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Fat Quantification in the Abdomen

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Abstract

Fatty liver disease is characterized histologically by hepatic steatosis, the abnormal accumulation of lipid in hepatocytes. It is classified into alcoholic fatty liver disease and non-alcoholic fatty liver disease, and is an increasingly important cause of chronic liver disease and cirrhosis. Assessing the severity of hepatic steatosis in these conditions is important for diagnostic and prognostic purposes, as hepatic steatosis is potentially reversible if diagnosed early. The gold standard for assessing hepatic steatosis is liver biopsy, which is limited by sampling error, its invasive nature, and associated morbidity. As such, non-invasive imaging-based methods of assessing hepatic steatosis are needed.

Ultrasound and CT are able to suggest the presence of hepatic steatosis based on imaging features, but are unable to accurately quantify hepatic fat content. Since Dixon's seminal work in 1984, MRI has been used to compute the signal fat fraction from chemical-shift-encoded imaging, commonly implemented as out-of-phase and in-phase imaging. However, signal fat fraction is confounded by several factors that limit its accuracy and reproducibility. Recently, advanced chemical-shift-encoded MRI methods have been developed that address these confounders and are able to measure the proton density fat fraction (PDFF), a standardized, accurate, and reproducible biomarker of fat content. The use of these methods in the liver, as well as in other abdominal organs such as the pancreas, adrenal glands, and adipose tissue will be discussed in this review.

Introduction

MRI has been used historically to detect and qualitatively assess the presence and degree of fat accumulation in the liver as well as the presence of fat in the adrenal glands, other organs, and fat-containing lesions ^{1,2}. Recently, advanced chemical-shift-encoded (CSE) methods have been developed that can quantify the proton density fat fraction (PDFF) in the liver as an accurate and precise biomarker of hepatic steatosis ^{3–7}. This biomarker has been studied extensively in recent years as an objective indicator for the presence and degree of liver fat accumulation, and it is now being used in clinical care and in clinical trials as an eligibility marker and study end point ^{8–10}. Advanced CSE methods are now being applied in investigational studies to assess PDFF in the pancreas but are not yet validated for this purpose ¹¹. Although CSE has been used to identify the presence of fat in the adrenal glands

to characterize adrenal nodules and differentiate lipid-rich adenomas from metastases, PDFF has not been investigated as a quantitative imaging biomarker of adrenal fat yet^{12–15}.

In addition to quantifying fractional fat content in solid organs, MRI has also been used to quantify whole body fat volume^{16–23}. However, most MRI techniques for this purpose have relied on manual segmentation, which is expensive, laborious, and impractical, limiting their use to small cohorts in the research setting^{19,24–26}. Recently, a technique based on 3D Dixon imaging has been proposed to quantify intra-abdominal adipose tissue as well as subcutaneous adipose tissue. The new method enables faster fat quantification and its large-scale feasibility has been demonstrated in the United Kingdom BioBank study^{23,27}.

In this article, we review advanced PDFF quantification methods for the liver and the scientific evidence supporting their use. We also briefly review their applications beyond the liver including quantification of fractional fat content in the pancreas and adrenals, and computation of adipose tissue volumes.

Fat Quantification in the Liver

Signal Fat Fraction Using Fat-Suppressed Techniques

Fat-suppression techniques quantify liver fat by acquiring two images, one with and one without a fat-saturation pulse. Applying chemical fat-saturation pulse sequences decreases the overall signal intensity in the liver by suppressing the signal attributable to fat. The image acquired with fat saturation represents water signal only, whereas that acquired without fat saturation represents the sum of fat and water signals. The fat signal is computed by subtracting signal intensities from the two sets of images, and the signal fat fraction is then calculated as the signal from fat divided by the combined signal from fat and water. This technique has been available since the 1990s, and in one study, was shown to correlate better with histological steatosis grade than conventional dual in-phase (IP) and out-of-phase (OP) imaging for assessing hepatic steatosis^{28,29}. However, since complete suppression of fat signal is not possible (due to B_0 magnetic field inhomogeneity), the water image is invariably contaminated by fat signal, which causes unavoidable errors in fat quantification. Fat-suppressed techniques are thus not suitable for PDFF measurement.

Signal Fat Fraction Using CSE and MRS Techniques

Since 1984, when Thomas Dixon published his seminal paper, the fat signal fraction has been calculated using CSE methods³⁰ by separating the MR signal into its water and fat components. There are two main CSE approaches: the magnitude-based approach which uses only magnitude data without the phase data, and the complex-based approach which uses both magnitude and phase data. The former magnitude-based method acquires images at two or more echo times, ideally where the water peak and the dominant fat peak are nominally IP and OP³¹. The signal fat fraction is the difference between the IP and OP signal intensities divided by double the IP signal intensity. Using the IP and OP data permits computation of the proportion of the dominant signal, however due to fat/water signal dominance ambiguity, the range of measurable signal fat fractions is 0 – 50%. The complex-based approach requires at least three echoes, with optimal separation between echoes of

$2\pi/3$, and the middle echo being centered at $\pi/2 + \pi k$, where k is an integer³². The use of magnitude and phase data together permits unambiguous separation of fat and water signals, allowing measurement of the signal fat fraction over a range of 0–100%. With either approach, the fat signal fraction is the signal from fat divided by the combined signal from fat and water.

In MR spectroscopy (MRS), data are generally acquired from a single anatomical location (referred to as the MRS voxel), and proton signal intensities from fat and water can be measured from the chemical peaks of their proton moieties. The relative contributions from fat and water can be quantified directly from the areas under their corresponding peaks in the acquired spectrum, and the fat fraction calculated.

The fat signal fraction is independent of radiofrequency coil sensitivity and B_0 magnetic field inhomogeneity, and – for MRI approaches – requires only a single breath-hold for entire liver coverage. However, the fat signal fraction can be confounded by a number of factors, including T1-weighting bias, T2 or T2* signal decay, the multi-peak spectral complexity of fat, noise bias, J-coupling effects, and eddy currents^{31,33}. Importantly, for many of these factors, the magnitude of the introduced errors depends on the individual scanner, scanner field strength, acquisition parameters, and biological factors such as iron overload. This means that fat signal fraction measurements are neither accurate nor reproducible. This limits their utility for clinical care and research, and prevents reliable pooling of results in meta-analyses.

Proton Density Fat Fraction Using CSE and MRS techniques

To accurately and reproducibly quantify fat content, advanced CSE MRI and MRS techniques have been developed to measure PDFF by addressing the factors that confound fat signal fraction estimation (Table). Below, we describe how these confounding factors are addressed, how the images are acquired, and how PDFF is calculated.

Accounting for Confounders—T1 bias refers to the phenomenon where increased T1-weighting causes amplification of signal from fat relative to water, because fat has shorter T1 time than water. Since the T1 time of water can be two or three times greater than that of fat, this bias causes PDFF overestimation. T1 bias can be addressed by using a long repetition time (TR) or a low flip angle in spoiled-gradient-echo acquisitions, leading to a proton density weighted acquisition. However, using a low flip angle reduces the signal-to-noise ratio (SNR). T1 bias may also be addressed by optimizing the flip angle (based on the Ernst angle) to maximize SNR and performing a T1-signal correction, which requires an additional acquisition to perform T1 mapping. T1 bias can also affect MRS and is usually minimized by using a long TR and minimum mixing time.

T2* decay causes increasing signal loss with increasing echo times after the initial radiofrequency excitation, leading to incorrect estimation of the water and fat signal amplitudes. T2* signal decay is accelerated by the presence of excess liver iron, which may occur in patients with fatty liver disease. If not corrected for, T2* decay results in fat content underestimation (if the first OP echo time is shorter than the first IP echo time) or overestimation (if the first OP echo time is longer than the first IP echo time). The

magnitude of the error depends on the degree of iron overload as well as other factors, and so is difficult to predict. Advanced techniques address this confounding effect by acquiring at least three adequately spaced echoes and incorporating the time-dependent signal decay into the signal model as $1/T2^* (R2^*)$ ^{33–35}. Inclusion of this parameter reduces SNR but is necessary for accurate PDFF estimation. In most implementations, fat and water are modeled to have the same $T2^*$ values (as opposed to modeling separate $T2^*$ values), which is a reasonable compromise between PDFF accuracy, SNR, and modeling simplicity. In addition, one group found that modeling the $T2^*$ values of fat and water had no significant effect on PDFF values overall, but created noisier PDFF maps ³⁶. For MRS, $T2$ decay needs to be taken into account when modeling observed fat and water signal intensities back to their proton-density-weighted signals. The $T2$ of fat and water can be modeled separately, but all fat peaks are assumed to have the same $T2$ relaxation time.

The concept of calculating the fat signal fraction with OP and IP imaging assumes that water and fat can each be described as a single resonance frequency whose relative signal intensities oscillate at regular periods. While this assumption is true for the water peak, it is not true for the fat peak, since hydrogen protons in the triglyceride molecule resonate at different frequencies depending on their exact positions within the triglyceride molecule; each position is associated with different electron shielding effects. For this reason, the fat spectrum consists of multiple peaks, the signals of which interfere with each other as well as with water. Due to this complex interference pattern, water and fat are never exactly OP and IP and signal fat fraction calculations based on a simplistic OP and IP model are intrinsically incorrect (Figure 1). The errors introduced by the multi-frequency effects of fat can be addressed by using a spectral model that specifies the chemical shifts and relative amplitudes of each fat peak derived from spectroscopic data by Hamilton et al ³⁷. It has been shown that the use of a multi-peak spectral model improves the accuracy of PDFF estimation ^{38–40}. Several slightly different spectral models have been proposed, with no particular model being shown to outperform any other ⁴¹. For MRS, although most of the spectrum can be observed, some portions of fat peak overlap with the water peak and cannot be visualized directly; accurate measurement of these peaks requires spectral modeling based on prior knowledge of the typical human triglyceride structure.

Noise bias results during the recombination of separated water and fat images into a fat-fraction image. It occurs because areas of low signal have only positive noise after the magnitude operation, and is thus most pronounced at low fat fractions. Noise bias can be mitigated by magnitude discrimination and phase-constrained reconstruction ⁴².

Eddy currents generated during rapid switching of magnetic gradients result in inaccurate phase data, which affects complex-based methods. This may be addressed with hybrid approaches, by acquiring additional calibration data, or by calculating and removing concomitant gradient effects ³¹.

In MRS, the hydrogen nuclei which are close to one another in a triglyceride molecule can affect each others' effective magnetic fields. This phenomenon is termed J-coupling and affects fat peaks in a TE-dependent manner, resulting in a biased $T2$ estimation and PDFF estimation when using MRS. This may be minimized by acquiring spectra at relatively short

TEs. J-coupling of fat peaks is not a significant confounder for most CSE MRI techniques that use low flip angle spoiled gradient echo sequences, but it may affect techniques that use fast spin-echo sequences ³¹.

Acquisition, Reconstruction, and Post-processing for CSE Techniques—PDF measurement is based on gradient-echo sequences, with magnitude-based approaches typically based on 2D gradient-echo imaging and complex-based approaches typically based on 3D gradient-echo imaging ³¹. These methods have been validated at both 1.5T and 3T ^{4,5}. A low flip angle and long TR are used to minimize the confounding effects of T1 weighting. Six echoes are typically collected in order to perform signal fitting to estimate T2* decay, although the use of as few as three and as many as sixteen echoes have been described ⁴³. In one study of magnitude-based techniques, accuracy relative to MR spectroscopy decreased with increasing numbers of echoes, presumably due to noise floor effects and/or modeling imperfections ⁴³.

The fat fraction is computed on a per-voxel basis to generate PDF maps (Figure 2).

Comparison of Magnitude-based and Complex-based CSE Techniques—Magnitude-based and complex-based techniques each have their own respective advantages and disadvantages. One advantage of magnitude-based techniques is greater availability, as the acquisition can be reproduced easily using standard available pulse sequences on many commercial MR scanners, though off-line processing may be necessary. Complex-based techniques are now available as commercial product sequences, but generally require purchase as add-ons, which has hampered their clinical adoption.

Since magnitude-based techniques do not use phase data, they are more robust to the confounding effects of eddy currents, which preferentially affect the accuracy of the phase data. In addition, by using a single amplitude value instead of the separate real and imaginary data components, these components are effectively averaged, which increases the signal-to-noise ratio ³³.

Conversely, by discarding phase data, magnitude-based techniques can only achieve a dynamic range of 0 – 50% due to fat-water signal ambiguity (Figure 2). Complex-based techniques can achieve the full dynamic range of 0 – 100% through incorporation of phase data (Figure 2). The assumption that water is the dominant signal is rarely violated in the assessment of hepatic steatosis, even in severe cases, but may not suffice when assessing tissues such as bone marrow or adipose tissue where fat is the dominant signal.

The lack of complete fat-water separation also implies that magnitude-based techniques cannot be used for fat-suppression imaging ⁴⁴. Magnitude images exhibit Rician distributions rather than Gaussian distributions, which creates a so-called “noise floor” ³³. These noise floor effects introduce greater bias in magnitude-based reconstructions, which becomes particularly prominent at lower fat fraction ranges and high T2* signal decay rates (such as in severe iron overload) where the signal-to-noise ratio is low ⁴⁵.

MR Spectroscopy

As with MRI-based quantification techniques, confounding factors must be accounted for in MR spectroscopy to compute PDFF rather than the fat signal fraction.

Two main types of MRS sequence are typically used for PDFF estimation: stimulated echo acquisition mode (STEAM) and point resolved spectroscopy (PRESS). For both, a single voxel (typically $2 \times 2 \times 2 \text{ cm}^3$) is placed in liver parenchyma, using images to avoid liver edges, large vessels, and large bile ducts. Spectra are generally acquired in a single breath-hold with no spatial or chemical saturation, and a long TR ($> 3000 \text{ ms}$) is used to minimize T1 weighting. To correct for T2 decay, signals are either acquired at a single short TE and corrected with predefined water and fat T2 values, or they are acquired at multiple TEs to calculate T2-corrected peak areas of water and fat (Figure 3). STEAM is preferred to PRESS because STEAM is capable of shorter minimum TE than PRESS. The shorter TE of STEAM also minimizes the confounding effects of J-coupling.

The fat signal fraction can be computed from the relative areas under the peaks corresponding to fat and water. Two of the fat peaks cannot be easily distinguished from the water peak, and their contribution to the water peak is corrected using a previously derived liver spectrum. Due to its high sensitivity and accuracy, MRS has been used as a reference standard for a number of studies which have validated the accuracy of MRI-based PDFF ^{4,5,36,39,46–50}. In some cases, MRS has been used for direct PDFF measurement as a biomarker of hepatic steatosis ^{8,51,52}. MRS has also been demonstrated to have high reproducibility ⁵³.

One of the disadvantages of MRS is that PDFF is only measured in a single anatomical location and analysis is complicated. Additionally, analysis of the collected spectrum must be performed offline and requires specialized skills and software. MRS has not been widely used clinically because of the necessary post-processing and the lack of anatomical information.

CT and Ultrasound

On non-contrast CT, the normal liver has slightly lower attenuation than the spleen and blood vessels ⁵⁴. Increasing fat content results in even lower attenuation of the liver, which can be assessed relative to the spleen and quantified as an attenuation difference in Hounsfield units (HU). Hepatic steatosis may be diagnosed if the attenuation of the liver is at least 10 HU less than that of the spleen ⁵⁵. Hepatic steatosis may also be diagnosed if the absolute attenuation of the liver is less than 40 – 50 HU ^{56,57} or if the unenhanced liver is lower in attenuation than the intrahepatic blood vessels (Figure 4). However, precise thresholds for making the diagnosis of steatosis vary from study to study. On contrast-enhanced CT examinations, the assessment of hepatic steatosis is dependent on the rate of contrast injection as well as the scan timing, making it a difficult tool to use in a standardized manner ^{58,59}. In one study, the qualitative assessment of hepatic steatosis on contrast-enhanced CT was highly specific, however had low sensitivity ⁶⁰. Although a practical tool for diagnosis of hepatic steatosis, CT is unable to quantitatively assess fat fraction accurately and precisely.

Similarly, the diagnosis of hepatic steatosis may be made on conventional ultrasound but cannot be assessed quantitatively (Figure 5). On ultrasound, hepatic steatosis is assessed qualitatively using a combination of imaging features such as liver-kidney contrast, vessel blurring, posterior beam attenuation, focal fat sparing, and gallbladder and diaphragm visualization^{61,62}. Ultrasonographic assessment of hepatic steatosis is limited by its low sensitivity and accuracy^{63,64}, especially at lower steatosis grades^{65,66}, and substantial inter-observer variability⁶⁷. Although hepatic steatosis may be assessed on ultrasound examinations performed for other clinical indications, it is not the diagnostic test of choice⁶⁸.

On ultrasound transient elastography, the controlled attenuation parameter (CAP) may be able to more quantitatively assess the degree of steatosis, however it has an unacceptably high technical failure rate of 8 – 35% in patients with non-alcoholic fatty liver disease^{69–71}. Hepatic steatosis may also be assessed using quantitative ultrasound (QUS) techniques which compute the backscatter coefficient^{72–74}. QUS may be more accurate than conventional ultrasound, but has not been widely studied to date⁷⁵.

Fat Quantification in the Pancreas

Pancreatic fat has been quantified using a variety of MR-based techniques, including two-point Dixon, three-point Dixon, complex-based CSE-MRI, and MRS in various clinical studies^{49,76–80}. It has been shown that fat in the pancreas tends to be evenly distributed and increases with age⁷⁶. The severity of pancreatic steatosis is associated with the severity of hepatic steatosis⁷⁷, and it is also associated with increasing BMI and decreased insulin secretion⁷⁹. In one study of complex-based CSE-MRI, it was found that the correlation between MRI and MRS was weaker in the pancreas than in the liver⁴⁹. This may be due to the smaller size of the pancreas and signal contamination from surrounding visceral fat in the MRS voxel.

Pancreatic fat may also be assessed using CT. In one study which quantified pancreatic steatosis by comparing pancreatic attenuation to splenic attenuation, the CT attenuation indices were associated with histological steatosis grade and impaired glucose metabolism⁸¹. However, this has not been further studied to date.

Fat Quantification in the Adrenal Glands

Detection of fat in the adrenal glands is important for distinguishing adrenal adenomas, which often contain fat, from malignant tumors^{12,14}. However, there is not an obvious clinical need for the quantification of fat in the adrenal glands. Some investigations have been published using dual-energy CT⁸² and double-echo CSE-MRI⁸³ for fat quantification in the adrenals for the abovementioned purpose, however reasonable performance for the diagnosis of lipid-rich adenomas is achievable with qualitative assessment of fat content using MRI.

Fat Quantification in Adipose Tissues

In addition to quantifying the fractional fat content in solid organs such as the liver, MRI has been used to quantify the volume of abdominal adipose tissue compartments^{19,24}.

Traditional MRI methods for quantifying adipose tissue volume were based on manual segmentation, which is expensive, laborious, and impractical for research studies and clinical practice. This has limited their use to a small number of image slices in the research setting, but numerous automated and semi-automated methods have been developed for adipose and muscle tissue segmentation recently²³. One of these techniques has recently been implemented in the United Kingdom BioBank study of over three thousand adults, which demonstrates its large-scale feasibility²⁷. These methods face two main challenges in binary tissue classification and 2D segmentation. The binary classification of each voxel as either strictly adipose or non-adipose tissue leads to underestimation of fat volume at tissue interfaces where sub-voxel fat is not included in the estimated fat volume because the whole voxel is classified as non-adipose tissue^{84,85}. 2D segmentation separates fat tissues on each individual slice without incorporating information from neighboring slices, resulting in segmentation errors that are more pronounced in morphologically complex fat structures or in the presence of imaging artifacts.

Conclusion

MR-based techniques for fat quantification include imaging with and without fat saturation, CSE imaging, and MRS. Ultrasound and CT allow qualitative assessment of fat content in the liver but do not provide accurate fat quantification. The advent of advanced CSE techniques that account for confounders of signal fat fraction have enabled the computation of PDFF, an accurate and reproducible imaging biomarker of fat content in tissues. PDFF quantification may use a magnitude-based approach which is based on MR magnitude data, or can use a complex-based approach which uses both the magnitude data and phase data. The main application of these techniques in the abdomen are for the assessment of hepatic steatosis, where liver biopsy is currently the gold standard for hepatic steatosis but is limited by sampling error and its invasive nature. These CSE techniques are also applicable to other abdominal organs/tissues such as the pancreas, adrenal glands, and adipose tissues, but are not as well investigated for these applications.

References

1. Brateman L. Chemical shift imaging: a review. *Am J Roentgenol.* 1986; 146(5):971–980. DOI: 10.2214/ajr.146.5.971 [PubMed: 3008543]
2. Heiken JP, Lee JK, Dixon WT. Fatty infiltration of the liver: evaluation by proton spectroscopic imaging. *Radiology.* 1985; 157(3):707–710. DOI: 10.1148/radiology.157.3.2997837 [PubMed: 2997837]
3. Reeder SB, Sirlin CB. Quantification of liver fat with magnetic resonance imaging. *Magn Reson Imaging Clin N Am.* 2010; 18(3):337–57. ix. DOI: 10.1016/j.mric.2010.08.013 [PubMed: 21094444]
4. Yokoo T, Bydder M, Hamilton G, et al. Nonalcoholic fatty liver disease: diagnostic and fat-grading accuracy of low-flip-angle multiecho gradient-recalled-echo MR imaging at 1.5 T. *Radiology.* 2009; 251(1):67–76. DOI: 10.1148/radiol.2511080666 [PubMed: 19221054]

5. Yokoo T, Shiehorteza M, Hamilton G, et al. Estimation of hepatic proton-density fat fraction by using MR imaging at 3.0 T. *Radiology*. 2011; 258(3):749–759. DOI: 10.1148/radiol.10100659 [PubMed: 21212366]
6. Tang A, Desai A, Hamilton G, et al. Accuracy of MR imaging-estimated proton density fat fraction for classification of dichotomized histologic steatosis grades in nonalcoholic fatty liver disease. *Radiology*. 2015; 274(2):416–425. DOI: 10.1148/radiol.14140754 [PubMed: 25247408]
7. Negrete LM, Middleton MS, Clark L, et al. Inter-examination precision of magnitude-based MRI for estimation of segmental hepatic proton density fat fraction in obese subjects. *J Magn Reson Imaging*. 2014; 39(5):1265–1271. DOI: 10.1002/jmri.24284 [PubMed: 24136736]
8. Le T-A, Chen J, Changchien C, et al. Effect of colessevelam on liver fat quantified by magnetic resonance in nonalcoholic steatohepatitis: a randomized controlled trial. *Hepatology*. 2012; 56(3): 922–932. DOI: 10.1002/hep.25731 [PubMed: 22431131]
9. Browning JD, Szczepaniak LS, Dobbins R, et al. Prevalence of hepatic steatosis in an urban population in the United States: impact of ethnicity. *Hepatology*. 2004; 40(6):1387–1395. DOI: 10.1002/hep.20466 [PubMed: 15565570]
10. Loomba R, Sirlin CB, Ang B, et al. Ezetimibe for the treatment of nonalcoholic steatohepatitis: assessment by novel magnetic resonance imaging and magnetic resonance elastography in a randomized trial (MOZART trial). *Hepatology*. 2015; 61(4):1239–1250. DOI: 10.1002/hep.27647 [PubMed: 25482832]
11. Idilman IS, Tuzun A, Savas B, et al. Quantification of liver, pancreas, kidney, and vertebral body MRI-PDFF in non-alcoholic fatty liver disease. *Abdom Imaging*. 2015; 40(6):1512–1519. DOI: 10.1007/s00261-015-0385-0 [PubMed: 25715922]
12. Adam SZ, Nikolaidis P, Horowitz JM, et al. Chemical Shift MR Imaging of the Adrenal Gland: Principles, Pitfalls, and Applications. *RadioGraphics*. 2016; 36(2):414–432. DOI: 10.1148/rg.2016150139 [PubMed: 26849154]
13. Inan N, Arslan A, Akansel G, Anik Y, Balci NC, Demirci A. Dynamic contrast enhanced MRI in the differential diagnosis of adrenal adenomas and malignant adrenal masses. *Eur J Radiol*. 2008; 65(1):154–162. DOI: 10.1016/j.ejrad.2007.03.012 [PubMed: 17466481]
14. Slapa RZ, Jakubowski W, Januszewicz A, et al. Discriminatory power of MRI for differentiation of adrenal non-adenomas vs adenomas evaluated by means of ROC analysis: Can biopsy be obviated? *Eur Radiol*. 2000; 10(1):95–104. DOI: 10.1007/s003300050012 [PubMed: 10663723]
15. Rodacki K, Ramalho M, Dale BM, et al. Combined Chemical Shift Imaging With Early Dynamic Serial Gadolinium-Enhanced MRI in the Characterization of Adrenal Lesions. *Am J Roentgenol*. 2014; 203(1):99–106. DOI: 10.2214/AJR.13.11731 [PubMed: 24951201]
16. Kullberg J, Karlsson A-K, Stokland E, Svensson P-A, Dahlgren J. Adipose tissue distribution in children: Automated quantification using water and fat MRI. *J Magn Reson Imaging*. 2010; 32(1): 204–210. DOI: 10.1002/jmri.22193 [PubMed: 20575078]
17. Poonawalla AH, Sjöberg BP, Rehm JL, et al. Adipose tissue MRI for quantitative measurement of central obesity. *J Magn Reson Imaging*. 2013; 37(3):707–716. DOI: 10.1002/jmri.23846 [PubMed: 23055365]
18. Thörmer G, Bertram HH, Garnov N, et al. Software for automated MRI-based quantification of abdominal fat and preliminary evaluation in morbidly obese patients. *J Magn Reson Imaging*. 2013; 37(5):1144–1150. DOI: 10.1002/jmri.23890 [PubMed: 23124651]
19. Wald D, Teucher B, Dinkel J, et al. Automatic quantification of subcutaneous and visceral adipose tissue from whole-body magnetic resonance images suitable for large cohort studies. *J Magn Reson Imaging*. 2012; 36(6):1421–1434. DOI: 10.1002/jmri.23775 [PubMed: 22911921]
20. Müller H-P, Raudies F, Unrath A, Neumann H, Ludolph AC, Kassubek J. Quantification of human body fat tissue percentage by MRI. *NMR Biomed*. 2011; 24(1):17–24. DOI: 10.1002/nbm.1549 [PubMed: 20672389]
21. Addeman BT, Kutty S, Perkins TG, et al. Validation of volumetric and single-slice MRI adipose analysis using a novel fully automated segmentation method. *J Magn Reson Imaging*. 2015; 41(1): 233–241. DOI: 10.1002/jmri.24526 [PubMed: 24431195]

22. Würslin C, Machann J, Rempp H, Claussen C, Yang B, Schick F. Topography mapping of whole body adipose tissue using A fully automated and standardized procedure. *J Magn Reson Imaging*. 2010; 31(2):430–439. DOI: 10.1002/jmri.22036 [PubMed: 20099357]
23. Borga M, Thomas EL, Romu T, et al. Validation of a fast method for quantification of intra-abdominal and subcutaneous adipose tissue for large-scale human studies. *NMR Biomed*. 2015; 28(12):1747–1753. DOI: 10.1002/nbm.3432 [PubMed: 26768490]
24. Brennan DD, Whelan PF, Robinson K, et al. Rapid Automated Measurement of Body Fat Distribution from Whole-Body MRI. *Am J Roentgenol*. 2005; 185(2):418–423. DOI: 10.2214/ajr.185.2.01850418 [PubMed: 16037514]
25. Karlsson A, Rosander J, Romu T, et al. Automatic and quantitative assessment of regional muscle volume by multi-atlas segmentation using whole-body water-fat MRI. *J Magn Reson Imaging*. 2015; 41(6):1558–1569. DOI: 10.1002/jmri.24726 [PubMed: 25111561]
26. Thomas MS, Newman D, Leinhard OD, et al. Test-retest reliability of automated whole body and compartmental muscle volume measurements on a wide bore 3T MR system. *Eur Radiol*. 2014; 24(9):2279–2291. DOI: 10.1007/s00330-014-3226-6 [PubMed: 24871333]
27. West J, Dahlqvist Leinhard O, Romu T, et al. Feasibility of MR-Based Body Composition Analysis in Large Scale Population Studies. Gonzalez-Bulnes A, ed. *PLoS One*. 2016; 11(9):e0163332.doi: 10.1371/journal.pone.0163332 [PubMed: 27662190]
28. Mitchell DG, Kim I, Chang TS, et al. Fatty liver. Chemical shift phase-difference and suppression magnetic resonance imaging techniques in animals, phantoms, and humans. *Invest Radiol*. 1991; 26(12):1041–1052. [PubMed: 1765436]
29. Qayyum A, Goh JS, Kakar S, Yeh BM, Merriman RB, Coakley FV. Accuracy of Liver Fat Quantification at MR Imaging: Comparison of Out-of-Phase Gradient-Echo and Fat-saturated Fast Spin-Echo Techniques—Initial Experience. *Radiology*. 2005; 237(2):507–511. DOI: 10.1148/radiol.2372040539 [PubMed: 16244259]
30. Dixon WT. Simple proton spectroscopic imaging. *Radiology*. 1984; 153(1):189–194. DOI: 10.1148/radiology.153.1.6089263 [PubMed: 6089263]
31. Reeder SB, Cruite I, Hamilton G, Sirlin CB. Quantitative assessment of liver fat with magnetic resonance imaging and spectroscopy. *J Magn Reson Imaging*. 2011; 34(4):729–749. DOI: 10.1002/jmri.22580 [PubMed: 21928307]
32. Reeder SB, Pineda AR, Wen Z, et al. Iterative decomposition of water and fat with echo asymmetry and least-squares estimation (IDEAL): application with fast spin-echo imaging. *Magn Reson Med*. 2005; 54(3):636–644. DOI: 10.1002/mrm.20624 [PubMed: 16092103]
33. Bydder M, Yokoo T, Hamilton G, et al. Relaxation effects in the quantification of fat using gradient echo imaging. *Magn Reson Imaging*. 2008; 26(3):347–359. DOI: 10.1016/j.mri.2007.08.012 [PubMed: 18093781]
34. Yu H, Shimakawa A, McKenzie CA, Brodsky E, Brittain JH, Reeder SB. Multiecho water-fat separation and simultaneous R^2 estimation with multifrequency fat spectrum modeling. *Magn Reson Med*. 2008; 60(5):1122–1134. DOI: 10.1002/mrm.21737 [PubMed: 18956464]
35. Yu H, McKenzie CA, Shimakawa A, et al. Multiecho reconstruction for simultaneous water-fat decomposition and T_2^* estimation. *J Magn Reson Imaging*. 2007; 26(4):1153–1161. DOI: 10.1002/jmri.21090 [PubMed: 17896369]
36. Bashir MR, Zhong X, Nickel MD, et al. Quantification of hepatic steatosis with a multistep adaptive fitting MRI approach: prospective validation against MR spectroscopy. *AJR Am J Roentgenol*. 2015; 204(2):297–306. DOI: 10.2214/AJR.14.12457 [PubMed: 25615751]
37. Hamilton G, Yokoo T, Bydder M, et al. In vivo characterization of the liver fat ^1H MR spectrum. *NMR Biomed*. 2011; 24(7):784–790. DOI: 10.1002/nbm.1622 [PubMed: 21834002]
38. Kühn J-P, Hernando D, Muñoz del Rio A, et al. Effect of multipoint spectral modeling of fat for liver iron and fat quantification: correlation of biopsy with MR imaging results. *Radiology*. 2012; 265(1):133–142. DOI: 10.1148/radiol.12112520 [PubMed: 22923718]
39. Hines CDG, Frydrychowicz A, Hamilton G, et al. $T(1)$ independent, $T(2)$ (*) corrected chemical shift based fat-water separation with multi-peak fat spectral modeling is an accurate and precise measure of hepatic steatosis. *J Magn Reson Imaging*. 2011; 33(4):873–881. DOI: 10.1002/jmri.22514 [PubMed: 21448952]

40. Meisamy S, Hines CDG, Hamilton G, et al. Quantification of hepatic steatosis with T1-independent, T2-corrected MR imaging with spectral modeling of fat: blinded comparison with MR spectroscopy. *Radiology*. 2011; 258(3):767–775. DOI: 10.1148/radiol.10100708 [PubMed: 21248233]
41. Wang X, Hernando D, Reeder SB. Sensitivity of chemical shift-encoded fat quantification to calibration of fat MR spectrum. *Magn Reson Med*. 2016; 75(2):845–851. DOI: 10.1002/mrm.25681 [PubMed: 25845713]
42. Liu C-Y, McKenzie CA, Yu H, Brittain JH, Reeder SB. Fat quantification with IDEAL gradient echo imaging: correction of bias from T(1) and noise. *Magn Reson Med*. 2007; 58(2):354–364. DOI: 10.1002/mrm.21301 [PubMed: 17654578]
43. Levin YS, Yokoo T, Wolfson T, et al. Effect of echo-sampling strategy on the accuracy of out-of-phase and in-phase multiecho gradient-echo MRI hepatic fat fraction estimation. *J Magn Reson Imaging*. 2014; 39(3):567–575. DOI: 10.1002/jmri.24193 [PubMed: 23720420]
44. Yokoo T, Browning JD. Fat and Iron Quantification in the Liver. *Top Magn Reson Imaging*. 2014; 23(2):129–150. DOI: 10.1097/RMR.000000000000016 [PubMed: 24690617]
45. Hernando D, Sharma SD, Aliyari Ghasabeh M, et al. Multisite, multivendor validation of the accuracy and reproducibility of proton-density fat-fraction quantification at 1.5T and 3T using a fat-water phantom. *Magn Reson Med*. Apr.2016 doi: 10.1002/mrm.26228.
46. Johnson BL, Schroeder ME, Wolfson T, et al. Effect of flip angle on the accuracy and repeatability of hepatic proton density fat fraction estimation by complex data-based, T1-independent, T2*-corrected, spectrum-modeled MRI. *J Magn Reson Imaging*. 2014; 39(2):440–447. DOI: 10.1002/jmri.24153 [PubMed: 23596052]
47. Kühn J-P, Hernando D, Mensel B, et al. Quantitative chemical shift-encoded MRI is an accurate method to quantify hepatic steatosis. *J Magn Reson Imaging*. 2014; 39(6):1494–1501. DOI: 10.1002/jmri.24289 [PubMed: 24123655]
48. Horng DE, Hernando D, Hines CDG, Reeder SB. Comparison of R2* correction methods for accurate fat quantification in fatty liver. *J Magn Reson Imaging*. 2013; 37(2):414–422. DOI: 10.1002/jmri.23835 [PubMed: 23165934]
49. Hu HH, Kim H-W, Nayak KS, Goran MI. Comparison of fat-water MRI and single-voxel MRS in the assessment of hepatic and pancreatic fat fractions in humans. *Obesity (Silver Spring)*. 2010; 18(4):841–847. DOI: 10.1038/oby.2009.352 [PubMed: 19834463]
50. Zhong X, Nickel MD, Kannengiesser SAR, Dale BM, Kiefer B, Bashir MR. Liver fat quantification using a multi-step adaptive fitting approach with multi-echo GRE imaging. *Magn Reson Med*. 2014; 72(5):1353–1365. DOI: 10.1002/mrm.25054 [PubMed: 24323332]
51. Szczepaniak LS, Nurenberg P, Leonard D, et al. Magnetic resonance spectroscopy to measure hepatic triglyceride content: prevalence of hepatic steatosis in the general population. *Am J Physiol Endocrinol Metab*. 2005; 288(2):E462–8. DOI: 10.1152/ajpendo.00064.2004 [PubMed: 15339742]
52. Tang A, Rabasa-Lhoret R, Castel H, et al. Effects of Insulin Glargine and Liraglutide Therapy on Liver Fat as Measured by Magnetic Resonance in Patients With Type 2 Diabetes: A Randomized Trial. *Diabetes Care*. 2015; 38(7):1339–1346. DOI: 10.2337/dc14-2548 [PubMed: 25813773]
53. van Werven JR, Hoogduin JM, Nederveen AJ, et al. Reproducibility of 3.0 Tesla magnetic resonance spectroscopy for measuring hepatic fat content. *J Magn Reson Imaging*. 2009; 30(2):444–448. DOI: 10.1002/jmri.21837 [PubMed: 19629974]
54. Piekarski J, Goldberg HI, Royal SA, Axel L, Moss AA. Difference between liver and spleen CT numbers in the normal adult: its usefulness in predicting the presence of diffuse liver disease. *Radiology*. 1980; 137(3):727–729. DOI: 10.1148/radiology.137.3.6934563 [PubMed: 6934563]
55. Limanond P, Raman SS, Lassman C, et al. Macrovesicular Hepatic Steatosis in Living Related Liver Donors: Correlation between CT and Histologic Findings. *Radiology*. 2004; 230(1):276–280. DOI: 10.1148/radiol.2301021176 [PubMed: 14695401]
56. Hamer OW, Aguirre DA, Casola G, Sirlin CB. Imaging Features of Perivascular Fatty Infiltration of the Liver: Initial Observations. *Radiology*. 2005; 237(1):159–169. DOI: 10.1148/radiol.2371041580 [PubMed: 16100085]

57. Yajima Y, Narui T, Ishii M, et al. Computed tomography in the diagnosis of fatty liver: total lipid content and computed tomography number. *Tohoku J Exp Med.* 1982; 136(3):337–342. [PubMed: 7071850]
58. Johnston RJ, Stamm ER, Lewin JM, Hendrick RE, Archer PG. Diagnosis of fatty infiltration of the liver on contrast enhanced CT: limitations of liver-minus-spleen attenuation difference measurements. *Abdom Imaging.* 1998; 23(4):409–415. DOI: 10.1007/s002619900370 [PubMed: 9663278]
59. Jacobs JE, Birnbaum BA, Shapiro MA, et al. Diagnostic criteria for fatty infiltration of the liver on contrast-enhanced helical CT. *Am J Roentgenol.* 1998; 171(3):659–664. DOI: 10.2214/ajr.171.3.9725292 [PubMed: 9725292]
60. Lawrence DA, Oliva IB, Israel GM. Detection of Hepatic Steatosis on Contrast-Enhanced CT Images: Diagnostic Accuracy of Identification of Areas of Presumed Focal Fatty Sparing. *Am J Roentgenol.* 2012; 199(1):44–47. DOI: 10.2214/AJR.11.7838 [PubMed: 22733892]
61. Yajima Y, Ohta K, Narui T, Abe R, Suzuki H, Ohtsuki M. Ultrasonographical diagnosis of fatty liver: significance of the liver-kidney contrast. *Tohoku J Exp Med.* 1983; 139(1):43–50. [PubMed: 6220488]
62. Ballestri S, Lonardo A, Romagnoli D, et al. Ultrasonographic fatty liver indicator, a novel score which rules out NASH and is correlated with metabolic parameters in NAFLD. *Liver Int.* 2012; 32(8):1242–1252. DOI: 10.1111/j.1478-3231.2012.02804.x [PubMed: 22520641]
63. Hamaguchi M, Kojima T, Itoh Y, et al. The Severity of Ultrasonographic Findings in Nonalcoholic Fatty Liver Disease Reflects the Metabolic Syndrome and Visceral Fat Accumulation. *Am J Gastroenterol.* 2007; 102(12):2708–2715. DOI: 10.1111/j.1572-0241.2007.01526.x [PubMed: 17894848]
64. Fishbein M, Castro F, Cheruku S, et al. Hepatic MRI for fat quantitation: its relationship to fat morphology, diagnosis, and ultrasound. *J Clin Gastroenterol.* 2005; 39(7):619–625. [PubMed: 16000931]
65. Dasarathy S, Dasarathy J, Khiyami A, Joseph R, Lopez R, McCullough AJ. Validity of real time ultrasound in the diagnosis of hepatic steatosis: A prospective study. *J Hepatol.* 2009; 51(6):1061–1067. DOI: 10.1016/j.jhep.2009.09.001 [PubMed: 19846234]
66. Saadeh S, Younossi ZM, Remer EM, et al. The utility of radiological imaging in nonalcoholic fatty liver disease. *Gastroenterology.* 2002; 123(3):745–750. [PubMed: 12198701]
67. Strauss S, Gavish E, Gottlieb P, Katsnelson L. Interobserver and intraobserver variability in the sonographic assessment of fatty liver. *AJR Am J Roentgenol.* 2007; 189(6):W320–3. DOI: 10.2214/AJR.07.2123 [PubMed: 18029843]
68. Bohte AE, van Werven JR, Bipat S, Stoker J. The diagnostic accuracy of US, CT, MRI and ¹H-MRS for the evaluation of hepatic steatosis compared with liver biopsy: a meta-analysis. *Eur Radiol.* 2011; 21(1):87–97. DOI: 10.1007/s00330-010-1905-5 [PubMed: 20680289]
69. Lédinghen V, Vergniol J, Foucher J, Merrouche W, Bail B. Non-invasive diagnosis of liver steatosis using controlled attenuation parameter (CAP) and transient elastography. *Liver Int.* 2012; 32(6): 911–918. DOI: 10.1111/j.1478-3231.2012.02820.x [PubMed: 22672642]
70. Myers RP, Pollett A, Kirsch R, et al. Controlled Attenuation Parameter (CAP): a noninvasive method for the detection of hepatic steatosis based on transient elastography. *Liver Int.* 2012; 32(6):902–910. DOI: 10.1111/j.1478-3231.2012.02781.x [PubMed: 22435761]
71. Forestier N, Gaus A, Herrmann E, et al. Acoustic radiation force impulse imaging for evaluation of antiviral treatment response in chronic hepatitis C. *J Gastrointest Liver Dis.* 2012; 21(4):367–373. [PubMed: 23256119]
72. Yao LX, Zagzebski JA, Madsen EL. Backscatter coefficient measurements using a reference phantom to extract depth-dependent instrumentation factors. *Ultrason Imaging.* 1990; 12(1):58–70. DOI: 10.1016/0161-7346(90)90221-I [PubMed: 2184569]
73. Han, A., Erdman, JW., Simpson, DG., Andre, MP., O'Brien, WD. Early detection of fatty liver disease in mice via quantitative ultrasound. 2014 IEEE International Ultrasonics Symposium; IEEE; 2014. p. 2363-2366.

74. Ghoshal G, Lavarello RJ, Kemmerer JP, Miller RJ, Oelze ML. Ex vivo Study of Quantitative Ultrasound Parameters in Fatty Rabbit Livers. *Ultrasound Med Biol.* 2012; 38(12):2238–2248. DOI: 10.1016/j.ultrasmedbio.2012.08.010 [PubMed: 23062376]
75. Lin SC, Heba E, Wolfson T, et al. Noninvasive Diagnosis of Nonalcoholic Fatty Liver Disease and Quantification of Liver Fat Using a New Quantitative Ultrasound Technique. *Clin Gastroenterol Hepatol.* 2015; 13(7):1337–1345. e6. DOI: 10.1016/j.cgh.2014.11.027 [PubMed: 25478922]
76. Li J, Xie Y, Yuan F, Song B, Tang C. Noninvasive Quantification of Pancreatic Fat in Healthy Male Population Using Chemical Shift Magnetic Resonance Imaging. *Pancreas.* 2011; 40(2):295–299. DOI: 10.1097/MPA.0b013e318201669f [PubMed: 21178651]
77. Patel NS, Peterson MR, Brenner DA, Heba E, Sirlin C, Loomba R. Association between novel MRI-estimated pancreatic fat and liver histology-determined steatosis and fibrosis in non-alcoholic fatty liver disease. *Aliment Pharmacol Ther.* 2013; 37(6):630–639. DOI: 10.1111/apt.12237 [PubMed: 23383649]
78. Livingstone RS, Begovatz P, Kahl S, et al. Initial clinical application of modified Dixon with flexible echo times: hepatic and pancreatic fat assessments in comparison with 1H MRS. *Magn Reson Mater Physics, Biol Med.* 2014; 27(5):397–405. DOI: 10.1007/s10334-013-0421-4
79. Kovanlikaya A, Mittelman SD, Ward A, Geffner ME, Dorey F, Gilsanz V. Obesity and fat quantification in lean tissues using three-point Dixon MR imaging. *Pediatr Radiol.* 2005; 35(6): 601–607. DOI: 10.1007/s00247-005-1413-y [PubMed: 15785930]
80. Yoon JH, Lee JM, Lee KB, et al. Pancreatic Steatosis and Fibrosis: Quantitative Assessment with Preoperative Multiparametric MR Imaging. *Radiology.* 2016; 279(1):140–150. DOI: 10.1148/radiol.2015142254 [PubMed: 26566228]
81. Kim SY, Kim H, Cho JY, et al. Quantitative Assessment of Pancreatic Fat by Using Unenhanced CT: Pathologic Correlation and Clinical Implications. *Radiology.* 2014; 271(1):104–112. DOI: 10.1148/radiol.13122883 [PubMed: 24475851]
82. Ju Y, Liu A, Dong Y, et al. The Value of Nonenhanced Single-Source Dual-Energy CT for Differentiating Metastases From Adenoma in Adrenal Glands. *Acad Radiol.* 2015; 22(7):834–839. DOI: 10.1016/j.acra.2015.03.004 [PubMed: 25957502]
83. Namimoto T, Yamashita Y, Mitsuzaki K, et al. Adrenal Masses: Quantification of Fat Content with Double-Echo Chemical Shift In-Phase and Opposed-Phase FLASH MR Images for Differentiation of Adrenal Adenomas. *Radiology.* 2001; 218(3):642–646. DOI: 10.1148/radiology.218.3.r01mr15642 [PubMed: 11230633]
84. Peng Q, McColl RW, Ding Y, Wang J, Chia JM, Weatherall PT. Automated method for accurate abdominal fat quantification on water-saturated magnetic resonance images. *J Magn Reson Imaging.* 2007; 26(3):738–746. DOI: 10.1002/jmri.21040 [PubMed: 17729369]
85. Ludwig UA, Klausmann F, Baumann S, et al. Whole-body MRI-based fat quantification: A comparison to air displacement plethysmography. *J Magn Reson Imaging.* 2014; 40(6):1437–1444. DOI: 10.1002/jmri.24509 [PubMed: 24449401]

Figure 1.

Plot demonstrating the simulated signal intensity over time at a PDF of 20% and an $R2^*$ value of 20 sec^{-1} . The red curve represents the simulated signal interference pattern of fat and water where fat is simplistically modeled as a single peak at 1.3 ppm. The superimposed blue curve represents the simulated signal interference pattern between fat and water where fat is modeled more realistically as six separate peaks, each with its own chemical shift and relative amplitude as described in the text.

Figure 2. Magnitude-based (left) and complex-based (right) proton density fat fraction (PDFF) estimation in a 44-year-old female. Within the co-localized regions of interest (squares), estimated PDFF was 38.1% and 40.0% respectively.

Figure 3.

MR spectrum using the STEAM sequence from the liver of the same 44-year-old female at the location demarcated in Figure 2. The water peak (W) is at 4.7 ppm. The six fat peaks (1 – 6) are at 5.3, 4.2, 2.75, 2.1, 1.3, and 0.9 ppm. Spectra were collected at five echo times ranging from 10 – 30 ms, allowing measurement of and correction for T2 decay. The estimated PDFF by MRS was 38.1%.

Figure 4.

Non-contrast CT from an 8-year-old male. The liver (21.1 HU) is substantially lower in attenuation than the spleen (59.8 HU), indicating hepatic steatosis. Notice that the unenhanced blood vessels are higher in attenuation than to the steatotic liver. Also notice a geographic region of relative fat sparing (arrow) in the lateral sector of the liver immediately anterior to the porta hepatis. Although these CT findings indicate steatosis, they do not permit accurate or precise quantification of fat content.

Figure 5.

Conventional ultrasound image in a 43-year-old female. The liver is noticeably more echogenic than the kidney. Also notice posterior beam attenuation with poor visibility of the diaphragm, as well as poor visibility of intra-hepatic blood vessels. Together, these qualitative features indicate hepatic steatosis. Although these conventional sonographic findings indicate steatosis, they do not permit accurate or precise quantification of fat content.

Table 1

Table of confounders that need to be addressed for PDFF and MRS techniques. MRI-M: magnitude-based MRI-PDFF; MRI-C: complex-based MRI-PDFF

Table of confounders that must be addressed for accurate PDFF estimation using MRI- and MRS-based techniques. MRI-M: magnitude-based MRI-PDFF; MRI-C: complex-based MRI-PDFF

Confounding factor	MRI-M	MRI-C	MRS
T1			
T2			
T2*			
Spectral complexity			
Phase errors			
Noise bias			
J-coupling			