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Quantitative Hepatic Fat Quantification in NAFLD using Ultrasound-Based Techniques: A Review of Literature and their Diagnostic Performance

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Abstract

Non-alcoholic fatty liver disease (NAFLD) is a condition that is characterized by the presence of >5% fat in the liver and affects over one billion people worldwide. If adequate and early precautions are not taken, NAFLD can progress to cirrhosis and death. The current reference standard for detecting hepatic steatosis is a liver biopsy. However, due to the potential morbidity associated with liver biopsies, non-invasive imaging biomarkers have been extensively investigated. Magnetic resonance imaging (MRI)-based methods have proven accuracy in quantifying liver steatosis; however, these techniques are costly and have limited availability. Ultrasound-based quantitative imaging techniques are increasingly utilized because of their widespread availability, ease of use, and relative cost-effectiveness. Several ultrasound-based liver fat quantification techniques have been investigated, including techniques that measure changes in the acoustic properties of the liver due to the presence of fat. In this review, we will focus on quantitative ultrasound approaches and their diagnostic performance in the realm of NAFLD.

Keywords

NAFLD; quantitative; ultrasound; attenuation; backscatter; CAP; speed of sound

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Introduction

Non-alcoholic fatty liver disease (NAFLD) is the most common liver disease with an estimated one billion patients globally (Loomba and Sanyal 2013). NAFLD is the most common form of hepatic steatosis and affects approximately 40% of men and 20% of women in the general population (Browning et al. 2004). Its prevalence is estimated to be 13–32% in the general population, and up to 90% in patients with diabetes or obesity as co-morbidities (Chalasani et al. 2018). NAFLD prevalence increases proportionally with obesity and other components of the metabolic syndrome and is expected to be the leading cause of liver transplantation in future (Byrne and Targher 2015; Wong et al. 2015).

NAFLD encompasses a wide spectrum of hepatic abnormalities from simple fat accumulation in greater than 5% of the hepatocytes (non-alcoholic fatty liver: NAFL) to more severe forms with pathological injury (non-alcoholic steatohepatitis: NASH) (Takahashi and Fukusato 2014). In NASH, lobular inflammation, hepatocyte ballooning and progression to fibrosis occur (Bedossa and Patel 2016). Hepatic steatosis can be present in other chronic liver diseases, like chronic hepatitis B and C, in which the rapid onset of the fibrosis process is more common (Yoon and Hu 2006). Although NAFLD does have certain pathognomonic features on a liver biopsy, it is generally considered a diagnosis of exclusion (e.g. steatosis without a known cause and in the absence of associated NASH features). Other causes of hepatic steatosis include metabolic, nutritional, and drug induced (chemotherapy and steroids) (Kneeman et al. 2012). NAFLD is accepted as the hepatic manifestation of metabolic syndrome and is strongly correlated with insulin resistance, atherosclerosis, obesity, dyslipidemia and hypertension (de Alwis and Day 2008; Targher 2007).

Risk stratification in NAFLD is performed by distinguishing NASH patients from simple steatosis patients, as NASH patients are at far higher long-term risk of cirrhosis, liver failure, and hepatocellular carcinoma (Stern and Castera 2017). The current reference standard for diagnosing NASH remains percutaneous biopsy, and biopsies currently play an essential role in staging hepatic steatosis and fibrosis (Chalasani et al. 2018). A common steatosis scoring system is the NASH Clinical Research Network (NASH CRN) scoring system: S0 (<5% hepatocytes), S1 (5%–33% hepatocytes), S2 (34%–66% hepatocytes), and S3 (>66% hepatocytes) (Kleiner et al. 2005). Unless otherwise stated, the steatosis staging system used in this review is the NASH CRN system.

A liver biopsy has well known limitations, including sampling variability and invasiveness (Goldstein et al. 2005; Nalbantoglu and Brunt 2014; Ratzliff et al. 2005). Liver biopsies are not suitable for large scale screening due to the relatively high prevalence of NAFLD/NASH in the general population (Chalasani et al. 2012).

Because of the increasing prevalence of NAFLD over the past decade, there is a growing interest in the non-invasive assessment of steatosis with two main approaches: serum biomarkers and imaging biomarkers (Noureddin and Loomba 2012). Accurate quantification of the fat profile of the liver is also critical in liver donor selection, as steatosis may cause

complications and is associated with perigraft mortality (Sharma et al. 2013). While there have been numerous articles looking at the NAFLD diagnostic performance of conventional imaging modalities and ultrasound approaches, there is a lack of literature on quantitative ultrasound approaches to hepatic steatosis quantification. The aim of this article is to briefly review the currently used imaging techniques to quantify hepatic fat, specifically focusing on potential advantages of ultrasound-based fat quantitation and summarize the diagnostic performance of quantitative ultrasound approaches to date. We searched the keywords 'steatosis', 'quantification', 'ultrasound' using the Pubmed search platform, and reviewed most recent papers. To understand the principal concepts, we used pioneer studies. To our knowledge, apart from review publications, all the citations below are based on IRB or IACUC approved studies. Area under the receiver operating curve (AUROC) value is extensively used in research to express discriminating power and diagnostic performance (Obuchowski 2004). In this review, we will use AUROC values to express the diagnostic performance of the techniques.

Overview of Conventional Imaging Modalities for Hepatic Fat Quantification

While CT and MRI are known to be able to detect and quantify liver fat, they are unsuitable for widespread use owing to multiple limitations.

Computerized Tomography (CT):

CT is known to detect liver steatosis in moderate to severe stages as reduced hepatic attenuation (Ricci et al. 1997). CT uses ionizing radiation and is therefore unsuitable for widespread use in asymptomatic patients. Furthermore, several factors, including iron, copper, and glycogen deposition, fibrosis and edema, may confound the ability of CT to diagnose hepatic fat (Limanond et al. 2004; Reeder et al. 2011). New CT-based modalities have been proposed to quantify hepatic fat, and these modalities are promising in terms of accuracy (Hyodo et al. 2017). However, given the high incidence of NAFLD and the ionizing radiation of CT imaging, CT is likely to remain unsuitable for widespread use.

Magnetic Resonance Imaging (MRI):

MRI based studies are accurate for quantification of fat, but are expensive and challenging to deploy across the large NAFLD population (Paige et al. 2017). In-phase and opposed-phased MRI and MRI Spectroscopy (MRS) have been extensively utilized for detecting liver fat (Longo et al. 1993; Mitchell et al. 1991; Satkunasingham et al. 2015). A newer MRI technique - proton density fat fraction (MR-PDFF) – offers great potential in quantifying liver fat with a diagnostic performance that may exceed liver biopsy, with the advantage of linear steatosis percentage staging (Le et al. 2012; Nouredin et al. 2013)(Figure1). MR-PDFF is superior to US and CT in diagnosing NAFL, particularly when used in combination with MRI Elastography (Bohte et al. 2011; Yoon et al. 2015). In addition, it has shown high correlation 0.69 ($p<0.001$) with liver biopsy evaluation (Tang et al. 2013) and 0.98 ($p<0.001$) with MR spectroscopy (Idilman et al. 2016). A study by Idilman et al. also showed high correlation of MRIPDFF and histology-determined steatosis ($r=0.743$, $p<0.001$) while MR Spectroscopy showed equally good results($r=0.712$, $p<0.001$) with no difference between them($z=0.19$, $p=0.849$)(2016). As a result, MR-PDFF is also increasingly relied upon as the

gold standard for hepatic fat quantification. Despite the high accuracy of MRI in hepatic fat quantification, the biggest limitations of MR-PDFF for the evaluation of NAFL and NASH are the limited availability and high cost of MRI.

Conventional Ultrasound (CUS):

CUS is the most commonly used technique to assess hepatic steatosis because of its accessibility and low cost (Dasarathy et al. 2009). In addition, ultrasound can be performed easily in conscious patients, which is an advantage when imaging pediatric patients or adults unable to tolerate MRI without sedation. Conventional ultrasound uses qualitative sonographic patterns to assess the severity of hepatic fat infiltration, including increased liver echogenicity, portal vein blurring, hepatic vein blurring, posterior beam attenuation, poor diaphragm visualization, and a tightly packed echo pattern (Joseph et al. 1979; Saadeh et al. 2002)(Figure 2). CUS has low accuracy to detect steatosis (Paige et al. 2017), has intra/inter-observer variability, and is often not feasible in patients with high body mass index(BMI) (Bohte et al. 2011; Bohte et al. 2012; Strauss et al. 2007; Williamson et al. 2011).

Quantitative Ultrasound (QUS) Approaches

Due to the limited utility of conventional ultrasound in quantifying hepatic steatosis, there has been a significant effort to develop quantitative ultrasound approaches for liver fat quantification.

Most QUS techniques use different approaches to identify tissue microstructure by measuring essential acoustic parameters (Ghoshal et al. 2012). Phantom studies have shown that quantitative US parameters are accurate, reproducible, and not operator dependent (Nam et al. 2012; Yao et al. 1990).

QUS techniques can essentially be divided into two groups: (1) image based analysis (sometimes referred to as envelope statistics and/or characterization) and (2) analysis based on the raw RF data acquired directly from the scanner. Development of the latter techniques has accelerated recently with the availability of research scanners given their ability to capture raw data including those from individual transducer elements. B-mode based techniques have been analyzed in many studies in the last few decades (Edens et al. 2009; Gaitini et al. 2004; Thijssen et al. 2008) and non-image based spectral techniques, including speed of sound, US backscatter and attenuation coefficients, have been studied for decades (Bamber et al. 1981; Chen et al. 1987; Goss et al. 1978; O'Brien Jr. et al. 1988). Summary of the studies using quantitative techniques, is presented in Table1. However, their acceptance into routine practice and into commercial scanners has been slow. The rapid advancement of computation in the last decade has improved some of the data analysis approaches. The aim of this article is to review these approaches, especially speed of sound estimation, backscatter coefficient and attenuation parameters, with a comparison of their diagnostic performance for hepatic fat quantification.

Speed of Sound

The measurement of the speed of sound in tissue has been of major interest not only for the potential of being able to diagnose disease, but also to improve ultrasound image quality. The majority of scanners today assume a constant speed of sound of 1540 m/s throughout the entire imaging domain. This assumption is demonstrably invalid in the average human but nonetheless its use in image formation results in reasonable image quality. New methods for the estimation of longitudinal wave speed (LWS) of sound in tissue and to establish the ability of such methods to stage the progression of steatosis and fatty infiltration are increasingly being studied. Both shear wave speed (current paradigm) and the longitudinal wave speed have similar mathematical relationships to the elastic properties of tissue. Various approaches to derive these have been studied on phantoms, animal models or excised human liver samples (Bamber et al. 1981; Chen et al. 1987; Ghoshal et al. 2012; Imbault et al. 2017; Lin et al. 1987)

With most image-based methods of speed of sound estimation, characteristics of the B-mode image are analyzed for brightness or sharpness (high frequency content) near the focal zone. The technical origins of this approach are based on the work of Burckhard et al and Wagner et al., who recognized the similarity between laser and ultrasound speckle, and were able to demonstrate analytically increased brightness and reduced speckle size in the focal region (Burckhardt 1978; Wagner et al. 1983). These insights have been taken advantage of in several settings involving speed of sound, for example, image quality improvement (Napolitano et al. 2006), aberration correction (Nock and Trahey 1985), as well as several efforts in liver steatosis estimation (Kumagai et al. 2014) or in general speed of sound measurements (Gyöngy and Kollár 2015). In addition to speckle based analysis, other researchers have used seismology based methods (Anderson et al. 2000), triangulation or biprisms (Chen et al. 1987; Robinson et al. 1991), and tomographically determined phase shifts within the imaged area from different viewing angles (Jaeger et al. 2015).

Speed of sound in normal healthy liver and fatty liver has been reported as a range of 1538–1588 m/s for normal liver, and from 1423–1567 m/s for fatty liver. There is a high negative correlation between speed of sound and the fat content of the liver, with increases in the fat content of the liver resulting in a proportional reduction in the speed of sound (Bamber et al. 1981; Chen et al. 1987; O'Brien Jr. et al. 1988). As a confounding factor, the effect of temperature has been assessed by research groups. The speed of sound in normal liver increases with temperature and shows a maximum value at around 50°C. For fatty liver, a negative correlation occurs (Bamber and Hill 1979). Mahmoud et al, introduced an ultrasound technique called ultrasound induced thermal strain imaging (US-TSI) to assess fat in *ex-vivo* mice liver by using Bamber and Hill's (1979) proposed speed-temperature theory(2014). US-TSI identifies fatty liver (20% fat) with 70% sensitivity, 90% specificity and an AUROC of 0.775 (Mahmoud et al. 2014). Most of the above reported studies used multiple acoustic windows with multiple transducers, but in one study, the same negative correlation between speed of sound and hepatic fat content was proposed with a single transducer (Kumagai et al. 2014).

In a recent study investigating a NAFLD population ranging from simple steatosis to cirrhosis, Imbault et al. used a complex technique including aberration correction, optimization of the spatial coherence of backscattered speckle noise for different speeds of sound thereby correcting for bias caused by variations in the intercostal layer thickness, with a reference standard of MR-PDFF and biopsy (2017). The speed of sound assessment technique proposed in this study indicated AUROC values of 0.942 and 0.952 ($p < 0.0001$ for both) in a 16-patient study, when compared with reference standards of MR-PDFF and biopsy, respectively. They defined the speed of sound cutoff value between healthy and fatty liver as $1.555 \text{ mm} \cdot \mu\text{s}^{-1}$ (Imbault et al. 2017).

These results are promising, and further clinical validation is needed for establishing speed of sound to quantify fat in the liver, especially for the diagnostic performance with accepting biopsy, MR-PDFF or MRS as reference. Furthermore, there is a need to ascertain clinical and biological confounders that may affect speed of sound estimation in the underlying tissue. Some of the factors that need to be accounted for include the subcutaneous fat layer overlying the liver and other pathophysiological processes that occur in the liver along with steatosis, such as fibrosis and inflammation.

Attenuation Coefficient

Ultrasound attenuation, the energy loss when a sound wave passes through a medium, depends on the frequency of the ultrasound wave and the nature of the tissue. Biochemical components of the tissue, including fat, glycogen and fibrotic tissue, directly affect the attenuation of the acoustic wave (Parker et al. 1988; Tuthill et al. 1989). The attenuation coefficient is a quantitative measure of the loss of ultrasound energy due to transmission within a medium (Lin et al. 2015). Attenuation has been studied by many research groups, and many different calculations and analyses have been proposed including spectral shift-zero crossing and sound field correction. The common point of these studies was the positive correlation between the attenuation coefficient and steatosis severity (Fujii et al. 2002; Itoh et al. 1988; Kuni et al. 1989; Taylor et al. 1986). Attenuation coefficient can be measured using various other techniques as well. For example, the spectral shift technique assumes a Gaussian spectral shape of the propagating pulse and echo and estimates the attenuation coefficient slope by measuring the downshift in the center frequency with respect to depth. A drawback of this method is that it does not account for diffraction effects. In order to remedy this, methods that use reference phantoms have been developed. One of these is the spectral difference method, which measures the decay of the power spectrum frequency components with respect to depth to estimate the attenuation coefficient as a function of frequency. Another reference-based technique is the spectral log difference method, which assumes that the attenuation has a linear frequency dependence and obtains an estimate of the attenuation coefficient slope by calculating the slope of the straight line that fits the log ratio (difference between log spectra) of the two power spectra from the proximal and the distal segments of the region of interest (ROI) (Labyed and Bigelow 2011). Additionally, the hybrid method is a recently developed technique that estimates the attenuation coefficient slope by measuring the downshift in the center frequency of the spectra that results from multiplying the power spectra of windowed segments at various depths of the ROI by a Gaussian filter (Labyed and Bigelow 2011). Some of these techniques have shown

promising results with AUROC values of 0.793 (95%CI, 0.676–0.911) to detect steatosis grade S1 vs S2 and 0.804 (95%CI, 0.696–0.913) to detect steatosis grade S2 vs S3 (Paige et al. 2017). It has also shown high correlation values $\rho=0.69$ (0.53–0.81) and $\rho=0.55$ (0.34–0.71), with reference standard steatosis diagnostic measurements obtained via MRI-PDFF and liver biopsy, respectively (Paige et al. 2017).

That being said, however, the use of attenuation coefficients to diagnose NAFLD/NASH does have its drawbacks. Attenuation is generally measured along the path of propagation, without providing the requisite spatial information. In the case of NAFLD and NASH, a bulk attenuation coefficient might prove impractical in identifying cirrhotic or inflamed regions of the liver (Labyed and Bigelow 2010). Additionally, the estimation of attenuation coefficients from backscattered echoes is greatly affected by the presence of aberrating layers (subcutaneous fat in obese patients) and diffraction effects within the insonified region. These effects modify the spectrum of the backscattered RF signals, leading to errors in the estimated values; these errors get progressively worse with increasing depths (Labyed and Bigelow 2010). In some instances (such as when using the Spectral Fit Algorithm), explicit knowledge of the scatterers within the insonified region (density, size, distribution etc.) is required when estimating the attenuation coefficients and might prove impractical for diagnosing such a widespread condition (Labyed and Bigelow 2010).

Controlled Attenuation Parameter

The most widely clinically studied attenuation assessment method is the controlled-attenuation parameter (CAP) implemented by FibroScan (Paris, France). With CAP, total attenuation at the central frequency of the regular or M (mono-element) probe of the Fibroscan (3.5 MHz) is calculated in units of dB/m and used to estimate steatosis severity (Sasso et al. 2010). The algorithm itself is proprietary, and details of it are restricted to Fibroscan. CAP has been shown to be useful in both adult and pediatric patients with NAFLD or alcoholic liver disease (Ahn et al. 2016; Desai et al. 2016; Sasso et al. 2010; Thiele et al. 2018). The XL probe, designed for obese patients, can be used when the conventional M probe is insufficient (Chan et al. 2017). CAP measurements with both M and XL probe, can successfully differentiate steatosis stages, at frequency value 3.5MHz (Sasso et al. 2016).

In a recent meta-analysis study of 19 CAP studies with histologic features as reference, CAP had overall AUROC values of 0.823 (95%CI, 0.809–0.837) to detect S0 vs. S1–S3, 0.865 (95%CI, 0.850–0.880) to detect S0–S1 vs. S2–S3 and 0.882 (95%CI, 0.858–0.906) to detect S0–2 vs. S3 level steatosis (Karlas et al. 2017). These results are concordant with other meta-analyses (Shi et al. 2014; Wang et al. 2015). A summary of some CAP studies is presented in Table 2. Other studies have shown that CAP is successful in the assessment of steatosis caused by multiple liver disease etiologies including viral, alcoholic and non-alcoholic (Ahn et al. 2016; Ferraioli et al. 2014b; Mi et al. 2014; Thiele et al. 2018). Kumar et al. also reported no difference between CAP acquisitions in HBV infected, HCV infected and NAFLD patients ($p=0.592$ for S0, $p=0.964$ for S1, $p=0.062$ for S2 and $p=0.728$ for S3) (2013).

Steatosis assessment is critical in the living-donor liver transplantation setting as hepatic steatosis is associated with graft loss (Stern and Castera 2017). A combination of CAP and elastographic liver fibrosis assessment with the transient elastography function of FibroScan (Figure 3) can be used preoperatively to comprehensively assess the graft liver condition (Mancia et al. 2015). Elastography attempts to estimate the speed of propagation of shear waves within a medium to estimate its stiffness (elasticity), which is often indicative of disease progression (Ozturk et al. 2018). CAP is a useful technique to exclude potential liver donor candidates with a steatosis level >33% (Hong et al. 2017).

CAP has been compared with other imaging modalities in steatosis assessment. Comparing CAP and conventional ultrasound (CUS) based Hamaguchi steatosis scoring system, Carvalhana et al. reported a correlation of $\rho=0.75$ ($P<0.001$) between ultrasound and CAP (2014). Several research groups compared the diagnostic accuracy rates of CAP and MR based methods (Imajo et al. 2016; Karlas et al. 2014; Park et al. 2017). Park et al. showed that MR-PDFF had diagnostic AUROC values of 0.90 (95% CI, 0.82–0.97) for diagnosing S2–S3 vs S0–1 and 0.92 (95% CI, 0.84–0.99) for diagnosing S3 vs S0–2, while CAP AUROC values were 0.70 (95% CI, 0.58–0.82) and 0.73 (95% CI, 0.58–0.89), respectively (2017). Direct comparison of these two techniques showed that MRI-PDFF is significantly superior at each steatosis grade ($p=0.0091$ for S1–3 vs S0, $p=0.0017$ for S2–3 vs S0–1, $p=0.0238$ for S3 vs S0–2) (Park et al. 2017).

CAP also correlates with several other biomarkers of hepatic fat: BMI ($\rho=0.55$), waist circumference ($\rho=0.62$), fatty liver index ($\rho=0.69$), Steatotest ($\rho=0.308$), triglyceride levels ($\rho=0.49$), HOMA-IR ($\rho=0.26$), cholesterol levels ($\rho=0.19$) and fasting C-peptide ($\rho=0.402$) levels (Carvalhana et al. 2014; Chon et al. 2016; de Ledinghen et al. 2012).

Although CAP is an accurate and feasible technique to quantify steatosis, it has some limitations that need to be considered. At the end stage of NAFLD fibrosis, cirrhosis, normal attenuation values may be observed, implying that attenuation may not be a reliable measure of steatosis in severe diffuse liver disease (Maklad et al. 1984). Other confounders for attenuation measurements as a measure of hepatic fat include: (1) attenuation coefficient changes with temperature, with 40 °C being a turning point (Bamber and Hill 1979), (2) Prolonged fatty diet (6 weeks) may increase the attenuation coefficient by 90% (Ghoshal et al. 2012), (3) High skin to capsule distance (SCD) may cause overestimation of steatosis level, although there is no significant difference between AUROC values in patient groups $SCD < 25\text{mm}$ and $SCD > 25\text{mm}$ (Shen et al. 2015) (4) CAP measurements are affected by the intake of meals prior to examination and as such, a minimum fast of 150 minutes is suggested prior to examinations (Ratchasettakul et al. 2017). (5) CAP value improvements occur after short term low-calorie diet and vitamin D correction (Arslanow et al. 2016; Papapostoli et al. 2016).

CAP has been shown to be more cost-effective but inferior to liver biopsy in the diagnosis of steatosis (Thavorn and Coyle 2015). CAP is available on the same platform that can perform transient elastography. Synchronous assessment of liver steatosis and fibrosis from the same region of the liver may be helpful when performing risk stratification in NAFLD.

Backscatter Coefficient (BSC)

Backscatter coefficient is the quantitative value of the ultrasound signals (echoes) returned from the tissue under examination (Lin et al. 2015). It is defined as the differential scattering cross-section per unit volume in the 180° direction (Sigelmann and Reid 1973). Generally, the higher the echogenicity observed, the higher the BSC values (Lin et al. 2015). In vivo and in vitro studies have shown positive correlation between backscatter and steatosis (Bamber et al. 1981; Boote et al. 1992; Zagzebski et al. 1993). Several techniques derived from backscatter coefficient including effective scatterer diameter (ESD) and effective acoustic concentration (EAC) have shown similar correlations (Ghoshal et al. 2012).

The diagnostic performance of BSC to detect steatosis grade S1 vs S2 was shown to have an AUROC value of 0.854 (95%CI, 0.748–0.961). The AUROC value for detecting steatosis grade S2 vs S3 was 0.830 (95%CI, 0.719–0.942) (Paige et al. 2017). BSC correlates with steatosis measured by MRI-PDFF and liver biopsy with Spearman correlation values $\rho=0.72$ (0.57–0.83) and $\rho=0.67$ (0.49–0.79) (Paige et al. 2017). In a study comparing healthy volunteers and patients with diffuse liver disease, Lu et al. reported 14 times higher BSC values for fatty liver than healthy liver ($6.8 \times 10^{-3} \text{cm}^{-1} \text{sr}^{-1}$ vs $0.5 \times 10^{-3} \text{cm}^{-1} \text{sr}^{-1}$, $p < 0.0001$) (1999). (Lu et al. 1999)

Shear Wave Dispersion

Dispersion is defined as frequency dependence of shear wave speed and shear wave attenuation (Barry et al. 2012). By evaluating the crawling wave pattern at different frequencies, shear wave velocity and attenuation can be monitored (Barry et al. 2012). Using this technique, researchers found that hepatic fat accumulation is associated with increased dispersion (Barry et al. 2012). The accepted unit for dispersion is 'm/s per Hz'. Current knowledge of shear wave dispersion is mainly from animal models, with limited clinical data available. Barry et al. showed increased dispersion with increasing steatosis in mice (2014). This finding suggests that dispersion measurement techniques may have a role in staging hepatic steatosis. However, a clinical study of 135 NAFLD patients demonstrated poor performance of dispersion for predicting steatosis, with an AUROC of 0.47 (Nightingale et al. 2015). Further studies are needed to validate this technique in clinical settings. A possible confounding factor in dispersion measurement is increased abdominal fat thickness (Barry et al. 2012). The accuracy of this technique in early hepatic steatosis as well as steatosis in the presence of concomitant fibrosis still require validation (Barry et al. 2014; Barry et al. 2015).

Conclusions/Discussion

Hepatic steatosis evaluation is important in the assessment of chronic liver disease, particularly for the NAFLD spectrum of disease (NAFL or NASH), metabolic syndrome, and alcoholic liver disease. The increasing incidence of NAFLD disease worldwide, and the realization that steatosis alone (NAFL) can progress to clinically significant fibrosis (McPherson et al. 2015; Sharma et al. 2015), make hepatic steatosis an important public health concern, with a risk of future cirrhosis requiring liver transplantation (Farrell and

Larter 2006). Percutaneous biopsy is not practical for large scale steatosis screening due to its invasive nature, high cost, and diagnostic limitations (Nalbantoglu and Brunt 2014). Several imaging biomarkers have been explored to detect and quantify hepatic steatosis, including ultrasound, CT and MRI based techniques. The non-invasive nature of these techniques is ideally suited to serial imaging assessment of steatosis and potentially provides a non-invasive endpoint of therapeutic efficacy. Conventional US is cost effective and easy to implement but lacks quantitative assessment (Lee and Park 2014). CT based modalities are accurate and sensitive but involve ionizing radiation exposure. MR based modalities like standard MRI, MR spectroscopy and MR-PDFF are the most accurate modalities; however, high cost and limited availability limit their broad use. Consequently, lower cost, easier to perform bedside tests such as serum biomarkers or ultrasound techniques are the biomarkers of choice for serial assessment of hepatic steatosis.

While imaging based ultrasound quantification methods hold promise, quantification methods using underlying ultrasound data acquisition are a more robust approach. Among these, CAP has been the most widely studied. This has resulted in the generation of clinical data regarding accuracy of the technique in hundreds of patients. Though some of these studies have shown good performance (AUROC value of 0.97) (Chan et al. 2014), others have not shown such good results (AUROC value of 0.65) (Kumar et al. 2013).

There is limited data for the performance of attenuation coefficient, backscatter coefficient and speed of sound techniques in the clinical setting; however, these quantitative ultrasound techniques are highly dependent on tissue structure and have shown high correlation with an increase in the histology-determined steatosis stage (Imbault et al. 2017; Lin et al. 2015; Paige et al. 2017). QUS techniques have the potential to be reliable techniques with minor inter-operator variability. CAP is also an operator friendly technique with a high inter-rater reliability concordance correlation coefficient (CCC) value of 0.82 (95%CI, 0.78–0.85) (Ferraioli et al. 2014a). Reliability of attenuation coefficient and backscatter coefficient have been studied with phantoms and in clinical settings (Han et al. 2017; Paige et al. 2017). Attenuation coefficient has high inter-rater reliability with 90% (79.5–96.2) agreement value between operators ($p < 0.0001$) (Paige et al. 2017). Backscatter coefficient has a relatively high inter-rater reliability with 71.7% (58.6–82.5) agreement value between operators ($p = 0.0012$) (Paige et al. 2017).

Differentiation of NASH from simple steatosis is also critical. Speed of sound, attenuation, CAP and BSC are promising in terms of sensitivity and feasibility to detect steatosis, but current studies have focused on NAFLD patients without attempting to discriminate NASH patients from simple steatosis. Inflammation in the liver may influence quantitative techniques (Matsushashi et al. 1996), so NASH discrimination may be a fruitful area for future research. In summary, quantification techniques using ultrasound based approaches hold significant promise. Larger clinical trials are needed to see if these approaches can be used in combination for achieving a robust hepatic fat quantification technique that provides an alternative to MR based approaches.

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Figure1.
MR-PDFF image with multiple region of interest (ROI) showing 6%, 6.9% and 4.8% fat accumulation (Courtesy of Amirkasra Mojtahed, MD).

Figure2.
Difference between healthy liver and fatty liver. Increased echogenicity and poor beam attenuation are visible in figure on the right.

Figure3. Time-motion(TM) mode, Amplitude(A) mode and shear wave propagation map, respectively. TM and A modes are used to locate ideal liver part for reliable acquisitions. Shear wave propagation image.y-axis is distance from skin, x-axis is time. Slope of the dashed line is shear wave speed(V_s). Median CAP shows 289dB/m, and median stiffness value shows 7.1kPa.

Figure4.

Spagetti plot of mean/median of attenuation values from multiple research groups using controlled attenuation parameter. X axis represents steatosis stage (S1–3). Y axis represents controlled attenuation parameter in dB/m units. Attenuation value increases at higher steatosis stages (Sasso et al. 2010, Myers et al. 2012, Kumar et al. 2013, Wang et al. 2014, Ferraioli et al. 2014, Chan et al. 2014, Shen et al. 2014, Chon et al. 2014, Mi et al. 2014, Karlas et al. 2014, Lupsor-Platon et al. 2015, Shen et al. 2015, Imajo et al. 2016, de Ledinghen et al. 2016, Ahn et al. 2016, Kwok et al. 2016, Andrade et al. 2017, Thiele et al. 2018).

Table1.

Technical summary of the research studies using various fat quantification methods. SoS-Speed of Sound, AC-Attenuation Coefficient, BSC-Backscatter Coefficient, SWD-Shear wave dispersion

Study	Assessed Parameter	Liver type	Ultrasound system	Probe	Frequency 1
Imbault et al. 2017	SoS	Phantom, healthy and CLD subjects	Supersonic imagine	XC 6–1 Curved probe	
Paige et al. 2017	AC and BSC	NAFLD subjects	Siemens ACUSON S3000	4C1 Curved probe	1–4.5
Jaeger et al. 2015	SoS	Phantom	Verasonics V1–64	HDI L7–4 linear probe	5 MHz
Barry et al. 2015	SWD	Rat liver	GE Logiq E9	L8–18i-D linear probe	150 Hz
Lin et al. 2015	BSC	Healthy and NAFLD subjects	Siemens ACUSON S3000	4C1 Curved probe	1–4.5
Barry et al. 2014	SWD	Phantoms and rat liver	Ultrasonix	L40–8/12	200–360 Hz
Mahmoud et al. 2014	SoS	Rat Liver	Ultrasonix SonixTOUCH	L14–5/38 linear Probe	5–14MHz
			FUJIFILM VisualSonics Vevo2100		3–24MHz
Kumagai et al. 2014	SoS	Rat Liver	Experimental setup	Panasonic linear Probe	7 MHz
Barry et al. 2012	SWD	Phantoms and rat liver	GE Logiq E9	M12L Linear Probe	100–400 Hz
Ghoshal et al. 2012	SoS, AC, BSC	Rabbit liver	Experimental setup	Olympus probe	20 MHz
Nam et al. 2012	AC and BSC	Phantom	Ultrasonix RP	L14–5/38	6MHz
			Siemens ACUSON S2000	18I6	10MHz
				9L4	9MHz
			Visualsonics Vevo2100	MS200	15 MHz
Thijssen et al. 2008	AC	Cow liver	Toshiba Power Vision 6000	Curved probe	4.2MHz
Gaitini et al. 2004	AC and BSC	CLD subjects	Philips HDI5000		2–5 MHz
Fujii et al. 2002	AC	Phantom and healthy subjects	Aloka SSD-5500		3.75MHz
Lu et al. 1999	AC and BSC	Phantom, healthy and CLD subjects	Siemens SL-1		3.5, 5MHz
Zagzebski et al. 1993	AC and BSC	Healthy subjects	Siemens Sonoline SL-1		3.5, 5, 7.5MHz
Boote et al. 1992	BSC	Phantom	Experimental setup		3–5MHz
Yao et al. 1990	BSC	Phantom	ATL Mark III		2.5–5.5
Kuni et al. 1989	AC	Healthy and CLD subjects			3.5MHz
Itoh et al. 1988	AC	Phantom, healthy and CLD subjects	Aloka SSD-270	Curved and linear probes	3.5MHz

Study	Assessed Parameter	Liver type	Ultrasound system	Probe	Frequency 1
Parker et al. 1988	AC	Healthy and CLD subjects	Ausonics Octoson		2.5MHz
O'Brien Jr. et al. 1988	SoS and AC	Rat Liver	Experimental setup		100 MHz
Lin et al. 1987	SoS	Excised human liver	Experimental device		5 MHz
Chen et al. 1987	SoS	Normal and CLD	UI Octoson		3 MHz
Taylor et al. 1986	AC	Phantom, healthy and CLD subjects	GE Datason		3 MHz
Bamber et al. 1981	SoS, AC, BSC	Excised human liver			1, 2.5, 4MHz

Summary of the research studies using CAP in patients with NAFLD. *, N/A, AUROC, LCI and UCI, denote; median values, Not available, Area under the curve, lower confidence interval and upper confidence interval respectively. S1, S2 and S3 represents fat accumulation in 5%–33%, 33%–66%, and >66% of hepatocytes, respectively.

Table2.

Study ID	N	Etiology	Reference method	Probe type	Steatosis Level	Mean/Median CAP value (dB/m)	Optimal cut-off value (dB/m)	AUROC	AUROC LCI	AUROC UCI	Sensitivity %	Specificity %
Friedrich-Rust et al. 2012	46	NAFLD	Biopsy	M	S1	241	N/A	N/A	N/A	N/A	N/A	N/A
					S2	298	245	0.78	0.58	0.99	97	67
					S3	319	301	0.72	0.57	0.86	76	68
Myers et al. 2012	153	NAFLD	Biopsy	M	S1	299*	289	0.79	0.71	0.87	68	88
					S2	319*	288	0.76	0.69	0.84	85	62
					S3	320*	283	0.7	0.6	0.81	94	47
Kumar et al. 2013	63	NAFLD	Biopsy	N/A	S1	213*	N/A	N/A	N/A	N/A	N/A	N/A
					S2	284*	258	0.79	N/A	N/A	78.4	73.1
					S3	291*	283	0.76	N/A	N/A	71.4	67.9
Chan et al. 2014	161	NAFLD	Biopsy	M	S1	305*	263	0.97	N/A	N/A	91.8	93.7
					S2	320*	263	0.86	N/A	N/A	96.9	67.7
					S3	324*	281	0.75	N/A	N/A	100	53.1
Karlvas et al. 2014	50	NAFLD	Biopsy	M	S1	253	233.5	0.93	0.86	1	93	87
					S2	321	268.5	0.94	0.88	0.99	97	81
					S3	335	301.2	0.82	0.7	0.93	82	76
Imajo et al. 2016	142	NAFLD	Biopsy	M	S1	262.9	236	0.88	0.8	0.95	82.3	91
					S2	289.6	270	0.73	0.64	0.81	64.3	73.6
					S3	304.9	302	0.7	0.58	0.83	64.3	73.6
Sasso et al. 2016	59	NAFLD	MRI fat fraction	M	S 2%	275	251	0.83	0.71	0.95	78	78
					S 8%	276	267	0.87	0.78	0.97	80	79
					S 16%	268	299	0.92	0.85	0.99	92	88
				XL	S 2%	279	254	0.84	0.73	0.95	83	78
					S 8%	272	270	0.90	0.82	0.99	88	79
					S 16%	275	301	0.91	0.83	0.99	92	81
de Ledinghen 2016	261	NAFLD	Biopsy	M	S1	264	N/A	N/A	N/A	N/A	N/A	N/A
					S2	331	310	0.8	0.73	0.86	79	71
					S3	336	311	0.66	0.59	0.72	87	47

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Study ID	N	Etiology	Reference method	Probe type	Steatosis Level	Mean/Median CAP value (dB/m)	Optimal cut-off value (dB/m)	AUROC	AUROC LCI	AUROC UCI	Sensitivity %	Specificity %
Lee et al. 2016	183	NAFLD	Biopsy	N/A	S1	265*	247	0.95	0.92	0.98	88.2	100
					S2	313*	280	0.85	0.79	0.91	84.7	80
					S3	322*	300	0.72	0.64	0.80	72.7	60.7
Chan et al. 2017	57	NAFLD	Biopsy	M	S1	324*	266	0.94	0.86	0.98	91.1	87
					S2	321*	266	0.80	0.69	0.88	91.1	87
					S3	330*	267	0.69	0.57	0.79	100	40.6
				XL	S1	339*	271	0.97	0.90	0.99	94.6	91.3
					S2	345*	271	0.81	0.71	0.89	95.3	61.1
					S3	345*	304	0.67	0.56	0.77	80	54.7
Park et al. 2017	104	NAFLD	Biopsy	M and XL	S1	N/A	261	0.85	0.75	0.96	71.8	85.7
					S2	N/A	305	0.70	0.58	0.82	63.3	68.8
					S3	N/A	312	0.73	0.58	0.89	63.6	70.1
Siddiqui et al. 2018	393	NAFLD	Biopsy	M and XL	S1	306*	285	0.76	0.64	0.89	80	77
					S2	340*	311	0.70	0.64	0.75	77	57
					S3	340*	306	0.58	0.51	0.64	80	40
Garg et al. 2018	76	NAFLD	Biopsy	XL	S1	320*	323	0.75	0.61	0.89	58.6	83.3
					S2	354*	336	0.74	0.62	0.86	73.9	75.5
					S3	362*	357	0.82	0.73	0.91	100	77.8
Caussy et al. 2018	119	NAFLD	MRI-PDFF	M and XL	5%	315	288	0.80	0.70	0.90	75	77.1
					10%	N/A	306	0.87	0.80	0.94	78.6	82.5
Chan et al. 2018		NAFLD	Biopsy	M	S1	293*	253	0.84	0.78	0.89	92.6	70.6
					S2	327*	294	0.76	0.69	0.82	84.8	58.8
					S3	330*	294	0.61	0.54	0.69	87.9	36.1
				XL	S1	302*	279	0.91	0.85	0.94	82.8	88.2
					S2	342*	303	0.78	0.71	0.84	79.5	64.7
					S3	351*	325	0.65	0.58	0.72	75.8	54.4
Runge et al. 2018	55	NAFLD	Biopsy	M	S1	N/A	260	0.77	0.63	0.87	90	60
					S2	N/A	296	0.78	0.65	0.88	92.3	55.2
					S3	N/A	334	0.78	0.65	0.88	77.8	76.1