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Quantification of Liver Proton-Density Fat Fraction in an 7.1 Tesla preclinical MR Systems: Impact of the Fitting Technique

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Abstract

Purpose—To investigate the feasibility of estimating the proton-density fat fraction (PDFF) using a 7.1 Tesla magnetic resonance imaging (MRI) system and to compare the accuracy of liver fat quantification using different fitting approaches.

Materials and Methods—Fourteen leptin-deficient *ob/ob* mice and eight intact controls were examined in a 7.1 Tesla animal scanner using a 3-dimensional six-echo chemical shift-encoded pulse sequence. Confounder-corrected PDFF was calculated using magnitude (magnitude data alone) and combined fitting (complex and magnitude data). Differences between fitting techniques were compared using Bland-Altman analysis. In addition, PDFFs derived with both reconstructions were correlated with histopathological fat content and triglyceride mass fraction using linear regression analysis.

Results—The PDFFs determined with use of both reconstructions correlated very strongly ($r=0.91$). However, small mean bias between reconstructions demonstrated divergent results (3.9%; CI 2.7%-5.1%). For both reconstructions, there was linear correlation with histopathology (combined fitting: $r=0.61$; magnitude fitting: $r=0.64$) and triglyceride content (combined fitting: $r=0.79$; magnitude fitting: $r=0.70$).

Conclusion—Liver fat quantification using the PDFF derived from MRI performed at 7.1 Tesla is feasible. PDFF has strong correlations with histopathologically determined fat and with triglyceride content. However, small differences between PDFF reconstruction techniques may impair the robustness and reliability of the biomarker at 7.1 Tesla.

Keywords

Chemical Shift Imaging; Liver Fat; Proton-Density Fat Fraction; Ultra-High-Field MRI

Introduction

Non-alcoholic fatty liver disease (NAFLD) is a precursor of the metabolic syndrome (1). Clinical and preclinical research focuses on elucidating the causal relationship and interaction of diseases related to the metabolic syndrome such as cardiovascular disease or diabetes, which are common in the western world (2-6). Radiological cross-sectional imaging is a useful tool in studying disease manifestations of the metabolic syndrome. Specifically, techniques for quantification of liver fat such as magnetic resonance imaging (MRI) can provide useful information (7-10).

Conventional chemical shift-encoded MRI using in-phase/out-of-phase imaging is a simple method for quantifying liver fat in the clinical setting. However, chemical shift-based liver fat quantification is confounded by several physical factors such as T1 bias (11), T2* decay (12), multispectral complexity of fat (13), eddy currents, and image noise (11). If these confounders are addressed, the calculated fat fraction is defined as proton-density fat fraction (PDFF) (14). PDFF determination has evolved into an accepted clinical approach for accurate quantification of liver fat using conventional MRI systems with a field strength of up to 3.0 Tesla (14).

Calculation of PDFF requires postprocessing of the acquired MR images by fitting a fat-water signal model to the acquired data, including correction for relevant confounding factors (e.g., B0 inhomogeneity, multi-peak fat spectrum, and R2* decay). Three main approaches are available for fitting the signal model to the data: complex fitting (where the phase of the data is used in the fitting), magnitude fitting (where the phase of the data is discarded), and a combination of both known as combined/hybrid technique. Complex fitting algorithms for PDFF calculation can quantify liver fat over the entire range of fat fractions from 0-100% with optimized noise performance (because all acquired data are used in the estimation). However, complex fitting techniques are sensitive to phase errors in the data (e.g., from eddy currents). This may be particularly problematic for MRI systems with high field strength, which often require high amplitude gradients with fast slew rates, and where chemical shift encoded imaging is typically performed using multiple interleaved echo trains (15). In contrast, magnitude-based techniques are insensitive to phase errors in the data (because the phase is discarded), but have poorer noise performance (15). As a result, magnitude-based techniques may yield falsely negative fat fraction values, especially in subjects with low liver fat content. In addition, magnitude fitting is generally limited to quantification of tissue fat in a range from 0% to 50% (16). Recent studies have demonstrated the advantage of techniques combining magnitude and complex fitting in one algorithm (15,16).

The advantages of MRI systems with higher field strengths, currently 7 Tesla and more, offer new options for preclinical and clinical imaging. These include, for example, options arising from the improved signal-to-noise ratio (SNR) compared to low-field scanners. A

better SNR can be used to increase the temporal and spatial resolution of images. In addition, at high field strength, there is an increased chemical shift (ability to separate peaks), which is a major advantage in MR spectroscopy. On the other hand, higher field strength leads to changes in several physical properties and effects such as B0/B1 inhomogeneity, changes in susceptibility (T2*) and increased eddy currents (17). These disadvantages introduce errors (e.g., phase errors) in the acquired signal and affect the performance of chemical shift-encoded water/fat separation, degrading the accuracy of PDFF for liver fat quantification. Therefore, authors recommend avoiding complex fitting alone for reconstruction of PDFF from images acquired at more than 3 Tesla.

Therefore, the purpose of this study was to investigate the feasibility of liver fat quantification at a field strength of 7.1 Tesla and to compare the accuracy of magnitude-based and combined approaches for PDFF quantification using histopathology and triglyceride content as the standard of reference.

Material and Methods

The feasibility of quantification of liver fat in an ultra-high-field MR system was investigated using a leptin-deficient *ob/ob* mouse model. This animal model is known to develop obesity and hepatic steatosis. The animal research authority of Mecklenburg-Vorpommern, Germany approved this study (7221.3-1.1-010/12).

Animals

Fourteen male leptin-deficient mice (*ob/ob* knockout, C57BL/6) with a mean age of 100.3 ± 26.2 days and a mean weight of 55.4 ± 4.4 g underwent MRI of the upper abdominal organs. Eight wild type mice (C57BL/6) with a mean age of 96.9 ± 14.9 days and a mean weight of 29.8 ± 2.6 g served as controls.

The mice were kept in specific pathogen-free (SPF) cages with a maximum of three mice per cage. *ob/ob* mice and controls were fed with a ssniff® diet (ssniff GmbH, Soest, Germany) and water ad libitum. MRI was performed when the mice were approximately 100 days old.

Magnetic Resonance Imaging

MRI was acquired under general anesthesia in prone, head-first position. Inhalation anesthesia was induced using a mixture of isofluran (CP-Pharma, Burgdorf, Germany) and oxygen. During the MRI examination, the isoflurane dosage was adjusted to the respiratory rate, which was kept between 30-40 breaths per minute.

Imaging was performed in a 7.1-Tesla animal MR system (Bruker, Ettlingen, Germany) using a mouse whole-body coil with 8 radiofrequency (RF) coil elements. The gradient field strength was 290mT/m and the slew rate was 1160T/m/s.

The mice were imaged using an ungated chemical shift-encoded three-dimensional six-echo gradient echo sequence with the following parameters: TR: 66ms; TE₁/TE₂/TE₃/TE₄/TE₅/TE₆: 2ms/3.5ms/4.4ms/5.4ms/6.3ms/7.3ms; flip angle: 3°;

bandwidth: $\pm 1950\text{Hz/pixel}$; matrix: 128×128 (interpolated to 256×256); field of view: $42 \times 42\text{mm}$; slices: 16; slice thickness: 1.5mm. Acquisition time was 3min 12sec. Echoes were acquired using one echo train and bipolar readout.

After MRI animals were sacrificed. The liver was extracted and divided into two parts: the right part was used for histopathological analysis and the left part for chemical analysis.

MRI Reconstruction

Confounder-corrected PDFF maps were calculated for each animal using Matlab (version R2014b, Mathworks, Natick, MA, USA). A home-made Matlab script was used to account for known confounders of MRI-based fat quantification including $R2^*$ bias, multispectral complexity of fat and noise bias. The initial pulse sequence was acquired using a relatively long TR of 66ms and a very low flip angle of 3° . Therefore, T1 bias was negligible in these acquisitions.

Signal fitting for PDFF mapping was performed including correction $R2^*$ decay and for multi-peak fat signals using the following signal model:

$$s(TE) = [s_W + s_F \cdot \sum_{p=1}^P a_p e^{i2\pi f_{f,p} TE}] \cdot e^{i\phi} \cdot e^{i2\pi f_B TE} \cdot e^{-R2^* \cdot TE} \quad (1)$$

where s_W and s_F are the water and fat amplitudes, respectively, fat is represented by a six-peak (i.e., $P=6$) fat model with frequency shifts ($f_{f,p}$ in Hz) relative to the water peak (ppm) of -3.80, -3.40, -2.60, -1.94, -0.39, and 0.60 and relative amplitudes (a_p) of 0.087, 0.694, 0.128, 0.004, 0.039, and 0.048, respectively, ϕ is the initial phase, and f_B is the local off-resonance frequency (in Hz) due to B0 inhomogeneities (18,19). Additionally, fitting included correction for $R2^*$ ($=1/T2^*$) decay using a single- $R2^*$ model (common $R2^*$ decay rate of water and fat signals) (12,20,21). Finally, PDFF maps were calculated with correction for noise bias effects using magnitude discrimination (11).

To assess the effects of phase errors on PDFF reconstruction, we generated parametric maps of liver PDFF for two different types of reconstruction: (A) magnitude-based fitting (discarding the signal phase) and (B) combined fitting (correction of water/fat ambiguity using phase imaging after magnitude fitting). Further details of the fitting techniques were as follows:

- A.** Magnitude fitting was performed by directly fitting the acquired signal magnitude (i.e., discarding phase) using a nonlinear least-squares fitting algorithm with signal model the magnitude of Eq. 1. Note that magnitude fitting results in a PDFF dynamic range of approximately 0-50%.
- B.** A combined fitting approach was implemented to obtain PDFF estimates with a full dynamic range of 0-100%. With this approach, fat-water separation was first performed using the acquired complex-echo images (i.e., including magnitude and phase). This step included regularized B0

field map estimation using a graph-cut algorithm with signal model as shown in Eq. 1 to avoid fat-water swaps (22). Subsequently, magnitude fitting was performed (with signal model the magnitude of Eq. 1), initialized with the results of complex fitting. The magnitude fitting served to derive PDFF estimates. Note that hybrid PDFF calculation (15) (where PDFF estimates from complex and magnitude fitting are directly combined using a weighted average to obtain the final PDFF estimate) was not performed here because we expected large PDFF errors in complex fitting as a result of the large phase errors observed.

Image Analysis

Image analysis was performed using Osirix (version 4.6; Pixameo, Bernex, Switzerland). Two observers assessed the PDFF of each liver. Observer 1 had more than 10 years of experience in liver imaging and 6 years of experience in animal imaging. Observer 2 had 1 year of experience. They were blinded to the results of histopathology and chemical analysis. A representative liver slice was selected from the raw dataset (first TE image), and the liver was outlined and completely segmented. A region of interest (ROI) was placed avoiding motion artifacts and large vessels. In addition, the observer evaluated the PDFF maps generated from the chosen slice to identify large local phase shifts. When regions with large phase shifts were identified, another slice was chosen. Using the copy and paste function, the observer transferred the ROI to the PDFF map reconstructed with the combined fitting technique. The PDFFs calculated using the magnitude and the combined fitting techniques for both observers were recorded. In addition, observer 1 assessed the ROI standard deviations for each animal and for both type of reconstructions.

Histopathology and Triglyceride Content

Liver fat content for each mouse was estimated by histopathological analysis using hematoxylin and eosin (HE) staining. One pathologist with more than 10 years of experience in liver pathology estimated liver fat content from 0 to 100% in steps of 5%.

In addition, triglyceride content was determined. Therefore, a hexane/isopropanol mixture (at a 3:2 ratio) was added to the liver tissue, followed by sodium sulfate. After centrifugation and vaporization of hexane, total lipid content of the tissue sample was weighed. To measure the triglyceride content a buffer containing sodium hydrogen phosphate, lubrol, distilled water and hydrochloric acid was added to the samples. A glycerol standard solution and a triolein standard solution served as references. All samples were mixed with lipase, and measurements were performed using an automatic system (Cobas C 311 Analyzer; Roche Diagnostics, Berlin, Germany).

Statistics

Data are reported as mean $\pm$ standard deviation. The data of observer one were defined as reference. In addition, quality control of observer one was performed with a second reading done by observer 2. Bland-Altman analysis was performed to assess differences between observers.

- A.** Bland-Altman analysis was used to identify differences between the two reconstruction techniques (magnitude versus combined fitting). Furthermore, the two approaches were compared using linear regression. Perfect agreement was defined as a slope of 1 and an intercept of 0%. Differences in slope and intercept were evaluated using a t-test. In addition, ROI standard deviation between fitting techniques were compared using a paired t-test.
- B.** PDFF was compared with the standards of reference. Since clinical assessment of liver fat is controversial, histopathological fat content and chemical triglyceride content were used as standards of reference in this study. The PDFFs determined with each reconstruction technique were compared with histopathology and triglyceride content using linear regression analysis. Due to the use of different metrics in PDFF and histopathology we were not able to calculate differences in slope and intercept from linear regression as done for the comparison with triglyceride content. Therefore, triglyceride content measured in mg/g was converted to a mass fraction (%).

Spearman correlation coefficient (r) was calculated and values were interpreted as $r=0-0.19$ indicating "very weak", $0.20-0.39$ "weak", $0.40-0.59$ "moderate", $0.60-0.79$ "strong" and $0.80-1.0$ "very strong" correlation. We used the Spearman r because it is more robust against outliers than the r derived from linear regression.

Results

MRI and postprocessing of both reconstructions as well as histopathological and chemical analysis were successfully performed in all mice. Comparison of the two observers revealed a low mean bias of -1.21% (CI $-6.27\% - 3.85\%$) for PDFF reconstruction using magnitude fitting, respectively 1.49% (CI $-5.69\% - 8.67\%$) for combined fitting.

An example of PDFF reconstructed with the magnitude and combined fitting technique is shown in Figure 1. Subjective image evaluation revealed significantly more artifacts such as local phase swaps in the PDFF maps reconstructed with the combined fitting approach, although a systematic review was not performed. In addition, these artifacts were not considered in quantitative image evaluation.

Direct comparison of both reconstruction techniques revealed very strong correlation of PDFF estimated from the magnitude fitting and from the combined fitting technique with a correlation coefficient of 0.910 ($p < 0.001$) (Figure 2). However, we calculated significant differences in intercept 3.28% ($p = 0.001$) and no statistical difference in slope (1.08 ; $p = 0.265$). PDFF reconstructed with the combined fitting technique yielded higher liver fat content compared with magnitude fitting. Mean bias between both techniques was 3.92% with CI of $2.71\% - 5.12\%$. ROI standard deviation was statistically significant higher for PDFF reconstructed with combined technique (mean $\pm 22.1\%$) compared to magnitude fitting (mean $\pm 18.7\%$); $p = 0.001$.

Correlation with fat content determined by histopathology was strong for both fitting techniques ($r=0.636$; $p=0.002$ for magnitude versus $r=0.607$; $p=0.003$ for combined fitting) (Figure 3). It must be noted that metrics between fat content determined by histopathology and MRI are fundamentally different (14), therefore we expected these two measurements to be strongly correlated but numerically different.

We also found strong correlations between PDFF and triglyceride content (magnitude fitting: $r=0.702$ ($p<0.001$); combined fitting: $r=0.790$ ($p<0.001$)) (Figure 4). Linear regression analysis demonstrated no statistically significant differences between PDFF and triglyceride content (magnitude fitting: intercept of -0.41% , ($p=0.827$); slope of 0.78 , ($p=0.151$), and combined fitting: intercept of 1.36% , ($p=0.433$); slope of 0.99 ($p=0.943$).

Discussion

In this study, we investigated the feasibility of in vivo quantification of liver fat from images acquired with a 7.1 Tesla preclinical MR system for animal imaging and compared two generally accepted types of reconstruction for PDFF (magnitude versus combined fitting technique) (14). We chose the magnitude approach as preferred fitting technique because it is well known that phase images are prone to multiple errors, particular in high-field MR scanners. While PDFF determination is feasible using ultra-high-field MRI, there appears to be a small difference between these two reconstruction techniques, suggesting that at least one fitting technique does not function accurately at 7.1 Tesla. This fact may impair the robustness of PDFF determination.

PDFF has become a clinically accepted method for MRI-based quantification of liver fat from images acquired at field strengths up to 3 Tesla. Recent studies confirm the accuracy, robustness, and especially the reliability of PDFF in quantification of tissue fat (23). In our study, we compared MRI-derived PDFF with histopathologically and chemically analyzed fat content. With both PDFF reconstruction techniques investigated here, we found strong correlations between PDFF and these two gold standards. This correlation at 7.1 Tesla MR imaging is comparable to the correlations between PDFF derived from images acquired with less than 3 Tesla and histopathology as well as triglyceride content found in earlier studies (24-27). These results corroborate that quantification of liver fat using a preclinical 7.1 Tesla MR system is feasible.

However, our study also revealed a small bias in combined fitting compared to magnitude fitting. There was a mean bias of 3.9% with higher absolute values for the PDFF maps derived with combined fitting. This bias may not be acceptable when PDFF is used as a biomarker for estimating liver fat content in a clinical or preclinical setting. Hepatic steatosis is diagnosed when PDFF is greater than 5.1% (26). A mean bias of nearly 4% in MRI-based liver fat quantification therefore may lead to a clinically relevant misinterpretation. Another point is that we occasionally obtained negative PDFF values, especially in mice with a very low PDFF reconstructed with magnitude fitting. Note that pixel-wise negative PDFF values are allowed in the PDFF mapping algorithm in order to avoid noise bias in ROI-based PDFF measures. However, a negative average PDFF over an entire ROI is physically meaningless and likely due to the presence of residual artifacts in the images (15).

The magnitude fitting technique is known to be robust as it discards phase information. Therefore, only fat contents in a range of 0 to 50% can be measured (28). Fitting techniques which include phase information such as complex or hybrid approaches are known to be susceptible to eddy currents and the resulting phase errors (15). Therefore, most investigators using complex fitting techniques apply specific phase correction (15,16,20,28), particularly when MRI is performed at 3T and the technique involves acquisition of multiple echo trains.

The phase errors induced by eddy currents can result in artifacts not only in complex fitting but also when a combined fitting approach is used to derive the PDFF. Additionally, 7 Tesla imaging typically suffers relatively high field inhomogeneities due to susceptibility effects. Both eddy currents and magnetic field inhomogeneities could degrade the assessment of liver fat in ultra-high-field MR systems. Our results suggest that field inhomogeneities and eddy currents become more relevant at 7 Tesla compared to MR systems operating at conventional field strengths of less than 3 Tesla, as reflected by artifacts in the PDFF maps, predominantly when the maps are generated with use of a fitting technique including phase information. We consider these artifacts a potential reason for the overestimation of hepatic fat content when the PDFF is derived from images obtained at 7 Tesla ultra-high field strength using a combined fitting approach.

It should be further investigated whether these differences between fitting techniques in estimating PDFF will also occur at 7 Tesla on MRI scanners for imaging humans. Therefore, further studies should confirm the robustness of PDFF in human high-field systems. Nevertheless, it is important to develop and validate 7-Tesla techniques for tissue fat quantification also for animal scanners.

Our study has several limitations. First, we used two standards of reference. We opted for this approach because it is still debated whether histopathology or chemical analysis such as determination of triglyceride content is the better biomarker to describe the amount of fat present in the liver. In the clinical setting, histopathology is the accepted reference standard. Our data further demonstrate a good correlation between histopathology and triglyceride content ($r=0.775$). In addition, feasibility studies of MRI-based fat quantification mainly use MR spectroscopy as another imaging-based standard of reference, which was not performed in this study.

Further, the resonance frequency of protons is proportional to the magnetic field strength used. At 7 Tesla, the difference in resonance frequencies between water and fat protons is 1040Hz, which means that in-phase and opposed-phase are about 0.5ms apart. With the currently available gradient technology, we were unable to achieve such close echo spacing due to gradient switching limitations. In addition, MRI data were acquired using non-uniformly spaced echoes with bipolar readout. The bipolar approach has many advantages such as improvement of the signal-to-noise ratio and reduction of the echo time increment (a reason why we chose this approach). On the other hand, bipolar readout may also cause phase errors resulting from eddy currents and sequence timing errors (29). However, this study sought to establish whether phase errors (known to introduce bias in complex fitting

PDFF quantification techniques) also result in bias in combined complex-magnitude fitting using 7 Tesla imaging.

Another major concern is that respiratory motion may degrade PDFF determination when images are acquired without scan triggering. All motion will affect the data phase TR-to-TR. Therefore, fitting techniques using phase images acquired without physiological triggering may have serious limitations. Last, we included a small number of mice in this project, and larger studies are needed in order to definitively answer these remaining questions.

In conclusion, quantification of liver fat using PDFF is feasible at 7T, as demonstrated by strong to very strong correlations of PDFFs with histopathology and triglyceride content. However, the discrepancies observed between the two established types of PDFF reconstruction may limit the robustness and reliability of this biomarker. Further development and studies are necessary for a more detailed investigation of the differences in PDFF resulting from the use of different fitting techniques (magnitude versus combined fitting) for determination of liver fat from images acquired with small animal 7.1 Tesla MR systems.

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Figure 1.

Hepatic steatosis of an *ob/ob* mouse confirmed by histopathology (70% fat content). The figure shows PDFF maps derived from images acquired at 7.1 Tesla. The map on the left was reconstructed with the magnitude-based algorithm and the map on the right with combined fitting. The combined fitting-based PDFF map shows phase error artifacts in liver, heart, and soft tissue (gray arrows), resulting in impairment of fat quantification in these regions. These phase swaps might impair fat quantification. In the present study, regions with large phase shifts were excluded from image analysis.

PDFF according to type of reconstruction

Figure 2.

Comparison of magnitude fitting and combined fitting reconstructions for calculation of the PDFF; left: Bland-Altman plot; right: linear regression (gray line = unity line representing identical values in both methods). Agreement between the two fitting techniques is good but not perfect with a mean bias of 3.9%.

Figure 3.

PDFF determined with the two reconstruction techniques in comparison to histopathological estimation of liver fat. There are different metrics between histopathology and PDFF and calibration is required. Calibration is complicated by the disagreement in PDFFs obtained with magnitude fitting and combined fitting.

Figure 4.
PDFF determined with the two reconstruction techniques in comparison to triglyceride content (depicted as mass fraction in %).