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In Vivo Measurement Reproducibility of Femoral Neck Microarchitectural Parameters Derived from 3-T Magnetic Resonance Images

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Abstract

Purpose—To evaluate the within-day and between-day measurement reproducibility of *in vivo* 3-D MRI assessment of trabecular bone microarchitecture of the proximal femur.

Materials and Methods—This HIPPA compliant, IRB approved study was conducted on eleven healthy subjects (mean age = 57.4 ± 14.1 years) with written informed consent. All subjects underwent a 3T MRI hip scan *in vivo* ($0.234 \text{ mm} \times 0.234 \text{ mm} \times 1.5 \text{ mm}$) at three time points: baseline, second scan same day (intra-scan), and third scan one week later (inter-scan). We applied digital topological analysis and volumetric topological analysis to compute the following microarchitectural parameters within the femoral neck: total bone volume, bone volume fraction, markers of trabecular number (skeleton density), connectivity (junctions), plate-like structure (surfaces), plate width, and trabecular thickness. Reproducibility was assessed using root-mean-square coefficient of variation (RMS-CV) and intraclass correlation coefficient (ICC).

Results—The within-day RMS-CVs ranged from 2.3% to 7.8%, and the between-day RMS-CVs ranged from 4.0% to 7.3% across all parameters. The within-day ICCs ranged from 0.931 to 0.989, and the between-day ICCs ranged from 0.934 to 0.971 across all parameters.

Conclusion—These results demonstrate high reproducibility for trabecular bone microarchitecture measures derived from 3-T MR images of the proximal femur. The measurement reproducibility is within a range suitable for clinical cross-sectional and longitudinal studies in osteoporosis.

Keywords

hip; osteoporosis; 3-T MRI; microarchitecture; digital topological analysis; volumetric topological analysis

INTRODUCTION

Fracture is the hallmark of osteoporosis, the most common bone disorder of individuals greater than 50 years old in Western society (1). Dual X-ray absorptiometry (DXA) estimation of areal bone mineral density (BMD) is the current standard-of-care test used to diagnose osteoporosis and assess fracture risk. However, the majority of patients who suffer osteoporotic fractures have non-osteoporotic BMD values (2). Bone microarchitecture -- the three-dimensional (3-D) arrangement of trabecular bone (TB) at the microstructural level -- is also a critical determinant of bone strength (1,3–5), and *in vivo* assessment of bone microarchitecture could play an important role in clinicians' ability to diagnose and treat osteoporosis (6,7). Indeed, deterioration of bone microarchitecture is included in the World Health Organization (WHO) disease definition of osteoporosis (8). The hip or proximal femur is the most devastating fracture site, with high morbidity and mortality in the first year after fracture (9). Computed tomography (CT) can assess the 3-D macrostructural properties of the proximal femur, and this may have value, beyond the 2-D information provided by DXA, for the diagnosis and monitoring of osteoporosis (10). However, because of limited spatial resolution and ionizing radiation dose restrictions, CT cannot depict individual trabeculae within the proximal femur; therefore, CT cannot evaluate the role of bone microarchitecture in hip fracture.

With the evolution of high-resolution magnetic resonance imaging (MRI) methods over the last fifteen years, noninvasive, quantitative assessment of bone microarchitecture *in vivo* has become feasible (11,12). The majority of these studies have been performed in the peripheral skeleton, such as the distal radius or the distal tibia. Recently, *in vivo* MR imaging of individual trabeculae within the proximal femur has become possible (13,14) secondary to the emergence of multichannel receive coils for improved MR signal detection in the hip (14) and the development of SNR efficient pulse sequences for improved data acquisition (15). In one clinical study, Chang et al. demonstrated that finite element analysis applied to MR images of proximal femur microarchitecture could detect lower bone strength in subjects with fragility fractures compared with controls who did not differ by BMD (16).

A new clinical test must not only be able to detect disease, but also have high measurement reproducibility. With this in mind, the goal of this study was to evaluate the within-day and

between-day *in vivo* measurement reproducibility for 3-D MRI assessment of trabecular bone microarchitecture within the proximal femur.

MATERIAL AND METHODS

Human Subjects

The local institutional review board approved this HIPPA compliant study, and we obtained written informed consent from all subjects. Eleven subjects (9 female, 2 male, mean age = 57.4 ± 14.1 years, range = 31 to 72 years) without history of fracture, osteoarthritis, Paget's disease, or bone metastasis participated in this study. Subjects were recruited from the Osteoporosis Center within the institution. The mean femoral neck BMD T-score for subjects was -2.3 ± 0.8 (range = -1.0 to -3.3) and time interval between MRI and BMD measurements was less than 60 days,

MRI Scanning

We scanned the non-dominant hip of all subjects on a 128-channel 3T MRI scanner (Siemens Skyra, Erlangen, Germany) three times: twice on one day (intra-session) and once one week later (inter-session). The subjects were repositioned between scans performed on the same day. We used a 26-element coil setup (Siemens, Erlangen, Germany, a flexible 18-element array coil anteriorly and 8 elements from a spine coil posteriorly) and a 3-D fast low angle shot (FLASH) sequence (TR/TE = 37ms/4.92ms, matrix = 512×512 , field of view = 12 cm, slice thickness = 1.5 mm, 60 coronal images, generalized auto calibrating partially parallel acquisition (GRAPPA) at an acceleration factor of two and scan time = 15 min 18 s) to acquire images.

Image Processing: Generation of Bone Volume Fraction Map and Computation of Microarchitectural Parameters Using Digital and Volumetric Topological Analysis

All subject data was randomized and de-identified prior to image processing, which was performed with in-house developed software. First, we generated bone volume fraction (BVF) maps by scaling voxel signal intensities from 0 to 100 (0 = pure marrow, 100 = pure bone) (16,17). The BVF corresponds to the fractional occupancy of bone within a voxel. A musculoskeletal radiologist (G.C., 4 years of experience) selected a $10 \text{ mm} \times 10 \text{ mm} \times 10 \text{ mm}$ volume of interest (VOI) within the femoral neck. The VOI was manually selected by first choosing the central coronal slice of the proximal femur images, and then choosing a point at the center of the femoral neck, which would serve as the center of the VOI. The VOI size was chosen in order to obtain sufficient coverage of the femoral neck while still being able to include subjects who had smaller proximal femurs.

Then, we applied digital topological analysis (DTA) and volumetric topological analysis (VTA) to compute several parameters of bone microarchitecture including: total bone volume (TBV), bone volume fraction (BVF), markers of trabecular number (skeleton density or Sk. D), connectivity (junctions or Junc), plate-like structure (surfaces or Surf), plate width (SWVTA), and trabecular thickness (Tb. Th). DTA (18,19) and VTA (20) are 3-D methods that determine the topological class of each individual location in a digitized 3-D trabecular bone volume of interest. Of note, VTA can provide a classification based on a

continuum between perfect plates and rods (20). In brief, these algorithms function by performing surface skeletonization of the digital structure, inspection of each bone voxel's neighboring voxels (i.e., the 26 other voxels within the voxel's $3 \times 3 \times 3$ kernel) along with subsequent topological classification, and finally, manifold distance transform and scale computation followed by volumetric feature propagation (VTA only) (18–20).

Statistical analysis

Statistical analysis was performed in SPSS (IBM, Somers, NY). The root-mean-square coefficient of variation (RMS-CV) across the eleven subjects was calculated (expressed as percentages) for each microarchitectural parameter for within-day scans (intra-scan), between-day scans (inter-scan), and across all scans (aggregate). RMS-CV indicates the average error of trabecular bone parameter measurements. One-way analysis of variance (ANOVA) was used to compute intraclass correlation coefficients (ICC) for within-day scans, between-day scans, and across all scans. The 95% confidence intervals for ICC were also reported. ICC is used to assess the reliability of the trabecular bone parameter measurement. Aggregate results were determined as estimators of the average overall variability for each parameter.

RESULTS

Bone volume fraction maps from the three scans of one subject are shown in Figure 1. Individual trabeculae are seen on the images, and there is similarity in the microarchitectural pattern within the femoral neck in the scans and bone volume fraction maps. Figure 2 provides scan-rescan (within-day and between-day) plots showing the correlations of baseline versus follow-up values for each microarchitectural parameter for each of the 11 subjects. For all parameters, scan-rescan correlations are moderately high, ($R^2 > 0.74$) thus illustrating the feasibility of serial reproducibility.

Table 1 provides the root-mean-square coefficients of variation for microarchitectural parameters measured within the femoral neck. The within-day RMS-CV values per parameter ranged from 2.3% (for Tb. Th) to 7.8% (for Junc). The between-day RMS-CV values per parameter ranged between 4.0% (for Sk. D) and 7.3% (for SWVTA). The overall variability of measurements across all three scans was slightly lower. The aggregate RMS-CV values per parameter, ranged from 3.6% (for Sk.D) to 6.8% (for Junc).

Table 2 provides the ICCs values for microarchitectural parameters measured within the femoral neck. The within-day ICC values per parameter ranged from 0.931 (for Sk. D) to 0.989 (for Tb. Th). The between-day ICC values per parameter ranged from 0.934 (for Sk. D) to 0.971 (for Surf). The aggregate ICC values per parameter ranged from 0.951 (for Junc) to 0.976 (for Tb. Th).

DISCUSSION

In this study, we report the *in vivo* measurement reproducibility for quantitative assessment of trabecular bone microarchitecture in the proximal femur using 3-D MRI at 3 Tesla. The

measurement reproducibility is within a range suitable for *in vivo* clinical studies of disease detection or disease progression/treatment response.

Previous work has shown the value of performing high-resolution MRI at distal skeletal sites for monitoring response to treatment with bone-strengthening drugs (21–24) or monitoring disease progression; for example, after renal transplantation (17). Other studies have also shown that microarchitectural assessment at distal skeletal sites has added value beyond BMD for discriminating subjects without and with fragility fractures (25,26). Therefore, given the high measurement reproducibility for MRI assessment of proximal femur microarchitecture reported in this study, the next step in the field would be to determine whether such assessment has value as a tool for fracture risk assessment or the monitoring of longitudinal changes in the hip during the course of treatment with bone-strengthening drugs.

The measurement reproducibility for assessment of proximal femur microarchitecture in this study is similar to that reported in prior high-resolution MRI studies performed at the distal radius and distal tibia. Our precision error for within-day and between-day scans was 7.8%, and the ICC values were > 0.9 across all conditions and parameters investigated. As a comparison, Gomberg et al. investigated the reproducibility of MRI-derived parameters of bone microarchitecture in the distal radius and distal tibia and reported an overall precision error of < 10% and an average ICC of 0.96 (27). In a more recent study by Wald et al., the reproducibility for measurement of microarchitectural parameters at the distal tibia was within a similar range (CV < 8.1%, ICC range: 0.75–0.99) (28).

The precision error ranges for measurements obtained on the same day and one week apart were similar. This is not surprising given that no changes in the bone microarchitecture would be expected during such a short time interval. Thus, any measurement variation that exists is likely due to variation related to the MRI system and data acquisition (e.g., image noise, motion artifact, patient positioning) or related to the image processing (e.g., selection of the volumes of interest).

We note that at the voxel size in this study ($0.082 \text{ mm}^3 = 0.234 \text{ mm} \times 0.234 \text{ mm} \times 1.5 \text{ mm}$) we cannot assess trabeculae that are smaller than the in-plane dimension of 0.234 mm. Because the proximal femur is a deep anatomic structure (6–10 cm distant from the radiofrequency coil placed on the patient to receive the MR signal), it will be difficult to achieve the same SNR and spatial resolution as for high-resolution MRI performed in the distal radius (as small as $0.137 \text{ mm} \times 0.137 \text{ mm} \times 0.4 \text{ mm}$), which is relatively superficial (0–2 cm from the radiofrequency coil). Since SNR decreases dramatically as the distance between the anatomy of interest and the receive coil increases, the close proximity of the distal radius to the coil allows much higher SNR and spatial resolution compared to imaging of the hip. Nevertheless, with the recent arrival of highly SNR efficient pulse sequences for proximal femur microstructure imaging (15) and given that the image analysis methods used in this study can actually perform reliably with an SNR as low as ~10 (12), analysis of proximal femur microarchitecture at smaller voxel sizes will be achievable in the future. Finally, we note that besides high-resolution MRI, there is no other way to obtain microarchitectural information noninvasively in the proximal femur *in vivo*. CT scans of the

hip have much larger voxels ($0.75 \times 0.75 \times 2.5 \text{ mm}^3$ or $1 \times 1 \times 1 \text{ mm}^3$) that cannot resolve trabeculae. It is also advantageous that MRI does not use ionizing radiation.

This study has limitations. First, the 26-element receive coil setup used to image the hip is not yet widely available. However, it is commercially sold, and we believe that such coils will only become more commonplace in the future. Second, the scan time is relatively long (15 minutes) compared to, for example, a CT scan (10–20 seconds). Nevertheless, we did not notice any motion artifact on images. This is probably because the hip is not mobile with the patient lying supine. In addition, the coil was secured to the patient and scan table by Velcro straps, helping to reduce motion artifact. However, immobilization of the hip may not be sufficient to correct for motion especially in long acquisition time scans where the risk for small involuntary displacements increases. In the future, to minimize motion artifacts, retrospective motion correction techniques (29) or SNR efficient pulse sequences with shorter scan times, such as fast large angle spin-echo (FLASE) or steady state free precession sequences (SSFP) (15) could be implemented. Third, we did not quantify the variation in measurements due to image postprocessing (as opposed to variation in imaging). To minimize variation in image post-processing in this initial study, a musculoskeletal radiologist (G.C) oversaw the image analysis and assigned the VOIs across all data sets. We believe that this VOI selection can be taught to a technologist; however, it will require training and the inter-user variation in VOI selection should be quantified. Fourth, larger patient studies performed at multiple sites and using scanners even from different vendors are needed to determine whether proximal femur microarchitectural assessment could be incorporated into patient care and used as a clinical tool, in addition to DXA, to improve the assessment of fracture risk and monitoring of disease progression/treatment response. Finally, microstructural MRI methods do not provide information about the material properties of bone, unlike CT or DXA. However, MRI methods to assess bone material properties do exist. For example, phosphorus MRI has potential as a method to assess bone mineral content in vivo, and ultra-short echo time (UTE) MRI methods can assess water bound to collagen, which is an important component of bone matrix.

In conclusion, this study reports high measurement reproducibility for quantitative assessment of bone microarchitecture in the proximal femur using 3-D MRI based methods. The measurement reproducibility is suitable for clinical cross-sectional or longitudinal studies and has the potential for widespread implementation, as it can be performed on a clinical 3-T MRI scanner using a commercially available radiofrequency coil and a widely available product sequence for data acquisition.

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Figure 1.

Representative scan-rescan bone-volume fraction map images derived from 3-T MR images ($0.234 \text{ mm} \times 0.234 \text{ mm} \times 1.5 \text{ mm}$) of the proximal femur from one subject. The red squares indicate the selected volume of interest ($10 \times 10 \times 10 \text{ mm}^3$) at the femoral neck.

Figure 2.

Scan-rescan plots of microarchitectural parameters derived from the trabecular bone volume at the femoral neck (n = 11, each parameter): *polygons* within-day scans (scan 1 – scan 2); *squares* between-day scans (scan 1 – scan 3).

Table 1

Reproducibility (RMS-CV, %) of morphological and topological trabecular parameters at the femoral neck.

Microarchitectural Parameter	Intra-scans	Inter-scans	Aggregate (i.e., intra- and inter-scans)
<i>Trabecular morphology</i>			
TBV	3.9	6.4	5.6
BVF	3.5	5.4	4.7
Tb. Th	2.3	6.5	5.0
<i>Trabecular topology</i>			
Sk. D	4.2	4.0	3.6
Surf	5.1	4.2	4.3
Junc	7.8	7.1	6.8
SWVTA	4.5	7.3	6.3

Values of the root-mean-square coefficient of variation in percentage (RMS-CV) are shown for intra-scans (same day scans with re-positioning in between), inter-scans (scans 7 days apart), and aggregate scans.

(*TBV* total bone volume, *BVF* bone volume fraction, *Tb. Th* trabecular thickness, *Sk. D* skeleton density, *Surf* surfaces, *Junc* junctions, *SWVTA* plate width).

Minimum and maximum RMS-CV values in each column highlighted in bold.

Table 2

ICCs (95% confidence intervals) for morphological and topological trabecular parameters at the femoral neck.

Microarchitectural Parameter	Intra-scans	Inter-scans	Aggregate (i.e., intra- and inter-scans)
<i>Trabecular morphology</i>			
TBV	0.972 (0.904–0.992)	0.970 (0.898–0.991)	0.969 (0.918–0.990)
BVF	0.969 (0.892–0.991)	0.963 (0.872–0.989)	0.973 (0.928–0.991)
Tb. Th	0.989 (0.963–0.997)	0.950 (0.834–0.986)	0.976 (0.938–0.993)
<i>Trabecular topology</i>			
Sk. D	0.931 (0.759–0.980)	0.934 (0.771–0.981)	0.952 (0.872–0.985)
Surf	0.941 (0.796–0.983)	0.971 (0.900–0.992)	0.955 (0.872–0.986)
Junc	0.939 (0.789–0.983)	0.951 (0.829–0.986)	0.951 (0.863–0.985)
SWVTA	0.970 (0.894–0.991)	0.963 (0.877–0.989)	0.972 (0.927–0.991)

Values of the intraclass-correlation-coefficient (ICC), with numbers in parenthesis representing 95% confidence intervals, are shown for intra-scans (same day scans with re-positioning in between), inter-scans (scans 7 days apart), and aggregate scans.

(*TBV* total bone volume, *BVF* bone volume fraction, *Tb. Th* trabecular thickness, *Sk. D* skeleton density, *Surf* surfaces, *Junc* junctions, *SWVTA* plate width).

Minimum and maximum ICCs values in each column highlighted in bold.