Whole spine vertebral bone marrow proton density fat fraction mapping: anatomical variation and gender-specific reference database

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Introduction: The bone marrow tissue as non-mineralized component of bone contributes to systemic and skeletal metabolism. It contains hematopoietic stem cells (red marrow), generating circulating blood and osteoclasts, and mesenchymal stem cells (yellow marrow), which can mature into osteoblasts and adipocytes. The assessment of bone marrow composition has recently gained significant attention. Firstly, increased vertebral bone marrow fat fractions have been correlated with visceral adipose tissue and HbA1c values in women with type 2 diabetes mellitus [1]. Secondly, myelosuppressive chemotherapy and radiation treatment suppress the hematopoietic function of the red marrow and increase the differentiation of mesenchymal stem cells toward adiposis leading to increased yellow marrow [2]. Thus, treatment-induced bone marrow damage has been reflected by greater bone marrow fat fractions. Lastly, bone marrow adiposity is associated with bone loss pathophysiology [3]. Proton single-voxel Magnetic Resonance Spectroscopy (MRS) has been the most widely used method to non-invasively quantify bone marrow fat in-vivo. Another emerging method for measuring vertebral bone marrow fat fraction is quantitative chemical shift encoding-based water-fat imaging. Water-fat imaging techniques are advantageous compared to single-voxel MRS, since they can provide quantitative and spatially resolved information on bone marrow water-fat composition. The water-fat imaging-based proton density fat fraction (PDFF) has been shown to be in good agreement with the MRS-based fat fraction in the bone marrow of the proximal femur [4]. However, little is known about the anatomical variation of PDFF over the whole spine and a reference database of PDFF values of young, healthy subjects has not been established yet. Therefore, the purpose of the present study was to (i) investigate the anatomical variation and (ii) establish a gender-specific reference database of the vertebral bone marrow fat by using chemical shift encoding-based water-fat MRI, and (iii) to assess the reproducibility of these measurements.

Methods: MR Imaging: The whole spine of 28 young, healthy subjects (17 males and 11 females, 26±4 years of age) was scanned on a 3 T whole-body scanner (Ingenia, Philips Healthcare, Best, Netherlands) using the built-in-the-table posterior coil elements (12-channel array). The MR exam consisted of three sagittal 3D spoiled gradient echo sequences placed on the cervical, thoracic, and lumbar spine respectively, in order to achieve whole spine coverage.

An eight-echo 3D spoiled gradient echo sequence was used for chemical shift encoding-based water-fat separation. The sequence acquired the eight echoes in two interleaves (4 echoes per TR) using flyback (monopolar) read-out gradients and the following imaging parameters: TR/TEmin/ΔTE = 15/1.47/1.05 ms, FOV = 220x220 mm^2, acquisition matrix = 124x122, slice thickness = 4 mm, slice locations = 20, receiver bandwidth = 1551 Hz/pixel, frequency direction = A/P (to minimize breathing artifacts), N_{avg} = 2. A flip angle of 3° was used to minimize T_1-bias effects.

Fat Quantification: The gradient echo imaging data were processed off-line using in house-built routines written in MATLAB (Mathworks, Natick, MA, USA). Specifically, a region-growing algorithm was first used to estimate the fieldmap variation. A complex-based water-fat decomposition was then performed using a single T_2* correction and a pre-calibrated fat spectrum, accounting for the presence of the multiple peaks in the fat spectrum. The pre-calibrated fat spectrum previously measured in the red bone marrow of the proximal femur was employed [4]. The imaging-based PDFF map was computed as the ratio of the fat signal over the sum of fat and water signals. Mean vertebral bone marrow fat fraction was determined by manually placing circular regions of interest (ROIs) on the PDFF map in the three most central slices depicting each vertebra from C3 to L5. Each ROI was placed in the ventral half of vertebrae, equidistant to both endplates, and covering two third of the vertebral height.

Reproducibility: Six subjects (4 males and 2 females) were scanned three times with repositioning to assess the reproducibility error of the PDFF measurements. The reproducibility error was expressed as root mean square absolute precision error in [%] (PDFF absolute units) and as root mean square coefficient of variation (RMSCV) in [%] (relative units).

Results: Typical whole spine fat fraction maps in a male and a female subject of the same age are shown in Fig. 1. Mean ± SD of PDFF of all subjects amounted to 31.6±8.6% (C3-L5) with increasing values from C3-7 (28.3±7.9%), T1-6 (30.6±8.7%), T7-12 (31.3±8.8%) to L1-5 (36.4±10.2%). PDFF values of C3-7 were significantly lower than those of T1-T6 (p=0.004) as well as PDFF values of T7-12 than those of L1-5 (p<0.001), while PDFF values of T1-6 and T7-12 were not significantly different (p=0.215). A correlation coefficient of r=0.66 (p=0.001) was observed for the association of vertebral level C3 to L5 and corresponding PDFF in all subjects (Fig. 2). Only mild correlation coefficients (r=0.42 to r=0.47; p<0.05) were obtained for the association of age versus PDFF of all subjects averaged over C3-L5, C3-7, T1-6, T7-12, and L1-5, respectively. PDFF averaged over C3-L5, C3-7, T1-6, T7-12, and L1-5 were significantly (p<0.05) greater in male compared to female subjects except for L1-5 (Table 1).

The root mean square absolute precision error of the PDFF measurements amounted to 1.7% (PDFF absolute units) averaged over C3-L5 (range: 0.5% in T2 to 3.3% in C7). The RMSCV of PDFF measurements amounted to 5.7% (relative units) averaged over C3-L5 (range: 1.7% in T2 to 10.4% in C7).

Discussion & Conclusion: An accurate extraction of the bone marrow PDFF requires the assessment of multiple effects that can confound the measurements. The present study considered strategies to address the most critical effects confounding the measurement of the vertebral bone marrow PDFF. Firstly, an eight-echo acquisition was presently adopted to reliably correct for T_2* decay effects. Secondly, the presence of multiple peaks in the fat spectrum was considered using a pre-calibrated fat spectrum previously characterized in the red bone marrow of the proximal femur [4]. Thirdly, T_1-bias effects were minimized by using a small flip angle excitation. In conclusion, whole spine marrow fat could be reliably assessed by using chemical shift encoding-based water-fat MRI. Vertebral bone marrow fat fraction showed anatomical variations with increasing values from C3 to L5. In the future, vertebral bone marrow changes might be classified by using the gender-specific reference database provided by the present study.

References: [1] Baum, J Magn Reson Imag 35:117, 2012, [2] Li, Br J Haematol 127:326, 2004, [3] Rosen, Nat Clin Pract Rheumatol 2:35, 2006, [4] Karampinos, Magn Reson Med 71:1158, 2014.

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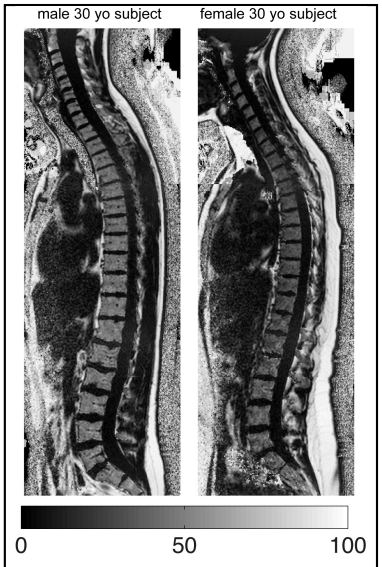

Fig. 1: Typical whole spine fat fraction maps in a male and a female subject of the same age. Colorbar represents fat fraction values in [%].

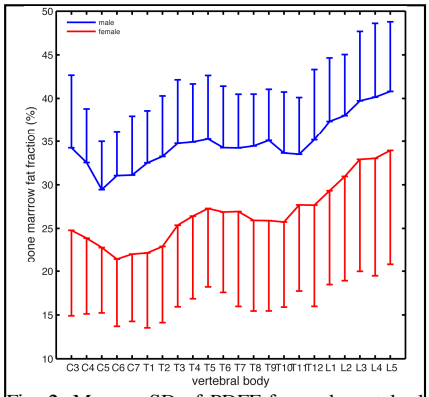

Fig. 2: Mean ± SD of PDFF for each vertebral level (C3-L5) in all subjects. Note the overall increase of the bone marrow fat fraction from C3 to L5 with a correlation coefficient of r=0.66 (p=0.001).

	males (n=17)	females (n=11)	p-value
C3-L5	34.8±6.4%	26.7±9.5%	**0.011**
C3-7	31.7±7.9%	23.0±7.8%	**0.002**
T1-6	33.8±6.8%	24.6±8.8%	**0.005**
T7-12	33.8±6.4%	26.1±6.4%	**0.023**
L1-5	38.8±7.6%	31.5±12.4%	0.063

Table 1: Mean ± SD of PDFF averaged over C3-L5, C3-7, T1-6, T7-12, and L1-5 in males and females, respectively. Gender differences were evaluated with t-tests.