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Emerging Quantitative Magnetic Resonance Imaging Biomarkers of Hepatic Steatosis

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In this issue of HEPATOLOGY, Nouredin et al. describe an innovative application of an emerging magnetic resonance imaging (MRI)-based biomarker, proton density fat-fraction (PDFF), for quantification of hepatic steatosis in patients with nonalcoholic steatohepatitis (NASH).¹ In this study, 50 patients with biopsy-proven NASH were enrolled in a randomized double-blinded placebo-controlled trial. Patients were randomized to receive placebo or colesevelam, an agent known to reduce elevated low-density lipoprotein (LDL) and to improve glycemic control in adults with type II diabetes. The authors performed cross-sectional comparisons of MRI-derived PDFF with MR spectroscopy (MRS)-derived PDFF and nontargeted liver biopsy, at baseline and after 24 weeks of treatment. This study demonstrated excellent agreement and correlation between MRI and MRS, and also demonstrated excellent correlation between both MRI and MRS with histology-derived steatosis grade. Perhaps most interesting, the authors determined that longitudinal changes in MRI-derived PDFF was more sensitive to detection of changes in liver fat than biopsy, with changes in liver fat paralleling changes in body weight and serum aminotransferases between baseline and week 24. These exciting results demonstrate the utility of quantitative MRI methods for treatment monitoring using a novel, noninvasive imaging-based biomarker of hepatic steatosis.

Biopsy is and will remain the clinical gold standard for the diagnosis, grading, and staging of diffuse liver disease. However, emerging imaging-based biomarkers of diffuse liver disease, such as MRI-derived PDFF, will play an important complementary role in the management of patients with liver disease. Although cost and the invasive nature of biopsy are relative barriers, the most important limitation of biopsy is its known sampling variability.² The high variability between repeated measurements limits the ability of biopsy to quantify longitudinal changes in features of diffuse liver disease during an intervention such as weight loss or drug therapy. Of course, biopsy plays a central diagnostic role given its ability to evaluate other features of diffuse liver disease such as inflammation, fibrosis, ballooning degeneration, etc. Biopsy can also characterize disease processes through the histological distribution of disease features at the level of the portal sinusoid. This characterization is beyond the capability of current radiological methods such as MRI.

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MRI is an established noninvasive method for performing a wide variety of diagnostic procedures including imaging of the abdomen, without the use of ionizing radiation. It is widely regarded as the best noninvasive method to assess focal liver lesions and, *qualitatively*, many features of diffuse liver disease, such as hepatic steatosis and iron overload, and, in the endstages, fibrosis. MRI works by magnetically polarizing the nuclear spin of protons in the body, which are in very high concentration in water and fat (~55M). Radiofrequency (RF) energy (64 MHz at 1.5T, 128 MHz at 3T) is transmitted into the body, and the resulting signals emitted from these “excited” protons are subsequently received using receive coils placed on the body. Because of higher electronic shielding of the protons in triglycerides, the proton signal from triglycerides is ~217 Hz slower than water (at 1.5T, 434 Hz at 3T). This “chemical shift” is exploited by “chemical shift encoded” MRI methods, such as that described by Nouredin et al. Using these methods, the relative concentration of signal from protons of water and fat can be determined.

It is with great serendipity that only the abnormal accumulation of fat (triglycerides in vacuoles) is visible with MRI. Protons from cholesterol, sphingolipids, phospholipids, and other fat molecules that comprise cell membranes and organelles yield no visible MRI signal and can only be detected using solid-state nuclear magnetic resonance (NMR) methods.

MRI is a rich modality whose signal depends on a large number of factors that can be exploited to generate a vast number of contrast mechanisms used for diagnosis. For example, MRI is sensitive to the presence of tissue water content, met-hemoglobin, oxygen concentration, the diffusion of water in tumors, tissue perfusion, blood flow in large vessels, melanin, fat, iron, and many other factors that make this modality such a versatile and powerful clinical tool.

Unfortunately, this dependence of the MRI signal on so many factors has, paradoxically, limited the ability of MRI to *quantify* features of disease, because many of these factors alter the MRI signal in unanticipated ways. As a result of these confounding factors, conventional MRI methods attempting to quantify triglyceride concentration have lacked robustness to changes in acquisition parameters. Historically, this has led to poor reproducibility across institutions, MRI platforms, MRI manufacturers, and also field strength (1.5T and 3T are the two most common field strengths used clinically). This lack of reproducibility has greatly limited the validity and applicability of conventional MRI to quantify tissue triglyceride concentration.

Fortunately, over the past 6–7 years there has been intensive work within the MRI research community on the development of robust and reproducible quantitative imaging biomarkers using MRI.^{3–6} Much of this work has focused on the identification of and development of methods to avoid or correct for various confounding factors that influence the MRI signal.^{7–12} Using “confounder-corrected” MRI methods, such as that described by Nouredin et al., accurate, precise, and reproducible estimates of triglyceride fat concentration can be achieved, *equivalent* to MRS-based methods, across different vendors, field strength, and site, as well as among children and adults.^{3–6,13} MRI-derived PDFF has been validated in phantom⁹ and animal studies,¹⁴ and has been demonstrated to have high repeatability (precision) in patients.¹⁵

Although MRS has been widely regarded as the noninvasive reference standard to measure tissue PDFF, it has important limitations. First, the MRS signal is typically acquired within a single small voxel, typically $\sim 2 \times 2 \times 2 \text{ cm}^3$ in size. Steatosis can have a very heterogeneous distribution within the liver, and for this reason, MRS suffers from sampling variability, similar to biopsy, and presents challenges for coregistering MRS voxels acquired in a patient at different time-points. Fortunately, MRI-derived PDFF does not suffer from this limitation and emerging methods can image the entire liver within an ~ 20 -second breath-hold. MRS also requires postprocessing by an experienced MR physicist, whereas reconstruction of PDFF maps using MRI can be fully automated and requires minimal computation time (< 1 minute) and no user input.

The most commonly used MRI- or MRS-derived biomarker of tissue fat concentration is the PDFF.¹⁶ PDFF is defined as the ratio of the density of mobile triglycerides to the total density of protons from mobile triglycerides and mobile water. It is essential to calculate a ratio or fraction of fat proton density, because MRI can only derive the relative signals from water and fat, rather than the absolute values, unless an external calibrated reference standard is included in the image.

Importantly, PDFF is a fundamental tissue property that reflects the concentration of fat within that tissue. While highly correlated with tissue triglyceride assays (measured in mg of triglyceride/g of tissue) these are *different* metrics, as the PDFF does not account for MR invisible species within tissue. Further, PDFF (reported as a percentage) does not correspond to the histological grading (also reported as a percentage). Steatosis is histologically graded as *the percentage of hepatocytes containing vacuoles of fat*, which can be subsequently binned into histological grades (grade 0: $< 5\%$, grade 1: $5\% - 33\%$, grade 2: $34\% - 66\%$, grade 3: $> 66\%$).¹⁷ While PDFF and histological grade are highly correlated, as demonstrated by Nouredin et al. and others,^{18,19} it is essential to understand that PDFF and histological grade are fundamentally different metrics, and agreement between the two should not be expected.

The U.S. Food and Drug Administration (FDA) has recently approved confounder-corrected MRI with the indication to quantify PDFF as a biomarker of triglyceride concentration.⁴ Although currently approved for only one major MRI manufacturer, all other major MRI manufacturers have viable prototypes and are expected to commercialize these methods in the near future. To the best of my knowledge, PDFF is the first quantitative MRI biomarker with proven accuracy, precision, and reproducibility. When widely available, this will allow, for the first time, multicenter clinical studies with meaningful comparisons across institutions and patient populations.

The cost-effectiveness of MRI to quantify fat is worth comment. First, the incremental cost of performing a single 20-second breath-hold during an MRI of the abdomen performed for other reasons is trivial. Second, a dedicated MRI exam for assessment of steatosis (single 20-second breath-hold) would require ~ 5 minutes of total time in the MRI suite. According to CMS.gov, the global Medicare reimbursement for a complete noncontrast MRI of the abdomen in 2013 is $\sim \$370$. Given that this examination typically requires 30–60 minutes of

time in the MRI suite, one can envision a total cost less than \$100–150, comparable to that of a panel of serum tests.

Despite the exciting prospects of MRI-derived PDFF as an emerging biomarker of tissue fat concentration, there are important limitations worth noting. First, MRI cannot distinguish between microvesicular and macrovesicular steatosis, since both are comprised of triglycerides. Isolated microvesicular steatosis can be a sign of mitochondrial toxicity often related to drug toxicity, and often suggests a more guarded prognosis²⁰ than slowly progressive diseases like nonalcoholic fatty liver disease (NAFLD). Further, MRI-derived PDFF does not evaluate for other important histological features of diffuse liver disease (e.g., inflammation) and should not replace biopsy for comprehensive evaluation of liver disease. Other limitations of MRI include contraindications to implants and metallic objects, although patients with pacemakers are increasingly being scanned under certain conditions.²¹ Further, claustrophobia and large body habitus are diminishing as barriers in clinical care given the widespread dissemination of 1.5T and 3T wide-bore magnets, with 500 lb (225 kg) patient limits, able to accommodate most obese patients who are at elevated risk of NAFLD.

In summary, the work by Nouredin et al. is an important advance, demonstrating the potential utility of MRI-derived PDFF for quantification of hepatic steatosis. The method described in this work offers great promise for the detection and treatment monitoring of fatty liver disease including longitudinal follow-up during pharmaceutical or other intervention (e.g., Fig. 1). Additional multicenter studies examining the role of MRI in outcomes and cost-effectiveness are needed. However, the imminent widespread clinical availability of MRI methods to measure PDFF in the clinical setting will undoubtedly play an important role in the study and clinical management of patients with diffuse liver disease.

Abbreviations

LDL	low-density lipoprotein
MRI	magnetic resonance imaging
MRS	MR spectroscopy
NASH	nonalcoholic steatohepatitis
NMR	nuclear magnetic resonance
PDFF	proton density fat-fraction

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Fig. 1.

Serial PDFF maps in a patient with recalcitrant hypertriglyceridemia (>10,000 at baseline) and severe hepatic steatosis, treated with plasmapheresis. Serial studies demonstrate not only a significant drop in the concentration of liver fat from 53% to 33% but also a decrease in the overall size of the liver. This example demonstrates the ability of MRI to monitor changes in hepatic steatosis during treatment.