Diffusion-Weighted,Triple-Fat-Suppressed Echo-Planar Imaging Provides 'Anomalous' Diffusion Metrics for Assessment of Muscle Quality in the Human Thigh

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TARGET AUDIENCE: Clinicians who are interested in novel measures of muscle quality and scientists who specialise in magnetic resonance parameter estimation.

PURPOSE: Diffusion-weighted imaging (DWI) has been used extensively to non-invasively probe the ultrastructure of human tissues. Previous studies have assumed monoexponential diffusion signal decay as a function of *b*-value; however, given the complexity of biologic tissue, multi-component diffusion may represent a more intuitive model, as has been seen in T2 decay of muscle[1]. Alternatively, non-Gaussian diffusion propagators, representing so-called 'anomalous' diffusion models, may better reflect the complex architecture of skeletal muscle than conventional Gaussian models. While multiexponential models describe multiple diffusion components, kurtosis and stretched exponential models permit description of a continuum of diffusion coefficients that reflect complex microstructure. **In the present study,** three alternative diffusion models are investigated in the human thigh, along with a conventional monoexponential model: 1) intravoxel incoherent motion (IVIM), an intrinsically biexponential model; 2) diffusional kurtosis; and 3) the stretched exponential. Since characterising these complex models is highly dependent upon the accuracy of observed data, adequate fat suppression is required. Accordingly, we implemented a triple-fat-suppressed spin echo echo-planar imaging (EPI) sequence, developed in-house.

METHODS: Imaging was conducted in 8 volunteers (median age=40, range=27-62 years) using a Philips Achieva 3.0T X-series system (Philips Healthcare, Best, NL) with a 32-channel cardiac coil for signal reception. Participants were positioned feet-first with a 10 cm bolster under their knees to align the legs parallel to the bore; they were then shifted laterally to place the left thigh as close to the isocentre as possible. After localisers, the entire left thigh was shimmed to second order, and a modified Dixon sequence was applied to visualise muscle and fat. Axial DWI acquisitions were performed using spin echo single-shot echo-planar imaging (EPI), with a trio of water-specific excitation, spectral attenuated inversion recovery (SPAIR), and slice-select gradient-reversal[2] for fat-suppression. The imaging plane was taken through the thickest part of the thigh, and water-fat shift was minimised by acquiring only a single slice. Parameters included: repetition time(TR)/echo time(TE) = 3000/71 ms, field-of-view = 270×270 mm, slice thickness = 22 mm, in-plane resolution = 2.7×2.7 mm, 8 averages, partial Fourier factor = 0.6 in ky, sensitivity encoding factor = 2, 1-4-6-4-1 composite excitation pulse, SPAIR delay = 220 ms. Diffusion gradients were applied in the slice-select direction in all 8 volunteers, and in the readout direction in 4 volunteers, with 16 logarithmically-spaced *b*-values (0, **10, 18, 33, 60, 110, 276**, 381, 525, 725, 1000, 1380, 1904, 2627, 3624, and 5000 s/mm^2; δ=27 ms and Δ=35 ms). DW images were analysed in MATLAB (MathWorks, Natick, USA), where they were registered to the Dixon anatomical scans, a composite water-fat image was used to mask residual olefinic fat, and the resulting masked DWI series was fit pixel-by-pixel with a trust-region-reflective least squares algorithm. Each of the models, other than IVIM, was fit after excluding short *b*-values (shown in bold, above). Explicitly, the four models fitted to the data were:

- **Monoexponential:** given by $S = S_0 exp(-bD) + n$, where S is the signal, S_0 is the signal at $b = 0$, D is the diffusion coefficient, and n is the fitted noise floor.
- **IVIM:** given by $S = S_0\left(\left(f_p exp(-bD^*)\right) + \left(1 - f_p\right)exp(-bD)\right) + n$, where f_p is the perfusion fraction and $D^*$is the perfusion coefficient. Diffusion and perfusion components were separated using a previously described multi-step approach[3].
- **Kurtosis:** given by $S = S_0 exp(-bD + b^2D^2K/6) + n$, where K is the excess kurtosis.
- **Stretched exponential:** given by $S = S_0 exp(-(bD)^\alpha) + n$, where α is the stretching parameter.

Maps were generated for diffusion/perfusion coefficients, f_p, K, α, root-mean-square error (RMSE), and the fitted noise floor. Regions of interest were drawn in the medial thigh muscles, and means and standard deviations were calculated. RMSE values were adjusted for the number of degrees of freedom in order to compare the different diffusion models.

RESULTS/DISCUSSION: Table 1 summarises the results; Figure 1 shows selected maps, and a water/fat reference image. Fat suppression was robust, eliminating aliphatic fat and leaving only low intensity, minimally-shifted olefinic fat. Diffusion coefficients were similar for all four models, and in the slice direction $K \approx 0$ and $\alpha \approx 1$, indicating Gaussian diffusion; however, in the read direction K and α showed non-Gaussian behaviour—the respective Gaussian propagator values of 0 and 1 being outside the 95% confidence intervals of the mean. This implies a more complex diffusion environment perpendicular to the muscle fibres as compared to parallel to the fibres. The stretched exponential also gave the best fit to the data, with a substantially smaller RMSE than the other models. Moreover, some inter-participant variation was seen for diffusion parameters and for stretching/kurtosis, meriting investigation in a larger sample.

CONCLUSION: Triple-fat-suppressed DWI determines diffusion parameters with minimal fat contamination, making it ideal for assessing anomalous diffusion models. Such models better represent the underlying signal decay as compared to Gaussian models, offering potential muscle quality metrics that can be applied to future studies on ageing and muscle function.

REFERENCES: [1] Saab G et al. (1999). *Magn. Reson. Med.* 42(1):150-7; [2] Park HW et al. (1987). *Magn. Reson. Med.* 4(6):526-36; [3] Luciani A et al. (2008). *Radiology* 249(3):891-9.

Diffusion Model	Diff. Coeff. (×10^3 mm^2/s)	Fraction/*K*/*α*	RMSE	
Monoexponential	2.1 [0.2]	—	1430 [681]	SLICE
IVIM (perfusion)	57.3 [10.3]	f_p = 10.6 [4.8]%	1658 [911]	SLICE
Kurtosis	2.2 [0.1]	K = 0.11 [0.07]	1270 [557]	SLICE
Stretched Exponential	2.2 [0.2]	α = 0.95 [0.04]	1077 [412]	SLICE
Monoexponential	1.6 [0.1]	—	2634 [960]	READ
IVIM (perfusion)	54.1 [14.7]	f_p = 9.7 [4.3]%	1996 [862]	READ
Kurtosis	1.6 [0.2]	K = 0.29 [0.03]	2037 [825]	READ
Stretched Exponential	1.6 [0.2]	α = 0.90 [0.03]	1357 [455]	READ

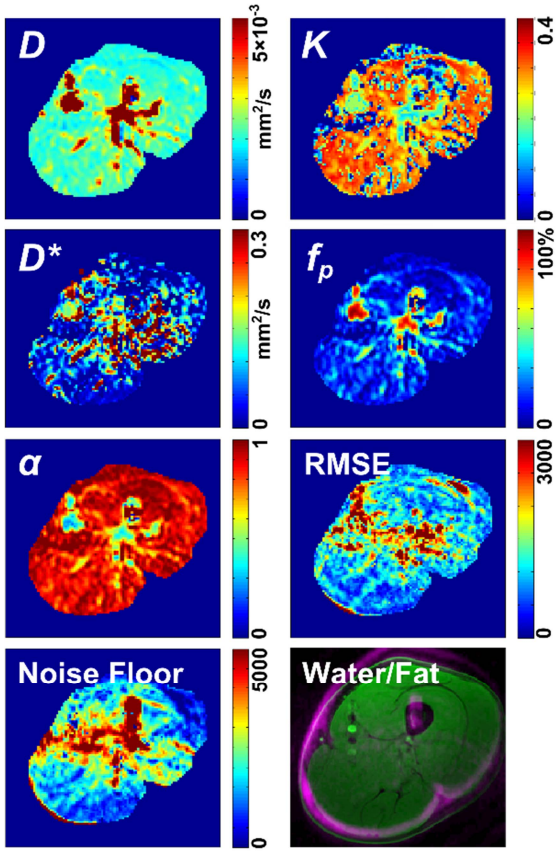

Figure 1. *Selected parameter maps and a water/fat ref. image, axial orientation (D/D* = diffusion/perfusion coeff, α = stretching parameter, K = excess kurtosis, RMSE = root-mean-square error). Maps are acquired with diffusion gradients played in the slice direction.*