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Multiparametric MRI in Patients With Nonalcoholic Fatty Liver Disease

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Nonalcoholic fatty liver disease (NAFLD) is a common cause of chronic liver disease in the world, affecting more than 25% of the adult population. NAFLD covers a spectrum including simple steatosis, in which lipid accumulation in hepatocytes is the predominant histological characteristic, and nonalcoholic steatohepatitis (NASH), which is characterized by additional hepatic inflammation with or without fibrosis. Liver biopsy is currently the reference standard to discriminate between hepatic steatosis and steatohepatitis. Since liver biopsy has several disadvantages, noninvasive diagnostic methods with high sensitivity and specificity are desirable for the analysis of NAFLD. Improvements in magnetic resonance imaging (MRI) technology are continuously being implemented in clinical practice, specifically multiparametric MRI methods such as proton density fat-fraction (PDFF), T2⁎, and T1 mapping, along with MR elastography. Multiparametric imaging of the liver has a promising role in the clinical management of NAFLD with quantification of fat content, iron load, and fibrosis, which are features in NAFLD. In the present article, we review the utility and limitations of multiparametric quantitative imaging of the liver for diagnosis and management of patients with NAFLD.

Level of Evidence: 5.
Technical Efficacy Stage: 3.
CHRONIC LIVER DISEASE is a worldwide health burden, mainly caused by alcoholic liver disease, viral infection, and nonalcoholic fatty liver disease (NAFLD). NAFLD has a global prevalence of 25% and represents a disease spectrum including simple steatosis, in which lipid accumulation in hepatocytes is the predominant histological characteristic, and nonalcoholic steatohepatitis (NASH), which is characterized by additional hepatic inflammation with or without fibrosis.1,2 NASH can further lead to advanced fibrosis and NASH-related cirrhosis, increasing the risk of hepatocellular carcinoma (HCC).3 NASH has an estimated prevalence between 1.5% and 6.5% in the general population and is expected to become the most common indication for liver transplantation in the near future.4 The diagnosis and classification of NAFLD traditionally relies on liver biopsy, which has several well-known disadvantages such as bleeding complications, sampling error, and observer-dependent variability.5,6 Since the majority of patients with NAFLD have uncomplicated isolated hepatic steatosis, a noninvasive diagnostic method would be preferable. Noninvasive screening tests for NAFLD are either based on mathematical quantification of blood-derived biomarkers or based on imaging. Risk calculations such as fatty liver-index and NAFLD liver fat score could be used as first-line triage in the primary care setting to identify individuals with increased risk for NAFLD.7 Following referral to second-line, blood-based biomarker tests have their limitations since the diagnostic yield is too low and further assessment may be needed, for example, by liver biopsy.8 Therefore, a clinical need exists to have reliable noninvasive biomarkers for diagnosis and follow-up of NAFLD. In the last decade, reliable noninvasive multiparametric magnetic resonance imaging (MRI) methods with a specific focus on liver diseases have been developed to predict clinically meaningful endpoints. The advantages of multiparametric MRI are the imaging of the whole organ to exclude sampling variability and assessment of organ-specific tissue quantification. A relatively new method is the application of multiparametric MRI for the diagnosis of NAFLD with specific liver tissue quantification of fat, iron, and fibrosis. Therefore, multiparametric MRI methods offer an attractive option for noninvasive liver assessment.9 In this review article, we focus on clinical interpretation on MR elastography (MRE) and specific multiparametric MRI methods such as proton density fat-fraction (PDFF), T2*, and T1 mapping for the assessment of fat, iron, and fibrosis in patients at risk of NAFLD.

CLINICAL PERSPECTIVE OF NAFLD
NAFLD is defined as >5.6% fat accumulation in hepatocytes on imaging or histology, in the absence of other causes of hepatic steatosis (such as excessive alcohol intake or the use of certain medications). Abdominal, particularly visceral, obesity leading to insulin resistance is strongly associated with NAFLD, via increased distribution of free fatty acids to the liver and increased hepatic lipogenesis associated with hyperglycemia and hyperinsulinemia.10 Therefore, NAFLD is closely related to type 2 diabetes mellitus (T2DM) and the metabolic syndrome.11 The prevalence of NAFLD is higher in patients with T2DM (33–66%) and severe obesity (>95%), and components of the metabolic syndrome (hyperglycemia, visceral obesity, dyslipidemia, and hypertension) also increase the risk of developing NAFLD. Due to the high prevalence of T2DM, obesity, Western lifestyle, and diet, it is estimated that the overall NAFLD prevalence will grow to one-third of the worldwide population.12,13 While the majority of patients with NAFLD will not develop advanced liver disease, patients with NASH and advanced fibrosis have increased risk of liver-related complications and progression to endstage liver disease.7 Identification and management of high-risk patients with fibrogenesis (especially NASH) are essential, since the fibrosis stage is associated with increased overall- and disease-specific mortality.14 If high suspicion of NASH is present, a specialist referral is indicated with an in-depth assessment of disease severity, exclusion of other liver pathology, and the initiation of therapy.7 In case of doubt regarding the clinical diagnosis, a liver biopsy may be considered. Lifestyle modification is the first and most important intervention for patients with NAFLD. In obese and nonobese patients, even moderate weight reduction is effective and is independently associated with remission of NAFLD.15 For patients with NASH, treatment with vitamin E or pioglitazone can be considered; however, additional clinical evidence is needed to strengthen this recommendation.7 Multiple pharmaco-therapeutic interventions are currently emerging from clinical trials.

FAT QUANTIFICATION
Methods of Liver Fat Measurement
Hepatic steatosis is graded from 0–3, depending of the parenchymal involvement of steatosis (0%, 5–33%, 33–66%, >66%) with the standardized histologic scoring system for NAFLD.16 The measurement of steatosis can be performed with various imaging modalities, including ultrasound (US), computed tomography (CT), vibration-controlled transient elastography (TE) with controlled attenuation parameter (CAP), and MR-based methods such as proton MR spectroscopy (1H-MRS) and PDFF.

Non-MRI Modalities for Fat Quantification
Conventional US is the most used noninvasive imaging modality of hepatic steatosis, since it is widely available, affordable, well tolerated, and cheap. Steatosis hepatitis manifests as increased echogenicity of liver tissue as compared to kidney tissue with the degree of steatosis classified as absent, mild, or
severe. However, US functionality is limited in patients with a body mass index (BMI) >40 kg/m² and has low sensitivity and specificity in determination of mild steatosis. Furthermore, conventional US is observer-dependent and a quantitative estimation of hepatic steatosis is not possible. CT detects hepatic steatosis but is not recommended due to low sensitivity for low-grade steatosis and exposure to ionizing radiation. TE measurement with CAP is a quick, noninvasive bedside imaging modality for assessment of liver stiffness and steatosis. During a fasting state, elastography reflects liver stiffness by measurement of US propagation through the liver. CAP measures the degree of US attenuation that correlates with the degree of hepatic fat, with values ranging from 100–400 dB/m. CAP measurements are reliable and reproducible, with CAP cutoff values 248–311 dB/m corresponding to grade 2 hepatic steatosis (57–96% sensitivity and 62–94% specificity). Liver fat measurement with CAP is easy to use, has point-of-care access, and gives direct test results. However, in comparison to MRI-based methods such as ¹H-MRS and PDFF, CAP is less accurate in detecting grades of steatosis and an optimal threshold for hepatic steatosis is not yet established. The diagnostic accuracy of CAP can be affected by multiple factors such as age, ascites, BMI, visceral fat, and intercostal space width.

**MRI Modalities for Fat Quantification**

MRI quantification of liver fat content can be performed with different techniques, of which ¹H-MRS and PDFF are the most used in clinical practice and research studies. For the last decade, ¹H-MRS has been considered the gold standard for the noninvasive quantitative assessment of liver fat concentrations in patients. By measuring the direct proton signal of water and accumulated triglycerides in hepatocytes, the percentage of liver fat can be estimated (Fig. 1a). ¹H-MRS can accurately quantify hepatic steatosis and has high correlation with histology-determined steatosis. The drawbacks of ¹H-MRS are the long acquisition time and complicated planning procedure and postprocessing.
The current reference standard for MRI assessment of hepatic fat content is PDFF measurement. PDFF reflects the excitable fat protons (fat) in relation to the total number of excitable protons (fat + water). It is independent of field strength, scanner manufacturer, or type of platform. In short, PDFF consists of a gradient echo sequence in which water signal is acquired in-phase. Separately, combined water and fat signal is measured out-of-phase. This is fitted into an algorithm that estimates fat and water proton densities, resulting in a liver fat percentage (Fig. 2). PDFF accurately reflects the triglyceride concentration in liver tissue compared to steatosis grading on a histologic basis with high intra- and interobserver agreement. In a prospective validation study, PDFF showed a strong correlation with histologic steatosis grading, with an area under the curve (AUROC) of 0.90–0.94. PDFF can detect grade 1 steatosis (>5.2%) with high sensitivity and specificity (90.0–93.3%). A recent meta-analysis concluded that PDFF has high diagnostic value for the assessment and classification of steatosis hepatitis in patients with NAFLD. Compared to CAP, PDFF allows superior detection and grading of hepatic steatosis. Furthermore, quantification of hepatic steatosis in patients with morbidly obese patients can be challenging, with low success rates for US and TE. In a recent study, the success rate of PDFF measurement in obese patients was 98.1%.

Table 1. Multiparametric MRI in the Liver. In the first row we show schematic drawing of the macroscopic liver, representing healthy liver, hemochromatosis, steatosis hepatitis and NASH. In the second row in the same representative liver states, we show an increase in fat percentage in steatosis hepatitis and NASH. In the third row we show iron quantification which is only reduced in hemochromatosis, in others it is normal. In the fourth row, fibrosis/inflammation is normal except in NASH.

<table>
<thead>
<tr>
<th>Multiparametric MRI of the liver</th>
<th>Healthy liver</th>
<th>Hemochromatosis</th>
<th>Steatosis hepatitis</th>
<th>NASH steatohepatitis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fat (PDFF)</td>
<td>2.0%</td>
<td>4.0%</td>
<td>11.2%</td>
<td>25.7%</td>
</tr>
<tr>
<td>Normal value: &lt;5.6%</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Iron (T₂⁻)</td>
<td>17.4ms</td>
<td>7.2ms</td>
<td>16.3ms</td>
<td>12.6ms</td>
</tr>
<tr>
<td>Normal value: &gt;12.5 msec</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fibrosis/inflammation (cT₁)</td>
<td>683ms</td>
<td>748ms</td>
<td>780ms</td>
<td>922ms</td>
</tr>
<tr>
<td>Normal value: 650–800 msec.</td>
<td></td>
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</table>
compared with an 85% success rate in the elastography group, implying that fat quantification in obese patients is favorable with PDFF, with the maximum weight for the MRI scanner being a limiting factor.26 PDFF is increasingly being accepted as an endpoint for hepatic steatosis in clinical trials in the last decade and evidence gathered since then has proven a strong case for the use of PDFF as a noninvasive biomarker.9,30-32 Table 1 illustrates that PDFF can be used to determine the grade of liver steatosis, with PDFF values above 5.6% commonly used as threshold for hepatic steatosis.

**IRON QUANTIFICATION**

The liver plays a vital role in iron metabolism and storage. Homeostasis and disturbances in iron regulation are frequently described in patients with chronic liver diseases.33 Hepatic iron overload, defined as accumulation of iron in the liver, causes chronic hepatocellular injury and is traditionally found in patients with primary hemochromatosis, a hereditary genetic disorder characterized by an increase in total body iron stores and accumulation of iron in the liver.34 Iron overload is also described in 4–65% of patients with alcoholic liver disease, viral liver disease, and autoimmune hepatitis.35 Ferritin, a storage protein for iron and acting as an acute phase protein, is increased in 30% of patients with NAFLD.36 More recently, hyperferritinemia has been shown to be associated with the dysmetabolic iron overload syndrome (DIOS), a syndrome defined by a mild increase of liver and body iron in patients with metabolic syndrome and NAFLD.37 In patients with NAFLD, hyperferritinemia seems to be more related to inflammation than classical iron overload, which has implications for further diagnosis and treatment. The reference standard for hepatic iron measurement is a liver biopsy, with a reference upper limit of 1.8 mg dry weight.38 However, this invasive procedure is reserved for patients with a high pretest likelihood for hepatocellular injury or advanced fibrosis. Regular follow-up is usually performed with serum biomarkers such as serum transferrin and ferritin, which do not necessarily correspond with liver iron stores.34,39 Therefore, noninvasive assessment with MRI can alternatively be used for the diagnosis and follow-up of patients with iron overload. Furthermore, multiparametric MRI can distinguish the distributions of iron and fat simultaneously by combining different sequences into one examination and is able to estimate the iron concentration within the liver.

**T2**

Hepatic iron can be detected using T2 MRI due to magnetic local field inhomogeneity, caused by the paramagnetic effect of hemosiderin particles.40 Magnetic susceptibility is increased by the presence of iron in the hepatic parenchyma, shortening tissue T2 relaxation time due to increased local magnetic field inhomogeneity. This results in an inverse correlation of T2 with liver iron content. A regression mode is used to derive a model for estimating hepatic iron concentration from T2 MRI maps represent T2 per pixel. Liver areas with increased iron content shows low signal intensity, reflecting the distribution of iron in the organ (Table 1).41 In patients with iron overload, T2 MRI measurement has an advantage, since it is less sensitive to differences in iron particle sizes and distributional variations of iron.42 Liver iron concentration measurement with T2 is noninvasive and has a low acquisition time. Reliability decreases in patients with high levels of liver iron content due to the rapid decay of the MRI signal.34 In a recent population study, reference values of the healthy population were measured. Elevated liver iron concentration was found in 4.82% of the included persons, defined as >1.8 mg/g. Factors with significant impact on elevated iron in the liver were age, sex, ethnicity, dietary intake of beef, BMI, and liver fat.34 In
Table 1, T2* was used to diagnose a patient with hereditary hemochromatosis. With a measurement of 7.2 msec, T2* was below the upper limit of normal (12.5 msec), indicating elevated iron content of the liver. If an elevated iron measurement is found in the absence of steatosis hepatis, further analysis is warranted, with measurement of serum ferritin and transferrin saturation and testing for genetic disorders such as primary hemochromatosis (Fig. 3).39

**Quantification of Fibrosis**

Steatosis, lobular inflammation, ballooning of hepatocytes, and development of fibrosis are important hallmarks for the histopathological evaluation of NASH. To distinguish between patients with simple steatosis and patients with NASH at risk of progression to advanced chronic liver disease, noninvasive methods to predict hepatic fibrosis and inflammation are needed. MRE and T1 mapping of the liver are two emerging techniques for the noninvasive diagnostic evaluation fibrosis in the liver. (Fig. 4)

**Magnetic Resonance Elastography (MRE)**

MRE is a noninvasive MRI method to detect and quantify liver fibrosis, producing representative liver stiffness maps in 2D or 3D planes. Using the same principle as TE, mechanical waves
“shear waves” are applied to the liver area by placing a passive driver to the anterior abdominal wall overlying the liver. The mechanical vibrations are produced by an active driver outside the MRI room and transported by a flexible tube to the passive vibration driver (Fig. 1c). During MRE acquisition, vibrations are continuously applied and typically range between 20 Hz and 500 Hz. The response to shear waves propagating through the tissue can be measured by a specific MRI sequence, resulting in a tissue stiffness map or elastogram. By detecting the difference in wavelength between normal liver tissue and fibrotic liver tissue, MRE is highly accurate in detecting and evaluating different stages of liver fibrosis. Although MRE does not reliably correlate with individual stages of fibrosis compared to histology, it has high AUROCs for fibrosis ≥1, ≥2, ≥3, and 4. Although the technique was developed initially in 2D sequence, measuring the shear waves only in the acquisition plane, recent developments in 3D MRE with multiple planes has improved sensitivity and specificity. A drawback of MRE is the need for additional hardware, thereby increasing procedure costs and limiting its wide application in clinical practice. Furthermore, MRE is less reliable in patients with iron overload of the liver due to interfering signal intensity.

**T1 Mapping**

T1 mapping is a novel multiparametric MRI method that can be used to assess liver tissue composition for the extent of fibrosis and inflammation of the liver, without the use of intravenous agents. Both fibrosis and inflammation cause distinctive increases of extracellular fluid in the liver, which can be measured by an increase of T1 relaxation time (Fig. 1d). However, accumulation of excess iron in liver tissue can be a
confounding factor by decreasing the measured T₁ relaxation time. To correct for this potential bias, iron can be quantified with parallel acquisition of T₂* in the same slice as T₁. LiverMultiScan software (Perspectum, Oxford, UK) uses a proprietary algorithm to combine the acquired T₁ and T₂* data, resulting in iron-corrected T₁ mapping (cT₁).48 Reference values of cT₁ in a healthy population were determined in a recent population study ranging from 573–852 msec, with median cT₁ values of 666 msec and 95% confidence intervals of 600–763 msec.49 cT₁ is already used as an endpoint in multiple clinical studies to assess different stages of diffuse liver disease and monitor response to treatment.26,49–51 In a study of 50 patients undergoing standard-of-care liver biopsy for NAFLD, cT₁ could accurately distinguish between patients with steatosis and NASH, although in the same cohort of patients cT₁ did not significantly discriminate between individual stages of fibrosis compared to histology.52

**Multiparametric MRI Clinical Algorithm**

The European Clinical Practice Guidelines for the management of NAFLD recommends active case finding of advanced NASH with fibrosis in high-risk individuals. Patients at risk of advanced disease are identified by age over 50 years and the presence of T2DM or metabolic syndrome (abdominal obesity, hyperglycemia, hypertension, high serum triglycerides, low serum high-density lipoprotein). In Fig. 5, we propose an algorithm for the risk assessment of liver fibrosis/inflammation in patients suspected of NAFLD. Patients with steatosis hepatitis and strongly elevated tissue stiffness or cT₁ values have increased risk of NASH and should be referred for comprehensive evaluation and monitoring. A liver biopsy can be considered on a case-by-case basis.

**Conclusion**

In summary, improvements in MRI technology in multiparametric quantitative imaging provide multiple MRI biomarkers for the diagnosis and clinical management of patients with NAFLD. MRI of the liver is noninvasive and repeated measurements can be performed without safety concerns. Compared with liver biopsy, multiparametric MRI of the liver has several advantages, such as quantitative assessment of the whole organ, low sampling variability, and high reproducibility. A disadvantage is the need for additional postimaging processing. Both ¹H-MRS and PDFF methods have high sensitivity and specificity for the diagnosis of steatosis hepatitis and correlate well with histological steatosis grade. T₂* measurement is an effective method for iron quantification of the liver. MRE is highly accurate in the detection and staging of liver fibrosis in clinical trials but is less practical in routine clinical use. cT₁ is sensitive to both fibrosis and inflammation, although larger studies are required to assess validated cutoff points for individual fibrosis and inflammation stages. Further studies are required to refine the sensitivity and specificity of these multiparametric MRI methods, the use of MRI in the noninvasive assessment in patients suspected for NAFLD, and the evaluation of their prognostic potential.

**Acknowledgments**

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**Conflict of Interest**

The authors declare no conflicts of interest.

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