Title: Assessment of proximal femur microarchitecture using ultra-high field MRI

Short title: Ultra-high field MRI of femur microarchitecture

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Abstract

Purpose: The purpose of this study was to investigate bone microarchitecture of cadaveric proximal femurs using ultra-high field (UHF) 7-Tesla magnetic resonance imaging (MRI) and to compare the corresponding metrics with failure load assessed during mechanical compression test and areal bone mineral density (ABDM) measured using dual-energy X-ray absorptiometry.

Materials and methods: ABDM of ten proximal femurs from five cadavers (5 women; mean age= 86.2 ± 3.8 (SD) years; range : 82.5-90 years) were investigated using dual-energy X-ray absorptiometry and the bone volume fraction, trabecular thickness, trabecular spacing, fractal dimension, Euler characteristics, Connectivity density and degree of anisotropy of each femur was quantified using UHF MRI. The whole set of specimens underwent mechanical compression tests to failure. Associations were searched using correlation tests and multiple regression analysis.

Results: the inter-rater reliability for bone microarchitecture parameters measurement was good with an intra-class correlation coefficient ranging from 0.80 and 0.91. ABDM and the whole set of microarchitecture metrics but connectivity density significantly correlated with failure load. Microarchitecture metrics correlated to each other but did not correlate with ABDM. Multiple regression analysis disclosed that the combination of microarchitecture metrics and ABDM improved the association with failure load, for example an improvement from $R^2 = 0.418$ to adjusted $R^2 = 0.688$ when combining ABDM and Euler characteristics.

Conclusion: Femur bone microarchitecture metrics quantified using UHF MRI significantly correlated with biomechanical parameters. The multimodal assessment of ABDM and trabecular bone microarchitecture using UHF MRI improved the information about fracture risk of femoral bone and might be of interest for future investigations of patients with undetected osteoporosis.

Keywords: femur; osteoporosis; magnetic resonance imaging; cancellous Bone; 7 Tesla

INTRODUCTION

Fracture of the proximal femur is a major health burden in post-menopausal women and elderly persons. It represents the main source of osteoporosis-related mortality and morbidity [1]. Osteoporosis is an age-related progressive skeletal disease characterized by a reduced bone mass and microarchitectural alterations resulting in an increased bone fragility and susceptibility to fracture [2]. Bone strength is routinely evaluated from areal bone mineral density (ABDM) measurements using dual-energy X-ray absorptiometry (DXA) [3, 4]. Patients are commonly diagnosed as osteoporotic on the basis of the ABDM T-score [5, 6]. A score lower than 2.5 standard deviations (SDs) below the mean ABDM value quantified in a group of young control subjects (< 30-year-old) of the same gender and ethnicity is considered as outside the normal range [5, 6]. However, the diagnostic value of DXA-based ABDM has been recognized as limited for the prediction of fracture risk thereby indicating that ABDM would not allow bone microarchitecture assessment. Accordingly, low ABDM values would account for only 28% of hip fractures [7]. Similarly, a significant percentage of fractures has been reported in women with ABDM values above the accepted threshold [8-10]. While microarchitecture deterioration has actually been included in the definition of osteoporosis this aspect is not assessed using

ABDM measurements [11]. Interestingly, bone microarchitecture can be assessed using high-resolution quantitative computed tomography (QCT) [12] but the corresponding tool is poorly available and has never been used for large groups of subjects [13].

Considering its non-radiating nature and the progress regarding radiofrequency coil technology and field strength, magnetic resonance imaging (MRI) of proximal femur microarchitecture has become possible [7, 14, 15]. It has been recently reported that post-menopausal women with a higher fracture risk can be distinguished from those with lower fracture risk on the basis of measurements obtained from ultra-high field (UHF) MRI [15]. On that basis, it has been suggested that UHF MRI can provide information about bone quality that are different and likely complementary than those provided by DXA. Although the very first results are promising, comparative analysis between MRI and biomechanical metrics are still very scarce with only one study performed at 1.5-T [14].

The purpose of this study was to investigate bone microarchitecture of cadaveric proximal femurs using UHF MRI and to compare the corresponding metrics with failure load assessed during mechanical compression tests and ABDM measured using DXA.

MATERIALS AND METHODS

Femoral specimens

Ten cadaveric proximal femora of 5 human donors (5 women; mean age= 86.2 ± 3.8 (SD) years; range : 82.5-90 years) were obtained within 10 days after death, according to the institutional safety and ethics regulations. Donor consent for research purposes was obtained prior to death. No information was available regarding the cause of death or previous diseases. Donors with scars in the region of proximal femur were excluded. All specimens were carefully cleaned of soft tissue and the femoral diaphysis was cut 10 cm below the lesser trochanter to facilitate bone attachment for mechanical testing. Specimens were stored at −20°C and progressively thawed at room temperature 6 hours before testing. A single defrosting cycle was required.

CT measurements

Each femur was scanned using a Light Speed® VCT 64 unit (General-Electric Healthcare) in order to detect femoral lesion (tumor) or fracture, and gas bubbles due to tissue degradation with the following parameters: field of view 12 cm slice thickness, 0.625; interval, 0.625 mm; tube current, 365 mA; and tube potential, 120 KV.

DXA measurements

Specimens were positioned similarly to what is conventionally done for *in vivo* examination with a mild internal rotation. They were placed in a vessel filled with tap water up to 15 cm in height to simulate soft tissue [16]. DXA measurements were performed with a Prodigy® Scanner

(General-Electric Healthcare). ABDM was measured in three regions of interest (ROIs) for each specimen (*i.e.,* femoral neck, intertrochanteric and greater trochanter regions). The total proximal ABDM was computed.

MRI

Each specimen was scanned using a 7-T whole-body MRI scanner (Siemens Healthineers) and a 28-channel proton coil. Once the initial MRI localized images were obtained for the three orthogonal planes, an interactive localized B_0 shimming was performed using the second-order shimming procedure provided by the manufacturer. High-resolution gradient recalled-echo images of each femur were acquired in the coronal plane using the following parameters: field of view, 140 × 140 mm²; acquisition matrix size, 832 × 832; contiguous slice thickness, 0.5 mm; TR/TE, 20/6 msec; flip angle, 15°; number of repetitions, = 3; number of slices, = 58; in-plane voxel size, 0.17 x 0.17 mm. The corresponding acquisition time was 37 min 36 s.

Each image was initially corrected for any remaining signal inhomogeneities using the N4 algorithm [17]. Using an open-source digital measurement software (ImageJ, NIH,) [18], images were binarized and thresholded as previously described [19]. For each slice, a 10 x 10 x 10 mm volume of interest (VOI) positioned at mid-distance between the top and the bottom of the greater trochanter was selected (*i.e.*, 60 x60 pixels in 20 slices) (Fig. 1). Bone volume fraction, trabecular thickness (Tb.Th), trabecular spacing (Tb.Sp), fractal dimension (FD), Euler characteristics, connectivity density and the degree of anisotropy (DA) were computed within the VOI using BoneJ an ImageJ module dedicated to bone images analysis.

Bone volume fraction corresponds to $\frac{Bone\ volume}{Total\ volume}$. Bone volume fraction is commonly related to porosity and has been considered as a surrogate of volumetric bone density rather than a strict measure of bone microarchitecture [20].

Fractal dimension is a bone texture parameter with the fractal dimension of bone-marrow surface giving some information on the degree of complexity or disorder of the bone microarchitecture. Fractal analysis expresses the roughness of the texture and characterizes the self-similarity of its gray-level variations over different scales [21]. Texture parameters have been reported as indirect indices of the 3D microarchitecture [22].

The number of connected structures in a network can be determined from the Euler characteristic [23]. Trabecular bone can be considered as a network and its connectivity density can be calculated from the ratio between the connectivity estimate and the volume of the sample (~ number of trabeculae per unit volume) [18].

Anisotropy corresponds to the preferential spatial directional organization of a material. Trabecular bone is typically an anisotropic material with variable mechanical properties according to the direction of the applied strength, the maximum resistance being parallel to the main line of spans. The spans which first disappear in osteoporosis are the ones which undergo the least mechanical strengths [22]

Analyses were performed by two independent operators, a 7-year-experience skeletal radiologist (D.G.) and a engineer doctor specialized in MRI (J.C.S.).

Mechanical testing

Each specimen was loaded to failure in a universal testing machine (Instron 5566, Instron). Femur orientation within the loading apparatus was chosen so as to simulate a sideways fall on the greater trochanter [24, 25]. Specimens were fixed in resin (Epoxy Axon F23) at 15° internal rotation and the femoral shaft was oriented at 10° adduction within the apparatus. The load was applied to the greater trochanter through a pad, which simulated a soft tissue cover, and the femoral head was molded with resin to ensure force distribution over a greater surface area. The load was applied to the greater trochanter at a displacement rate of 10 mm/min. Failure load (in Newton) was defined as the first local maximum after which the load declined by more than 10%. Then, fractures were visually classified according to clinical criteria (femoral neck, intertrochanteric, subtrochanteric, or isolated greater trochanteric fractures) [26].

Statistical analysis

Each parameter was described using mean and standard deviation (SD), median and quartiles [Q1; Q3]. We firstly verified that the distribution of the parameters was not statistically different from the normal distribution using the Kolmogorov-Smirnov with exact *P*-value.

The inter-rater reliability of microarchitecture characterization was assessed with the intraclass correlation coefficient (ICC) for each microarchitecture variable. The average coefficient of variation between rater was presented as CV.

Then, we assessed the correlation between failure load and each of the parameters and between the parameters themselves using Pearson correlations coefficients (r) after having verified the linear relationship with scatter plots. The level of significance was set at $P < 0.05$.

To evaluate whether microarchitecture parameters combined to ABDM improved the accuracy of the model multivariate ridge regressions analyses (with femoral failure as the dependent factor) were performed. We used the coefficient of determination of the model (R^2) to compare quality of the model with ABDM alone (R^2) vs ABDM and different combinations of microarchitecture parameters (adjusted R^2 named adjR^2). The R^2 indicates the percentage of the variance in the dependent variable (the femoral failure) that the independent variables (microarchitecture parameters and ABDM) explain collectively. We first reported the R^2 of the univariate linear regression with ABDM as the only independent variables (R^2). Then, we reported the R^2 of the multivariate linear ridge regression with ABDM combined with one of the microarchitecture parameters adjusted (adjR^2). For each microarchitecture parameters, we measured the % of improvements of the R^2 using the following computation:

$$\frac{adjR^2 model\ with\ ABMD\ and\ one\ microarchitecure\ parameter - R^2 with\ ABMD\ only}{R^2 with\ ABMD\ only}.$$

The % of improvement measures to what extent the addition of each of microarchitecture parameters allows to better explain the variation of the femoral failure. The ridge regression was used to take account for co-linearity due to correlation between microarchitecture parameters.

Finally, a multivariate ridge regression analysis was performed with the whole set of microarchitecture parameters and ABDM as independent variables. We used a backward stepwise analysis (elimination one parameter after the other) to only include parameters significantly associated with femoral failure at the *P* value <0.05. Statistical analyses were performed using SPSS V20 and ridge regression was performed using the SAS® software.

RESULTS

The mean ABDM for the total hip in our cohort was 0.72 ± 0.1 (SD) g/cm^2 (range: 0.62 - 0.86 g/cm^2). During the compression test, a fracture could be detected for a mean failure load of 1238.5 ± 507.4(SD) N (range: 710.6 - 2113 N) (mean=1034 N, Q1= 809.6, Q3= 1776.3). We observed 1 femoral neck and 9 intertrochanteric fractures. No subtrochanteric or isolated greater trochanteric fracture was observed. Microarchitecture metrics are reported in Table 1 along with the corresponding descriptive statistics.

The ICCs for the microarchitecture measurements performed in the greater trochanter were 0.90 (CV = 6.2%) for bone volume fraction, 0.89 (CV=6.6%) for trabecular thickness, and 0.80 (CV = 5.6%) for trabecular spacing, 0.81 (CV = 10.1%) for the degree of anisotropy, 0.88 (CV=9.5%) for connectivity density, 0.91 (CV = 4.7%) for fractal dimension and 0.88 (CV = 6.2%) for Euler characteristics.

All of the microarchitecture metrics but connectivity density were significantly correlated with failure load and with each other (Table 1; Fig.2). Bone volume fraction had the highest correlation with failure load (r= 0.736; *P*=0.01) Most of the microarchitecture parameters strongly correlated with each other but only the degree of anisotropy correlated with trabecular thickness (Table 2). The connectivity parameters (*i.e.*, Euler characteristics and connectivity density) significantly correlated with each other (*P*=0.0001). Euler characteristics was significantly correlated with load failure (*P*=0.044) whereas connectivity density was not (*P*=0.063).

Ridge regression analysis demonstrated that correlation with fracture load prediction could be significantly increased from R^2=0.418 to adjR^2=0.69 when bone microarchitecture parameters metrics were combined with ABDM (Table 3). More specifically, Euler characteristics was the variable with the largest influence on the R^2 increase when combined to

ABDM: when ABDM was combined with Euler characteristics the adjR^2 yielded the value of 0.69 (improvement of 64.6%).When connectivity density was combined to ABDM, the adjR^2 yielded the value of 0.67 (60.3% of improvement); while fractal dimension was combined with ABDM, the adjR^2 yielded the value of 0.69 (62.9% of improvement). Similarly, improvement in failure load correlation was 54.3% when combining bone volume fraction and ABDM, 60.5% when combining trabecular spacing and ABDM, 22.2%when combining trabecular thickness and ABDM, and 7.6% when combining the degree of anisotropy and ABDM.

Using a ridge multivariate regression analysis including all the microarchitecture metrics and ABDM and after a backward elimination of the non-significant parameters (at alpha level equal to 0.05), fractal dimension was the single eliminated parameter.

DISCUSSION

In the present study we assessed proximal femoral bone microarchitecture using UHF-MRI and compared the corresponding results with those from DXA and mechanical compression tests. The correlations between bone microarchitecture parameters and mechanical compression tests were better than in those reported in further studies.

In our study, ABDM significantly correlated with failure load in line with two previous studies [16, 27]. The microarchitecture (bone volume fraction, trabecular thickness, trabecular spacing, the degree of anisotropy and Euler characteristics) and texture metrics (fractal dimension) also significantly correlated with bone strength in line with previous study [15]. In addition, ABDM and microarchitecture metrics were not related thereby indicating, as previously suggested, that MRI and DXA provide different information regarding bone quality and fracture

risk [15]. Interestingly, the statistical power of the correlation between the microarchitecture and the mechanical metrics was improved when both ABDM and a microarchitecture variable were combined further supporting that both indices are not providing similar information and that the combination can be of diagnostic interest [15].

Among the microarchitecture metrics, bone volume fraction displayed the largest correlation with failure load. These results further support those from previous MRI studies conducted in the distal radius, ankle, distal femur, wrist and vertebrae [14, 28, 29]. On the basis of 1.5-T MRI measurements (slice thickness = 300 µm, in plane resolution = 117 µm), Majumdar *et al*. reported a lower bone volume fraction in the distal radius of subjects with fragility fractures (mean bone volume fraction = 0.23) as compared to controls (mean bone volume fraction = 0.29) while Link *et al*. showed similar results in the calcaneal bone and in the proximal femur (mean bone volume fraction=0.33) [14, 28, 29]. In our population of women cadavers without femoral fractures, mean bone volume fraction at the proximal femur was slightly larger i.e. 0.37 and the same as mean values reported by Chang *et al*. in women with fragility fractures [30]. In a study conducted at 3-T in 60 postmenopausal women, the authors did not report significant bone volume fraction difference between the control group and the group with osteoporotic fractures thereby illustrating that the higher resolution obtained at UHF might account for this apparently paradoxical result [15]. Link *et al.* found a significant correlation between bone volume fraction measured in the great trochanter and biomechanical testing in the femoral neck (r= 0.62) [14]. This correlation was validated when measurements were performed using 0.9 mm thickness MRI slices but not when thickness was reduced to 0.3 mm (r = 0.32) likely resulting from a reduced signal-to-noise ratio. In the present study, strong correlations

were found between bone volume fraction and other microarchitecture metrics suggesting a potential overlap between these variables for the assessment of bone quality.

Trabecular thickness and trabecular spacing were also very significantly correlated with failure load with correlation coefficient larger than those computed using ABDM values. This result supports those from previous studies which have illustrated that trabecular volume and trabeculae space both increased with age [31]. Combining trabecular spacing with ABDM significantly improved the failure load identification whereas combining trabecular thickness with BMD did not, probably due to a lack of power of the study. Both Euler characteristic (64.8%). and connectivity density (60.3%) had a large impact on the fracture identification from the combination between microarchitecture metrics and ABDM thereby illustrating a great potential for the assessment of bone strength *in vivo* from combined measurements. One can be surprised by this result because connectivity density was not significantly correlated to failure load ($r=0.606$, $p=0.063$), maybe due to a lack of power of the study because p is close to significance. Nevertheless, in our study, connectivity density and ABDM did not correlate ($r=0.145$, $P=0.688$), they therefore provide different information on the failure load. And when adjusted on ABDM, connectivity density provides significant information on failure load.

In our study, the degree of anisotropy was significantly correlated with failure load in agreement with previous results indicating that anisotropy is one of the main accounting factors of the bone mechanical resistance [28]. Combining the degree of anisotropy and ABDM did not significantly improve the relationship between the microarchitecture and mechanical parameters in agreement to what has been previously suggested [28]. Indeed, in our study the degree of anisotropy and ABDM are significantly linked ($r= 0.637$, $P=0.048$), that is why the degree of anisotropy does not provide any additional information on failure load vs. ABDM.

In the present study, fractal dimension was strongly correlated with both other microarchitecture metrics and failure load, and the failure load information was improved if fractal dimension was combined to ABDM. These results confirm those obtained from DXA measurements and using the trabecular bone score indicating that trabecular bone score combined with ABDM incrementally improved fracture assessment in postmenopausal women [32].

The VOIs used for the microarchitecture measurements were positioned in the greater trochanter according to previous results [15] and given the high image quality there. Gas bubbles were present in the region of the femoral neck likely due to the metabolic processes occurring in *ex-vivo* specimen. Those gas bubbles generate important artifacts in MRI. A small VOI (1x1x1cm) similar as the recent study of Chang et al. [15] was chosen in order to avoid bubbles. In addition, during the biomechanical tests, most of the femoral fractures occurred in the intertrochanteric region (only one in the femoral neck). Considering that our in-plane resolution was within the range of trabecular size, microstructure metrics could have been slightly biased due to partial volume effects. As previously indicated, the resolution we obtained might have caused artefactual widening of trabeculae. However, the correlative analyses with mechanical variables are still valid and of high interest. In addition, the resolution we obtained using UHF MRI (voxel size = 0.17 x 0.17 x 0.5mm) was almost equivalent to the resolution that can be achieved using HR-QCT [33] and similar to the resolution previously reported at 7-T [34]. Due to image blurring and X-ray exposure, HR-QCT cannot be used in clinical routine so that UHF MRI could be considered as an interesting alternative [12]. Acquisition time (37 min) was still too long for a clinical context but might be shortened using other MRI pulse sequences such as 3D fast spin-echo with out-of-slab cancellation [35].

Our study has some limitations. Our results have been obtained from a small number of specimens, although this number is similar to the amount used in some other studies [29]. Samples preparation including a freezing-defreezing process and soft tissue removal might have altered the cadaveric samples and biased the corresponding results. Considering that the range of ABDM values reported in the present study was similar to those previously published *ex-vivo* [16, 28,] this bias might be considered as minor. As hematopoietic bone marrow could be detected *in vivo*, one can wonder about a potential contamination of hematopoietic bone marrow for the signal processing [14]. In our old cadaveric specimens, active red marrow is not expected and corresponding hyperintensities were not observed.

In conclusion, the results of the present study demonstrate that microarchitecture metrics quantified from excised proximal femur using UHF MRI are correlated with biomechanical strength and could provide an additional assessment tool of bone quality. Combined with ABDM values, these parameters might improve the prediction of load failure in previously undetected osteoporotic patients.

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Figure Legend

Figure 1: Typical coronal MRI of a cadaveric femur in saline. A is the original image and B is the same image after bias correction. The white square indicates the volume of interest (VOI) location for further measurements, the VOI left top corner has been set to be in the middle of the

axes defined by the top and bottom point of the greater trochanter (white line). The corresponding image is shown in C. D and E are the images obtained after contrast enhancement and binarization.

Figure 2: Graph displaying the relation observed between bone volume fraction (BVF) on abscissa) and the femoral failure load (in Newton, ordinate) in 10 specimens.

Table legend

Table 1: Mean, standard deviation (SD), quartile Q1 and Q3, median, for each imaging variable and Pearson correlation (r) between imaging variables and failure load. Areal bone mineral density (ABDM), bone volume fraction (BVF), trabecular thickness (TT), trabecular spacing (TS), fractal dimension (FD), Euler characteristics (EC), connectivity density (CD), degree of anisotropy (DA).

Table 2: Pearson's correlation coefficient between vertebral microarchitecture parameters and areal bone mineral density (ABMD). Correlation coefficients between bone volume fraction (BVF) and other microarchitecture parameters trabecular thickness (TT), trabecular spacing (TS), fractal dimension (FD), Euler Characteristics (EC), connectivity density (CD), degree of anisotropy (DA) obtained at UHF-MRI, and ABDM measured by DXA.

Table 3: Multiple regression analysis of combinations of ABDM and microarchitecture parameters used to explain the femoral failure load. *significant difference between adjusted R^2 of ABDM alone and ABDM + microarchitecture parameters, *P* value < 0.05