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Advanced MRI Methods for Assessment of Chronic Liver Disease

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Abstract

MRI plays an increasingly important role for assessment of patients with chronic liver disease. MRI has numerous advantages, including lack of ionizing radiation and the possibility of performing multiparametric imaging. With recent advances in technology, advanced MRI methods such as diffusion-, perfusion-weighted MRI, MR elastography, chemical shift based fat-water separation and MR spectroscopy can now be applied to liver imaging. We will review the respective roles of these techniques for assessment of chronic liver disease.

Keywords

Liver disease; MRI; fibrosis; cirrhosis; fat; iron

INTRODUCTION

Chronic liver diseases encompass many different etiologies including mainly viral infections, non alcoholic fatty liver disease (NAFLD), alcohol abuse, primary sclerosing cholangitis, primary hemochromatosis and autoimmune disease. Chronic liver diseases can lead to hepatic fibrosis, cirrhosis, end-stage liver disease, portal hypertension and hepatocellular carcinoma (HCC), and constitute an important cause of morbidity, mortality, and health care costs [1]. In the United States, two emerging etiologies of chronic liver disease will be discussed in this review: chronic hepatitis C viral infection (HCV) and NAFLD.

HCV infection accounts for approximately 40% of all chronic liver disease, results in estimated 8000–10,000 deaths annually, and is the most frequent indication for liver transplantation [2–4]. Simulations for the years 2010–2019 suggest that morbidity and mortality associated with HCV will increase dramatically, resulting in 165,900 deaths from chronic liver disease, 27,200 deaths from HCC and \$10.7 billion in direct medical costs [5–7]. Progression to cirrhosis occurs in 20% to 30% of HCV infected patients, with disease duration up to 20 years [8]. The early detection of fibrosis and cirrhosis has important clinical implications in these patients. Antiviral treatment of chronic HCV can eradicate the infection, increase patient survival and reduce the need for liver transplantation [9].

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The prevalence of **NAFLD** has also dramatically increased, reflecting the obesity epidemic [10,11]. It afflicts an estimated 90-100 million (>30%) people in the United States [12,13] including 10% of children [14-18]. With the current epidemic of obesity and diabetes, NAFLD is widely expected to overtake chronic HCV infection as the leading indication for liver transplantation in the next decade. NAFLD includes a spectrum of liver abnormalities ranging from liver steatosis to nonalcoholic steatohepatitis (NASH) [19]. Up to 25% of patients with NAFLD can progress to inflammation and liver injury, leading to fibrosis and cirrhosis, with the ultimate risk of developing HCC [20,21]. NAFLD is closely linked to the “metabolic syndrome”, a constellation of conditions that includes obesity, diabetes and insulin resistance. As shown in Fig. 1, insulin resistance leads to an intracellular accumulation of triglycerides and fatty acids (steatosis) [22,23]. Fatty acids are known to cause oxidative stress that can injure the liver, activating stellate cells that are responsible for hepatic injury and fibrosis. Why some patients with steatosis develop inflammatory and fibrotic changes, while others do not, is not well understood. Day proposed a “two-hit” model, hypothesizing that steatosis is the first “hit” [24]. An unknown form of oxidative stress (eg. iron overload, infection, genetic predisposition) forms the second “hit” and is necessary for progression to fibrosis. A vicious self-perpetuating cycle of steatosis, insulin resistance, and fibrosis ensues, eventually leading to cirrhosis [21]. Steatosis is the earliest biomarker of NAFLD and is a necessary feature of disease for the development of fibrosis. It is also essential to quantify liver injury through the measurement of fibrosis in order to differentiate simple steatosis from NASH. Early detection of steatosis, the hallmark and earliest feature of NAFLD, would facilitate early diagnosis and intervention before liver damage is irreversible, and thus, there has been great interest in the development of accurate quantitative biomarkers of steatosis with MRI. Steatosis is also an important disease feature in other types of chronic liver diseases [25-27].

Role of liver biopsy for assessment of chronic liver disease

The typical histological features of chronic HCV are variable degrees of hepatocellular necrosis and inflammation (activity or grade of disease) and fibrosis (stage of disease), with possible associated fat or iron deposition [28,29]. Several semiquantitative methods have been proposed to assess fibrotic changes and histological activity in chronic hepatitis [30-33], but the most generally accepted one is the METAVIR classification [33]. The histopathologic findings have a role for assessing prognosis, guiding antiviral therapy, and predicting treatment efficacy in viral hepatitis [29,34]. Clinically significant fibrosis is generally defined by fibrosis stage $\geq$ F2 (on the METAVIR scale from F0 to F4, F4 being cirrhosis) [33]. Advanced fibrosis or cirrhosis (F3-F4) on initial liver biopsy is associated with a decreased likelihood of sustained virologic response to treatment [35,36]. Repeat liver biopsies can also be useful to evaluate the progression of the disease in patients who have opted against treatment or in patients who did not respond to their initial therapy and are considering another course of therapy. In NAFLD, in addition to the fat grading, liver biopsy can assess for the presence of inflammation and fibrosis [37].

Limitations of liver biopsy

Although liver biopsy is a relatively safe procedure when performed by experienced clinicians, it has poor patient acceptance, is not risk free and difficult to repeat. Prior studies have suggested a risk of hospitalization of 1% to 5%, with up to 0.57% risk of severe complications, and reported mortality rates of 1:1000 to 1:10000 [38-42], in relation with liver biopsy. In addition, liver biopsy is prone to inter-observer variability and sampling errors [43-46], and is relatively expensive compared to MRI. In contrast, MRI is relatively inexpensive, non-invasive, safe, and avoids the use of ionizing radiation, making it a very attractive cost-effective alternative for early diagnosis and subsequent disease monitoring during therapy.

In this review, we discuss the acquisition, results and limitations of functional MRI methods for assessment of chronic liver disease. Focal liver lesion detection will not be discussed.

NON INVASIVE DIAGNOSIS OF LIVER FIBROSIS AND CIRRHOSIS

Hepatic fibrogenesis is a complex dynamic process, which is mediated by necroinflammation and activation of stellate cells [47], with abnormal collagen deposition resulting from increased collagen synthesis and decreased collagen degradation. A reliable and reproducible non invasive marker of hepatic fibrosis is strongly needed, and such a tool would reduce biopsy-related risks and costs, could be useful for guiding antiviral treatment, monitoring treatment efficacy, and for clinical evaluation of new types of antiviral and antifibrotic drugs.

Furthermore, identification of occult advanced fibrosis or cirrhosis, may direct further management, and has essential prognostic implications.

- **Serological markers:** Liver function tests are known to be poorly correlated with the degree of fibrosis. For example, a study showed that up to 40% of patients with advanced fibrosis have persistently normal alanine aminotransferase (ALT) [48]. Serological markers of hepatic fibrosis developed recently such as aspartate aminotransferase (AST)/ ALT ratio, platelet count and prothrombin index have a variable accuracy [1]. Imbert-Bismuth and colleagues [49] have developed a score based on a combination of basic serum markers, known as FibroTest (combination of alpha2 macroglobulin, alpha2 globulin, γ globulin, apolipoprotein A1, γ GT, and total bilirubin). This test panel performed with 75% sensitivity and 85% specificity for diagnosis of stage F2 and higher. In a subsequent study, the same group reported a lower performance of the FibroTest and Actitest (activity index, which incorporates ALT) in HCV treated patients, with an area under the curve of 0.76 [50].
- **Transient elastography:** sonographic elastography (FibroScan-Echosens, France) [51-54] has been recently developed to measure liver stiffness in chronic hepatitis, showing strong correlation between measured stiffness and increasing degrees of fibrosis. For example, an AUC of 0.83 was reported for diagnosis of fibrosis $\geq$ F2 using this method [53], which is still not FDA approved in the US.
- **Conventional MRI:** MRI has become an increasingly important imaging modality for the investigation of patients with chronic liver disease. Several morphologic criteria have been described for the diagnosis of cirrhosis [55-58]. However, most of these findings can be subjective, subject to inter-observer variability, and limited in sensitivity and specificity. Awaya et al [59] have described a quantitative morphologic parameter for diagnosis of early cirrhosis: the caudate to right lobe ratio measured on contrast-enhanced images, which showed a limited value for diagnosing cirrhosis (sensitivity, specificity, and accuracy of 71.7%, 77.4%, and 74.2%, respectively, when using a caudate to right lobe ratio > 0.90).
- **Functional MRI methods:** Due to recent advances in MRI, there is a growing interest in optimizing and applying functional MRI methods for assessment of liver disease. These methods include (but are not limited to) diffusion-weighted MRI (DWI), perfusion-weighted MRI (PWI), MR Elastography (MRE) and MR spectroscopy (MRS).

➤ Diffusion-weighted MRI (DWI)

DWI is based on intravoxel incoherent motion, and provides non invasive quantification of water diffusion and microcapillary/blood perfusion [60]. DWI does not require gadolinium contrast, which is attractive in patients with renal dysfunction at risk for nephrogenic systemic fibrosis [61-63].

DWI acquisition—DWI is performed optimally on systems with high performance gradients usually using a single shot echoplanar imaging (SS EPI) sequence with diffusion gradients applied in 3 orthogonal directions [frequency-encoding (x), phase-encoding (y), section-select directions (z)]. Breath-hold or free breathing or respiratory triggered EPI sequences can be performed in conjunction with parallel imaging to improve image quality [64,65]. A free breathing or respiratory triggered acquisition allows the use of multiple levels of diffusion weighting (b-values) in a single acquisition, with improved image quality compared to breath-hold acquisition, however at the expense of longer acquisition time [66]. The selection of b-values is based on a compromise between image quality and adequate diffusion-weighted contrast [67]. At least 3 b-values should be used to obtain a good fit for apparent diffusion coefficient (ADC) calculation.

DWI processing—The process of ADC calculation is usually automated on most clinical systems. This is achieved by performing a mono-exponential fit between the liver signal intensity (in logarithmic scale) and the b-values as follows: $ADC = \ln(SI_0/SI)/b$ (in which SI_0 is signal intensity for $b=0$, and SI is for higher b_0 -value). The slope of the line which describes this relationship in each voxel represents the ADC. In diffuse liver disease, ADC values should be calculated in multiple locations within the liver (excluding the lateral left lobe which could be affected by cardiac related artifacts) by placing regions of interest (ROIs) to measure ADC values.

DWI results in liver fibrosis and cirrhosis—Several studies have demonstrated that ADC of cirrhotic liver is lower than that of normal liver [67-72] (Fig. 2). Koinuma et al [73] demonstrated a significant negative correlation between hepatic ADC and fibrosis score in a large population of patients ($n=163$) using a low b-value (128 s/mm^2). However, their results showed no correlation between ADC and inflammation grades. Lewin et al. [74] investigated the role of DWI (using b-values of $400\text{-}800 \text{ s/mm}^2$) compared to FibroScan and serum markers in a large series of HCV patients ($n=54 + 20$ healthy volunteers), and demonstrated an excellent performance of DWI for prediction of moderate and severe fibrosis, and prediction of severe fibrosis and cirrhosis. Patients with moderate-to-severe fibrosis (F2-F4) had hepatic ADC values lower than those without or with mild fibrosis (F0-F1) and healthy volunteers: 1.10 ± 0.11 vs. 1.30 ± 0.12 vs. $1.44 \pm 0.02 \times 10^{-3} \text{ mm}^2/\text{s}$, respectively. For the discrimination of patients with fibrosis stage F3-F4 from F0-F2, the areas under the curves (AUCs) were 0.92 for DWI, 0.92 for FibroScan, 0.79 for FibroTest, and 0.86-0.87 for other blood tests. Sensitivity, specificity, positive predictive value, and negative predictive value were 87%, 87%, 72%, and 94%, respectively, for DWI (using ADC cutoff of $1.21 \times 10^{-3} \text{ mm}^2/\text{s}$). In addition, they found a significant relationship between ADC and inflammation scores, and suspected a possible associated influence of steatosis on ADC values. Girometti et al [75] reported lower ADC in cirrhotic livers compared to healthy controls, and showed an area under the curve (AUC) of 0.93, with sensitivity of 89.7% and specificity of 100% for diagnosing cirrhosis (using b-values of $0\text{-}150\text{-}250\text{-}400 \text{ s/mm}^2$). In our experience, we have found ADC to be a significant predictor of fibrosis stage ≥ 1 (sensitivity 88.5% and specificity 73.3%) and inflammation grade ≥ 1 (sensitivity 75% and specificity 78.6%) [76]. In a separate study, we showed a decrease in liver ADC in significant and severe fibrosis using b-values $\geq 500 \text{ s/mm}^2$ [77] with the best correlation demonstrated with $b=700 \text{ s/mm}^2$.

The mechanism of diffusion restriction in patients with chronic liver disease is not clearly understood, and is likely multifactorial; possibly related to the presence of increased connective tissue in the liver (which is proton poor) and from decreased blood flow. A recent animal study [78] showed that rats with hepatic fibrosis demonstrate reduced ADC values in vivo but not when DWI was performed ex vivo, which suggests that decreased perfusion had the primary effect on decreased apparent diffusion. In addition, recently published work by Luciani et al [79], based on intravoxel incoherent motion MR (IVIM) [80-84], has also suggested that

restricted diffusion observed in patients with cirrhosis reflects diminished capillary perfusion and to a much lesser extent pure molecular diffusion. Their analysis of 37 patients demonstrated lower ADC values between cirrhotic and normal livers ($ADC = 1.23 \pm 0.4$ vs. $1.39 \pm 0.2 \times 10^{-3} \text{ mm}^2/\text{s}$) which they attributed primarily to reduced perfusion in cirrhotic livers.

➤ Perfusion-weighted MRI (PWI)

Liver perfusion can be assessed by following the uptake and washout of Gd based contrast agents using high temporal resolution T1-weighted imaging. Because of the lack of ionizing radiation, PWI can be used to quantify perfusion of the whole liver, with the possibility of repeating the study after treatment. However, with the recent recognition of the risk of nephrogenic systemic fibrosis [61-63], gadolinium based contrast agents should be avoided in patients with severe renal dysfunction.

PWI acquisition—With state of the art systems, it is possible to cover the entire liver with good spatial and temporal resolution. The majority of prior liver PWI studies have relied on a 2D acquisition limited to a single axial slice in order to preserve high spatial and temporal resolution [85-87]. The initial experimental work on PWI by Scharf et al. in 1999 [85] on pigs (at 1.0T) demonstrated a good correlation between MR perfusion parameters and a reference thermal diffusion probe in the setting of partial portal vein occlusion. Materne et al and Annet et al [86,87] performed PWI at 1.5T using a single axial slice at the level of the portal vein, using cardiac triggering, which enabled high temporal resolution. At our institution, we perform whole liver perfusion imaging at 1.5-T or 3T using a 3D interpolated spoiled gradient-recalled echo sequence in the coronal plane, with an acceleration factor of 3 [88]. One to three volume acquisitions are performed prior to IV contrast administration [10 ml of gadopentetate dimeglumine (Magnevist; Berlex Laboratories, Wayne, NJ) or 10 ml of gadobenate dimeglumine (MultiHance; Bracco Diagnostics, Princeton, NJ)]. Approximately 36 to 40 coronal slices are acquired every 3 to 5 seconds (depending on the liver size). The images are acquired first during a breath-hold and then during quiet free breathing, for a total acquisition time of 3 to 5 minutes.

PWI processing—By placing regions of interest (ROIs) in the tissue of interest, SI (signal intensity) vs. time curves are obtained (Fig. 3). ROIs are placed in the main portal vein, proximal abdominal aorta (used as a surrogate for the hepatic artery) and liver parenchyma to measure SI. To simplify the perfusion quantification, a linear relationship between SI and [Gd] (Gadolinium concentration) can be assumed for the range of expected concentrations in the liver and blood, based on prior work on measurement of Gd-DTPA concentration in vivo and in vitro [89]. However, it is also possible to perform a potentially more accurate non-linear conversion of SI to [Gd] using either analytic expressions [90], calibration curves from phantom studies, or pre-contrast T1 measurements [89,91]. A dual-input single compartmental model, which has been validated previously using radiolabeled microspheres in rabbits [86], can be used to fit the resulting time-activity curves in the liver. This model reflects the dual blood supply from the portal vein and hepatic artery received by the liver. Details on the model can be obtained elsewhere [87,88]. The following parameters can be obtained: absolute arterial blood flow (F_a) (in ml/min), absolute portal venous blood flow (F_p) (in ml/min), arterial fraction (ART, in %) = $100 \times F_a / (F_a + F_p)$, portal venous fraction (PV, in %) = $100 - \text{ART}$, distribution volume (DV in %) of Gd through the liver, and mean transit time (MTT in sec: average time it takes a Gd molecule to traverse the liver from arterial/portal venous entry to the hepatic venous exit).

PWI results for the diagnosis of liver fibrosis and cirrhosis—Liver fibrosis and cirrhosis are associated with alterations in liver perfusion secondary to pathophysiologic alterations including endothelial defenestration and collagen deposition in the space of Disse.

In a rabbit model of liver fibrosis, Van Beers et al [92] demonstrated increased liver MTT using a low molecular contrast agent and decreased DV using a high molecular contrast agent that correlated with the collagen content in the liver. In a study of 46 patients with cirrhosis, Annet et al [87] demonstrated altered arterial, portal and total liver perfusion, as well as increased MTT in cirrhotic livers compared to non cirrhotic livers, and found a correlation with severity of disease as assessed by the Child-Pugh class and degree of portal hypertension. Our group performed a prospective study assessing liver perfusion parameters, and we demonstrated increased arterial flow, MTT and DV, and decreased portal venous flow in patients with advanced fibrosis and cirrhosis (n=27) [88]. DV, MTT and arterial flow (Fa) had the best sensitivity (76.9-84.6%) and specificity (71.4-78.5%) for the diagnosis of advanced fibrosis, as determined by histological examination. The increased DV in patients with cirrhosis may be related to increased interstitial volume. The increase in MTT may be explained by collagen deposition in the extracellular space of Disse restricting diffusion of small particles.

➤ MR Elastography (MRE)

MRE is an emerging diagnostic imaging technique for quantitatively assessing the mechanical properties of tissue [93]. Normal liver human liver tissue is very soft to palpation at surgery, similar to subcutaneous adipose tissue. In contrast, it is well known that the liver becomes very firm or even hard to palpation in patients with cirrhosis. Based on these considerations, investigators have developed techniques for applying MRE for evaluating the liver and have tested the usefulness of the technique for diagnosing hepatic fibrosis. MRE involves a three-step process: (i) generating mechanical waves within the tissues of interest, (ii) imaging the micron-level displacements caused by propagating waves using a special MRI technique with oscillating motion-sensitizing gradients, and (iii) processing the wave images using an “inversion” algorithm to generate quantitative maps of mechanical properties. MRE can be implemented on a standard MR system by installing a device for generating mechanical vibration in the liver under MR scanner control, a special MRE pulse sequence, and processing software to generate the diagnostic MRE images, which are called “elastograms”. In a typical implementation, a simple, drum-like “passive” acoustic driver is placed over the right anterior chest wall and coupled to a source of low frequency sound wave by a flexible tube (Fig. 4). Vibrations at 40-90 Hz are generated in the abdomen with this device. The waves are imaged with a modified phase contrast MRI pulse sequence. Imaging time can be as short as approximately 15 seconds, using parallel acquisition techniques and is done during suspended respiration. Because the incremental imaging time is so small, MRE can readily be added to standard abdominal MRI protocols. MRE data are processed with a special inversion algorithm to generate a quantitative image showing the elasticity of the liver. Clinical studies by multiple investigators have established that MRE is an accurate method for diagnosing hepatic fibrosis [94-101] (Fig. 5). MRE-measured hepatic stiffness increases systematically with fibrosis stage. In a study encompassing 50 patients with biopsy-proven liver disease and 35 normal volunteers, ROC analysis showed that, with a shear stiffness cut-off value of 2.93 kPa, the predicted sensitivity and specificity for detecting liver fibrosis is 98% and 99%, respectively [98]. ROC analysis also provided evidence that MRE can discriminate between patients with moderate and severe fibrosis (stages 2–4) and those with mild fibrosis (stages 0-1) with sensitivity of 86% and specificity of 85%. Importantly, hepatic stiffness is not systematically influenced by the presence of steatosis [98]. A study comparing MRE and ultrasound transient elastography (FibroScan) in a series of 141 patients with chronic liver disease demonstrated that the rate of technical success for MRE was higher (94%) than that of FibroScan (84%), and that MRE had better diagnostic accuracy [101]. The presence of ascites or obesity can cause FibroScan to fail, whereas these conditions have little effect on MRE [102]. Due to the global view of the liver provided by MRE, it is also potentially less affected by sampling error than biopsy and FibroScan [102]. Studies of patients with chronic liver disease have shown a correlation between the MRE-measured stiffness of the spleen and the biopsy-proven grade of hepatic

fibrosis. It is possible that this may reflect the presence of portal hypertension, with the spleen becoming stiffer as pulp pressure increases. If true, this points to the possibility that MRE may be useful for estimating portal venous pressure.

DIAGNOSIS AND QUANTIFICATION OF HEPATIC STEATOSIS WITH MRI

For over 20 years, MRI has been an established method to detect the presence of hepatic steatosis [103]. MRI exploits the fact that fat resonates more slowly than water, by 210 Hz at 1.5T [103,104].

➤ MR Spectroscopy (MRS)

¹H MRS is considered to be a non-invasive gold standard method for measuring hepatic fat content, with many studies showing strong correlations demonstrated between MRS and histologic grade of steatosis [105-112]. Most methods use single voxel spectroscopy (SVS) approaches such as PRESS [113] or STEAM [114] and are easily performed within a few breath-holds. The main disadvantage of SVS is that a single, large voxel (typically $2.0 \times 2.0 \times 2.0 = 8.0 \text{ cm}^3$) is interrogated and it cannot provide volumetric evaluation of the fat content of the liver. It is well known that hepatic steatosis is often heterogeneous, and thus SVS cannot provide a comprehensive evaluation of hepatic steatosis. However, 2D CSI (chemical shift imaging) methods are being developed. In addition, MRS methods must use long TR values to avoid T1 related bias, and in theory must correct for differential T2 decay between water and fat. Because MRS methods are spin-echo based, there is concern for the effects of J-coupling [115] that could influence the relative amplitudes of fat vs. water signal and bias estimates of fat fraction. Finally, unlike image based fat quantification methods that automatically generate a fat fraction image from which fat content can be assessed, MRS requires relatively complex post-processing involving some user interaction in order to measure the fat fraction from the acquired spectrum.

➤ Dixon methods

“In-phase” and “out-of-phase” (IOP) imaging was first described by Dixon in 1984 [116] and is commonly used for the detection of fat, acquiring in-phase images at TE=4.6 ms (at 1.5T) when signal from water and fat add, and out-of-phase images at TE=2.3ms when signal from water and fat subtract. Fig. 6 shows examples of mild and severe hepatic steatosis confidently diagnosed with conventional IOP imaging. However, a precise measure of fat concentration in the liver is difficult to discern from these images. Fishbein et al [117], and more recently Hussain et al [118] as well as others [119,120] have described the use of IOP imaging for quantification of steatosis. This method measures the signal decrease in “out-of-phase” (OP=W-F) images relative to “in-phase” (IP=W+F) images. Using these images, fat-signal fraction is calculated:

$$\eta = \frac{F}{F+W} = \frac{IP - OP}{2IP} \quad (1)$$

These investigators have shown excellent correlation between fat fraction and the fat measured with MRS. Unfortunately, conventional IOP imaging suffers from three drawbacks. First, fat fractions over 50% cannot be assessed reliably [118,121], because separation of water and fat signals is necessary to measure fat fractions from 0-100%. Hepatic fat fractions greater than 50% are very uncommon, however. As a result of this ambiguity, more recent approaches have employed chemical shift based water-fat separation methods in order to generate separate water and fat images that allow direct calculation of fat fraction images with a complete dynamic range from 0-100% [112,122,123]. The second major drawback of conventional IOP imaging is that it is highly dependent on T₁ and T₂*. Although fat fraction measurements made with IOP

imaging demonstrates excellent correlation with other measures of hepatic steatosis (MRS, biopsy, phantoms, etc), the estimates of fat fraction made with IOP imaging do not represent a biologically based estimate of the fat concentration in the liver.

Fat fraction estimates are highly dependent on acquisition parameters such as TR, TE, flip angle, and field strength, all of which alter the degree of T_1 and T_2^* weighting. Differences in T_1 between fat and liver tissue lead to over estimation of fat if the acquisition is T_1 weighted. T_2^* decay corrupts the signal evolution of both water and fat as TE increases, leading to errors in fat fraction estimation. The confounding effects of T_1 and T_2^* were recognized by Fishbein et al [117] and Hussain et al [118]. More recently, Liu et al [124] and Bydder et al [125] proposed a low flip angle approach that avoids T_1 related bias by making the fat fraction estimates T_1 independent. Correction for T_2^* decay has been addressed by Hussain et al [118] who used a second acquisition to measure and correct for T_2^* . More recently, Yu et al [126] and Bydder et al [125], have developed T_2^* correction approaches in combination with 6 echo acquisition strategies. By directly estimating the T_2^* as part of acquisition itself, the effects of T_2^* are removed and more accurate estimates of water and fat (and subsequently fat fraction) can be made. Lack of correction for T_2^* decay can lead to very large errors. For example, in a liver with no fat, and $T_2^*=25\text{ms}$, the apparent fat fraction with IOP imaging is 5%, which is an unacceptably high error, especially if we consider a 5.6% detection threshold. In addition, abnormally elevated intra-hepatic stores of iron are common in NAFLD. Hepatic iron overload is well known to create oxidative stress that leads to end-stage cirrhosis, liver failure and the development of hepatocellular carcinoma [127], which is a major cause of death in patients with primary hemochromatosis [127].

Recent studies have demonstrated that up to 40% of NAFLD patients have concomitant iron overload [128,129], with a strong association between iron and aggressive histology [129, 130]. Regardless of the role of iron, its presence has important implications for MRI methods attempting to quantify steatosis. Iron results in accelerated signal decay (T_2^* decay), further accelerating signal decay and leading to larger errors in fat fraction estimates. Therefore, any MRI method that attempts to quantify hepatic steatosis must decouple the effects of iron overload.

The final disadvantage of conventional IOP fat fraction imaging, as well as conventional chemical shift based water separation methods is the spectral complexity of fat. Historically, IOP imaging and most chemical shift based fat-water separation methods model water and fat both as single NMR peaks. While the spectral peak of water is a well defined single peak, fat is well known to contain at least 6 well defined peaks, at least two of which are very close to the water peak [131]. As a result, it is not possible to accurately separate water and fat signals if fat is modeled as a single resonance. Recently, Bydder et al [125] and Yu et al [132] introduced methods that accurately model spectral modeling of fat that accounts for the different chemical shifts of each fat peak as well as the relative amplitudes of these peaks. The use of accurate spectral modeling has been demonstrated to greatly improve the agreement between the measured fat fraction with imaging and gold standards such as MR spectroscopy [133,134]. Methods that provide accurate estimation of fat content in the liver that are biologically based and have broad applicability across multiple platforms and field strengths, must be T_1 independent, correct for T_2^* decay and accurately model the NMR spectrum of fat.

Fig. 7 shows a fat fraction image obtained from a T_1 independent acquisition with T_2^* correction and accurate spectral modeling, based on a 6-echo IDEAL (Iterative Decomposition of water and fat with Echo Asymmetry and Least squares estimation) acquisition [122,126, 132], demonstrating close agreement with single voxel MR spectroscopy [133]. Fig. 8 shows fat fraction images acquired with a T_1 independent acquisition with T_2^* correction and accurate spectral modeling based on 6 magnitude images acquired in-phase and out of phase

[125]. In this example, an approximately 20% decrease in liver fat concentration is nicely demonstrated in a morbidly obese patient undergoing rapid weight loss. Of note, this method is a magnitude-based approach and therefore cannot resolve fat fractions greater than 50%, which is why subcutaneous fat appears dark in these fat fraction images. However, this approach, as well as the IDEAL based method both been shown to have excellent agreement with MRS, indicating that measurements of liver fat are biologically based and directly measure the fat concentration in the liver [133,134]. An interesting and important advantage of T2* correction methods such as those by Yu et al [126] and Bydder et al [125] is that R2* ($=1/T2^*$) images are estimated. As discussed below, T2* measurements in the liver provide accurate measures of liver iron content, and thus, T2* correction fat quantification methods have the added benefit of simultaneous iron quantification in the liver.

The main disadvantage to both the magnitude based and IDEAL based approach is that it requires at least six echoes in order to accurately estimate and correct for T2*. This necessarily increases scan time and limits coverage of the liver within a breath-hold, requiring acceleration methods such as parallel imaging methods. In addition, although initial studies have shown excellent correlation with MRS, no large-scale studies comparing these image-based fat quantification methods with biopsy have been performed to verify their accuracy.

DIAGNOSIS AND QUANTIFICATION OF HEPATIC SIDEROSIS WITH MRI

Iron overload in the liver can result from a variety of causes, but is most commonly encountered in patients with genetic hemochromatosis, transfusional hemosiderosis and a chronic inflammatory state (eg. NASH, viral hepatitis, alcohol, etc). Increased iron stores are toxic to the liver and are well known to be carcinogenic in patients with hemochromatosis [127]. Although serum markers provide indirect measures of iron overload, accurate evaluation of liver iron content requires liver biopsy and biochemical extraction of iron from the biopsy specimen. This process has the associated risks and expense of biopsy and is limited for repeated follow-up evaluation of liver iron content. Thus, it would be highly desirable to have a relatively inexpensive, non-invasive method, such as MRI for accurate quantification of liver iron content.

Conventional T2 and T2* weighted imaging provides an excellent means for qualitative detection of hepatic iron overload. For example, Fig. 9 demonstrates the effects of iron overload in two patients, one with transfusional hemosiderosis and the other with genetic hemochromatosis. In addition, iron overload can also be diagnosed with conventional IOP imaging, as shown in Fig. 10. Paradoxical signal dropout is seen on the in-phase image, because this image is acquired at a longer TE than the out of phase image and iron accelerates T2* and T2 decay. Of note, this paradoxical dropout explicitly demonstrates why iron confounds the ability of IOP imaging to quantify fat: iron and fat have the opposite effect on signal dropout. The pattern of signal dropout in different organs can be used to distinguish the type of iron overload. For example, genetic hemochromatosis generally affects the liver and pancreas, and spares the spleen and bone marrow, while hemosiderosis (eg. from transfusional iron overload) affects the liver, bone marrow and spleen, while leaving the pancreas unaffected.

In recent years, MRI methods have been developed for the quantification of hepatic iron overload based on both T2* and T2-weighted imaging methods. A widely accepted and commonly used approach is that developed by Gandon et al [135], based on an imaging-biopsy correlation study in 174 patients. This protocol uses a combination of 2D gradient echo images acquired with proton density weighting, T1 weighting, and escalating T2* weighting. SI measured with this protocol are fed into a calibration curve that provides accurate estimates of hepatic iron concentration. Although this approach is widely accepted and used, it has the disadvantage that it requires specific scanner dependent parameters such as TR, TE, flip angle

and field strength (1.5T). This method also requires several breath-holds and multiple signal intensity measurements. A convenient website is available where signal intensities can be entered and estimates of hepatic iron concentration are provided [136]. More recent approaches for iron quantification have focused on direct measurement of $T2^*$ or $R2^*$ ($=1/T2^*$) mapping. Using a 3D multi-echo gradient echo acquisition, Wood et al recently performed a study in 102 patients undergoing biopsy demonstrating a linear correspondence between $R2^*$ and hepatic iron concentration [137]. This work provides a useful calibration between $R2^*$ and hepatic iron concentration. The primary advantage of this approach is that a fundamental tissue property ($R2^*$) is measured and is, in principle, independent of acquisition parameters such as TR, TE and flip angle. The calibration between $R2^*$ and iron concentration will be dependent on field strength of course, and many investigators are currently evaluating the use of $R2^*$ measurements at 3T for iron quantification [138]. Another primary advantage of $R2^*$ mapping is that rapid 3D multi-echo gradient echo sequences are now available for rapid $R2^*$ measurements within a single breath-hold. $R2^*$ values can be fit from the data in a fully automated manner, requiring no user input other than measuring $R2^*$ from the images and determining hepatic iron concentration from the calibration curve. Fig. 10 also shows an $R2^*$ map from the same location calculated using the $T2^*$ approach described by Yu et al [126], explicitly showing the iron overload in the liver, while sparing the spleen. These approaches can also be used to monitor therapy for patients with hemochromatosis, such as that seen in Fig. 11 demonstrating a decrease in $R2^*$ (increase in $T2^*$) after phlebotomy therapy. Finally, Fig. 12 shows images from a patient with biopsy proven steatosis and iron overload, acquired with a $T2^*$ corrected water-fat separation method [126]. No apparent change in SI is seen in the IOP images. The fat fraction image, however, demonstrates 9% fat and a shortened $T2^*$ (15.1ms), explicitly demonstrating the need to methods to separate the effects of fat and iron. If fat and iron are both present they will confound the ability of conventional IOP imaging to detect and quantify the other.

LIMITATIONS OF MRI METHODS

Some general limitations of the methods described above include limited availability, complex acquisition and processing, and a learning curve. Some of these methods (eg, MRE) are still limited to few centers, and should be rapidly expanding as more data is available, and as MR vendors will make some of these methods commercially available. In addition, large multi-institutional studies are desirable to prove the role of these methods alone or combined for the diagnosis of liver fibrosis and cirrhosis, and for fat and iron quantification.

Specific limitations for each method are discussed below:

DWI: Image quality needs to be improved, especially at higher field. The use of different sequence parameters and hardware makes it difficult to compare between studies and DWI requires more standardization [139]. Liver fat and iron deposition may also alter diffusion measurements, and should be assessed. Other technical factors such as cardiac motion limiting evaluation of the left hepatic lobe and respiratory motion effecting ADC values in the right lobe need to be addressed with respiratory triggered techniques.

PWI: Similarly to DWI, the selection of imaging parameters and perfusion models vary widely among studies, and limit the comparison of PWI results from study to study. The intensive post-processing required to obtain perfusion parameters is a barrier to the widespread clinical use of PWI.

MRE: The most common cause of technical failure of MRE is the presence of hepatic iron overload. The resulting low signal intensity of the liver can prevent adequate visualization of mechanical waves. Alternative MRE pulse sequences can be developed to address this problem.

FUTURE DIRECTIONS

Multiparametric imaging combining conventional sequences with some of the above discussed techniques (alone or in combination) could enable a comprehensive examination of the liver, including the information on the presence of fat, iron and fibrosis, as well as HCC and portal hypertension, and could represent the future of liver imaging, possibly replacing the liver biopsy, at least for follow-up studies. This would constitute an important clinical tool. In addition, this could be used as a non invasive tool for prospective drug trials assessing antiviral and antifibrotic trials.

The use of 3T imaging provides higher SNR and theoretically improved image quality. However, at higher fields, DWI using SS EPI is limited by increased susceptibility, which limits the use of higher b-values. Optimized fat-water imaging at 3T should also be standardized.

CONCLUSIONS

With the continued increased prevalence of liver disease (mostly due to NAFLD and HCV infection), MRI will play an increasingly important role in the evaluation of patients with chronic liver disease, due to the lack of ionizing radiation, and the possibility of performing multiparametric imaging combining conventional and functional sequences. However, more clinical evidence is needed to determine which method or combination of methods achieves the best accuracy for assessment of fibrosis, fat and iron deposition.

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Abbreviations (in alphabetical order)

ALT	alanine aminotransferase
ART	arterial fraction (%)
AST	aspartate aminotransferase
AUC	area under the curve
DV	distribution volume (%)
DWI	diffusion-weighted imaging
Fa	absolute hepatic arterial flow (ml/100g/min)
Fp	absolute hepatic portal venous flow (ml/100g/min)
Gd	gadolinium chelates
[Gd]	Gd concentration (mM/L)
HCV	hepatitis C virus
IDEAL	Iterative Decomposition of water and fat with Echo Asymmetry and Least squares estimation
IOP	in- and out-of-phase
IVIM	intravoxel incoherent motion MR
MRE	magnetic resonance elastography
MRS	magnetic resonance spectroscopy

MTT	mean transit time (sec.)
NAFLD	non alcoholic fatty liver disease
NASH	non alcoholic steatohepatitis
PV	portal venous fraction
PWI	perfusion-weighted imaging
SI	signal intensity

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Figure 1.

Although the pathophysiology of NAFLD (non alcoholic fatty liver disease) is not entirely understood, it is generally thought that insulin resistance leads to the intracellular accumulation of triglycerides and fatty acids, which are known to cause oxidative stress. The presence of an unknown second "hit" leads to the development of inflammation (NASH: non-alcoholic steatohepatitis), injury and fibrosis, an ultimately cirrhosis. Like all patients with cirrhosis, those with NASH are at increased risk of liver failure or HCC.

Figure 2.

52 year-old male with chronic hepatitis C without evidence of fibrosis at liver biopsy (F0-top row) and 67 year-old female with cirrhosis secondary to chronic hepatitis C (F4-bottom row). Breath-hold fat suppressed TSE T2-weighted image and breath-hold fat suppressed single shot echoplanar diffusion-weighted images for $b=0$, and $b=700 \text{ mm}^2/\text{s}$ and ADC map (using $b=0$ and $700 \text{ mm}^2/\text{s}$) are shown. In the patient without fibrosis, hepatic ADC was within normal range, measuring $1.6 \times 10^{-3} \text{ s/mm}^2$, the liver appearing brighter than the spleen (which is known to have low ADC). In the cirrhotic patient, T2-weighted image shows minimal morphologic changes in relation with cirrhosis. However, hepatic ADC was decreased (reaching the spleen ADC), measuring $1.0 \times 10^{-3} \text{ s/mm}^2$ (according to the ADC values described by Taouli et al [77]).

Figure 3.

54-year old female with cirrhosis secondary to chronic hepatitis C. Perfusion MR images of the liver (top) obtained using a coronal 3D interpolated spoiled gradient-recalled echo sequence covering the entire liver before and after injection of 10 ml of Gd-DTPA with a temporal resolution of approximately 3 sec. Selected time points from 35 measures are shown in chronological order (top to bottom, left to right). Progressive opacification of the aorta, hepatic artery, portal vein and liver parenchyma are observed. Signal intensity vs. time curve (bottom) obtained by placing regions of interest (ROIs) in the aorta (used as a surrogate for the hepatic artery), portal vein and liver parenchyma. Visually, there is evidence for delayed enhancement of the liver parenchyma. A dual input single compartmental model [87,88] was used to compute the perfusion parameters, which showed increased arterial fraction (36%), hepatic arterial flow (14.5 ml/100g/min), distribution volume (27%) and mean transit time (40 sec), and decreased hepatic portal venous flow (29 ml/100g/min) consistent with advanced fibrosis/cirrhosis [88] .

Figure 4.

Magnetic resonance elastography as performed in a standard scanner. A plastic drum-like passive driver device is placed over the liver to generate shear waves that can be imaged with a special phase-contrast MRI sequence. The abdominal acoustic driver is powered by a speaker-like device (on left) that can be placed outside the magnet room and connected to the passive driver by flexible tubing. Propagating shear waves are imaged and then the information is processed to generate elastograms, which quantitatively depict the stiffness of tissues.

Figure 5. Assessment of hepatic fibrosis with MRE (magnetic resonance elastography) in three patients with chronic liver disease

Left column: T2-weighted anatomic images. Middle column: MRE wave images. Right column: MR elastograms, stiffness of liver tissue. Top Row: The liver has normal appearance in the anatomic image, and the wave image shows that shear waves at 60 Hz have a short wavelength, consistent with the normally soft mechanical characteristics of normal liver tissue. The elastogram shows a mean stiffness value of 2.1 kPa, well below the upper limit of normal (2.9 kPa), indicating the absence of hepatic fibrosis. Middle row: This patient also has a normal-appearing liver, but the wave images show relative prolongation of the visualized shear waves. The elastogram shows an abnormally high mean stiffness value of 4.8 kPa, consistent with moderate hepatic fibrosis. Biopsy demonstrated stage 1 fibrosis. Bottom row: Third patient has an abnormal hepatic contour and ascites, consistent with chronic liver disease. The wave image shows marked lengthening of the visualized shear waves. The elastogram shows that liver stiffness is markedly heterogeneous, with many confluent areas measuring more than 8 kPa in stiffness. Biopsy confirmed the presence of moderate to advanced fibrosis.

Figure 6. In-phase (left) and out of phase (right) images in two patients with hepatic steatosis. Marked dropout on out-of-phase images is present in patient 1, consistent with qualitatively severe steatosis. Mild signal dropout is seen on the out of phase image of patient 2, with focal fatty sparing near the gallbladder fossa, consistent with mild steatosis (white arrow).

Figure 7.

Fat fraction MR image (left) obtained using a T_1 independent, T_2^* corrected acquisition with accurate spectral modeling using the IDEAL (Iterative Decomposition of water and fat with Echo Asymmetry and Least squares estimation) water-fat separation methods [122,124,126, 132] demonstrates close agreement with single voxel MR spectroscopy from a $2 \times 2 \times 2$ cm voxel from the posterior segment of the right lobe of the liver (square). Fatty sparing in the gallbladder fossa (white arrow) is noted incidentally. At least six discrete fat spectral peaks (denoted by *) can be seen in the spectrum.

Figure 8.

Fat fraction MR image in a 350 lb woman before (left) and after (right) a 27 lb weight loss in 27 days, acquired using Bydder's T_1 independent, T_2^* corrected method with accurate spectral modeling [125]. Overall fat fraction was variable throughout the liver, but demonstrated changes of approximately 3-5% from an initial fat fraction of 16-24%. Fat in adipose tissue appears black because of the inherent ambiguity of fat fractions greater than 50%, however, excellent quantification of hepatic steatosis can be achieved using this method (Image courtesy Masoud Shiehmorteza, Liver imaging Group, UCSD).

Figure 9.

T2* weighted (TE=10ms) gradient echo image of a patient with transfusional hemosiderosis (left) qualitatively demonstrates iron overload through decreased signal in the spleen (short arrow) and bone marrow (arrowhead) in addition to the liver. Note also the sparing of the pancreas (thin arrow). In contrast, the right image shows a T2 weighted fast spin-echo (TE=80ms) image from a patient with genetic hemochromatosis demonstrating decreased signal in the pancreas (thin arrow) in addition to the liver, with sparing of the spleen (short arrow) and bone marrow (arrowhead). The patterns of signal dropout are easily depicted on these conventional imaging methods, which are very helpful in distinguishing the etiology of these two forms of iron overload. However, assessing the severity of disease requires quantitative methods.

Figure 10.

In-phase (left) and out of phase (middle) images in a patient with genetic hemochromatosis demonstrates paradoxical signal drop out of the liver on the in-phase image. This occurs because the TE of the in-phase image (4.6ms) is longer than the out of phase image (2.3ms) leading to signal dropout from accelerated T2* decay in the presence of iron overload. Note the lack of signal dropout in the spleen, which is characteristic of genetic hemochromatosis. An R2* map acquired from the same patient using the method of Yu et al [126] is shown on the right, demonstrating a markedly abnormal $R_2^* = 240\text{s}^{-1}$ ($T_2^* = 4.1\text{ms}$).

Figure 11.

R₂* images measured using the method of Yu et al [126], in a patient with genetic hemochromatosis, before (left) and after (right) one year of phlebotomy therapy. Before therapy, R₂*=192s⁻¹ (T₂*=5.2ms) and after one year of phlebotomy, R₂*=106s⁻¹ (T₂*=9.4ms), demonstrating a treatment response that correlates with a drop in serum ferritin from 184 ng/ml to 91 ng/ml.

Figure 12.

In-phase and out of phase (left) images in a patient with biopsy proven hepatic iron overload and steatosis. Signal intensities in the in-phase and out of phase images were nearly identical (846 AU and 851 AU, respectively) suggesting neither fat nor iron. However, simultaneous estimation of fat and $R2^*$ using the method of Yu et al [126] indicates abnormal level of steatosis (9%) and shortened $T2^*$ (15.1ms, normal = 25-30ms). Also note the shortened $T2^*$ in the spleen (9.7 ms), which can also be inferred through signal drop out in the spleen on the in-phase image (white arrow).