Title
Accelerated Bone Loss in Older Men: Effects on Bone Microarchitecture and Strength

Journal
Journal of Bone and Mineral Research, 33(10)

ISSN
0884-0431

Authors
Cauley, Jane A
Burghardt, Andrew J
Harrison, Stephanie L
et al.

Publication Date
2018-10-01

DOI
10.1002/jbmr.3468

Peer reviewed

HHS Public Access

Author manuscript

J Bone Miner Res. Author manuscript; available in PMC 2019 October 01.

Published in final edited form as:

J Bone Miner Res. 2018 October ; 33(10): 1859–1869. doi:10.1002/jbmr.3468.

Accelerated bone loss in older men: Effects on bone microarchitecture and strength

J.A. Cauley[1], **A.J. Burghardt**[2], **S.L. Harrison**[3], **P.M. Cawthon**[3], **A.V. Schwartz**[4], **E. Barrett Connor**[5], **Kristine E. Ensrud**[6,7,8], **Lisa Langsetmo**[6], **S. Majumdar**[2], **E. Orwoll**[9], and **the Osteoporotic Fractures in Men (MrOS) Research Group**

[1]Department of Epidemiology, University of Pittsburgh, Pittsburgh, PA;

[2]Department of Radiology and Biomedical Imaging, University of California, San Francisco, San Francisco, CA;

[3]California Pacific Medical Centre, San Francisco, CA;

[4]Department of Epidemiology and Biostatistics, University of California, San Francisco, San Francisco, CA;

[5]University of California, San Diego, La Jolla, CA;

[6]Department of Medicine Community Health, University of Minnesota, Minneapolis, MN

[7]Division of Epidemiology & Community Health, University of Minnesota, Minneapolis, MN;

[8]Center for Chronic Disease Outcomes Research, VA Health Care System, Minneapolis, MN;

[9]Oregon Health & Science University, Portland OR

Abstract

Accelerated bone loss (ABL) shown on routine dual-energy X-ray absorptiometry (DXA) may be accompanied by microarchitectural changes, increased cortical porosity and lower bone strength. To test this hypothesis, we performed a cross-sectional study and used high resolution peripheral quantitative computed tomography (HR-pQCT) scans (SCANCO, Inc., Switzerland) to measure estimated bone strength and microarchitecture in the distal radius and distal and diaphyseal tibia. We studied 1628 men who attended the Year 14 exam of the Osteoporotic Fractures in Men (MrOS) study. We retrospectively characterized areal (a) bone mineral density (BMD) change from the Year 7 to Year 14 exam in 3 categories: “accelerated” ≥10% loss at either the total hip or femoral neck, (N=299, 18.4%); “expected” loss, <10%, (N=1061, 65.2%) and “maintained” BMD, ≥0%, (N=268, 16.5%). The ABL cutoff was a safety alert established for MrOS. We used regression models to calculate adjusted mean HR-pQCT parameters in men with ABL, expected loss or maintained BMD. Men who experienced ABL were older and had a lower body mass index and aBMD and experienced greater weight loss compared to other men. Total volumetric BMD and trabecular and cortical volumetric BMD were lower in men with ABL compared to the

Corresponding author: Jane A. Cauley, DrPH, University of Pittsburgh, Graduate School of Public Health, 130 DeSoto Street, Crabtree A510, Pittsburgh, PA 15261, jcauley@pitt.edu,.

Drs. Cauley, Cawthon, Schwartz, Ensrud, Langsetmo, Stefanick, Majumdar, Orwoll and Mr. Burghardt and Ms. Harrison have no conflicts.

expected or maintained group. Men with ABL had significantly lower trabecular bone volume fraction (BV/TV), fewer trabeculae and greater trabecular separation at both the distal radius and tibia than men with expected loss or who maintained aBMD, all p trend <0.001. Men with ABL had lower cortical thickness and lower estimated bone strength but there was no difference in cortical porosity except at the tibia diaphyseal site

Abstract

In summary, men with ABL have lower estimated bone strength, poorer trabecular microarchitecture and thinner cortices than men without ABL but have similar cortical porosity. These impairments may lead to an increased risk of fracture.

INTRODUCTION

Low areal bone mineral density (aBMD) is an established risk factor for fracture in both men and women [1,2] even over 25 years [3]. In contrast, *changes* in BMD have been shown to predict fractures in some [4–8] but not all studies [9–11]. In the Osteoporotic Fractures in Men (MrOS) study, we showed that accelerated decrease in aBMD was a strong independent risk factor for hip and non-spine fractures [12].

High resolution peripheral quantitative computed tomography (HR-pQCT) enables a non-invasive assessment of bone microarchitecture. HR-pQCT provides essential information on both cortical and trabecular volumetric (v) BMD as well as bone microarchitecture, and estimated strength. The aim of the current analysis was to test the hypothesis that accelerated bone loss (ABL) by dual-energy X-ray absorptiometry (DXA) is associated with microarchitectural deterioration in bone, cortical porosity and loss of estimated bone strength. We performed a cross-sectional study of 1628 men who attended the Year 14 exam of the MrOS study and had HR-pQCT scans of the distal radius, distal tibial and diaphyseal tibia and aBMD scans of the femoral neck and/or total hip.

METHODS

Study Population

A total of 5994 community-dwelling men ≥65 years old were enrolled from 2000 to 2002 in the prospective MrOS study [13]. Participants were recruited in six regions of the United States [14]. Individuals with a history of bilateral hip replacement or the inability to walk without the assistance of another person were not eligible to participate. The institutional review board at each participating institution approved the study protocol and written informed consent was obtained from all participants. The analytic sample for this analysis consisted of 1628 men, Figure 1.

Measurement of aBMD

At all study visits, participants who attended the clinic visit had hip DXA scans completed on Hologic 4500 scanners (Hologic, Waltham, MA, USA) as previously described [12]. Briefly, centralized quality-control procedures, certification of DXA operators, and standardized procedures for scanning were used to ensure reproducibility of DXA

measurements. Each clinic scanned a spine and hip phantom throughout the study to monitor longitudinal changes in measures of aBMD, and correction factors were applied to participant data as appropriate. To adjust for inter-clinic differences, statistical models include indicator variables for clinical center. The precision of DXA scans of the spine and hip is 1% to 2% in clinical settings [15]; the coefficient variation of the MrOS DXA scanners estimated using a central phantom ranged from 0.3% to 0.7% for the total hip (data not shown). Each participant's right hip was scanned unless there was a fracture, implant, hardware, or other problem preventing the right hip from being scanned; in those instances, the left hip was scanned.

MrOS investigators established a safety alert for ABL that was used to identify men who need to be referred to their personal physical. This safety alert was approved the MrOS Observational Study Monitoring Board. Men whose bone loss exceeded this threshold were informed by study physician/nurses and encouraged to see their physician. ABL was defined as ≥10% loss at either the total hip or femoral neck from the Year 7 to Year 14 exam, an average of 7.3 years apart. Men whose bone loss was <10% were considered to have experienced "expected" aBMD loss. Men whose aBMD change was ≥0% were considered to have "maintained/increased" BMD.

Measurement of HR-pQCT Parameters

HR-pQCT scans were completed using XtremeCT II machines (SCANCO Medical AG, Brüttisellen, Switzerland), which have nominal voxel size of 61μm. Operators were centrally trained and certified to perform the imaging protocol, including an online scan positioning operator calibration procedure that has been shown to reduce inter-operator measurement error for bone outcomes by approximately 50% [16]. Operators acquired scans of the distal radius (9 mm from the articular surface), distal tibia (22 mm from the articular surface), and diaphyseal tibia (centered at 30% of tibial length, as externally measured from tibial plateau proximally to the tibial malleolus at the distal end) [17]. The radius from the non-dominant arm and the tibia from the ipsilateral leg were scanned except in the case of prior fracture, metal shrapnel or implant, amputation or recent complete non-weight bearing period >6 weeks during the previous 12 months. Machines were calibrated and a single cross-calibration density phantom was circulated among the study sites. The between site calibration coefficients were all <0.6%, and therefore pooled data were used without transformations [18]. The standard local density phantom was scanned on a daily basis to monitor for values that fell outside of the nominal range (8 mg HA/cm^3). Centralized quality assurance (QA) and standard analysis of all image data, including micro finite element analysis (μFEA), was performed.

A central observer read all images for motion artifacts and used an established semi-quantitative 5-point grading system (1=superior, 5=poor) to score image quality. Images scored with 4 or 5 were deemed to be of insufficient quality and were excluded from the analytic data set (97% of scans image grade ≤3) [19]. A fully automated analysis pipeline was developed to segment the radius and tibia for quantification of bone density and structure[20]. For this study, an automated QA algorithm was developed to detect bone segmentation errors. The slice-wise variation in total cross-sectional area was measured to

identify contours that failed to locate the outer cortical perimeter of the radius or tibia; cases with an absolute slice-wise difference of 2 mm^2 at the diaphysis, and 4 mm^2 at the distal sites, were visually reviewed and manually corrected, as needed. Observed failure rates were <2% and <6%, for diaphyseal and distal scans, respectively.

Volumetric BMD (vBMD) and cross sectional area of the total, cortical, and trabecular compartments were measured. Cortical porosity and thickness, and trabecular thickness, separation and number were calculated directly [21,22]. Of note, there are significant differences in how the SCANCO software measure trabecular thickness and trabecular spacing in the second generation XtremeCT scans. However, the scales of our measures are consistent with the XtremeCT II validation data reported by Manke et al [22] and differences compared to the first generation XtremeCT scanner are consistent with comparisons reported by Agarwal et al [23]. Linear elastic micro-finite element analysis of a 1% uniaxial compression was performed using a homogenous elastic modulus of 10 GPa and a Poisson's ratio of 0.3 (SCANCO FE Software v1.12, SCANCO Medical). The failure load or estimated bone strength was estimated by calculation of the reaction force at which 7.5% of the elements exceed a local effective strain of 0.7% [24].

All participants with outliers (difference from mean >3 SDs) were reviewed and those with abnormal anatomic findings at a given skeletal site (e.g. severe inflammatory arthritis, osteolytic lesions, injuries with ossification, unreported fracture) were excluded. Scans with motion and other scans that were identified for exclusion by our QA process (e.g., scan positioning error/problem) were also excluded (distal radius n=61, distal tibia n=47, diaphyseal tibia n=58) from the analysis for that skeletal site.

Other Measurements

Covariates were measured at the Year 14 exam with the exception of date of birth and race/ethnicity which were collected at baseline. All men who attended the Year 14 exam completed questionnaires and were interviewed about health status. Physical activity was assessed using the Physical Activity Scale for the Elderly (PASE) [25]. Body weight (indoor clothing without shoes) was measured on balance beam or digital scales; height was measured using a Harpenden stadiometer (Dyved, UK). Body mass index (BMI) was calculated as weight (kg)/height (m^2). Weight change was calculated by subtracting Year 7 weight from Year 14 weight and expressed as a percentage of the Year 7 value. Weight change was categorized as moderate weight loss (loss ≥10%), mild weight loss (loss 5% to <10%), stable weight (<5% loss or gain) or weight gain (gain ≥5%) based on standard cut-offs for clinically relevant weight changes in older adults and availability of sufficient numbers of participants in each category [26,27].

Medical history included self-reported physician diagnosis of chronic obstructive pulmonary disease (COPD), hypertension, myocardial infarction (MI), congestive heart failure (CHF), stroke and diabetes. Information on fall history in the past 12-months and alcohol consumption was obtained. Men self-reported their health as excellent/good, fair, poor or very poor. Men also reported limitations in 5 instrumental activities of daily living (IADL) including meal preparation, shopping, housework, walking 2–3 blocks and climbing 10 steps. Participants were asked to bring all current (any use within in the past 30 days)

prescription medications with them to the clinic. All prescription medications were recorded in an electronic medication inventory database and matched to its ingredients based on the Iowa Drug Information Service drug vocabulary (College Pharmacy, University of Iowa, Iowa City, USA) [28]. Osteoporosis medications included bisphosphonates, parathyroid hormone and denosumab.

STATISTICAL ANALYSES

Differences in the characteristics of 1628 men in the analytic cohort across aBMD loss categories were compared using chi-squared tests for categorical variables and ANOVA for continuous variables. We used linear regression models to calculate least square mean HR-pQCT parameters in men who experienced ABL, expected loss in aBMD and who maintained their aBMD with tests for trend. Base models adjusted for age, clinic and limb length. The multivariate (MV) models also adjusted for height, weight, health status, physical activity, difficulty with any IADL, alcohol consumption and a history of CHF or diabetes. To test whether the association between aBMD loss and HR-pQCT parameters was independent of aBMD at Year 7, we further adjusted models for femoral neck aBMD. We have previously shown that weight loss was associated with lower bone strength and greater aBMD loss in a non-linear manner [29]. Thus, to test whether the associations were mediated by weight change, we adjusted for the four categories of weight change. A small number of men self-reported using osteoporosis medications at the Year 7 and/or Year 14 exam. In additional analyses, we adjusted for osteoporosis medication use, (Supplemental Table 1). We performed additional analyses of HR-pQCT data across quartiles of changes in femoral neck aBMD, (Supplemental Table 2a and 2b).

RESULTS

About 18% of men experienced ABL and 16.5% maintained or increased their aBMD between the Year 7 and Year 14 exam, Table 1. Men with ABL were older (mean age 86 years) compared to men who maintained or experienced expected aBMD loss (mean age 84 years), Table 1. The majority (≈92%) of men were white. Men who experienced ABL had lower weight, height and BMI at Year 14 and experienced greater weight loss from the Year 7 visit and from baseline. They were less likely to self-report their health as excellent/good, drink alcohol and had lower physical activity. Almost half of these men had difficulty with at least one IADL compared to about 30% of the other men. There was no difference in the prevalence of smoking, COPD, hypertension, MI or stroke. Men who experienced ABL were twice as likely to self-report CHF but were less likely to report diabetes than men who maintained their aBMD. A higher proportion of men who experienced ABL reported falling at least once in the past year. aBMD at the femoral neck and total hip were lower in men with ABL at both the Year 7 and Year 14 exam, p trend=0.0001. The average change in aBMD from the Year 7 to year 14 exam was 11% at the total hip and 13% at the femoral neck among men with ABL compared to about a 3–4% decline among men with “expected” aBMD loss and 3% gain among men who were considered “maintainers”. A higher proportion of men with ABL reported use of osteoporosis medications. There were no differences in the use of corticosteroids across aBMD loss categories. A small number of men (n=6) reported androgen deprivation therapy (ADT) and the number of men on ADT

was greatest in men with ABL. Thus, we excluded all men reporting ADT from further analyses.

Distal Radius

Total area did not differ in men who experienced ABL, expected loss or who maintained their aBMD. Total, trabecular and cortical vBMD were all significantly lower in men who experienced ABL. vBMD decreased in a graded fashion comparing men who maintained, experienced expected aBMD loss and men with ABL, p trend <0.0001. The differences in the MV models were for total BMD (13% lower), trabecular vBMD (10% lower) and cortical vBMD (5% lower) comparing men with ABL to men who maintained their aBMD.

The cortical area was 5% smaller among men with ABL compared to men who maintained their aBMD. The mean cortical thickness was 11% lower in men who experienced ABL compared to men who maintained their aBMD. There was no difference in cortical porosity across the aBMD change groups. The microarchitecture of the distal radius revealed 6% lower trabecular number, 9% greater trabecular separation and 11% lower trabecular bone volume fraction among men who experienced ABL compared to men who maintained or increased their aBMD, Table 2. There was no difference in trabecular thickness across aBMD loss groups.

Estimated failure load was 15.2% lower in men with ABL compared to men who maintained their aBMD and almost 11% lower than men who experienced expected aBMD loss, p trend, <0.0001. Further adjustment for femoral neck aBMD had no effect on our results.

Distal Tibia

There were modest differences (3%, p=0.008) in total area between men with ABL compared to men who maintained their aBMD, Table 3. The total, trabecular and cortical vBMD were 12%, 7%, 6%, respectively (MV models) lower in men with ABL compared to men who maintained their aBMD. Cortical area was almost 13% lower in men with ABL compared to men who maintained aBMD, p <0.0001. Cortical thickness was 11% lower in men with ABL but there was no difference in cortical porosity across aBMD groups. Similar to results for the distal radius, the trabecular number was 3% lower, trabecular separation, 4% higher, and trabecular bone volume fraction, 6% lower among men who experienced ABL compared to men who maintained their aBMD, Table 3. The estimated failure load was significantly 12% lower in men who experience ABL compared to men who maintained their aBMD. Further adjustment for aBMD had little effect on our results.

Diaphyseal Tibia

Results were similar at the tibial diaphyseal with significantly lower vBMD, lower cortical area, lower cortical thickness and lower estimated failure load in men who experienced ABL, in comparison to men who maintained aBMD or experienced expected loss (all p trend <0.05), Table 4. Cortical porosity was 12% greater in men with ABL compared to the maintained group, p trend, 0.014. Further adjustment for aBMD had no effect on our results.

Additional Analyses

We additionally adjusted for use of osteoporosis medications at the Year 7 and/or Year 14 exam. Results were essentially unchanged (Supplemental Table 1). We also adjusted for weight change from Year 7 to Year 14 but since we included Visit 14 weight in the models (final weight), adjusting for weight change had no effect (data not shown). Finally, we examined the HR-pQCT parameters across quartiles of change in femoral neck aBMD and results were generally similar, (Supplemental Table 2).

DISCUSSION

Our current cross-sectional results suggest that ABL is accompanied by low vBMD, poor microarchitecture, lower estimated bone strength as measured by finite element analysis. Results were consistent at both the radius and tibia suggesting that the loss of microarchitecture and strength is consistent at weight bearing and non-weight bearing skeletal sites. This suggests that other factors in addition to mechanical loading, such as, age related declines in hormones and lean mass may underlie these associations [30]. Results were consistent for both trabecular and cortical vBMD. There was little difference in the overall size of the bone across aBMD loss groups but men who experienced ABL had significantly lower cortical area and cortical thickness. There was no difference in trabecular thickness or cortical porosity at either the distal radius or distal tibia. In summary, ABL is accompanied by changes in microarchitecture, density and strength that may contribute to an increased fracture risk.

Measures of microarchitecture and estimated strength have been prospectively linked to incident fractures in both men [31] and women [32,33]. One standard deviation decrease in cortical area, cortical bone mass and trabecular bone volume fraction were associated with a 1.6–2.0 fold increased risk of fracture independent of aBMD [31]. In MrOS, lower failure load at the diaphyseal tibia and distal radius were associated with an increased risk of fractures, independent of the Fracture Risk Assessment Tool (FRAX®) with aBMD [34]. Thus, our results suggest that ABL is accompanied by these microarchitecture and strength changes that have been prospectively linked to increased fracture risk.

Men who experienced ABL differed from men who experienced expected loss or maintained/increased their aBMD. They were older, had lower BMI, were less likely to self-report excellent/good health, reported more falls in the past years, had lower physical activity, were less likely to drink alcohol, and more IADL disability. All of these characteristics suggest an overall poorer health status among men with ABL. However, we adjusted for health status in our MV models. Of importance, men with ABL started out with lower hip aBMD at Year 7. Nevertheless, ABL was associated with lower vBMD, poor microarchitecture and lower estimated bone strength independent of aBMD.

We have recently shown a non-linear association between weight change and failure load at the radius and tibia in MrOS [29]. Greater weight loss was also associated with lower cortical thickness and cortical vBMD (but not trabecular vBMD or trabecular microarchitecture). One-third of men with ABL experienced moderate weight loss (≥ 10% weight loss) since the Year 7 visit, compared to 7% of men who maintained or increased their aBMD. However,

adjustment for weight change had no effect on our results likely because all models included the final weight at Visit 14.

Men who experienced ABL had lower cortical thickness and cortical vBMD at all 3 skeletal sites but there was no difference in cortical porosity except at the diaphyseal tibia. This latter finding may have occurred by chance, but it could reflect the larger cortical areal at the diaphyseal tibia site and improved detection of cortical porosity. The lack of a difference in cortical porosity at the distal radius and distal tibia is surprising since cortical porosity is a main determinant of cortical density and we saw large differences in cortical density. In older men with ABL, minimal measurable cortical bone remains at distal sites due to sustained intra- and endo- cortical bone loss that has led to trabecularization of the cortex. Highly trabecularized cortical bone is not included in the cortical compartment. With increasing trabeculization, the residual cortex leaves less measurable porosity. Older men may also simply have cortices that are too thin or too trabecularized to properly measure this parameter. But it may also reflect the limitations of even second generation HR-pQCT scanners or the associated algorithms in detecting cortical porosity at these skeletal sites.

Increases in bone turnover markers, specifically, higher C-terminal crosslinking telopeptide of Type I collagen (CTX), and collagen Type I N-terminal propeptide (PINP) were associated with faster cortical and trabecular bone loss at the femoral neck and proximal femur in both older men and women [35]. Increases in CTX and PINP were also associated with periosteal expansion at the femoral neck in men only. Other studies have shown that increasing bone turnover markers predict rates of bone loss in women transitioning menopause [36] and in older women [37]. Thus, ABL may lead to these microarchitecture, and strength changes because of accelerated bone turnover. We were unable to test this hypothesis because we do not have measures of bone turnover at Year 7 or 14.

We have shown in MrOS that men with lowest estradiol, lowest testosterone and highest sex hormone binding globulin experience faster rates of bone loss [38]. Men who had serum 25-hydroxyvitamin D <20 ng/ml also experienced faster rates of bone loss [39]. Chronic low grade inflammation may also contribute to faster rates of bone loss [40]. Thus, there are many physiological factors that could lead to ABL and contribute to these microarchitectural and estimated strength changes.

To our knowledge, there have been few studies of sex steroid hormones, vitamin D and vBMD, microarchitectural and estimated strength as measured by HR-pQCT. A small study of 72 obese men with metabolic syndrome showed that men with estradiol below the median (43 pmol/L) had lower trabecular number, greater trabecular separation and lower bone volume fraction than men with higher estradiol levels but these comparisons were unadjusted for body weight [41]. A study of postmenopausal women reported positive associations between estradiol and trabecular vBMD, cortical area and estimated strength of the ultra-distal forearm but these associations were not significant in the MV model [42]. Bioavailable testosterone was also related to cortical area in the univariate analysis. A study of 109 subjects (62% women) showed little relationship between 25(OH)D and HR-pQCT parameters in the radius or tibia [43]. Among patients with primary hyperparathyroidism,

there was no relationship of 25(OH)D and any HR-pQCT measure [44]. More is clearly needed on the physiological factors that contribute to skeletal integrity.

It is quite remarkable that 18% of men maintained or increased their aBMD into their 9th decade of life indicating that bone loss may not be an inevitable consequence of aging in older men. There is substantial heterogeneity in the manner that individuals age and it will be important to understand what factors contributed to their maintenance of aBMD. Only a small number of men who maintained their aBMD reported use of osteoporosis medications at either the Year 7 or Year 14 exam. It is unlikely that the low prevalence of osteoporosis medications accounted for the larger group of men who maintained aBMD. We have no information on sex steroid hormones, but given the higher body weight among men who maintained aBMD, it is possible that these men who had maintained their aBMD had higher circulating estradiol levels than men who experienced accelerated loss. There are likely other factors that contribute, such as, maintenance of muscle mass greater physical activity. Maintenance of aBMD in older women was associated with lower mortality [45] and may also represent a phenotype of successful aging in older men.

A higher percentage of men with ABL reported taking medications for osteoporosis. However, the overall use of these medications was low and adjustment for these medications had little effect on our results.

This study has several strengths. We studied a large cohort of men in their ninth decade of life with longitudinal assessment of aBMD loss over 7 years. Measures of HR-pQCT in this cohort are unique. Centralized QA and standard analysis of HR-pQCT image data were performed. We adjusted for important covariates. However, this study also has several limitations. The cohort was predominately Caucasian community dwelling men, so results may not be generalizable to other groups. Multiple statistical comparisons were performed and some of the observed associations may have occurred by chance alone. However, for the most part our results were consistent across the 3 skeletal sites. We were unable to test whether the ABL is due to low sex steroid hormones, low vitamin D, or higher bone turnover because these biomarkers are not available at the year 7 or 14 exam. Finally, we used an observational study design and the possibility of residual confounding by unmeasured factors remains.

In conclusion, men with ABL have poorer microarchitecture, thinner cortices and lower estimated strength than men without ABL. These impairments may lead to an increased risk of fracture and deserves further examination.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgment

The Osteoporotic Fractures in Men (MrOS) Study is supported by National Institutes of Health funding. The following institutes provide support: the National Institute on Aging (NIA), the National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS), the National Center for Advancing Translational Sciences (NCATS), and NIH Roadmap for Medical Research under the following grant numbers: U01 AG027810, U01 AG042124,

U01 AG042139, U01 AG042140, U01 AG042143, U01 AG042145, U01 AG042168, U01 AR066160, and UL1 TR000128.

References

1. Cummings SR, Cawthon PM, Ensrud KE, Cauley JA, Fink HA, Orwoll ES. BMD and risk of hip and nonvertebral fractures in older men: a prospective study and comparison with older women. J Bone Miner Res. 2006;21(10):1550–6. [PubMed: 16995809]
2. Marshall D, Johnell O, Wedel H. Meta-analysis of how well measures of bone mineral density predict occurrence of osteoporotic fractures. Bmj. 1996;312(7041):1254–9. [PubMed: 8634613]
3. Black DM, Cauley JA, Wagman R, et al. The Ability of a Single BMD and Fracture History Assessment to Predict Fracture Over 25 Years in Postmenopausal Women: The Study of Osteoporotic Fractures. J Bone Miner Res. 2018;33(3):389–95. [PubMed: 28719727]
4. Hillier TA, Stone KL, Bauer DC, et al. Evaluating the value of repeat bone mineral density measurement and prediction of fractures in older women: the study of osteoporotic fractures. Arch Intern Med. 2007;167(2):155–60. [PubMed: 17242316]
5. Nguyen TV, Center JR, Eisman JA. Femoral neck bone loss predicts fracture risk independent of baseline BMD. J Bone Miner Res. 2005;20(7):1195–201. [PubMed: 15940372]
6. Crandall CJ, Hovey KM, Andrews CA, et al. Bone Mineral Density as a Predictor of Subsequent Wrist Fractures: Findings From the Women's Health Initiative Study. J Clin Endocrinol Metab. 2015;100(11):4315–24. [PubMed: 26367200]
7. Leslie WD, Brennan-Olsen SL, Morin SN, Lix LM. Fracture prediction from repeat BMD measurements in clinical practice. Osteoporos Int. 2016;27(1):203–10. [PubMed: 26243362]
8. Leslie WD, Majumdar SR, Morin SN, Lix LM. Change in Bone Mineral Density Is an Indicator of Treatment-Related Antifracture Effect in Routine Clinical Practice: A Registry-Based Cohort Study. Ann Intern Med. 2016;165(7):465–72. [PubMed: 27428723]
9. Berry SD, Samelson EJ, Pencina MJ, et al. Repeat bone mineral density screening and prediction of hip and major osteoporotic fracture. JAMA. 2013;310(12):1256–62. [PubMed: 24065012]
10. Berger C, Langsetmo L, Joseph L, et al. Association between change in BMD and fragility fracture in women and men. J Bone Miner Res. 2009;24(2):361–70. [PubMed: 18847328]
11. Leslie WD, Morin SN, Lix LM, Manitoba Bone Density P. Rate of bone density change does not enhance fracture prediction in routine clinical practice. J Clin Endocrinol Metab. 2012;97(4): 1211–8. [PubMed: 22278427]
12. Cawthon PM, Ewing SK, Mackey DC, et al. Change in hip bone mineral density and risk of subsequent fractures in older men. J Bone Miner Res. 2012;27(10):2179–88. [PubMed: 22648990]
13. Orwoll E, Blank JB, Barrett-Connor E, et al. Design and baseline characteristics of the osteoporotic fractures in men (MrOS) study--a large observational study of the determinants of fracture in older men. Contemp Clin Trials. 2005;26(5):569–85. [PubMed: 16084776]
14. Blank JB, Cawthon PM, Carrion-Petersen ML, et al. Overview of recruitment for the osteoporotic fractures in men study (MrOS). Contemp Clin Trials. 2005;26(5):557–68. [PubMed: 16085466]
15. Cummings SR, Bates D, Black DM. Clinical use of bone densitometry: scientific review. JAMA. 2002;288(15):1889–97. [PubMed: 12377088]
16. Bonaretti S, Vilayphiou N, Chan CM, et al. Operator variability in scan positioning is a major component of HR-pQCT precision error and is reduced by standardized training. Osteoporos Int. 2017;28(1):245–57. [PubMed: 27475931]
17. Bonaretti S, Majumdar S, Lang TF, Khosla S, Burghardt AJ. The comparability of HR-pQCT bone measurements is improved by scanning anatomically standardized regions. Osteoporos Int. 2017;28(7):2115–28. [PubMed: 28391447]
18. Burghardt AJ, Pialat JB, Kazakia GJ, et al. Multicenter precision of cortical and trabecular bone quality measures assessed by high-resolution peripheral quantitative computed tomography. J Bone Miner Res. 2013;28(3):524–36. [PubMed: 23074145]
19. Pialat JB, Burghardt AJ, Sode M, Link TM, Majumdar S. Visual grading of motion induced image degradation in high resolution peripheral computed tomography: impact of image quality on measures of bone density and micro-architecture. Bone. 2012;50(1):111–8. [PubMed: 22019605]

20. Burghardt AJ, Buie HR, Laib A, Majumdar S, Boyd SK. Reproducibility of direct quantitative measures of cortical bone microarchitecture of the distal radius and tibia by HR-pQCT. Bone. 2010;47(3):519–28. [PubMed: 20561906]
21. Hildebrand T, Laib A, Muller R, Dequeker J, Ruegsegger P. Direct three-dimensional morphometric analysis of human cancellous bone: microstructural data from spine, femur, iliac crest, and calcaneus. J Bone Miner Res. 1999;14(7):1167–74. [PubMed: 10404017]
22. Manske SL, Zhu Y, Sandino C, Boyd SK. Human trabecular bone microarchitecture can be assessed independently of density with second generation HR-pQCT. Bone. 2015;79:213–21. [PubMed: 26079995]
23. Agarwal S, Rosete F, Zhang C, et al. In vivo assessment of bone structure and estimated bone strength by first- and second-generation HR-pQCT. Osteoporos Int. 2016;27(10):2955–66. [PubMed: 27155883]
24. Mueller TL, Christen D, Sandercott S, et al. Computational finite element bone mechanics accurately predicts mechanical competence in the human radius of an elderly population. Bone. 2011;48(6):1232–8. [PubMed: 21376150]
25. Washburn RA, Ficker JL. Physical Activity Scale for the Elderly (PASE): the relationship with activity measured by a portable accelerometer. J Sports Med Phys Fitness. 1999;39(4):336–40. [PubMed: 10726435]
26. Ensrud KE, Harrison SL, Cauley JA, et al. Impact of Competing Risk of Mortality on Association of Weight Loss With Risk of Central Body Fractures in Older Men: A Prospective Cohort Study. J Bone Miner Res. 2017;32(3):624–32. [PubMed: 27739103]
27. Newman AB, Yanez D, Harris T, et al. Weight change in old age and its association with mortality. J Am Geriatr Soc. 2001;49(10):1309–18. [PubMed: 11890489]
28. Pahor M, Chrischilles EA, Guralnik JM, Brown SL, Wallace RB, Carbonin P. Drug data coding and analysis in epidemiologic studies. Eur J Epidemiol. 1994;10(4):405–11. [PubMed: 7843344]
29. Ensrud KE, Vo TN, Burghardt AJ, Schousboe JT, Cauley JA, Taylor BC, Hoffman AR, Orwoll EO, Lane NE, Langsetmo L, for the Osteoporotic Fractures in Men (MrOS) Research Group Weight Loss in Men in Late Life and Bone Strength and Microarchitecture: A Prospective Study. Osteoporosis International (submitted). 2017.
30. Cauley JA, Ewing SK, Taylor BC, et al. Sex steroid hormones in older men: longitudinal associations with 4.5-year change in hip bone mineral density--the osteoporotic fractures in men study. J Clin Endocrinol Metab. 2010;95(9):4314–23. [PubMed: 20554716]
31. Ohlsson C, Sundh D, Wallerek A, et al. Cortical Bone Area Predicts Incident Fractures Independently of Areal Bone Mineral Density in Older Men. J Clin Endocrinol Metab. 2017;102(2):516–24. [PubMed: 27875059]
32. Boutroy S, Khosla S, Sornay-Rendu E, et al. Microarchitecture and Peripheral BMD are Impaired in Postmenopausal White Women With Fracture Independently of Total Hip T-Score: An International Multicenter Study. J Bone Miner Res. 2016;31(6):1158–66. [PubMed: 26818785]
33. Sornay-Rendu E, Boutroy S, Duboeuf F, Chapurlat RD. Bone Microarchitecture Assessed by HR-pQCT as Predictor of Fracture Risk in Postmenopausal Women: The OFELY Study. J Bone Miner Res. 2017;32(6):1243–51. [PubMed: 28276092]
34. Langsetmo L, Peters K, Burghardt AJ, et al. Volumetric Bone Mineral Density and Failure Load of Distal Limbs Predict Incident Clinical Fracture Independent of FRAX and Clinical Risk Factors Among Older Men. 2017 (under review).
35. Marques EA, Gudnason V, Lang T, et al. Association of bone turnover markers with volumetric bone loss, periosteal apposition, and fracture risk in older men and women: the AGES-Reykjavik longitudinal study. Osteoporos Int. 2016;27(12):3485–94. [PubMed: 27341810]
36. Shieh A, Ishii S, Greendale GA, Cauley JA, Lo JC, Karlamangla AS. Urinary N-telopeptide and Rate of Bone Loss Over the Menopause Transition and Early Postmenopause. J Bone Miner Res. 2016;31(11):2057–64. [PubMed: 27322414]
37. Ivaska KK, Gerdhem P, Vaananen HK, Akesson K, Obrant KJ. Bone turnover markers and prediction of fracture: a prospective follow-up study of 1040 elderly women for a mean of 9 years. J Bone Miner Res. 2010;25(2):393–403. [PubMed: 19961336]

38. Cauley JA, Parimi N, Ensrud KE, et al. Serum 25-hydroxyvitamin D and the risk of hip and nonspine fractures in older men. J Bone Miner Res. 2010;25(3):545–53. [PubMed: 19775201]

39. Ensrud KE, Taylor BC, Paudel ML, et al. Serum 25-hydroxyvitamin D levels and rate of hip bone loss in older men. J Clin Endocrinol Metab. 2009;94(8):2773–80. [PubMed: 19454586]

40. Cauley JA, Danielson ME, Boudreau RM, et al. Inflammatory markers and incident fracture risk in older men and women: the Health Aging and Body Composition Study. J Bone Miner Res. 2007;22(7):1088–95. [PubMed: 17419681]

41. Ornstrup MJ, Kjaer TN, Harslof T, et al. Adipose tissue, estradiol levels, and bone health in obese men with metabolic syndrome. Eur J Endocrinol. 2015;172(2):205–16. [PubMed: 25416724]

42. Melton LJ, 3rd, Riggs BL, Muller R, et al. Determinants of forearm strength in postmenopausal women. Osteoporos Int. 2011;22(12):3047–54. [PubMed: 21308363]

43. Boyd SK, Burt LA, Sevick LK, Hanley DA. The relationship between serum 25(OH)D and bone density and microarchitecture as measured by HR-pQCT. Osteoporos Int. 2015;26(9):2375–80. [PubMed: 25851697]

44. Walker MD, Nishiyama KK, Zhou B, et al. Effect of Low Vitamin D on Volumetric Bone Mineral Density, Bone Microarchitecture, and Stiffness in Primary Hyperparathyroidism. J Clin Endocrinol Metab. 2016;101(3):905–13. [PubMed: 26745256]

45. Cauley JA, Lui LY, Barnes D, et al. Successful skeletal aging: a marker of low fracture risk and longevity. The Study of Osteoporotic Fractures (SOF). J Bone Miner Res. 2009;24(1):134–43. [PubMed: 18715137]

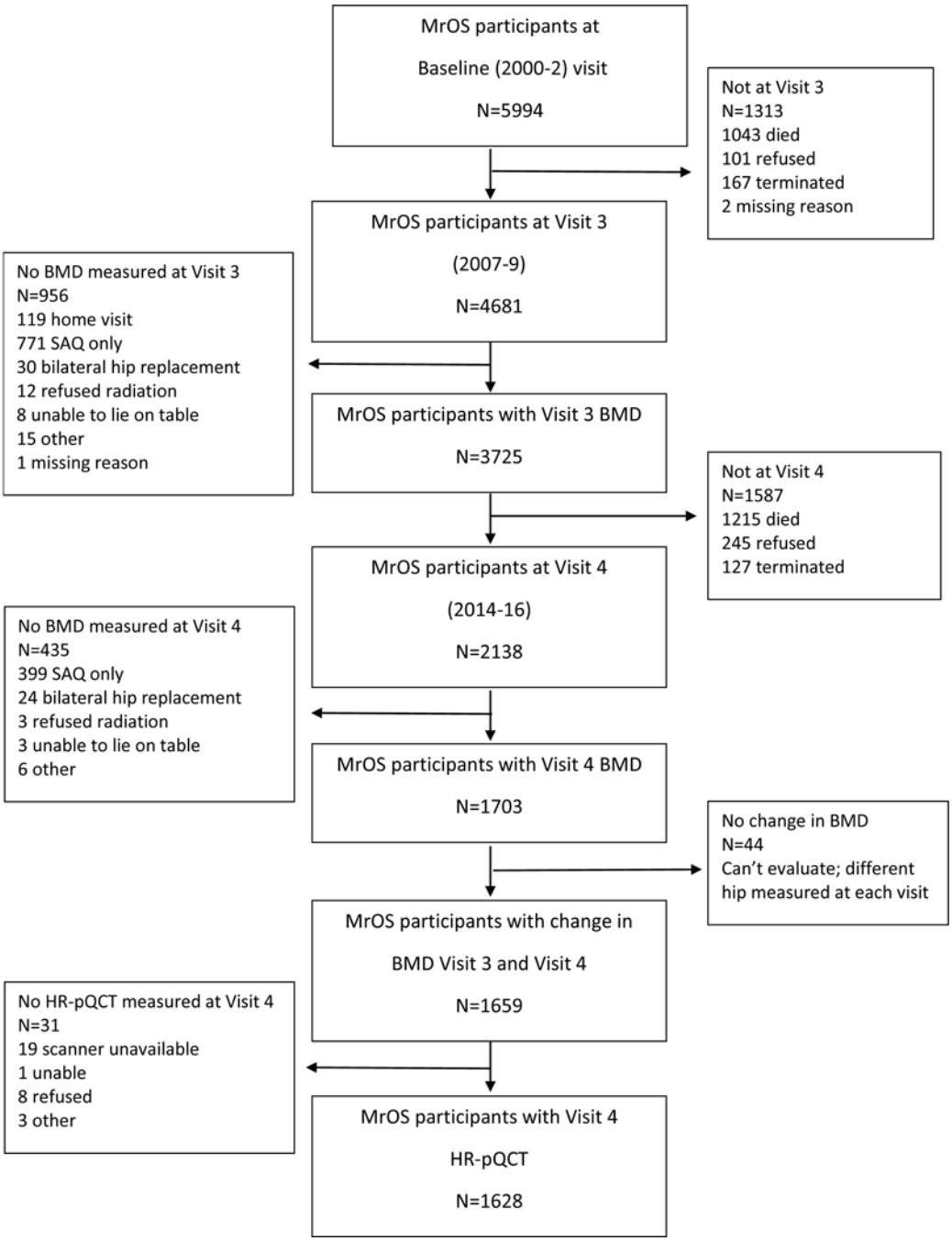

Figure 1:
Participant flow: Analytic sample.

Table 1.

Characteristics of men at Year 14 across bone mineral density (BMD) change categories (Year 7 to Year 14)

Characteristics	Accelerated BMD Loss 10% or more decrease in BMD (N= 299/ 18.4%)	Expected BMD Loss <10% decrease in BMD (N= 1061/ 65.2%)	Maintained or increased BMD (≥0 BMD change) (N= 268/ 16.5%)	p-value
Age (y), mean +/− SD	86.0 +/− 4.7	84.1 +/− 4.0	84.2 +/− 4.1	<0.0001
Race (white vs. other)	277 (92.6)	978 (92.2)	246 (91.8)	0.93
BMI (kg/m2), mean +/− SD	25.8 +/− 3.5	26.7 +/− 3.6	28.1 +/− 3.7	<0.0001
Weight (kg), mean +/− SD	75.6 +/− 11.5	79.5 +/− 12.0	84.4 +/− 13.0	<0.0001
Height (cm), mean +/− SD	171.2 +/− 7.3	172.3 +/− 6.7	173.3 +/− 7.2	0.0018
Change in weight since Year 7 visit (%)				
≥10% weight loss	100 (33.4)	118 (11.1)	20 (7.5)	<0.0001
5%−9% weight loss	92 (30.8)	258 (24.3)	44 (16.4)	
Weight gain or loss ≥5%	94 (31.4)	605 (57.1)	161 (60.1)	
≥5% WEIGHT GAIN	13 (4.4)	79 (7.5)	43 (16.0)	
Change in weight since Year 7 visit (%)	−7.2 +/− 7.5	−3.2 +/− 5.9	−0.7 +/− 6.3	<0.0001
Change in weight since baseline (%)	−11.7 +/− 10.6	−5.3 +/− 8.3	−2.4 +/− 8.0	<0.0001
Self-reported health (excellent/good), n (%)	249 (83.8)	957 (90.8)	234 (87.3)	0.0022
Drinks per week, n (%)				
No use	134 (45.1)	402 (38.1)	97 (36.6)	0.0088
<13 Drinks/week)	157 (52.9)	604 (57.3)	148 (55.9)	
≥14 Drinks/week)	6 (2.0)	48 (4.6)	20 (7.6)	
Smoking				
None	126 (47.0)	494 (47.2)	157 (52.9)	0.18
Past	117 (43.7)	430 (41.1)	103 (34.7)	
Current	25 (9.3)	123 (11.7)	37 (12.5)	
Physical Activity for the Elderly (PASE) score, mean +/− SD	99.1 +/− 64.0	118.6 +/− 64.7	115.8 +/− 68.5	<0.0001
Difficulty with >1 instrumental activity of daily living, n (%)	146 (49.7)	303 (28.8)	79 (29.6)	<0.0001
chronic obstructive pulmonary disease, n (%)	40 (13.4)	118 (11.1)	32 (11.9)	0.56
Hypertension, n (%)	148 (49.5)	532 (50.2)	149 (55.6)	0.25
Myocardial infarction, n (%)	49 (16.4)	145 (13.7)	30 (11.2)	0.20
Congestive heart failure, n (%)	43 (14.4)	82 (7.7)	16 6.0)	0.0003

J Bone Miner Res. Author manuscript; available in PMC 2019 October 01.

Characteristics	Accelerated BMD Loss 10% or more decrease in BMD (N= 299/ 18.4%)	Expected BMD Loss <10% decrease in BMD (N= 1061/ 65.2%)	Maintained or increased BMD (≥0 BMD change) (N= 268/ 16.5%)	p-value
Diabetes, n (%)	53 (17.7)	146 (13.8)	53 (19.8)	0.0267
Stroke, n (%)	19 (6.4)	55 (5.2)	12 (4.5)	0.58
Fallen in past 12 months, n (%)	133 (44.5)	393 (37.1)	92 (34.3)	0.027
Total hip BMD (gm/cm^2) (Year 7)	0.92 +/−0.13	0.97 +/− 0.13	0.99 +/− 0.15	<0.0001
Total hip BMD (gm/cm^2) (Year 14)	0.82 +/− 0.13	0.94 +/− 0.13	1.02 +/− 0.53	<0.0001
Change in total hip BMD				
Year 7 to Year 14	−11.44 +/− 5.6	−3.00 +/− 3.1	2.77 +/− 2.2	<0.0001
Baseline to Year 14	−14.05 +/− 7.2	−4.27 +/− 7.2	2.47 +/− 4.6	<0.0001
Femoral neck BMD (Year 7)	0.75 +/− 0.12	0.79 +/− 0.12	0.81 +/− 0.1	<0.0001
Femoral neck BMD (Year 14)	0.65 +/− 0.11	0.76 +/− 0.12	0.84 +/− 0.51	<0.0001
Change in femoral neck BMD				
Year 7 to Year 14	−12.98 +/− 5.2	−3.01 +/− 3.9	4.11 +/− 4.0	<0.0001
Baseline to Year 14	−15.3 +/− 7.2	−4.68 +/− 6.0	3.13 +/− 7.1	<0.0001
Osteoporosis meds				
Year 7, n (%)	23 (8.6)	43 (4.1)	10 (3.3)	0.0035
Year 14, n (%)	13 (4.9)	34 (3.2)	4 (1.4)	0.0570
Corticosteroid use, n (%)	34 (12.7)	156 (14.7)	42 (14.1)	0.69
Antiandrogen use, n (%)	3 (1.1)	1 (0.1)	2 (0.7)	0.0059

Table 2:

HR-pQCT parameters at the Distal Radius across categories of bone mineral loss (BMD) *

Parameters	BMD Loss, Mean (95% confidence interval)			P trend
	Accelerated (≥10% decreased BMD)	Expected (<10% decreased BMD)	Maintained/Increased (≥0 BMD change)	
Total vBMD (mg/cm^3)				
Base[1]	254.6 (247.7, 261.5)	276.2 (272.6, 279.7)	289.3 (282.1, 296.4)	<0.0001
MV[2]	255.7 (248.6, 262.7)	276.0 (272.4, 279.6)	288.3 (281.1, 295.6)	<0.0001
MV + FNBMD[3]	258.3 (252.0, 264.7)	275.6 (272.4, 278.8)	287.0 (280.4, 293.5)	<0.0001
Total area (mm^2)				
Base[1]	393.2 (386.0, 400.3)	397.5 (393.8, 401.2)	396.9 (389.5, 404.2)	0.47
MV[2]	398.8 (391.9, 405.7)	397.2 (393.7, 400.7)	390.6 (383.6, 397.7)	0.11
MV + FNBMD[3]	398.8 (391.9, 405.7)	397.2 (393.7, 400.7)	390.7 (383.6, 397.7)	0.12
Trabecular vBMD (mg/cm^3)				
Base[1]	160.3 (155.7, 164.9)	170.8 (168.5, 173.2)	178.5 (173.8,183.3)	<0.0001
MV[2]	160.9 (156.2, 156.7)	170.9 (168.5, 173.7)	176.9 (172.1, 181.8)	<0.0001
MV + FNBMD[3]	162.9 (158.8, 167.0)	170.6 (168.5, 172.7)	176.0 (171.7, 180.2)	<0.0001
Cortical vBMD (mg/cm^3)				
Base[1]	773.0 (765.3, 780.8)	797.3 (793.3, 801.3)	811.3 (803.3, 819.3)	<0.0001
MV[2]	775.0 (767.1, 783.0)	796.9 (792.9, 800.9)	812.3 (804.2, 820.4)	<0.0001
MV + FNBMD[3]	776.3 (768.5, 784.1)	796.7 (792.8, 800.6)	811.7 (803.7, 819.7)	<0.0001
Trabecular area (mm^2)				
Base[1]	336.9 (329.5, 344.3)	335.6 (331.8, 339.4)	332.6 (325.0, 340.3)	0.43
MV[2]	341.5 (334.3, 348.8)	335.5 (331.8, 339.1)	327.2 (319.8, 334.6)	0.0081
MV + FNBMD[3]	340.9 (333.7, 348.1)	335.6 (331.9, 339.2)	327.5 (320.1, 334.9)	0.0127
Cortical area (mm^2)				
Base[1]	60.9 (59.2, 62.5)	66.5 (65.7, 67.4)	68.9 (67.2, 70.5)	<0.0001
MV[2]	62.0 (60.4, 63.7)	66.4 (65.5, 67.2)	68.0 (66.3, 69.7)	<0.0001
MV + FNBMD[3]	62.5 (61.0, 64.1)	66.3 (65.5, 67.1)	67.8 (66.2, 69.3)	<0.0001
Trabecular volume fraction, mm^3				
Base[1]	0.222 (0.216, 0.229)	0.238 (0.235, 0.242)	0.249 (0.242, 0.256)	<0.0001
MV[2]	0.223 (0.216, 0.230)	0.238 (0.235, 0.242)	0.247 (0.240, 0.254)	<0.0001
MV + FNBMD[3]	0.226 (0.220, 0.232)	0.238 (0.235, 0.241)	0.245 (0.239, 0.252)	<0.0001

Parameters	BMD Loss, Mean (95% confidence interval)			P trend
	Accelerated (≥10% decreased BMD)	Expected (<10% decreased BMD)	Maintained/Increased (≥0 BMD change)	
Trabecular number, mm^{-1}				
Base[1]	1.35 (1.32, 1.37)	1.40 (1.39, 1.42)	1.46 (1.43, 1.48)	<0.0001
MV[2]	1.36 (1.33, 1.38)	1.41 (1.39, 1.42)	1.44 (1.42, 1.47)	<0.0001
MV + FNBMD[3]	1.36 (1.34, 1.39)	1.40 (1.39, 1.42)	1.44 (1.41, 1.46)	<0.0001
Trabecular separation, (mm)				
Base[1]	0.734 (0.717, 0.752)	0.691 (0.681, 0.700)	0.658 (0.640, 0.676)	<0.0001
MV[2]	0.731 (0.713, 0.749)	0.690 (0.681, 0.699)	0.665 (0.646, 0.683)	<0.0001
MV + FNBMD[3]	0.725 (0.709, 0.742)	0.691 (0.682, 0.699)	0.668 (0.651, 0.685)	<0.0001
Trabecular thickness, mm				
Base[1]	0.246 (0.244, 0.248)	0.247 (0.246, 0.248)	0.248 (0.246, 0.251)	0.20
MV[2]	0.246 (0.244 (0.248)	0.247 (0.246, 0.248)	0.249 (0.247, 0.251)	0.10
MV + FNBMD[3]	0.247 (0.245, 0.249)	0.247 (0.246, 0.248)	0.248 (0.246, 0.251)	0.24
Cortical thickness (mm)				
Base[1]	0.887 (0.861, 0.914)	0.965 (0.951, 0.978)	0.995 (0.968 1.022)	<0.0001
MV[2]	0.895 (0.869, 0.922)	0.962 (0.949, 0.976)	0.993 (0.965, 1.020)	<0.0001
MV + FNBMD[3]	0.903 (0.878, 0.928)	0.961 (0.948, 0.974)	0.989 (0.963, 1.015)	<0.0001
Cortical porosity(%)				
Base[1]	1.52 (1.42, 1.61)	1.60 (1.55, 1.65)	1.61 (1.51, 1.71)	0.17
MV[2]	1.52 (1.42, 1.62)	1.59 (1.54, 1.64)	1.61 (1.51, 1.71)	0.19
MV + FNBMD[3]	1.53 (1.43, 1.63)	1.58 (1.54, 1.63)	1.61 (1.51, 1.71)	0.28
Estimated failure load (n)				
Base[1]	4338.7 (4185.3, 4492.0)	4913.3 (4834.2, 4992.5)	5198.3 (5040.3, 5356.3)	<0.0001
MV[2]	4434.1 (4279.1, 4589.1)	4905.6 (4827.2, 4984.0)	5106.4 (4947.8, 5265.0)	<0.0001
MV + FNBMD[3]	4499.3 (4364.0, 4634.6)	4896.2 (4827.8, 4964.6)	5073.5 (4935.1, 5211.9)	<0.0001

[*] 6 men on androgen deprivation therapy excluded.

[1] Base model adjusted for age, clinic and limb length.

[2] Multivariate (MV) models also adjusted for height, weight, health status, physical activity, difficulty with any instrumental activity of daily living (IADL), alcohol consumption and a history of congestive heart failure (CHF) or diabetes.

[3] MV + Femoral Neck BMD at Year 7.

Table 3:

HR-pQCT parameters at the Distal Tibia across categories of bone mineral loss (BMD): Least square means (95% confidence interval)*

Parameters	BMD Loss, Mean (95% confidence interval)			P trend
	Accelerated (≤10% decreased BMD)	Expected (≤10% decreased BMD)	Maintained/Increased (≥0 BMD change)	
Total vBMD (mg/cm^3)				
Base[1]	258.4 (252.4, 264.4)	281.8 (278.7, 285.0)	293.5 (287.2, 299.8)	<0.0001
MV[2]	260.2 (254.1, 266.4)	281.6 (278.5, 248.8)	291.2 (284.7, 297.7)	<0.0001
MV + FNBMD[3]	263.8 (258.4, 269.2)	281.1 (278.3, 283.8)	289.4 (283.8, 295.1)	<0.0001
Total area (mm^2)				
Base[1]	897.9 (884.3, 911.5)	890.0 (882.9, 897.1)	899.0 (884.7, 913.3)	0.96
MV[2]	909.9 (897.2, 922.7)	890.3 (883.8, 896.9)	885.7 (872.3, 899.1)	0.0106
MV + FNBMD[3]	909.5 (896.7, 922.3)	890.4 (883.9, 897.0)	885.9 (872.5, 899.4)	0.0132
Trabecular vBMD (mg/cm^3)				
Base[1]	176.3 (171.8, 180.7)	185.8 (183.5, 188.1)	189.6 (185.0, 194.3)	<0.0001
MV[2]	176.6 (172.1, 181.1)	185.9 (183.6, 188.2)	188.3 (183.5, 193.0)	0.0005
MV + FNBMD[3]	179.2 (175.2, 183.2)	185.5 (183.5, 187.5)	187.0 (182.8, 191.2)	0.0083
Cortical vBMD (mg/cm^3)				
Base[1]	748.2 (739.7, 756.7)	781.8 (777.4, 786.3)	805.8 (796.9, 814.7)	<0.0001
MV[2]	753.9 (745.3, 762.6)	780.9 (776.5, 785.3)	802.4 (793.3, 811.4)	<0.0001
MV + FNBMD[3]	756.0 (747.5, 764.4)	780.6 (776.3, 784.9)	801.4 (792.5, 810.3)	<0.0001
Trabecular area (mm^2)				
Base[1]	778.9 (764.4, 793.3)	756.1 (748.5, 763.6)	757.6 (742.4, 772.8)	0.04
MV[2]	787.8 (773.9, 801.8)	756.7 (749.5, 763.8)	747.2 (732.5, 761.9)	0.0001
MV + FNBMD[3]	785.9 (772.0, 799.8)	757.0 (749.9, 764.1)	748.2 (733.6, 762.7)	0.0003
Cortical area (mm^2)				
Base[1]	125.2 (121.7, 128.6)	140.0 (138.2, 141.8)	147.5 (143.9, 151.2)	<0.0001
MV[2]	128.3 (124.8, 131.7)	139.8 (138.0, 141.6)	144.6 (141.0, 148.2)	<0.0001
MV + FNBMD[3]	129.8 (126.6, 133.0)	139.6 (137.9, 141.2)	143.8 (140.5, 147.2)	<0.0001
Trabecular volume fraction, mm^3				
Base[1]	0.257 (0.251, 0.263)	0.269 (0.266, 0.273)	0.275 (0.268, 0.281)	0.0001
MV[2]	0.257 (0.251, 0.263)	0.270 (0.267, 0.273)	0.273 (0.266, 0.279)	0.0006

Parameters	BMD Loss, Mean (95% confidence interval)			P trend
	Accelerated (≤10% decreased BMD)	Expected (≤10% decreased BMD)	Maintained/Increased (≥0 BMD change)	
MV + FNBMD[3]	0.261 (0.255, 0.266)	0.269 (0.266, 0.272)	0.271 (0.265, 0.277)	0.0088
Trabecular number, mm^{-1}				
Base[1]	1.31 (1.28, 1.33)	1.35 (1.34, 1.36)	1.37 (1.34, 1.39)	0.0013
MV[2]	1.31 (1.29, 1.34)	1.35 (1.34, 1.36)	1.35 (1.33, 1.38)	0.04
MV + FNBMD[3]	1.33 (1.30, 1.35)	1.35 (1.34, 1.36)	1.35 (1.32, 1.37)	0.18
Trabecular separation, (mm)				
Base[1]	0.763 (0.745, 0.781)	0.725 (0.715, 0.734)	0.716 (0.697, 0.735)	0.0003
MV[2]	0.760 (0.742, 0.779)	0.724 (0.715, 0.734)	0.726 (0.707, 0.745)	0.0104
MV + FNBMD[3]	0.753 (0.736, 0.770)	0.726 (0.717, 0.734)	0.730 (0.712, 0.748)	0.0630
Trabecular thickness, mm				
Base[1]	0.272 (0.269, 0.274)	0.272 (0.271, 0.273)	0.273 (0.270, 0.275)	0.59
MV[2]	0.271 (0.268, 0.274)	0.272 (0.271, 0.274)	0.273 (0.271, 0.276)	0.26
MV + FNBMD[3]	0.272 (0.269, 0.275)	0.272 (0.271, 0.273)	0.273 (0.270, 0.276)	0.58
Cortical thickness (mm)				
Base[1]	1.36 (1.32, 1.39)	1.49 (1.47, 1.50)	1.54 (1.50, 1.58)	<0.0001
MV[2]	1.37 (1.34, 1.41)	1.48 (1.46, 1.50)	1.52 (1.48, 1.56)	<0.0001
MV + FNBMD[3]	1.39 (1.36, 1.42)	1.48 (1.46, 1.50)	1.51 (1.48, 1.55)	<0.0001
Cortical porosity(%)				
Base[1]	4.29 (4.10, 4.48)	4.27 (4.17, 4.37)	4.29 (4.08, 4.49)	0.98
MV[2]	4.26 (4.06, 4.45)	4.28 (4.18, 4.38)	4.32 (4.11, 4.53)	0.68
MV + FNBMD[3]	4.27 (4.07, 4.46)	4.28 (4.17, 4.38)	4.32 (4.11, 4.52)	0.74
Estimated failure load (n)				
Base[1]	12300.1 (11972.1, 12628.1)	13639.8 (13468.6, 13811.0)	14431.0 (14085.6, 14776.4)	<0.0001
MV[2]	12584.0 (12260.9, 12907.2)	13634.8 (13469.3, 13800.7)	14137.2 (13797.8, 14476.6)	<0.0001
MV + FNBMD[3]	12793.0 (12521.3, 13064.8)	13602.6 (13463.6, 13741.5)	14031.9 (13746.8, 14316.9)	<0.0001

*6 men on androgen deprivation therapy excluded.

[1]Base model adjusted for age, clinic and limb length.

[2]Multivariate (MV) models also adjusted for height, weight, health status, physical activity, difficulty with any instrumental activity of daily living (IADL), alcohol consumption and a history of congestive heart failure (CHF) or diabetes.

[3]MV + Femoral Neck BMD at Year 7.

Table 4:

HR-pQCT parameters at the Diaphyseal Tibia across categories of bone mineral loss (BMD) least square means (95% confidence interval) *

Parameters	BMD Loss, Mean (95% confidence interval)			P trend
	Accelerated (≤10% decreased BMD)	Expected (≤10% decreased BMD)	Maintained/Increased (≥0 BMD change)	
Total vBMD (mg/cm^3)				
Base[1]	704.1 (694.7, 713.4)	735.2 (730.4, 740.1)	746.1 (736.3, 755.8)	<0.0001
MV[2]	705.1 (695.6, 714.6)	735.0 (730.1, 739.9)	744.7 (734.7, 754.7)	<0.0001
MV + FNBMD[3]	708.9 (700.0, 717.8)	734.4 (729.8, 739.0)	742.8 (733.4, 752.2)	<0.0001
Total area (mm^2)				
Base[1]	440.6 (434.6, 446.6)	439.2 (436.0, 442.3)	439.1 (432.9, 445.4)	0.74
MV[2]	445.7 (439.8, 451.5)	439.0 (436.0, 441.9)	434.4 (428.3, 440.5)	0.0098
MV + FNBMD[3]	446.3 (440.5, 452.1)	438.9 (435.9, 441.8)	434.1 (428.0, 440.1)	0.005
Cortical vBMD (mg/cm^3)				
Base[1]	993.7 (989.4, 997.9)	996.6 (994.4, 998.8)	999.9 (995.5, 1004.3)	0.045
MV[2]	991.9 (987.8, 996.1)	996.7 (994.6, 998.8)	1002.0 (997.6, 1003.4)	0.001
MV + FNBMD[3]	992.9 (988.8, 997.0)	996.5 (994.5, 998.6)	1001.5 (997.2, 1005.8)	0.005
Cortical area (mm^2)				
Base[1]	299.6 (294.9, 304.2)	314.2 (311.8, 316.7)	318.2 (313.3, 323.1)	<0.0001
MV[2]	304.2 (299.7, 308.7)	313.9 (311.6, 316.2)	313.7 (309.0, 318.4)	0.004
MV + FNBMD[3]	306.1 (301.9, 310.3)	313.6 (311.4, 315.7)	312.7 (308.3, 317.1)	0.031
Cortical thickness (mm)				
Base[1]	5.80 (5.70, 5.91)	6.21 (6.15, 6.26)	6.30 (6.19, 6.41)	<0.0001
MV[2]	5.86 (5.76, 5.97)	6.20 (6.14, 6.23)	6.24 (6.13, 6.35)	<0.0001
MV + FNBMD[3]	5.91 (5.81, 6.00)	6.19 (6.14, 6.24)	6.22 (6.12, 6.32)	<0.0001
Cortical porosity(%)				
Base[1]	2.27 (2.13, 2.42)	2.09 (2.01, 2.16)	1.95 (1.79, 2.10)	0.003
MV[2]	2.24 (2.10, 2.39)	2.09 (2.01, 2.17)	1.96 (1.80, 2.12)	0.012
MV + FNBMD[3]	2.21 (2.07, 2.36)	2.10 (2.02, 2.17)	1.98 (1.82, 2.13)	0.03
Estimated failure load (n)				
Base[1]	19202.9 (18892.3, 19513.5)	20236.9 (20074.2, 20399.6)	20462.4 (20135.8, 20789.0)	<0.0001

Parameters	BMD Loss, Mean (95% confidence interval)			P trend
	Accelerated (≤10% decreased BMD)	Expected (≤10% decreased BMD)	Maintained/Increased (≥0 BMD change)	
MV[2]	19493.3 (19118.5, 19798.1)	20214.7 (20058.2, 20371.2)	20186.1 (19866.5, 20505.8)	0.002
MV + FNBMD[3]	19629.8 (19348.8, 19910.7)	20194.3 (20050.3, 20338.3)	20115.0 (19820.8, 20409.2)	0.018

[*] 6 men on androgen deprivation therapy excluded.

[1] Base model adjusted for age, clinic and limb length.

[2] Multivariate (MV) models also adjusted for height, weight, health status, physical activity, difficulty with any instrumental activity of daily living (IADL), alcohol consumption and a history of congestive heart failure (CHF) or diabetes.

[3] MV + Femoral Neck BMD at Year 7.