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Bone Mineral Density and Prevalent Osteoarthritis of the Hip in Older Men for the Osteoporotic Fractures in Men (MrOS) Study Group

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Abstract

Background—We evaluated the association of BMD measured by DXA and quantitative computerized tomography (QCT) (integral, cortical and trabecular volumetric BMD (vBMD)) and radiographic hip OA (RHOA) in a cohort of elderly men.

Methods—A cross-sectional analysis was conducted within the Study of Osteoporotic Fractures in Men (MrOS), a prospective cohort study of 5,995 U.S. men age ≥ 65 yrs. Standing pelvic x-rays were done in 4024 subjects and scored for prevalent RHOA severity. DXA was done in 3886 subjects and aBMD and vBMD associations were compared with RHOA score using linear regression, adjusting for covariates.

Results—Both moderate and severe RHOA groups had significantly higher aBMD at all BMD sites (range: 3.7 – 10.0% difference, p-value 0.0012 and p-value < 0.005) compared to the control group with no RHOA. The difference remained strong after adjusting for co-variables. While the total hip and lumbar spine cortical vBMD measurements of subjects with moderate or severe RHOA was increased compared to controls, trabecular vBMD was not.

Conclusion—Older men, with both moderate or severe RHOA had significantly higher aBMD and integral vBMD at the hip and lumbar spine compared to controls without RHOA.

Osteoarthritis (OA) is a leading cause of disability in the elderly (1) and a growing number of adults are expected to be affected with large joint (hip or knee) OA as the population ages (2). The risk of large joint OA has been shown to increase with increasing bone mineral density (BMD) in both cross-sectional and longitudinal epidemiological studies (3– 6). For the hip, higher BMD has been described at sites both near and distant from the OA site (3, 4).

BMD measured at sites distant from the site of hip OA have been found to be associated with both prevalent and incident hip OA (3, 4, 7). An association of high lumbar spine BMD and radiographic hip or knee OA has been attributed to potential osteophytosis in the lumbar spine (LS), a systemic increased skeletal response to loading or, potentially, a hereditary component of bone turnover regulation (4,7). This association has not been assessed in a large population of elderly men.

In addition to higher systemic BMD, elevated BMD and altered bone metabolism has also been reported adjacent to joints with OA (8,9). Higher BMD at the femoral neck of hip OA subjects may reflect subcortical remodeling such as buttressing, which is reported in association with more advanced disease (10). In a large prospective study, baseline femoral neck BMD was associated with radiographic hip OA (RHOA) in men and with incident knee OA in both women and men with no initial OA measured approximately 6 years after the initial visit (3). Similarly, prevalent hip OA has also been associated with a higher femoral neck BMD in elderly Caucasian women (4).

To date, most published studies of BMD and hip OA have used dual energy X-ray densitometry (DEXA) to obtain a measure of areal BMD (aBMD), defined as the bone mineral content (BMC) corrected for assessed bone area (11). Measures of aBMD may be influenced by bone size, with larger bone having a higher areal BMD (11,12), thereby introducing a measurement bias. In contrast, quantitative CT (QCT) measures a true volumetric BMD (vBMD), independent of bone dimensions. QCT also provides separate vBMD measures of the cortical and trabecular compartments of bone. One small study (n=27 cases) of vBMD measured by MRI found no difference in vBMD between men with and without prevalent hip OA (13).

The purpose of this study was to examine the association of both aBMD and vBMD at the hip and lumbar spine in elderly men with RHOA, to better understand the pathogenesis of hip OA.

Materials and Methods

Study subjects and population

The Study of Osteoporotic Fractures in Men (MrOS) is a prospective cohort study of 5,995 U.S. men recruited from 2000–2002 at six clinical center sites that were geographically dispersed across the United States: Birmingham, Minneapolis, Palo Alto, Pittsburgh, Portland and San Diego.

To be eligible, men had to be ≥65 years old, ambulatory, and without bilateral hip replacements. Subjects included in this analysis were drawn from the population of 4,531 MrOS participants who returned for a second clinic visit (visit 2), conducted between 2004–2006 and averaging approximately 4.6 years after the baseline visit. From the 4,157 men who consented for a pelvic x-ray at visit 2, 4,032 x-rays were digitized and available at the time of this analysis, with 4,025 men also having DXA values available; however, 20 of these subjects were excluded because of hip fracture, leaving 4,012 subjects with available radiographs; 4,005 of these remaining subjects had DXA scans available, with 2,429 also having QCT measurements available. We then excluded 82 subjects with DXA measurements that had total hip replacements (THRs) resulting in 3,929 that were included in the final aBMD analyses. We also excluded 45 subjects with THRs that had QCT measurements, resulting in 2,384 that were included in the final vBMD analyses.

For the purposes of this study, all variables were obtained from the first follow-up visit, which is referred to as visit 2 unless otherwise specified.

Radiography and Interpretation

At visit 2, standing pelvis x-rays were done using a standardized footmat with toes internally rotated 15 degrees, and the x-ray beam positioned two inches above the pubis symphysis. Hip radiographs were assessed for five individual radiographic features (IRFs) of OA: 1) joint space narrowing (JSN 0 – 4) laterally and medially, 2) osteophyte formation (0 – 3) (femoral or acetabular and either inferiorly or superiorly in each location, 3) cysts (0 – 3), 4) subchondral sclerosis (0 – 3) and 5) femoral head deformity (0 – 3) (14,15). Atlas figures were consulted during the readings to improve reliability (14). These methods used have been published elsewhere (4, 14, 15).

A summary grade for radiographic hip OA severity of 0 – 4, modified from Croft (15, 16) was assigned to each hip based on individual radiographic features. Grade 0 hips had no individual radiographic features (IRFs) or were defined as normal. Grade 1 hips required either the presence of possible JSN or osteophytes (severity grade =1). Grade 2 hips required the presence of definite (severity grade = 2) JSN or osteophytes plus at least one other feature (cysts or subchondral sclerosis). Grade 3 hips required definite JSN or osteophytes plus at least two other features. Grade 4 hips met the criteria for grade 3, and also had femoral head deformity. Minimum joint space was measured in millimeters using electronic calipers (4, 15, 16).

Prior to the formal radiographic scoring, the primary reader (a trained radiologist) read 30 films with an experienced reader (NEL) to become familiar with the previously validated scoring system. The radiographs were initially read and measured by the primary reader, blinded to subjects' clinical characteristics. All of the radiographs with either definite osteophytes or definite narrowing (severity score = 2) in any location on the initial reading were jointly evaluated by 2 readers to reach consensus on the radiographic score. Intra-rater reliability for the radiographic readings was evaluated from a random sample of N= 414 films; the kappa for the maximum definite joint space narrowing and definite osteophyte score was 0.76, the kappa was 0.63 for femoral osteophytes, and for lateral or medial JSN osteophytes the kappa was 0.77.

Definitions of radiographic hip OA

The definitions of prevalent RHOA have been described previously (15). Hips were considered to have RHOA if a summary grade of ≥ 2 was present in either hip. RHOA cases were further categorized as having either moderate RHOA (summary score = 2 in the worst hip and the contralateral hip with a summary score = 1). Severe RHOA was defined as a summary score = 3 in the worst hip and the contralateral hip with a summary score = 2, or a summary score = 2 in one hip and the contralateral hip with a THR for OA, as verified by medical records). Subjects with RHOA grades of 0 - 1 made up the control group. Subjects with a unilateral THR were excluded from DXA

In addition, a subgroup of hips with RHOA that were defined by two distinct RHOA phenotypes: osteophytic (osteophyte-predominant), and atrophic (JSN-predominant) were examined. The hips classified as “osteophytic” had a femoral osteophyte score ≥ 2, and JSN (lateral and medial) = 1; hips classified as atrophic were those with lateral JSN ≥ 2 or medial JSN ≥ 3, with femoral and acetabular osteophytes = 1. These phenotypic definitions are similar to other reports that have classified phenotypes of RHOA on the absence or predominance of JSN or osteophytes (4).

DXA Scanning and areal BMD Measurements

DXA measurements were obtained at the lumbar spine, total hip, femoral neck and trochanteric sites using a QDR 4500 Hologic machine (Waltham, MA) at all six MrOS

clinical sites. Standardized methods were used to position subjects, all densitometry technicians were centrally certified, and all scanners were calibrated at visit 2 and daily quality control scans were performed (17). Areal BMD was calculated as BMC (grams) divided by the 2-dimensional bone area scanned (cm^2).

QCT Scanning and Volumetric BMD Measurements

QCT of the hip and lumbar spine were performed at baseline visit (4.7 years before visit 2) on the first consenting 650 participants at each clinical site and on all consenting minority participants (18). All sites used a standard protocol in which the pelvic region was scanned from the superior aspect of the femoral head to a level 3.5 cm below the lesser trochanter. Calibration standards with known hydroxyapatite concentrations (150, 75, and 0 mg/cm^3 ; Image Analysis, Columbia, KY) were included with each participant's scan. All scans were reviewed for quality control and analyzed at the Department of Radiology at the University of California, San Francisco. QCT scans of the hip were obtained for 3,684 participants; however, 112 (3.0%) of these hip scans were not available for processing, because they were lost or corrupted during transfer to the UCSF MrOS Coordinating Center, leaving 3,572 hip scans. QCT scans of the lumbar spine were obtained in 3,783 subjects, 249 (6.6%) of which were not available for processing due to loss or corruption during transfer, an insufficient number of images, metal interference, miscalibration, or fracture at the region of interest. Of the 3,534 QCT lumbar spine scans which were processed, 3,495 men had complete data in the L1 and L2 region of interest (ROI) however hip radiographs were obtained on only 2,327 of these men at visit 2.

Image processing and analysis of volumetric BMD was performed using a software program designed specifically for this purpose (18, 19). At the lumbar spine, the integral vBMD ROI was defined as the entire L1 vertebra, including the transverse processes, similar to the region of interest for an AP DXA scan. The total hip ROI was manually defined from the minimum cross section of the femoral neck to the postero-lateral boundary of the greater trochanter. The hip QCT images were reformatted manually along the neutral axis of the femur from the coronal and sagittal reformations of the CT volumes, giving an effective voxel size of 0.9375 mm. The periosteal border was delineated from soft tissue using a region-growing algorithm. The maximum and minimum cross sectional area (CSA) of the femoral neck were identified. For each ROI the integral volume was comprised of the volume of tissue within the periosteal boundary. An erosion process with a fixed number of iterations was employed to shrink the periosteal boundary to a point fully contained within the endosteal margin. The cortical region of interest was delineated from the trabecular region of interest by applying a vBMD threshold of $-0.35 \text{ g}/\text{cm}^3$ to all voxels between the eroded boundary and the periosteal boundary (18, 19). The total hip integral vBMD, trabecular and cortical compartments vBMD were analyzed and reported separately.

Assessment of Potential Confounders

All participants completed a visit 2 questionnaire at the time the pelvic radiographs were obtained that collected self-reported information on a number of subject characteristics including, age, health comorbidities, current and past medication use, current alcohol use (average drinks/week), tobacco use (current, past or ever), and hip pain over the past 30 days. Subject height was measured in the clinic using a Harpenden stadiometer (Holtain Ltd., Crymych, UK), and weight was determined using a standard balance beam or digital scale (17). Body mass index (BMI) was calculated in weight in kg divided by height in meters squared. Subject activity was assessed by the Physical Activity for the Elderly Scale (PASE) (20), an activity scale that specifically measures occupational, household and leisure-time activity in the elderly. A comorbidity score was calculated as the sum of the

following self reported medical conditions; history of myocardial infarction, angina, COPD, hypertension, osteoarthritis, stroke and diabetes.

Statistical Analyses

The unit of analysis was person-based, with each subject contributing only one hip measurement to the analyses. In cases with bilateral OA (RHOA = 2 on both sides), the hip with the worse RHOA summary score was included. For analyses of the association of BMD with the summary RHOA score, summary scores of 0–1 were used as the referent (control) group. For the analyses of the osteophytic and atrophic phenotypes and their differences, the referent group included all subjects with IRF scores = 1 on all other individual radiographic features with the exception of cysts, deformity, buttressing and sclerosis, which were restricted to 0. Comparisons of baseline characteristics for subjects with and without RHOA were done using ANOVA for continuous variables and chi-squared tests for binary and categorical variables. Non-parametric tests were done for skewed continuous variables. Differences between the adjusted mean aBMD and vBMD for the cases and controls were examined using a generalized linear model to generate the adjusted least squares mean, standard error of the mean (SEM) and p-values. Associations of BMD and RHOA were determined using generalized linear regression models adjusting for age and the following covariates: age, BMI, height, race, physical activity level based on the PASE score, clinical site and muscle strength (Nottingham maximum power, 6 meter walk speed and inability to do chair stands). Adjusted percent differences and 95% confidence intervals were calculated by dividing the multivariate regression beta estimates and 95% confidence intervals by the mean BMD value of the reference group. All analyses were done using SAS software version 9 (SAS Institute, Inc., Cary, NC).

Results

Baseline Characteristics

Subject characteristics at visit 2 were generally similar among the three groups, with a few exceptions (Table 1). Compared to controls, the moderate and severe RHOA groups were slightly older ($p < 0.05$), the moderate group was less active, had a higher comorbidity score ($p < 0.05$), and the percentage of non-white participants was higher in the severe RHOA group ($p < 0.05$). The distribution of RHOA cases and controls differed between the six MrOS clinical sites ($p < 0.005$).

aBMD results measured by DXA

The mean hip aBMD of subjects with severe RHOA was significantly higher than that of men with little or no RHOA (See Table 2). The percent differences in aBMD in the RHOA groups was also higher compared to subjects with no RHOA, with a trend towards greater differences in aBMD in those subjects with the higher RHOA summary scores (See Figure 1). Multivariate linear regression, adjusting for age, BMI, height, PASE activity level, clinical site, muscle strength and race showed a strong association with aBMD across all measured hip sites in both moderate and severe RHOA cases. Adjustment for the visit 2 comorbidity score did not alter these results.

The greatest difference in aBMD was seen at the femoral neck and lumbar spine sites in subjects in both the moderate and severe RHOA groups compared to controls. Compared to the control group, the moderate RHOA group had a 6.4% higher adjusted aBMD at the femoral neck site and a 5.6% higher adjusted aBMD at the lumbar spine site; the severe RHOA group had a 9.8% higher adjusted aBMD at the femoral neck site, and a 10.3% higher adjusted aBMD at the lumbar spine site (See Figure 1).

There were also significant differences in the hip and lumbar spine aBMD measurements for the two radiographic RHOA phenotypes compared to the control group (all IRFs = 1). The osteophytic (osteophyte-predominant) RHOA group had a higher aBMD at all sites compared to the control group: +3.9% at the total hip ($p = 0.002$); +8.5% at the femoral neck ($p < 0.0001$); +4.6% at the trochanter site ($p = 0.002$); and +7.2% at the lumbar spine ($p = 0.0003$). In contrast, the atrophic phenotype was not significantly associated with any difference in aBMD compared to subjects with all IRFs graded = 1 (See Figure 2).

QCT Results

The means of the hip and spine vBMD measurements were significantly higher in both the moderate and the severe RHOA groups when each was compared to the controls (See Table 2). Multivariate linear regression analyses showed a strong association for all integral and cortical hip site measurements in severe RHOA, while no significant differences in the mean vBMD values were found for the hip trabecular measurements. Additionally, no significant differences in vBMD were found for all measurement sites in the moderate RHOA group. Adjustment for the visit 2 co-morbidity score did not change these results. Compared to the control group, the percent difference in vBMD in the severe RHOA group differed at the total hip integral and cortical site vBMD measurements and the lumbar spine integral vBMD measurement (See Figure 3). The percentage difference for total hip trabecular vBMD was not significant compared to the mean of the controls (See Figure 3).

An additional analysis of radiographic phenotypes showed that the vBMD hip and spine measurements in the osteophytic group was significantly higher at cortical-predominant sites compared to the control group (subjects with all IRF = 1). The greatest difference in the vBMD was in the total hip cortical and L1 integral measurements; the adjusted percent differences in the vBMD measurement were 2.6 % ($p\text{-value} = 0.006$) higher at the total hip cortical site, and 4.7 % ($p\text{-value} = 0.03$) higher at the L1 integral measurement site, when each was compared to measurements in the control group. The percent differences at the total hip integral and trabecular vBMD sites in the osteophytic group were not significantly different from the controls. In the atrophic group, the percent differences in vBMD at different sites were not significantly different compared to the mean of the control group (Figure 4).

Discussion

We found that higher aBMD and vBMD were associated with prevalent RHOA in this cohort of elderly men, and that these differences in BMD measurements were greater in subjects with severe versus moderate RHOA. While aBMD was higher at all measurement sites (total hip, femoral neck, trochanter and lumbar spine) in RHOA groups compared to the controls, a greater percentage difference in vBMD was seen at sites which were composed of predominantly cortical bone. In addition, osteophytic, or osteophyte-predominant, RHOA was associated with a higher vBMD in cortical-predominant sites, while the atrophic RHOA phenotype was not.

These aBMD and vBMD results support previous reports of an association between increased BMD and large joint radiographic OA in subject groups with RHOA compared to those without RHOA. These BMD differences were found both at the site of the OA and distal to it. Nevitt et al (4) reported a nearly 10% increase in aBMD at the hip in elderly Caucasian women with RHOA, and similarly, Burger et al (3) reported a higher (3 - 8% increase) in femoral neck aBMD in male subjects with RHOA. A positive association was reported between femoral neck aBMD and hip OA in monozygotic and dizygotic twins, as well (21). Our vBMD findings differ from a study by Arokoski et al. (11) that evaluated the association of vBMD measured by MRI and hip OA. The investigators studied 57 men and

reported no association between aBMD by DXA or MRI and hip OA, but did find a positive association between BMC and hip OA. Differences in sample size, the technique of vBMD measurement and case definition may account for the different findings between the two studies.

A positive association of osteoarthritis of other large joints, such as the knee, and BMD has also been reported. Female subjects in the Framingham cohort with higher BMD were at greater risk of developing incident knee OA over an 8 year follow-up period than women with low BMD (20). Similarly, systemic BMD has been reported to be higher in subjects who develop incident knee OA (7, 23). The present results confirm these reported associations between radiographic OA in a large joint and higher BMD at the site of OA.

We also found aBMD and vBMD to be higher in RHOA subjects compared to controls at the lumbar spine, a site that is anatomically distant from the hip joint. These results are similar to several published reports of lumbar spine aBMD and large joint OA (4, 5, 7), and suggest that a skeletal phenotype with high BMD may alter loading across large joints and accelerate joint degeneration. However, adjusting for the BMI and physical activity, which should be associated with a possible skeletal phenotype effect, did not change our results.

We also found a significant association between the osteophytic phenotype and both aBMD and vBMD; of note, our DXA and QCT regions of interest were distal to the region of the femoral head where femoral or acetabular osteophytes would be located. Our findings are consistent with other reports (4, 23) and underscore the potentially different pathophysiology between these two OA phenotypes. One possible explanation for the differences may be explained by the contrasting actions of the wnt pathway on cartilage and bone. The wnt system is a large family of extracellular cysteine-rich glycoproteins, which help regulate embryogenic formation, and in adult cartilage and bone repair. There is evidence from animal studies that wnt signaling has different effects on cartilage compared to bone (24, 25). Higher serum levels of the wnt antagonist Dickkopf-1 (Dkk-1) have been found to be protective against the progression of RHOA in older women (26) and secreted frizzled-related protein 3 (sFRP-3), another wnt antagonist, may be protective against cartilage injury (26, 27). These results are intriguing, and the role of wnt signaling in cartilage and bone in relation to the osteophytic and atrophic phenotypes requires further study.

In our study, we used QCT to measure vBMD and examine its association with RHOA. Most published reports on the association of BMD and OA have utilized DXA and reported on aBMD. The development of OA is often characterized by an increase in osteophyte formation at the joint margins and cortical bone modeling resulting in increased cortical thickness on the medial side of the femoral neck; this increased cortical thickness can, in turn, change the size and shape of the bone. These bone changes can lead to inaccuracies in a 2-dimensional measurement of BMD by DXA. In contrast, BMC measures may be less affected by changes in bone size and shape, and may be a more accurate 2-dimensional assessment of bone status in patients with and without OA. This difference may explain why subjects with OA are sometimes found to have increases in BMC but not BMD compared to subjects without OA (28).

The lumbar spine QCT vBMD measurement is not affected by inaccuracies of DXA scans such as the inclusion of osteophytes, sclerosis or adjacent aortic calcification (29). QCT allows the measurement of the cortical and trabecular compartments both together and separately. This distinction is especially relevant as trabecular bone has been reported to be more sensitive to changes in stress loading and subsequent remodeling than cortical bone compartment (30, 31). QCT may be a more sensitive method to assess pathophysiologic

changes in bone as disease evolves. For example, studies of the effect of glucocorticoid use on bone have used QCT to demonstrate a rapid loss in trabecular vBMD followed by a slower loss of cortical vBMD (32).

Our aBMD and vBMD findings support a potential role for both trabecular and cortical bone changes in the pathogenesis of OA. Our finding that aBMD was higher in the femoral neck of the hip with prevalent RHOA is consistent with previous reports (3, 4), and suggests that local trabecular thickening of the principal compressive region (33) may contribute to higher femoral neck aBMD. Histomorphometric studies support the hypothesis that trabecular bone remodelling in the femoral neck contributes in part to the buttressing the proximal femur against increased hip joint loading (34).

We reported that the vBMD in the cortical compartment in the hip was significantly increased compared to controls, and the trabecular compartment vBMD was not. However these results must be interpreted with caution as the proportional change in cortical bone volume was only 3.3% between severe RHOA and mild RHOA, while it was 5.8% in the trabecular compartment. Since the sequence in which trabecular bone changes and cartilage loss occurs is unclear (35 - 37), further investigation is needed to clarify the role of trabecular and cortical changes associated with different phases of RHOA. The relative location and changes in cortical and trabecular vBMD suggest that the pathogenic changes seen in RHOA may be associated with a redistribution of load across the proximal femur.

Our study has several strengths including a well-characterized cohort of elderly men with comprehensive radiographic hip OA and bone mineral density assessments. However there are also a number of weaknesses. The software program's threshold for measurement of cortical bone volume of 350mg/cm³ may not be optimal as the study by Poole et. al (38) clearly demonstrates that our threshold may over-estimate the cortical bone volume in the hip. However, we used the same threshold for the cases of RHOA and controls, and we detected a significant difference. Therefore, the direction of the association is probably valid but the magnitude of the difference may be different with different software analyses programs. Future studies are needed to confirm and elucidate this association will use different thresholds for cortical bone for a more accurate assessment of the two bone compartments.

Another weakness was that this study was cross-sectional, and associations could only be made with prevalent RHOA. The QCT measurements were done 4.6 years prior to the pelvic radiograph and DXA scans obtained at Visit 2. To insure that no incident RHOA cases were included, QCT scout films of all cases from the baseline visit were reviewed to confirm the presence of RHOA in all cases. While CT is a sensitive measurement of bone features, the scout films were not taken specifically for the assessment of the subject's hip OA status, and could have been a source of potential bias through inadvertent inclusion of incident RHOA cases. Lastly, this was a cohort of largely Caucasian (91%) older men, and the results are therefore not generalizable to other populations.

In summary, both areal BMD and volumetric BMD of the hip are associated with prevalent hip OA in elderly men. Furthermore, vBMD at the hip was increased only in the cortical compartment, suggesting that there may be different roles for trabecular and cortical bone remodeling in different stages of the pathogenesis of RHOA. Additional longitudinal studies with QCT scans of the hip would be needed to explore this hypothesis.

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Figure 1.

Percent Increases in aBMD Measurements in Subjects by RHOA Summary Grade Compared to Mean aBMD in Subjects with Summary Grade 0–1. †

†Adjusted for age, BMI, height, activity level (PASE), Nottingham maximum power, 6 meter walk speed, inability to do chair stands, clinic site and race. RHOA= 2 (n= 209); RHOA ≥ 3 (n= 185).

*Significant at P-value < 0.005. (See Table 2A for exact P-values).

Figure 2.

Percent Differences in aBMD in the Osteophytic and Atrophic Phenotypes compared to Mean aBMD in Subjects with IRF scores ≥ 1 .†

†Adjusted for age, BMI, height, activity level (PASE), Nottingham maximum power, 6 meter walk speed, inability to do chair stands, clinic site and race. Osteophytic (n= 134); Atrophic (n= 120).

* P-value < 0.005 compared to referent group.

Figure 3. Percent Differences in vBMD Measurements in Subjects by RHOA Summary Grade compared to Mean vBMD in Subjects with Summary Grade 0–1.†

†Adjusted for age, BMI, height, activity level (PASE), Nottingham maximum power, 6 meter walk speed, inability to do chair stands, clinic site and race. RHOA=2 (n= 149); RHOA ≥ 3 (n= 122).

*Significant at P-value < 0.05. (See Table 2B for exact P-values).

Figure 4.

Percent Differences in vBMD Measurements in Subjects by radiographic phenotype compared to Subjects with IRF < 1.†

†Adjusted for age, BMI, height, activity level (PASE), Nottingham maximum power, 6 meter walk speed, inability to do chair stands and race. Osteophytic (n= 100); Atrophic (n= 67).

P-value <0.005 compared to referent group.

Table 1

Baseline Characteristics of Subjects by Summary Grade of Worse Hip

Variables (Mean ±	No RHOA (Summary Grade 0-1) (n= 3529)	Prevalent RHOA (Summary Grade 2) (n= 209)	(Prevalent RHOA Summary Grade 3-4) (n= 185)
Age (years)	77.17 ± 5.33	78.93 ± 5.53 [†]	78.63 ± 5.65 [†]
Weight (kg)	82.06 ± 13.46	82.54 ± 13.03	83.31 ± 14.19
Height (cm)	173.35 ± 6.83	173.01 ± 6.74	173.73 ± 7.38
BMI (kg/ m2)	27.27 ± 3.95	27.55 ± 3.88	27.55 ± 4.03
Race (% Caucasian)	90.34%	90.43%	95.14% [†]
Corticosteroid Use (Previous) (% Yes)	2.12%	3.83%	2.16%
Vitamin D use (% Yes)	65.08%	66.99%	63.24%
Bisphosphonate Use (% Yes)	5.36%	4.78%	3.78%
NSAID Use (% Yes)	15.89%	15.31%	20.08%
Activity Level (PASE Score)	137.88 ± 68.45	128.51 ± 64.12 [†]	132.08 ± 69.19
Self-rated Health Status (Good vs. Poor)	87.50%	80.38% [†]	81.08% [†]
Nottingham maximum power (watts)	191.15 ± 63.74	175.28 ± 58.55 [‡]	170.78 ± 58.35 [‡]
6 meter Walk Speed (m/s)	1.20 ± 0.24	1.11±0.24 [‡]	1.10 ±0.25 [‡]
Inability to complete chair stands	6.94 %	13.04% [‡]	15.22% [‡]
Comorbidity Score [*]	1.15 ± 1.11	1.43 ± 1.22 [‡]	1.48 ± 1.13 [‡]
Clinic Site [‡]			
Birmingham	16.27%	6.27%	8.11%
Minneapolis	18.56%	17.22%	20.23%
Palo Alto	15.54%	10.05%	14.05%
Pittsburgh	15.13%	33.01%	24.32%
Portland	16.27%	6.70%	15.14%
San Diego	18.28%	16.75%	19.46%

[†] Significant at P-value < 0.05 compared to referent group (subjects with summary grade 0-1).[‡] Significant at P-value < 0.005 compared to referent group (subjects with summary grade 0-1).^{*} Comorbidity score was calculated as the sum of the following medical conditions: history of myocardial infarction, angina, COPD, hypertension, osteoarthritis, stroke, diabetes mellitus.

Table 2

Adjusted mean aBMD (g/cm^2) (DXA) and adjusted mean vBMD (g/cm^3) (QCT) and summary RHOA hip score (Adjusted Mean $\pm$ SEM) [†]

DXA Results	Mild or No RHOA (Summary Grade 0–1) (n= 3529)	Moderate RHOA (Summary Grade = 2) (n= 209)	Severe RHOA (Summary Grade = 3) (n= 185)
aBMD (g/cm^2)			
Total Hip	0.944 $\pm$ 0.002	0.981 $\pm$ 0.961	0.994 $\pm$ 0.011
Femoral Neck	0.770 $\pm$ 0.002	0.822 $\pm$ 0.009	0.845 $\pm$ 0.010
Trochanter	0.757 $\pm$ 0.002	0.790 $\pm$ 0.010	0.810 $\pm$ 0.010
Lumbar Spine	1.20 $\pm$ 0.005	1.27 $\pm$ 0.022	1.33 $\pm$ 0.024
QCT Results	Mild/No RHOA (Summary Grade 0–1) (n= 2113)	Moderate RHOA (Summary Grade = 2) (n= 149)	Severe RHOA (Summary Grade = 3) (n= 122)
vBMD (g/cm^3)			
Total Hip, Integral	0.279 $\pm$ 0.001	0.284 $\pm$ 0.005	0.296 $\pm$ 0.005
Total Hip, Cortical	0.521 $\pm$ 0.001	0.529 $\pm$ 0.004	0.538 $\pm$ 0.005
Total Hip, Trabecular	0.104 $\pm$ 0.001	0.102 $\pm$ 0.003	0.110 $\pm$ 0.003
L1 Integral	0.203 $\pm$ 0.001	0.208 $\pm$ 0.004	0.219 $\pm$ 0.004
		P-value *	P-value *
		0.341	0.001
		0.052	0.0002
		0.615	0.080
		0.169	0.0001

[†] Adjusted for age, BMI, height, activity level (PASE), and race, 6 meter walk pace, Nottingham muscle strength, inability to do chair stands, clinic site and race.

* Compared to the Referent Group: RHOA 0–1 group.