

Single- versus multipeak modeling of Dixon images to determine the fat fraction in patients with Duchenne muscular dystrophy

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Introduction:

Duchenne muscular dystrophy (DMD) is characterized by progressive loss of muscle function and a decreased life expectancy. Over the last few years, many possible therapeutic options for the disease have been developed^{1,2}. The current gold standard for the assessment of therapy effectiveness is a muscle biopsy which is invasive and only provides focal information. Consequently, non-invasive methods for longitudinal therapy follow-up become increasingly important. A useful marker for therapy follow-up could be the fat fraction in the muscle, which is known to increase during the course of the disease³. For quantitative analysis of the fat fraction in the muscle multiecho chemical-shift based water-fat separation^{4,5} can be used. However, for this technique the fat signal is usually modeled as a single-peak whereas in reality the fat signal consists of multiple peaks⁶, resulting in underestimation of the true fat fraction in a sample^{7,8}. In DMD patients eligible for therapeutic trials, an underestimation of the fat fraction could potentially influence inclusion in clinical studies¹ as well as the results of therapy follow-up if the fat fraction were to be used as an outcome measure. It is currently unknown how multipeak, as compared to single peak, fitting behaves in heavily fat infiltrated muscles. In this study we compared single- and multipeak fitting in muscle MR images from Duchenne patients and healthy controls.

Methods:

Six DMD patients (age $9.5 \text{ years} \pm 1.5 \text{ years}$) and five age-matched healthy controls (age $11 \text{ years} \pm 1 \text{ year}$) were included. Images were acquired from the upper and lower leg on a 3T Philips Achieva scanner (Best, NL) using a 14 cm two-element coil placed directly below the patella for the analysis of the lower leg and directly above the patella for analysis of the upper leg. The scanning protocol consisted of a T1 weighted (twenty five 5 mm slices, 0.5mm gap, TR 600, TE 16) and a 3-point Dixon scan (twenty five 5 mm slices, 0.5mm gap, TR 400, TE 4.41, FA 8°) for both the upper- and the lower leg.

Dixon images were reconstructed with the fat signal modeled as a single peak and using the multipeak method described by Yu et. al. with frequencies $f_p = [94, -318, -420]$ Hz, amplitudes $A_p = [0.08, 0.15, 0.78]$. Regions of interest (ROIs) were manually drawn in eleven muscles in the upper leg and seven muscles in the lower leg, the subcutaneous fat and bone marrow using MIPAV⁹ on the co-registered T1 images, resulting in 220 datapoints (fig.1.). Fat fraction was obtained as $SI_{fat} / (SI_{fat} + cSI_{water})$, where the factor c corrects for the differences in both proton density and T2 values of fat and water¹⁰. The fat fraction per muscle was calculated using the mean of ten slices in the lower- and twelve slices in the upper leg.

Results:

The fat fraction in muscle in healthy controls ranged from 4.5% to 11% using multipeak fitting and 1.9% to 7.3% using single peak fitting. In patients values ranged from 4.9% to 89% using multipeak and 2.8% to 86% using single peak fitting. In both patients and controls the single peak model consistently showed a lower fat fraction than the multipeak model (fig.2.). The difference was most apparent in the range of 30% to 50% fat, where differences up to 20% were present. In tissue with either low or high fat fractions, the differences were smaller. A Runs test showed a significant deviation from linearity with $p < 0.0001$.

Conclusions:

Our study shows that multiple peak fitting of Dixon chemical shift based water-fat separation is feasible in patients with DMD and results in a considerable increase of the estimated fat fraction in muscles of these patients. Even though the 'true' fat fraction in the muscles is unknown, results from phantom studies suggest that multipeak fitting is more consistent with the actual fat fraction⁸. The main contributions to this difference are assignment of part of the fat signal to the water component, in particular the olefinic fat protons, as well as internal dephasing of fat signal components as a function of TE. Although the latter effect has been countered by fitting a T2* term to fat for single peak methods, it is readily included in the multipeak analysis.

Differences in fat fractions compared to single peak fitting were most pronounced in the mid-range of fat fractions. Especially in this mid-range accurate assessment of the fat fraction is important, as a cut-off value of at least 50% muscle tissue has been used for inclusion in clinical trials based on visual assessment of T1-weighted images¹. Quantitative assessments, such as chemical-shift based water-fat separation could be of potential use for patient inclusion and follow-up in clinical trials, where implementing the multipeak fitting method could prevent inclusion of less responsive patients.

References: [1] Van Deutekom et al. *N Engl J Med*, 357(26), 2677-2686 (2007) [2] Kinali et al. *Lancet Neurology* 8, 918-928 (2009) [3] Liu et al, 186 475-480 (1993) [4] Dixon WT *Radiology* 153, 189-194 (1984) [5] Wren et al *AJR J Roentgenol.*, 190, W8-W12 (2008) [6] Brix et al., *Magn. Reson Imaging* 11 997-91 (1993) [7] Yu et al. *Magn. Reson. Med.*, 60, 1122-1134 (2008) [8] Hernando et al. *MRM* 64 1122-1134 (2010) [9] <http://mipav.cit.nih.gov> [10] Reeder SB, et al. *Proc. Intl. Soc. Mag. Reson. Med.* 17, 211 (2009)

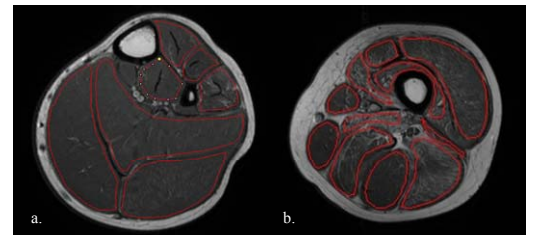


Fig.1. Image of lower leg (a) and upper leg (b) with ROIs of the analyzed muscles

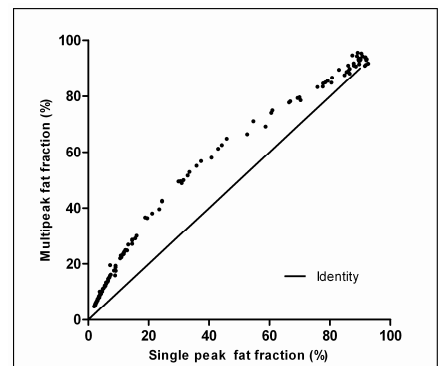


Fig.2. Fat fraction (%) obtained with single peak versus multipeak fitting. Differences are especially apparent in the midrange of fat fractions