Collaboration, Not Competition: The Role of Magnetic Resonance, Transient Elastography, and Liver Biopsy in the Diagnosis of Nonalcoholic Fatty Liver Disease

The global obesity pandemic necessitates characterization of nonalcoholic fatty liver disease (NAFLD) in an extremely large and growing number of patients. This disease subsumes hepatic fat, inflammation, and fibrosis. Fibrosis is of particular interest, being the strongest predictor of mortality, and noninvasive techniques for assessing its severity are becoming part of routine care, at least in Asia and Europe. As we endeavor to understand NAFLD more fully, steatosis quantification has become increasingly successful, although we are still struggling to understand its clinical implications. Nonalcoholic steatohepatitis (NASH) is a strong indicator of disease progression; until now, however, only liver biopsies were sufficiently reliable for diagnosing inflammatory activity.

In this month’s issue of Gastroenterology, Park et al compared 2 major noninvasive approaches, magnetic resonance and transient elastography (TE), in biopsy-proven NAFLD patients. Fibrosis was staged using magnetic resonance elastography (MRE)- and TE-based liver stiffness measurements and steatosis was graded with proton density fat fraction (PDFF) and the TE-based controlled attenuation parameter (CAP). This interesting study was the first to do so using an important TE probe combination (so-called M and XL probes), appropriate to an obese cohort. The authors concluded that MRE and PDFF are more accurate than TE and CAP for diagnosing fibrosis and steatosis, respectively.

A head-to-head comparison of this sort is necessary and certainly useful, but only part of the picture. There are various requirements and needs to be considered, and one cannot optimize all of them with a single approach.

a. The clinical need is risk stratification, so long as effective therapeutic options are available. “Risk” means progression of liver disease and, finally, liver-related and overall mortality.

b. The huge number of NAFLD patients who might be considered for screening necessitates a low-threshold point-of-care technique that should be inexpensive and easy to handle.

c. Existing infrastructure and resources need to be exploited to their best potential.

NAFLD diagnosis currently requires proof of steatosis, which relies on imaging techniques in clinical practice. To address the diagnosis of the huge number of putative patients, studies of serum and anthropometry-based approaches are already underway. Similar strategies can also be used for further risk stratification because they are related to clinical outcomes. Biopsy is not viable for the many patients who then qualify for in-depth evaluation with higher specificity. Without question MRE/PDFF and TE/CAP could help to close this gap and a sophisticated discussion of their merits and drawbacks can be found in Friedrich-Rust et al. MRE is not yet as well evaluated as TE and the complex data acquisition and processing implies that standardization across different centers presents challenges. A recent comparable paper to that of Park et al was also able to show that MRE/PDFF is more accurate than TE/CAP in 142 NAFLD patients, but the very different cutoffs for staging fibrosis suggest that the conclusions require further verification. The European Association for the Study of the Liver guidelines recently proposed an algorithm based on...
liver enzymes and ultrasound imaging to select patients for specialist referral and assessment of disease severity. This algorithm can be used either by hepatologists or by other physicians treating NAFLD patients. Future guidelines will have to find the appropriate place for MRE/PDFF and TE/CAP in patient management also considering cost and logistics, which vary between health care systems.

The diagnostic properties of different options will certainly play a role, which shows the importance of research such as that published here by Park et al or by Imajo et al. TE and CAP cannot differentiate adjacent stages of fibrosis and steatosis with high precision, but potentially provide high negative predictive values for excluding advanced disease with respectable throughput. Use of MRE/PDFF and TE/CAP in clinical practice relies on harmonization, where important steps have been taken for TE liver stiffness measurement and are underway for CAP, but with limited evidence for pure NAFLD cohorts.

NAFLD has been recognized as a distinct etiology for 2 decades now, but specific treatment has not gone much beyond lifestyle intervention. As new pharmaceutical agents are developed, clinical endpoints must be defined and tested. The relatively slow progression of the disease means that surrogate endpoints will probably be most appropriate during early phases of drug development. MRE/PDFF and TE/CAP have yet to prove themselves in this regard, but are promising. In particular, repeated frequent observations can be performed with noninvasive techniques, but not with biopsy. The objective quantification on continuous scales would enable such studies to detect small changes, not discernible in histologic grading and staging. However, within the spectrum of NAFLD, NASH seems to forebode later complications, but effective noninvasive methods for diagnosing hepatic inflammation are still lacking, and liver biopsy remains the reference standard.

To recapitulate, MRE/PDFF and TE/CAP will certainly both have a role to play in management of NAFLD patients and drug development. Park et al have published an important comparison that will help to find precisely how to use each approach to its best advantage, though there are aspects of the study that warrant critical discussion. These include a transparent presentation of why many patients are missing from the main comparison of steatosis results and thoughts on the meaning and relevance of steatosis grade S0 for the NAFLD etiology. There are gaps to be filled before either of the above options can be used optimally and some may prove to be serious obstacles. Biopsy is clearly inappropriate for screening, but remains the reference for diagnosis, especially of NASH, and for endpoint prediction. It must, however, be kept in mind that histologic assessment, MRE/PDFF, and TE/CAP evaluate distinct aspects of “steatosis” and “fibrosis”: percentage of affected hepatocytes and distribution of extracellular matrix proteins on the one hand, and physical properties like fat molecule resonance spectra, tissue stiffness, and the attenuation of an ultrasound signal, on the other. The clinical relevance of each should be tested separately. At the moment, we definitely need “two to tango”—biopsy and noninvasive techniques—to further develop the active field of NAFLD and NASH.

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References


