Review Article

Update on Imaging-based Noninvasive Methods for Assessing Hepatic Steatosis in Nonalcoholic Fatty Liver Disease

CME Credits

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Abstract

Nonalcoholic fatty liver disease (NAFLD), among the most common chronic liver diseases worldwide, affects approximately 25% of the global population. Its incidence is increasing owing to various risk factors, including genetic variation, metabolic health, dietary habits, and microbiota. Hepatic steatosis is a critical histological characteristic of NAFLD. Evaluating liver fat content is vital for identifying and following up with patients at risk of developing NAFLD. NAFLD includes simple liver steatosis and more severe forms such as inflammation, nonalcoholic steatohepatitis, fibrosis, and cirrhosis. The early assessment of fatty liver is important for reversing liver disease progression. Metabolic (dysfunction)-associated fatty liver disease recently replaced NAFLD as the most common hepatic disease worldwide. This article reviews the current state of noninvasive imaging, especially ultrasound, for liver fat quantification.

Keywords: Nonalcoholic fatty liver disease, noninvasive, ultrasound

Introduction

Nonalcoholic steatohepatitis (NASH), first coined by Ludwig in 1980, is characterized by hepatitis that historically presents with striking fatty changes as well as evidence of lobular hepatitis, focal necrosis, and mixed inflammatory infiltrates.[1] After several years, a new classification, known as nonalcoholic fatty liver disease (NAFLD), emerged. First described by Shaffner and Thaler in 1986, NAFLD is a fatty liver disease that occurs without significant alcohol intake.[2,3] It is the most common chronic hepatic disease worldwide, affecting more than 25% of the global population.[4] The annual medical cost directly attributable to NAFLD in the United States is approximately 100 billion USD. Hepatic steatosis, the abnormal buildup of fat in the cytoplasm of hepatocytes, is considered one of the primary features or hallmarks of NAFLD and can be detected using different methods, including histological and noninvasive imaging techniques. The disease course of NAFLD involves various stages ranging from simple steatosis (fatty liver) to more severe forms such as NASH, liver fibrosis, liver cirrhosis, and even hepatocellular carcinoma (HCC). Clinically, there are two crucial purposes for managing NAFLD: to diagnose NAFLD; and identify the degree of advanced fibrosis. The degree of fibrosis is strongly linked to various adverse outcomes including mortality, cardiovascular disease, HCC, and extrahepatic neoplasms.[5] In recent years, an international panel of experts consisting of hepatologists and researchers suggested the term "metabolic (dysfunction)-associated fatty liver disease" (MAFLD) as a replacement for NAFLD. MAFLD highlights the strong association between fatty liver disease and metabolic dysfunction, replacing NAFLD as the most common hepatic disease worldwide.[6] This article focuses on the role of ultrasonography in quantifying liver fat and discusses the currently available and emerging imaging modalities.

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Liver Biopsy

Liver biopsy histology has become the gold standard diagnostic procedure for assessing the severity of fatty liver diseases including hepatic steatosis, liver tissue inflammation, and liver fibrosis.[4] Liver steatosis on biopsy is graded based on the rate of fat deposition within hepatocytes: Grade 0 (normal, <5%), Grade 1 (mild liver steatosis, 5%–33%), Grade 2 (moderate liver steatosis, 34%–66%), and Grade 3 (severe liver steatosis, >66%). However, biopsy is an invasive procedure that can feature rare, but serious complications (such as bleeding, perforation, infection, and death); moreover, only a small area of the liver can be collected, which may lead to variable findings from pathologists. Hence, noninvasive techniques have been developed to assess fatty liver disease.

Magnetic Resonance Imaging-derived Proton Density Fat Fraction

Magnetic resonance imaging-derived proton density fat fraction (MRI-PDFF) is a feasible choice for liver biopsy that provides a precise and reproducible noninvasive imaging modality for quantifying liver fat content.[4] Moreover, MRI-PDFF can quantify the lipid content across the entire liver, enabling a comprehensive assessment of the disease burden. The MRI-PDFF is calculated as the fraction or percentage of mobile proton density from fat to the total mobile proton density from both fat and water within the liver tissue. This ratio provides an estimate of triglyceride concentration, a key indicator of liver fat content.[7] Several research studies demonstrated the significant correlation between liver fat quantification as assessed by MRI-PDFF and steatosis graded by hepatic histology.[8,9] The area under the receiver operating characteristic curve (AUROC) values of MRI-PDFF for classifying mild (Grade 1), moderate (Grade 2), and severe (Grade 3) histological steatosis range from 0.91 to 0.98.[10] MRI-PDFF has the potential to replace liver biopsy in evaluating liver fat content and the longitudinal monitoring of NAFLD/MAFLD. MRI-PDFF is considered the most precise noninvasive imaging approach for quantitatively measuring liver fat.[11] However, its cost can be prohibitive for many individuals, and access to MRI facilities may be limited in certain regions or health-care settings. Access to MRI as a routine diagnostic tool for assessing liver fat content is limited for most of the global population.

Conventional B-Mode Ultrasonography

Conventional B-mode ultrasonography is the most common imaging modality used for screening and health examinations because of its accessibility, ease of performance and interpretation, and relatively low cost. For liver imaging, ultrasound can provide valuable information regarding the presence of hepatic steatosis, including the brightness of the liver parenchyma, reduced contrast between the liver and adjacent kidney, attenuation of the deep beam, and brightness of the vessel walls and the gallbladder wall. One or more of these ultrasound characteristics suggests hepatic steatosis (fatty liver). Hepatic steatosis grading by conventional B-mode ultrasound is commonly performed using a semi-quantitative scale, particularly: Grade 0 (no steatosis), normal right lobe liver echogenicity compared to the right kidney cortex; Grade 1 (mild steatosis), mildly diffused increased liver echogenicity with slightly increased brightness of the liver parenchyma compared to the kidney, but with normal visualization of the diaphragm and intrahepatic vessel borders; Grade 2 (moderate steatosis), moderately diffuse increase in liver echogenicity with more pronounced brightness compared to the kidney and slightly impaired visualization of intrahepatic vessels and diaphragm; and Grade 3 (severe steatosis), marked increase in liver echogenicity with the liver appearing significantly brighter than the kidney and poor or no visualization of the diaphragm, intrahepatic vessel borders, and posterior part of the right lobe of the liver. Although conventional B-mode ultrasonography is a widely available non-invasive imaging technique used to diagnose hepatic steatosis, its sensitivity and specificity are 53%–76% and 76%–93%, respectively.[12]

Artificial Intelligence Deep Learning Techniques for Measuring Steatosis

The use of artificial intelligence (AI)-assisted interpretation is currently trending, and few studies have combined traditional ultrasound with AI deep learning techniques to assist in the assessment of fatty liver disease severity. It is possible to train an AI system capable of distinguishing and quantifying the degree of liver steatosis. A retrospective study involving 2070 patients and 21,855 ultrasound images used AI neural network models (ResNet-50 v2) to determine the severity of fatty liver in each image. The AUROC were 0.974 (mild steatosis vs. others), 0.971 (moderate steatosis vs. others), 0.981 (severe steatosis vs. others), 0.985 (any severity vs. normal), and 0.996 (moderate-to-severe steatosis/clinically abnormal vs. normal-to-mild steatosis/clinically normal).[13] Another retrospective cohort study used 3310 patients, 19,513 studies, and 228,075 images to train a deep-learning algorithm to diagnose steatosis stages. The deep learning system shows good cross-scanner agreement, stable diagnostic performance, and higher AUROC values (0.92–0.97 vs. 0.80–0.92) and accuracies (77%–91% vs. 62%–68%) than controlled attenuation parameter (CAP).[14] Research to date confirmed that training AI using deep learning techniques can achieve good sensitivity, specificity, positive predictive value, negative predictive value, and accuracy.[15] There are still many limitations to be overcome (e.g., speckle noise, semantic gap, computational time, dimensionality reduction, and accuracy of images retrieved from a large dataset) that will require additional research data.

Hepatorenal Index

The hepatorenal index (HRI) is defined as the echogenicity or brightness ratio of the liver parenchyma and the renal cortex on the same ultrasound image. Using B-mode ultrasonography, calculating the HRI can potentially improve the detection and

grading of fatty liver disease. In studies comparing HRI with histology, which is considered the reference standard for the diagnosis of hepatic steatosis, the sensitivity and specificity of HRI are 62.5%–100% and 54%–95%, respectively.[12] The adequate cutoff values of HRI for detecting fatty liver can vary within a range, for example, HRI ranges from 1.28 to 2.01 for mild steatosis. The accuracy of HRI for detecting hepatic steatosis varies across studies, to which several factors, including ultrasound equipment, underlying liver disease, and fatty liver severity, can contribute.

Controlled Attenuation Parameter

A new ultrasound-based technology that was recently developed to quantify hepatic steatosis has overcome the limitations of B-mode ultrasonography and HRI [Table 1]. Ultrasound-based CAP, first available in 2010, is a simple and convenient noninvasive technique that calculates the degree of attenuation (weakening) of ultrasound signals as they pass through the liver, enabling estimation of the amount of fat accumulated in the liver.[12] The CAP value, expressed in decibels per meter (dB/m), is 100–400 dB/m and can be used to quantify hepatic steatosis. CAP values correlate well with the histological assessment of hepatic steatosis in liver biopsies. The optimal cutoff values for liver steatosis grades >S0, >S1, and >S2 were >248, 268, and 280 dB/m, respectively.[12] However, CAP has certain limitations in the detection of hepatic steatosis. CAP has low sensitivity for differentiating fatty from nonfatty liver, with a sensitivity as low as 68.8% and a specificity of 82.2%.[13] In addition, obesity, diabetes, body mass index, the presence of inflammation or fibrosis, and operator dependency can impact CAP values.

Newer Ultrasound-guided Fat Quantification Techniques

In addition to CAP, several other ultrasound-guided technologies have been developed by various manufacturers to quantitatively assess hepatic steatosis [Table 1]. These advanced technologies are often integrated into high-end or technically sophisticated sonography equipment to provide additional tools for evaluating liver health.[12] The principles for new fat quantification techniques involve assessing the attenuation of ultrasound signals, which are influenced by the absorption, reflection, refraction, and scattering of ultrasound waves as they pass through liver tissue.[16,17] Different manufacturers have their own patent algorithms to transform attenuation signals into markers of the degree of liver steatosis. Absorption is the reduction in the power of sound waves as they pass through a tissue. The reflection of a sound wave occurs when the wave passes through the tissue, and part of the wave turns back. Scattering occurs when a sound wave hits a structure and becomes scattered in different directions with decreasing power. Refraction occurs when a wave passes through the interface between two media at an angle other than 90° and is refracted [Figure 1].

Some of these technologies, including attenuation imaging (ATI), attenuation coefficient (ATT), and ultrasound-guided attenuation parameter (UGAP), are used to assess the attenuation of radiofrequency signals in hepatic steatosis to quantify the hepatic fat content. The backscatter coefficient (BSC) is another novel quantitative technique that characterizes the scattering of ultrasonic pulses as they propagate through tissues. This value represents the amount of ultrasound energy scattered back toward the ultrasound probe after passing through the liver parenchyma.

Quantitative ultrasonography techniques for fat fraction estimation have been developed to assess liver fat content quantitatively using backscatter parameters. These techniques utilize specific algorithms and analytical methods to extract information from backscattered ultrasound signals and estimate the fat fraction within the liver. A detailed introduction and recommended guidelines for the various ultrasound techniques

Table 1: Characteristics of each noninvasive imaging modality for detecting hepatic steatosis

Modality	Advantages	Limitations	Cost	Quantitative
Conventional B-mode ultrasonography	High availability High sensitivity to moderate to severe steatosis	Technician dependent Low sensitivity for mild steatosis (<30%)	Low	No
HRI	Better than US alone	Technician dependent Low sensitivity for mild steatosis (<30%) Additional program required to calculate HRI	Low	No
CAP	Widely validated with high evidence Offering defined cutoff values for different grades of steatosis	High rate of measurement failure in very obese patients No detailed information about the distribution or location of fat within the liver	Low	Yes
Newer fat quantification techniques (ATI, ATT, BSC, UGAP)	Integrated in high-end devices measurement on B-mode US images Potentially high sensitivity	Low evidence, limited number of studies	Low	Yes
MRI-PDFF	High accuracy Whole-liver assessment	Limited availability	High	Yes

ATI: Attenuation imaging, ATT: Attenuation coefficient, BSC: Backscatter coefficient, CAP: Controlled attenuation parameter, HRI: Hepatorenal index, MRI-PDFF: Magnetic resonance imaging-proton density fat fraction, UGAP: Ultrasound-guided attenuation parameter, US: Ultrasonography

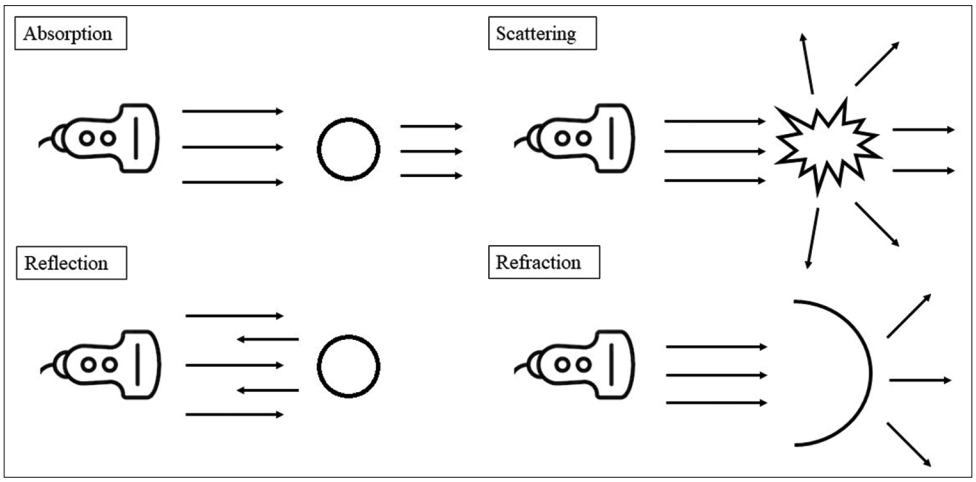

Figure 1: Main principles of quantitative ultrasound attenuation for assessing hepatic steatosis. The principles for new fat quantification techniques involve assessing the attenuation of ultrasound signals, which are influenced by the absorption, reflection, refraction, and scattering of ultrasound waves, as they pass through liver tissues. Different manufacturers have their own patented algorithms to transform attenuation signals into the degree of liver steatosis

currently used for hepatic fat quantification were provided by the World Federation of Ultrasound in Medicine and Biology.[12,17]

Owing to the novelty of CAP, only a few studies exist on its diagnostic accuracy of liver fat quantification compared to that of MRI or histology. In a study using ATI measurements that contrasted the performance of ATI with that of CAP using MRI-PDFF as the benchmark, the correlation between ATI and MRI-PDFF was stronger than that between ATI and CAP (r = 0.81 vs. r = 0.65, respectively). ATI exhibited greater accuracy than the CAP, and this distinction was statistically significant for cases of S > 1 (P = 0.04).[18] A multicenter prospective study examined 351 patients with various underlying causes of liver disease. All patients underwent liver biopsy and ATT measurements on the same day. The percentage of fat area in the biopsy samples was measured. ATT showed a moderate correlation with fat area (r = 0.50, P < 0.001). The AUROC values for S ≥ 1, S ≥ 2, and S = 3 were 0.79, 0.87, and 0.96, respectively.[19] In a prospective study of 163 patients with chronic liver disease, UGAP measurements were positively correlated with the percentage of steatosis (r = 0.78, P < 0.001). The AUROC values for UGAP in predicting S ≥ 1, S ≥ 2, and S = 3 were 0.90, 0.95, and 0.96, respectively.[20]

The precision of BSC measurements for diagnosing and quantifying hepatic steatosis was assessed among a cohort of 204 individuals with versus without NAFLD. MRI-PDFF was used as a benchmark for comparison. The participants were randomly divided into training and validation sets. A substantial correlation was observed between MRI-PDFF and BSC (Spearman's r = 0.80, P < 0.0001). The AUROC of BSC for identifying steatosis stood at 0.98 within the training group.[21] The diagnostic accuracy of hepatic fat quantification can vary depending on various factors, including specific studies, methods, and chosen cutoff values[4,12,17,22] with a sensitivity of 68%–88% and a specificity of 62%–100%.[23-25] These new quantitative techniques show good diagnostic accuracy for the detection of moderate and severe steatosis. However, for detecting mild steatosis, the diagnostic accuracy is considered fair, but not excellent. To date, no study has compared the superiority of one product over another.

The quantification of liver steatosis is important for several reasons.[4,12] First, detecting steatosis is crucial for diagnosing fatty liver disease. Second, higher grades of steatosis are known risk factors for fibrosis progression;[4,26] thus, it is possible to identify high-risk patients. Third, quantitative measurements of liver fat content can be used for the follow-up and monitoring of treatment responses, although caution is required when interpreting changes in liver fat content during follow-up. A reduction in hepatic steatosis does not necessarily correlate with disease improvement. In some cases, particularly in progressive liver diseases such as NAFLD or NASH, liver fibrosis can continue to progress even if the liver fat content decreases. Therefore, to fully assess disease progression or improvement, it is important to evaluate the degree of fibrosis during follow-up.[4,26]

Conclusion

Ultrasound-based technology for liver fat content quantification is very important for the early diagnosis, follow-up, and monitoring of treatment responses in hepatic steatosis diseases such as NAFLD, MAFLD, or MAFLD. Conventional B-mode ultrasound effectively detects moderate and severe steatosis, but not quantitatively. The use of newer techniques, including HRI, CAP, and quantitative ultrasound methods, has shown promise in improving the identification of patients with steatosis. Further studies are necessary to increase our understanding of the confounding factors and ability to optimize quantitative ultrasound techniques.

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Conflicts of interest

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