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Magnetic resonance imaging and transient elastography in the management of Nonalcoholic Fatty Liver Disease (NAFLD)

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Abstract

Introduction: Nonalcoholic fatty liver disease (NAFLD) is the most common cause of chronic liver disease and cirrhosis worldwide and the second most common cause of liver transplantation in major medical centers. Because liver steatosis and fibrosis severity are related to disease morbidity and mortality, the extent of disease, and disease progression, they need to be assessed and monitored. In addition, innovation with new drug developments requires disease staging and monitoring in both phase 2 and 3 clinical trials. Currently, disease assessment in both clinical practice and research is mostly performed by liver biopsy, an invasive, procedure with risks. Noninvasive, highly accurate tests are needed that could be used in clinical trials as surrogate endpoints and in clinical practice for monitoring patients.

Area Covered: We discuss noninvasive tests, transient elastography (TE) with controlled attenuation parameter (CAP), magnetic resonance imaging (MRI), and MR elastography (MRE), summarize the available evidence of their usefulness for assessing steatosis and fibrosis. Therefore they could be used as clinical trials outcomes and in disease monitoring in clinical practice.

Expert Commentary: TE with CAP, MRI and MRE are highly accurate noninvasive diagnostic tools for quantifying hepatic steatosis and fibrosis. Therefore they could be used as clinical trials outcomes and in disease monitoring in clinical practice.

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Declaration of interest

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Keywords

Nonalcoholic fatty liver disease; nonalcoholic steatohepatitis; magnetic resonance imaging proton density fat fraction; magnetic resonance elastography; transient elastography; controlled attenuation parameter

1. Introduction

Nonalcoholic fatty liver disease (NAFLD) is now the most common cause of chronic liver disease and cirrhosis [1–3], a major risk factor for hepatocellular carcinoma [4], the second most common cause of liver transplantation in major medical centers [5], the most likely cause of abnormal liver enzymes in Western countries and an increasingly common cause of liver disease-associated morbidity [6–8] as well as cardiovascular disease [9]. It develops when fat accumulates in the liver cells leading to abnormal liver enzymes and/or abnormal findings on imaging. The majority of NAFLD patients have simple hepatic steatosis with or without minimal inflammation, termed nonalcoholic fatty liver (NAFL). However, a subset of patients with NAFLD develops nonalcoholic steatohepatitis (NASH) in which the fat accumulation is accompanied by hepatocellular injury, inflammation and/or fibrosis [10]. NASH can lead to progressive disease including cirrhosis and hepatocellular carcinoma [10,11].

A diagnostic workup for NAFLD is routinely prompted by detecting abnormalities in liver enzymes, especially in those with established risk factors such as obesity, mixed hyperlipidemia, metabolic syndrome, diabetes, as well as in those who are in high-risk ethnic groups such as Hispanics, those with risk alleles for specific genetic polymorphisms, and those who are members of what has been termed ‘NAFLD families’ [12]. However, liver enzymes can be normal in NAFLD patients [13–15]. NAFLD is also sometimes incidentally detected by ultrasound during routine medical checkups. Other causes of liver disease should be excluded and an imaging study should be performed to assess steatosis [14]. Liver tissue biopsy remains the reference standard both to diagnose NAFLD and to differentiate NAFL from NASH and determine the amount of fibrosis [14,16]. However, liver biopsy is an invasive test that may be associated with adverse events and sample errors [17]. Although ultrasound remains the first step for detecting steatosis in NAFLD patients in clinical practice, it has a limited role in follow up. Other diagnostic approaches such as computerized tomography (CT) scans have shown limited benefit in diagnosis and follow-up [18–20]. Prospective cohort studies have clearly demonstrated that liver fibrosis severity is the strongest predictor of both the liver-related complications of NAFLD and of important extrahepatic diseases, including cardiovascular disease and extrahepatic malignancies [1,9]. Thus, there is considerable interest in noninvasive imaging techniques that would avoid the possible adverse effects of liver biopsy while accurately determining the extent of liver fibrosis.

Transient elastography (TE) is of emerging interest for noninvasive assessment of liver tissue stiffness. The US FDA approved TE in April 2013 for the noninvasive assessment of liver disease at the point of care [21,22]. Initially, it was used to assess the level of liver fibrosis through liver stiffness measurement (LSM) in chronic viral hepatitis. It was shown to be

better for identification of liver cirrhosis than advanced fibrosis (mean AUROC 94% vs. 84%, respectively) among viral hepatitis patients [23,24]. Investigations regarding TE assessment of liver fibrosis have been carried out in patients with chronic viral hepatitis as well as patients with chronic liver disease of several other etiologies [25]. Most recently, it has been shown to be beneficial for evaluation of liver fibrosis in NAFLD.

Magnetic resonance imaging (MRI) has also been assessed and shown to be accurate for detecting fat in the liver. MR spectroscopy (MRS) was shown to be precise for quantifying liver steatosis and became the reference standard; however, it has biases and is mainly used in research studies [26]. MRI-determined proton density fat fraction (MRI-PDFF) is a novel technique that reduced the biases seen with MRS and has been shown to be highly correlated with MRS [27,28]. It has been demonstrated that MRI-PDFF is accurate for quantification of liver fat and we have shown that MRI-PDFF correlated highly with MRS in quantifying liver fat in patients enrolled in a clinical trial for NASH [27,29]. MR elastography (MRE) is an emerging technique that has been shown to have a role in detecting fibrosis in NAFLD patients and probably in predicting NASH [30]. In this review, we highlight recent advances in TE and MRI techniques and their usefulness for evaluation of NAFLD patients.

Ultrasound shear wave elastography is a technique for fibrosis assessment that is still emerging; with little data available to date, it is outside the scope of this review.

2. Transient elastography

Liver stiffness is measured by TE with the FibroScan device (Echosens, Paris, France) using transducer-induced vibrations at low frequency (50 Hz) and amplitudes [31]. The propagation of the shear wave through the liver parenchyma is followed by pulse-echo ultrasound to measure the average velocity using Hook's law. The resulting values range from 2.5 to 75 kPa with the value inversely proportional to liver elasticity [32,33]. In chronic hepatic disease, more than 10 measurements and a success rate of >60% are required for reliable evaluations [34]. In addition to its usefulness for the assessment of liver stiffness, the most recent FibroScan model measures a novel physical parameter termed the controlled attenuation parameter (CAP), a proprietary algorithm based on the ultrasonic attenuation coefficient of transient elastography's shear wave, an estimate of the total ultrasonic attenuation at 3.5 MHz, with values ranging from 100 to 400 dB/m. Since fat affects ultrasound propagation, CAP measurement has been shown to reliably quantify hepatic steatosis [35,36]. Studies have shown that liver steatosis can be detected with CAP in multiple chronic liver diseases [37–40].

2.1. Transient elastography with liver stiffness measurement to predict hepatic fibrosis stage in NAFLD

Multiple studies have compared LSM and liver biopsy for their usefulness in identifying different stages of liver fibrosis in NAFLD patients; Table 1 shows a summary of these studies that included only NAFLD patients [41–50,53]. In these studies, LSM cut-off values for F 2 range from 6.2 to 11 kPa, with 65–90% sensitivity, 45–91% specificity, 60–97% positive predictive value and 59–94% negative predictive value. LSM cut-off values for F 3 range from 7.3 to 11.4 kPa, with 78–100% sensitivity, 61–97% specificity, 45–75%

positive predictive value and 92–100% negative predictive value. LSM cut-off values for F4 range from 6.9 to 20 kPa with 63–100% sensitivity, 62–98.4% specificity, 15–83% positive predictive value and 95–100% negative predictive value.

Studies from the US have been limited. In one study, the median LSM for patients without advanced versus those with advanced fibrosis (F3–F4) were 6.6 kPa (5.3 – 8.9) and 14.4 kPa (12.1 – 24.3), respectively [52]. The authors suggested that the ideal LSM cut-off for advanced fibrosis was 9.9 kPa (sensitivity 95%, specificity 77%). In a meta-analysis that estimated the diagnostic accuracy of TE it was shown that TE has moderate accuracy (79% sensitivity and 75% specificity using cut-off 6.7–7.7kPa) for diagnosing F2 while it has excellent accuracy for diagnosing F3 (85% sensitivity and 82% specificity using cut-off 8–10.4kPa) and F4 (92% sensitivity and 92% specificity using cut-off 10.3–17.5kPa) [51]. Based on the meta-analysis and previous studies, we suggest the following ranges: 7–9.9 kPa for F2, 10–13 kPa for F3 and 14 kPa for F4.

A major limitation of these studies was the unsuccessful measurement of LSM in obese patients and the unknown accuracy of LSM in obese patients. Wong et al. compared M and XL probes for accurately identifying fibrosis in 193 NAFLD patients [53]. By intention-to-diagnose analysis, the areas under the receiver operating characteristics curves (AUROCs) of the M probe and the XL probe were 0.56 and 0.74 for F2 or higher, 0.57 and 0.78 for F3 or higher, and 0.53 and 0.86 for F4 disease, respectively; when stratified by body mass index (BMI), the M probe performance was shown to be particularly poor in obese patients. The XL probe generated lower liver stiffness values than the M probe in the same patient, requiring a different set of cut-off values. An improved LSM success rate by XL probe was predominantly observed in obese patients, with 10 valid measurements achieved in 93% of patients with BMI ≥ 30 kg/m² with the XL probe, but only in 60% of these patients with the M probe. Overall, it appears that TE with the XL probe allows a higher proportion of reliable examinations in obese patients but not in nonobese patients [54]. However, a tendency was shown for the XL probe to over-estimate liver fibrosis in patients with BMI of > 35 kg/m². It will be important to remember that liver stiffness in NAFLD can be influenced by BMI, as well as by severe steatosis ($>33\%$) and diabetes mellitus [55,56]. A recent U.S. cross-sectional study by Park et al. used the M probe initially for all patients and then, when indicated by the equipment, rescanned some of the patients using the XL probe [50]. The study showed that the performance of TE without adjustment for the probe type (AUC 0.67) and that of TE with adjustment for the probe type (AUC 0.62) were not significantly different ($p = .29$). This is contradictory to previous studies and needs to be confirmed with additional studies. As most cut-off values are based on the M probe, further studies on obese patients using XL probes are also needed.

Regarding the precision and reliability of TE, in a cross-sectional study that analyzed findings from two experienced operators assessing 195 patients on the same day, the interobserver intraclass correlation coefficient was 0.940 (95% CI 0.863–0.967) and measurements made by operators correlated [Spearman's $\rho = .924$; $p < .001$] [57]. However, there was interobserver variability, with discordance of 35% between operators for at least one stage of fibrosis and 5% for two or more stages.

Overall, TE is a highly accurate, easily performed noninvasive test for advanced fibrosis exclusion and a moderately accurate test for significant fibrosis exclusion. Suzuki et al. have suggested that disease progression in NAFLD can be monitored by LSM based on their study in which the LSM at year 4 was compared to the initial LSM assessment and to other noninvasive markers [58]. The change in LSM was well correlated with changes in the FIB4 index ($r = .519$, $p = .0011$) and in the aspartate aminotransferase- to- platelet ratio index (APRI) ($r = .346$, $p = .0412$), but not with changes in other noninvasive markers. The study did not perform liver biopsy to prove their findings. Therefore, additional prospective studies are required in order to confirm the usefulness of TE for monitoring disease progression.

2.2. Transient elastography with controlled attenuation parameter for the prediction of hepatic steatosis grade in NAFLD

Histologically, the severity of liver steatosis is graded by the percentage of hepatocytes with fat. Studies have used different CAP cut-off values to identify the level of steatosis in NAFLD only patients by liver biopsy, summarized in Table 2 [36,42,44,50,59]. S₁ indicates 10% of hepatocytes with fat, S₂ indicates 33% of hepatocytes with fat, and S₃ indicates 66% of hepatocytes with fat. CAP cut-off values for S₁ ranges from 236 to 263 dB/m with sensitivity of 72–92%, specificity of 86–100%, positive predictive value of 96–100%, and negative predictive value of 23–88%. CAP cut-off values for S₂ ranges from 263 to 310 dB/m with sensitivity of 63–97%, specificity of 50–81%, positive predictive value of 56–86% and negative predictive value of 59–97%. CAP cut-off values for S₃ ranges from 281 to 311 dB/m with sensitivity of 64–100%, specificity of 53–74%, positive predictive value of 17–86% and negative predictive value of 59–100%. From these studies, CAP is a fairly sensitive and specific test to detect different grades of steatosis. Although the exact cut-off values remain to be explored, a recent pooled analysis of data from 19 studies containing histology verified CAP data for grading of steatosis in patients with liver disease stemming from multiple etiologies (37% hepatitis B, 36% hepatitis C, 20% NAFLD/NASH, 7% other) has shown that optimal cut-offs were: (1) 248 dB/m (237–261) for S₀ vs. S₁-S₃ with sensitivity of 69%, specificity of 82% and AUROC of 0.82; (2) 268 for S₀-S₁ vs. S₂-S₃ with sensitivity of 77%, specificity of 81% and AUROC of 0.86; and (3) 280 dB/m (268–294) for S₀-S₂ vs. S₃ with sensitivity of 88%, specificity of 78% and AUROC of 0.88 [60].

Similar to LSM, all these studies have used the M probe, regardless of BMI, excluding the benefits of using XL probes. In 2014, De Ledingham et al. conducted a study to determine the factors influencing the failure of CAP measurement in chronic liver disease of various etiologies [40]. The study revealed that female gender, metabolic syndrome and BMI >30 kg/m² were associated with CAP measurement failure by multivariate analysis. In the study already mentioned in which the M probe was used initially for all patients and then some patients were rescanned using the XL probe, there was no significant difference in the performance of CAP with adjustment for type of probe and with nonadjusted models given AUC of 0.85 for both models ($p = .9774$). Therefore, an additional large cohort prospective investigation using both M and XL probes is needed to compare accuracies and resolve the CAP measurement limitations. Interobserver reliability has been shown to be satisfactory with ICC 0.84 (95% confidence interval: 0.77–0.88) for hepatic steatosis

measurements [61]. Thus, CAP is a noninvasive, reliable and easy test to perform to detect hepatic steatosis.

3. Magnetic resonance elastography

Magnetic resonance elastography (MRE) has recently emerged as a noninvasive method for the measurement of liver stiffness. MRE uses low frequency propagating waves with a phase contrast technique. The wave information is processed to produce quantitative images demonstrating mechanical properties such as tissue stiffness [62]. MRE can accurately detect early and advanced fibrosis [63–66]. MRE can be successfully performed in most patients, including those with ascites and anatomical variants, and liver transplant recipients [22,62,67]. The accuracy of MRE has been shown to be better than VCTE [50,68,69], although the number of clinical cross-sectional studies that compare the two methods is small. However, it is expensive and less practical than TE (Table 3). It is currently used to stage patients with NAFLD and is increasingly being used in clinical trials of NASH.

3.1. Magnetic resonance elastography for the prediction of hepatic fibrosis stage in NAFLD

Multiple studies have shown the diagnostic accuracy of MRE for quantification of hepatic fibrosis in NAFLD (Table 4) [42,50,70–75]. Among the studies using 2D MRE, for F₂, cut-off values for liver stiffness range from 2.86 to 3.6 kPa with sensitivity of 63%–87%, specificity of 81%–95%, positive predictive values of 66–88% and negative predictive values of 8–89%. For F₃, cut-off values for liver stiffness range from 2.99–4.8 with sensitivity of 75%–92%, specificity of 80%–94%, positive predictive values of 48–75% and negative predictive values of 81–98%. For F₄, cut-off values for liver stiffness range from 3.35 to 6.7 kPa with sensitivity of 70–89%, specificity of 81%–95%, positive predictive values of 27.3%–57% and negative predictive values of 97–99%. In one retrospective study that included 58 biopsy-proven NAFLD patients, there was good correlation between liver stiffness and fibrosis stage with a correlation coefficient of 0.651, using 4.58 kPa for F₂, 5.55 kPa for F₃, and 5.82 kPa for F₄ [76]. In a pooled analysis of NAFLD patients, diagnostic accuracy was high, with AUC of 0.9 (95% CI 0.84–0.94) for identification of advanced stage 3 and 4 fibrosis, using cut-off values of 3.77 kPa and 4.09 kPa, respectively [75]. A more advanced version of 3D-MRE was used in a recent prospective study which demonstrated that 3D-MRE at 40 Hz has the highest accuracy for diagnosis of NAFLD advanced fibrosis while both 2D- and 3D-MRE at 60 Hz, the standard shear-wave frequency, are also very accurate for diagnosis of NAFLD advanced fibrosis [73].

Interobserver agreement with MRE for hepatic fibrosis has been shown to be higher (ICC 0.99, 95% CI 0.98–1) than that of pathologist staging (ICC 0.91, 95% CI 0.86–0.94) [77]. Based on these studies, MRE is highly accurate for detecting hepatic fibrosis, with less interobserver variation and without influence from patient demographics.

3.2. New MRI modalities to measure hepatic steatosis in NAFLD patients

Recently, advances in MRI and MRS techniques have reduced the biases seen with traditional MRI methods [78]. This has been achieved by measuring the proton density fat

fraction which reflects the fraction of mobile protons in the liver attributable to fat, rather than measuring the signal fat fraction [78,79]. As well as reducing the biases mentioned above, this technique is platform and scans parameter independent and is highly correlated with the degree of hepatic steatosis. It can be used with both MRS and MRI [80]. MRI-PDFF uses a gradient echo sequence with a low flip angle to minimize T1 bias and acquire multiple echoes where fat and water signals are nominally in phase or out of phase relative to each other. Data acquired at each echo is then passed to a fitting algorithm that estimates and corrects T2 effects, models the fat signal, and measures the fat and water proton densities; the fat content is then calculated [81]. MRS-PDFF measures the fat fraction in a single location in the liver, whereas MRI-PDFF measures the fat fraction in all segments. In addition, MRS requires special coils, software and expertise, is time consuming and is mainly a research tool [27]. In contrast, MRI-PDFF is easier to apply and is now commercially available. In addition, MRI-PDFF requires less time and is cheaper compared to MRS [78]. We have found that MRI-PDFF is highly correlated with MRS, which has been previously used as a reference standard for liver fat quantification [27]. Indeed, MRI-PDFF was more accurate than liver biopsy in detecting liver fat changes over 24 weeks of follow-up in NASH patients who were enrolled in a randomized clinical trial [82]. Most of the current MRE research indicates that hepatic stiffness is influenced by fibrosis and necroinflammatory effects, whereas steatosis has little effect and therefore MRE is not affected by the degree of steatosis [76,83].

3.3. Magnetic resonance imaging-proton density fat fraction for the prediction of hepatic steatosis grade in NAFLD

MRI-PDFF has high accuracy in detecting hepatic steatosis and quantifying the degree of steatosis in NAFLD (Table 5). There is a strong correlation between MRI-PDFF and liver histology grading of hepatic steatosis as shown by Permutt et al. [84], Tang et al. [28] and Bannas et al. [85] ($r^2 = .54$, $p < .001$; $r^2 = .69$, $p < .001$, and $r^2 = .85$, $p < .001$ respectively). Imajo et al. [42], Tang et al. [28] and Park et al. further demonstrated AUC of 0.82–0.98 for grade 1 steatosis, AUC of 0.83–0.9 for grade 2 steatosis, and severe steatosis grade 3, AUC of 0.79–0.89, suggesting the high diagnostic accuracy of MRI-PDFF for differentiating various grades of hepatic steatosis in NAFLD. These findings were validated by Idilma et al. [86] and Bannas et al. [85] with the correlation between MRI-PDFF and liver biopsy ($r^2 = .82$) and explant ex vivo liver histology ($r^2 = .85$). Idilma et al. again demonstrated that MRI-PDFF was accurate in differentiating moderate to severe steatosis from no to mild steatosis (AUC 0.95) [86]. Sensitivity, specificity, positive predictive values and negative predictive values to discriminate moderate to severe steatosis from no to mild steatosis were 93%, 85%, 91% and 88%, respectively (Table 5). Studies further demonstrated that patient demographics (age, sex, BMI), hepatic disease component (inflammation, iron deposition and concomitant hepatic disease) and technical factors have no significant influence on MRI-PDFF assessment in NAFLD [87–89].

The precision and reproducibility of MRI-PDFF assessment have been further explored. Negrete et al. showed high inter-examiner agreement in obese subjects for each hepatic segment (ICC 0.992; SD 0.66%; range 1.24%), lobe (ICC 0.998; SD 0.34%; range 0.64%), and the whole liver (ICC = 0.999; SD 0.24%; range 0.45%) [90]. Similar

excellent intra- and inter-examination precision in overweight and obese subjects was demonstrated by Tyagi et al. [91]. Bannas et al. further demonstrated significantly smaller variance with excellent intra- and inter-observer agreement and repeatability for MRI-PDFF compared to histologic steatosis grading ($p < .001$) [85].

4. Conclusion

Transient elastography with CAP and LSM is a noninvasive, easy-to-perform test that is useful for screening for NAFLD and hepatic fibrosis. There have been advances in MRI modalities for assessing NAFLD patients. The new PDFF technique has reduced the biases seen with conventional MRI. MRE is an emerging technique for measuring hepatic fibrosis. Liver biopsy should be considered in those in whom there is a suggestion of advanced fibrosis on MRE or TE for treatment consideration and to allow participation in a clinical trial. These techniques can also be used for long-term follow up in clinical practice.

5. Expert commentary: clinical applications

Management of NAFLD is mainly based on the risk factors for progression to NASH and advanced fibrosis. Patients with NASH are more likely to progress to cirrhosis than are those with NAFL [92]. Features of metabolic syndrome, type 2 diabetes mellitus, persistently elevated aspartate aminotransferase (AST) and alanine aminotransferase (ALT) levels, and increasing age and BMI are known risk factors associated with the presence of NASH [93,94]. Another key risk factor that increases risk of liver-associated outcomes and death is the degree of fibrosis [1,9].

The most recent AASLD guideline in 2012 recommends that liver biopsy should be considered in high risk patients with NAFLD and patients with an increased risk of NASH and advanced fibrosis [14]. Clinical studies suggest that both transient elastography (TE) and magnetic resonance elastography (MRE) can detect the degree of hepatic fibrosis. The feasibility of using TE in clinical practice was assessed in a prospective study in which liver fat and fibrosis were assessed by CAP and LSM using FibroScan at a diabetic center for patients from primary care and hospital clinics, using CAP cut-off 222 dB/m to detect steatosis and LSM 11 kPa to detect advanced fibrosis [95]. Of the 1799 patients with valid CAP data, 72.8% had increased CAP of 222 dB/m, indicating steatosis; the CAP values indicated that 5.1% had grade 1 steatosis, 29.6% had grade 2, and 38.0% had grade 3. Of 1770 patients with reliable LSM by the M probe, 17.1% had advanced fibrosis or cirrhosis. Because TE only evaluates a portion of the liver its usefulness is limited by the possibility of unreliable measurements and failure in patients with a body mass index $>30 \text{ kg/m}^2$, significant ascites and hepatic inflammatory activity or hepatic congestion [47,96–98].

In addition to research studies and clinical trials, MRI can be used to follow up patients with fatty liver disease and to quantify their liver fat changes longitudinally. Nouredin et al. demonstrated that patients with either a decrease (1%) or increase (1%) in MRI-PDFF showed a parallel decrease or increase in their body weight and serum alanine aminotransferase and aspartate aminotransferase levels, suggesting that MRI-PDFF can be used clinically to accurately detect improvement or worsening of liver fat [82]. MRI-PDFF

has been used in clinical trials by assessing three co-localized regions of interest (ROI) measuring ($\sim 300\text{--}400\text{ mm}^2$) in each of the nine liver segments counting for a total of 27 separate ROI at baseline and end of the trial [99,100]. This allowed an accurate measurement of responsiveness by co-localizing the ROIs between the time baseline and end of treatment.

It is worth mentioning that the cut-off point for the MR liver fat fraction and steatosis grades should be standardized. It has been shown that the hepatic fat fraction decreases in advanced stages of fibrosis (stage 3 and beyond) [84]; this should always be considered when conducting MRI techniques. MRE can assess hepatic fibrosis and can be coupled with MRI-PDFF to give accurate assessments of the grade (steatosis) and stage (fibrosis) of NAFLD. The randomized double-blind placebo-controlled MOZART Trial that compared treatment of NASH with ezetimibe and placebo demonstrated the usefulness of co-localization of MRI-PDFF-derived fat maps and MRE-derived stiffness maps of the liver to noninvasively assess treatment response [101]. In a prospective study of 100 type 2 diabetics, MRI-PDFF and MRE were shown to be feasible for screening for NAFLD and advanced fibrosis [102]. The high prevalence of NAFLD (65%, defined as MRI-PDFF $\geq 5\%$) and advanced fibrosis (7.1%, defined as MRE $\geq 3.6\text{ kPa}$) found in this population points to the importance of screening diabetics for NAFLD.

Finally, an emerging imaging technique called multiparametric magnetic resonance imaging has recently emerged. The multiparametric MRI includes T1 mapping for fibrosis/inflammation imaging and T2 mapping for liver iron quantification and proton magnetic resonance spectroscopy for hepatic steatosis quantification. The T1 measurements were adjusted for the iron level, as high iron levels in the presence of fibrosis can lead to falsely normal T1 values. This MRI modality is a quick (completed in 23 min), noninvasive test that does not require special hardware, technical complexity or injection of any intravenous contrast agent. The proof-of-concept prospective study by Banerjee et al. demonstrated a high correlation of hepatic fibrosis ($r = 0.69$, $p < 0.0001$) and hepatic steatosis ($r = 0.89$, $p < 0.0001$) measured by this MR with histology findings, and high diagnostic accuracy with AUC of 0.94 for any degree of fibrosis and 0.93 for steatosis [103]. In addition to diagnosis, fibrosis/inflammatory scores detected by multiparametric MRI were shown to predict risk of disease progression and decompensation in a retrospective study [104]. Although these studies provide promising data, further validation is required to confirm the findings.

Based on the clinical trials and clinical applications, we propose an algorithm to follow patients and monitor disease progression in Figure 1.

6. Five-year view

Although a few cross-sectional studies have shown better accuracy of MRE and MRI-PDFF in comparison to TE and CAP, additional larger longitudinal studies will be required to show the magnitude of these differences. In addition, cost analysis studies should be performed. In our algorithm we take into consideration the practicality and cost of each technique in addition to their accuracy. It is worth mentioning that we still suggest performing liver biopsy when noninvasive imaging shows increased stiffness which is suggestive of more

advanced forms of the disease (NASH with or without fibrosis). The requirement of liver biopsy is mainly driven by the current guidelines and the fact that clinical trials and drug approval by the FDA and other agencies still consider it essential. Nevertheless, we expect that noninvasive imaging or future highly accurate blood biomarkers may replace liver biopsy to monitor disease progression.

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Key Issues

- Transient elastography with CAP and LSM is an accurate noninvasive easy-to-perform test that is useful for screening for NAFLD and hepatic fibrosis.
- Patients' body habitus and selection of TE probes remain a challenge for diagnostic accuracy.
- MRI-PDFF and MRE provide promising accuracy in assessment of hepatic steatosis and fibrosis in NAFLD patients.
- A few cross-sectional studies have shown that MRI modalities are better than TE; this needs to be confirmed by large prospective studies in the future.
- TE, MRI-PDFF and MRE may be used for longitudinal follow up in NAFLD.

Figure 1.

Algorithm for risk stratification of patients to monitor disease progression of NAFLD
Abbreviations: AASLD, American Association for the Study of Liver Diseases; CAP, controlled attenuation parameter; ALT, alanine aminotransferase; MRE, magnetic resonance elastography; MR PDFF, magnetic resonance imaging-proton density fat fraction; NAFLD, nonalcoholic fatty liver disease; NASH, nonalcoholic steatohepatitis; Pio, pioglitazone; RCT, consider enrollment in appropriate randomized controlled trial; Vit E, Vitamin E, SE: side effects, HCC: Hepatocellular carcinoma, EGV: Esophageal gastric varices. F/U: Follow up..

Table 1.
Performance of liver stiffness measurement by TE compared with liver biopsy in the detection of fibrosis in NAFLD patients.

Study	Design	Probe	Cut-off (kPa)	AUC	Sensitivity (%)	Specificity (%)	PPV	NPV	Number of patients with liver biopsy
Fibrosis stage F2									
Park et al. [50] (2016)	Cross-sectional prospective	M, XL	6.9	0.86	79	85	70	90	104
Imajo et al. [42] (2016)	Cross-sectional	M	11	0.82	65	88.7	89	88	127
Lee et al. [44] (2016)	Cross-sectional prospective	M	8	0.89	83	85	64	94	183
Pathik et al. [46]	Cross-sectional prospective	M	9.1	NA					110
Yoneda et al. [48] (2007)	Cross-sectional prospective	M	6.65	0.88	82	91	90	84	67
Cassinotto et al. [41] (2016)	Retrospective	M	6.2	0.82	90	45			291
Wong et al. [47] (2010)	Cross-sectional prospective	M	7	0.84	80	76	70	84	246
Lupsor [45] (2010)	Cross-sectional prospective	M	6.8	0.789	67	84	60	88	72
Yoneda [49] (2008)	Cross-sectional prospective	M	6.65	0.87	86	89	97	59	97
Kumar [43] (2013)	Cross-sectional prospective	M	7	0.85	77	78	75	81	205
Wong [53] (2012)	Cross-sectional prospective	M	5.8	0.56	72	35	47	61	130
Wong [53] (2012)	Cross-sectional prospective	XL	4.8	0.74	87	35	52	77	63
Fibrosis stage F3									
Park et al. [50] (2016)	Cross-sectional prospective	M, XL	7.3	0.8	78	78	45	94	104
Imajo et al. [42] (2016)	Cross-sectional	M	11.4	0.88	86	84	75	92	127
Lee et al. [44] (2016)	Cross-sectional prospective	M	9	0.97	96	86	55	99.3	183
Pathik et al. [46]	Cross-sectional prospective	M	12	0.9	90	80	72	93	110
Yoneda et al. [48] (2007)	Cross-sectional prospective	M	8	0.91	88	84	64	96	67
Cassinotto et al. [41] (2016)	Retrospective	M	8.2	0.86	90	61			291
Wong et al. [47] (2010)	Cross-sectional prospective	M	8.7	0.93	84	83	60	95	246
Lupsor [45] (2010)	Cross-sectional prospective	M	10.4	0.98	100	97	71	100	72
Yoneda [49] (2008)	Cross-sectional prospective	M	9.8	0.9	85	81	64	93	97
Kumar [43] (2013)	Cross-sectional prospective	M	9	0.94	85	88	68	95	205
Wong [53] (2012)	Cross-sectional prospective	M	7.9	0.57	65	57	39	80	193
Wong [53] (2012)	Cross-sectional prospective	XL	5.7	0.78	86	51	42	90	193
Fibrosis stage F4									
Park et al. [50] (2016)	Cross-sectional prospective	M, XL	6.9	0.69	63	66	15	95	104

Study	Design	Probe	Cut-off (kPa)	AUC	Sensitivity (%)	Specificity (%)	PPV	NPV	Number of patients with liver biopsy
Imajo et al. [42] (2016)	Cross-sectional prospective	M	14	0.92	100	76	73	100	127
Lee et al. [44] (2016)	Cross sectional prospective	M	11	0.97	100	90	45	100	183
Pathik et al. [46]	Cross-sectional prospective	M	20	NA					110
Yoneda et al. [48] (2007)	Cross-sectional prospective	M	17	0.99	100	98.4	83.3	100	67
Cassinotto et al. [41] (2016)	Retrospective	M	9.5	0.87	92	62			291
Wong et al. [47] (2010)	Cross-sectional prospective	M	10.3	0.95	92	88	26	99	246
Yoneda [49] (2008)	Cross – sectional prospective	M	17.5	0.99	100	97	75	100	97
Kumar [43] (2013)	Cross-sectional prospective	M	11.8	0.96	90	88	41	98	205
Wong [53] (2012)	Cross-sectional prospective	M	10.3	0.53	52	69	20	91	193
Wong [53] (2012)	Cross-sectional prospective	XL	7.2	0.86	88	67	28	97	193

Table 2.
Performance of controlled attenuation parameter compared with liver biopsy for the detection of steatosis in NAFLD patients.

Study	Design	Probe	Cut-off (dB/m)	AUC	Sensitivity (%)	Specificity (%)	PPV	NPV	Number of patients with liver biopsy
Steatosis grade 1									
Chan et al. [59] (2014)	Prospective	M	263	0.97	92	94	96	88	101
Imajo et al. [42] (2016)	Cross-sectional	M	236	0.88	82	91	99	67	127
Lee et al. [44] (2016)	Prospective	M	247	0.95	88	100	100	63	183
Park et al. [50] (2016)	Cross-sectional prospective	M,XL	261	0.85	72	86	98	23	104
Steatosis grade 2									
Chan et al. [59] (2014)	Prospective	M	263	0.86	97	68	67	97	101
Imajo et al. [42] (2016)	Cross-sectional	M	270	0.73	78	81	73	75	127
Lédinghen et al. [36] (2016)	Prospective	M	310	0.8	79	71	86	59	261
Lee et al. [44] (2016)	Prospective	M	280	0.85	85	50	83	82	183
Park et al. [50] (2016)	Cross-sectional prospective	M,XL	305	0.7	63	69	56	75	104
Steatosis grade 3									
Chan et al. [59] (2014)	Prospective	M	281	0.75	100	53	17	100	101
Imajo et al. [42] (2016)	Cross-sectional	M	302	0.7	64	74	76	94	127
Lédinghen et al. [36] (2016)	Prospective	M	311	0.66	79	71	86	59	261
Lee et al. [44] (2016)	Prospective	M	300	0.73	73	61	29	91	183
Park et al. [50] (2016)	Cross-sectional prospective	M,XL	312	0.73	64	70	26	92	104

Table 3.

Benefits and limitations of transient elastography and MRI techniques.

	Transient elastography (TE)	MRI techniques
Benefits	<ul style="list-style-type: none"> ● Reliable ● Easy to perform ● Well tolerated ● Portable ● Relatively inexpensive ● Widely available ● Available to physicians at point of service 	<ul style="list-style-type: none"> ● Highly reliable even in those with high BMI and ascites ● Captures large portion of the liver ● High inter-examiner precision ● Validated as outcome measure in RCTs ● Anatomic images are captured
Limitations	<ul style="list-style-type: none"> ● Unreliable measures and failure in: <ol style="list-style-type: none"> 1. BMI>30 kg/m² (now being improved with XL probe) 2. Significant ascites 3. Hepatic congestion ● Selection of probe ● No anatomic images captured ● Not validated as outcome measure in RCTs 	<ul style="list-style-type: none"> ● Require special hardware ● Technical complexity ● Limited availability (mostly academic centers) ● Contraindicated in claustrophobic patients ● Costly

Table 4.

Performance of liver stiffness measurement by MRE compared with liver biopsy in the detection of fibrosis in NAFLD patients.

Study	Design	Cut-off (kPa)	AUC	Sensitivity (%)	Specificity (%)	PPV	NPV	Number of patients with liver biopsy
Fibrosis stage F2								
Imajo et al. [42] (2016)	Cross-sectional	3.4	0.89	87	85	88	84	142
Singh [75] (2016)	Pooled analysis	3.54	0.87	79	81	4.14 (LR)	0.27 (LR)	232
Loomba et al. [74] (2014)	Cross sectional Prospective	3.58	0.86	63	92	76	85	117
Cui et al. [71] (2016)	Cross sectional	3.62	0.89	67	95	85	89	125
Chen et al. [76] (2011)	Retrospective	4.58						58
Loomba et al. [73] (2016)	Cross-sectional	1.77	0.86					
Park et al. [50] (2016)	Cross-sectional prospective	2.86	0.89	79	82	66	90	104
Fibrosis stage F3								
Kim et al. [72] (2013)	Retrospective	4.15	0.95	85	93			142
Imajo et al. [42] (2016)	Cross-sectional	4.8	0.89	75	87	75	81	142
Singh [75] (2016)	Pooled analysis 6 studies	3.77	0.9	83	86	5.93 (LR)	0.19 (LR)	232
Loomba et al. [74] (2014)	Cross sectional Prospective	3.64	0.95	82	91	67	96	117
Cui et al. [70] (2015)	Cross sectional prospective cohort, comparative effectiveness	3.64	0.96	92	90	69	98	102
Cui et al. [71] (2016)	Cross section	3.62	0.93	91	93	73	98	125
Chen et al. [76] (2011)	Retrospective	5.55						58
Loomba et al. [73] (2016)	Cross-sectional	2.43	0.98	92	94	71	98	100
Park et al. [50] (2016)	Cross-sectional prospective	2.99	0.87	78	80	48	94	104
Fibrosis stage F4								
Imajo et al. [42] (2016)	Cross-sectional	6.7	0.97	91	95	59	99	142
Singh [75] (2016)	Pooled analysis	4.09	0.91	88	87	6.5 (LR)	0.14 (LR)	232
Loomba et al. [74] (2014)	Cross sectional Prospective	4.67	0.89	70	93	57	97	117
Cui et al. [71] (2016)	Cross sectional	4.15	0.86	89	91	44	99	125
Chen et al. [76] (2011)	Retrospective	5.82						58
Loomba et al. [73] (2016)	Cross-sectional	2.38	0.99					100
Park et al. [50] (2016)	Cross-sectional prospective	3.35	0.87	75	81	27	97	104

Table 5.
Performance of PDFF compared with liver biopsy for the detection of steatosis in NAFLD patients.

Study	Design	Cut-off (%)	AUC	Sensitivity (%)	Specificity (%)	PPV	NPV	Number of patients with liver biopsy
Steatosis grade 1								
Imajo et al. [42] (2016)	Cross-sectional	5.2	0.96	90	93.3	89.2	51.5	127
Permutt et al. [84] (2012)	Cross-sectional prospective	8.9	N	N	N	N	N	51
Tang et al. [28] (2013)	Cross-sectional prospective	6.4	0.98	97	100	100	71	77
Bannas et al. [85] (2015)	Cross-sectional prospective	NA						
Heba et al. [87] (2016)	Cross-sectional prospective	NA						
Park et al. [50] (2016)	Cross-sectional prospective	3.71	0.99	96	100	100	70	104
Steatosis grade 2								
Imajo et al. [42] (2016)	Cross-sectional	11.3	0.9	79	84	85	78	127
Permutt et al. [84] (2012)	Cross-sectional prospective	16.3 %	N	N	N	N	N	51
Tang et al. [28] (2013)	Cross-sectional prospective	17.4%	0.83	61	90	90	61	77
Park et al. [50] (2016)	Cross-sectional prospective	13.03%	0.9	80	83	75	87	104
Steatosis grade 3								
Imajo et al. [42] (2016)	Cross-sectional	17.1	0.79	74	81	63	95	127
Permutt et al. [84] (2012)	Cross-sectional prospective	25%	N	N	N	N	N	51
Tang et al. [28] (2013)	Cross-sectional prospective	22.1%	0.89	68	91	72	90	77
Idilman et al. [86] (2013)	Retrospective	15%	0.95	93	85	91	88	70
Park et al. [50] (2016)	Cross-sectional prospective	16.37%	0.92	82	84	45	97	104