The porous system model suitable to investigate the structural properties of the cancellous bone by using diffusion techniques: validation in calcaneus and femoral neck

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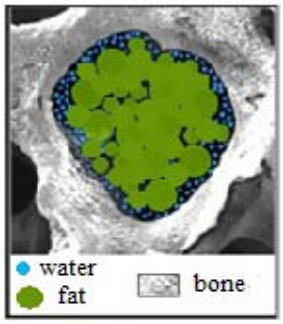
Purpose: My aim was to describe and to validate a porous system model suitable to investigate the structural properties of the cancellous bone by using diffusion techniques. Toward this goal I described cancellous bone model on the basis of some recent evidences obtained in both calf bone samples[1] and human vertebrae [2,3]. Then, I examined the calcaneus and the femoral neck of healthy (H), osteopenic (OPE) and osteoporotic (OPO) subjects, as classified by the bone mineral density (BMD) parameter, by measuring the apparent diffusion coefficient (ADC), together with the marrow fat content (Mfc) and assessing associations between, BMD, Mfc and ADC.

Methods: *Model***:** The cancellous bone model suitable for obtaining microstructural information in cancellous bone by using diffusion (**Fig.1**) was derived from the following recent evidences: -1- water is more prevalent in the boundary zone while fat occupies primarily the central zone of each cancellous bone pore[1]. -2- the molecular dynamic associated with fat protons is much slower than that of water. Indeed, ADC values of fat component in bone marrow are approximately two orders of magnitude lower than those of water molecules[1]. As a consequence bone-marrow water diffuses in the interstitial space between bone and fat[1] -3- bone marrow fat increases from axial skeleton (vertebral site) to peripheral skeletal sites. Mfc values extracted from the vertebrae, the femoral neck and the calcaneus of postmenopausal women was found to range from 50% to 70%, 60% to 88%, 78% to 98%, respectively[2,3,4].

Subjects: Thirty postmenopausal women (mean age, 64.5±5.8 y) underwent both quantitative computer tomography (QCT) to assess BMD in lumbar vertebrae L1-L3 and diffusion weighted imaging (DWI) investigation in calcaneus. A second group of postmenopausal women (mean age, 71.5±4.2 y) underwent both dual energy X-ray absorptiometry (DXA) to assess femoral BMD and DWI investigation in femoral neck. The study was approved by the local Ethics Committee, and written informed consent was obtained from all subjects. T-scores were calculated for each woman, and subjects were grouped into three categories (H, OPE and OPO subjects) according to the diagnostic classification criteria based on QCT BMD and DXA BMD. *Experiments*: ADC in calcaneus was evaluated from DWI images acquired in a single sagittal section of the calcaneus using a 3T Allegra Siemens scanner. A spin-echo segmented echo-planar imaging (EPI) sequence (repetition time, TR=1500ms, echo time, TE=86 ms; field of view, FOV=192x192 mm^2; matrix, 128x128; epi factor, 7; diffusion gradient along the anterior-posterior direction) at two different b-values (b=0 and 8000 sec/mm^2) was run[1]. ADC in femoral neck was evaluated from DWI images acquired in coronal section of the femur using a 3T Achieva, Philips scanner. A segmented EPI sequence (TR/TE=2500/104ms; FOV= 160x142mm^2; matrix, 72x49; epi factor, 7; diffusion gradient along left-right direction) at two different b-values (b=0 and 2500 sec/mm^2) was run. A volume of interest (voxel size, 15x15x15 mm^3) in the central zone of the calcaneus and the femoral neck was also selected for collecting ^{1}H spectra (TR/TE=5000/22 ms; number of signal-averages NS=32) using a single-voxel spectroscopy PRESS sequence. *Analysis*: ADC values were obtained from DWI images, using the relation: $I_b=I_0 \cdot \exp(-b \cdot ADC)$, where I_0 and I_b are the mean signal intensities at b=0 s/mm^2 and b=2500 s/mm^2 or b=8000 s/mm^2 for the femoral neck and the calcaneus, respectively. All ^{1}H spectra were analyzed using the LC Model method. Mfc was calculated for all subjects according to the following equation: $Mfc = [I_{fat}/(I_{fat} + I_{wat})] \cdot 100$, where I_{wat} is the water peak area (at about 4.7 ppm) and I_{fat} is the sum of partially overlapping lipid peaks[1].

All measured variables in the calcaneus and in the femoral neck were compared between the three bone density groups by a one-way analysis of variance (one-way ANOVA). Pearson correlation coefficients (r) were calculated to assess linear correlation between pairs of variables for all subjects and for all subjects belonging to each bone density group. A P value less than 0.05 was considered statistically significant.



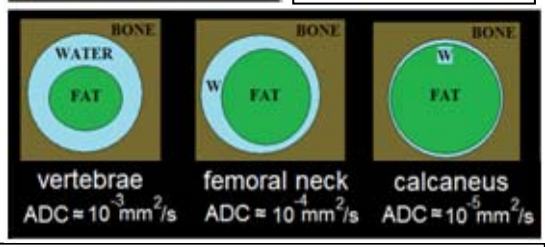


Fig.1
The porous model suitable for obtaining micro-structural information in cancellous bone by using diffusion.

Results: Mfc values in calcaneus were not significantly different between H, OPE and OPO subjects (**Table1**). Moreover, no significant correlation was observed between Mfc and T-scores. On the other hand, significant correlation was observed between Mfc and T-scores in femoral neck and Mfc values were significantly different between H and OPO, and between OPE and OPO subjects. A significant negative correlation was found between ADC and T-scores, while no-correlation was found between ADC and Mfc in calcaneus. Moreover, ADC values measured in calcaneus were significantly different between H, OPE and OPO subjects. Conversely, a significant positive correlation was found between ADC and T-scores in femoral neck together with a significant correlation between ADC and Mfc. Furthermore, ADC values obtained in femoral neck were significantly different between H and OPE and between H and OPO subjects.

Discussion: ADC results obtained in both calcaneus and femoral neck validated the cancellous bone model proposed here. Because, in calcaneus, Mfc doesn't increase from H to OPO subjects, patients with osteoporosis compared to age-matched controls showed significantly higher ADC values. These findings may be a consequence of pore enlargement and increase in interconnections between adjacent pores in the trabecular bone network due to perforations of trabecular plates. As a consequence, ADC values in calcaneus are strictly related to pore enlargement and trabecular network degradation. Conversely, because femoral Mfc shows an increasing trend from H to OPO subjects, ADC values as a function of T-score in femoral neck show a reversed trend compared to that in calcaneus. Mean ADC values shown in **Table 1**, indicate that water is confined in a mean displacement distance ($d=(2Dt)^{1/2}$) approximately equal to 3 μm and to 10 μm, in the calcaneus and in the femoral neck, respectively. Moreover, using vertebral ADC values obtained from literature[2,3] a distance d approximately equal to 15 μm can be estimated. These findings, together with vertebral ADC behavior in H and OPO subjects extracted from literature[2,3] are in agreement with the cancellous bone model depicted in **Fig. 1**. Moreover, ADC and Mfc results shown that, with the development of osteoporosis two main mechanisms occur in femoral neck and vertebral sites: an increase of the marrow fat which decreases the ADC value and a microstructure deterioration with a pore enlargement that increases ADC. On the other hand only the latter mechanism is present in the calcaneus.

Table 1
MR data in calcaneus and femoral neck of healthy, osteopenic and osteoporotic group

Parameter	Skeletal site	1 (H) (n = 10)	2 (OPE) (n = 10)	3 (OPO) (n = 10)	*P* Value (1 vs 2)	*P* Value (2 vs 3)	*P* Value (1 vs 3)
Mfc (%)	Calcaneus	86.44±4.70	88.01±3.32	87.50±2.00	ns	ns	ns
ADC (*10^{-10} m^2/s)	Calcaneus	0.40±0.08	0.52±0.15	0.68±0.16	**	*	***
Mfc(%)	Femoral neck	73.42±5.34	80.14±7.78	83.86±4.94	*	ns	***
ADC (*10^{-10} m^2/s)	Femoral neck	4.12±0.56	2.12±1.14	2.15±0.41	***	ns	***

Data are mean ±SD. n=number of subjects. ns ($P \geq 0.05$); *($P < 0.05$); **($P < 0.01$); ***($P < 0.001$).

Conclusion: ADC and Mfc results, obtained in different skeletal locations, validate the model proposed to investigate cancellous bone by exploiting bone-marrow water diffusion. From a more speculative perspective, on the basis of the model here proposed, diffusion assessment**,** in combination with ^{1}H Magnetic Resonance Spectroscopy investigations obtained in large populations, might increase our pathophysiological understanding of osteoporosis.

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