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Fat spectral modeling on triglyceride composition quantification using chemical shift encoded magnetic resonance imaging

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ABSTRACT

Purpose: To explore, at a high field strength of 7T, the performance of various fat spectral models on the quantification of triglyceride composition and proton density fat fraction (*PDFF*) using chemical-shift encoded MRI (CSE-MRI).

Methods: MR data was acquired from CSE-MRI experiments for various fatty materials, including oil and butter samples and in vivo brown and white adipose mouse tissues. Triglyceride composition and *PDFF* were estimated using various a priori 6- or 9-peak fat spectral models. To serve as references, NMR spectroscopy experiments were conducted to obtain material specific fat spectral models and triglyceride composition estimates for the same fatty materials. Results obtained using the spectroscopy derived material specific models were compared to results obtained using various published fat spectral models.

Results: Using a 6-peak fat spectral model to quantify triglyceride composition may lead to large biases at high field strengths. When using a 9-peak model, triglyceride composition estimations vary greatly depending on the relative amplitudes of the chosen a priori spectral model, while *PDFF* estimations show small variations across spectral models. Material specific spectroscopy derived spectral models produce estimations that better correlate with NMR spectroscopy estimations in comparison to those obtained using non-material specific models.

Conclusion: At a high field strength of 7T, a material specific 9-peak fat spectral model, opposed to a widely accepted or generic human liver model, is necessary to accurately quantify triglyceride composition when using CSE-MRI estimation methods that assume the spectral model to be known as a priori information. CSE-MRI allows for the quantification of the spatial distribution of triglyceride composition for certain in vivo applications. Additionally, *PDFF* quantification is shown to be independent of the chosen a priori spectral model, which agrees with previously reported results obtained at lower field strengths (e.g. 3T).

1. Introduction

Chemical-shift encoded magnetic resonance imaging (CSE-MRI) water-fat separation has recently emerged as a useful method for the quantification of triglyceride composition in fatty tissues. In comparison to magnetic resonance spectroscopy (MRS), which only allows for the quantification of the average triglyceride composition in a localized volume of interest, CSE-MRI water-fat separation techniques allow for the quantification of triglyceride composition over an entire volume of interest with high spatial resolution [1–6]. Water-fat separation techniques, in general, have also been shown to produce results that are comparable to those obtained using spectroscopy methods [3, 7–14]. The ability to non-invasively quantify the spatial distribution of triglyceride composition may provide valuable clinical information about the development of obesity related diseases and assist in the evaluation of obesity related treatments through the monitoring of brown adipose tissue (BAT) activation and white adipose tissue (WAT) beiging, which have been shown to change triglyceride composition [15–18] and occur heterogeneously throughout the tissue [19–22].

CSE-MRI water-fat separation techniques have primarily been used to only separate the water and fat components of the MR signal to quantify proton density fat fraction (*PDFF*) [23–32] and has focused

Abbreviations: CSE-MRI, Chemical shift encoded magnetic resonance imaging; *PDFF*, Proton density fat fraction; *ndb*, Number of double bonds per molecule; *nmidb*, Number of methylene-interrupted double bonds per molecule; *cl*, Fatty acid chain length; BAT, Brown adipose tissue; WAT, White adipose tissue; iBAT, Intercapsular brown adipose tissue; iWAT, Intercapsular white adipose tissue; igWAT, Inguinal white adipose tissue

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Table 1
Theoretical 9 fat peak model [41, 42].

Water-fat chemical shifts (ppm)	Theoretical peak amplitudes (Number of protons)
0.59	2*ndb
0.49	1
−0.50	4
−1.95	2*nmidb
−2.46	6
−2.68	4*(ndb-nmidb)
−3.10	6
−3.40	6*(cl-4)-8*ndb + 2*nmidb
−3.80	9

A theoretical 9 fat peak model with theoretical amplitudes of each fat resonance peak given in terms of the number of double bonds per molecule (*ndb*), the number of methylene-interrupted double bonds per molecule (*nmidb*), and the fatty acid chain length (*cl*) [41, 42]. The 6-peak model combines the peaks located at 0.49 and 0.59 ppm, −2.46 and −2.68 ppm, and −3.10 and −3.40 ppm into common peaks located at 0.60, −2.60, and −3.40 ppm, respectively.

mostly on the study of nonalcoholic fatty liver disease and hepatic steatosis [9, 10, 12, 13, 33], as well as liver iron quantification [34–40]. These methods generally assume the liver fat spectral model (chemical shifts and relative amplitudes of the fat resonance peaks) to be known a priori, and therefore, the triglyceride composition is also assumed to be known a priori. The triglyceride composition determines the relative amplitudes of the fat peaks in the spectral model based upon three parameters: 1) the number of double bonds per molecule (*ndb*), which is associated with monounsaturated fatty acid composition, 2) the number of methylene-interrupted double bonds per molecule (*nmidb*), which is associated with polyunsaturated fatty acid composition, and 3) the fatty acid chain length (*cl*) [41, 42] (Table 1).

Hamilton et al. [41–43] has shown using MRS that the triglyceride compositions of brown, white, surface and deep subcutaneous, and visceral adipose tissue differ from that of liver tissue, and significant variations in triglyceride composition were observed across subjects [43]. Additionally, Leporq et al. [5, 6] has shown the presence of spatial variability in triglyceride composition within human liver tissue and murine visceral adipose tissue. This raises questions as to whether or not previously published fat spectral models can provide accurate results when used across various biological tissues, and even if using a tissue specific model, how natural spatial variability within the tissue and variability across subjects, as well as dynamic processes, such as BAT activation and WAT beiging, can affect triglyceride composition estimations.

In modeling the CSE-MR signal for adipose tissues, many different multi-fat peak models have been proposed [14, 30, 41, 42, 44, 45]. NMR spectroscopy performed at higher magnetic fields (e.g. 7T) has shown that the fat spectrum of adipose tissue may consist of as many as 10 different resonance peaks [45], with the chemical shifts being relatively fixed for all types of fatty tissues and materials, while the relative amplitudes of the peaks vary from sample to sample (Fig. 1) based on triglyceride composition (Table 1). Despite availability of this 10-peak model, many studies have used fat spectral models containing less than 10 peaks to minimize errors arising from nonuniform excitation profiles and difficulties differentiating nearby fat resonance peaks due to spectral profile broadening at lower field strengths (e.g. 1.5 T and 3 T) [44, 45]. The two most commonly used fat spectral models are a 6-peak model and a 9-peak model [42], which are provided in the ISMRM fat-water toolbox (https://www.ismrm.org/workshops/FatWater12/data.htm). The relative amplitudes provided in this toolbox are specific to human liver tissue, and these models have become widely accepted and are often used generically for other types of fatty tissues.

Recent works have made comparisons between the performances of different fat spectral models when estimating *PDFF* and the effective transverse relaxation rate (R_2^*) using CSE-MRI. Wang et al. [14] has shown that when evaluating *PDFF* in the human liver at 3T using various published fat spectral models containing a range of 3 to 9 peaks, no particular model proved to be superior, and all models produced results that correlated well with MRS-*PDFF*. Using a 6-peak model with fixed chemical shifts, Hong et al. [46] evaluated the variability in the estimations of both *PDFF* and R_2^* in the human liver at 3T using 60 variant relative amplitude models. Increasing variations in the estimates of *PDFF* and R_2^* were reported with increasing *PDFF* and R_2^*; however, these variations weren't considered to be significant. These studies were both performed at low field strengths (e.g. 3T) and have focused on obtaining estimations solely within the human liver, which typically has a *PDFF* of less than 40%.

The aim of this paper is to further explore, for materials with higher *PDFF*s and at a high field strength (e.g. 7T), the effect and performance of using different 6- and 9-peak fat spectral models when estimating triglyceride composition (*ndb*, *nmidb*, and *cl*) and *PDFF* with a specific focus on differences in the relative amplitudes of the fat peaks. MRI and NMR spectroscopy experiments were conducted using oil and butter samples and an in vivo mouse model to evaluate the importance of using a material specific fat spectral model and to evaluate the variability in the estimations of triglyceride composition and *PDFF* obtained using various fat spectral models.

2. Material and methods

2.1. NMR spectroscopy experiments

Three samples (corn oil, olive oil, and butter) were obtained from local grocery stores and prepared with a chloroform solvent (CDCl3). Then standard proton (^{1}H) NMR spectroscopy (rectangular excitation pulse followed by immediate acquisition) was performed on each sample using a 300 MHz Mercury Spectrometer (Varian Medical Systems, Palo Alto, CA) (flip angle $FA = 45^\circ$, repetition time TR = 2.7 s, spectral width $sw = 4800$ Hz, pulse width $pw = 4.75$ μs, and 8 acquisitions for averaging).

The intercapsular brown adipose tissues (iBAT) from three 2-month-old C57/BL6 mice ($n = 3$) were surgically removed and prepared using a standard NMR procedure [47]. Standard water suppressed ^{1}H NMR spectroscopy was then performed on each sample using a 600 MHz Varian Inova Spectrometer ($FA = 90^\circ$, TR = 2 s, $sw = 6600$ Hz, $pw = 6.3$ μs, and 16 acquisitions for averaging).

Assuming a 9-peak spectral model (Table 1) [41, 42], the relative amplitudes of the fat peaks for all acquired spectra were determined by performing multiplet analysis using MNOVA (Mestrelab Research, S.L., Santiago de Compostela, Spain). Estimates of *ndb, nmidb,* and *cl* were obtained from the relative amplitudes using the mldivide algorithm provided by Matlab (Mathworks Inc., Natick, MA) to solve the linear system of equations associated with the theoretical peak amplitudes given in Table 1 [41, 42]. For the iBAT tissues, the average relative amplitudes of the three mice were used in estimating *ndb, nmidb,* and *cl*.

2.2. MRI experiments

For phantom experiments, three small 5-ml vials (one filled with each oil or butter sample) were placed into a larger cylindrical tube (28 mm in diameter, 114 mm in length) filled with water. Then using a 7 T Varian Magnex MRI Scanner, the tube containing the three samples was scanned with a 38 mm volume coil and a 2D multi-echo gradient-echo sequence with a unipolar readout gradient (TR = 200 ms, $FA = 20^\circ$, initial echo time $TE_i = 1.7$ ms, echo spacing $\Delta TE = 0.7$ ms, 12 echoes, matrix size of 64 × 64, field of view $FOV = 35 \times 35$ mm, slice thickness $thk = 1$ mm, and 6 acquisitions for averaging).

In vivo experiments were also performed to scan the iBAT and inguinal white adipose tissue (igWAT) of two two-month old C57/BL6