Editorial

# Ultrasound imaging in nonalcoholic liver disease: current applications and future developments

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## Introduction

In 1980, Ludwig described non-alcoholic liver disease (NAFLD) in patients who did not drink alcohol, but whose liver histology showed alcoholic-like liver disease (1). NAFLD includes a range of diseases from nonalcoholic fatty liver (NAFL) to nonalcoholic steatohepatitis (NASH). The prevalence of NAFLD is highest in the Middle East (31.8%), followed by Asia (27.4%), USA (24.1%) and Europe (23.7%), to the lowest (13.5%) in Africa (2). Accordingly, NAFLD has emerged as the most common chronic liver disease worldwide. The overall global economic burden increases as the clinical consequences of NAFLD grow, including liver-specific, cardiovascular disease and overall mortality (3). Compared to the effective anti-viral treatments for viral chronic hepatitis, the management of NAFLDs is still under development. Although there is no universal consensus, many scientific communities have developed guidelines for diagnosis and treatment.

## Ultrasound in NAFLD clinical management

Previously, liver biopsy was considered the golden standard for NAFLD diagnosis. According to histological characteristics, when hepatic steatosis presents ≥5% without existence of hepatocellular injury is defined as NAFL. NASH is characterized by the presence of ≥5% hepatic steatosis, with hepatocyte inflammation and ballooning, with or without any fibrosis. However, liver biopsy is impractical due to the limitations of sampling error, subjective biopsy interpretation, complication and high cost. Therefore, it is infeasible to perform liver biopsy in large numbers of at-risk patients (4). Given the prevalence of 20–30%, it is important to have a simple non-invasive method for the management of NAFLD.

The first clinical challenge is "Who should be screened for NAFLD?". Although systemic screening of the general population still lacks strong evidence, highlighting the suspicion for NAFLD and NASH in high-risk groups, such as type 2 diabetes or obesity, is emphasized (5,6). Conventional ultrasonography (US) is often the first imaging modality used in screening clinically due to availability and low cost, compared to magnetic resonance-based or computed tomography techniques. However, the qualitative and subjective results, low sensitivity and specificity and inability to differentiate NAFL and NASH can limit application in a clinical setting. Several semi-quantitative scoring systems provide more objective evaluation (*Table 1*) by using liver-kidney contrast, attenuation of liver parenchyma, vessel and gallbladder wall blurring, etc. Although some of these tools show high correlations to metabolic characteristics (7,8), they

**Table 1** The semi-quantitative scoring system for nonalcoholic liver disease (NAFLD)

| Hamaguchi *et al.* | Ballestri *et al.* | Liang *et al.* | Saadeh *et al.* |
|---|---|---|---|
| Japanese group, 46.5±8.8 yrs (range, 18–78 yr) | Italian group, 45.1±12.7 yrs | Taiwan, morbid obese (BMI >40) for laparoscopic bariatric surgery | United States, middle adult (47.5±3 yrs for NASH and 43.3±3 yrs for steatosis) |
| NAFLD: score ≥2 (total score: 6); AUC for NAFL*: 0.98 (Sen: 91.7%, Spe: 100%) | NAFLD: score ≥2 (total score: 8); Correlation (r) to steatosis (%): 0.745; to Fibrosis stage: 0.198 (P=0.147); AUC for NASH#: 0.7635–0.796 | Total score: 10; NASH diagnosis: r=0.464; Sen 81%, Spe: 66% | Echogenicity severity: 0–5; sonographic pattern grade: 0–5; 33% liver fat was the optimal threshold for detecting steatosis; None of variable |

*NAFL, non-alcoholic fatty liver, steatosis was diagnosed when macrovesicular steatosis ≥10%; #NASH, non-alcoholic steatohepatitis, Brunt's criteria or NAFLD activity score ≥5; Sen, sensitivity; Spe, specificity, AUC, area under the curve of receiver operating characteristic curve.

cannot detect low degree of liver steatosis. The predict value for hepatic steatosis would become significant with liver steatosis ≥20% (9,10), which is much higher than the definition of NAFL (≥5% hepatic steatosis). The amount of liver fat is associated with the risk of cardiac complications and cardiovascular disease mortality. Nevertheless, the scales of these semi-quantitative scoring systems are not sufficient to stratify risky subjects into different levels. Human visual inspection of US images to identify liver fat amount, NASH or liver fibrosis is not effective. Strauss *et al.* presented that the using US images to detect the presence of increased liver fat had the agreement rates of 72% and 76% for inter- and intra-observer, respectively. Besides, intra-observer agreement for severity of fatty liver was between 55% to 68% (11). Fishbein *et al.*, also found the magnetic resonance imaging (MRI) and US measurements showed different correlations to liver biopsy steatosis. MRI had equal correlation with fat content in macrovesicular steatosis (r=0.92 *vs.* r=0.90) but better performance in microvesicular steatosis than US (0.77 *vs.* 0.41) (12). This reflect that grading of liver fat are highly depending on the examiners' subjective impression. Accordingly, a new quantitative US to measure liver fat and fibrosis objectively and precisely is highly desirable as liver fat and liver fibrosis are considered strong evidence for clinical poor outcome.

## The quantitative ultrasound (QUS) for liver steatosis

Because of the limitations of conventional US, different QUS approaches have been developed to measure acoustic parameters to recognize tissue microstructure. Several studies have shown when more fat accumulate in the liver, the evidences of hepatic inflammation/fibrosis are more likely to be found in histology (13-15). Therefore, precise quantification of liver fat is of high clinical relevance. Gaitini *et al.* reported that the inflammation or fibrosis in severe NAFLD changed the ultrasound backscattering properties and weakened the discrimination of the pathology in normal livers (13). The quantitative technique can be classified as image-based analysis and the raw-radiofrequency data acquiring from the scanner directly (16). The non-image-based parameters, such as US backscatter, attenuation coefficients and speed of sound, have been studied for many years. The estimations of attenuation coefficients were different in previous studies due to various system settings, different ultrasound imaging platforms and datasets. For instance, Taylor *et al.* presented that the average attenuation coefficients were 0.52 dB/cm/MHz in a normal liver and 0.77 dB/cm/MHz in a fatty liver were, respectively (14). Lin *et al.* showed the value increased with the grading of liver steatosis from 0.71 to 1.22 dB/cm/MHz (17). Lu *et al.* pointed out the mean attenuation of fatty livers was higher at 3 MHz than that in healthy subjects (2.54 and 1.66 dB/cm, respectively) (18). Similar results were also reported by Fujii *et al.* The average attenuation coefficients were 0.80 and 0.59 dB/cm/MHz for fatty liver and normal liver, respectively (19). In the paper by Thijssen *et al.* (20), residual liver attenuation coefficient was 1.19 dB/cm in high fat liver, comparing to 0.76 dB/cm in medium fat liver. Nevertheless, the correlation between the attenuation coefficient and the amounts of liver fat is positive unanimously.

Combining different types of parameters can increase the accuracy and detect the severity of NAFLD and small liver fat quantity when the semi-quantitative scoring system shows normal (no hepatic steatosis) (21). Most quantitative US parameters are based on the assumptions of a statistical

 

model, such as Homodyned-K, Nakagami and Rayleigh distributions, etc. (22). Similarly, non-model-based statistical parameters including Kurtosis *K* and entropy have also been used for the quantification of hepatic steatosis (22,23) and associations with metabolic factors (24). Gaitini *et al.* found the best results using the sum entropy and entropy of the gray-level co-occurrence matrix (GLCM) among the 18 textural indices to characterize fatty liver (13). Yeh *et al.* extracted texture features from GLCM and nonseparable wavelet transform, and their results showed an accuracy of 90.5% for the classification of steatosis and non-steatosis but decreased to 82.6% when steatosis was divided into four classes (25).

However, the acceptance of QUS in clinical routine practice is still low. The most widely clinically used technique is controlled-attenuation parameter (CAP) with M probe and XL probe (for obese patients) implemented by FibroScan™ (Paris, France) (16,26). CAP is recognized as a tool for hepatic steatosis assessment in clinical guidelines and trials of pharmacotherapy for NASH (27). Thanks to the contributions of the CAP in clinical applications, the role and importance of acoustic attenuation in the assessment of hepatic steatosis has attracted more and more attention of researchers. For example, the technique of ultrasound attenuation imaging was recently proposed and implemented in the Aplio™ i800 ultrasound system (Canon Medical Systems, USA) as a diagnostic tool for the evaluation of hepatic steatosis. Concurrently, the Aplio™ i800 system also combines shear wave elastography imaging, contrast vector imaging, and shear wave dispersion measurement into a liver analysis package, enabling a more comprehensive evaluation of the liver.

## The QUS for liver fibrosis

Currently, the clinical application of QUS to evaluate advanced liver fibrosis is more important than the quantification of hepatic steatosis because liver fibrosis has been noted for the single most important factor determining long-term outcome in NAFLD patients (28). NAFLD and NASH induce fibrosis progression, leading to cirrhosis and related clinical complications, although absence of cirrhosis has been reported in 30–50% of NAFLD-associated hepatocellular cancer (29). Because liver fibrosis induces the mechanical changes of the liver, the physical characteristics can be provided for the measurement of QUS. Among different QUS for liver fibrosis, the most common technique was elastography. Petitclerc *et al.* described three clinical widely-used US shear-wave elastography: 1D transient elastography, focal point shear-wave elastography, and super-sonic shear-wave elastography (30). Of these techniques, 1D transient elastography has been commercialized as FibroScan™, which is the most widely used worldwide and shows good accuracy for significant fibrosis (≥ F3 and cirrhosis, AUC: 0.93, 95% CI: 0.89–0.96) and with a negative predictive value of 90% to rule out cirrhosis. In particular, FibroScan™ was suggested to replace liver biopsy for evaluating liver fibrosis because it provides quantitative measure of liver stiffness in patients with HBV or HCV to indicate the initiation for anti-viral treatment (4). The focal point shear-wave elastography and super-sonic shear-wave elastography also have been commercialized as acoustic radiation force-based elastography (ARFI) and Supersonic Imagine, respectively. The diagnostic accuracy of ultrasound elastography has been assessed in numerous studies and pooled in meta-analyses. The reported diagnostic accuracy for various ultrasound elastography techniques (FibroScan™ and ARFI) has an AUC in the range of 0.84–0.87 for fibrosis stage ≥F2, 0.89–0.91 for fibrosis stage ≥F3, and 0.93–0.96 for fibrosis stage F4 (31-33). Only one review in children and adolescents reported that Supersonic Imagine has an AUC of 0.91 for fibrosis stage ≥ F2 (34). Although CAP of FibroScan™ has been approved for hepatic steatosis measurement, the relationship between hepatic steatosis and ARFI (or shear wave) is still unclear and controversial (5).

It should be noted that liver fibrosis not only increases the tissue stiffness but also results in microstructural changes, which alter the statistical distribution of ultrasound backscattering. The acoustic structure quantification (ASQ) technique is a useful tool for characterizing the liver parenchyma by analyzing the ultrasound backscattered statistics (35). The resolvable scatterers (e.g., fibrotic structures and nodules) with the dimensions larger than the wavelength gradually develop during the formation of liver fibrosis, making the scattering cross-sections vary significantly between scatterers. In this condition, the backscattered statistics measured from the liver deviate from the Rayleigh distribution, resulting in coarse and heterogeneous speckle patterns. This is why the ASQ algorithm works for assessing liver fibrosis. More importantly, the ASQ analysis is less affected by the inflammatory activity compared with ultrasound elastography (35). However, some inconsistent conclusions published previously questioned the diagnostic value of ASQ in the assessment of liver fibrosis. For example, the

 

studies of Kramer *et al.* (36) and Keller *et al.* (37) found that changes in ASQ parameters are less dependent on the progress of liver fibrosis. In contrast, more and more papers gradually support the usefulness of ASQ in the assessment of hepatic steatosis (38-40).

To the best of our knowledge, early detection of liver fibrosis is still an unmet need in the clinical diagnosis of liver diseases; for the time being, no more effective methods or determinant strategies have been further developed yet to satisfy the above purpose universally and stably although FibroScan™ is currently a well-accepted modality. In the future, multimodality imaging approaches may be taken into account to provide various aspects of physical meanings associated with liver tissues, making an early evaluation of liver fibrosis possible.

## Challenge and future development

Current guidelines for the management of NAFLD provide different algorithms to screen, diagnose and follow-up. Actually, other indirect tools are recommended in addition to ultrasound. For example, Fatty Liver Index (FLI) and NAFLD liver fat score are easily calculated to assess the presence of hepatic steatosis. Fiborsis-4 (FIB-4) score and NAFLD fibrosis score are used to identify patients at risk of fibrosis by using serum test results, history taking and anthropometric measurement.

Due to the development of several noninvasive assessment tools for NAFLD, the need for liver biopsy is reduced sharply (4). Hence, it is important to have a new strategy of noninvasive risk stratification for liver fibrosis by combing indirect tools and new QUS techniques. The goal is to thus categorize patients into low, indeterminate and high likelihood of advanced fibrosis, especially in the primary care clinic. Then, the patient with a high risk for advanced fibrosis should be referred to a liver specialist. Meanwhile, this will also be helpful for guiding treatment decisions based on the overall risk of advanced fibrosis (e.g., the patients with advanced QUS parameter and abnormal alanine aminotransferase levels).

Nowadays, there are numerous agents for the treatment of NAFLD and NASH being developed in phase II and III clinical trials (41). Some studies have shown the promising treatment effects on improvements of steatosis, inflammation and fibrosis, which are assessed with histological endpoints. When new agents are approved for the market, the clinical surveillance of patient requires affordable, safe and convenient tools instead of liver biopsy to follow steatosis, inflammation and fibrosis change. As a surrogate of liver histopathology, the role of QUS assessments is gaining momentum despite it being premature according to the current technology. Despite the wide use of FibroScan™ CAP, its accuracy in reflecting liver steatosis over time has not been demonstrated (27). Furthermore, nowadays there is no evidence of QUS being the surrogate marker of the inflammation in liver. Consequently, QUS is combined with inflammatory biomarkers and a panel [apoptosis markers, e.g., serum cytokeratin18 (CK-18) fragment M30 and surface antigen FAS (sFAS)] to enhance the accuracy of detection for NASH (42). Based on the mechanisms of action of the treatments (or drugs), the use of different QUS parameters and imaging or serum biomarkers can demonstrate improvement in the clinical intervention of NAFLD and NASH. However, well-suited combinations still need further analysis.

## Conclusions

Even though QUS is a surrogate measurement for liver steatosis and fibrosis, it does not reflect the nature and definition of NASH in histopathology. The core components of NASH are inflammation and hepatic injury (hepatocyte ballooning), which cannot be detected by QUS. Moreover, the data of pipeline agents for NASH show that the fibrosis is prevented, while the feature of NASH may worsen (or vice versa). These complicated outcomes interfere with the application of QUS in clinical fields. Furthermore, the nature history of NAFLD has not been elucidated completely and there have not been any longitudinal follow-up cohorts with repeated QUS assessment. The dynamic change of QUS parameters accompanied with disease situation also warrants further evaluation. The use of QUS for the management of NAFLD is likely to increase in the coming future.

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## Footnote

*Conflicts of Interest:* The authors have no conflicts of interest to declare.

 

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