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Evaluation of Trabecular Micro-Architecture in Non-Osteoporotic Post-Menopausal Women With and Without Fracture

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Abstract

Purpose—To compare microscopic magnetic resonance imaging (μ MRI) parameters of trabecular micro-architecture between postmenopausal women with and without fracture who have normal or osteopenic bone mineral density (BMD) on dual-energy x-ray absorptiometry (DXA).

Methods—The study included 36 post-menopausal Caucasian women 50 years of age and older with normal or osteopenic BMD (T-scores better than -2.5 at the lumbar spine, proximal femur, and one-third radius on DXA). Eighteen women had a history of low-energy fracture, while 18 women had no history of fracture and served as an age, race, and ultra-distal radius BMD-matched control group. A three-dimensional fast large-angle spin-echo (FLASE) sequence with $137 \mu\text{m} \times 137 \mu\text{m} \times 400 \mu\text{m}$ resolution was performed through the non-dominant wrist of all 36 women using the same 1.5T scanner. The high resolution images were used to measure trabecular bone volume fraction, trabecular thickness, surface-to-curve ratio, and erosion index. Wilcoxon signed rank tests were used to compare differences in BMD and μ MRI parameters between post-menopausal women with and without fracture.

Results—Post-menopausal women with fracture had significantly lower ($p < 0.05$) trabecular bone volume fraction and surface-to-curve ratio and significantly higher ($p < 0.05$) erosion index

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Study Conduct: R.K., M.T., D.K., and N.B. contributed to study conduct.

Data Collection: R.K., M.T., D.K., and N.B. contributed to data collection.

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R.K., M.T., and N.B. take responsibility for the integrity of the data analysis

DISCLOSURES/CONFLICTS OF INTEREST

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than post-menopausal women without fracture. There was no significant difference between post-menopausal women with and without fracture in trabecular thickness ($p=0.80$) and BMD of the spine ($p=0.21$), proximal femur ($p=0.19$), one-third radius ($p=0.47$), and ultra-distal radius ($p=0.90$).

Conclusions—Post-menopausal women with normal or osteopenic BMD who had a history of low energy fracture had significantly different ($p<0.05$) μ MRI parameters than an age, race, and ultra-distal radius BMD-matched control group of postmenopausal women with no history of fracture. Our study suggests that μ MRI can be used to identify individuals without a DXA-based diagnosis of osteoporosis who have impaired trabecular micro-architecture and thus a heretofore-unappreciated elevated fracture risk.

Keywords

Osteoporosis; Trabecular Micro-Architecture; Magnetic Resonance Imaging; Fracture

INTRODUCTION

Osteoporosis is a multi-factorial disease of low bone mass and impaired bone micro-architecture which results in decreased bone strength and increased fracture risk (1). The disease becomes extremely common with advancing age with 40% to 50% of women and 25% of men sustaining an osteoporosis-related fracture during their lifetime (2, 3). Currently an estimated 1.5 million fractures occur annually in the United States (4) which produce high morbidity and mortality and cause substantial healthcare expenditures (5–9). While the current disability and economic burden associated with osteoporosis is enormous, the future burden will be considerably higher with the increasing age of the population worldwide (10). As such, a pressing need exists to optimally identify those individuals at elevated fracture risk.

The clinical standard for osteoporosis diagnosis is bone mineral density (BMD) measurements obtained using dual-energy x-ray absorptiometry (DXA) (11). In fact, the World Health Organization (WHO) T-score based system classifying individuals as normal, osteopenic, or osteoporotic (12) directly applies only to BMD as measured by DXA (11). DXA has proven to be a valuable clinical tool as it identifies individuals at elevated fracture risk, and subsequent treatment of men and women with low BMD reduces fracture risk (13–17). However, BMD accounts for only 50% to 65% of variations in the mechanical strength of bone (18, 19). Furthermore, large prospective studies have found that less than 50% of individuals who sustain low-energy fractures have a diagnosis of osteoporosis based upon BMD measurements (20–22). Thus, clinical need exists to identify factors other than BMD that influence bone strength and fracture risk.

Bone strength is the result of bone density and “bone quality”, a complex amalgamation including macro- and micro-architecture, mineralization, turnover, and damage accumulation. Bone remodeling is a component of normal human physiology which prevents fatigue damage accumulation and contributes to mineral homeostasis (23, 24). Remodeling is carried out by a coupled team of cells, osteoclasts which excavate remodeling lacunae and osteoblasts which produce and mineralize osteoid (25, 26). Ideally, osteoblasts precisely replace the amount of bone resorbed by osteoclasts via a complex coupling process (27). However, with aging, osteoclastic activity exceeds osteoblastic activity leading to trabecular thinning and perforation and conversion of trabecular plates to rods (28). The resultant micro-architecture deterioration leads to reduced bone strength and increased fracture risk (29).

The recognition of impaired trabecular micro-architecture as a risk factor for fracture was originally based on iliac crest biopsy histomorphometry (30–32). However, histomorphometry is invasive and provides imperfect micro-architectural assessment since histological sections are two-dimensional and trabecular micro-architecture is inherently three-dimensional and highly anisotropic (33). Non-invasive three-dimensional assessment of trabecular micro-architecture has recently become possible using high resolution imaging techniques such as peripheral quantitative computed tomography (pQCT) and microscopic magnetic resonance imaging (μ MRI). pQCT can acquire images of the peripheral skeleton with voxel sizes as low as $82\ \mu\text{m} \times 82\ \mu\text{m} \times 82\ \mu\text{m}$ with minimal radiation exposure (34), while μ MRI can acquire images with voxel sizes as low as $137\ \mu\text{m} \times 137\ \mu\text{m} \times 225\ \mu\text{m}$ for the wrist (35–37) and $234\ \mu\text{m} \times 234\ \mu\text{m} \times 1500\ \mu\text{m}$ for the proximal femur (38). The high resolution images can be used to measure various micro-architectural parameters including the fractional volume and thickness of trabecular bone and the degree of connectivity of the trabecular network (39–42).

Multiple previous studies have shown that trabecular micro-architectural parameters measured using both pQCT (43) and μ MRI (44–50) are superior to BMD for distinguishing between osteoporotic individuals with and without fracture (44–50). However, no previous study has investigated the ability of these parameters to assess fracture risk in individuals without a DXA-based diagnosis of osteoporosis. Thus, this study was performed to compare μ MRI parameters of trabecular micro-architecture between postmenopausal women with and without fracture who have normal or osteopenic bone mineral density (BMD).

METHODS

Subjects

The prospective study was performed in compliance with HIPAA regulations and with approval from our Institutional Review Board. All subjects signed written consent prior to participation in the study.

The study included 36 post-menopausal Caucasian women 50 years of age and older with normal or osteopenic BMD (T-scores better than -2.5 at the lumbar spine, proximal femur, and one-third radius on DXA). Eighteen women had a history of low-energy fracture which was defined as a clinically symptomatic fracture occurring with everyday activities including a fall from standing height or less. Five subjects had ankle fractures, 2 subjects had rib fractures, 6 subjects had vertebral body fractures, one subject had a humerus fracture, and 4 subjects had dominant side wrist fractures. All fractures were documented either through the medical records or actual review of the imaging studies. The mean interval between the time the subjects sustained a fracture and the time they were enrolled in the study was 4.8 years with a range between 0.1 and 17.1 years and a standard deviation of 4.4 years. Eighteen women had no history of low-energy fracture and served as an age, race, and ultra-distal radius BMD-matched control group. Age between subjects was matched to within 6 months, and BMD in grams/cm^2 at the non-dominant ultra-distal radius was matched within 5%. Subjects were excluded from the study if they had a history of metabolic bone disease, malignancy, renal failure, use of medications which alter bone turnover, diseases/conditions leading to non-dominant arm disuse, and contraindications to μ MRI examination.

Subjects were recruited through an Institute on Aging Volunteer Registry at our institution which was searched for potential eligible volunteers. Following phone screening, potential eligible subjects underwent standard spine, proximal femur, and non-dominant forearm DXA scans (Lunar iDXA densitometer, GE Healthcare, Madison, WI). Quality assurance precision data obtained from repeat BMD measurements on 30 post-menopausal women

showed a coefficient of variance of 1.2% for the spine, 0.6 % for the proximal femur, 2.4% for the distal radius, and 3.9% for the ultra-distal radius. DXA images were used to exclude the presence of prior trauma, osteoarthritis, or inflammatory or crystalline induced arthritis of the non-dominant wrist which may influence trabecular micro-architecture. A DXA vertebral fracture assessment (VFA) image of the thoracolumbar spine was obtained to document vertebral fracture status to assure that unappreciated vertebral fractures did not exist in subjects in the control group. Blood was drawn to obtain a routine chemistry panel to demonstrate the absence of systemic conditions indicative of bone disease. Subjects meeting inclusion/exclusion criteria with a history of low energy fracture and those determined to be an appropriate match were included in the study.

μMRI Examination

All subjects underwent a μMRI examination of the non-dominant wrist on the same 1.5T scanner (Signa Hdx, GE Healthcare, Madison, WI) using a specially designed transmit-receive elliptical birdcage coil (Insight MRI, Worcester, MA). All subjects were imaged with their arm positioned at the side and their wrist centered within the coil. The coil was placed in the middle of an immobilizing vacuum bag (VacFix™, Soule Medical Systems, Inc., Tampa, FL) and attached to the base of a positioning device. The vacuum bag was secured around the arm using Velcro straps and inflated to minimize wrist movement during the μMRI examination (37, 51, 52).

All μMRI examinations consisted of a three-dimensional fast large-angle spin-echo (FLASE) sequence. Intermittent navigator echoes were incorporated into the sequence to allow for motion correction. The FLASE sequence was performed using a TR/TE of 80ms/10ms, 140° flip angle, 7.0 cm x 5.3 cm field of view, 512 x 384 matrix, 0.4 mm slice thickness, one excitation, 137 μm x 137 μm x 400 μm voxel size, and 12:30 minute scan time. Images were acquired through a 7.0 cm x 5.3 cm x 7.0 cm volumetric slab which was centered on the distal radius 7 mm proximal to the tip of the epiphyseal line (37, 51, 52).

Image Analysis

Image analysis was performed by an experienced research technologist from MicroMRI, Inc. (Langhorne, PA) using a previously described semi-automated virtual bone biopsy system (33). Motion-corrected images were generated from the raw data using estimates of patient motion obtained from the navigator echoes (53). A three-dimensional volume-of-interest through the distal radius was selected to exclude areas of artifact but to include as much of the bone marrow space as possible. The volume-of-interest was processed using a bone volume fraction mapping technique to generate noiseless parametric images where each voxel represented the trabecular bone volume fraction (bone volume/trabecular volume) (54).

The average trabecular thickness on the bone volume fraction maps was measured using a fuzzy distance transform algorithm (55). The bone volume fraction maps then underwent subvoxel processing to improve resolution which resulted in a voxel size of 69 μm x 69 μm x 103 μm (56). The maps were binarized and skeletonized to produce a model of the trabecular network consisting of surfaces and curves which represented the lower-dimensional counterparts of plates and struts respectively (42). Digital topological analysis was used to classify each voxel within the volume-of-interest into a surface (S), curve (C), or their mutual junction (CC, SC, and SS). Further classification was used to distinguish between voxels located in the interior or edge of the respective curves or surfaces (CI, SI, CE, and SE) (35, 57).

The topological parameters surface-to-curve ratio and erosion index were calculated to describe the integrity of the trabecular network. The surface-to-curve ratio represented the relative plate-like versus rod-like character of the trabecular network and was defined as the sum of all surface-type voxels (SE, SI, SC, SS) divided by the sum of all curve-type voxels (CE, CI, and CC). The erosion index represented the degree of connectivity of the trabecular network and was defined as the sum of all surface-type voxels expected to increase with bone resorption (CI, CE, CC, and SE) divided by the sum of all surface-type voxels expected to decrease with bone resorption (SI, SC, and SS) (35, 57).

A preliminary pilot study was performed at our institution by MicroMRI, Inc. (Langhorne, PA) to document the precision of the FLASE sequence and virtual bone biopsy system for measuring μ MRI parameters. μ MRI examinations were performed twice on separate days on 10 healthy volunteers (four male with average age of 27.8 years and six females with an average age of 28.3 years) using the previously described imaging protocol. μ MRI parameters of trabecular microarchitecture were measured using the previously described methods. The mean coefficient of variance for repeat measurements was 2.4% for bone volume fraction, 2.1% for trabecular thickness, 6.2% for surface-to-curve ratio, and 4.1% for erosion index which was similar to values reported at other institutions (37, 58).

Statistical Analysis

All statistical analysis was performed using the R programming environment (R Development Core Team; Vienna, Austria; Version 2.3.1; 2006; <http://www.R-project.org>). Wilcoxon signed rank tests were used to compare differences between post-menopausal women with and without fracture in age, height, weight, body mass index, BMD measurements (lumbar spine, proximal femur, one-third radius, and ultra-distal radius), laboratory values (calcium, phosphate, creatinine, albumen, alkaline phosphatase, and alanine aminotransferase), and μ MRI parameters (trabecular bone volume fraction, trabecular thickness, surface-to-curve ratio, and erosion index). For all statistical tests, differences were considered to be statistically significant if the p-value was less than 0.05.

RESULTS

There was no statistically significant difference ($p=0.13-0.99$) between post-menopausal with and without fracture in age, height, weight, body mass index, BMD measurements, and laboratory values (Table 1). However, post-menopausal women with fracture had significantly lower ($p<0.05$) trabecular bone volume fraction and surface-to-curve ratio and significantly higher ($p<0.05$) erosion index than post-menopausal women without fracture. There was no significant difference ($p=0.80$) in trabecular thickness between post-menopausal women with and without fracture (Table 2).

DISCUSSION

Our study found a significantly lower bone volume fraction in post-menopausal women with fracture when compared to post-menopausal women without fracture. Link and associates compared μ MRI parameters of the calcaneus (46) and Majumdar and associates compared μ MRI parameters of the wrist (50) in post-menopausal women with and without hip fracture and also found significantly lower trabecular bone volume fraction in subjects with fracture. In addition, Wehrli and associates found significantly lower trabecular bone volume fraction of the wrist in post-menopausal women with vertebral body fracture when compared to post-menopausal women without fracture (35). However, in those prior studies, a significant difference in BMD between subjects with and without fracture was present which may have served as a confounding variable in fracture risk assessment (35, 46, 50). In our study, low trabecular bone volume fraction was found to be a risk factor for fracture independent of

BMD since our post-menopausal women with and without fracture had similar BMD measurements at all body sites and were specifically matched for BMD at the ultra-distal radius where μ MRI parameters were measured.

Our study found a significantly lower surface-to-curve ratio and significantly higher erosion index in post-menopausal women with fracture when compared to post-menopausal women without fracture. Post-menopausal bone loss is characterized by conversion of trabecular plates to rods due to excessive osteoclastic activity eventually leading to plate perforation (59). Differences in topological parameters in our study indicate a more rod-like trabecular network and greater trabecular erosive changes in post-menopausal women with fracture. Wehrli and associates also found significantly lower surface-to-curve ratio and significantly higher erosion index of the wrist in post-menopausal women with vertebral body fracture when compared to post-menopausal women without fracture. However, subjects with and without fracture also showed significant BMD differences which may have served as a confounding variable in the study (50). A later study by Ladinsky and associates found a significant correlation between surface-to-curve ratio and erosive index of the wrist and vertebral body fracture burden in post-menopausal women which was independent of vertebral body BMD (48).

Our study found no significant difference in trabecular thickness between post-menopausal women with and without fracture. This is consistent with prior work demonstrating that bone loss in post-menopausal women is characterized by trabecular perforation rather than the trabecular thinning which is more commonly observed in aging men (60, 61). Similarly, Link and associates found no significant difference in trabecular thickness of the calcaneus (46) and Majumdar and associates found no significant difference in trabecular thickness of the wrist (50) between post-menopausal women with and without hip fracture. However, Ladinsky and associates found a significant correlation between trabecular thickness of the wrist and vertebral body fracture burden in post-menopausal women which was independent of vertebral body BMD (48). Difference in the results of our study and the study performed by Landinsky and associates may be partly explained by differences in patient populations. Our study included only post-menopausal women with a T-score better than -2.5 at the lumbar spine, proximal femur, and one-third radius on DXA, while the study by Landinsky and associates included only post-menopausal females with a T-score between -1.5 and -3.5 at the lumbar spine and proximal femur.

Our study is the first to investigate the role of trabecular micro-architectural parameters in assessing fracture status exclusively in individuals with normal or osteopenic BMD. All previous studies have shown that parameters of trabecular micro-architecture measured using pQCT (43) and μ MRI (44–50) can distinguish between osteoporotic individuals with and without fracture (44–50). However, individuals with a DXA-based diagnosis of osteoporosis would meet the current U.S. National Osteoporosis Foundation guidelines for receiving pharmacologic therapy to increase BMD and reduce fracture risk regardless of whether their trabecular microarchitecture was normal or abnormal. Our study demonstrates that μ MRI can be used as a non-invasive method to identify individuals without a DXA-based diagnosis of osteoporosis who have a heretofore-unappreciated elevated fracture risk. As micro-architectural deterioration profoundly reduces bone strength, it is apparent that clinical application of tools capable of identifying such structural deterioration may enhance targeting of fracture prevention therapy.

Our study has several limitations. One limitation was the wide variety of low energy fractures sustained by our post-menopausal women which may have resulted in a rather heterogeneous study group. However, this is reflective of the real-life clinical scenario in which individuals with low BMD sustain a variety of low energy fractures. A second

limitation of our study was the suboptimal resolution of the FLASE sequence used to evaluate trabecular micro-architecture. In particular, the $137\ \mu\text{m} \times 137\ \mu\text{m} \times 400\ \mu\text{m}$ resolution may have been insufficient to accurately measure trabecular thickness which typically ranges between $100\ \mu\text{m}$ and $150\ \mu\text{m}$ (34). Thus, the inability of our study to detect a significant difference in trabecular thickness between subjects with and without fracture may be partly due to resolution-dependent inaccuracies in the measurement of this micro-architectural parameter. Another limitation of our study was the relatively small number of subjects. Additional studies using a larger number of subjects and perhaps higher resolution imaging techniques should be performed to further compare trabecular micro-architectural parameters between postmenopausal women with and without fracture who do not have a DXA-based diagnosis of osteoporosis. A final limitation of our study was that the μMRI examination was performed only on the non-dominant wrist of post-menopausal females. Previous studies have also measured μMRI parameters in the calcaneus (45, 46), tibia (50, 62, 63), and proximal femur (38). It is possible that μMRI parameters measured at these sites may be more useful for distinguishing between subjects with and without fracture than μMRI parameters measured at the wrist.

In conclusion, our study found that post-menopausal women with normal or osteopenic BMD who had a history of low energy fracture had significantly lower trabecular bone volume fraction and surface-to-curve ratio and significantly higher erosion index than an age, race, and ultra-distal radius BMD-matched control group of postmenopausal women with no history of fracture. Our study suggests that μMRI can be used to identify individuals without a DXA-based diagnosis of osteoporosis who have a heretofore-unappreciated elevated fracture risk. In the future, μMRI may potentially enhance targeting of fracture prevention therapy to include individuals with normal or osteopenic BMD who have impaired trabecular micro-architecture. For example, patients without a DEXA-based diagnosis of osteoporosis who have a family history of low-energy fracture or an elevated fracture risk according to the World Health Organization Fracture Risk Assessment Tool (FRAX) could be further evaluated with μMRI . If such individuals were found to have substantial micro-architectural deterioration, it seems logical that pharmacologic therapy could reduce subsequent fracture risk. However, before μMRI can be used as decision making tool in clinical practice, additional studies are first needed to delineate the population distribution of normal and abnormal μMRI parameters and to determine clinical thresholds at which these parameters are sufficiently abnormal to indicate the need for pharmacologic therapy to reduce fracture risk.

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Table 1

Characteristics of post-menopausal women with and without fracture.

Characteristic	Mean (Standard Deviation)		Difference Between Groups
	Fracture Group	Non-Fracture Group	
Age	60.9 years (+/- 6.4 years)	61.1 years (+/- 6.8 years)	P= 0.13
Height	65.0 cm (+/- 2.8 cm)	64.5 cm (+/- 3.0 cm)	P= 0.60
Weight	160.4 lbs (+/- 26.2 lbs)	147.7 lbs (+/- 23.2 lbs)	P= 0.68
Body Mass Index	27.0 kg/m ² (+/- 5.6 kg/m ²)	25.1 kg/m ² (+/- 4.2 kg/m ²)	P= 0.26
Lumbar Spine BMD	1.122 g/cm ² (+/- 0.098 g/cm ²)	1.169 g/cm ² (+/- 0.128 g/cm ²)	P= 0.21
Proximal Femur BMD	0.827 g/cm ² (+/- 0.067 g/cm ²)	0.865 g/cm ² (+/- 0.095 g/cm ²)	P= 0.19
One-Third Radius BMD	0.831 g/cm ² (+/- 0.086 g/cm ²)	0.810 g/cm ² (+/- 0.086 g/cm ²)	P= 0.17
Ultra-Distal Radius BMD	0.376 g/cm ² (+/- 0.059 g/cm ²)	0.377 g/cm ² (+/- 0.055 g/cm ²)	P= 0.90
Calcium	9.5 mg/dL (+/- 0.4 mg/dL)	9.4 mg/dL (+/- 0.4 mg/dL)	P= 0.15
Phosphate	3.8 mg/dL (+/- 0.6 mg/dL)	3.7 mg/dL (+/- 0.4 mg/dL)	P= 0.96
Creatinine	0.8 mg/dL (+/- 0.1 mg/dL)	0.8 mg/dL (+/- 0.1 mg/dL)	P= 0.99
Albumen	4.3 mg/dL (+/- 0.2 mg/dL)	4.4 mg/dL (+/- 0.2 mg/dL)	P= 0.63
Alkaline Phosphatase	74.3 mg/dL (+/- 16.0 mg/dL)	79.3 mg/dL (+/- 54.4 mg/dL)	P= 0.74
Alanine Aminotransferase	26.0 mg/dL (+/- 43.5 mg/dL)	32.1 mg/dL (+/- 19.7 mg/dL)	P= 0.99

Table 2

μMRI parameters in post-menopausal women with and without fracture.

μMRI Parameter	Mean (Standard Deviation)		Difference Between Groups
	Fracture Group	Non-Fracture Group	
Trabecular Bone Volume Fraction	9.3% (+/- 1.1%)	10.2% (+/- 0.9%)	P< 0.001
Trabecular Thickness	85.5 μm (+/- 8.0 μm)	85.7 μm (+/- 6.3 μm)	P= 0.80
Surface-to-Curve Ratio	5.1 (+/- 1.0)	5.9 (+/- 1.0)	P= 0.04
Erosion Index	1.4 (+/- 0.2)	1.2 (+/- 0.2)	P= 0.03