Full Length Article

Bone mineral density, structure, distribution and strength in men with prostate cancer treated with androgen deprivation therapy

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ABSTRACT

Androgen deprivation therapy (ADT) improves survival in men with advanced prostate cancer (PCa), but has been associated with compromised skeletal health and increased fracture risk. However, limited previous research has investigated determinants of bone strength beyond DXA-derived areal bone mineral density (aBMD) in this population group. The aim of this cross-sectional study was to investigate the effects of ADT in men with PCa on BMD, bone structure, estimates of whole bone strength and cortical bone distribution. A total of 70 ADT-treated men, 52 PCa controls and 70 healthy controls had DXA lumbar spine and proximal femur aBMD and pQCT distal (4%) and proximal (66%) tibia and radius cortical and trabecular volumetric BMD (vBMD), bone structure, strength and cortical bone distribution assessed. Analyses included BMI and/or tibia/radius length as covariates. On average, ADT-treated men had a higher BMI than PCa ($P < 0.05$) but not healthy controls. ADT-treated men had 7.2–7.8% lower lumbar spine aBMD than PCa ($P = 0.037$) and healthy controls ($P = 0.010$), with a trend for a lower total hip aBMD in the ADT-treated men ($P = 0.07$). At the distal tibia, total bone area was 6.2–7.3% greater in ADT-treated men than both controls ($P < 0.01$), but total vBMD was 8.4–8.7% lower in ADT-treated men than both controls ($P < 0.01$). Moreover, bone strength index (BSI) was 10.8% lower relative to healthy controls only ($P < 0.05$). At the distal radius, ADT-treated men had lower total and trabecular vBMD (10.7–14.8%, $P < 0.05$) and BSI (23.6–27.5%, $P < 0.001$) compared to both controls. There were no other differences in bone outcomes at the proximal tibia or radius. In conclusion, ADT treatment for PCa was associated with lower BMD and estimated compressive bone strength, particularly at trabecular skeletal sites (lumbar spine, and distal tibia and radius), compared to controls, but there were no consistent differences in cortical bone structure, distribution or bending strength.

1. Introduction

Prostate cancer (PCa) is the most commonly diagnosed male cancer in the developed world, but with improving detection and treatment, the survival rate of PCa is among the highest of all cancers [1–3]. Androgen deprivation therapy (ADT) is a mainstay in the treatment of locally advanced and metastatic prostate cancer, with evident benefit in controlling PCa progression and improving overall survival when prescribed appropriately [4]. However, hypogonadism induced by ADT is associated with a range of adverse effects on cardiovascular and metabolic health, sexual function and musculoskeletal health [5–8]. Regarding skeletal health, most cross-sectional studies have reported lower dual-energy x-ray absorptiometry (DXA) areal bone mineral density (aBMD) at various skeletal sites in ADT-treated men compared to PCa patients not treated with ADT and to healthy older adults [9–12], while others have reported no differences [13,14]. Longitudinally, ADT-treated men have been shown to have up to a five-fold greater rate of decline in aBMD compared to normal age-related losses [8,15–17]. However, little research has investigated the effects of ADT on other key determinants of bone strength beyond aBMD, such as cortical volumetric BMD (vBMD) and its distribution which provides an indication of whole bone and regional bone material properties (mineralization and/or porosity), cortical bone structure and mass distribution or trabecular bone properties. This is important because changes in whole bone strength can occur without a measurable change in aBMD, justifying their independent assessment when evaluating

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skeletal health [18–20]. The assessment of cortical bone mass and density distribution is also important given that cortical bone vBMD is not uniform throughout the cortex, and that cortical bone distribution changes with age leading to regional variations in the porosity, degree of mineralization and osteon population density [21–26]. Indeed, it has been reported that around 70% of the age-related loss in cortical vBMD is due to increased porosity, particularly on the inner endosteal surface [23,27]. Whether ADT leads to a preferential loss or change in cortical bone mass or density distribution has not been examined.

Peripheral quantitative computed tomography (pQCT) is an established technique that is able to assess bone geometric properties such as bone size and shape at peripheral skeletal sites, distinguish cortical and trabecular components, provide an estimate of bone strength as well as measure region-specific changes in the distribution of cortical bone within a given cross-section [18–20]. Longitudinally, one study using high-resolution pQCT (HR-pQCT) reported marked declines (1.5–12.5%) in cortical and trabecular vBMD as well as in cortical area at both the distal tibia and radius during the first 12-months of ADT [20]. This is an important study as it was the first to report deleterious effects of ADT on bone microarchitecture [20]. These results are supported by a longitudinal study in older men that reported more rapid declines in HR-pQCT assessed cortical bone outcomes of the distal tibia and radius among a subsample of men treated with ADT ($N = 16$), compared to those not treated with ADT ($N = 779$) [28]. The current study adds to this previous research by comparing ADT-treated men to both non-ADT men with prostate cancer and healthy controls and by assessing proximal sites of the tibia and radius that are predominantly comprised of cortical bone, as well as cortical bone distribution, which has not been previously investigated in this population. Therefore, the aim of this study was to investigate DXA areal BMD and pQCT cortical and trabecular vBMD, cortical bone structure, distribution and estimates of whole bone strength in PCa survivors treated with ADT compared to PCa survivors not treated with ADT and to healthy older men.

2. Materials and methods

2.1. Participants

This was a cross-sectional study that included 70 men treated with ADT for PCa, 52 men treated with non-hormonal therapies (including active surveillance) for PCa (PCa controls) and 70 men not diagnosed with PCa (healthy controls). Men treated with ADT in this analysis were involved in a larger randomised controlled trial involving exercise training and nutritional supplementation [29]. This cross sectional study includes the baseline data from these ADT-treated men. 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, 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 (> 1 session/week) or regular weight bearing impact exercise (> 150 min/week) in the past three months, were current smokers, had a weight > 159 kg or had any absolute contraindications to exercise testing according to the American College of Sports Medicine guidelines [30]. Specific to ADT-treated men, treatment must have been pharmacological (surgical orchiectomy excluded) and administered for > 12 weeks at enrolment.

ADT-treated men were recruited between April 2014 and November 2017 via clinician referral from Alfred Health (Melbourne, Australia), Peter MacCallum Cancer Centre (Victoria, Australia) and six private urology practices (Victoria, Australia), as well as from 32 PCa support groups (Victoria, Australia) and advertisements in state/local newspapers. PCa and healthy controls were recruited between October 2014

and February 2016 from PCa support groups and advertisements in state/local newspapers. The study was conducted in accordance with Declaration of Helsinki and was approved by the human research ethics 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.

2.2. Measurements

2.2.1. Areal bone mineral density (aBMD)

Lumbar spine (L_1-L_4) and proximal femur (femoral neck and total hip) aBMD (g/cm^2) were assessed using DXA (Lunar iDXA, GE Lunar Corp., Madison, WI, USA) and analysed using enCORE software (version 12.30.008), by a researcher blinded to group allocation. All scans were reviewed for artefacts or local structural abnormalities known to influence BMD and where necessary, artefacts were marked and excluded from analysis. For the lumbar spine, T-scores from adjacent vertebrae were reviewed to determine any large differences in BMD from one vertebrae to the next. Individual vertebrae affected by structural abnormalities causing artificial elevation of BMD (T-score ≥ 2 SDs different to adjacent vertebrae) were excluded from the analysis such that the overall lumbar spine BMD results included only the remaining vertebrae ($N = 11$ participants with verterbrae excluded). Additionally, two participants (PCa control, N = 1; healthy control, N = 1) with hip arthroplasty were excluded from the analysis of proximal femur sites. One ADT-treated participant was excluded from analysis of total hip aBMD due an abnormally high value (T-score of 7.3). The short-term coefficient of variation (CV) for aBMD measures range from 0.6% to 1.0% within our laboratory. The lowest T-score of the lumbar spine, femoral neck and/or total hip was used to classify participants with osteoporosis (T-score ≤ −2.5) or osteopenia (T-score between −2.5 and −1), consistent with World Health Organization criteria [31].

2.2.2. Volumetric BMD, bone structure and strength

Proximal (66%) and distal (4%) sites of the non-dominant radius and dominant tibia were scanned using pQCT (XCT 3000, Stratec Medizintechnik GmbH, Pforzheim, Germany). Volumetric BMD (total and cortical vBMD [mg/cm^3]), structure (total, cortical and medullary area [mm^2]) and strength (density-weighted polar cross-sectional moment of inertia [I_{polar}, mg/cm]) at proximal sites as well as vBMD (total and trabecular vBMD [mg/cm^3]), bone size (total area [mm^2]) and strength (bone strength index [BSI, mg^2/mm^4]) at distal sites were assessed. The slice thickness was 1 mm and voxel size was 0.5 mm at a scanning speed of 20 mm/s. pQCT images were analysed in the Fiji image analysis platform [32] using the BoneJ plugin [33] as previously reported [22]. Distal radius and tibia (4%) total bone area were analysed based on thresholding at 169 mg/cm^3. Trabecular density was determined by peeling single layers of pixels until 55% of the total bone area was peeled away. The remaining inner 45% of the total bone area was considered to be exclusively trabecular bone. BSI was calculated as follows: BSI = total area multiplied by the square of total vBMD [34]. For the 66% proximal radius and tibia, the periosteal surface was determined based on a threshold of 280 mg/cm^3, and cortical bone a threshold of 550 mg/cm^3. Medullary area was calculated by subtracting cortical area from total area. I_{polar} was determined using the bone threshold of 480 mg/cm^3 [35]. Three participants (ADT-treated, $N = 1$; PCa controls, N = 1; healthy control, N = 1) did not complete pQCT scans due to maintenance of the scanner at the time of testing. Scans at each site were reviewed for errors and excluded according to the visual inspection rating scale of participant movement [36,37]. Distal tibia scans of 10 participants (ADT-treated men, $N = 3$; PCa controls, N = 3; healthy controls, $N = 4$), proximal tibia scans of three participants (ADT-treated men, N = 3), the distal radius scan of one ADT-treated participant and the proximal radius scans of nine participants (ADT-

Table 1

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

	Healthy controls	PCa controls	ADT-treated men	P-value
N	70	52	70	–
Age (years)	69.1 ± 7.3	68.8 ± 5.9	71.3 ± 6.2	0.073
Height (cm)	175.7 ± 6.5	176.1 ± 7.2	175.1 ± 6.5	0.730
Weight (kg)	85.1 ± 12.3	82.5 ± 13.5	88.5 ± 17.1	0.074
Body mass index (kg/m^2)	27.5 ± 3.2	26.6 ± 4.0	28.8 ± 5.1*	**0.013**
Ethnicity, N (%)				
Caucasian	66 (94.3)	51 (98.1)	68 (97.1)	0.422
Asian	4 (5.7)	1 (1.9)	1 (1.4)	
African	0 (0.0)	0 (0.0)	1 (1.4)	
Comorbidities[b], N (%)	61 (87.1)	42 (80.8)	62 (88.6)	0.441
If yes, total (N)	2 ± 1	2 ± 1	3 ± 1	0.372
Prescription medication, N (%)	45 (64.3)	34 (65.4)	55 (78.6)	0.132
If yes, total (N)	3 ± 2	3 ± 2	3 ± 2	0.201
Physical activity (kJ/d)	3016 ± 1698	3199 ± 1960	2634 ± 1706	0.192
Diet				
Energy (kJ/d)	8571 ± 2354	8316 ± 2151	8666 ± 2579	0.727
Protein (g/d)	99 ± 31	103 ± 34	93 ± 31	0.239
Carbohydrate (g/d)	218 ± 66	203 ± 67	214 ± 87	0.508
Fat (g/d)	73 ± 29	76 ± 32	77 ± 34	0.683
Calcium (mg/d)	879 ± 340	763 ± 365	841 ± 374	0.211
Time since PCa diagnosis (months)	–	71 ± 58	69 ± 70	0.889[a]
Stage of PCa, N (%)				
Localised/removed	–	44 (84.6)	20 (28.6)	**< 0.001**[a]
Advanced	–	6 (11.1)	45 (64.3)	
Unknown	–	2 (3.7)	5 (7.1)	
ADT duration (months), median (IQR)	–	–	12 (5–23)	–
Previous prostatectomy, N (%)	–	36 (69.2)	34 (48.6)	**0.022**[a]
Previous radiotherapy, N (%)	–	12 (23.1)	48 (68.6)	**< 0.001**[a]
Previous chemotherapy, N (%)	–	0 (0.0)	11 (15.7)	**0.003**[a]
Current active surveillance, N (%)	–	8 (15.4)	–	–

Data are: mean ± standard deviation unless stated otherwise.

[a] ADT-treated men compared to PCa controls only.

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

* $P < 0.05$ compared to PCa controls.

treated men, $N = 5$; PCa controls, $N = 2$; healthy controls, $N = 2$) were excluded from the analysis of vBMD, bone structure and strength as the scan quality did not allow for accurate analysis of these outcomes. The short-term CVs for repeated measures in a sample of healthy premenopausal women range from 0.9% to 2.2% for the 4% radius, 0.7% to 2.5% for the 4% tibia and 0.6% to 1.8% for the 66% tibia outcome measures [38].

2.2.3. Cortical bone distribution

Cortical bone density distribution was calculated from the pQCT scans of the proximal tibia and radius. As we have previously reported [22], radial bone density distribution within the bone cross-section was calculated by measuring the average bone density for three concentric rings (endocortical, midcortical and pericortical) from the centre of bone mass to the outer bone edge. The short-term CVs for repeated measures of endocortical, midcortical and pericortical vBMD in samples of healthy men range from 1.6% to 4.3% for the radius [39] and 1.4% to 2.4% for the tibia [22].

2.2.4. Anthropometry, physical activity and diet

Height and body mass was assessed using a portable stadiometer (SECA, Hamburg, Germany) and scales (A&D, Tokyo, Japan) respectively, with participants wearing light clothing and no shoes. Body mass index (BMI) was calculated as body mass (kg) divided by height (m) squared (kg/m^2). The Community Healthy Activities Model Programme for Seniors (CHAMPS) physical activity questionnaire was used to assess to total habitual activity levels (kJ/d) based participation in a comprehensive list of low, moderate and vigorous physical and leisure activities [40]. Diet was assessed using a 24-hour food recall. Dietary analysis was performed using Australia-specific dietary analysis software (FoodWorks, Xyris software, Highgate Hills, Australia).

2.3. Statistical analysis

All statistical analyses were performed using Stata statistical software (Version 15, Stata, College Station, TX, USA). Initially, all outcome 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. Outcomes with non-normally distributed residuals (lumbar spine aBMD, distal tibia total area and BSI, distal radius total and trabecular vBMD, total area, medullary area, cortical vBMD and I_{polar} of the proximal tibia and radius, and endocortical, midcortical and pericortical vBMD of the proximal tibia and radius) were transformed using natural logarithms prior to analysis and percentage differences were calculated on the natural log transformed data for those outcomes [41]. One-way analyses of variance/covariance (ANOVA/ANCOVA) were used to compare continuous variables between groups. Chi-squared tests, or Fisher's exact test for small expected frequencies, were used to compare categorical variables between groups. BMI was included as a covariate in analyses of all outcomes, and tibia and radius length were included as covariates in analyses of all tibia and radius pQCT outcomes, respectively. Bonferroni corrected pairwise comparisons were used where appropriate to further investigate any significant main effects between groups. Subgroup analysis was completed to compare ADT-treated men with treatment duration less than and > 12-months. This cut-point was chosen as bone loss with ADT is shown to be greatest within the first 12-months of treatment [13,42]. Spearman rank-order correlation coefficients were used to investigate the relationship between ADT duration and bone outcomes. Continuous data were reported as mean ± standard deviation (or mean [95% confidence intervals] for adjusted values), 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.

3. Results

3.1. Participant characteristics

The characteristics of the 192 men included in the three groups are shown in Table 1. For ADT-treated men, the median (IQR) treatment duration was 12 (5–23) months. ADT-treated men had 7.9% higher BMI than PCa controls ($P = 0.012$), but not healthy controls. ADT-treated men were more likely to have advanced PCa and be previously treated with radiotherapy or chemotherapy compared to PCa controls, while PCa controls were more likely to have had a prostatectomy. There were no other differences between groups for other demographic, diet, physical activity or medical treatment outcomes.

3.2. Areal BMD

ADT-treated men had 7.2% and 7.8% lower lumbar spine aBMD compared to PCa ($P = 0.037$) and healthy controls ($P = 0.010$), respectively (Table 2). While there was a significant main effect for total hip aBMD between groups ($P = 0.040$), corrected pairwise comparisons revealed only a trend for lower (5.9%) total hip aBMD in ADT-treated men compared to PCa controls ($P = 0.068$). Although ADT-treated men had 2.8% to 3.8% lower femoral neck aBMD compared to PCa and healthy controls, there were no significant differences between groups. There were also no differences in aBMD between PCa and healthy controls at any site. Overall, 7.1% of ADT-treated men were classified as osteoporotic compared to 1.4% and 1.9% of PCa and healthy controls, respectively. However, the prevalence of osteoporosis and osteopenia

did not differ significantly between groups.

3.3. Volumetric BMD, bone structure and strength

At the distal tibia, total area was 7.3% and 6.2% higher in ADT-treated men compared to PCa ($P = 0.005$) and healthy controls ($P = 0.009$), respectively (Table 2 and Fig. 1). In contrast, total vBMD of the distal tibia was 8.4% and 8.7% lower in ADT-treated men compared to PCa ($P = 0.003$) and healthy controls ($P < 0.001$), respectively. There were no significant group differences in trabecular vBMD of the distal tibia, despite ADT-treated men having 4.5% to 4.6% lower vBMD compared to both control groups ($P = 0.160$). BSI of the distal tibia was 10.8% lower in ADT-treated men compared to healthy controls ($P = 0.030$), but not PCa controls. There were no significant differences between groups for any bone structure, density or strength outcomes at the proximal tibia.

At the distal radius, total area did not differ between groups, despite being 3.5% to 4.5% higher in ADT-treated men compared to controls. In contrast, ADT-treated men had significantly lower distal radius total vBMD (14.4% and 12.2%, both $P = 0.001$) and trabecular vBMD (14.8%, $P = 0.003$; 10.7%, $P = 0.029$) compared to PCa and healthy controls, respectively. BSI of the distal radius was 27.5% and 23.6% lower in ADT-treated men compared to PCa and healthy controls, respectively (both $P < 0.001$). There were no significant differences between groups for any bone structure, density or strength outcomes at the proximal radius. Similarly, there were no differences between PCa and healthy controls for any vBMD, structure or strength outcomes at the tibia or radius Fig. 2.

Table 2
Adjusted mean (95% CI) areal and volumetric bone mineral density (BMD), bone structure and strength in men with prostate cancer (PCa) treated with androgen deprivation therapy (ADT), PCa controls and healthy controls.

	N	Healthy controls	N	PCa controls	N	ADT-treated men	P-value
DXA aBMD							
Lumbar spine (g/cm^2)	70	1.341 (1.293, 1.389)	52	1.333 (1.276, 1.389)	70	**1.243 (1.195, 1.292)**[a,d]	**0.006**[#]
Femoral neck (g/cm^2)	69	0.986 (0.957, 1.015)	51	0.976 (0.942, 1.011)	70	0.950 (0.920, 0.979)	0.220
Total hip (g/cm^2)	69	1.067 (1.035, 1.100)	51	1.078 (1.039, 1.116)	69	1.018 (0.985, 1.051)	**0.040**
pQCT							
Distal tibia (4%)							
Total area (mm^2)	65	1291 (1254, 1327)	48	1279 (1236, 1322)	66	**1369 (1331, 1407)**[b,e]	**0.002**[#]
Total vBMD (mg/cm^3)	65	323 (314, 332)	48	322 (311, 332)	66	**297 (288, 306)**[c,e]	**< 0.001**
Trabecular vBMD (mg/cm^3)	65	250 (242, 258)	48	250 (240, 260)	66	239 (231, 248)	0.160
BSI (mg^2/mm^4)	65	1.356 (1.285, 1.427)	48	1.325 (1.241, 1.409)	66	**1.218 (1.144, 1.292)**[a]	**0.030**[#]
Proximal tibia (66%)							
Total area (mm^2)	69	898 (872, 923)	51	867 (837, 896)	66	878 (851, 905)	0.281[#]
Cortical area (mm^2)	69	389 (379, 400)	51	393 (380, 405)	66	399 (387, 410)	0.533
Medullary area (mm^2)	69	508 (481, 535)	51	474 (442, 506)	66	479 (450, 508)	0.222[#]
Total vBMD (mg/cm^3)	69	528 (511, 545)	51	543 (523, 563)	66	541 (523, 560)	0.456
Cortical vBMD (mg/cm^3)	69	997 (987, 1008)	51	996 (984, 1009)	66	995 (984, 1007)	0.959[#]
I$_{polar}$ (mg/cm)	69	9846 (9446, 10,245)	51	9458 (8987, 9929)	66	9657 (9227, 10,086)	0.467[#]
Distal radius (4%)							
Total area (mm^2)	69	438 (420, 455)	51	431 (411, 452)	68	451 (433, 469)	0.335
Total vBMD (mg/cm^3)	69	359 (345, 373)	51	366 (350, 383)	68	**317 (303, 332)**[c,f]	**< 0.001**[#]
Trabecular vBMD (mg/cm^3)	69	208 (198, 219)	51	213 (201, 226)	68	**186 (175, 197)**[a,e]	**0.003**[#]
BSI (mg^2/mm^4)	69	0.558 (0.526, 0.591)	51	0.576 (0.538, 0.615)	68	**0.452 (0.418, 0.485)**[c,f]	**< 0.001**
Proximal radius (66%)							
Total area (mm^2)	67	193 (186, 201)	49	186 (177, 195)	64	189 (182, 197)	0.505[#]
Cortical area (mm^2)	67	113 (109, 116)	49	113 (109, 118)	64	110 (106, 114)	0.448
Medullary area (mm^2)	67	81 (74, 87)	49	72 (65, 80)	64	80 (73, 86)	0.146[#]
Total vBMD (mg/cm^3)	67	674 (651, 698)	49	709 (681, 737)	64	672 (647, 697)	0.106
Cortical vBMD (mg/cm^3)	67	1016 (1001, 1031)	49	1024 (1005, 1042)	64	1015 (999, 1031)	0.778[#]
I$_{polar}$ (mg/cm)	67	473 (444, 501)	49	451 (417, 485)	64	451 (421, 481)	0.759[#]

Data are adjusted means with 95% confidence interval, and results are adjusted for BMI and tibia or radius length (for pQCT outcomes). [a]$P < 0.05$, [b]$P < 0.01$, [c]$P < 0.001$ compared to healthy controls. [d]$P < 0.05$, [e]$P < 0.01$, [f]$P < 0.001$ compared to PCa controls. [#]Analyses completed using natural log-transformed data. DXA, dual-energy X-ray absorptiometry; pQCT, peripheral quantitative computed tomography; vBMD, volumetric bone mineral density; BSI, bone strength index; I$_{polar}$, density-weighted polar cross-sectional moment of inertia.

Table 3

Adjusted mean (95% CI) cortical bone density distribution in men with prostate cancer (PCa) treated with androgen deprivation therapy (ADT), PCa controls and healthy controls.

	N	Healthy controls	N	PCa controls	N	ADT-treated men	P-value[a]
Proximal tibia (66%)							
Endocortical vBMD (mg/cm^3)	61	993 (979, 1005)	46	991 (976, 1007)	62	990 (976, 1005)	0.964
Midcortical vBMD (mg/cm^3)	61	1122 (1110, 1133)	46	1120 (1107, 1134)	62	1111 (1099, 1123)	0.423
Pericortical vBMD (mg/cm^3)	61	1136 (1125, 1147)	46	1125 (1112, 1137)	62	1120 (1108, 1132)	0.148
Proximal radius (66%)							
Endocortical vBMD (mg/cm^3)	65	930 (914, 946)	45	947 (927, 967)	62	933 (916, 950)	0.379
Midcortical vBMD (mg/cm^3)	65	1146 (1129, 1162)	45	1163 (1142, 1183)	62	1147 (1130, 1165)	0.390
Pericortical vBMD (mg/cm^3)	65	988 (976, 1000)	45	1001 (986, 1016)	62	990 (977, 1003)	0.376

Data are adjusted mean with 95% confidence interval, and results adjusted for BMI and tibia or radius length. vBMD, volumetric bone mineral density.

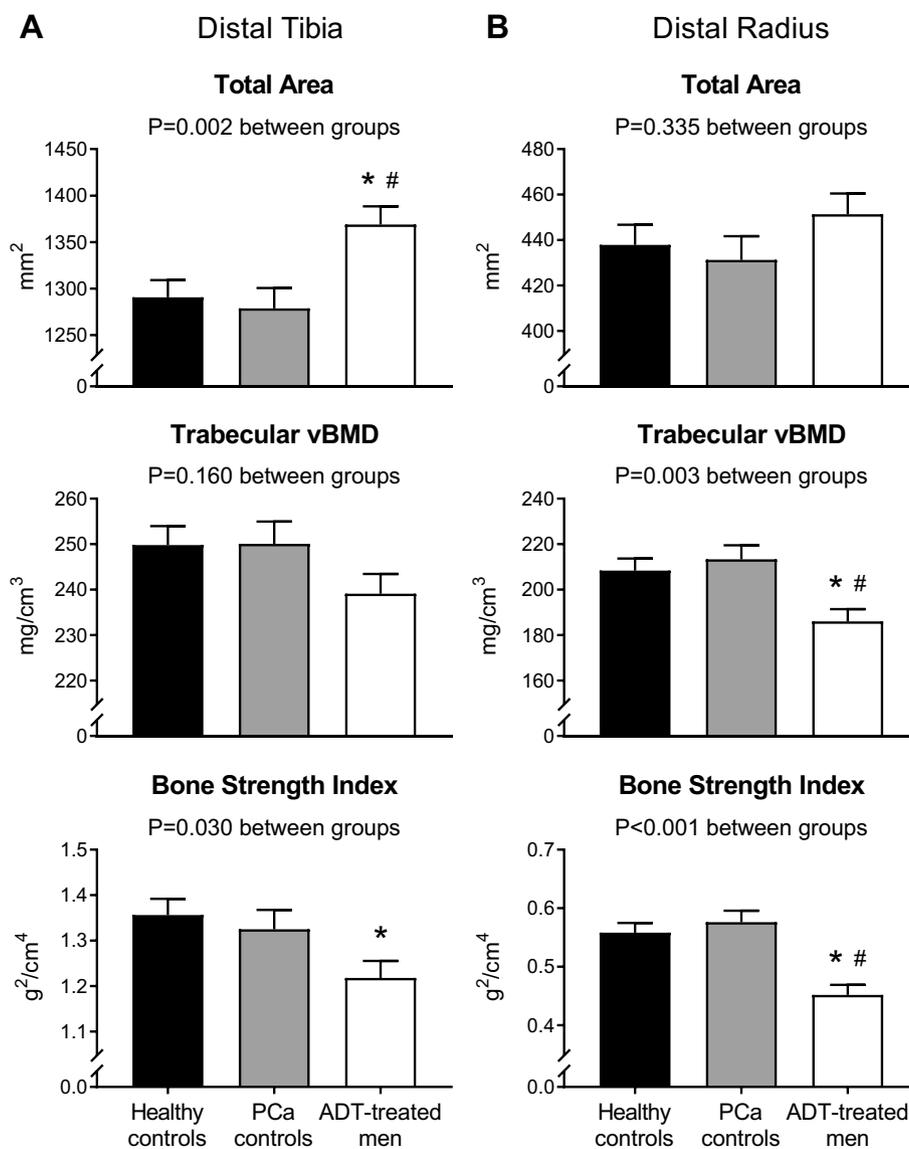[a] Analyses completed using natural log-transformed data.

Fig. 1. Mean (± standard error) pQCT-derived outcomes at distal sites of the A) tibia and B) radius in healthy controls, PCa controls and ADT-treated men, adjusted for BMI and tibia or radius length. *P < 0.05 compared to healthy controls, #P < 0.05 compared to PCa controls. vBMD, volumetric bone mineral density; PCa, prostate cancer; ADT, androgen deprivation therapy; pQCT, peripheral quantitative computed tomography.
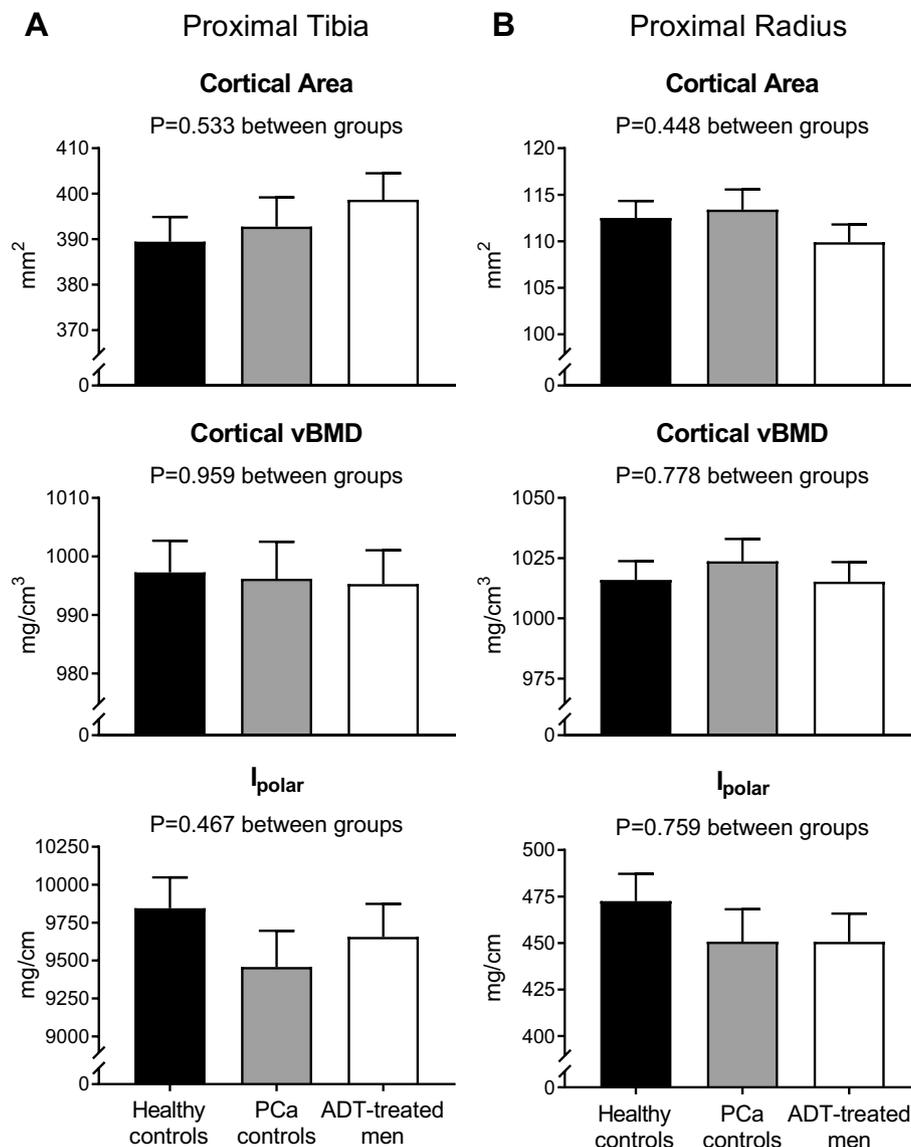
A   Proximal Tibia

Cortical Area
P=0.533 between groups

B   Proximal Radius

Cortical Area
P=0.448 between groups

Cortical vBMD
P=0.959 between groups

Cortical vBMD
P=0.778 between groups

I$_{polar}$
P=0.467 between groups

I$_{polar}$
P=0.759 between groups

Fig. 2. Mean (± standard error) pQCT-derived outcomes at proximal sites of the A) tibia and B) radius in healthy controls, PCa controls and ADT-treated men, adjusted for BMI and tibia or radius length. vBMD, volumetric bone mineral density; I$_{polar}$, density-weighted polar cross-sectional moment of inertia; PCa, prostate cancer; ADT, androgen deprivation therapy; pQCT, peripheral quantitative computed tomography.

3.4. Cortical bone distribution

There were no differences between groups for average endocortical, midcortical or pericortical vBMD of either the proximal tibia or radius (Table 3). There were also no differences between PCa and healthy controls for any cortical bone distribution outcomes.

3.5. ADT duration

To assess the effect of ADT duration on the results, men in the ADT group treated for < 12 months ($N = 35$, median [IQR] duration = 5.3 [4.1–8.2] months) were compared to those treated for > 12 months (N = 35, median [IQR] duration = 23.4 [15.3–59.4] months). Participant characteristics other than ADT duration and time since PCa diagnosis were equivalent between men treated for less than and > 12 months. There were no differences in any bone outcomes according to duration of ADT use, with the exception that men treated for < 12 months had 2.4% and 2.2% lower midcortical and pericortical vBMD of the proximal tibia, respectively compared to those treated for > 12 months. There were no significant correlations between ADT duration

and any bone outcomes, other than a weak negative correlation ($r = -0.26$, $P < 0.05$) with pericortical vBMD of the proximal tibia.

4. Discussion

The main finding from this study was that ADT treatment in men with PCa was associated with lower pQCT-derived total and trabecular vBMD and compressive bone strength at distal skeletal sites as well as lower DXA-derived lumbar spine, and to a lesser extent hip aBMD compared to PCa and healthy controls. In contrast, there were no differences in cortical bone density, structure or bending strength between groups, which suggests that treatment with ADT may predominantly affect trabecular bone sites.

To our knowledge, there are few studies that have quantified the effects of ADT on other determinants of whole bone strength and fracture risk beyond aBMD. Prospective studies assessing the distal tibia and radius using HR-pQCT have reported a marked loss in cortical and trabecular vBMD (1.5% to 11.3% per annum) and cortical area (11.5% to 12.5% per annum) over the first 12-months of ADT [20], and an accelerated decline in cortical area, thickness and vBMD in ADT treated

compared to non-ADT treated men [28]. In part support of these findings, we found that ADT-treated men had significantly lower compressive bone strength (BSI) at distal sites, which is likely due to lower total and/or trabecular vBMD compared to controls, particularly at the distal radius. However, the current study adds to this previous study by comparing ADT-treated men to control groups and by assessing proximal cortical bone sites of the tibia and radius. A key finding from our study was that there was no consistent evidence that cortical bone structural outcomes and bone strength (polar moment of inertia) were impaired at any site in our cohort of ADT treated men compared to controls. This suggests that ADT may predominantly affect trabecular bone, particularly at non weight-bearing sites.

Trabecular bone is suggested to be more responsive to rapid bone loss, as occurs with hypogonadism induced by ADT, than cortical bone due to a greater surface area for bone resorption or remodelling making trabecular bone more metabolically active [14,43]. In part support of this notion, hypogonadal men have been shown to have impaired QCT-derived trabecular density of the lumbar spine [44,45] and trabecular microarchitecture of the tibia assessed by micro-MRI [46]. Furthermore, these outcomes have been shown to improve with testosterone replacement therapy [44,47,48], supporting the importance of androgens in maintaining trabecular bone. Testosterone therapy for 12-months in hypogonadal older men has been shown to increase QCT-assessed vBMD and estimated bone strength at both the spine and hip, with greater increases observed in the spine compared to the hip [48]. Lumbar spine aBMD was also shown to increase to a greater extent than total hip and femoral neck aBMD with testosterone therapy compared to placebo [48]. Evidence from mice studies suggest that the mechanisms responsible for trabecular and cortical bone loss differ following acute sex steroid deficiency [49], potentially explaining why lower trabecular vBMD was not accompanied by lower cortical vBMD in the current study. The differences in trabecular bone in the ADT-treated men in our study may also be related to the relatively short duration of ADT use in our men. Weak negative associations between ADT duration and trabecular bone indices of the distal radius assessed by HR-MRI have been reported previously [50]. Overall, 50% of the men in the ADT group were treated for < 12-months, and thus it is possible that longer term treatment may lead to observable changes in cortical bone outcomes. While the comparison between men treated for < 12 months and > 12 months showed negligible differences in most bone outcomes, the analysis may have been limited by the modest sample size.

Although cortical bone structural outcomes at proximal skeletal sites did not differ in ADT-treated men compared to controls in our study, an unexpected finding was that ADT-treated men had higher total bone area of the distal tibia but lower vBMD. Previous research has reported that periosteal bone apposition may occur during aging to partially offset endocortical bone resorption to maintain cortical thickness and bone strength [51]. Thus, the higher total area in ADT-treated men in this study may therefore represent a compensatory response to the lower total vBMD to maintain bone strength. Indeed, a small increase in the size or outer diameter of the bone can lead to large increases in bone strength because the resistance of bone to bending or torsional forces is related exponentially (to the 4th power) to its diameter [19]. In contrast to these findings, distal radius total bone area did not differ between the groups, despite both total and trabecular vBMD being lower in ADT-treated men compared to controls. These contrasting results may be due to the fact that the distal radius is a non-weight-bearing site. It is well established that mechanical loading is a potent stimuli for skeletal adaptation [52], and that the tibia is subjected to regular loading. However, despite the greater total bone area, distal tibia bone strength was still lower in ADT-treated men compared to healthy controls, suggesting that the greater bone size did not compensate for the lower vBMD in this study. Additionally, sex steroids may influence the sensitivity of bone to mechanical loading [49]. Mouse models suggest that estrogen deficiency may decrease the sensitivity, whereas androgen deficiency does not impair and may even increase the skeletal response to mechanical loading [49]. Prospective studies are required to further investigate changes in vBMD, bone structure and strength during ADT and to confirm the results of the current study.

An additional novel aspect of this study was the assessment of cortical bone density distribution at proximal sites to evaluate whether ADT was associated with regional-specific changes in cortical bone density. This is important because previous research has reported that cortical bone mass and density are not uniform throughout the cortex [21,22] and change with age [22,23]. For example, a study investigating mid-tibia cortical bone vBMD in young compared to older men reported that despite equivalent whole bone cortical bone vBMD, older men had lower endocortical vBMD and higher pericortical vBMD compared to young men [22]. Any variations in cortical density are likely to be related to changes in intracortical remodelling that alters the porosity and/or mineralization of bone [22]. In this study, we found that cortical bone density distribution across the cortex of both the proximal tibia and radius did not differ in ADT-treated men compared to controls. Given that it has been reported that about 70% of the age-related reduction in cortical vBMD is due to increased porosity [27], these findings suggests ADT does not appear to adversely affect cortical porosity. However, further studies using more advanced high resolution imaging techniques such as HR-pQCT are needed to address this question.

Although previous cross-sectional studies investigating DXA aBMD in ADT-treated men compared to control groups have reported mixed results [9–14], we found that lumbar aBMD was ~7–8% lower in the ADT-treated men compared to PCa and healthy controls. This is consistent with the findings from several studies which also observed that lumbar spine aBMD in ADT-treated men was 8% to 23% lower compared to PCa controls [9,11,12] or healthy controls [9]. In contrast, we observed no significant differences in aBMD at proximal femur sites, which is consistent with a number of studies reporting no differences in total hip [9,11,13], femoral neck [10,13,14], or trochanter aBMD [10,13] in ADT-treated men compared to PCa and/or healthy controls. Although some previous studies have reported 7% to 12% lower total hip [10,12] and femoral neck aBMD [12] in ADT-treated men compared to PCa controls, the contrasting results with regard to DXA aBMD may be related to a number of factors, including differences in the duration of ADT use and sample sizes used which may have limited the statistical power to detect any significant between group differences. For instance, Stoch et al. [10] included 19 ADT-treated men and reported no significant differences in lumbar spine and femoral neck BMD, despite being 6.5% and 8.3% lower respectively compared to PCa controls. The lower aBMD of the lumbar spine but not of the femoral neck observed in ADT-treated men compared to controls supports our pQCT results that suggest ADT may primarily affect trabecular bone, given that the lumbar spine contains a higher proportion of trabecular bone than the proximal femur.

There are several strengths to our study. This is the first study to use robust measures to assess estimates of bone strength and its determinants at distal and proximal skeletal sites, including vBMD, bone structure, strength and cortical bone density distribution, in ADT-treated men. In addition, the inclusion of both non-ADT treated PCa men and healthy controls allowed for the effects of ADT to be compared independently of any effects of a PCa diagnosis or any non-hormonal PCa treatment. However, there are also a number of limitations that should be considered. Firstly, the cross-sectional design of the study means that causality cannot be established for the outcomes assessed. Secondly, although the sample size was relatively large compared to previous studies, this study may still have been underpowered to detect some differences in the pQCT-derived outcomes given that changes in bone geometry tend to occur more slowly over time compared to density. The sample size was further reduced for certain pQCT outcomes due to limitations in scan analysis and acquisition. Thirdly, it is possible that some hypogonadal men may have been included in the

control groups. However, the prevalence of middle-aged and older men having total testosterone levels below 200 ng/dL (considered androgen deficient) is reported to be very low (~2.0%) [53]; this would be even lower if using the castrate threshold of 50 ng/dL typically achieved by ADT [4,54]. Additionally, factors such as ADT adherence and efficacy may influence skeletal health, however we did not collect treatment information other than ADT duration. Finally, volunteer bias due to the way in which participants were recruited may limit the generalisability of the results. ADT-treated men included in this study were involved in a larger RCT, so all volunteered to potentially be allocated to a 52-week exercise training and nutritional supplementation intervention. It is therefore possible that only ADT-treated men who were capable of completing the intervention volunteered for the study, and as a result, they may represent a healthier subsection of the broader population of ADT-treated men. Conversely, PCa and healthy control group participants were recruited for a single testing session promoted as a 'free health assessment'. It is therefore possible that men with an existing health issue or concern were more likely to volunteer, so participants in the control groups may have been less healthy than the general population.

In conclusion, ADT treatment in men with PCa was associated with lower aBMD and vBMD and reduced estimated compressive bone strength, particularly at distal trabecular skeletal sites, compared to non-ADT treated PCa and healthy controls. In contrast, there were no differences in cortical bone density, structure or bending strength at proximal sites between groups, which suggests that treatment with ADT may predominantly affect trabecular bone.

Declaration of Competing Interest

None.

Authors' roles

Study design: PO, RD, SF. Study conduct: JDV, PO, NM. Data collection: JDV, PO, NM. Data analysis: JDV, PO, RD, TR. Data interpretation: JDV, RD, SF. Drafting manuscript: JDV. Revising manuscript content: JDV, RD, PO, NM, TR, SF. Approving final version of manuscript: JDV, RD, PO, NM, TR, SF. JDV takes responsibility for the integrity of the data analysis.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.bone.2019.06.005.

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