−0.50, −0.05)***	−0.08 (−0.33, 0.17)
Back (kg)	48.7 ± 11.3	52.1 ± 9.5	56.2 ± 11.2	**0.002**	−3.4 (−8.9, 2.1)	**−7.5 (−12.5, −2.5)****	−4.1 (−9.6, 1.4)
Back/weight (kg/kg)	0.56 ± 0.12	0.65 ± 0.10	0.66 ± 0.10	**<0.001**	**−0.10 (−0.15, −0.04)*****	**−0.11 (−0.16, −0.06)*****	−0.01 (−0.07, 0.04)

Data are unadjusted mean ± standard deviation and unadjusted mean difference (95% confidence interval). 3-RM, three-repetition maximum. Bold = statistical significance.
*$P < 0.05$.
**$P < 0.01$.
***$P < 0.001$.

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regions, respectively, than age-matched healthy weight men (mean BMI, 23.4 kg/m^2).[15] Considering these findings, and the observation of greater amounts of fat mass in the ADT-treated men in our study compared with both controls, there is a need to adjust muscle outcomes for adiposity in this cohort of men to gain a greater understanding of potentially masked treatment-related adverse effects.

To date, there have been several methods proposed to adjust lean mass for adiposity and/or body size, including ALM_{BMI} and ALMI.[16–18] When ALM was adjusted for BMI in our study, we found that men treated with ADT had 7.8–9.4% lower ALM_{BMI} than both controls. In contrast, no difference was observed between groups for ALMI, which adjusts for height squared as an index of body size. To our knowledge, only one other study in men treated with ADT examined ALMI and observed that 30 ADT-treated men (mean age, 72 years) and 25 age-matched non-ADT hypogonadal controls had similar results (mean, both 7.5 kg/m^2). These findings in hypogonadal men (regardless of whether induced by ADT or not) were of a similar magnitude to the mean ALMI in our study (mean, 8.07 kg/m^2). However, to our knowledge, adiposity-based adjustments are yet to be applied in men treated with ADT when compared with controls, but some studies have considered adjustment for body size (e.g. total body per cent lean mass). For instance, Clay *et al*.[26] reported that 42 men treated with chronic ADT (greater than 6 months; mean age, 73 years) had 4.4% and 4.5% lower total body per cent lean mass compared with PCa and healthy controls, respectively. Similarly, a cohort of 29 chronic ADT-treated men (greater than 6 months; mean age, 73) were shown to have 3.9% and 5.4% less total body per cent lean mass when compared with PCa and healthy controls, respectively.[27] When we expressed total body lean mass as a percentage of total body weight, men treated with ADT had 4.8–5.4% less total body per cent lean mass when compared with controls. Our findings that adiposity-adjusted total body and regional lean mass were required to detect differences between groups support the use of these adjustments when considering these men and their susceptibility to treatment-induced increases in adiposity.

Another novel aspect of this cross-sectional study was the assessment of forearm and lower leg muscle CSA assessed via pQCT, which is important as this technique can provide an accurate measure of muscle size.[29] However, consistent with the absolute lean mass DXA findings, minimal difference was observed between the three groups for absolute muscle CSA at either the forearm or lower leg. Whilst no previous studies have assessed the effects of ADT on pQCT-derived muscle CSA at these sites, several prospective studies examining absolute muscle CSA at different sites (i.e. paraspinal, quadriceps, rectus femoris, and sartorius) observed decrements of 3.2–5.5% in paraspinal muscles and 15–22% in muscles of the upper leg over 15–48 weeks of therapy.[30–32] Unfortunately, these studies did not include comparison control groups and did not account for known confounding variables, such as physical activity and diet.[30–32] A noteworthy observation in our study was that when muscle CSA was expressed as a percentage of total arm or leg area, men treated with ADT had 3.0–6.0% lower muscle CSA than controls at both sites. This suggests that relative to body size, men treated with ADT have smaller forearm and lower leg muscle size, which adds further support to our findings that it is important to account for any adiposity (or size) when evaluating body composition (muscle) in ADT-treated men.

As with muscle mass, there is some evidence that increased adiposity has been associated with greater muscle strength in healthy older men,[14] and thus, muscle strength is often normalized to body weight (e.g. expressed as strength per kilogram of body weight). In our study, when measures of muscle strength were expressed relative to weight, we found that men treated with ADT had lower handgrip (15–17%), chest (15%), and back (15–16%) muscle strength compared with both controls. Moreover, ADT-treated men had 15% lower leg muscle strength per kilogram of body weight compared with healthy controls, but not PCa controls. These findings suggest that treatment with ADT may have systemic effects on muscle strength when normalized to body weight. Whilst our study is the first to report muscle strength per kilogram of body weight in men treated with ADT, similar adjustments were applied in a sample of 1129 men aged 70–79 years after it was observed that for every standard deviation increase in fat mass (approximately 7.1 kg), leg muscle strength was 3.0–4.7 Nm greater.[14] Additionally, leg muscle strength per kilogram of body weight was 0.6–0.9 Nm/kg lower per standard deviation increase in fat mass.[14] This suggests that despite having greater absolute leg muscle strength, relative to body weight, men with greater body size were weaker. Potential reasons for these observations may include the accumulation of fat around and/or within muscle tissue or potential neurological changes associated with ADT-induced hypogonadism. Indeed, in healthy older men, there is evidence that an increase in skeletal muscle fat infiltration is associated with lower muscle strength.[33] It has also been reported that age-related losses in muscle strength were only weakly associated with changes in muscle CSA.[34] This may be related to various age-related neurological changes, including a decrease in the number of functional motor units and the rate in which these can be maximally discharged, as well as a reduction in spinal excitability.[35] Previous research has reported that androgens, such as testosterone, can enhance neural excitability[36,37]; thus, hypogonadism may impair neural function in men treated with ADT that may influence muscle strength. Therefore, despite men with ADT having similar absolute muscle strength values compared with PCa and healthy controls, men treated with ADT appear to possess compromised weight-adjusted muscle strength, with these deleterious effects potentially extending beyond a loss of lean mass and/or muscle CSA alone.

A strength of this study is inclusion of both PCa and healthy controls that allowed for the effects of ADT to be quantified independent of PCa diagnosis, non-hormonal PCa treatment, and ageing. Moreover, this study used robust measures of lean and fat mass via DXA and muscle CSA via pQCT; of which the latter provided the first known measurements of the forearm and lower leg in men treated with ADT compared with both PCa and healthy controls. However, several limitations also need to be considered when interpreting results. First, volunteer bias may have yielded results that were not representative of the broader population. Men treated with ADT in this analysis were involved in a larger RCT; all agreed to be allocated to a 52 week exercise training and nutritional supplementation intervention, which may have limited the study sample to only those capable and willing to complete such an intervention; therefore, participants may have been healthier than the average man treated with ADT. Conversely, PCa and healthy controls were recruited for a single visit promoted as a 'free health assessment', thus potentially increasing the likelihood that those with pre-existing medical conditions or concerns would volunteer; hence, these individuals may have had compromised health when compared with the general population. Second, the cross-sectional design of the current study precludes inference of causality and in particular the potential that reverse casualty was observed cannot be excluded (e.g. increased fat mass may have led to PCa progression and thus the need for ADT).[38] Third, the modest sample size in comparison with the previous population-based studies, as well as the large heterogeneity in the duration of treatment among ADT-treated men in the current study, should be considered when interpreting these data. Notably, an exploratory multivariate analysis revealed ADT duration (independent of age, disease severity, BMI, protein intake, previous chemotherapy, and previous radiotherapy) was not associated with outcomes of absolute lean mass or muscle strength. Finally, although applied in previous studies to account for the confounding role of adiposity, there are limited long-term prospective studies that have established the ability of adiposity-adjusted muscle outcomes to predict risk in older men, particularly in men treated with ADT, and thus the inference of risk associated with these outcomes should be made with caution and therefore warrants further research of a prospective design.

Conclusion

The main finding from this study was that men treated with ADT had greater fat mass and compromised total and ALM, muscle CSA, and muscle strength compared with non-ADT-treated men with PCa and healthy controls after accounting for their increased adiposity. On this basis, we suggest that adiposity-based adjustments be considered when assessing muscle-related outcomes in men treated with ADT.

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Conflict of interest

The authors declare no conflicts.

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