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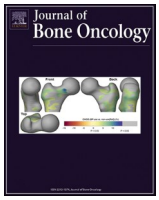

Research Paper

The impact of androgen deprivation therapy on bone microarchitecture in men with prostate cancer: A longitudinal observational study (The ANTELOPE Study)

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HIGHLIGHTS

- The ANTELOPE study has demonstrated the value of HR-pQCT imaging in assessing prostate cancer treatment bone loss when used in combination with more traditional bone investigation approaches such as DXA.
- ADT resulted in microstructural deterioration, a reduction in estimated bone strength, an increase in bone turnover and a decrease in bone mineral density in men with prostate cancer receiving 12 months treatment with ADT.
- An increase in frailty and a decrease in physical performance and strength was also observed.
- The use of HR-pQCT should be considered when studying the effects of anti-androgens and other novel PC treatments on bone and in studies to devise strategies for the prevention of bone loss.

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ABSTRACT

Introduction: Androgen Deprivation Therapy (ADT) for prostate cancer (PC) has substantial negative impacts on the musculoskeletal system and body composition. Many studies have focused on the effects of ADT on areal bone mineral density (aBMD), but aBMD does not capture key determinants of bone strength and fracture risk, for example volumetric bone density (vBMD), geometry, cortical thickness and porosity, trabecular parameters and rate of remodelling. More specialist imaging techniques such as high-resolution peripheral quantitative computed tomography (HR-pQCT) have become available to evaluate these parameters. Although it has previously been demonstrated that bone microarchitectural deterioration occurs in men undergoing ADT, the aim of the ANTELOPE study was to examine longitudinal changes in bone microstructure alongside a range of musculoskeletal parameters and frailty, comparing men with PC receiving ADT alone or ADT plus chemotherapy for metastatic disease, with a healthy age-matched population.

Methods: We used HR-pQCT to investigate effects of 12 months of ADT on vBMD and microstructural parameters, complemented by assessment of changes in aBMD, serum bone turnover markers, sex hormones, body composition, grip strength, physical and muscle function, frailty and fracture risk. We studied three groups: Group A – men with localised/locally advanced PC due to commence ADT; Group B – men with newly diagnosed hormone-sensitive, metastatic PC, starting ADT alongside docetaxel chemotherapy and steroids; Group C – healthy, age-matched men. The primary endpoint was change in vBMD (Group A vs Group C) at the distal radius.

Results: Ninety-nine participants underwent baseline study assessments (Group A: n = 38, Group B: n = 30 and Group C: n = 31). Seventy-five participants completed all study assessments (Group A (29), Group B (18), Group C (28). At baseline, there were no significant differences between Groups A and C in any of the BMD or bone microstructure outcomes of interest. After 12 months of ADT treatment, there was a significantly greater decrease in vBMD ($p < 0.001$) in Group A (mean 12-month change = -13.7 mg HA/cm^3, −4.1 %) compared to Group C (mean 12-month change = -1.3 mg HA/cm^3, −0.4 %), demonstrating achievement of primary outcome.

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Similar effects were observed when comparing the change in vBMD between Group B (mean 12-month change = -13.5 mg HA/cm^3, −4.3 %) and Group C. These changes were mirrored in aBMD. ADT resulted in microstructural deterioration, a reduction in estimated bone strength and an increase in bone turnover. There was evidence of increase in total fat mass and trunkal fat mass in ADT-treated patients, with marked loss in upper limb mass, along with BMI gain. Frailty increased and physical performance and strength deteriorated in both ADT groups, relative to the healthy control group.

Conclusion: The study showed that ADT has profound effects on vBMD, aBMD, bone microstructure and strength and body composition, and important impacts on frailty and physical performance. Whilst DXA remains a valuable tool (changes in aBMD are of the same magnitude as those observed for vBMD), HR-pQCT should be considered for assessing the effects of anti-androgens and other newer PC therapies on bone, as well as potential mitigation by bone-targeted agents.

1. Introduction

Prostate cancer (PC) is the second most commonly diagnosed cancer in men worldwide [1] with 1.4 million new cases and 375,000 deaths each year. Improved survival has resulted in a large proportion of men with PC living with the condition for many years. The long-term consequences of treatment are therefore of increasing importance. Both PC and its treatment have significant consequences on bone health and body composition. These effects occur in addition to normal age-related changes in bone mineral density (BMD) and bone structure. Men with PC already have a cancer-linked increased risk of fracture, compared with age- and sex-related controls, even before PC treatment initiation.

Androgen deprivation therapy (ADT) is a mainstay of treatment for both early and advanced PC and leads to a rapid and profound reduction in circulating sex steroids. ADT is associated with a reduction in BMD [2–4] that is most marked in the first 12 months (when there may be a high prevalence of vertebral fractures [5]), but continues for the duration of treatment. In addition to ADT, other systemic treatments such as chemotherapy and anti-androgens have become standard components of the PC treatment pathway and may require concomitant glucocorticoids, which themselves are a common cause of secondary osteoporosis [6].

Most studies examining the effects of ADT on bone have focused on changes in areal BMD (aBMD) assessed using dual energy x-ray absorptiometry (DXA) [7]. However, there is increasing evidence that bone strength is determined by factors that are independent of aBMD and fractures can occur in those subsequently found to have normal aBMD. Bone strength is also dependent on whole bone geometry (e.g. volumetric BMD (vBMD), bone size and mass, cortical thickness), microstructure (e.g. cortical porosity and trabecular parameters), bone tissue material properties, and the rate of bone remodelling. High resolution peripheral quantitative computed tomography (HR-pQCT) can be used to study bone microstructure, geometry and estimated strength parameters [8].

Although it has previously been demonstrated that bone microarchitectural deterioration occurs in men with PC undergoing ADT [9–11], there are few, if any, previous clinical studies which have comprehensively assessed the longitudinal effects of ADT on bone microarchitecture, related musculoskeletal parameters and frailty in the same patients. We now report such a study in three distinct participant groups, men with non-metastatic PC receiving ADT, men with metastatic PC receiving ADT and chemotherapy and a group of age-matched healthy volunteers.

ADT also predisposes men to sarcopenic obesity, with detrimental effects on muscle function, physical performance and falls risk. In men with metastatic PC, sarcopenia may reduce tolerance to chemotherapy and has been associated with worse cancer-specific survival [12].

Frailty commonly occurs with ageing and is defined as vulnerability to the poor resolution of homeostasis following a stressor event [13]. It is the consequence of cumulative deficits across multiple physiological systems, and has been associated with adverse outcomes in cancer patients, including increased mortality and intolerance to cancer treatment [14]. Notably, PC occurs mainly in older men (peak incidence around age 70), who are susceptible to sarcopenia and often have co-morbidities. In older cancer patients, the median frailty prevalence has been estimated to be 42 % and a substantial proportion are pre-frail [14]. There is also considerable overlap between the known physical toxicities of ADT (e.g. sarcopenic obesity, fatigue and changes in muscle strength) and frailty. ADT may either be a direct cause of, or exacerbate, pre-existing frailty or pre-frailty [15].

This study aimed to characterise the 12-month longitudinal change in vBMD, bone microstructure, estimated bone strength, aBMD, markers of bone turnover (BTMs), body composition, physical functioning, fracture risk and frailty in men with localised or locally advanced PC commencing ADT compared to healthy men without PC. As an exploratory arm, we also investigated a group of patients who had newly diagnosed hormone sensitive metastatic PC, starting docetaxel chemotherapy and steroids alongside ADT. There have been few such studies in this group, where chemotherapy may affect bone metastases favourably, whilst the concurrent glucocorticoids may have adverse spinal effects.

2. Materials and methods

2.1. Study design

The ANTELOPE study was a prospective, longitudinal cohort study, designed with the participation of a local prostate cancer Patient and Public Involvement group. The study was registered on the ClinicalTrials.gov website (https://clinicaltrials.gov/), Project ID = NCT02785627).

Our primary objective was to compare the 12-month change in total distal radius vBMD in men with localised or locally advanced PC commencing ADT (Group A) with changes in age-matched healthy men without PC (Group C). Secondary objectives were to determine 12-month changes in (i) radius bone microstructure, stiffness and strength, (ii) spine and hip aBMD, (iii) serum BTMs, (iv) sex hormones, (v) body composition and (vi) physical functioning. Secondary objectives included all of the above for an exploratory group of patients (Group B) who were newly diagnosed with hormone sensitive metastatic PC starting docetaxel chemotherapy and steroids alongside ADT.

2.2. Study population

We recruited participants aged 50–85 years with WHO performance status 0–2. Androgen deprivation was achieved by use of GnRH agonists or antagonists. All participants in Groups A and B required histological confirmation of PC. Men were excluded if they had any condition(s) or were taking any medication known to affect bone metabolism; had experienced a fracture or undergone orthopaedic surgery within the past 12 months; showed evidence of significant abnormal organ function on standard laboratory testing or had a body mass index (BMI) outside the range 18.5 – 35.0 kg/m^2.

After giving fully informed, written consent, participants in Groups A and B were recruited from urology and oncology outpatient clinics, in Sheffield, UK (serving a regional population of 1.5 million). Group C participants were recruited from a database of healthy volunteers who

had participated in previous Sheffield studies or from responders to poster adverts and email advertising. Group C participants were individually matched to Group A participants during the study by age within +/- 5 years, height within +/- 5 cm and BMI within +/- 5 kg/m^2. Ethical approval was obtained from the South Yorkshire Research Ethics Committee in October 2016 (IRAS ID 206171) and participants were recruited between January 2017 and November 2018. All study procedures were carried out in accordance with the 1964 Declaration of Helsinki and later amendments, and with the International Conference on Harmonisation Good Clinical Practice (ICH GCP) guidelines.

All participants underwent study procedures at baseline (within 4 weeks of ADT initiation for Group A participants, and within 12 weeks for Group B) and at 12 months, unless otherwise stated and completed a standardised questionnaire which included risk factors for osteoporosis, fractures and frailty. Although it would have been desirable to include all Group B participants (newly diagnosed) within 4 weeks of starting ADT, this could not be mandated because of logistical issues in transfer of Group B patients from urology to oncology care.

2.3. HR-pQCT

HR-pQCT examinations of the distal radius were performed at baseline and repeated at 12 months using the XtremeCT (Scanco Medical AG, Bassersdorf, Switzerland) and in accordance with previously reported standard operating procedures [16]. In order to minimise any confounding effects arising from the possible presence of bone metastases, microstructural parameters were only assessed in the radius, since previous work in breast cancer has shown that, although metastases are uncommon in the peripheral skeleton, the prevalence was significantly lower in the radius (0.3 %), than the tibia (2.8 %) [17]. All examinations were performed on the non-dominant limb except for when a participant had sustained a prior fracture of the non-dominant radius, in which case the contralateral limb was imaged. A stack of 110 parallel CT slices was acquired over 9.8 mm in each participant, by two highly trained operators. A maximum of one repeat scan of the distal radius was performed in the event of patient movement [18]. The quality of the HR-pQCT scan images was assessed by the operator at the time of scan acquisition, using the visual grading system reported by Engelke et al [19].

HR-pQCT image segmentation and analysis were performed (again by two highly trained operators) using the standard in-built software (version 6.0, Scanco Medical AG, Bassersdorf, Switzerland). For the standard analysis, the 2D registration technique, incorporated into the Scanco Medical AG software, was utilised to match the baseline and 12 month scans. Extended cortical bone analysis techniques were applied to the segmented scans following the approach described by Burghardt et al [20]. Measures of estimated bone strength in the distal radius were determined by finite element analysis (FEA) using software developed by Scanco Medical AG (version 1.13; FE-solver included in the Image Processing Language) [21]. The outcome measures of interest were (i) total, trabecular, and cortical vBMD (mgHA/cm^3), (ii) bone area (mm^2), (iii) cortical thickness (mm), porosity (%) and perimeter (mm), (iv) trabecular thickness (mm), number (mm^{-1}), separation (mm), (v) trabecular bone volume fraction (Trab.BV/TV) and (vi) FEA estimates of stiffness (kN/mm), failure load (kN), Von Mises stresses (MPa) and trabecular/cortical load (%).

2.4. Dual energy X-ray absorptiometry (DXA)

aBMD of the lumbar spine (LS), proximal femur (total hip (TH) and femoral neck (FN)) and total body was measured at baseline and 12 months by dual energy x-ray absorptiometry (DXA) using a Hologic bone densitometer (a Discovery A, software version 13.4.2:3), or a Horizon A, software version 13.6.0.5:3, Hologic Inc, Bedford MA). Participants were scanned on the same densitometer at baseline and 12 months. Bone area (cm^2), bone mineral content (BMC (g)) and aBMD (g/cm^2) were measured at each anatomical site. T-scores were calculated in accordance with the 2023 International Society for Clinical Densitometry (ISCD) Official Positions Adult [22] using male reference data. Patients in any group found to have a T score $\leq$ -2.5 (i.e. at high risk of fracture and requiring osteoporosis treatment) were withdrawn from further study participation and referred for a Fracture Risk Assessment. Vertebra with obvious abnormalities such as fracture or bone metastasis were excluded on the lumbar spine scan. A T-score difference of more than 1 standard deviation between adjacent vertebrae was also indicative that the aBMD was likely to be inaccurate. A minimum of two evaluable vertebrae were required for analysis. One participant in group B had extensive lumbar vertebral metastases at baseline and was excluded from further participation. Participants were also excluded if the metastases were located within the total hip or femoral neck regions of interest.

Body composition (whole body and sub-regional lean and fat mass) was also assessed by DXA (data available in Supplementary Table 4).

2.5. Biochemical markers

Overnight fasting blood samples were obtained for real-time measurement of renal and thyroid function. The remaining samples were stored at −80 °C until all participant visits had been completed and then batch analysis was conducted. Serum testosterone, oestradiol, vitamin D and sex hormone binding globulin (SHBG) were measured using a Cobas e801 automated electrochemiluminescent immunoassay (ECLIA, Roche Diagnostics, Penzberg, Germany). Bone turnover markers including C-terminal telopeptide of type I collagen (CTX), N-terminal propeptide of type I procollagen (PINP), and osteocalcin were also measured using a Cobas e411 automated ECLIA (Roche Diagnostics, Penzberg, Germany, inter-assay CVs = 5.1 %, 3.3 % and 6.4 % respectively). Serum sclerostin was measured using an enzyme-linked immunosorbent assay (ELISA) (Cat no: BI-20492, Biomedica, Vienna, Austria, inter-assay CV = 7.3 %), and tartrate-resistant acid phosphatase (TRAcP 5b) was measured using the BoneTRAP® ELISA (Cat no: SB-TR201A, Immunodiagnostic Systems Ltd, Boldon, United Kingdom, inter-assay CV = 5.9 %).

2.6. Muscle function, physical functioning

Maximal grip strength was measured using a digital hand dynamometer (Saehan Corporation, Masan, Kyungsangnam-Do, South Korea). The short physical performance battery (SPPB) score [23] was calculated from a six metre walk, a narrow walk test and a chair stand test. Participants were given scores for each of these based upon their quartile results amongst all participants.

2.7. Fracture risk assessment (baseline only)

The FRAX fracture risk tool [24] was used to estimate the 10-year risk of hip fracture and major osteoporotic fracture (MOF) in all participants at baseline only. The risk was calculated both with, and without BMD data, and did not include ADT as a risk factor for secondary osteoporosis.

2.8. Frailty assessment

Frailty was defined using criteria from the Fried phenotype model [25] (slow gait speed, exhaustion, low physical activity, unintentional weight loss and poor handgrip strength) where frailty is defined as the presence of three or more of these.

2.9. Statistical considerations

The sample size calculation was based on the findings of a previous study [9] that measured bone structural change in men with PC. With 90 % power and 5 % two-sided significance, 24 participants were required in each of Groups A and C to detect a standardised difference of

0.96 mgHA/cm^3 in distal radius vBMD (primary outcome). To allow for a 10 % drop out rate, and also in anticipation of the fact that some men in Group B (with more advanced disease) would have disease progression during the study period, we aimed to recruit 30 participants to each group. Any participant that was excluded at baseline or lost to follow-up was replaced by additional recruitment. Participants in Group B that developed progressive disease, requiring a change in treatment during the study period, could have their 12-month visit brought forward, provided that they had been on the study for at least 6 months.

At baseline, independent samples t-tests were used to compare BMD, microstructure, FE analysis, body composition and fracture risk measurements between ADT groups and the control group. These data were normally distributed hence parametric statistical approaches were employed during these analyses. The Mann-Whitney *U* test was used to compare serum BTMs and hormone measurements. Non-parametric statistical testing was used as these data were not normally distributed. Paired samples t-tests were used to analyse the mean change from baseline for density, microstructure and body composition outcomes. Changes were compared between the ADT and control group using repeated measures ANOVA including an interaction between time and group. The Hodges-Lehmann median difference (non-parametric) was calculated for changes from baseline for serum measurements. Further analysis compared the measurements at 12 months between the ADT and control groups using ANCOVA including the 12-month measurement as the dependent variable, a fixed factor for group, and the baseline measurement as a covariate, adjusting for age and BMI. For the serum biomarker and hormone data the measurements were log transformed with the difference between groups presented as the ratio of geometric means (non-parametric statistical approaches were employed when analysing these data).

3. Results

3.1. Study participants

Fig. 1 shows a summary of ANTELOPE screening, recruitment and retention and Table 1 shows baseline demographics. There were no significant baseline differences in participant age, height, weight, BMI or fracture risk factors when comparing the three study groups. Few participants reported the use of dietary vitamin D (n = 5, 5 %) and calcium (n = 14, 16 %) supplements.

3.2. Prostate cancer treatment

Participants in Group A had a median PSA of 27.4 ng/ml at the time of their PC diagnosis. Two thirds had a Gleason score of 8 or 9, and the majority had T3 disease. Four participants in Group A had loco-regional lymph node involvement (N1). Twenty-seven participants in Group A received radical radiotherapy to the prostate or the prostate and pelvis during the 12-month study. The median duration of ADT before the baseline visit was 20 days (range 2 to 32 days). Group B participants had a median PSA of 98.6 ng/ml at the time of their PC diagnosis. All had metastatic disease and 21 participants had bone involvement. Of those who had a biopsy, 90 % had a Gleason score of $\geq$ 9. The median time from ADT initiation to the baseline study visit was 57 days (range 0 to 82 days). All Group B participants received chemotherapy and glucocorticoids as standard of care, although three participants received fewer than 5 cycles due to disease progression or unacceptable toxicity. The median dose of prednisolone (or equivalent) administered as concomitant treatment during chemotherapy was 2460 mg (range = 820 to 2460 mg).

3.3. Assessment of bone microstructural properties by HR-pQCT

Data from baseline and 12-month distal radius HR-pQCT scans were available for 56 participants (75 %). Two participants were not scanned at baseline – one due to an equipment fault and a second when the participant's arm could not be positioned correctly within the scanner gantry. One participant did not receive a follow-up scan at 12 months due to wrist swelling. Any other missing data were due to movement artefact that prevented image analysis – a well-recognised limitation of HR-pQCT. This was minimised by protocol-defined allowance of one

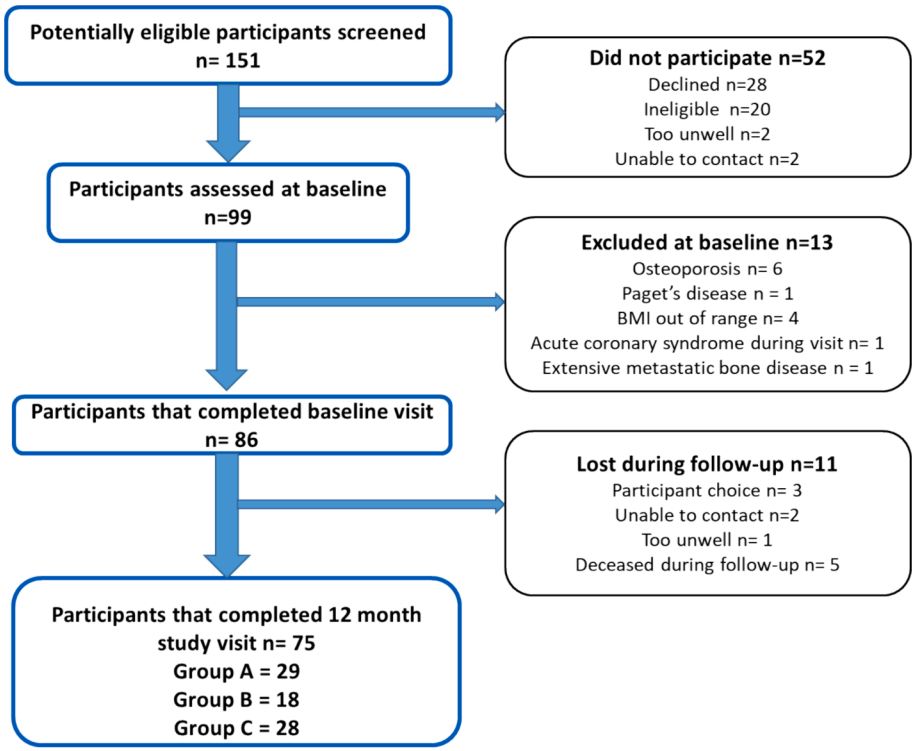

Fig. 1. Summary of ANTELOPE screening, recruitment and retention.

Table 1
Demographics and fracture risk at baseline.

	Group A (ADT) n = 31	Group B (ADT + chemo) n = 25	Group C (controls) n = 30	Difference between groups (ANOVA)
Median age	73	71	73	p = 0.8
(range)	(64–82)	(56–78)	(53–82)	
Height in cm	173.9	172.1	175.1	p = 0.69
(median, range)	(160.7–191.1)	(163.1–190.4)	(159.8–192.3)	
Weight in kg	81	81.3	81	p = 0.73
(median, range)	(60.3–119)	(56.7–103)	(58–116.2)	
BMI (kg/m^2)	26.9	26.8	26.3	p = 0.59
(median, range)	(21.9–34.4)	(19.8–32.5)	(20.4–34.9)	
Smoking status				
Current	2	2	2	
Previous	15	12	17	
Never	14	11	11	
Median PSA (ng/ml)	27.4	98.6	N/A	
Bone metastasis	0	21	N/A	
Glucocorticoids	0	25	N/A	
GNRH agonists/antagonists	31	25	N/A	
Median time, ADT to baseline (days)	20	57	N/A	
Previous major fracture	0	3	6	
Parental hip fracture	5	6	5	
FRAX 10-year risk				
FRAX MOF risk without BMD	6.60 (2.62)	7.24 (3.43)	7.25 (3.22)	
MOF risk with BMD	5.22 (2.5)	6.69 (3.92)	3.92 (2.89)	
Hip fracture risk without BMD	2.74 (2.64)	2.61 (2.48)	2.47 (1.34)	
Hip fracture risk with BMD	1.62 (2.13)	2.17 (3.42)	1.61 (1.33)	

repeat scan at each study visit. Participants with significant movement artefact on both baseline scans did not have a 12-month follow-up scan. HR-pQCT results are summarised in Table 2 and given in detail in Supplementary Table 1. At baseline, there were no significant differences in microstructural bone properties between Groups A and C.

By month 12, decreases in radius total vBMD were greater for the two

Table 2
Change in microarchitecture and finite element outcomes from HR-pQCT (distal radius).

Outcome	Group A (ADT) (n = 18)	Group B (ADT + chemo) (n = 15)	Group C (Controls) (n = 23)	Mean difference Groups A Vs C	P value *
Total vBMD					
12-month change in vBMD (mg HA/cm^3)	**−13.7**	**−13.5**	**−1.3**	**−11.7**	<0.001
(95 % CI)	(−17.8, −9.6)	(−21.6, −5.4)	(−4.3, 1.7)	(−16.7, −6.7)	
% change	4.1	4.3	0.4		
Cortical parameters					
12-month change in cortical vBMD (mg HA/cm^3)	**−27.1**	**−31.8**	**−7.5**	**−20.5**	<0.001
(95 % CI)	(–33.2—21.0)	(−46.8, −16.8)	(−12.7, −2.4)	(−28.7, −12.3)	
12-month change in cortical area (mm2)	**−5.9**	**−6.6**	**−1.6**	**−4.0**	<0.001
(95 % CI)	(−7.5, −4.3)	(−10.1–3.1)	(−2.9–0.3)	(−6.1, −1.9)	
12-month change in cortical thickness (mm)	**−0.07**	**−0.07**	**−0.02**	**−0.05**	0.001
(95 % CI)	(−0.09,-0.05)	(−0.11, −0.03)	(−0.03,0.004)	(−0.07, −0.02)	
12-month change in cortical perimeter (mm)	**0.1**	**0.2**	**0.2**	**−0.02**	0.911
(95 % CI)	(−0.2, 0.4)	(−0.2, 0.7)	(−0.1, 0.5)	(−0.46, 0.41)	
12-month change in cortical porosity **(%)**	**0.008**	**0.006**	**0.001**	**0.007**	0.002
(95 % CI)	(0.005, 0.012	(0.001, 0.012)	(−0.002,0.004)	(0.003, 0.011)	
Trabecular parameters					
12-month change in trabecular vBMD	**−2.2**	**−2.5**	**0.4**	**−2.6**	0.016
(95 % CI)	(−4.2, −0.3)	(−5.7, 0.7)	(−0.8, 1.5)	(−4.8, −0.5)	
12-month change in trabecular area	**3.6**	**2.2**	**0.9**	**2.7**	0.02
(95 % CI)	(2.0, 5.2)	(−2.3, 6.8)	(−0.6, 2.4)	(0.4, 4.9)	
12-month change in trabecular number	**−0.05**	**0.07**	**0.06**	**−0.09**	0.13
(95 % CI)	(−0.12,0.02)	(−0.06, 0.20)	(−0.04, 0.16)	(−0.22, 0.03)	
12-month change in trabecular thickness	**0.001**	**−0.004**	**−0.002**	**0.003**	0.18
(95 % CI)	(−0.001, 0.004)	(−0.008, 0.001)	(−0.006, 0.001)	(−0.001, 0.007)	
		−0.008	**−0.013**	**0.02**	
12-month change in trabecular separation	**0.012**	(−0.032, 0.016)	(−0.030, 0.005)	(−0.001, 0.05)	0.06
(95 % CI)	(−0.003, 0.027)	**−0.002**	**0.0002**	**−0.002**	
		(−0.005, 0.001)	(−0.001, 0.001)	(−0.004, −0.0002)	
12-month change in Trab.BV/TV	**−0.002**				0.03
(95 % CI)	(−0.003,-0.0001)				
Finite element analysis					
12-month change in mean stiffness (kN/mm)	**−4.4**	**−8.0**	**−2.4**	**−1.8**	0.24
(95 % CI)	(−6.1, −2.7)	(−12.9, −3.1)	(−5.0, 0.1)	(−4.8, 1.2)	
12-month change in mean ultimate failure load (kN)	**−0.24**	**−0.37**	**−0.10**	**−0.14**	0.032
(95 % CI)	(−0.32, −0.17)	(−0.60, −0.14)	(−0.21, 0.01)	(−0.26, −0.01)	

*ANCOVA with the 12-month measurement set as the dependent variable, with a fixed factor for group, and the covariates of age, BMI and baseline measurement.

ADT groups, Group A (mean change = -13.7 mgHA/cm^3 (4.1 %)) and Group B (mean change = -13.5 mgHA/cm^3 (4.3 %)) than for healthy age-matched men in Group C (mean change = -1.3 mgHA/cm^3 (0.4 %)). For primary outcome, there was a significantly greater decrease in vBMD in Group A versus Group C (mean difference = -11.7 mgHA/cm^3, 95 % CI = -16.7 to −6.7 mgHA/cm^3, $p < 0.001$).

Twelve months of ADT resulted in larger decreases in radius cortical vBMD in Group A (mean change = -27.1 mgHA/cm^3, (5.9 %)) and Group B (mean change = -31.8 mgHA/cm^3, (6.6 %)) than in Group C (mean change = -7.5 mgHA/cm^3 (1.6 %)). The decreases in cortical vBMD, observed between baseline and 12 months, were significantly larger for Group A than for Group C (mean difference = -20.5 mg HA/cm^3, 95 % CI = -28.7 to −12.3 mg HA/cm^3, $p < 0.001$). There were also significant differences in the mean 12-month change for cortical area ($p < 0.001$), cortical thickness ($p < 0.001$) and porosity ($p = 0.002$) when comparing Groups A and C (Table 2). Similar results were observed for trabecular vBMD (Supplementary Table 1).

Finite element analysis was performed in participants with both baseline and 12-month HR-pQCT scans (n = 56). At baseline, there were no between group differences in measures of estimated bone strength. By 12 months, decreases in estimated ultimate failure load and stiffness in all three study groups were evident − these were larger for Group B (mean changes = -0.37 kN and −8.0 kN/mm for estimated ultimate failure load and stiffness, respectively). Only the mean decrease in estimated ultimate failure load was significantly greater ($p = 0.03$) for Group A than that for Group C (mean difference = -0.14 kN, 95 % CI = -0.26 to −0.01 kN).

3.4. Change in aBMD using DXA

There were no significant between-group differences in aBMD at baseline, for all skeletal sites measured. Summary data for 12-month changes in aBMD are shown in Table 3 and displayed in full in Supplementary Table 2. Over the 12 months, participants in both ADT groups experienced a decrease in aBMD at all skeletal sites with the lumbar spine being most affected. Decreases in LS aBMD were significantly larger in Group A than in control Group C ($p < 0.001$). Areal BMD 12-month losses at the proximal femur were largest in Group A and were significantly greater than those observed in Group C for the femoral neck ($p < 0.001$) and total hip ($p < 0.001$) (Table 3, Supplementary Table 2).

A decrease was observed in Groups A and B in total body aBMD (−3.1 % and −3.2 %, respectively) and BMC (−3.3 % and −3.5 %, respectively). No significant changes in total body aBMD and BMC were apparent in Group C. Decreases in total body aBMD and BMC were significantly greater for Group A versus Group C ($p < 0.001$ and $p < 0.001$, respectively).

3.5. Serum sex hormones

At baseline, castration levels of serum testosterone (<1.7 nmol/L) were present in 11 (38 %) and 16 (89 %) participants in Group A and B, respectively. Group A had a baseline median serum testosterone of 2.0 nmol/L. By 12 months, this had decreased to below the lower limit of detection (<0.04 nmol/L). Participants in Group B had testosterone levels < 0.04 nmol/L at both baseline and 12 months. The controls (Group C) had serum testosterone levels within the normal reference range at both baseline (median = 15.7 nmol/L) and 12 months (median = 15.4 nmol/L). There were no significant changes in SHBG over the 12-month study period in any group and all SHBG results remained within the normal reference range limits.

Serum oestradiol levels were below the limit of assay detection (<91.8 pmol/L) at baseline in 23 (79 %) of Group A participants, and in 28 participants (97 %) at 12 months. They were below the limit of detection for all Group B participants at both time points. Oestradiol levels did not change in Group C participants (baseline median 96.0 pmol/L) and were within normal limits for healthy men.

Table 3
12-month change in aBMD using DXA.

Outcome	Group A (ADT) n = 29	Group B (ADT + chemo) n = 18	Group C (controls) n = 28	Mean difference A Vs C (95 % CI)	p value*
Change in mean femoral neck BMD (g/cm^2) (95 % CI)	−0.031 (−0.043, −0.02)	−0.029 (−0.059, 0.001)	0.005 (−0.003, 0.014)	−0.034 (−0.048 to −0.019)	<0.001
% change from baseline	**3.8**	**3.5**	**0.6**		
Change in mean total hip BMD (g/cm^2) (95 % CI)	−0.035 (−0.044, −0.026)	−0.029 (−0.052,-0.006)	0.001 (−0.005, 0.008)	−0.036 (−0.048 to −0.025)	<0.001
% change from baseline	**3.3**	**2.8**	**0.1**		
Change in lumbar spine BMD (g/cm^2) (95 % CI)	−0.045 (−0.061, −0.029)	−0.070 (−0.119,-0.021)	0.024 (0.012, 0.035)	−0.072 (−0.092 to −0.052)	<0.001
% change from baseline	**3.9**	**5.9**	**2.2**		
Change in mean total body BMD (g/cm^2) (95 % CI)	−0.038 (−0.050,-0.026)	−0.039 (−0.054,-0.024)	0.008 (−0.004,0.019)	−0.044 (−0.061 to −0.028)	<0.001
% change from baseline	**3.1**	**3.2**	**0.7**		
Change in bone mineral content (g) (95 % CI)	−94.3 (−120.9,-67.7)	−92.2 (−127.1, −57.3)	16.4 (−11.4, 44.2)	−110.5 (−147.6 to −73.5)	<0.001
% change from baseline	**3.3**	**3.5**	**0.6**		

*ANCOVA with the 12-month measurement set as the dependent variable, with a fixed factor for group, and the covariates of age, BMI and baseline measurement.

3.6. Changes in serum biomarkers of bone turnover

Data are summarised in Table 4 and presented in full in Supplementary Table 3. At baseline, serum PINP and CTX levels were similar in Groups A and C and highest in Group B (as expected in metastatic disease). After 12 months, there was a significant increase in PINP in Group A compared to control Group C (ratio of geometric means = 2.20, 95 % CI = 1.93 to 2.51, p < 0.001), but a corresponding increase in CTX (Group A vs Group C) did not reach significance. For Group B, CTX levels increased slightly after 12 months, but PINP levels appeared to decrease (Table 4).

At baseline, serum osteocalcin levels were similar in all three groups. By month 12, the largest change was observed in Group A. These changes were significantly greater for Group A than for Group C (ratio of geometric means = 1.43, 95 % CI = 1.16 to 1.75, p = 0.001). Outcomes for serum TRAP5b or sclerostin (Table 4) did not differ significantly between groups.

3.7. Muscle function and strength

At baseline, the maximal grip strength was similar between groups (Fig. 2 and Supplementary Table 4). Over 12 months, grip strength deteriorated in all groups with the greatest mean decreases being observed in Groups A and B. These decreases were significantly greater for Group A than for Group C (mean difference −4.9 kg, 95 % CI = -7.3 to −2.5 kg, p < 0.001). The total SPPB scores were similar between groups at baseline. By month 12, Group A experienced a significantly greater reduction in SPPB score than Group C (after adjustment for baseline SPPB score, age, and BMI).

3.8. Changes in body composition

ADT was associated with a significant 12-month increase in BMI (mean difference = +1.1 kg/m^2 Group A versus Group C, 95 % CI = +0.4 to + 1.7 kg/m^2, p = 0.001), despite similar baseline BMI (Fig. 3, Supplementary Table 5). By month 12, total fat mass and body fat percentage had increased in Groups A and B (Fig. 3). The largest changes were in Group A and were significantly greater than in Group C. Trunk fat mass increased significantly with ADT (mean difference = +1530 g, 95 % CI = +648 g to + 2413 g, p = 0.001, for Group A versus C), with the greatest increase in Group B (mean change = +1466 g).

No significant changes in the total body lean mass were evident over 12 months in any group. However, there was a notable decrease in upper limb lean mass (mean difference = -264 g, 95 % CI = -423 g to −105 g, p = 0.002 − for Group A versus C) and an increase in upper limb fat mass (mean difference = +627 g, 95 % CI = +453 g to + 803 g, p < 0.001, for Group A versus C) (Fig. 3, Supplementary Table 5).

Table 4
Serum hormones and biomarkers of bone turnover.

12-month change in biomarkers of bone turnover (median difference, IQR)	**Group A (ADT)** (n = 29)	**Group B (ADT + chemo)** (n = 18)	**Group C (controls)** (n = 28)	**Ratio of Geometric Means A Vs C** (95 % CI)	**p value***
PINP (ng/mL) (95 % CI)	51.7 (40.6, 62.3)	−54.9 (−211.9, 45.1)	0.4 (−2.8, 4.2)	2.20 (1.93, 2.51)	<0.001
CTX (ng/mL) (95 % CI)	0.36 (0.2, 0.54)	0.14 (−0.27, 0.43)	0.09 (0.02, 0.17)	1.43 (0.99, 2.08)	0.059
TRAP5b (U/L) (95 % CI)	1.36 (0.71, 1.98)	0.47 (−0.86, 2.01)	0.74 (0.25, 1.32)	0.99 (0.65, 1.52)	0.973
Osteocalcin (ng/mL) (95 % CI)	13.0 (9.0, 36.7)	3.4 (−19.9, 16.0)	2.6 (0.5, 4.5)	1.43 (1.16, 1.75)	0.001
Sclerostin (ng/mL (95 % CI)	5.2 (2.1, 9.9)	3.0 (−3.5, 8.6)	2.6 (−1.8, 6.8)	1.06 (0.94, 1.19)	0.348

*P-Value from ANCOVA model with log-transformed measurement as the dependent variable, including a fixed factor for group and baseline measurement, age and BMI as covariates.

3.9. Fracture risk

At baseline, there was no significant difference in hip fracture risk between groups, as determined using the FRAX fracture risk tool [20] both with and without BMD data (Table 1). Compared with the control group (Group C), participants in Group B had an increased risk of major fragility fracture when FN aBMD data were included in the FRAX fracture risk assessment. When calculated with clinical risk factors alone (i.e. FN aBMD not included in the assessment), no differences in hip fracture risk were evident. In all groups, including the healthy volunteers (Group C), more than 75 % of participants had a fracture risk above the UK National Osteoporosis Guideline intervention threshold for recommended bone targeted treatment.

3.10. Frailty

At baseline, frailty was prevalent in 32 % and 10 % of men in Groups B and C respectively. No participants in Group A were characterised as being frail and few as pre-frail (Fig. 4). After 12 months of ADT, the prevalence of frailty increased from baseline in Groups A and B, and almost all participants were either frail or pre-frail. In Group C, there was no significant change in the prevalence of frailty.

4. Discussion

Development of HR-pQCT in recent years has enabled more sophisticated clinical investigation of *in vivo* bone structure and related properties than was previously possible. In this study, we have demonstrated that HR-pQCT, used alongside a range of other more established techniques, including DXA, provides a comprehensive insight into of the effects of ADT on the skeletal health of men with PC.

4.1. Musculoskeletal data

This study has identified a significant 12-month decrease in distal radius vBMD (primary endpoint) (Table 2) in men with localised/locally advanced PC receiving ADT (Group A) compared to healthy matched controls (Group C). Similar effects were observed in men with more advanced PC receiving ADT and chemotherapy (Group B). Both cortical and trabecular vBMD contributed to the decrease in vBMD, with decreases in cortical vBMD accounting for the majority of this effect. We observed a slight decrease in vBMD in Group C that is consistent with previous findings reported by Riggs et al. [26].

ADT also resulted in a significant decrease in cortical area (7.9 %) and thickness (8.2 %) and an increase in cortical porosity in both Groups A and B compared to Group C. This is consistent with data from mouse models, where orchiectomy decreases cortical density and thickness [27]. However, we must recognise that our comparison with mouse models may not be completely appropriate as mice lack Haversian canals and do not undergo intracortical bone remodelling. Our results are also consistent with those from a longitudinal patient study, in which ADT led to a reduction in cortical area of 5.1 % after 6 months and of 11.5 % after 12 months [9]. The two likely mechanisms underlying the

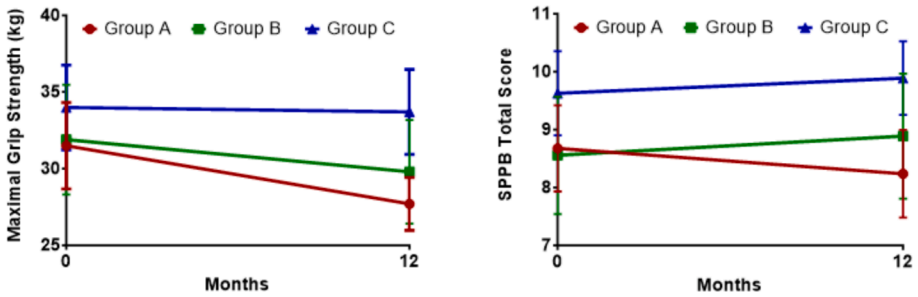

Fig. 2. 12-month change in maximal grip strength and total SPPB score. Group A, red line; Group B, green line; Group C, blue line. Error bars show 95% confidence intervals. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

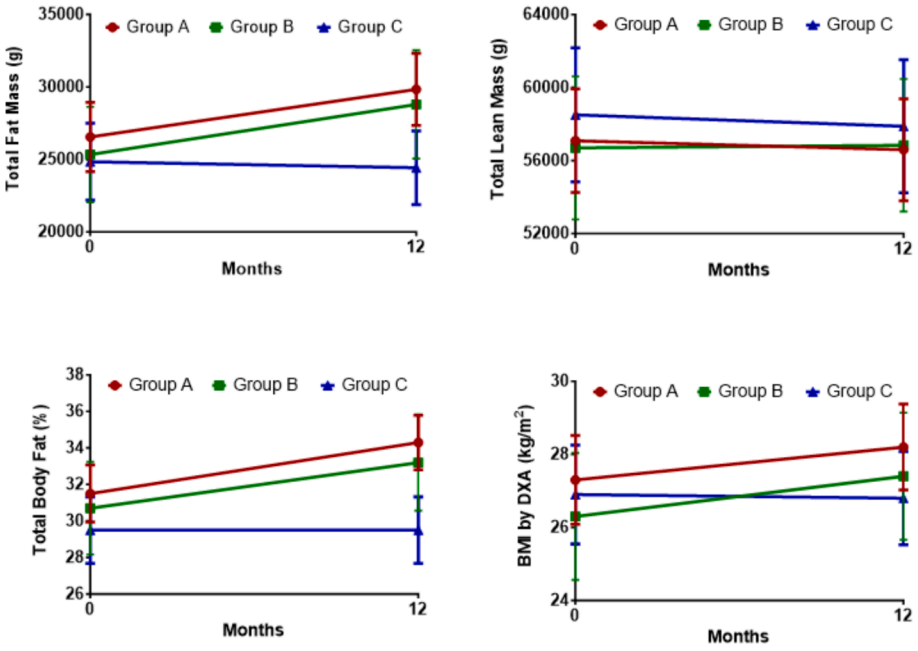

Fig. 3. 12-month change in body composition Group A, red line; Group B, green line; Group C, blue line. Error bars show 95% confidence intervals. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

cortical bone loss are an increase in cortical porosity and increased endocortical bone loss. Significant increases in trabecular area and decreases in Trab.BV/TV were observed in Group A when compared with Group C, and there was a tendency towards increased trabecular separation. Although previous knowledge of bone microstructural changes in men with PC receiving ADT is limited (and especially so in patients with metastatic disease receiving chemotherapy), Trab.BV/TV and duration of ADT have previously been correlated with total BMD at the ultradistal radius and ADT has also been associated with increased trabecular area [9,10] and a study (N = 78) by Russell et al included 26 % of participants with metastatic disease [11].

As expected, we found that 12 months of ADT resulted in a significant decrease in aBMD and aBMC at the lumbar spine, proximal femur and in total body ($p < 0.001$). The largest decreases in aBMD were in the lumbar spine (Group A = -3.9 % and Group B = 5.9 %). Group B losses may have been accentuated by the corticosteroids given with chemotherapy.

ADT reduced estimated bone stiffness and estimated ultimate failure load, although only the latter reached significance when comparing Group A with Group C. To our knowledge, there are no previously published data regarding FE analysis outcomes for estimated bone strength in men receiving ADT. Recent studies reported bone strength index (BSI) [28], calculated from peripheral quantitative computed tomography (pQCT) scans, in ADT and non-ADT treated men [29]. BSI at the distal radius was reduced by between 23.6 % and 27.5 % in men treated with ADT when compared to healthy men and PC controls ($p < 0.001$). However, BSI is a less sophisticated measure of estimated bone strength than FE analysis and may be affected by loss in total and trabecular vBMD. The largest decreases in distal radius stiffness and strength occurred in Group B. This may be a consequence of using ADT and glucocorticoid in combination. In an earlier study, central HR-QCT FEA evaluation of vertebra in men with glucocorticoid-induced osteoporosis found that estimated bone strength showed the most significant association with vertebral fracture [30].

Compared to the control group, 12 months of ADT resulted in an increase in BMI, total fat mass and total percent body fat with a large increase in trunk fat mass in both ADT groups. A decline in grip strength was also observed and may be explained by the loss in upper limb lean mass and gain in fat mass for Group A. Several studies have demonstrated accelerated loss of lean body mass and gain in body fat in men during the first 12 months of ADT. This sarcopenic obesity predisposes men to frailty, falls and fractures [31]. Our results show an increase in trunk fat mass associated with ADT, in agreement with studies reporting gains of + 1.4 to + 1.9 % in waist circumference after 6–12 months of ADT [32,33]. Our results are also consistent with cross-sectional data that have demonstrated an overall ADT-induced decline in upper body strength [34]. The SPPB score was calculated out of 12 points, and only small 12-month changes were observed, possibly because all

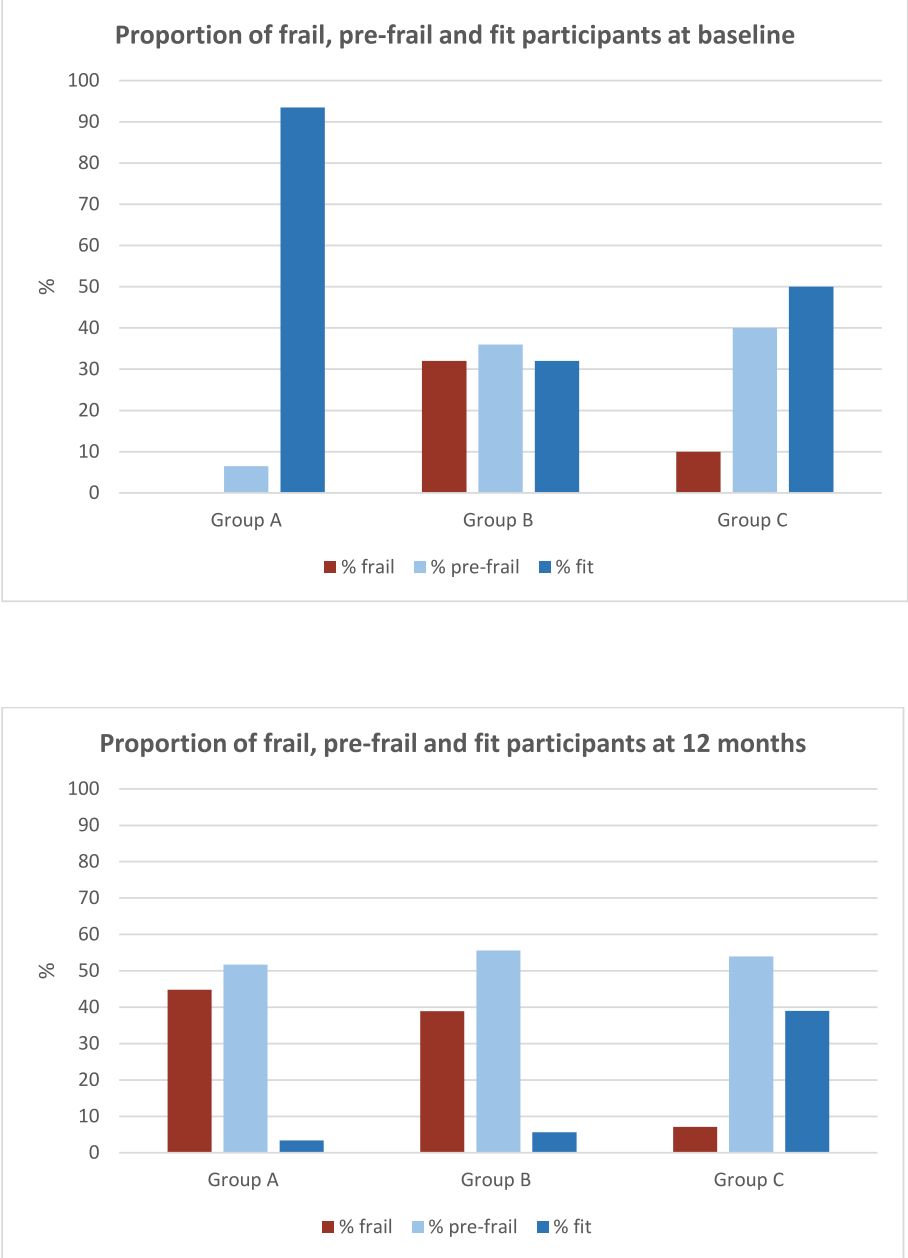

Fig. 4. 12-month change in prevalence of frailty.

participants in all groups scored the maximum of 4 points for the assessment of balance. Nevertheless, the decrease in SPPB score observed for Group A appeared to be significantly greater than that observed for Group C ($p = 0.001$). This finding could be explained by the ADT-induced loss in lean mass and gain in fat.

4.2. Serum data

Serum testosterone levels in Groups A and B were already low at baseline and this reflects the time between start of ADT and baseline assessments, as testosterone levels decrease rapidly after initiation of ADT. Ideally, study assessments would have been undertaken at the same time as ADT initiation, however this was not possible due to logistical restrictions (see Methods section).

The 12-month increases in both formation (PINP and Osteocalcin) and resorption (CTX) markers in Group A versus Group C are consistent with the expected ADT-induced increase in bone turnover. The resultant imbalance in bone remodelling correlates with the observed pathophysiological effects of deterioration of bone microstructure and BMD, measured in the same patients.

As expected, due to bone metastases, the baseline levels of PINP and CTX were high in Group B compared with Groups A and C. Interestingly, over the 12 months, PINP levels decreased considerably in Group B, most likely reflecting the response to docetaxel chemotherapy. In contrast to PINP and CTX, there was no significant change in TRAP5b levels between Groups A and C over the 12 months, indicating that TRAP5b may not be a sensitive marker of ADT-induced changes in bone turnover. Osteocalcin (a marker of osteoblast function which is raised during periods of high bone turnover) increased over the 12 months in Group B (relative to Group C), but to a lesser extent than in Group A. This lesser increase in Group B versus Group A is again likely to be due to the use of glucocorticoids in Group B participants. We observed a two-fold greater 12-month increase in sclerostin (an inhibitor of bone formation) in Group A versus Group C. However, this did not reach

statistical significance when adjusting for age and BMI at baseline. A previous cross sectional study reported higher sclerostin levels in men with non-metastatic PC when compared to healthy controls. Sclerostin levels were also higher in men with PC receiving ADT compared to men with PC not receiving ADT [35].

4.3. Frailty and fracture risk

Baseline prevalence of frailty was highest in Group B (participants with advanced PC). By month 12, pre-frailty and frailty increased in both ADT groups relative to Group C with the largest change in Group A. Thus, our study confirms that ADT accelerates the development of frailty in men with PC. Given the association of frailty with important clinical outcomes such as hospitalization and death, this consequence of ADT use should be considered carefully when initiating ADT treatment in older men with PC. Further studies are needed to identify risk factors for frailty in men receiving ADT and to explore effective interventions that can reduce ADT-associated decline in frailty status.

More than three-quarters of our study participants had a calculated fracture risk above the recommended threshold for treatment in osteoporosis. This is in keeping with previously reported findings from a study in 363 men receiving ADT, where 76.6 % of those aged 70–79 years met the criteria for treatment, and where age had a significant impact on the recommendations for treatment. The estimated hip fracture risk in our study is similar to published data from large studies in male populations [36,37] and in men with PC, where the hip fracture risk was between 1–3 % [38,39]. In more than 6,000 men participating in the STAMPEDE trial, the FRAX risk of hip fracture in men with hormone sensitive PC starting ADT was 3.06 % and the risk of MOF was 8.7 %, when clinical risk factors were used without BMD. The inclusion of BMD has been shown to produce a lower estimate of fracture risk than FRAX without BMD data. Currently, there is a lack of prospective, robust data in large, multi-ethnic cohorts. Future studies which examine the association between FRAX and fracture end points, compare FRAX in ADT and non-ADT treated men, and explore the relationship between fracture risk and duration of ADT, are required.

4.4. Strengths and limitations

This study has used a combination of established and novel techniques to investigate longitudinal changes in bone turnover, density, structure and strength in ADT-treated men with PC – including men with metastatic hormone sensitive PC, treated with chemotherapy.

A key strength of ANTELOPE is the prospective study design, and inclusion of a longitudinal control group that were well-matched by age and BMI. However, the study had limitations. We allowed for 10 % of participants to be excluded or lost to follow-up. Unsurprisingly, the greatest loss to follow-up was in Group B patients with more advanced disease. Furthermore, logistics caused some delays between ADT initiation and baseline assessment, though this is unlikely to have significantly affected the longer-term bone changes. An additional challenge to the final sample size arose from motion artefact on HR-pQCT scans, though the extent of this was similar to that reported in non-PC studies. In it also important to acknowledge that since there is no slice matching for FEA and cortical porosity assessment, the differences observed for estimated bone strength and cortical porosity, between the two scans may be subject to errors.

It is also possible that a 12-month follow-up period may not be sufficient to detect changes in some factors. However, for a study involving an advanced prostate cancer population, longer times could involve substantial drop out. Interestingly, Table 2 shows that the 12 month changes (Group A vs Group C) in trabecular vBMD and BV/TV reach statistical significance, whilst the trabecular changes in number, thickness and separation do not. In part at least, the discrepancy may be due to the accuracy with which the small differences in some of the parameters can be measured. Also, not all of the parameters are directly measured, but are derived by different means [40].

4.5. Conclusions

The ANTELOPE study has demonstrated the value of HR-pQCT imaging in assessing PC treatment bone loss when used in combination with more traditional bone investigation approaches such as DXA, though the latter remains a valuable tool, since the changes of areal BMD are of the same magnitude as those observed for volumetric BMD with HR-pQCT.

The use of the HR-pQCT technique should be considered when studying the effects of anti-androgens and other novel PC treatments on bone and in studies to devise strategies for the prevention of bone loss.

5. Data statement

The data that support the findings of this study are available on reasonable request from the corresponding author. All requests will be reviewed by relevant stakeholders on the basis of a controlled access approach. The data are not publicly available due to privacy or ethical restrictions.

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CRediT authorship contribution statement

Catherine Handforth: Writing – review & editing, Writing – original draft, Visualization, Validation, Methodology, Investigation, Formal analysis, Data curation. **Margaret A. Paggiosi:** Writing – review & editing, Writing – original draft, Validation, Supervision, Resources, Project administration, Methodology, Investigation, Formal analysis, Data curation. **Richard Jacques:** Writing – review & editing, Visualization, Validation, Formal analysis, Data curation. **Fatma Gossiel:** Writing – review & editing, Visualization, Validation, Methodology, Investigation. **Richard Eastell:** Writing – review & editing, Visualization, Validation, Formal analysis, Data curation. **Jennifer S. Walsh:** Writing – review & editing, Validation, Supervision, Project administration, Methodology, Investigation, Funding acquisition, Data curation, Conceptualization. **Janet E. Brown:** Conceptualization, Data curation, Formal analysis, Funding acquisition, Investigation, Methodology, Project administration, Resources, Supervision, Visualization, Writing – original draft, Writing – review & editing, Validation.

Declaration of competing interest

CH – Fellowship funding from Weston Park Cancer Charity MAP – none RJ – none FG – none RE receives consultancy funding from Immunodiagnostic Systems, Sandoz, Samsung, CL Bio, CureTeQ, Biocon, Takeda, UCB, meeting presentations for Pharmacosmos, Alexion, UCB and Amgen, and grant funding from Alexion and Osteolabs. JSW – none JEB – has served as a consultant or adviser for Novartis, Ipsen, Amgen, Merck Sharp & Dohme, Bristol-Myers Squibb, and Bayer; honoraria from Novartis, Ipsen, Amgen, Merck Sharp & Dohme, BristolMyers Squibb, and Bayer; research funding paid to their institution from the National Institute for Health and Care Research and Weston Park Cancer Charity; and travel expenses from Ipsen.

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Appendix A. Supplementary data

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