Lipidic profile of bone marrow in peripheral skeleton sites assessed by 1H-MRSpectroscopy: looking for instrumental biomarkers of osteoporosis.

Giulia Di Pietro[1,2], Vincenzo Vinicola[3], Guglielmo Manenti[4], Mauro Rebuzzi[2], Gisela Hagberg[5], Salvatore Masala[4], Giovanni Simonetti[4], Marco Bozzali[5], and Silvia Capuani[2,6]

[1]IIT@Sapienza, Physics Department, Rome, Rome, Italy, [2] "Sapienza" University of Rome, Physics Department, Rome, Rome, Italy, [3]Rehabilitation Hospital IRCCS Santa Lucia Foundation, Rome, Italy, [4]Department of Diagnostic Imaging and Interventional Radiology, University of "Tor Vergata", Rome, Italy, [5]Neuroimaging Laboratory, Santa Lucia Foundation, Rome, Italy, [6]CNR IPCF UOS Roma, Physics Department, Rome, Italy

Introduction: Osteoporosis is a metabolic and systemic disease characterized by low bone mass and micro architectural deterioration of bone tissue, leading to enhanced bone fragility and a consequent increase of bone fracture risk [1]. Bone marrow (BM) adiposity plays an important role in affecting bone quality [2]. Several studies suggest that differentiation of mesenchymal stem cell (SMCs) is a mutually exclusive process with commitment to either the fat or bone lineage. This observation is supported by studies in the elderly, where bone loss is associated with increase in bone marrow fat content percentage (Mfc%), suggesting a preferential differentiation of SMCs into marrow fat at the expense of bone-forming osteoblast [3]. As a consequence, BM fats quantification, performed by using ^{1}H-MRS, has recently gained increasing attention as a potential biomarker for bone quality and then as a biomarker for early diagnosis of osteoporosis. Previous studies performed on vertebrae, demonstrated that there is a clear relationship between Mfc% and bone mineral density (BMD) measured by DXA. In particular, in vertebral BM, subjects with osteopenia and osteoporosis present with a significant higher Mfc% than subjects with normal bone density [4-5]. However all studies reported in literature have evaluated the total Mfc% as derived from the main fat resonance at 1.3 ppm. Aim of this study was to characterize, using ^{1}H-MRS, the lipidic profile of BM in the calcaneus and the femoral neck of postmenopausal healthy (H), osteopenic (OPE) and osteoporotic (OPO) women. The final goal was to assess whether specific metabolite profiles are able to discriminate between individuals affected by osteoporosis and healthy subjects

Methods and Materials: A total of 86 women (preliminarily screened and classified using BMD assessments performed by QCT and DXA) were investigated using a 3.0T MR system. Specifically, the calcaneus of 62 women and the femoral neck of 24 woman were studied. The cohort of subjects for calcaneus investigation included: 11 H women (mean-age=60.0±4.1 years), 33 OPE (mean-age=62.0±6.4 years) and 18 OPO (mean age=63.6±4.7 years) patients. The cohort of subjects for femoral neck investigation included: 7 H women (mean-age=66.2±8.9 years), 9 OPE (mean-age=69.8±6.1 years), and 8 OPO (mean age=73.6±6.3 years) patients. Single-Voxel-^{1}H-MR-Spectroscopy (PRESS, TE/TR=22ms/5s) was employed to investigate the BM from calcaneus and/or femur of each recruited subject. ^{1}H-spectra were analyzed using the LCModel tool for *in vivo* quantification of bone-marrow spectra. Mfc% were derived from the resonances at 5.3, 4.1, 4.3, 28, 2.3, 2.1, 1.6, 1.3 and 0.9 ppm. The total fat content (TL) was also estimated in each subject (Fig.1). Mean ± SD values were computed for each resonance, and between-group differences (H, OPO and OPE) were assessed by Student's t-tests for independent samples (statistical threshold set to p values <0.05)

Results: TL of femoral neck was significantly lower in OPE compared to OPO patients. When Mfc% of each resonance was considered, the resonance at 5.3 ppm was significantly lower in H compared to OPE subjects. In H subjects all resonances were significantly lower than those observed in OPO subjects. Mfc% of resonances L16+L09+L13, L16+L13, L09, L53+L52, L43 and L41 were significantly lower in OPE subjects as compared to OPO patients (Fig2 (B)).

In calcaneus, Mfc% of L16 was significantly lower in H compared to that in OPE subjects. Moreover Mfc% of L43 and L4 were significantly lower in H compared to OPO subjects, and Mfc% of L28+L23+L21 was significantly lower in OPE compared to OPO subjects (Fig 2 (A)).

Conclusion: Our preliminary data obtained in femur, indicate that L53 (methine protons resonance) is a biomarker suitable for identifying H subjects, while L09 (CH$_3$- resonance) is the best marker to identify OPO subjects. Taken together, these ^{1}H-MRS measures might provide a sensitive and specific test for screening of populations at risk for osteoporosis. This is the basis for cost-effective programs of preventive medicine. Additionally, in calcaneus, the simul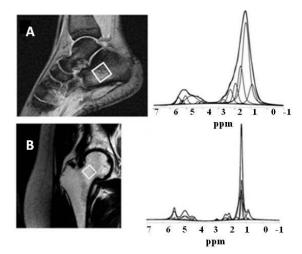taneous quantification of resonances L09,L43, L41 and L28+L23+L21 offers a chance to increase the diagnostic confidence of osteoporosis in low cost dedicated spectrometers.

Fig 1: T1-w images used for voxel positioning in the calcaneus (A) and femur (B). Correspondent ^{1}H-MR spectra, obtained from a H subject and fitted by LcModel are shown on the right. Each peak was analyzed as a sum of model peaks with different positions, widths and shapes.
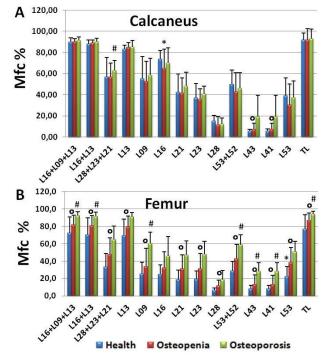

Fig.2: Histograms of calcaneal (A) and femoral (B) Mfc% in the different bone density groups, to show differences between groups (healthy, H, osteopenic, OPE, osteoporotic, OPO). * Statistically significant differences in marrow fat content (Mfc%) between H and OPE subjects. ° Statistically significant differences in Mfc% between H and OPO subjects. # Statistically significant differences in Mfc% between OPE and OPO subjects.

References: [1] WHO - TRS(843).1994: X-129. [2] Rosen CJ et al. Nat Clin Pract Rheumatol. 2006, 2: 35-43. [3] Bredella MA. et al. Skeletal Radiol. 2010, 39: 729-731. [4] Yeung DKW et al. J Mag Reson Imaging. 2005, 22: 279-285. [5] Griffith JF et al. Radiology. 2006, 241: 831-838.