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Abnormal Microarchitecture and Stiffness in Postmenopausal Women with Isolated Osteoporosis at the 1/3 Radius

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Abstract

Background: Postmenopausal women with isolated osteoporosis at the 1/3 radius (1/3RO) present a therapeutic dilemma. Little is known about whether these patients have generalized skeletal fragility, and whether this finding warrants treatment. The aim of this study was to investigate the biochemical and microarchitectural phenotype of women with 1/3RO compared to women with classic postmenopausal osteoporosis by DXA at the spine and hip (PMO), and controls without osteoporosis at any site.

Methods: This cross-sectional study enrolled 266 postmenopausal women, who were grouped according to densitometric pattern. Subjects had serum biochemistries, areal BMD (aBMD) measured by DXA, trabecular and cortical vBMD, microarchitecture, and stiffness by high resolution peripheral QCT (HR-pQCT, voxel size ~82 μm) of the distal radius and tibia.

Results: Mean age was 68±7 years. DXA T-Scores reflected study design. By HR-pQCT, 1/3RO had abnormalities at both radius and tibia compared to controls: lower total, cortical and trabecular vBMD, cortical thickness and trabecular number, higher trabecular separation and heterogeneity, and lower whole bone stiffness. In contrast, the magnitude and pattern of abnormalities in vBMD, microarchitecture and stiffness in 1/3RO were similar to those in PMO; the difference compared to controls was similar among the two groups. Serum calcium, creatinine, parathyroid hormone, 25-hydroxyvitamin D, and 24-hour urine calcium did not differ.

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Conclusions: Although aBMD appeared relatively preserved at the spine and hip by DXA, women with 1/3RO had significant microarchitectural and biomechanical deficits comparable to those in women with typical PMO. Further study is required to guide treatment decisions in this population.

Keywords

Osteoporosis; high resolution peripheral QCT; DXA; postmenopausal; microarchitecture

Introduction

Approximately 34 million Americans have osteoporosis and more than two million fragility fractures occur each year (1). Over 15 billion dollars are spent annually on health care costs related to osteoporosis and fragility fractures (1-3), which result in considerable morbidity and increased mortality (1, 4-9). While there are several available pharmacologic therapies that effectively lower fracture risk, identification of those patients at high risk for fracture remains a challenge. Treatment decisions are relatively straightforward in patients with osteoporosis at the spine and hip by DXA (10). However, the management of patients who have osteoporosis only at the 1/3 radius site is less clear. These patients present a therapeutic dilemma for several reasons. Little is known about fracture risk in patients who have isolated osteoporosis at the radius or whether isolated osteoporosis at this site reflects more widespread skeletal fragility. Moreover, data is lacking regarding the efficacy of anti-fracture treatment in these patients.

In this study, we investigated the biochemical and microarchitectural phenotype of women with isolated osteoporosis at the 1/3 radius using high resolution peripheral computed tomography (HR-pQCT). We compared the biochemical and structural characteristics of these women to those of women with classic postmenopausal osteoporosis by DXA at central sites, the spine and hip, and to postmenopausal controls without osteoporosis at any site. We hypothesized that women with isolated osteoporosis at the 1/3 radius have low volumetric bone mineral density (vBMD) and abnormal microarchitecture, with predominantly cortical bone deficits. We further hypothesized that microarchitectural abnormalities are less pronounced in these women compared with women who have osteoporosis at the spine and hip.

Methods

Patients

Postmenopausal women, over age 60 or more than 10 years postmenopause, were recruited at Columbia University Medical Center (CUMC; New York, NY) or Helen Hayes Hospital (HHH; West Haverstraw, NY) by advertisement, self- or physician referral. Potential subjects were excluded if they had a history of abnormal mineral metabolism (e.g., primary hyperparathyroidism, osteomalacia), endocrinopathy (e.g., untreated hyperthyroidism, Cushing's syndrome, prolactinoma), celiac or other gastrointestinal diseases, malignancy (except for skin cancer), and drug exposures that could affect bone metabolism (e.g., glucocorticoids, anticonvulsants, anticoagulants, methotrexate, aromatase inhibitors,

thiazolidinediones, strontium). Women with stage 4 or 5 chronic kidney disease were excluded. Women who had ever used teriparatide, denosumab, or who had taken bisphosphonates for more than one year were excluded. Women using hormone replacement therapy or raloxifene were not excluded. At the study visit, past medical history, reproductive history, and medication use were assessed. A physical exam was performed including height by Harpenden stadiometer and weight, and body mass index (BMI) was calculated. All subjects provided written informed consent and the Institutional Review Board of Columbia University Medical Center approved this study.

Areal bone mineral density (aBMD) and spine radiographs

Areal BMD was measured by DXA (QDR-4500, Hologic Inc., Marlborough, MA at CUMC; Lunar Prodigy, GE, Madison, WI at HHH) at the lumbar spine (LS: L1-4), total hip (TH), femoral neck (FN), and 1/3 radius (1/3R). Lumbar vertebrae with significant deformity, osteosclerosis, osteophytes or degenerative disease were excluded from the analysis. T-scores compared subjects with young-normal populations of the same race and sex, as provided by the manufacturer. Spine radiographs were performed at the study visit to evaluate prevalent vertebral fractures. Vertebral fracture severity was determined using the semi-quantitative method of Genant *et al.*(11). Women were classified into groups by densitometric pattern after DXA data had been obtained, specifically as: isolated osteoporosis at the 1/3 radius (1/3RO), postmenopausal osteoporosis at the hip and/or spine (PMO), and controls without osteoporosis at any site. Women with osteoporosis by DXA at the spine or hip (TH or FN) were classified as PMO regardless of wrist BMD. Among this group, 39% had osteoporosis only at the spine, 30% only at the hip, 31% at both the spine and hip. In addition, 40% had osteoporosis at the wrist as well as at the spine or hip.

HR-pQCT and Image-Based μFEA of the distal radius and tibia

HR-pQCT (XtremeCT1, voxel size 82 μm, Scanco Medical AG, Brüttisellen, Switzerland) was performed at CUMC. The non-dominant forearm and ipsilateral tibia (or non-fractured arm or leg in subjects with prior wrist or ankle fracture) was immobilized in a carbon fiber shell. Scans were performed as we have described in prior publications (12-17). Briefly, the region of interest was defined on a scout film by manual placement of a reference line at the endplate of the radius or tibia; with the first slice 9.5 mm and 22.5 mm proximal to the reference line at the radius and tibia, respectively. A stack of 110 parallel CT slices was acquired at the distal end of both sites using an effective energy of 40 keV, image matrix size 1024 x 1024, with a nominal voxel size of 82 μm. This provided a 3D image of approximately 9 mm in the axial direction. Attenuation data were converted to equivalent hydroxyapatite (HA) densities. The European Forearm Phantom was scanned daily for quality control. All scans were acquired by the same technician. HR-pQCT data were used to calculate whole bone stiffness, a measure of bone's resistance to force using finite element analysis. The analysis methods have been described, validated (18-20), and applied in several clinical studies (21-28). Bone tissue was modeled as an isotropic, linearly elastic material with a Young's modulus (E_s) of 15 GPa and a Poisson's ratio of 0.3 (29). A uniaxial displacement equaling 1% of the bone segment height was applied perpendicularly to the distal surface of the radius or tibia while the proximal surface was imposed with zero displacement along the same direction. Both ends of the tibia were allowed to expand

freely in the transverse plane. The total reaction force was calculated from the linear μFE analysis, and the axial stiffness was calculated as the reaction force divided by the imposed displacement.

Biochemistries

Fasting morning serum was collected from all subjects. Serum was archived at −80 degrees C and analyzed in one batch after all visits were completed. Laboratory assays were performed in the Core Laboratory of the CUMC Clinical and Translational Research Center. Serum calcium, albumin, and creatinine were measured using automated techniques. Serum 25-hydroxyvitamin D_2 and D_3 were measured by Ultra-performance Liquid Chromatography combined with tandem mass spectrometry (UPLC-MS/MS) using a 1290 UPLC and a 6410 Tandem Mass Spectrometer (Agilent, Santa Clara, CA). Inter-assay coefficient of variation (CV) was 2.9% for $25OHD_2$ and 5.4% for $25OHD_3$. Intact parathyroid hormone (iPTH) was measured by chemiluminescent immunoassay (CLIA, Siemens Healthcare Diagnostics, Deerfield, IL; CV 8.3%). Serum C-terminal telopeptide of type 1 collagen (CTX) was measured by ELISA (Immunodiagnostics Systems, Scottsdale AZ; CV <10%). Serum osteocalcin was measured by ELISA (Immunodiagnostic Systems, Scottsdale, Arizona; CV 2.7%). Serum bone alkaline phosphatase was measured by ELISA (Quidel Corp, Sand Diego, CA; CV 7.6%).

Statistical Methods

Analyses were conducted with STATA version 9.0 (Stata Corp, College Station, Texas) and SAS version 9.1 (SAS Institute Inc., Cary, North Carolina). Two-sided p values < 0.05 were considered to indicate statistical significance. Normality testing (Kolmogorov-Smirnov) was performed and variables that were not normally distributed were logarithmically transformed prior to group comparisons. Differences among the three groups were assessed by ANOVA with Scheffe test for multiple comparisons. Comparison of HR-pQCT parameters among groups after adjustment for age and BMI was performed using ANCOVA. Mean percent difference and the standard error of the difference between each osteoporosis group (1/3RO and PMO) and controls was calculated using multiple T-tests.

Results

Study Subjects

This study enrolled 266 postmenopausal women. Characteristics of the subjects in the three groups are detailed in Table 1. The majority of women were White Non-Hispanic (78%). The mean age was 68 ± 7 years. Controls were younger than the other two groups. Mean BMI was in the normal or overweight range for all groups, and was highest among controls. Tobacco and alcohol use were similar. There was no difference in use of calcium and vitamin D supplements or in mean intake between groups. Less than 10% of women were currently using HRT; use was higher among controls. Approximately half of the women in the overall cohort (56%) had a history of fragility fracture or a prevalent vertebral fracture by spine radiographs. There was no difference in overall clinical fracture history between the three groups. The prevalence of extremity fractures (wrist, ankle or humerus) appeared higher in patients with 1/3RO but the difference was not significant between

groups. Vertebral fracture prevalence appeared higher in patients with PMO but was not significantly different between groups. Among patients with a vertebral fracture, there was no difference according to group in either the presence of multiple vertebral fractures or fracture severity.

Biochemical Data

Calciotropic hormones and bone turnover markers are detailed in Table 2. Calcium and intact parathyroid hormone (iPTH) were in the normal range and did not differ between groups. Kidney function assessed by creatinine and estimated Glomerular Filtration Rate (eGFR) calculated by MDRD (30), was in the normal range and similar between groups. Urinary calcium excretion, measured as 24 hour urine calcium/creatinine ratio was also similar. Serum 25OHD levels were above 20 ng/ml in all groups. Although 25OHD was numerically lower in the 1/3RO group compared to controls and PMO this difference was not significant. Bone formation markers, serum osteocalcin and bone specific alkaline phosphatase were higher in 1/3RO. Bone resorption, assessed by serum CTX was also higher in 1/3RO.

Areal BMD

As expected according to our study design, mean T-Scores were lowest in PMO at all central sites compared to both controls and 1/3RO, lumbar spine (LS: −2.6 ± 1.1), total hip (TH: −2.0 ± 0.6) and femoral neck (FN: −2.4 ± 0.6). At the 1/3 radius, mean T-Score was −3.1 (± 0.5) among 1/3RO but higher and above the osteoporosis threshold in PMO (−2.3 ± 1.3). Values for 1/3RO fell within the osteopenic range at all other sites, the LS (−1.2 ± 1.0), TH (−1.5 ± 0.6), and FN (−1.9 ± 0.4). Controls had average T-Scores in the normal range at the LS (−0.8 ± 1.2), TH (0.8 ± 0.9) and 1/3R (−0.7 ± 1.0), and in the osteopenic range at the FN (−1.4 ± 0.8).

Volumetric BMD, Microarchitecture and Stiffness

Bone size, vBMD, cortical and trabecular microarchitecture were assessed by HR-pQCT (Figure 1A and 1B). Raw data are detailed in Table 3. Compared to controls, 1/3RO had substantial abnormalities in cortical and trabecular bone at both radius and tibia. At the radius, 1/3RO had lower total vBMD (−18%; $p<0.001$), cortical vBMD (−5%; $p<0.01$) and trabecular vBMD (−24%; $p<0.001$). They had lower cortical thickness (−14%; $p<0.01$), lower trabecular number (−22%; $p<0.001$), greater trabecular separation (+46%; $p<0.05$), and greater heterogeneity (+75%; $p<0.05$). Abnormalities were observed in vBMD and microarchitecture in women with 1/3RO at the tibia as well; compared to controls, 1/3RO had lower total vBMD (−16%; $p<0.001$), cortical vBMD (−6%; $p<0.01$) and trabecular vBMD (−16%; $p<0.001$). They had lower cortical thickness (−15%; $p<0.05$), lower trabecular number (−16%; $p<0.001$), greater trabecular separation (+24%; $p<0.001$), and greater heterogeneity (+49%; $p<0.01$). Trabecular thickness did not differ significantly at either site.

As expected, vBMD and microarchitecture were worse in PMO compared with controls as well. Specifically, at the radius, PMO had lower total vBMD (−17%; $p<0.001$), trabecular vBMD (−22%; $p<0.001$), and cortical vBMD (−5%; $p<0.001$). They had lower cortical

thickness (−19%; p<0.001) and trabecular number (−19%; p<0.001), greater trabecular separation (+40%; p<0.001), and greater heterogeneity (+91%; p<0.001). At the tibia, PMO had lower total vBMD (−15%; p<0.001), trabecular vBMD (−16%; p<0.001), and cortical vBMD (−5%; p<0.001) compared to controls. They had lower cortical thickness (−17%; p<0.001) and trabecular number (−16%; p<0.001), greater trabecular separation (+24%; p<0.001), and greater heterogeneity (+49%; p<0.001).

Interestingly, the extent of abnormalities in vBMD and microarchitecture were similar among 1/3RO and PMO. There were no significant differences between these groups in any cortical or trabecular parameter. Both groups had substantial deficits at both the radius and the tibia. When compared with controls, the same parameters were significantly worse in 1/3RO and PMO and differences from controls were of similar magnitude.

Biomechanical properties of bone were worse in both groups compared to controls. At the radius, whole bone stiffness was lower in both 1/3RO (−13%; p<0.01) and PMO (−21%; p<0.001) compared to controls. At the tibia, stiffness was lower in 1/3RO (−13%, p<0.01) and PMO (−17%, p<0.001). As observed with vBMD and microarchitecture, stiffness did not differ between women with 1/3RO and PMO.

Differences between groups were further compared after adjustment for age and BMI. The previously observed significant differences in vBMD, microarchitecture, and stiffness between the 1/3RO and the other groups remained statistically significant after adjustment.

Volumetric BMD and microarchitecture in women with 1/3RO with and without a history of fracture were compared. While no parameter was significantly different between the groups, radial total and trabecular vBMD tended to be lower among fracture subjects (p=0.06 and p=0.07 respectively).

Discussion

In this study, we investigated the microarchitectural and biochemical phenotype of women with isolated osteoporosis at the 1/3 radius by DXA compared to women who manifested the more typical pattern of osteoporosis at the spine and hip, and controls without osteoporosis. We found that women with 1/3RO had substantial abnormalities in vBMD, microarchitecture, and stiffness compared to controls. Significantly, the deficits documented by HR-pQCT at the radius and tibia in women with 1/3RO mirrored those detected in women with central osteoporosis at the spine and hip. These results suggest that the finding of isolated osteoporosis at the wrist by DXA is indicative of deteriorated microarchitecture and compromised biomechanical properties of bone similar to those seen in women with central osteoporosis at the spine and hip.

As the 1/3 radius is a predominantly cortical site, we hypothesized that women with 1/3RO would have cortical abnormalities compared to controls. In support of this, we found that they had lower cortical vBMD and thinner cortices. However, interestingly, they had substantial trabecular deficits as well, with lower trabecular vBMD, and fewer, more widely and irregularly spaced trabeculae at the radius. Moreover, the trabecular deficits were more marked than the cortical deficits. It could be postulated that small bone size might

contribute to the finding of 1/3RO as 2-dimensional DXA measurements are artifactually lower in patients with smaller bones (31), however, we observed that bone size measured as cross-sectional area by HR-pQCT was not smaller among women with 1/3RO compared to controls or PMO.

Microarchitectural differences between women with 1/3RO and controls were apparent at both radius and tibia. Although the site assessed by HR-pQCT is distal to the 1/3 radius site by DXA, the finding that patients who have lower values at the DXA 1/3 radius site have microarchitectural abnormalities at the radius is not unexpected. More surprising were the number and extent of abnormalities that were also observed at the tibia. This observation suggests that the microarchitectural deficits are generalized, at least throughout the peripheral skeleton, rather than limited to the 1/3 radius. While we observed differences at both radius and tibia, a limitation of our study is that we did not use modalities other than DXA to evaluate central sites. Other studies have shown that peripheral HR-pQCT measurements correlate with central QCT measurements in young women with osteoporosis (32). Future studies using higher-order imaging techniques at the spine and hip will help to elucidate how pervasive skeletal abnormalities are in the postmenopausal population.

While vBMD and microarchitecture were similar between women with 1/3RO and PMO, forearm DXA measurements were higher in the women with PMO. Work from our group and others has shown that peripheral HR-pQCT measurements are predictive of fragility at central sites (14, 17, 26). Peripheral DXA, in contrast, may not be as sensitive to these abnormalities. It is well established that low aBMD at the hip and spine are highly correlated with fracture risk (33-37). Current guidelines recommend that central DXA be used primarily as the reference of osteoporosis for postmenopausal women, as they are more reliable than peripheral measures (36). However, there are many instances when peripheral measures may be necessary. In the older population, spine measurements are often artifactually high because of degenerative disease. In the growing population of patients who have had orthopedic procedures involving hardware at the spine and the hip, these sites may not be evaluable. As a result, in some patients only wrist measurements are available. Studies have shown that aBMD at the wrist does correlate with aBMD at the spine and the hip (38). In the NORA trial, patients with osteoporosis at peripheral sites, including the wrist, had a higher rate of fracture at both the wrist and hip compared to patients with higher aBMD at these peripheral sites (39). Our results suggest that wrist DXA measurements provide valuable information even when central measurements are available, as they allow for identification of patients with microarchitectural abnormalities who might otherwise be missed if only spine and hip values are considered.

Subjects were classified in this study based upon densitometric pattern alone, and there were subjects with a history of fragility fracture included in each of the groups. Overall fracture prevalence was similar between the groups. As might be expected, a greater proportion of women with 1/3RO had fractures of the extremities, and more women in the PMO group had vertebral fractures. However, these differences were not significant, possibly due to our small number of woman with 1/3RO. This pattern of differences in fracture suggests that 1/3RO may represent a specific entity of peripheral skeletal abnormalities, with a particular

susceptibility to extremity fractures. Further, larger studies are needed to confirm these observations.

We investigated biochemical differences between the groups to determine whether there were differences in calciotropic hormones or bone turnover markers that might provide an underlying mechanism for the observed phenotype. Bone turnover was elevated in the 1/3RO women compared to the other groups which may have contributed to the microarchitectural abnormalities observed. No underlying metabolic abnormalities were observed to explain this increase in turnover or the structural abnormalities in 1/3RO. Although women with overt hyperparathyroidism and known renal disease were excluded from this study, we hypothesized that more subtle elevations in PTH, secondary to vitamin D deficiency, inadequate calcium intake, or mild chronic kidney disease, might contribute to cortical bone loss and 1/3RO, however we did not find this to be the case. We found that 25OHD levels were sufficient in the majority of subjects (>20 ng/ml). While values were numerically lower among 1/3RO, they did not differ significantly between groups. Calcium intake was similar between groups and 24-hour urine calcium was normal in these women, making it unlikely that inadequate calcium intake or a renal calcium leak played a role in the development of 1/3RO. Renal function, assessed by creatinine and MDRD did not differ. These results suggest that factors other than these biochemistries are responsible for the densitometric and microarchitectural abnormalities seen in women with 1/3RO. Genetic factors could play an important role.

Our study is limited by its cross-sectional design and the relatively small population of women with 1/3RO. We were unable to investigate the relationship between the structural abnormalities observed and prediction of fractures at peripheral or central sites. Studies from our group and others have shown that vBMD, microarchitecture and stiffness can discriminate fracture status in multiple populations. Recently HR-pQCT measurements predicted fracture in a longitudinal study (40). Whether the abnormalities that we detected in our cohort with isolated 1/3RO are directly related to fracture risk is an important topic for future work. Whether the higher remodeling rate observed in the 1/3RO contributed to the microarchitectural abnormalities cannot be determined in our cross-sectional study but is an important question to be addressed in future prospective work. There were differences in some demographic factors, age and BMI between our groups. While we did adjust for these differences in our analyses, it is possible that multiple factors may have contributed to the observed differences in microarchitecture. Further, although all HR-pQCT measurements were performed on one machine, DXA measurements were performed at two sites, one using a Hologic (CUMC) and the other a Lunar (HHH) system. We used T-Scores to reduce the confounding introduced by this variability (41) however, some disparities likely still existed and 1/3 radius measurements may be more variable between manufacturers than other sites. Finally, we enrolled women on the basis of aBMD and therefore women with fractures were included in each group of our cohort. Although the presence of a fragility fracture should prompt consideration of treatment regardless of aBMD, in practice treatment is often not initiated. Our subjects were not treated and many, despite their fracture history had never been told that they had osteoporosis, underscoring the reliance of many practitioners on DXA for assessment of bone health.

In conclusion, we found that postmenopausal women with isolated osteoporosis at the 1/3 radius have low volumetric BMD, abnormal cortical and trabecular microarchitecture and low stiffness at both radius and tibia compared to controls. In addition, these women had similar deficits in volumetric density, microarchitecture and stiffness to those observed in women with osteoporosis at the spine and hip. Our results suggest that although aBMD appears relatively preserved at the spine and hip by DXA, women with 1/3RO have substantial microarchitectural and biomechanical deficits throughout their extremities. Further study is required investigate the extent of these abnormalities throughout the axial skeleton and to guide treatment decisions in this population.

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Highlights

- Isolated osteoporosis at 1/3 radius (1/3RO) presents a therapeutic dilemma
- Women with 1/3RO had microarchitectural and biomechanical deficits
- The skeletal abnormalities in 1/3RO were similar to those in classic PMO

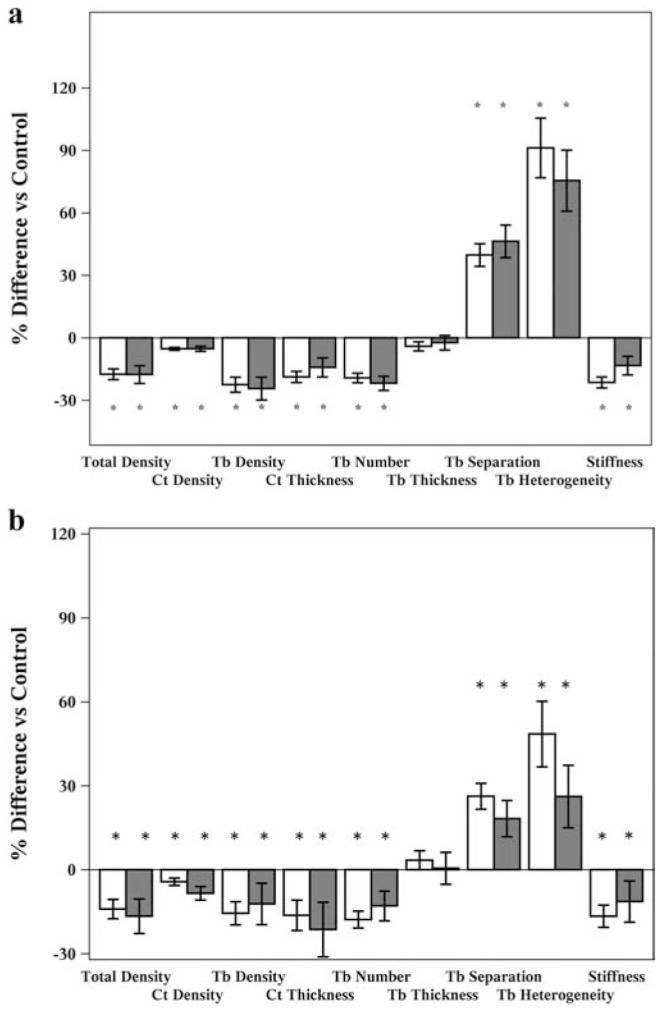

Figure 1.

A. Percent differences +/− SEM in vBMD, microarchitecture and whole bone stiffness at the radius compared to controls for women with 1/3RO (white bars) and PMO (grey bars) * P-value<0.05.

B. Percent differences +/− SEM in vBMD, microarchitecture and whole bone stiffness at the tibia compared to controls for women with 1/3RO (white bars) and PMO (grey bars). * P-value<0.05.

Table 1.

Characteristics of the study population

	1/3 RO N=27	PMO N=81	Control N=158	P-value
Age (years)	70 ± 8	71 ± 8[a]	67 ± 6	<0.01
Race – Caucasian (%)	81	75	79	0.58
BMI (kg/m^2)	26 ± 4[a]	24 ± 4[a]	28 ± 6	<0.001
History of fragility fracture (clinical + radiographic %)	63	58	54	0.62
Wrist Fracture (%)	30	26	18	0.18
Humerus fracture (%)	7	4	3	0.54
Ankle fracture (%)	15	10	11	0.77
Any extremity fracture (%)	48	37	30	0.16
Vertebral fracture (%)	11	21	13	0.27
Family history of osteoporosis (%)	55	47	47	0.76
Tobacco use –				
Never (%)	61	56	42	0.06
Former (%)	36	40	52	
Current (%)	3	4	5	
Alcohol use (beverages per day)	1 ± 1	1 ± 1	1 ± 1	0.71
Calcium supplements – total daily dose (mg)	732 ± 489	658 ± 540	600 ± 578	0.53
Vitamin D supplements – total daily dose (IU)	864 ± 300	952 ± 176	880 ± 125	0.94
HRT – Past (%)	48	34[a]	49	0.05
HRT - Current (%)	0	1[a]	9	0.02
Raloxifene (%)	4	6	2	0.14
Thyroxine (%)	8	21	18	0.76

Data shown as mean ± SD. Abbreviations: 1/3RO (isolated osteoporosis at the 1/3 radius by DXA), PMO (osteoporosis at the spine or hip by DXA), HRT (Hormone Replacement Therapy).

[a]statistically different from controls

Table 2.

Biochemical Data

	1/3RO	PMO	Control	P-value
Serum Calcium (8.6-10.2 mg/dL)	9.4 ± 0.5	9.5 ± 0.3	9.5 ± 0.4	0.80
Creatinine (0.5-1.2 mg/dL)	0.9 ± 0.3	0.8 ± 0.2	0.9 ± 0.3	0.29
Estimated GFR (ml/min)	74 ± 26	77 ± 17	75 ± 20	0.80
iPTH (11-67 pg/mL)	41 ± 16	47 ± 26	46 ± 27	0.57
24 hour urine calcium (mg/g Cr)	119 ± 57	155 ± 78	158 ± 87	0.23
25OHD (20-50 ng/ml)	27 ± 8	37 ± 16	36 ± 12	0.07
Osteocalcin (8.4-33.9 ng/mL)	25 ± 11[a]	21 ± 8	18 ± 8	<0.001
BSAP (11.5-29.6 U/L)	29 ± 14	27 ± 8	24 ± 10	<0.03
CTX (0.11-0.74 ng/mL)	0.6 ± 0.2[a]	0.4 ± 0.2	0.4 ± 0.2	<0.02

Data shown as mean ± SD with normal ranges in parentheses. Abbreviations: 1/3RO (isolated osteoporosis at the 1/3 radius by DXA), PMO (osteoporosis at the spine or hip by DXA), GFR (glomerular filtration rate), iPTH (intact parathyroid hormone), BSAP (bone specific alkaline phosphatase), CTX (C-telopeptide).

[a] statistically different from controls in pairwise comparison after an omnibus F-test is significance at the 0.05 level.

Table 3.

Raw Values of vBMD and Microarchitecture by HR-pQCT

HR-pQCT Parameter	Radius			Tibia		
	1/3RO	PMO	Control	1/3RO	PMO	Control
Total Area (cm^2)	235 ± 7	234 ± 3	234 ± 3	693 ± 21	645 ± 12	683 ± 9
Cortical Area (cm^2)	41 ± 2	38 ± 1	48 ± 1	78 ± 5	74 ± 3	91 ± 2
Trabecular Area (cm^2)	196 ± 8	183 ± 5	186 ± 3	615 ± 22	571 ± 12	593 ± 10
Total Density ($mgHA/cm^3$)	244 ± 12	244 ± 7	295 ± 5	205 ± 9	209 ± 5	245 ± 4
Cortical Density ($mgHA/cm^3$)	810 ± 13	810 ± 8	854 ± 5	742 ± 13	746 ± 8	786 ± 6
Cortical Thickness (mm)	0.62 ± 0.30	0.59 ± 0.02	0.73 ± 0.01	0.74 ± 0.05	0.73 ± 0.03	0.87 ± 0.02
Trabecular Density ($mgHA/cm^3$)	98 ± 7	100 ± 4	129 ± 3	147 ± 3	123 ± 4	147 ± 3
Bone Volume Fraction (BV/TV %)	0.08 ± 0.01	0.08 ± 0.00	0.11 ± 0.00	0.10 ± 0.01	0.10 ± 0.00	0.12 ± 0.00
Trabecular Number (1/mm)	1.41 ± 0.07	1.45 ± 0.04	1.80 ± 0.03	1.52 ± 0.06	1.51 ± 0.03	1.81 ± 0.03
Trabecular Thickness (mm)	0.06 ± 0.00	0.06 ± 0.00	0.06 ± 0.00	0.07 ± 0.00	0.07 ± 0.00	0.07 ± 0.00
Trabecular Separation (mm)	0.75 ± 0.05	0.72 ± 0.03	0.52 ± 0.01	0.62 ± 0.02	0.62 ± 0.01	0.50 ± 0.01
Trabecular Heterogeneity (mm)	0.43 ± 0.05	0.47 ±0.03	0.24 ± 0.01	0.34 ± 0.03	0.34 ± 0.02	0.23 ± 0.01
Stiffness (N/mm)	27643 ± 1354	25059 ± 792	31888 ± 612	82840 ± 3625	78886 ± 2052	95195 ± 1597

Mean ± SEM