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Magnetic resonance elastography assessment of fibrosis in children with NAFLD: promising but not perfect

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In the United States, NAFLD-related cirrhosis is now second among indications for adult liver transplantation.(1) Until recently, detecting histological progression before overt liver dysfunction largely relied on liver biopsy assessment. Over the past decade, however, promising new imaging technologies have emerged for noninvasively detecting advanced fibrosis. The most validated techniques involve measuring liver stiffness through ultrasound-based (US) modalities, vibration-controlled transient elastography (TE) and shear wave elastography (SWE), or through magnetic resonance elastography (MRE). While US elastography is less costly and available at point-of-care (TE), MRE may more accurately detect advanced fibrosis, particularly in adults with NAFLD.(2, 3) MRE is less influenced by abdominal adiposity, interrogates a much larger liver volume, and is highly reproducible across readers, field strengths, and imaging platforms.(4, 5) While highly sensitive and specific for detection of advanced fibrosis in adults with NAFLD, very little is known about the accuracy of MRE in children with NAFLD.

To address this gap, Schwimmer *et al.* conducted a prospective, multi-center, cross-sectional analysis of the performance of MRE in children with NAFLD.(6) They recruited 114 children, ages 8–17 years, at two sites in the NASH Clinical Research Network (NASH CRN). All had undergone clinically-indicated liver biopsies with robust phenotyping of histological liver disease. The analysis cohort comprised 90 children, mean age 13 ± 2 years, with 60% having no fibrosis, 27% stage 1, 7% stage 2, 6% stage 3 and 1% stage 4 fibrosis. Two-dimensional MRE was performed and manually analyzed at two independent reading centers as well as using a novel automated analysis technique. Inter-reader agreement and correlation between analysis methods were assessed. Twenty-four of the 114 participants (21%) were excluded from analysis, either due to unavailable software at time of scan ($n=7$), or due to problems completing the scan ($n=5$) or breathing artifact ($n=12$). The 16% failure rate in attempted MRE is unusually high compared to a $<5\%$ MRE failure rate in other published adult and pediatric cohorts.(7, 8) In the present study, the 17 children with

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excluded MRE had more NASH and stage 3 fibrosis vs. the analysis cohort, but no other significant differences. In a consecutive series of liver MRE in 468 children (mean age 13 ± 4 years), age or BMI did not differ between patients with successful (n=450) or unsuccessful MRE (n=18), but histological data were not provided.(8)

There are several salient findings. First, MRE had comparable sensitivity and specificity for detecting any fibrosis (stage 1) vs. no fibrosis compared to adult cohorts. At preset specificity of 90%, the optimal threshold for detecting any vs. no fibrosis was 2.69–2.78 kPa, varying slightly by analysis method. However, as in adults, liver stiffness values overlapped considerably between stage 0 and 1, resulting in low sensitivity of 44–47%.(2, 7) The overall cross-validated accuracy for discriminating between any vs. no fibrosis was 72% (95% CI: 62–81%). By comparison, in a study of MRE in 35 children with chronic liver disease, predominantly NAFLD (77%), a cutoff of 2.71 kPa provided maximal sensitivity (88%) and specificity (85%) for detecting significant fibrosis (stage 2) with AUROC of 0.92 (95% CI: 0.79–1.00; P = .02).(9)

Consistent with findings in adults, MRE performed better at classifying advanced fibrosis (stage 3) with optimal threshold of 3.03–3.33 kPa and cross-validated accuracy of 87–90%, depending on analysis method. However, the high negative predictive value of ~95% (at preset specificity of 90%) came at cost of very low sensitivity (33–50%) and positive predictive value (20–30%). In contrast, a pooled analysis of MRE in adults with NAFLD found a specificity for detecting advanced fibrosis of 0.86 (95% CI: 0.81–0.96) and sensitivity of 0.83 (95% CI: 0.53–0.90).(7) Although the authors concluded that MRE performs less well in children in detecting advanced fibrosis, this should be interpreted cautiously given the low prevalence of stage 3 fibrosis (7%). Had the 9 additional patients with advanced fibrosis but unreliable/incomplete MRE been included, the prevalence would have approximated other pediatric NASH CRN cohorts (~14–16% advanced fibrosis).

Notably, the cut-offs for detecting advanced fibrosis in children were lower compared to optimal thresholds of 3.45–4.8 kPa in adults with NAFLD.(2, 7) Apart from fibrosis, factors such as age, increased central venous pressure and associated passive liver congestion, inflammation, and possibly steatosis may influence liver stiffness.(10) Given the variance in reported thresholds, further validation and standardization is needed to determine optimal cut-offs, particularly in children. The correlation between MRE results from independent analyses at the two reading centers and the automated analyses was high, though results were not identical. All three MRE analysis methods correlated moderately well with increasing stages of fibrosis. Refining automated post-processing and analysis techniques should make this technology more accessible and reliable across centers, reducing a source of potential variability.

In summary, this is the largest pediatric study to date of MRE in children with NAFLD, with the additional strengths of well-characterized clinical and histological characteristics, and the assessment of a novel automated analysis technique. However, the cohort was limited by the very low prevalence of advanced fibrosis. It is also unclear if these children were involved in any interventions that may have influenced liver histology. Mean time between MRE and liver biopsy ranged from 62–115 days, but significant change in fibrosis is

unlikely in this time span. Both MRE and US-based elastography are most accurate at discriminating extremes of fibrosis (none vs. advanced), leaving a gap in our ability to accurately discriminate earlier stages of fibrosis. Monitoring early fibrosis is important in clinical care to identify patients at greater risk of adverse outcomes, as well as in clinical trials to evaluate fibrosis endpoints. The development and validation of noninvasive imaging biomarkers is increasingly focused on assessing hepatic inflammation, steatosis, and fibrosis using a variety of MR measures, termed “multi-parametric” MRI imaging. Examples include T1 mapping (corrected and uncorrected for T2* effects), T1 rho imaging, advanced forms of diffusion weighted imaging, and texture mapping (Figure 1).(11) Unlike MRE, these techniques do not require any special equipment (active and passive drivers).

Noninvasive imaging of liver disease has tremendous potential to illuminate the natural history of NAFLD and to accelerate identification of effective treatments. While MRE is a significant step forward, further studies must determine optimal thresholds for detecting advanced fibrosis in populations of different ages and in specific liver diseases, as varying pathophysiology and histological patterns may influence liver stiffness. Liver biopsy is also subject to sampling bias and relies on ordinal categorization of fibrosis patterns, while MRE and US-based elastography methods assess a continuum of liver stiffness. These factors may prevent achieving perfect correlation between elastography and histologic staging of fibrosis. Longitudinal studies should determine the relationship between change in the continuous measure of liver stiffness over time to histological progression and to clinical outcomes. Combining MRE with novel serum biomarkers and/or multi-parametric MRI measures may also enhance our ability to noninvasively monitor histological progression in NAFLD, as well as other chronic liver diseases.

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Figure 1. illustrates examples of multi-parametric MRI measures. The upper panels depict conventional T2-weighted fast spin echo (1A), MRE with normal hepatic shear stiffness of 2.22 kPa (1B), and corrected T1 time of 879 msec (1C) in a healthy child without evidence of liver disease. The lower panels show corresponding images in a child with biopsy-confirmed primary sclerosing cholangitis. The T2-weighted fast spin echo image (1D) shows heterogeneously increased liver signal due to fibrosis that can be quantified using texture mapping. MRE (1E) shows increased hepatic shear stiffness of 3.96 kPa. The corrected T1 time (1F) is increased to 1048 msec likely due to a combination of fibrosis and inflammation.