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ORIGINAL RESEARCH

Does Use of Androgen Deprivation Therapy (ADT) in Men with Prostate Cancer Increase the Risk of Sarcopenia?

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Abstract

Androgen deprivation therapy (ADT) for prostate cancer (PCa) can compromise muscle health. Hence, we aimed to quantify the prevalence of sarcopenia (i.e., compromised lean mass, muscle strength, and physical function) in ADT-treated (> 12 week) men ($n = 70$) compared to similarly aged non-ADT-treated PCa ($n = 52$) and healthy controls ($n = 70$). Lean and fat mass were quantified by dual-energy X-ray absorptiometry. Muscle strength and function were measured using handgrip dynamometry and gait speed, respectively. Sarcopenia was defined as low adjusted appendicular lean mass [ALM; height-adjusted (ALMI), body mass index-adjusted (ALM_{BMI}) and height and fat mass-adjusted (ALM_{HFM})] with weak handgrip strength and/or slow gait speed according to the following criteria: European Working Group on Sarcopenia in Older People [EWGSOP; both 2010 (EWGSOP1) and 2018 (EWGSOP2)], Foundation for the National Institutes of Health (FNIH) and International Working Group on Sarcopenia (IWGS). Overall the prevalence of sarcopenia was low and did not differ between the three groups. Only two (3.2%) ADT-treated men presented with sarcopenia as per EWGSOP1 and FNIH criteria, whereas no cases were observed using EWGSOP2 and IWGS criteria. The prevalence of low ALM_{BMI} was greater in ADT-treated men (32%) compared to PCa (15%; $P = 0.037$) and healthy controls (7.1%; $P < 0.001$). Similarly, low ALM_{HFM} was greater in ADT-treated men (29%) compared to healthy controls only (13%; $P = 0.019$). There was also a low prevalence of weak muscle strength and slow gait speed (0.0–11%) in all men, with no differences between the groups. Based on these findings, an adiposity-based adjustment of ALM is recommended to quantify risk of adverse outcomes associated with ADT in these men.

Keywords Atrophy · Prostatic neoplasms · Body composition · Muscle · Adiposity

Introduction

Prostate cancer (PCa) remains one of the most commonly diagnosed male cancers in developed nations, including Australia [1, 2]. In addition to cancer-related mortality [1], the diagnosis and treatment of PCa may predispose men to a myriad of comorbidities. Androgen deprivation therapy (ADT), and the associated hypogonadism, is one treatment that may result in compromised outcomes of muscle and fat [3, 4]. Given that older men with low lean mass (e.g.,

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two standard deviation (SD) below normative values) are twice as likely to develop insulin resistance and have a six-fold greater risk of mobility limitations during activities of daily living [5, 6], detecting those in need of appropriate strategies (e.g., exercise training and diet [3]) for reducing the risk of ADT-induced adverse effects on muscle health is of clinical relevance. To date, attempts to quantify ADT-treated men at risk of these complications have primarily relied upon singular outcomes of lean mass or muscle strength alone, which are limited given the somewhat inconsistent findings between studies. For example, one study observed total body lean mass to be approximately 3.8 kg lower in 67 ADT-treated men (mean age, 71 years) compared to both healthy and PCa controls [7], whereas another observed no difference between men treated with ADT (mean age, 70 years) and referents [8]. Moreover, muscle strength assessed by handgrip dynamometry was shown to be similar [9] or 29% lower [10] in ADT-treated men compared to age-matched healthy controls. Given the potential limitations of single-measure approaches, risk stratification in this clinical population group may benefit from the application of composite measures of muscle mass, strength, and function, which collectively represent the muscle disease sarcopenia.

Sarcopenia was initially defined as the loss of muscle (lean) mass associated with ageing [11], but now includes measures of muscle strength and/or functional capacity, most commonly assessed via handgrip dynamometry and gait speed, respectively [12–15]. A recent meta-analysis showed that the worldwide prevalence of sarcopenia, based on definitions that included concurrently compromised dual-energy X-ray absorptiometry (DXA) assessed appendicular lean mass (ALM) with either weak muscle strength or poor physical function, was 8.0% in men aged ≥ 60 years [16]. However, there is ongoing debate surrounding the clinical criteria and cut-offs for diagnosing sarcopenia and thus no consensus definition exists. Notable definitions include those proposed by the 2010 and 2018 European Working Group on Sarcopenia in Older People (EWGSOP; low muscle strength, muscle quantity/quality [e.g., ALM adjusted for height (ALMI)] and physical performance [13, 14]), Foundation for the National Institutes of Health (FNIH; low ALM adjusted for body mass index [BMI; ALM_{BMI}] and low handgrip strength [12]) and the International Working Group on Sarcopenia (IWGS; low ALMI and slow gait speed) [15]. Indeed, non-ADT-treated men diagnosed with sarcopenia have been shown to be at greater risk of falls [17–19], fractures [17, 20, 21], functional impairment [5, 17, 22–24], and mortality [17, 22, 25, 26]. However, no studies have investigated the prevalence of sarcopenia in men with PCa treated with ADT. Therefore, the aim of this study was to compare the prevalence of sarcopenia in men with PCa treated with ADT when compared to non-ADT-treated PCa controls and healthy controls.

Methods

Participants

This cross-sectional study was conducted parallel to baseline of a randomised controlled trial [27–29] and included 70 men treated with pharmacological (surgical orchiectomy excluded) ADT (with or without prior chemotherapy) for PCa, 52 PCa controls (diagnosed and/or treated with non-ADT therapies currently or previously) and 70 healthy controls (not diagnosed with PCa). 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(s) known to affect bone, muscle, calcium or vitamin D metabolism (other than ADT-induced hypogonadism), were currently receiving pharmacological intervention known to affect bone or muscle metabolism (other than ADT), had supplemented with protein, calcium (> 600 mg/day) or vitamin D (> 1000 IU/day) in the past 3 months, had undertaken progressive resistance training (> 1 session/week) or regular weight-bearing impact exercise (> 150 min/week) in the past 3 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 [30]. Only those treated with pharmacological ADT for greater than 12 weeks at enrolment were included.

ADT-treated men were recruited via clinician referral and private urology practices, as well as from PCa support groups and state/local newspaper advertisements. PCa and healthy controls were also recruited from PCa support groups and advertisements in state/local newspapers.

Measurements

Lean and Fat Mass

Total and regional lean and fat mass (kg) and total body percent fat mass (%) were assessed by DXA and analysed using software version 12.30.008 (Lunar iDXA, GE Lunar Corp., Madison, USA). Patient positioning and manual segmentation using custom regions of interest followed previously established protocols [31]. All imaging analyses were conducted blinded to group allocation. ALM was calculated as the aggregate of lean mass in both arms (kg) plus both legs (kg). ALMI was calculated as ALM (kg) divided by height (m) squared. ALM_{BMI} was calculated as ALM (kg) divided by BMI (kg/m^2). ALM adjusted for height and fat

mass (ALM_{HFM}) was calculated using an established regression equation method [32] adapted to the current study sample ($ALM_{HFM} = -34.35 + 31.83 \times$ height [m] $+ 0.14 \times$ total body fat mass [kg]). Short-term coefficient of variation (CV) for repeated measures of total body lean and fat mass were 1.0–1.7% in our laboratory.

Handgrip Strength

Handgrip strength (kg) was assessed using a digital handheld dynamometer (Jamar Plus Digital, Lafayette Instrument Company, Lafayette IN, United States of America [33]). Participants were seated with their forearm resting on the arm of the chair whilst maintaining a 90° angle at the elbow joint. Participants were asked to squeeze the dynamometer with maximal effort. Six trials were completed (three with each hand, alternating between hands). The highest single score of the six trials was recorded as the outcome. A CV of 6.3% was previously reported for this method in an advanced cancer population group [34].

Gait Speed

The four metre usual walk test was used to measure gait speed [35]. Participants were instructed to walk at their usual pace between two cones eight metres apart (2 m acceleration zone, 4 m timed zone, and 2 m deceleration zone). The time (to the nearest millisecond) to complete the timed zone was recorded with a stopwatch with the results expressed as meters per second (m/s). Three trials were completed, with the fastest single gait speed recorded as the outcome. This method had an ICC of 0.96 within our laboratory when compared to timing gates. Short-distance gait speed tests were shown to have a CV of 6.7% in a cohort of ADT-treated men [36].

Sarcopenia

Low ALM was defined as low adjusted ALM alone based on established criteria derived from previous studies, as well as an adapted ALM_{HFM} cut-off of ≤ -1.816 which identified those in the current study sample within the lowest 20th percentile (Table 1). Sarcopenia was defined by both low ALM and weak handgrip strength (muscle weakness) and/or slow gait speed (functional impairment) based on established definitions by EWGSOP1 (2010) [13], EWGSOP2 (2018) [14], FNIH [12], and IWGS [15] (Table 1).

Statistical Analysis

All analyses were performed using SPSS 25.0 (IBM Corp, Chicago IL, United States of America). Between-group comparisons were assessed by analyses of variance (ANOVA) or Chi-square tests. Post-hoc analyses applied the Bonferroni correction. Continuous data were reported as mean ± SD, whereas categorical variables were reported as frequency and percentage, unless stated otherwise. A significance level of $P < 0.05$ was adopted for all statistical tests.

Table 1 Definitions of sarcopenia and its components

	Lean mass (kg/m^2)	Handgrip strength (kg)	Gait speed (m/s)
EWGSOP1 [13]	ALMI ≤ 7.26	< 30	< 0.8
EWGSOP2 [14]	ALMI ≤ 7.0	< 20	< 0.8
IWGS [15]	ALMI ≤ 7.23	–	< 1.0
FNIH [12]	$ALM_{BMI} \leq 0.789$	< 26	–
Residual method[a] [32]	$ALM_{HFM} \leq -1.816$	–	–

ALM_{BMI} appendicular lean mass adjusted for body mass index, *ALM_{HFM}* appendicular lean mass adjusted for height and fat mass, *ALMI* appendicular lean mass index, *EWGSOP* European Working Group on Sarcopenia in Older People, *FNIH* Foundation for the National Institutes of Health, *IWGS* International Working Group on Sarcopenia

[a]Adjusted for current study sample

Results

Participant Characteristics

The characteristics of the participants are shown in Table 2. Age, height, and weight were similar between the three groups, but BMI was significantly 2.2 and 1.3 kg/m^2 higher in ADT-treated men than PCa and healthy controls, respectively. For ADT-treated men, the median (interquartile range) for ADT duration was 12 (20) months.

Prevalence of Sarcopenia

Overall, only two participants (1.0%) in the total sample were classified as having sarcopenia according to the FNIH definition, both of which were men treated with ADT (Table 3). When using the EWGSOP1 definition, a total of 4 (2.1%) men (2 men treated with ADT, 1 PCa control and 1 healthy control) were classified as having sarcopenia. No men were identified as sarcopenic using the EWGSOP2 or IWGS definition.

Low ALM

The prevalence of low ALM was significantly greater in ADT-treated men (32%) compared to PCa (15%) and

Table 2 Participant characteristics of men treated with androgen deprivation therapy (ADT) for prostate cancer (PCa), PCa controls (PCON) and healthy controls (HCON)

	ADT ($n=70$)	PCON ($n=52$)	HCON ($n=70$)	P value
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**
Physical activity (kJ/d)	2634 (1706)	3199 (1960)	3016 (1698)	0.192
Comorbidities, n (%)[b]	62 (88.6)	42 (80.8)	61 (87.1)	0.441
If yes, total (n)	3 (1)	2 (1)	2 (1)	0.372
Stage of PCa, n (%)[a]				
Localised/removed	45 (64.3)	6 (11.1)	–	**< 0.001**
Advanced	5 (7.1)	2 (3.7)	–	
Unknown	20 (28.6)	44 (84.6)	–	
Duration of ADT (months)	25 (36)	–	–	–
Type of ADT				
Goserelin	40 (57.1)	–	–	–
Leuprorelin	14 (20)	–	–	–
Goserelin and bicalutamide	5 (7.1)	–	–	–
Leuprorelin and bicalutamide	3 (4.3)	–	–	–
Triptorelin	3 (4.3)	–	–	–
Degarelix	2 (2.9)	–	–	–
Abiraterone	1 (1.4)	–	–	–
Degarelix and bicalutamide	1 (1.4)	–	–	–
Enzalutamide	1 (1.4)	–	–	–
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)	–	–
ALMI (kg/m^2)	8.07 (0.95)	8.13 (0.86)	8.36 (0.78)	0.119
ALM_{BMI}	0.875 (0.117)	0.961 (0.128)	0.946 (0.117)	**< 0.001**
Handgrip (kg)	37.9 (6.5)	41.7 (6.7)	43.3 (8.0)	**< 0.001**
Gait speed (m/s)	1.43 (0.20)	1.48 (0.19)	1.50 (0.22)	0.094

Bold values indicate statistical significance

Data are mean (standard deviation) and number (percentage)

[a]Men treated with ADT versus PCa controls only

[b]Comorbidities included asthma/respiratory problems, chronic bronchitis, muscle/ligament problems, back pain, angina/stroke/heart condition, diabetes, hypertension and hypercholesteromaemia

healthy controls (7.0%) for ALM_{BMI} (both $P < 0.05$). ADT-treated men also had a higher prevalence of low ALM_{HFM} compared to healthy controls (29% vs 13%, $P < 0.05$; Table 3; Fig. 1). No between-group differences were observed for various cut-offs of ALMI.

Muscle Weakness and Slow Gait Speed

No significant between-group differences were noted for the prevalence of muscle weakness or slow gait speed using established cut-offs (Table 3). Among the three groups, the handgrip strength cut-offs of < 30 kg (EWGSOP1) and < 26 kg (FNIH) only identified 11 and four men with muscle weakness, respectively. In contrast, the cut-off of < 20 kg (EWGSOP2) failed to identify any men across the total sample. Measures of gait speed were also limited in their ability to classify men as functionally impaired, with only two cases observed among the total sample, regardless of cut-offs considered (both ADT-treated men).

Table 3 Group prevalence and between-group differences in sarcopenia and its components in men with prostate cancer treated with androgen deprivation therapy (ADT), prostate cancer controls (PCON) and healthy controls (HCON)

	ADT ($n=70$)	PCON ($n=52$)	HCON ($n=70$)	*P* value	*P* value		
					ADT versus PCON	ADT versus HCON	PCON versus HCON
EWGSOP1	2 (3.2)	1 (1.9)	1 (1.4)	0.771	0.665	0.489	0.832
ALMI, ≤ 7.26 kg/m^2	9 (13.0)	6 (11.5)	6 (8.6)	0.694	0.804	0.396	0.586
Handgrip strength < 30 kg	7 (11.3)	2 (3.8)	2 (2.9)	0.093	0.142	0.055	0.762
Gait speed < 0.8 m/s (also EWGSOP2)	1 (1.6)	0 (0.0)	0 (0.0)	0.378	0.362	0.290	–
EWGSOP2	0 (0.0)	0 (0.0)	0 (0.0)	–	–	–	–
ALMI, ≤ 7.00 kg/m^2	6 (8.6)	3 (5.8)	3 (4.3)	0.570	0.558	0.301	0.708
Handgrip strength < 20 kg	0 (0.0)	0 (0.0)	0 (0.0)	–	–	–	–
IWGS	0 (0.0)	0 (0.0)	0 (0.0)	–	–	–	–
ALMI, ≤ 7.23 kg/m^2	9 (13.0)	6 (11.5)	6 (8.6)	0.694	0.804	0.396	0.586
Gait speed < 1.0 m/s	2 (3.2)	0 (0.0)	0 (0.0)	0.141	0.195	0.133	–
FNIH	2 (3.2)	0 (0.0)	0 (0.0)	0.137	0.191	0.130	–
ALM_{BMI}, < 0.789	22 (31.9)	8 (15.4)	5 (7.1)	**0.001**	**0.037**	**< 0.001**	0.145
Handgrip strength < 26 kg	3 (4.8)	0 (0.0)	1 (1.4)	0.182	0.108	0.254	0.387
Residual method[a]							
ALM_{HFM}, ≤ − 1.816	20 (29.0)	9 (17.3)	9 (12.9)	**0.049**	0.136	**0.019**	0.493

Bold values indicate statistical significance

Data are number of cases (percentage)

ALM_{BMI} appendicular lean mass adjusted for body mass index, ALM_{HFM} residual of appendicular lean mass adjusted for height and fat mass, *ALMI* appendicular lean mass index, *BMI* body mass index, *EWGSOP* European Working Group on Sarcopenia in Older People (EWGSOP1, 2010 criteria; EWGSOP2, 2018 criteria), *FM%* total body percent fat mass, *FNIH* Foundation for the National Institutes of Health, *IWGS* International Working Group on Sarcopenia

[a]Adjusted for the current study sample

Discussion

The main finding from this study was that the prevalence of sarcopenia was low (0–2%) according to current definitions in men with PCa treated with or without ADT and healthy controls. However, we found that the prevalence of low ALM_{BMI} was significantly greater in ADT-treated men (32%) compared to PCa (15%) and healthy controls (7.1%). Similarly, the prevalence of low ALM_{HFM} was greater in men treated with ADT (29%) compared to healthy controls only (13%), but ALM adjusted for height (ALMI) did not differ between groups. This suggests that it is important to account for adiposity when evaluating ALM in this cohort. Finally, the prevalence of weak muscle strength and slow gait speed was low in all men (0.0–11% depending on the different cut-offs) and did not differ significantly compared to controls. Collectively, these findings suggest that ADT adversely effects appendicular lean mass when adjusting for adiposity, but not muscle strength or function.

Globally sarcopenia is now recognised as a clinical disease characterised by varying combinations of slow gait speed, weak muscle strength and low ALM [12–15]. Although there remains a lack of consensus internationally with regard to the precise clinical cut-offs for each of these measures, based on the most widely adopted criteria we found that the prevalence of sarcopenia in our cohort of ADT men and controls was 0.0% using the IWGS or EWGSOP2 definitions, 1.4–3.2% for the EWGSOP1 and 0.0–3.2% for the FNIH definitions. To our knowledge, no previous studies in men with PCa treated with ADT have evaluated the prevalence of sarcopenia (defined as concurrently low ALM with low muscle strength or slow gait speed). However, when considering the EWGSOP1 definition [13] in cohorts of community-dwelling older men (mean age range, 67–86 years; sample size range, 66–568 older men) the prevalence of sarcopenia varied from 2.6 to 27% [25, 37–43]. Of those that utilised DXA to quantify ALM, to overcome limitations associated with less robust measures such as bioelectrical impedance and mid-arm circumference, the prevalence of sarcopenia was 4.6–11% [38, 40]. The low prevalence of sarcopenia in our study compared to previous cohorts of healthy older men could be partially attributed to selection bias, that is, the ADT-treated men included in our study were recruited on the basis of involvement in an exercise training trial. Thus, it is possible that they were healthier as men with absolute contraindications to exercise

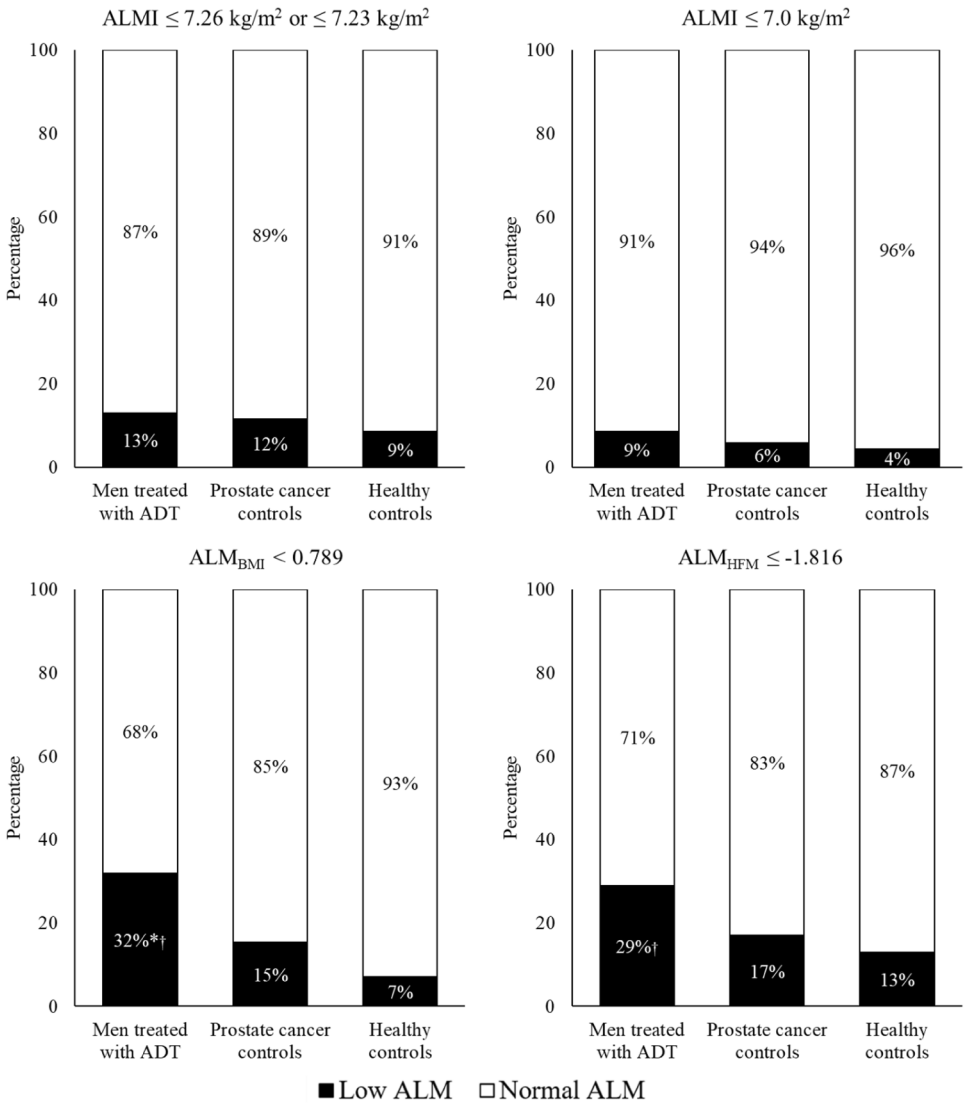

Fig. 1 Prevalence (percentage) of low appendicular lean mass (ALM) according to established (European Working Group on Sarcopenia in Older People 2010 and 2018, Foundation for the National Institutes of Health and International Working Group on Sarcopenia) and adapted criteria in men with prostate cancer (PCa) treated with androgen deprivation therapy (ADT), PCa controls and healthy controls; *$P < 0.05$ compared to PCa controls; †$P < 0.05$ compared to healthy controls

were excluded from participation. This notion is supported by the lack of difference between the three groups in terms of the total number of comorbidities. Moreover, ADT-treated men in our study participated in similar amounts of physical activity compared to controls, which conflicts previous findings that showed a 72-min per week reduction in a cohort of 59 older men (mean age, 65 years) recently diagnosed with PCa [44].

In addition to examining the prevalence of sarcopenia in men with PCa treated with ADT in our study, we also examined whether there were any between-group differences for each of the individual sarcopenia components. For ALM alone, we found that a significantly higher proportion of men treated with ADT had low ALM adjusted for adiposity (ALM_{BMI} and ALM_{HFM}), but not ALM adjusted for height (ALMI), when compared to controls. Discrepancies in the prevalence of sarcopenia between definitions were also shown in a cohort of 1435 healthy older men (mean age, 74 years), with 8.9% of overweight (BMI, 25–29 kg/m^2) and 0.0% of obese (BMI ≥ 30 kg/m^2) men diagnosed with low ALMI (< 7.23 kg/m^2), compared to 15% and 12% of overweight and obese men, respectively, when the residual method of ALM_{HFM} was applied [32]. Similarly, in a cohort of 7113 older men aged 65 years or greater, only 1.4% of obese men (BMI ≥ 30 kg/m^2) were shown to have low ALMI (< 7.23 kg/m^2), whereas 40% of obese men had low ALM_{BMI} (< 0.789) [45]. Collectively, these findings support that the prevalence of low ALM is markedly increased in cohorts with excess fat mass, such as men treated with ADT in our study, after accounting for adiposity, but not height alone (i.e., ALMI). Therefore, the adiposity-adjusted definitions and cut-offs for low ALM, such as ALM_{BMI} and ALM_{HFM}, may have increased sensitivity to identify ADT-treated men with low ALM, which may otherwise be undetected due to the concurrent accumulation of adiposity associated during therapy.

Regardless of cut-off for low handgrip strength, we observed no difference between the three groups, with 11% of ADT-treated men observed to have low handgrip strength based on the EWGSOP1 (< 30 kg) criteria [13] and no men with low values using the EWGSOP2 (< 20 kg) criteria [14]. To our knowledge, these cut-offs have not been applied in men treated with ADT; however, the < 30 kg cut-off was shown to identify 8.0% of 5934 healthy older men aged 65 years or older [17]. In contrast, the prevalence of low handgrip strength using the same cut-off was 18% among 611 healthy Australian men aged 65 years or greater [46]. Therefore, our findings appear to suggest that men treated with ADT do not have compromised handgrip strength. Potential reasons may include the relationship between adiposity and muscle, whereby the increased fat mass may serve as greater resistance during activities of daily living, such as locomotion, which results in increased lean mass and subsequently greater muscle strength [47]. As part of the FNIH sarcopenia project, the authors evaluated the clinical relevance of different grip strength cut-offs that included an alternative definition utilising low grip strength divided by BMI defined as < 1.002 kg/kg/m^2 for men [48]. Although they found that grip strength alone was a better predictor of mobility impairment in men, 16% of ADT-treated men in the current study were below this cut-off, compared to 3.8% and 1.4% of PCa and healthy controls, respectively. This suggests that adiposity-adjusted cut-offs should also be considered for muscle strength outcomes in this susceptible population group.

Among ADT-treated men, only one (1.6%) and two (3.2%) cases of slow gait speed were observed using the cut-offs of 0.8 [13, 14] and 1.0 m/s [15], respectively. Conversely, in a sample of 5934 healthy older men aged 65 years or older, slow gait speed using cut-offs of 0.8 and 1.0 m/s identified 4.4% and 17%, respectively [17]. Moreover, when these data were pooled into a sample of 11,427 older men (mean age, 82 years) across nine total studies, 10% and 29% had slow gait speed as determined by the cut-offs of 0.8 and 1.0 m/s, respectively. Hence, our observations suggest that gait speed is not impaired in men treated with ADT. Notably, the most recently proposed operational definition of sarcopenia (EWGSOP2 [14]) suggests gait speed should be used for quantifying the severity of diagnosed sarcopenia; thus, our findings also support the notion that the identification of severe sarcopenia may be limited in ADT-treated men.

There are a number of limitations of this study that should be considered when interpreting the results. First, recruitment bias may have also influenced participation of healthy controls in addition to the ADT-treated men, given the former were recruited as part of a single visit promoted as a health assessment, which may have prompted those with health concerns to participate (supported in part by a similar prevalence of total number of comorbidities compared to the two groups diagnosed and treated for PCa). Second, the sarcopenia cut-offs utilised within our study were based on those previously developed in cohorts that likely differ demographically from our own study sample. To overcome this limitation, we adapted the residual methods to our own cohort, although these values should be interpreted with caution given their novelty and that previous epidemiological research has primarily utilised established cut-offs to determine the associated risk of further adverse outcomes pertaining to compromised muscle health. Finally, these results should be interpreted with caution given the heterogeneity in the duration of ADT. Although an exploratory multivariate analysis showed that ADT duration, independent of age, disease severity, BMI, protein intake, previous chemotherapy and previous radiotherapy, was not associated with outcomes of muscle mass and strength.

In men with PCa treated with or without ADT and healthy controls, the prevalence of sarcopenia based on current definitions that included composite measures of ALM, handgrip strength and/or gait speed was non-existent to low. Further investigation into each of the individual sarcopenia components revealed that the prevalence of low muscle strength and slow gait speed was not compromised in ADT-treated men compared to controls. In contrast, the prevalence of low adiposity-adjusted ALM, but not height-adjusted ALM, was markedly increased in ADT-treated men. Based on these findings, we recommend that adiposity-based adjustments of ALM should be considered when attempting to quantify the risk of adverse muscle-based outcomes associated with ADT in this susceptible population group.

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Compliance with Ethical Standards

Conflict of interest Patrick Owen, Robin Daly, Jack Dalla Via, Niamh Mundell, Patricia Livingston, Timo Rantalainen, and Steve Fraser declare that they have no conflict of interest.

Human and Animal Rights and Informed Consent The study was ethically approved by the human research ethic committees at Deakin University (HREC: 2013-184), Alfred Health (Project No: 455/15) 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.

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