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Precision of volumetric assessment of proximal femur microarchitecture from high-resolution 3T MRI

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Abstract

Purpose—To evaluate the precision of measures of bone volume and bone volume fraction derived from high-resolution 3T MRI of proximal femur bone microarchitecture using non-uniformity correction.

Methods—This HIPAA compliant, institutional review board approved study was conducted on six volunteers (mean age 56 ± 13 years), and written informed consent was obtained. All volunteers underwent a 3T FLASH MRI hip scan at three time points: baseline, second scan same day (intrascans), and third scan one week later (inter-scans). Segmentation of femur images and values for total proximal femur volume (T), bone volume (B), and bone volume fraction (BVF) were calculated using in-house developed software, FireVoxel. Two types of non-uniformity corrections were applied to images (N3 and BiCal). Precision values were calculated using

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Conflict of interest The authors of this article, Alexandra Hotca, Shreyas Ravichandra, Artem Mikheev, Henry Rusinek, and Gregory Chang, declare that they have no conflict of interest.

Ethics standard All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1975, as revised in 2008.

absolute percent error (APE). Statistical analysis was carried out using one-sample one-sided t test to observe the consistency of the precision and paired t test to compare between the various methods and scans.

Results—No significant differences in bone volume measurements were observed for intra- and inter-scans. When using non-uniformity correction and assessing all subjects uniformly at the level of the lesser trochanter, precision values overall improved, especially significantly ($p < 0.05$) when measuring bone volume, B . B values using the combination of N3 or BiCal with CLT had a significant consistent APE values of less than 2.5 %, while BVF values were all consistently and significantly lower than 2.5 % APE.

Conclusion—Our results demonstrate the precision of high-resolution 3D MRI measures were comparable to that of dual-energy X-ray absorptiometry. Additional corrections to the analysis technique by cropping at the lesser trochanter or using non-uniformity corrections helped to improve precision. The high precision values from these MRI scans provide evidence for MRI of the proximal femur as a promising tool for osteoporosis diagnosis and treatment.

Keywords

3T MRI; Bone microarchitecture; Osteoporosis; Bone volume; Non-uniformity correction; MR reproducibility

Introduction

Osteoporosis is characterized by low bone mass and microarchitectural deterioration of bone tissue, leading to weak bone and a higher risk of fracture [1,2]. Osteoporosis affects 10 million Americans, resulting in approximately 2 million fractures per year, a number far greater than heart attacks, strokes, and breast cancer combined [3]. In particular, proximal femur fractures have the most devastating consequences; the chances of dying are 20–24 % in the first year after hip fracture [4].

The current standard of care test used to diagnose osteoporosis is dual-energy X-ray absorptiometry (DXA) estimation of areal bone mineral density in the proximal femur and lumbar spine [5]. DXA provides a marker of fracture risk [6], and it has high reproducibility; for a single femur, measurement precision may approach 2–3 % for well-calibrated devices [5].

However, there are limitations associated with DXA. Population studies have shown that DXA poorly discriminates between individuals with and without fragility fractures [7]. Also, since DXA is a 2-dimensional (2D) planar projection technique, it cannot account for overlying soft tissue, calcifications, or the 3D properties of bone, which could lead to measurement inaccuracy [8]. Furthermore, because it is a low-resolution technique, DXA is unable to assess bone microarchitecture, which is included in the disease definition of osteoporosis. These limitations provide motivation for more sensitive risk assessment tools that may be better equipped to more accurately assess bone quality, especially at the microstructural level.

With the advent of high-resolution 3 Tesla (3T) MRI and the development of high-resolution imaging sequences, in vivo bone microstructural analysis has become possible. Several previous studies have validated the utility of high-field magnetic resonance imaging (MRI) as a tool to assess bone microarchitecture [9-12]. Until now, most of current investigations are limited to imaging of distal extremities, and only a few MRI studies have been conducted of proximal femur microarchitecture [13-16] due to limitations in signal-to-noise ratio (SNR) that arise when imaging deeper anatomy [17].

Taking advantage of the higher SNR provided by multichannel receiver coils, we have recently showed the ability to visualize the trabecular bone structure of the proximal femur (Fig. 1) [14]. However, as of yet, the precision of proximal femur-related measures from high-resolution MRI has not been investigated.

The goal of this study was to estimate the precision values of two measures reflective of bone mass: (1) total proximal femur bone volume (B) and (2) bone volume fraction (BVF), which is defined as B/T , where T is the total proximal femur volume (i.e., bone plus bone marrow filled space), using high-resolution MRI. Bone volume was estimated by the analysis of the signal intensity of images within the manually segmented proximal femur. The precision was evaluated from serial 3T MRI scans of six subjects scanned three times within one week. During such a short period of time, no true changes in B and BVF are expected. This precision and interscan agreement was measured through statistical analysis. We have investigated the effect of MR signal non-uniformity on the precision by applying retrospective bias field correction techniques. We have also attempted to improve the precision by limiting the extent of the proximal femur to an anatomically defined landmark (lesser trochanter). Our key objective was to determine whether the precision of B and BVF measures with high-resolution MRI is competitive with the 2–3 % precision range of 2D DXA.

Material and methods

Human subjects

The local institutional review board approved this HIPAA compliant study, and written informed consent was obtained from all subjects. Six volunteers (5 females and 1 male, mean age $=56 \pm 13$ years) participated in this study. All volunteers underwent serial 3T MRI exams. Three MRI scans of each subject were performed over a time interval of one week, twice on one day (intra-scans), and the third several days later (inter-scans). The patients were repositioned and relocalized between scans.

MRI protocol

All MRI scanning was performed on a 128-channel 3T MRI scanner (Siemens Skyra, Erlangen, Germany). We used a 26-element coil setup composed of a flexible 18-element array coil anteriorly and 8 elements from a spine coil posteriorly (Siemens, Erlangen, Germany). We scanned the dominant hip of subjects using a 3D fast low angle shot sequence (TR/TE = 37 ms/4.92 ms, matrix = 512×512 , field of view = 12 cm, slice

thickness = 1.5 mm, 60 coronal images) using generalized auto calibrating partially parallel acquisition (GRAPPA) at acceleration factor of two (scan time = 15 min 18 s).

Segmentation of the proximal femur

The proximal femur was segmented on original 3D MR images by an experienced operator and a musculoskeletal radiologist in a consensus session (Fig. 2). The femur was outlined using an adjustable paintbrush/eraser tool driven by computer mouse. The operator could zoom on the image subregions and interactively switch between painting and erasing modes. Filling and morphing tools were also available to speed up the segmentation process. The femur mask involved 30–40 (average 33 ± 3.07) coronal slices. The mask included cortical bone but not the cartilage.

Correction of MR signal non-uniformity

MR signal intensity is affected by signal inhomogeneity, or shading artifacts, manifested as smooth spatially varying signal intensity distortions. Non-uniformity is attributed to inhomogeneous RF fields, inhomogeneous reception sensitivity, and electromagnetic interaction with the object being scanned. Correction of this effect is often required for successful tissue segmentation.

N3 method—The fully automatic algorithm [17] (commonly called N3) assumes that (a) non-uniformity blurring of the MR signal intensity (SI) can be modeled as a smooth multiplicative field and that (b) tissue intensities are independent identically distributed random variables $V(x, y, z)$. The software uses the histogram of unprocessed MR data to estimate V . It then performs an iterative estimation of the multiplicative bias field to “sharpen” the histogram. The coefficient of variation in the ratio between subsequent field estimates at a predetermined subraster of the field of view is used as the measure to terminate the iterations. The bias field estimate is smoothed within each iteration according to user-defined parameters. N3 was applied with maximum number of iterations = 75, subsampling = 2, field smoothness = 10 mm, assumed noise level = 1 %. Figure 3b shows one slice of the femur after applying N3 algorithm to the acquired FLASH image in Fig. 3a.

BiCal method—We have recently developed a new method, BiCal (Bias Calculation), for non-uniformity correction that involves 3D edge detection and expansion of the logarithm of the bias field into Legendre polynomials. The process begins by detecting 3D edges. Voxels identified as edges and adjacent voxels are marked. Also marked are background voxels, identified by regions of a distance of greater than 5 mm away from the region of interest (proximal femur mask). Unmarked voxels constitute a single binary mask H . We next search for a slowly varying analytic scalar field $L(x, y, z) = \ln(B)$ represented as the linear combination of 3D Legendre polynomials of degree N . The value of N , set to 5 in this study, controls the maximal spatial frequency of the resulting bias field. Next, the logarithm volume $P(x, y, z) = \ln(SI)$ is calculated. We have $dP/dr = dL/dr$ within H . We optimize polynomial coefficients of $L(x, y, z)$ over region H so that the analytical partial derivatives $\{d/dx, d/dy, d/dz\}$ provide the least squares fit of discrete partial derivatives of P . Discrete derivatives are preconditioned by a constrained Gaussian smoothing. Since the cost function is linear, the corresponding linear system is solved exactly using singular value

decomposition. Finally, the resulting field $B(x, y, z) = \exp(L)$ is normalized so that its average value over H is unity. Figure 3c illustrates the result of applying BiCal process to femur images.

Assessment of the proximal femur in the same relative anatomic location—In order to assess the proximal femurs of different subjects in the same relative anatomic location, we chose the inferior margin of the lesser trochanter as a landmark to crop or truncate the images (Fig. 4). We refer to this as the cropped lesser trochanter (CLT).

Segmentation of cortical and trabecular bone

The cortical and trabecular bone is characterized by low-intensity signal. The mean value M of the signal in the entire proximal femur is first computed. A threshold, defined as $0.9 M$, was then used to compute automatically the bone mask (Fig. 5b). The absolute bone volume B was defined by multiplying the number of bone voxels by the known voxel volume of 0.088 mm^3 , followed by unit conversion to cm^3 . Relative bone volume fraction, BVF, was then measured as B / T where T is the total femur mask volume shown in red in Fig. 5a. Measures B and BVF were computed for the original MR image, then recomputed under different scenarios: for uniformity corrected images, after N3 and BiCal processing, and after the combination of non-uniformity correction with CLT processing steps.

Software implementation

All image analyses were carried out using locally developed software *FireVoxel*, developed using Microsoft Visual Studio C++ compiler and Intel Vtune optimizer. The user interface is based on Microsoft Foundation Class Libraries. The code exploits multimedia extensions MMX, SIMD, SIMD2 and takes advantage of parallel multi-core processing.

Reproducibility measurements

Precision was calculated using the equations:

$$|B_{\text{baseline}} - B_{\text{follow-up}}| / [\text{mean}(B_{\text{baseline}}, B_{\text{follow-up}})] \quad (1)$$

$$|BVF_{\text{baseline}} - BVF_{\text{follow-up}}| / [\text{mean}(BVF_{\text{baseline}}, BVF_{\text{follow-up}})] \quad (2)$$

The values calculated from these equations were converted to percentage and labeled as absolute percent error (APE). Precision was assessed separately for original MRI, for uniformity corrected MRI, for CLT processing, and for combination of processing steps.

Statistical analysis

Means of the absolute percent error for each parameter were computed and compared for various conditions using Student's two-tailed paired t test at a level of significance of $p < 0.05$. One-sample t test was used to test the key hypothesis, namely that the precision of bone measures from MRI can be better than a predetermined precision level of 3 and 2.5 %. Two-sample paired t tests were used to compare the mean precision between two different post-processing methods. One of the study's main interests was to observe whether bone

volume precision measures could be improved with non-uniformity correction or non-uniformity correction with CLT, i.e., truncated femur images.

Results

Subjects data

From the initial MRI scans of the subject data, the average bone volume mass, defined as 90 % of the mean signal intensity for the baseline MRI for all 6 subjects, was $48.7 \pm 8.3 \text{ cm}^3$ (Table 1). Figure 1 shows an example patient MR image; Fig. 1b is a close-up image of the highlighted boxed region in (a). The high-resolution allows for the visibility of the individual trabeculae. ROIs were drawn manually on the proximal femur for multiple slices (Fig. 2); these ROIs were used for segmentation of the bone. Figure 3 shows a comparison of the different correction methods (N3 and BiCal processing) used after acquiring the MRI image. Each processing methods results in different non-uniformity corrections and masking of the signals as observed on Fig. 3 when using N3 and Fig. 3c when using BiCal. Figure 5 shows the process for measuring the bone volume as the red region highlights a bone mask that was used to calculate the total proximal femur volume (Fig. 5a). The mask is used to differentiate fat tissue volume from the bone volume through a signal intensity threshold. Figure 5b shows the different tissues using a binarized bone mask with the yellow representing the fat tissue volume and blue representing bone volume (cortical and trabecular).

Statistical comparisons of the measurements

Table 2 shows comparison of the bone volume measurement differences between intra- and inter-scans at the proximal femur. Mean absolute percent error (APE) values, between baseline and follow-up scans, were calculated using Eqs. (1) and (2) to measure precision. No significant differences were observed between the precision values for the two different scan times as indicated by the p values using a paired *t* test. In view of this finding, we combine intra-scan and inter-scan data in further analyses.

Table 3 and Fig. 6 present the distribution of APE in percentage (mean value and standard error of the mean SEM) for total proximal femur, segmented bone volume, and bone volume fraction within the proximal femur. APE is shown for original MRI and four post-processing methods, i.e., using N3 or BiCal non-uniformity correction alone or combined with CLT. Mean precision values for all measures and all scenarios were all better than 3%. Results were generally improved (lower APE and smaller SEM) when using a combination of BiCal or N3 with CLT compared to original measurements. The use of non-uniformity correction alone did not appear to improve APE.

In addition, based on the precision values calculated, most measurements have consistent precision values of less than 2.5% as indicated by the significant findings from one-sample *t* test in Table 4. For *B*, APE values were significantly under 2.5 % when using either non-uniformity correction plus CLT. Meanwhile, all BVF values were significantly under 2.5 % for all methods.

Discussion

The results of this first study of the reproducibility of proximal femur bone measurement using high-resolution 3T MRI show that high precision, similar to DXA, can be achieved when measuring B and BVF from MRI scans. Due to temperature changes, drifts in magnetic field gradient shims, and unwanted phase shifts in the RF transceiver chain, day-to-day variations in MR images can potentially be larger than within-day variations. However, no statistical differences were observed between the different time points (intra- vs inter-scans) allowing us to use all 12 scans for comparison (Table 2).

Our results show that using a combination of nonuniformity correction (N3 or BiCal) with spatial cropping of the proximal femur at a precise anatomic location (CLT) in general improved the precision for both B and BVF. The average precision error was low, and its variability as expressed by SEM was tight. In particular, BiCal with CLT showed average precision of 1.3 % for proximal femur bone volume and 1.0% for bone volume fraction. As seen in Table 3, greater improvements in precision were observed for calculating B compared to BVF when using the correction methods. This indicates that cropping the lesser trochanter seems necessary for B measurements; however, the overall improvements indicate that using CLT is useful.

Interestingly, the non-uniformity correction, N3, does not appear as helpful for precise measurement of B or BVF. This may be due to the central location of the femur in the reconstructed field of view and spatial distribution of non-uniformities in MRI scans. Non-uniformity is most pronounced for tissue located near radiofrequency coil, and it is less of a factor for deeper anatomic structures of the hip, which are more distant from the radiofrequency coil and where spatial changes in the SNR are not as pronounced as in superficial locations [14]. Also it is interesting to note that BVF calculations seem more precise in general compared to just bone volume, B , alone. This could be because BVF limits analysis to just the bone tissue alone, thereby avoiding errors from other tissues such as the fat.

The one-sample t test shows that many of the measurements, especially for BVF and its various correction methods, are significantly under 2.5 % APE. These results indicate that MRI can potentially obtain consistently low precision values that are comparable to DXA results of 2–3 % [5]. The combination of using both a non-uniformity correction and CLT also improved the measurement consistency, obtaining values below the 2.5 % error for bone volume measurements. This shows the utility of using such corrections and a closer examination of these methods in a larger study is therefore warranted.

This study has limitations. First, it was based on only six healthy subjects, each examined at three time points. The results provide motivation for larger reproducibility/precision studies that also includes patients with bone pathologies. Second, in the future, scanning patients with and without osteoporotic fractures as well as a longitudinal study will allow us to determine the sensitivity/specificity of the method to detect disease. In addition, due to low contrast between femur and the background and relatively low SNR, standard automatic segmentation algorithms failed on this acquisition protocol. Finally, we note that we did not

validate the measures with the gold standard of microcomputed tomography, though previous studies have shown a strong correlation between measures of bone microarchitecture obtained between high-resolution MRI and microcomputed tomography [18].

Overall, this study describes the high reproducibility of MRI for quantifying the volume of proximal femur bone microarchitecture in vivo. The high precision of the MRI scans may support the use of MRI as a potential useful adjunct tool to diagnose osteoporosis, as well as to monitor disease progression and response to therapy in longitudinal studies.

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Fig. 1.
a Representative high-resolution 3-T MRI image of proximal femur using FLASH MRI sequence **b** and image centered around the femoral neck region showing visible individual trabeculae

Fig. 2.

Example of a multiple slice view of a 3D MRI image in one subject after drawing manually regions of interest (ROI) shown in *red*

Fig. 3.

a Acquired 3-T MRI image of the proximal femur corrected for non-uniformity **b** with N3 processing, and **c** or with BiCal processing

Fig. 4.
Local identification (*white arrow*) of the inferior aspect of the lesser trochanter on a representative 3-D MRI image of proximal femur

Fig. 5.

a Bone mask in red representing total proximal femur volume and **b** signal intensity threshold shown as a binarized bone mask. *Yellow* represents fat tissue volume and *blue* represents bone volume (cortical and trabecular)

Fig. 6.
Comparison of mean absolute percent error (APE in %) for each volumetric measure (cm^3) between original measurements and **a** applied N3 or **b** applied BiCal symbols: * P value < 0.05 ** P value = 0.10

Table 1

Volumetric measures (cm^3) and bone volume fraction from the original MRI (baseline, follow-up same day, and follow-up several days later)

MRI timeline	Total proximal femur volume (cm^3)$\pm$ SD	Bone volume (cm^3)$\pm$ SD	Bone volume fraction $\pm$ SD
Baseline	119.07 $\pm$ 21.29	48.70 $\pm$ 8.31	0.41 $\pm$ 0.02
Follow-up same day	117.92 $\pm$ 22.40	47.82 $\pm$ 8.66	0.41 $\pm$ 0.03
Follow-up several days later	118.34 $\pm$ 21.66	48.29 $\pm$ 8.72	0.41 $\pm$ 0.03

Mean volumetric measures $\pm$ standard deviation (SD), and mean bone volume fraction $\pm$ SD values are given

Bone volume fraction was calculated dividing bone volume over the total proximal femur volume

Table 2

Comparison of volume measurements and bone volume fraction between intra- and inter- scans at the proximal femur

	Total proximal femur volume		Bone volume		Bone volume fraction	
	Intra-scans	Inter-scans	Intra-scans	Inter-scans	Intra-scans	Inter-scans
Mean APE (%)	1.60 ± 0.34	1.92 ± 1.00	2.61 ± 0.79	2.63 ± 1.60	0.49 ± 0.17	1.30 ± 0.46
<i>P</i> value	<i>P</i> = 0.8		<i>P</i> = 1.0		<i>P</i> = 0.1	

Mean absolute percent error ± standard error mean (APE ± SEM) values given in percentage; *Intra-* (scans taken within the same day); *Inter-*(scans taken several days apart)

Table 3

Absolute percent error of volume measurements between two consecutive scans (baseline—follow-up) for each applied method

Measure	Methods	APE (%) $\pm$ SEM
Total proximal femur volume	T	1.76 ± 0.51
	T + CLT	0.94 ± 0.22
Bone volume	B	2.62 ± 0.85
	B + N3	2.65 ± 0.58
	B + N3 + CLT	1.73 ± 0.33
	B + BiCal	2.64 ± 0.70
	B + BiCal + CLT	1.31 ± 0.31
Bone volume fraction	BVF	0.90 ± 0.26
	BVF + N3	0.96 ± 0.25
	BVF + N3 + CLT	0.94 ± 0.36
	BVF + BiCal	1.64 ± 0.35
	BVF + BiCal + CLT	1.00 ± 0.21

Mean absolute percent error (APE $\pm$ SEM) values in percent relative to baseline MRI for each corresponding method (CLT, N3, and BiCal) are given

Abbreviations: *T*—total proximal femur volume; *B*—bone volume; *BVF*—bone volume fraction (*B/T*); *CLT*—crop at lesser trochanter; *N3* and *BiCal*—different methods for non-uniformity correction

Table 4

Results of one-sample *t* test to assess if precision measured with APE in % was <2.5% and <3.0% (to compare with DXA [5])

Method	<i>P</i> value with 2.5%	<i>P</i> value with 3%
B	0.890	0.665
B + N3	0.797	0.114
B + N3 + CLT	0.040	0.003
B + BiCal	0.844	0.618
B + BiCal + CLT	0.002	0.000
BVF	0.000	0.000
BVF + N3	0.000	0.000
BVF + N3 + CLT	0.001	0.000
BVF + BiCal	0.034	0.003
BVF + BiCal + CLT	0.000	0.000

Bold values indicate a statistically significant APE with a $P < 0.05$