

WJG 20th Anniversary Special Issues (12): Nonalcoholic fatty liver disease**Radiologic evaluation of nonalcoholic fatty liver disease**

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Abstract

Nonalcoholic fatty liver disease (NAFLD) is a frequent cause of chronic liver diseases, ranging from simple steatosis to nonalcoholic steatohepatitis (NASH)-related liver cirrhosis. Although liver biopsy is still the gold standard for the diagnosis of NAFLD, especially for the diagnosis of NASH, imaging methods have been increasingly accepted as noninvasive alternatives to liver biopsy. Ultrasonography is a well-established and cost-effective imaging technique for the diagnosis of hepatic steatosis, especially for screening a large population at risk of NAFLD. Ultrasonography has a reasonable accuracy in detecting moderate-to-severe hepatic steatosis although it is less accurate for detecting mild hepatic steatosis, operator-dependent, and rather qualitative. Computed tomography is not appropriate for general population assessment of hepatic steatosis given its inaccuracy in detecting mild hepatic steatosis and potential radiation hazard. However, computed tomography may be effective in specific clinical situations, such as evaluation of donor candidates for hepatic

transplantation. Magnetic resonance spectroscopy and magnetic resonance imaging are now regarded as the most accurate practical methods of measuring liver fat in clinical practice, especially for longitudinal follow-up of patients with NAFLD. Ultrasound elastography and magnetic resonance elastography are increasingly used to evaluate the degree of liver fibrosis in patients with NAFLD and to differentiate NASH from simple steatosis. This article will review current imaging methods used to evaluate hepatic steatosis, including the diagnostic accuracy, limitations, and practical applicability of each method. It will also briefly describe the potential role of elastography techniques in the evaluation of patients with NAFLD.

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Key words: Nonalcoholic fatty liver disease; Nonalcoholic steatohepatitis; Liver steatosis; Magnetic resonance spectroscopy; Magnetic resonance imaging; Ultrasonography; Computed tomography; Elastography

Core tip: Ultrasonography is a cost-effective imaging technique for the diagnosis of hepatic steatosis in clinical practice. Magnetic resonance spectroscopy and magnetic resonance imaging are the most accurate and reliable methods of quantifying liver fat, especially for longitudinal follow-up of patients with nonalcoholic fatty liver disease. Ultrasound elastography and magnetic resonance elastography are promising imaging methods to evaluate the degree of liver fibrosis and to differentiate nonalcoholic steatohepatitis from simple hepatic steatosis.

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INTRODUCTION

Nonalcoholic fatty liver disease (NAFLD) is one of the most common causes of chronic liver diseases in Western countries, occurring in approximately 30% of the general population^[1,2]. NAFLD consists of a spectrum of diseases, including simple steatosis, nonalcoholic steatohepatitis (NASH), liver fibrosis, and liver cirrhosis^[3,4]. Although the exact risk or incidence of progression from simple hepatic steatosis to advanced stages of fatty liver disease has yet to be determined, the progression of simple hepatic steatosis to cirrhosis through the development of steatohepatitis (NASH) and fibrosis has been established^[2,5-11]. NASH, characterized by hepatocyte injury, inflammation, and fibrosis, is a clear risk factor for progression to cirrhosis, and such progression has been reported in up to 25% of patients^[6,7,9]. NASH is also associated with an increased risk of liver cancer and death from cardiovascular diseases or liver-related causes^[2,6,9,10,12]. NAFLD is closely related to obesity, insulin resistance, hypertension, and dyslipidemia and is now regarded as a hepatic manifestation of the metabolic syndrome^[4,13,14]. NAFLD also adversely affects disease progression and response to treatment in patients with viral hepatitis C^[15] and has negative effects on the prognosis of hepatic transplant recipients^[16].

Liver biopsy is regarded as the gold standard for the assessment of NAFLD and is the only reliable method for differentiating NASH from simple steatosis. This method, however, is invasive and is, therefore, unsuitable for screening large numbers of subjects at risk, or for follow-up of patients with NAFLD after therapeutic intervention. Furthermore, as liver biopsy samples are small in size, they are subject to sampling variability^[17,18]. The clinical importance of NAFLD and the limitations of liver biopsy have increased the need for accurate and noninvasive imaging methods to evaluate NAFLD. To date, various imaging methods have been utilized to evaluate patients with NAFLD, including ultrasonography (US), computed tomography (CT), magnetic resonance imaging (MRI), and magnetic resonance spectroscopy (MRS), with these methods mostly used to quantify hepatic steatosis. Each imaging method has its own advantages and disadvantages which are summarized in Table 1. More recently, several imaging methods that measure liver stiffness have been investigated for their usefulness in assessing inflammation and fibrosis in patients with NAFLD. This article will review the imaging methods currently utilized for the evaluation of NAFLD and discuss their practical applicability.

US FOR EVALUATING HEPATIC STEATOSIS

Hepatic steatosis on US appears as a diffuse increase in hepatic echogenicity, or “bright liver”, due to increased reflection of US from the liver parenchyma, which is caused by intracellular accumulation of fat vacuoles.

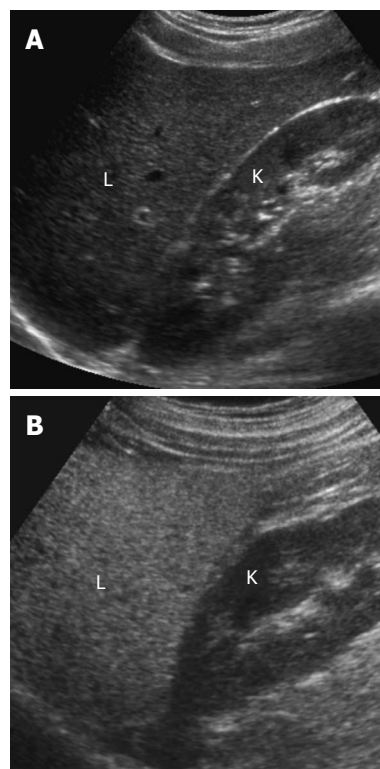


Figure 1 Ultrasonography evaluation of hepatic steatosis. A: Ultrasonography (US) image of a normal liver, showing that the echogenicity of liver parenchyma (L) and kidney cortex (K) is similar; B: US image of a steatotic liver, showing increased echogenicity of the liver parenchyma (L) which is clearly brighter than the kidney cortex (K).

US evaluation of hepatic steatosis typically consists of a qualitative visual assessment of hepatic echogenicity, measurements of the difference between the liver and kidneys in echo amplitude, evaluation of echo penetration into the deep portion of the liver, and determination of the clarity of blood vessel structures in the liver (Figure 1). Severity is usually graded clinically using a four-point scale, as follows: normal (grade 0), mild (grade 1), moderate (grade 2), and severe (grade 3)^[19-21]. The diagnostic performance of US in detecting hepatic steatosis has been reported to vary, depending on the exact definition of steatosis and the presence of coexisting chronic liver disease. In patients without coexisting liver disease, US offers a fairly accurate diagnosis of moderate-to-severe hepatic steatosis (*i.e.*, defined as histologic degree $\geq 30\%$ or 33%), with reported sensitivity ranging from 81.8% to 100.0% and specificity as high as 98%^[19,20]. In contrast, US was not accurate in diagnosing hepatic steatosis when all degrees of steatosis were considered (*i.e.*, $\geq 3\%$ or 5%), with a reported sensitivity ranging from 53.3% to 66.6% and specificity ranging from 77.0% to 93.1%^[19,21-23]. As hepatic fibrosis may also increase hepatic echogenicity^[24,25], the presence of underlying chronic liver disease may reduce the accuracy of US in the diagnosis of hepatic steatosis. For example, one study that included hepatitis C patients^[25] found that US had a sensitivity of 60% and a specificity of 73% in detecting histologically proven moderate-to-severe he-

Table 1 Advantages and disadvantages of imaging techniques for evaluating hepatic steatosis

Techniques	Advantages	Disadvantages	Clinical applications
US	Widely available, easy to perform, less expensive	Operator dependency, limited accuracy in diagnosing mild hepatic steatosis, rather qualitative nature	Population screening, initial examination for subjects with suspected nonalcoholic fatty liver disease
CT	Widely available, easy to perform	Potential radiation hazard, limited accuracy in diagnosing mild hepatic steatosis	Detecting moderate-to-severe hepatic steatosis in donor candidates for liver transplantation
MRI	Highly accurate and reproducible for measuring hepatic fat	High cost, long examination time	Follow-up of response after therapy in practice or clinical trials
MRS	Highly accurate and reproducible for measuring hepatic fat	High cost, long examination time, evaluation of small portion of the liver, expertise required for data acquisition and analysis	Follow-up of response after therapy in practice or clinical trials

US: Ultrasonography; CT: Computed tomography; MRI: Magnetic resonance imaging; MRS: Magnetic resonance spectroscopy.

hepatic steatosis.

One major limitation of US is the substantial intra- and inter-observer variability. A retrospective study of 168 US examinations showed intra- and inter-observer agreements of 54.7%-67.9% and 47.0%-63.7%, respectively, when assessing the severity of hepatic steatosis using the traditional four-point visual grading system^[26]. These findings are consistent with the results of a prospective study of 161 potential liver transplant donors^[19], in that the results of 21.7% US examinations differed between two independent readers, with the two radiologists differing significantly in diagnosing hepatic steatosis by US^[19]. These results indicate that US is highly dependent on the operator. Another limitation of US is the qualitative nature of the current four-point grading system. Although this grading system is the most widely used for US evaluation of hepatic steatosis in practice, it is too simplistic to account for small alterations in steatosis severity on follow-up. Thus, US may be inadequate for evaluating patients with NAFLD after therapeutic intervention. To overcome the limitations of US, computer-assisted quantitative US techniques were developed for the assessment of hepatic steatosis^[27-29]. These techniques employ dedicated post-processing software programs to analyze US echo amplitude, attenuation, and/or texture-based information. The most robust parameter is the computerized hepatorenal index, defined as the ratio of the echo intensities of the liver and renal cortex. The results of two related studies were very promising, with this index demonstrating sensitivities of 92.7% and 100% and specificities of 91% and 92.5% in diagnosing hepatic steatosis $\geq 5\%$ ^[28,29].

In summary, US is an established imaging technique for screening subjects at risk of NAFLD, with acceptable sensitivity and specificity in detecting moderate-to-severe hepatic steatosis. As US is easy to perform and less costly than other imaging methods, US is probably currently the most widely used imaging method for detecting hepatic steatosis in asymptomatic patients with elevated liver enzymes and suspected NAFLD^[30]. However, because of its low accuracy in detecting mild steatosis, its operator dependency, and its qualitative nature in the absence of dedicated image post-processing,

US may not be an adequate tool for monitoring NAFLD patients after therapeutic interventions. Computerized quantitative analysis methods for US may be able to overcome these limitations, but they require further clinical validation.

CT FOR EVALUATING HEPATIC STEATOSIS

CT evaluation of hepatic steatosis is based on the attenuation values of the liver parenchyma, evaluated as Hounsfield units (HUs), and dependent on tissue composition. As the attenuation value of fat (*i.e.*, approximately -100 HU) is much lower than that of soft tissue, hepatic steatosis lowers the attenuation of liver parenchyma. Although a few studies reported that contrast-enhanced venous phase CT and unenhanced CT scan had comparable diagnostic accuracy in the diagnosis of hepatic steatosis^[31,32], unenhanced CT scans are usually preferred to avoid the potential errors in contrast-enhanced CT caused by variations in liver attenuation related to contrast injection methods and scan timing. Several quantitative CT indices have been used to assess hepatic steatosis, with the two most frequently used being the absolute liver attenuation value (*i.e.*, HU_{liver}) and the liver-to-spleen difference in attenuation (*i.e.*, CT_{L-S}) (Figure 2). Despite HU_{liver} showing a stronger correlation with histologic degree of hepatic steatosis than CT_{L-S}, HU_{liver} may be subject to errors resulting from variations in attenuation values across CT scanners from different vendors^[33,34]. This error can be avoided, however, by using CT_{L-S}, which incorporates spleen attenuation as an internal control^[33].

Although the accuracy of CT in diagnosing hepatic steatosis was found to vary, CT was quite accurate for the diagnosis of moderate-to-severe steatosis but was not as accurate for detecting mild steatosis. The threshold values of CT indices for the diagnosis of hepatic steatosis were also quite variable, depending on the methods and populations used^[19,21,35]. In one study, which included 154 potential living liver donor candidates^[35], a threshold CT_{L-S} value of -9 had a specificity of 100% and a sensitivity of 82% in detecting moderate-

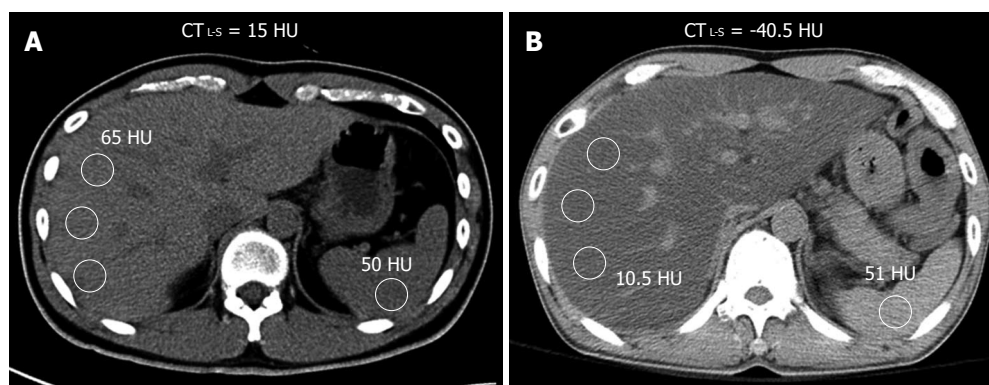


Figure 2 Computed tomography evaluation of hepatic steatosis using computed tomography_{L-S} index. A: Computed tomography (CT) image of a normal liver, showing that its attenuation (65 HU) measured using regions-of-interest (white circles) was higher than that of the spleen (50 HU), and the CT_{L-S} value was 15 HU, which lies within the normal reference range; B: CT image of a steatotic liver, showing hepatic attenuation (10.5 HU) much lower than that of the spleen (51 HU), making the CT_{L-S} value -40.5 HU, far below the normal reference range and indicating moderate-to-severe hepatic steatosis.

to-severe hepatic steatosis. Another study reported that a threshold CT_{L-S} of 3.2 had a sensitivity of 72.7% and a specificity of 91.3%^[19]. The variability in these reported threshold values limits the ability to generalize from the results of previous studies. To establish a more generalized threshold value of CT indices for the diagnosis of hepatic steatosis, a normal reference range for CT_{L-S} (1-18 HU) was established using histologically proven, non-steatotic healthy livers^[36]. An HU_{liver} of 48 and a CT_{L-S} of -2 were found to be threshold values for a 100% specific diagnosis of moderate-to-severe hepatic steatosis.

Several factors other than hepatic fat can influence liver attenuation on CT, including the presence of excess iron in the liver and the ingestion of certain drugs such as amiodarone^[33,36,37]. Unlike conventional CT, dual-energy CT can differentiate among several chemical components in tissue, by using X rays at two different energy levels. This method has been applied to the evaluation of hepatic steatosis because it may more accurately evaluate hepatic steatosis in the absence of other factors affecting CT hepatic attenuation. To date, however, the theoretical advantage of dual-energy CT has not been established clinically. A recent study in animals using an up-to-date, dual-source, dual-energy CT scanner reported that the use of dual-energy CT did not improve the accuracy of conventional single-energy CT in assessing hepatic steatosis^[38], reconfirming the results of a similar study in humans^[39].

The low accuracy of CT in detecting a mild degree of hepatic steatosis suggests that this method may not be suitable for the evaluation of NAFLD because patients with NAFLD frequently have a mild degree of steatosis^[9,40]. Moreover, the potential hazard of ionizing radiation makes CT unsuitable for use in children or for longitudinal monitoring of patients with NAFLD. CT for longitudinal follow-up of hepatic steatosis is also uncertain, due to a lack of knowledge about the reproducibility of serial CT measurements and the assay sensitivity of CT indices in detecting small changes in the severity of hepatic steatosis. Therefore, CT may not be appropriate for the evaluation of NAFLD, although

it may be useful in evaluating hepatic steatosis in specific clinical scenarios. For example, CT can be used successfully to detect moderate-to-severe hepatic steatosis in donor candidates for liver transplantation^[35,36,41], and CT measurement of fat in the liver may be useful for patients at risk of metabolic syndrome^[42,43].

MAGNETIC RESONANCE METHODS FOR EVALUATING HEPATIC STEATOSIS

Unlike CT and US, which evaluate hepatic steatosis through proxy parameters (echogenicity and attenuation, respectively), MRI and MRS can more directly measure the quantity of hepatic fat. MRI and MRS both measure proton density fat fraction (PDFF), defined as the amount of protons bound to fat divided by the amount of all protons in the liver, including those bound to fat and water. The basic magnetic resonance (MR) physics used in both techniques to differentiate protons in fat from those in water is the chemical-shift phenomenon, *i.e.*, the difference in MR frequency between the protons in fat and water. The chemical-shift effect is directly visible on MRS spectra, displaying signals at their respective resonance frequencies. Moreover, the chemical-shift effect is used in a number of MRI techniques to generate MR images, with signal intensities reflecting the magnitude of protons bound to fat. Accurate quantitative measurement of hepatic steatosis using MRS and MRI premises that MR signal intensities from fat and water are entirely created by proton densities of fat and water without any influence from other factors. However, in reality, the differences in T₁, T₂, and T₂* relaxation times between fat and water inevitably affect the signal intensities of fat and water on MRS and/or MRI. Therefore, various techniques have been developed to minimize the confounding effects. Several clinically feasible MRS and MRI techniques are introduced in the following sections.

MR spectroscopy: Technical aspects

MRS measures proton signals as a function of their res-

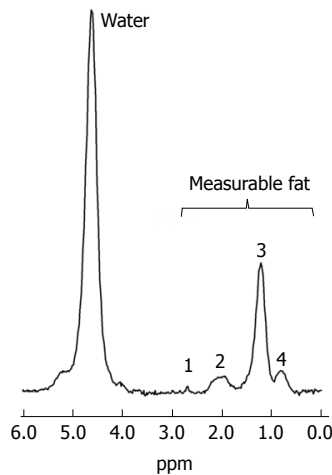


Figure 3 Magnetic resonance spectroscopy spectrum of hepatic fat. Water and fat peaks are displayed at different frequencies; water appears as a single peak at 4.7 ppm, whereas fat appears as four peaks, including the dominant methylene (CH₂) peak at 1.3 ppm (3), a methyl (CH₃) peak at 0.9 ppm (4), an α -olefinic and α -carboxyl peak at 2.1 ppm (2), and a diacyl peak at 2.75 ppm (1); the areas of these four fat peaks and the water peak can be measured by spectral tracing. Proton density fat fraction can be calculated as (sum of fat peaks) \div (sum of fat peaks + water peak)^[45,82].

onant frequency and displays multiple peaks at different locations, according to the chemical structure of protons in these frequency domains. On MRS spectra of the liver, where fat and water are the most abundant proton-containing materials, most of the identifiable peaks are derived from water and fat, with water appearing as a single peak at 4.7 ppm and fat as multiple peaks due to the presence of various chemical bonds between the protons and adjacent atoms in fat, *e.g.*, a methylene (CH₂) peak at 1.3 ppm and other smaller peaks at various locations (Figure 3). The signal intensities of fat and water peaks can be directly quantified by the spectral tracing of each peak, and PDFF can be calculated as the ratio of the sum of the signal intensities of the fat-derived peaks divided by the sum of the signal intensities of all fat- and water-derived peaks.

For hepatic fat quantification, MRS data is usually collected from a single voxel (typically 2 cm \times 2 cm \times 2 cm to 3 cm \times 3 cm \times 3 cm in size), manually placed in the liver parenchyma using 3-plane localizing images. Shimming is necessary to achieve a homogeneous magnetic field across the voxel. Either a stimulated echo acquisition mode (STEAM) or a point-resolved spectroscopy (PRESS) sequence can be used to acquire MRS spectra, with PRESS sequences providing a higher signal-to-noise-ratio (SNR) than STEAM sequences. STEAM, however, is considered more appropriate for fat quantification, as this sequence is less susceptible to a J-coupling effect and results in more reliable PDFF quantification^[44,45]. As water and fat peaks are acquired, water or fat suppression must not be used to quantify liver fat using MRS. Unlike brain MRS, which requires multiple acquisitions of data to achieve a sufficiently high SNR to detect minute metabolites, MRS of the

liver can be performed successfully with a single acquisition^[45,46]. Therefore, MRS of the liver with a single acquisition can be performed in a short time during a single breath-hold, effectively avoiding respiratory movement-related problems; this method is currently preferred^[47-51].

For unbiased fat quantification, MRS sequences should be optimized to minimize relaxation effects. A long repetition time (TR), *i.e.*, typically longer than 3000 ms at 1.5T, can minimize T₁-relaxation effects. T₂-relaxation effects can be reduced by using the shortest possible echo times (TEs). However, multi-echo MRS, which corrects for T₂-relaxation effects using multiple spectra acquired at different TEs, allows for a more complete T₂ correction^[49,52]. Multi-echo MRS techniques are typically performed within a single breath-hold, with five single averaged spectra acquired at five different TEs^[47,48,50,52].

MR imaging: Technical aspects

Several different MRI methods have been introduced to quantify hepatic fat, including chemical-shift imaging (CSI), fat saturation, and fat-selective excitation approaches^[45,53,54]. The CSI approach is most widely used because of its easy applicability and higher accuracy. Unlike MRS, which shows signals from fat and water at different locations on frequency domains, MRI displays the signal intensity of an image pixel as the vector sum of all signals from fat and water. CSI techniques separate MR signals into water and fat components based on the same MR physics as MRS (*i.e.*, the chemical shift between fat and water), but in a different way by using the chemical-shift-induced signal interference between the protons in fat and water.

The difference in resonance frequency between the dominant fat peak (*i.e.*, the methylene peak at 1.3 ppm) and the water peak (4.7 ppm) is 3.4 ppm, indicating that the water peak resonates 3.4 ppm faster than the methylene peak. Therefore, the protons in both methylene and water oscillate regularly and are positioned in opposed phase (OP) or in in-phase (IP) at certain TEs. The TEs corresponding to OP and IP depend on field strength: at 1.5T, the first OP and IP occurs at 2.3 ms and 4.6 ms, respectively, and OP and IP repeat at multiples of 4.6 ms after their first occurrence. At IP, the signals of methylene and water add constructively but, at OP, their signals cancel each other. Therefore, the difference in signal intensities between OP and IP images reflects the amount of fat (Figure 4).

Since their initial description^[55], OP and IP image-based CSI techniques have improved. Dual-echo CSI utilizes a pair of OP and IP images for fat quantification. Although this technique is widely used for clinical MR imaging of the liver, fat quantification using dual-echo CSI is subject to bias from T₁- and T₂*-relaxation effects. In addition to the proton densities of fat and water, the difference in T₁-relaxation times between fat and water affects the signal intensities on IP and OP images. Because of the difference in TEs between OP and IP, T₂*-related signal decay during the interval from OP

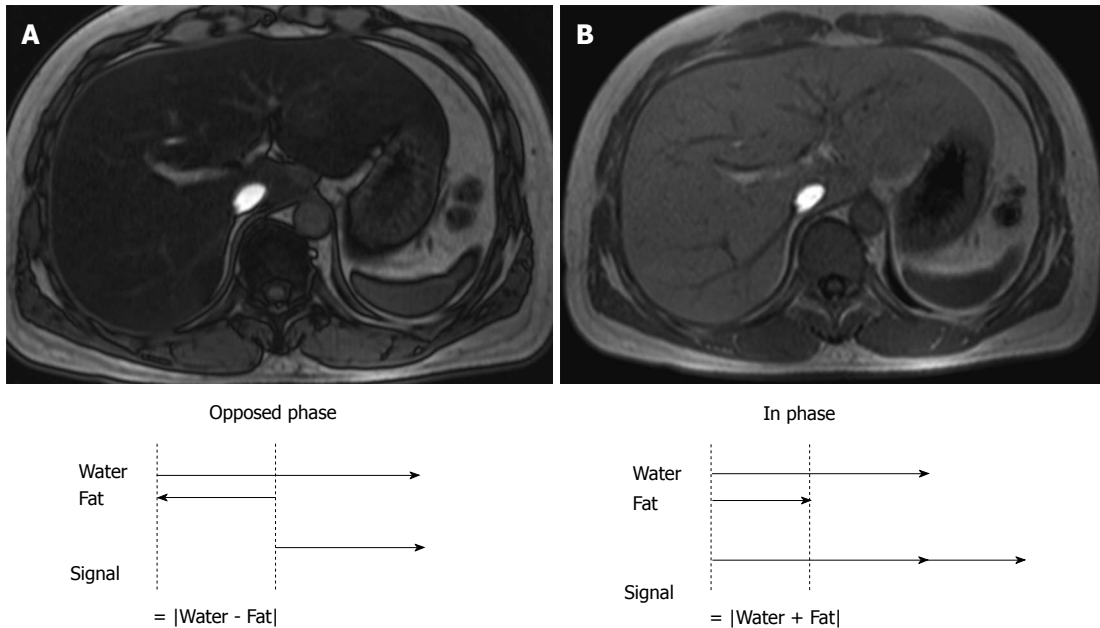


Figure 4 Dual-echo opposed-phase and in-phase chemical shift images of steatotic liver. A: At opposed-phase (OP) (echo time = 2.3 ms at 1.5T), the protons in water and those in methylene (the largest fat moiety) are placed in opposite directions, so that the signals of these two components cancel each other. Therefore, the liver appears dark (*i.e.*, decreased signal); B: At in-phase (IP), the protons in water and those in methylene are positioned in the same direction so that their signals are added. Liver fat fraction can be calculated based on signal intensities on OP and IP images as $(\text{signal at IP} - \text{signal at OP}) \div 2 \times \text{signal on IP}$; the signal fat fraction calculated with dual-echo chemical shift images was not corrected for the T2* effect, and therefore may not accurately determine proton density fat fraction.

to IP also causes signal differences between OP and IP images. As these relaxation effects may lead to inaccurate quantification of fat^[47,56,57], various techniques have been developed for correction. The T1 effect can be minimized with a low flip angle, whereas the T2*-effect can be corrected with triple or multiple echo acquisitions. Triple-echo CSI acquires a second IP echo in addition to the pair of first OP and IP echoes. The signal intensities of the first OP and IP echoes are corrected for the T2* effect using the T2* time estimated from the signal decay between the first and second IP echoes, followed by a calculation of the T2*-corrected PDFF. Multiple-echo CSI acquires three or more consecutive pairs of OP and IP echoes. Through signal modeling of multiple echoes, this technique allows for the estimation of the T2* time of the liver and T2*-corrected PDFF. These T1-independent, T2*-corrected CSI methods have shown higher accuracies in fat quantification than the classic dual-echo CSI method, resulting in unbiased fat quantification even in the presence of excess hepatic iron deposition^[47,50-52,58,59]. Recently, an algorithm for accurate spectral modeling of fat was developed and implemented in the T1-independent T2*-corrected multi-echo CSI technique. This technique is based on fat having a complex chemical spectrum, consisting of multiple peaks with different resonance frequencies, and models the signal intensities on OP and IP images using the signal interferences among water and multiple fat peaks, not between water and a single methylene peak. Since all the aforementioned OP and IP image-based CSI methods use only the signal intensity information on images without phase information, they cannot deter-

mine whether fat or water is dominant in tissues. Thus, the signal intensities of OP and IP images are nearly the same for tissues containing 30% and 70% fat. Therefore, the dynamic range of PDFF is 0%-50% hepatic steatosis for these OP and IP image-based CSI methods.

The IDEAL (iterative decomposition of water and fat with echo asymmetry and least-squares estimation) method is a chemical-shift-based, water-fat separation method using both magnitude and phase information. To separate water and fat signals, this technique measures the local field map and demodulates it from the signal in the source images using three or more echoes at different TEs. Although technically complex, the use of phase information for the IDEAL method allows PDFF to be measured over a full dynamic range of 0%-100% hepatic steatosis. Following its initial development, the algorithms for reducing T1- and noise-related bias, for T2*-correction, and for spectral modeling of fat, were implemented with the IDEAL method, allowing for T1-independent, T2*-corrected estimation of PDFF^[48,60-62].

CSI with MRI and MRS measures the same physical quantity (*i.e.*, PDFF) for the assessment of hepatic steatosis. Therefore, provided that CSI with MRI and MRS are correctly performed and interpreted, the PDFFs measured by the two techniques should be the same. As MRS estimates PDFF by directly measuring each water and fat peak, whereas CSI indirectly estimates PDFF using the signal interference between water and fat peaks, MRS has been considered more accurate than CSI in measuring PDFF. The feasibilities and accuracies of CSI methods were, therefore, initially validated by comparison with PDFF measured with MRS as the reference

standard. The results of these studies demonstrated that PDFF estimated using CSI techniques with T2*-correction and spectral fat modeling algorithms resulted in the most perfect agreement with MRS-derived PDFF, for both image-based and IDEAL-based approaches. Dual-echo CSI has been reported to generally underestimate PDFF, especially when excessive iron deposition is present^[50-52,63]. These findings were recently reconfirmed by comparing PDFFs measured by CSI techniques and MRS with the histologic degree of hepatic steatosis^[47,64]. This comparison found that multiple-echo CSI with T2*-correction and spectral fat modeling was as accurate as MRS in fat quantification, with no confounding effects of subjects' demographic factors and coexisting histologic abnormalities^[47,64]. In contrast, dual-echo CSI was less accurate than MRS and multi-echo CSI in fat quantification and is confounded by the degree of hepatic iron deposition^[47].

Clinical application of the MR techniques

Previous studies have compared the accuracies of MR techniques and other imaging modalities in the assessment of hepatic steatosis, with histologic grading as the reference standard^[19,21]. These studies consistently demonstrated that MRS and MRI outperform CT and US in the diagnosis and grading of hepatic steatosis, even when MRS and MRI were performed without any of the sophisticated corrective methods described above (*i.e.*, correction of T2 or T2* effects)^[19,21]. The MRI sensitivities and specificities in detecting histologic steatosis $\geq 5\%$ were 76.7%-90.0% and 87.1%-91%, respectively, and the corresponding MRS performances were 80.0%-91.0% and 80.2%-87.0%, respectively^[19,21]. MRS and MRI have several additional advantages over CT and US in the assessment of hepatic steatosis. MRS and MRI can evaluate hepatic steatosis in an objective manner using the quantitative index (*i.e.*, PDFF). PDFF measurements using MRS and MRI have been reported very reproducible^[1,50,51,65]. In one study, the standard deviation of PDFF values over repeated measurement was less than 1% for both MRS and MRI^[51]. Another study found that the reproducibility of PDFF measurements was high across scanners with different field strengths and from different vendors: the 95% Bland-Altman limits-of-agreement between MRI-determined PDFF on 1.5 and 3.0T scanners were approximately 2%-4%^[65].

Although histologic degree of hepatic steatosis has been used as the "gold standard" for comparisons, recent studies suggest that MRS- and MRI-derived PDFF can actually serve as a better reference standard for the amount of fat in the liver than histological evaluation, due to the high accuracy and reproducibility of these MR techniques^[66-68]. Studies assessing fat content in liver samples by computerized analysis of microscopic images or biochemical lipid assays found that the fat content in these liver samples was better correlated with MRI- or MRS-determined PDFF than with the pathologist's assessment of hepatic steatosis^[66-68]. Histologic assessment

of steatosis, including visual determination of percent hepatocytes containing fatty vacuoles or percent hepatic parenchymal area replaced by fat, is subject to large inter-observer variability^[17] and may not accurately reflect the physical quantity of hepatic fat^[66-68]. In addition, the traditional histological cutoffs categorizing the severity of steatosis (5%, approximately 30%, and approximately 60%) may be too blunt, especially in longitudinal follow-up. These findings and the inherent limitations of liver biopsy, including its invasiveness and ability to obtain very small samples, suggest that MRS and MRI may be the methods of choice, both as reference standards in research studies and in clinical practice, especially in the longitudinal follow-up of patients with hepatic steatosis after therapeutic intervention^[69-74]. A recent study has validated the efficacy of MRI- or MRS-determined PDFF as an imaging biomarker to quantify changes in the amount of liver fat and to assess the effects of drug therapy in patients with NAFLD^[71].

From a practical viewpoint, MRI appears to have several advantages over MRS. The acquisition and analysis of MRS data requires expertise and is time-consuming. Single-voxel MRS, the typical MRS method used to assess hepatic steatosis, collects data from a small portion of the liver (within a voxel $\leq 3 \text{ cm} \times 3 \text{ cm} \times 3 \text{ cm}$), which may be subject to sampling error, although it is much larger than a biopsy sample. By comparison, MRI is widely available, easily applicable, and can evaluate the entire liver within a short breath-hold. Since the scale of MRS- or MRI-determined PDFF (%) differs from the histologic degree (%) of hepatic steatosis (although both use percentages), clinical thresholds for MRS- or MRI-determined PDFF are needed. The largest MRS study to date, involving 2349 subjects in a general population, suggested that a PDFF value of 5.56% was the upper normal margin, as determined from the 95th percentile of PDFF in 345 subjects with no identifiable risk factors for hepatic steatosis^[1].

IMAGING DIAGNOSIS OF NASH AND ELASTOGRAPHY

Hepatic steatosis can progress to fibrosis and cirrhosis through a development of steatohepatitis (NASH), which is a clear risk factor for liver cirrhosis and liver-related mortality^[9,10,75]. Therefore, it is clinically important to diagnose the development of steatohepatitis in patients with NAFLD. In general, no imaging examinations have been found to accurately diagnose NASH, making liver biopsy the only reliable method of distinguishing NASH from simple steatosis. US elastography and MR elastography, however, are emerging as promising methods to diagnose NASH. US elastography and MR elastography evaluate liver stiffness by measuring the velocity of shear wave using US (US elastography) or MRI (MR elastography). Several US elastography techniques have been described, which differ in methods of shear wave generation and/or detection, including transient

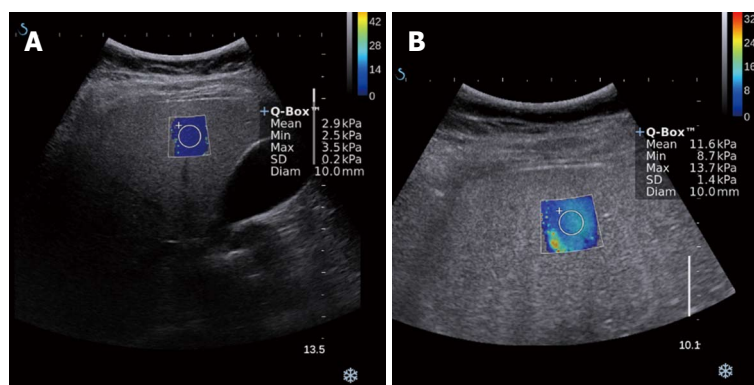


Figure 5 Supersonic shearwave elastography of simple steatosis vs nonalcoholic steatohepatitis. A: Supersonic shearwave elastography image of the liver with simple steatosis shows a mean liver stiffness value of 2.9 kPa, which lies within the normal reference range; B: Supersonic shearwave elastography image of the liver with nonalcoholic steatohepatitis shows an elevated mean liver stiffness value of 11.6 kPa.

elastography, acoustic radiation force impulse elastography, supersonic shearwave elastography (Figure 5), and real-time tissue elastography. These techniques were first applied to the evaluation of liver fibrosis in patients with chronic viral hepatitis, and their clinical application has recently been expanded to other liver diseases, including NAFLD. US elastography techniques have demonstrated very promising results for the diagnosis of liver fibrosis in NAFLD^[76-80]. They have shown a stepwise increase in liver stiffness as the severity of histologic liver fibrosis increased, and have been highly accurate in differentiating advanced liver fibrosis from mild liver fibrosis, with sensitivities ranging from 88.9% to 100% and specificities ranging from 75.0% to 100%^[76-80]. Liver stiffness value did not correlate with the degree of hepatic steatosis or with hepatic inflammation^[76-80], indicating that US elastography can assess hepatic fibrosis associated with steatosis without confounding by steatosis but would not be able to assess hepatic inflammation^[76-80]. A study of MR elastography in 58 patients with NAFLD showed that liver stiffness in patients with steatosis and lobular inflammation was significantly higher than in patients with steatosis only, and significantly lower than in patients with steatosis and fibrosis^[81]. Taken together, these results indicate that US elastography or MR elastography may play a potential role in screening for NASH and/or advanced fibrosis in patients with NAFLD.

CONCLUSION

US is a well-established and cost-effective imaging technique for screening subjects at risk of NAFLD with a reasonable sensitivity and specificity in detecting moderate and severe hepatic steatosis, despite its limited accuracy for mild hepatic steatosis and operator dependency. CT is inaccurate in detecting mild hepatic steatosis and involves a potential radiation hazard, making it inappropriate for assessing hepatic steatosis, especially for longitudinal follow-up of patients with NAFLD. CT, however, may be effective in specific clinical situations, such as the evaluation of hepatic donor candidates for transplantation. MRS is currently the most accurate im-

aging method used to diagnose hepatic steatosis. MRI, if performed and analyzed correctly, has a comparable accuracy to MRS, is more practical, and can cover the entire liver. Technical optimization of MRS and MRI may result in accurate and unbiased hepatic fat quantification. Both MRS and MRI are very reproducible and accurate in quantifying hepatic fat and may replace liver biopsy as the reference standard for research studies. US elastography and MR elastography can diagnose liver fibrosis associated with NAFLD and may play a role in identifying NASH or NAFLD patients who are at greater risk of progressive liver disease.

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