Removing the confounding effect of the fat component in ADC quantification of the vertebral bone marrow water component

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Target audience: Scientists working in diffusion of bone marrow and clinical researchers interested in biomarkers of bone health

Purpose: The water apparent diffusion coefficient (ADC_w) of vertebral bone marrow has been proposed as a useful biomarker for differentiating between benign and malignant vertebral compression fractures [1] and for indirectly investigating BMD changes in patients with osteoporosis [2,3]. A major challenge for a reliable quantification of ADC_w in bone marrow is the presence of a strong fat component. The main portion of the fat spins has a resonance frequency between 0 ppm and 3 ppm (Fig. 1) and thus can be efficiently suppressed by using a spectrally selective fat suppression technique, e.g. SPAIR. However, the olefinic at 5.3 ppm (* in Fig. 1) and glycerol at 4.2 ppm (** in Fig. 1) fat peaks have a resonance frequency close to the one of the water peak (Fig. 1) and cannot be suppressed using a spectrally selective technique. Neglecting the presence of the secondary fat peaks close to the water peak could lead to a significant bias in the quantification of the ADC_w, because the ADCs of water and fat differ by orders of magnitude (Fig. 1) [4,5]. Diffusion-weighted single-voxel MRS measurements can reliably extract the diffusion coefficients of all water and fat components, but only averaged over a single voxel [6]. Therefore, purpose of the present work was to develop an MRI protocol combined with a post-processing framework to measure the ADC map of the water component in vertebral bone marrow, free of the confounding effect of fat, and validate the proposed methodology with the ADC_w from diffusion-weighted single-voxel MRS measurements.

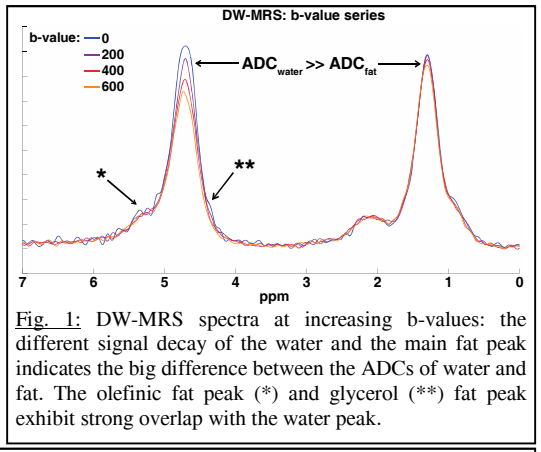

Fig. 1: DW-MRS spectra at increasing b-values: the different signal decay of the water and the main fat peak indicates the big difference between the ADCs of water and fat. The olefinic fat peak (*) and glycerol (**) fat peak exhibit strong overlap with the water peak.

Methods: Signal analysis**:** If we assume that spectrally selective fat suppression perfectly suppresses the fat peaks in the region between 0 and 3 ppm, then the diffusion-weighted signal at b-value b and echo time TE for a voxel with proton density fat fraction equal to PDFF, containing water and fat components with apparent diffusion coefficients ADC_w and ADC_f respectively and T_2 relaxation times equal to T_{2w} and T_{2f}, respectively, can be given by the following equation:

$$S(b) = \alpha S_{f_0} e^{-TE/T_{2f}} e^{-bADC_f} + S_{w_0} e^{-TE/T_{2w}} e^{-bADC_w}$$
$$= (S_{w_0} + S_{f_0}) \left[\alpha PDFF e^{-TE/T_{2f}} e^{-bADC_f} + (1 - PDFF) e^{-TE/T_{2w}} e^{-bADC_w} \right]$$

with α being the fraction of the unsuppressed fat spectrum energy that is located close to the water peak, S_{w0} and S_{f0} the proton density signal of the water and the fat component. The parameter α was assumed to be constant across subjects and determined equal to 0.12 based on a previous bone marrow MRS study [7]. It was also assumed that T_{2f} = 70 ms and ADC_f = 0 mm^2/s across all subjects. In order to extract ADC_w from the diffusion-weighted signal at different b-values, additional MRI sequences were used to obtain PDFF and T_{2w} maps. These parameters were needed as input for a signal model that was used to fit for ADC_w (Fig. 2). The MRI signal of the DWI sequence was averaged over a cube-shaped ROI inside the vertebral bone marrow for each b-value. The resulting average b-value-specific signal intensities as well as the previously estimated PDFF and T_{2w} parameters were put in to an exponential fitting routine yielding the ADC_w. Vertebral bone marrow MRS using the identical ROIs was used as a reference to validate the results of the described MRI-based ADC_w quantification.

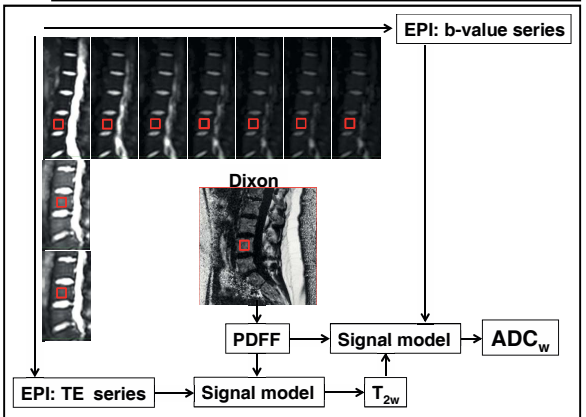

Fig. 2: Schematic display of the proposed MRI protocol and post-processing framework to remove the confounding effect of unsuppressed bone marrow fat: PDFF and T_{2w} are measured with a Dixon and TE series sequence, respectively, and used as input for the fitting routine that yields the ADC_w.

MRI/MRS measurements: The lumbar spine of four healthy subjects was scanned in an Ingenia 3.0T scanner (Philips Healthcare, Best, Netherlands). The imaging protocol included an 8-point Dixon sequence and a reduced-FOV DW-EPI sequence (to reduce geometric distortions) [8]. The Dixon data were processed using a water-fat-separation algorithm accounting for T_2* effects and the presence of multiple fat peaks to obtain PDFF maps [9]. The EPI sequence used SPAIR to suppress the fat signal between 0 ppm and 3 ppm and acquired data at TE = 52.5 ms and multiple b-values (b = 0/200/400/600/800 s/mm^2) and at TEs = 26/36/46 ms without diffusion weighting (b = 0 s/mm^2). Ten signal averages were acquired for each b. The EPI images at multiple TEs and b = 0 and the estimated PDFF were used to estimate the T_{2w}. The combined scan time of the Dixon and the non-diffusion weighted EPI sequences was 6 min, increasing the total scan time to 18 min. MRS was performed in the bone marrow of the L3 and L5 vertebral bodies. Spectra were acquired with two different sequences: (i) STEAM sequence at multiple echo times (TE = 11/15/20/25 ms, b = 0 s/mm^2) to estimate T_2 times and PDFF, (ii) diffusion weighted STEAM sequence at multiple b-values (b = 0/200/400/600/800 s/mm^2, TE = 25 ms) to estimate ADC_w. In order to reliably extract the water peak from the overlapping fat peaks, the area of those peaks were restricted to the area of the main fat peak during the peak fitting [7].

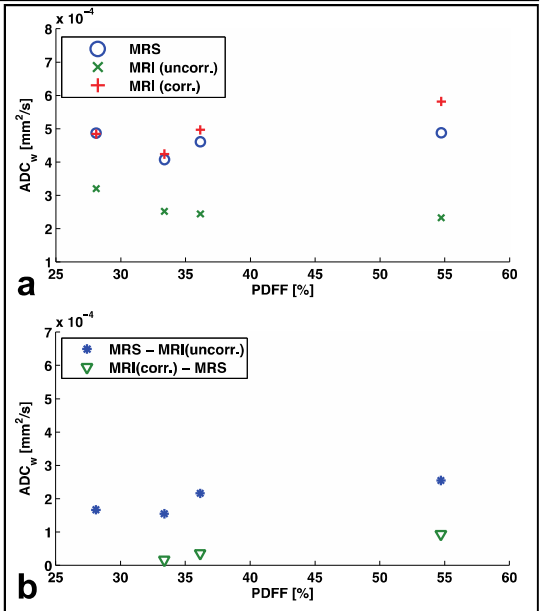

Fig. 3: ADC_w quantification results of the L3 vertebral body of four different subjects ordered by PDFF: (a) comparison between MRS, uncorrected MRI and corrected MRI results; (b) error between the reference value (MRS) and the values obtained with corrected and uncorrected MRI, respectively.

Results: Figure 3 shows the results of the ADC_w quantification for four different subjects with different PDFF exemplifying two main findings: (i) compared to MRS-based quantification the ADC_w is significantly underestimated (up to 52%) if a conventional DWI-based quantification method is used that does not take into account unsuppressed fat signal; (ii) the proposed quantification method is able to correct this underestimation substantially and yields ADC_w values closer to the reference.

Discussion & Conclusion: DWI-based quantification of bone marrow water ADC is strongly biased by unsuppressed fat signal. The present results show that the underestimation of the ADC_w due to incomplete fat suppression becomes stronger for higher PDFF values (Fig. 3). The proposed methodology combining the DW-EPI acquisition with a multi-TE EPI acquisition and a multi-echo gradient echo acquisition (for measuring T_{2w} and PDFF maps) shows that it can correct for the bias in bone marrow ADC_w caused by incomplete fat suppression.

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