EDITORIAL

Magnetic Resonance Imaging/Elastography Is Superior to Transient Elastography for Detection of Liver Fibrosis and Fat in Nonalcoholic Fatty Liver Disease

See "Magnetic resonance imaging more accurately 1 classifies steatosis and fibrosis in nonalcoholic fatty liver disease than transient elastography," by Imajo K KT, Honda Y, Tomeno W, et al on page 000.

Nonalcoholic fatty liver disease (NAFLD) is the most common cause of chronic liver disease with an estimated prevalence worldwide ranging from 25% to 45%. In the United States, it is estimated that 75–100 million individuals may have NAFLD.[1] NAFLD has recently emerged as the second cause of liver transplantation in the United States.[2] The prevalence of the disease has nearly doubled over the last 20 years among adults, and among children the incidence increased 174%, in parallel with the obesity epidemic and its related metabolic disorders. Although pure steatosis is considered benign with a low risk of progression to more severe liver disease, approximately 20% of NAFLD patients have histologic signs of necroinflammation with or without fibrosis, indicating nonalcoholic steatohepatitis (NASH), and are at risk of developing cirrhosis, end-stage liver failure and hepatocellular carcinoma. It has also been suggested that NAFLD may promote diabetes and cardiovascular disease. NAFLD is a condition that remains underrecognized in clinical practice as recently shown in a recent series of NAFLD patients, in which only 21.5% had NAFLD mentioned as a possible diagnosis in their medical records.[3] These results underline the need for screening populations at risk for NAFLD, such as obese or type 2 diabetic patients, with accurate noninvasive methods.

Liver biopsy remains the gold standard for distinguishing simple steatosis from NASH, for assessment of fibrosis, and for staging the disease. The diagnosis of NASH is based on histologic features combining steatosis, hepatocyte ballooning, and lobular inflammation. Several diagnostic scores have been proposed, the NAS score developed by Kleiner et al[4] and the more recent Steatosis, Activity, Fibrosis score.[5] Liver histology seems to be an accurate tool for assessing prognosis of NAFLD patients and for the assessment of therapeutic efficacy. Longitudinal studies evaluating the prognostic value of histologic features for long-term clinical outcomes in NAFLD patients have shown that fibrosis was the best independent predictor, followed by portal inflammation, diagnosis of NASH, and ballooning.[6] In clinical trials, liver histology remains a major endpoint for evaluating the efficacy of new therapies for NASH. However, it remains unknown whether histologic improvement, such as reversion of NASH, is associated with clinical improvement. Liver biopsy has several limitations in the management of NAFLD patients. First, because of its invasiveness, associated discomfort, the small but not negligible risk of complications, and cost, liver biopsy cannot be applied easily in clinical practice. Second, screening of NAFLD using liver biopsy in large populations is not a reasonable option. Third, sampling bias has been reported in patients with NAFLD and might affect both diagnosis and staging of the disease. Given these limitations, a number of noninvasive markers have been evaluated in NAFLD patients to detect and quantify steatosis, NASH, and fibrosis, including both serologic and imaging methods.

In this issue of *Gastroenterology*, Imajo et al[7] have compared the accuracy of MRI including MR elastography (MRE) to that of transient elastography (TE) for grading steatosis and fibrosis in 142 patients with biopsy-proven NAFLD. All subjects were evaluated by TE (using the M probe), MRI using multiecho Dixon technique, and MRE as well as 5 different clinical scoring systems. They observed higher area under the receiver operating characteristic curve (AUROC) using MRE versus TE for predicting F2-F4 fibrosis (0.91 vs 0.82; $P = .001$) and cirrhosis (0.97 vs 0.92; $P = .049$), with no difference for predicting F1-F4 and F3-F4 fibrosis. The performance of proton density fat fraction (defined as the ratio of density of mobile fat protons and the total density of protons from mobile fat and water protons, measured with MRI)[8] was superior to that of TE-based controlled attenuated parameter measurement for detecting all grades of steatosis (AUROC range, 0.79-0.96 for performance of proton density fat fraction vs 0.70-0.88 for TE-controlled attenuated parameter). Of note, serum markers (serum K18 fragments and alanine aminotransferase) did not provide additional information over imaging markers. TE failed in 15 patients (10% of the study cohort); MRE measurements were successful in all included subjects.

Several noninvasive imaging modalities for noninvasive detection and staging of liver fibrosis have been recently developed in the hopes of decreasing the number of liver biopsies. These include ultrasound (US)-based methods such as TE and shear wave elastography techniques (acoustic force radiation force imaging and supersonic imaging) and MRI methods, which include diffusion-weighted imaging, dynamic contrast-enhanced MRI, and MRE. US elastography and MRE provide quantitative information on stiffness properties of tissues and reflect changes in tissue stiffness related to pathologic conditions.

TE has been validated in large cohort studies for the diagnosis and staging of liver fibrosis, including NAFLD patients.[9,10] TE is limited by the possibility of unreliable measurements and failure in patients with a body mass

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	US elastography	MRI/MRE
Benefits	Cheap	Large sampling (better than US elastography)
	Widely available	High accuracy for fat quantification
	Can be combined with HCC screening (except for Fibroscan)	Can be combined with HCC diagnosis
Limitations	Limited accuracy for fat quantification	Not easily available, expensive
	Failure (obesity, steatosis, ascites)	Failure (iron) for gradient echo sequence; contra-indications in some patients
	Limited sampling (better than biopsy)	Parameters not fixed (some variability across series)

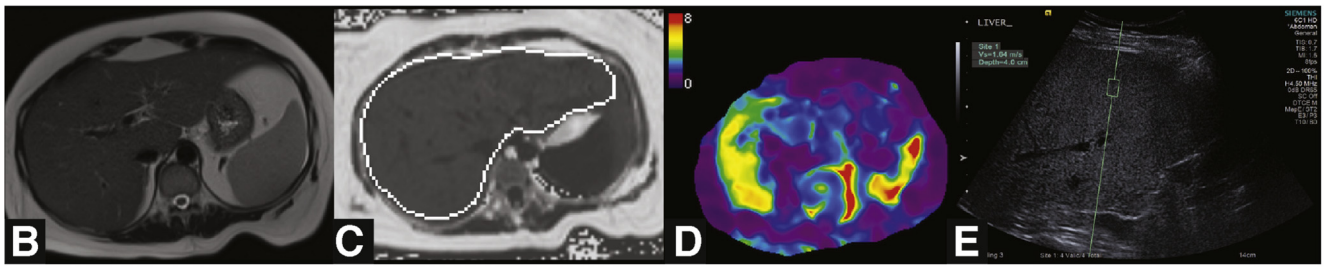

Figure 1. (*A*) *Top:* Benefits and limitations of US elastography and MRI/MR elastography (MRE) for detection of liver fibrosis and fat. *Bottom:* A 52-year-old female patient with nonalcoholic steatohepatitis assessed with shear-wave ultrasound elastography and MRI/MRE. (*B*) Axial T2-weighted image demonstrates normal liver morphology. (*C*) T2* corrected proton density fat fraction (PDFF) image obtained with multiecho Dixon sequence demonstrates mild steatosis (PDFF 13.5%). (*D*) Stiffness map obtained with MRE demonstrates increased liver stiffness (5.43 kPa) indicating advanced liver fibrosis, while liver stiffness measured with shear wave acoustic force radiation force imaging ultrasound (*E*) was not increased (2.79 kPa). Liver biopsy demonstrated hepatocyte ballooning, inflammation grade 3, fibrosis stage 3 and steatosis.

index of >28 kg/m^2, which may be improved using the new XL probe.[11] Despite lack of data in NAFLD, the evolution of liver stiffness may also be able to predict the long-term mortality as shown in patients with chronic hepatitis C infection. MRI systems are equipped for MRE by installing special driver hardware to generate low-frequency mechanical waves in the abdomen during imaging, a pulse sequence with cyclic motion encoding gradients to image the propagating waves, and software to automatically process the data to generate parametric stiffness maps. The MRE examination is fast (<1 minute) and the implementation and postprocessing protocols are relatively simple. It has been shown that MRE has excellent accuracy for detection of fibrosis in several studies, with reported AUROC of >0.9,[12–17] outperforming TE and serum markers in a few studies comparing the 2 techniques,[13,17,18] as in Imajo et al,[7] and as illustrated by the finding in one of our patients (Figure 1). Of note, published MRE data are smaller than those of TE, because MRE has been applied more recently than TE, with much less availability.

Specifically in NAFLD, the data on MRE are very encouraging, although limited.[14–17] A recent study combining NAFLD data from 9 centers reported high diagnostic accuracy for fibrosis detection, with AUROCs of 0.87 and 0.90 for diagnosing significant and advanced fibrosis, respectively, with no effect of body mass index on MRE performance,[19]

One of the benefits of MRE is that it allows a much larger sampling compared with US techniques and liver biopsy. The differences between MRE and TE relate to the mechanism of wave propagation and the imaging reconstruction algorithm. It has been proven that MRE generally provides more reliable measurements and less failure in patients with obesity or ascites. In a recent retrospective review of a large series of 1377 MRE cases from the Mayo Clinic, the reported failure rate was less than 6%, with no effect of body mass index on failure rate.[20] MRE may also be a better candidate than US elastography for assessing response to new therapies for NASH.

Limitations of MRE include the possibility of failure in patients with iron deposition (using gradient echo sequence), cost/availability, and possible contraindications (Figure 1). However, all major vendors now propose MRE capabilities, and new sequences such as echoplanar imaging have been shown to decrease failure rate in the presence of hepatic iron deposition.

The standard B-mode US is unreliable for diagnosing liver steatosis, given the nonspecific appearance of increased liver echogenicity, which can also be observed in fibrosis, with no possibility of quantification. Recently, TE