PhD Thesis Title: Fat unsaturation quantification, including ω-3 measures, with *in-vivo* magnetic resonance spectroscopy

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ABSTRACT:

Fat composition is relevant to disease and can be assessed non-invasively using Magnetic Resonance Spectroscopy (MRS). MRS studies do not usually account for the ω-3 (omega-3) fat content because of its low prevalence in human adipose tissue (≈ 1 %) and because the ω-3 (≈ 1.0 ppm) and non-ω-3 (≈ 0.9 ppm) methyl proton signals overlap at field strengths even as high as 9.4 T (Tesla). However, ω-3 fat content is altered in disease; therefore, there is motivation to quantify it non-invasively. Fat unsaturation can be estimated with MRS *in vivo* using the olefinic resonance (≈ 5.4 ppm). The thesis objectives are to enable relative ω-3 fat quantification at 9.4 T and 3 T and to enhance aspects of relative fat unsaturation assessment at 3 T.

High field strengths, including 9.4 T, have been used to investigate animal fat composition. When employing the standard short TE (echo time) *in-vivo* MRS pulse sequences, the ω-3 and non-ω-3 methyl resonances overlap at 9.4 T, rendering relative ω-3 fat quantification challenging. The presented research uses product operator formalism to establish a PRESS (Point RESolved Spectroscopy) TE of 109 ms that separately quantifies the two methyl resonances at 9.4 T (the TE minimized signal from the side peaks of the methyl triplets). The optimized method measured the relative differences in the ω-3 fat content in the abdominal tissue of mice fed varying amounts of ω-3 fat. A coefficient of determination (R^2) of 0.96 was calculated when assessing the MRS results against the content measured with gas chromatography of the excised mouse tissue.

Relative ω-3 fat quantification was also investigated at the clinical field strength of 3 T. The more weakly-coupled ω-3 methyl triplet includes side peaks that vary sinusoidally with TE. The response of the methyl resonances as a function of PRESS and STEAM (STimulated Echo Acquisition Mode, TM (mixing time) of 20 ms) TE was investigated. It was found that a TE of 160 ms with both sequences yields ω-3 methyl side peaks that are positive in-phase and broaden the collective methyl linewidth, correlating methyl linewidth to the relative ω-3 fat content in the oil phantoms. The optimized methods yielded R^2 values ≥ 0.9 when compared to the expected oil compositions obtained using 16.5 T high field NMR.

In addition, using MRS to quantify relative levels of fat unsaturation at 3 T *in vivo* was explored. PRESS (TE = 180 ms) and STEAM (TE = 120 ms, TM = 20 ms) yielded olefinic to methyl ratios that differed by 0.2 % and -1.8 %, respectively, from literature-obtained values for tibial bone marrow. The optimal timings depend on combined effects from J-coupling evolution and T_2 relaxation. Apparent (including J-coupling effects) T_2 relaxation times in several subjects were investigated in tibial bone marrow, subcutaneous and breast adipose tissue, to assess if the determined TE values in tibial bone marrow can be used to compare fat unsaturation measurements in the anatomical regions without applying correction factors for T_2 relaxation. Olefinic proton T_2 relaxation times were significantly higher in tibial bone marrow than in breast adipose. Fat unsaturation measures in the three tissues were also measured using olefinic to methylene (1.3 ppm) ratios. Fat unsaturation measures in the breast have not been explored extensively. This thesis examined the use of an inversion recovery pulse prior to a PRESS sequence (delay = 613 ms, TE = 40 ms) for minimizing water

contamination of the olefinic resonance when using a short TE. The technique yielded 5.9 times higher olefinic signal to noise ratio compared to using the previously determined long-TE of 200 ms, which relies on water T_2 relaxation to resolve the olefinic resonance.

Often, the glycerol CH (≈ 5.2 ppm) resonance contribution to that of the olefinic is ignored. This research estimates glycerol contaminations of ≈ 13 % for PRESS with a TE of 40 ms and ≈ 20 % for STEAM with a TE of 20 ms (TM = 20 ms) at 3 T. Furthermore, the response of the glycerol proton to PRESS and STEAM TE was studied to determine that PRESS with a TE of 200 ms and STEAM with a TE of 90 ms (TM = 20ms) minimizes the glycerol resonance area. The technique efficacies were verified on tibial bone marrow *in vivo.*

References to author publications that relate specifically to the dissertation:

Manuscripts

1. **Fallone, C.J.**, Tessier, A.G. and Yahya, A. (2022). Fat unsaturation measures in tibial, subcutaneous and breast adipose tissue using short and long TE MRS at 3 T. Magn Reson Imaging 86: 61-69. DOI: 10.1016/j.mri.2021.11.007

2. **Fallone, C.J.,** Tessier, A.G., Field, C.J. and Yahya, A. (2021). Resolving the omega-3 methyl resonance with long echo time magnetic resonance spectroscopy in mouse adipose tissue at 9.4 T. NMR Biomed 34: e4455 (11 pages). DOI: 10.1002/nbm.4455

3. **Fallone, C.J.** and Yahya, A. (2019). Effect of triglyceride glycerol CH signal on olefinic resonance quantification with proton magnetic resonance spectroscopy at 3 T. Biomed Phys & Eng Express 5: 027004 (10 pages). DOI:10.1088/2057-1976/ab05ab

4. **Fallone, C.J**., McKay, R.T. and Yahya, A. (2018). Long TE STEAM and PRESS for estimating fat olefinic/methyl ratios and relative ω-3 fat content at 3 T. J Magn Reson Imaging 48: 169-177. https://doi.org/10.1002/jmri.25920

Conference Abstracts

1. **Fallone, C.J.** and Yahya, A. (in press). Inversion recovery for resolving the olefinic resonance in spinal bone marrow at 3 T. In proceedings of the International Society for Magnetic Resonance in Medicine (ISMRM) Annual Meeting & Exhibition, number 1446.
2. **Fallone, C.J.**, Tessier, A.G., Field, C.J. and Yahya, A. Comparing omega-3 content in adipose tissue of mice and rats fed a high omega-3 diet with MRS at 9.4 T. (2021) In proceedings of the ISMRM Annual Meeting & Exhibition, number 3851.
3. **Fallone, C.J.** Yahya, A. Investigating using water inversion recovery (IR) to resolve the olefinic resonance from water in breast *in vivo* with magnetic resonance spectroscopy at 3 T. (2020). Med Phys 47:BReP-SNAP-I-29, e396. American Association of Physicists in Medicine (AAPM) 62nd Annual Scientific Meeting.
4. **Fallone, C.J.,** Tessier, A.G., Field, C.J. and Yahya, A. Apparent transverse relaxation times of omega-3 and non-omega-3 fat methyl protons in mouse adipose tissue at 9.4 T. (2020). Med Phys 47: PO-GeP-I-34, e515. AAPM 62nd Annual Scientific Meeting.
5. **Fallone, C.J.,** Tessier, A.G., Field, C.J. and Yahya, A. Optimized PRESS echo time for quantifying relative ω-3 fat content at 9.4 T *in vivo*. (2020). In proceedings of ISMRM 28th Annual Scientific Meeting & Exhibition, number 2872.
6. **Fallone, C.J.** and Yahya, A. Determining relative T_2 relaxation rates of breast and tibial bone marrow fat tissue with magnetic resonance spectroscopy at 3 T. (2019). Med Phys 46:TU-E-221AB-07, e348. AAPM 61st Annual Scientific Meeting.

7. **Fallone, C.J**. and Yahya, A. Assessing the glycerol proton contamination on fat unsaturation quantification using magnetic resonance spectroscopy at 3 T. (2018). Med Phys 45:SU-L-205-01, e384. AAPM 60th Annual Scientific Meeting.
8. **Fallone, C.J.** and Yahya, A. Improving *in vivo* fat quantification using magnetic resonance spectroscopy. (2017). Med Phys 44:4398. Canadian Organization of Medical Physicists (COMP) 63rd Annual Scientific Meeting.
9. **Fallone, C.J.** and Yahya, A. Improving *in-vivo* fat unsaturation quantification using olefinic to methyl ratios obtained with magnetic resonance spectroscopy. (2017). MAGMA 30: S482-S483. European Society for Magnetic Resonance in Medicine and Biology (ESMRMB) 34th Annual Scientific Meeting.
10. **Fallone, C.J.** and Yahya, A. Quantification of relative ω-3 fatty acid levels with localized magnetic resonance spectroscopy at 3 T. (2017). MAGMA 30: S481-S482. ESMRMB 34th Annual Scientific Meeting.