

Multiparametric Magnetic Resonance Elastography Improves the Detection of NASH Regression Following Bariatric Surgery

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Disease monitoring in nonalcoholic steatohepatitis (NASH) is limited by absence of noninvasive biomarkers of disease regression or progression. We aimed to examine the role of multiparametric three-dimensional magnetic resonance elastography (3D-MRE) and magnetic resonance imaging proton density fat fraction (MRI-PDFF) in the detection of NASH regression after interventions. This is a single-center prospective clinical trial of 40 patients who underwent bariatric surgery. Imaging and liver biopsies were obtained at baseline and 1 year after surgery. The imaging protocol consisted of multifrequency 3D-MRE to determine the shear stiffness at 60 Hz and damping ratio at 40 Hz, and MRI-PDFF to measure the fat fraction. A logistic regression model including these three parameters was previously found to correlate with NASH. We assessed the model performance in the detection of NASH resolution after surgery by comparing the image-predicted change in NAFLD activity score (delta NAS) to the histologic changes. A total of 38 patients (median age 43, 87% female, 30 of 38 with $NAS \geq 1$, and 13 of 38 with NASH) had complete data at 1 year. The NAS decreased in all subjects with $NAS \geq 1$ at index biopsy, and NASH resolved in all 13. There was a strong correlation between the predicted delta NAS by imaging and the delta NAS by histology ($r = 0.73$, $P < 0.001$). The strength of correlation between histology and the predicted delta NAS using single conventional parameters, such as the fat fraction by MRI-PDFF or shear stiffness at 60 Hz by MRE, was $r = 0.69$ ($P < 0.001$) and $r = 0.43$ ($P = 0.009$), respectively. **Conclusion:** Multiparametric 3D-MRE and MRI-PDFF can detect histologic changes of NASH resolution after bariatric surgery. Studies in a nonbariatric setting are needed to confirm the performance as a composite noninvasive biomarker for longitudinal NASH monitoring. (*Hepatology Communications* 2020;4:185-192).

SEE EDITORIAL ON PAGE 141

Noninvasive diagnosis of steatohepatitis is one of the most important challenges in nonalcoholic fatty liver disease (NAFLD). Nonalcoholic steatohepatitis (NASH) is present in approximately 20%–30% of those with NAFLD⁽¹⁾ and

60% of those with an indication for liver biopsy.⁽²⁾ As the aggressive form of NAFLD, NASH is an established risk factor for liver fibrosis and progression to cirrhosis.⁽³⁾ Therefore, the identification of patients with NASH is a crucial first step in risk stratification. However, the current gold-standard diagnostic modality is liver biopsy, which is limited by

Abbreviations: 3D, three-dimensional; AUROC, area under the receiver operating characteristic curve; CI, confidence interval; DR, damping ratio; FF, fat fraction; Hz, hertz; IQR, interquartile range; MRE, magnetic resonance elastography; MRI, magnetic resonance imaging; NAFLD, nonalcoholic fatty liver disease; NAS, NAFLD activity score; NASH, nonalcoholic steatohepatitis; PDFF, proton density fat fraction; ROI, region of interest; SS, shear stiffness.

Received July 31, 2019; accepted October 4, 2019.

Supported by the American College of Gastroenterology (Junior Faculty Development Grant), National Institute of Biomedical Imaging and Bioengineering (EB001981, EB017197), National Institute of Diabetes and Digestive and Kidney Diseases (K23DK115594, P30DK084567), and National Institute on Alcohol Abuse and Alcoholism (AA021171 and AA26887).

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invasiveness, sampling error, poor interrater reliability, complications, and cost. Moreover, serial liver biopsies are impractical for longitudinal monitoring of NASH after lifestyle and therapeutic interventions.

Due to the large volume of patients at risk and potential upcoming treatment agents, there is a substantial need for accurate and noninvasive methods to identify NASH and assess for regression after weight loss or response to therapy. Such methods would enable early NASH recognition, timely intervention, and assessment of response before onset of advanced fibrosis, when weight loss or treatment could have a higher impact.

Recent published evidence indicates that novel biomarkers identified by multifrequency three-dimensional magnetic resonance elastography (3D-MRE) have potential to predict early NASH and disease activity by NAFLD activity score (NAS) in a cohort of bariatric surgery candidates at risk for NASH.⁽⁴⁾ In this study, a protocol combining 3D-MRE measuring shear stiffness at 60 Hz, damping ratio at 40 Hz, and magnetic resonance imaging proton density fat fraction (MRI-PDFF) detected NASH with area under the receiver operating characteristic curve (AUROC) = 0.73 (95% confidence interval [CI] 0.65-0.81) and disease severity by NAS with AUROC = 0.82 (95% CI 0.77-0.87), using intraoperative liver biopsy as reference. This represents a significant improvement in the performance of standard two-dimensional MRE (2D-MRE) technology using shear stiffness at 60 Hz, which predicted NASH with AUROC = 0.61 (95% CI 0.53-0.69) and

disease activity by NAS with AUROC = 0.64 (95% CI 0.58-0.70) in the same cohort.

We hypothesized that the multiparametric protocol described can be used as a dynamic composite biomarker to detect histologic improvement of NASH after weight-loss surgery. Therefore, this work is a follow-up study of the prospectively enrolled bariatric cohort, to examine the performance of multifrequency 3D-MRE and MRI-PDFF for the detection of changes in liver histology 1 year after weight-loss surgery.

Patients and Methods

STUDY SUBJECTS AND DESIGN

Adults who were scheduled to undergo weight-loss surgery for medically complicated obesity were prospectively enrolled in a clinical trial (NCT02565446⁽⁵⁾) between October 2015 and June 2017, designed to determine the diagnostic accuracy of 3D-MRE in the diagnosis of NASH, as previously described.⁽⁴⁾ Exclusion criteria included excessive alcohol consumption (>21 units/week for men and >14 units/week for women), steatogenic medications (e.g., amiodarone, methotrexate, corticosteroids), presence of liver disease other than NAFLD, contraindications to MRI (e.g., claustrophobia, metallic aneurysm clips, spinal stimulators), or patients at high operative risk in whom a liver biopsy might lead to complications in the investigator's opinion. The subjects underwent MRI per the protocol described subsequently prior

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DOI 10.1002/hep4.1446

Potential conflict of interest: Dr. Ehman received grants from, owns intellectual property rights, and owns stock in Resoundant, Inc. Dr. Glaser received grants from, owns intellectual property rights, and owns stock in Resoundant, Inc. Dr. Yin owns stock in Resoundant, Inc.

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to the surgery, followed by intraoperative liver biopsy from the right lobe. Subsequently, they were contacted to participate in the follow-up study at 1 year after bariatric surgery, when they underwent repeat MRI by the same protocol followed by percutaneous liver biopsy.

MRI PROTOCOL

The imaging protocol consisted of 3D-MRE at 40 Hz and 60 Hz to estimate the damping ratio and shear stiffness, respectively, along with MRI-PDFF to estimate the proton density fat fraction. Magnetic resonance examinations were performed on 1.5T whole-body scanners (GE Healthcare, Milwaukee, WI) at the Mayo Clinic. Details regarding the protocol were previously described.⁽⁴⁾ Briefly, after a fasting period of at least 4 hours, patients were imaged in the supine position with the passive driver placed against the anterior body wall over the right lobe of the liver, held in place with an elastic band wrapped around the body. The waves were delivered at two separate frequencies (40 Hz and 60 Hz) in three to six 20-second breath-holds at the end of expiration, for a total imaging time of approximately 15 minutes.

All 3D-MRE data were processed to calculate the complex shear modulus $G^* = G' + iG''$. Several mechanical properties can be derived from G^* , including the storage modulus (G'), loss modulus (G''), shear stiffness ($|G^*|$), and the damping ratio ($\zeta = G''/[2G']$). For each subject, these parameters were reported as the mean and SD of a single volumetric region of interest (ROI) manually drawn to encompass as much of the liver as possible that had substantial wave propagation based on visual evaluation by 2 experienced analysts (M.Y. and J.L.). PDFF was measured from a single 16-second breath-hold 3D volumetric imaging sequence. Six gradient echoes were applied to reconstruct water and fat images, relative fat fractions (PDFFs), and $R2^*$ maps (IDEAL-IQ; GE Healthcare). For each subject, the PDFF and $R2^*$ measurements were reported as the mean of 9 ROIs manually drawn in 9 anatomic segments by 2 experienced analysts (S.K.V. and M.L.W.).

HISTOLOGIC ASSESSMENT

All liver biopsy specimens were reviewed by Mayo Clinic liver pathologists as part of the clinical service.

In addition, 1 study pathologist with NASH expertise provided a second interpretation while blinded to the results of the first interpretation and to imaging. There were no discrepancies in NASH diagnosis between the two evaluations. NASH was defined histologically by the presence of steatosis with (1) hepatocellular ballooning or (2) lobular inflammation with associated fibrosis. The disease severity was estimated using the NAS.⁽⁶⁾

STATISTICAL ANALYSIS

We used the logistic regression model of NAS prediction, including shear stiffness at 60 Hz (coefficient 0.64), damping ratio at 40 Hz (coefficient 0.70), and fat fraction (coefficient 2.46), as previously developed.⁽⁴⁾ The NAS values predicted by 3D-MRE/MRI-PDFF were obtained for each subject at the two time points of interest: bariatric surgery and 1-year follow-up. To evaluate the performance of 3D-MRE combined with MRI-PDFF to detect changes in NAS ($\Delta \text{NAS} = \text{NAS at baseline} - \text{NAS at 1 year}$), we plotted the predicted ΔNAS by imaging (y-axis) compared with the actual ΔNAS by histology (x-axis). Similar plots were obtained for each of the individual components of the model: fat fraction by MRI-PDFF, shear stiffness at 60 Hz by 3D-MRE, and damping ratio at 40 Hz by 3D-MRE. Pearson correlation was used as a statistical measure of performance. The strength of association can be interpreted as small if $r < 0.3$, moderate if $r = 0.3-0.5$, and strong if $r > 0.5$.

Statistical analyses were performed in SAS v9.4 (SAS Institute, Cary, NC) and R statistical software, version 3.2.0 (R Foundation for Statistical Computing, Vienna, Austria). This prospective study was approved by the Institutional Review Board of the Mayo Clinic.

Results

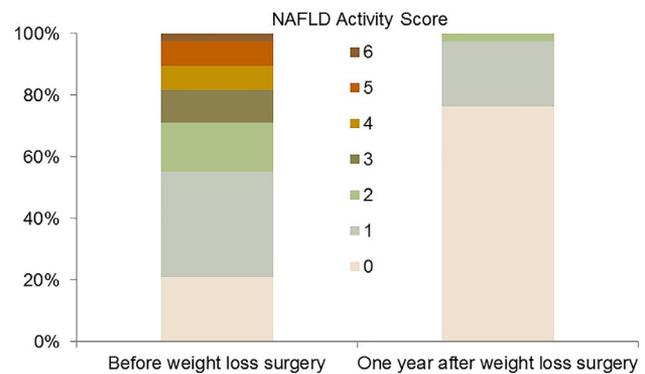
Of the 40 patients enrolled in the 1-year follow-up study, 2 were excluded due to missing data (1 liver biopsy and 1 imaging). The characteristics of the 38 patients included in the analysis are given in Table 1. The median (interquartile range [IQR]) age at the time of surgery was 50 (42-57), and 87% were women. The median time interval between liver biopsies and

TABLE 1. PATIENT CHARACTERISTICS (N = 38) AT THE TIME OF BARIATRIC SURGERY AND AT 1-YEAR FOLLOW-UP

	At Bariatric Surgery	One Year After Bariatric Surgery
Age, median (IQR)	50 (42-57)	51 (43-58)
Female sex	33 (87%)	33 (87%)
Body mass index	44.6	32.4
Liver histology		
NASH	13 (34%)	0
NAS		
0	8 (21%)	29 (76%)
1	13 (34%)	8 (21%)
2	6 (16%)	1 (3%)
3	4 (11%)	0
4	3 (8%)	0
5	3 (8%)	0
6	1 (3%)	0
7	0	0
8	0	0
Steatosis grade		
0	12 (32%)	36 (95%)
1	18 (47%)	2 (5%)
2	4 (10.5%)	0
3	4 (10.5%)	0
Lobular inflammation grade		
0	20 (53%)	30 (79%)
1	17 (45%)	8 (21%)
2	1 (2%)	0
3	0	0
Ballooning grade		
0	27 (71%)	38 (100%)
1	9 (24%)	0
2	2 (5%)	0
Fibrosis stage		
0	33 (87%)	36 (95%)
1	1 (3%)	1 (3%)
2	3 (8%)	0
3	1 (3%)	1 (3%)
Multiparametric MRE parameters, median (IQR)		
Shear stiffness at 60 Hz	2.3 (2.1-2.5)	2.2 (2-2.4)
Damping ratio at 40 Hz	0.1 (0.1-0.2)	0.2 (0.1-0.2)
Fat fraction	10.0 (6.4-19.6)	2.7 (2.2-4.0)

MRE was 6 (IQR = 1-14) days. The median sample length was 1.6 (IQR = 1.0-1.9) cm.

The median body mass index decreased from 45 kg/m² to 32 kg/m² after surgery. Changes in individual histologic and imaging parameters after weight-loss surgery are given in Table 1. There was improvement in all histologic parameters, with normalization of

**FIG. 1.** Distribution of NAFLD activity scores before and after weight-loss surgery.

liver biopsy in all but 2 (5%) patients who had persistent steatosis and 8 (21%) with mild nonspecific lobular inflammation. Fibrosis improved in the 4 patients with stage 2 or lower and remained stable in the patient with stage 3 at the time of surgery. NASH resolved in all 13 (34%) patients. The distribution of NAFLD activity scores before and after weight loss surgery is shown in Fig. 1. The number of patients with a 1, 2, 3, 4, and 5-point decrease in NAS after surgery were 11, 5, 7, 2 and 2, respectively (Fig. 2).

There was a strong correlation between the predicted delta NAS by 3D-MRE and MRI-PDFF and the actual change in NAS by histology ($r = 0.73$, $P < 0.001$) (Fig. 3A). The strength of correlation between histology and the predicted delta NAS using currently available technologies, such as the fat fraction by MRI-PDFF or shear stiffness at 60 Hz by MRE was $r = 0.69$ ($P < 0.001$) and $r = 0.43$ ($P = 0.009$), respectively (Fig. 3B,C). These data suggest that improvement in NASH disease activity after treatment is identified by the multiparametric MRE and MRI-PDFF with the highest accuracy, whereas MRI-PDFF alone tends to underestimate the degree of NAS changes, and shear stiffness as a single parameter is insufficient in patients without advanced fibrosis.

Figure 4 shows examples of predicted probabilities of NASH as a binary outcome (yes/no) and NAS value on a continuous scale ranging from 0 to 8 (the sum of all probabilities is 100) by 3D-MRE and MRI-PDFF before and after weight-loss surgery in 4 study subjects. The highest probabilities within the 68% CI were chosen to generate a range of predicted

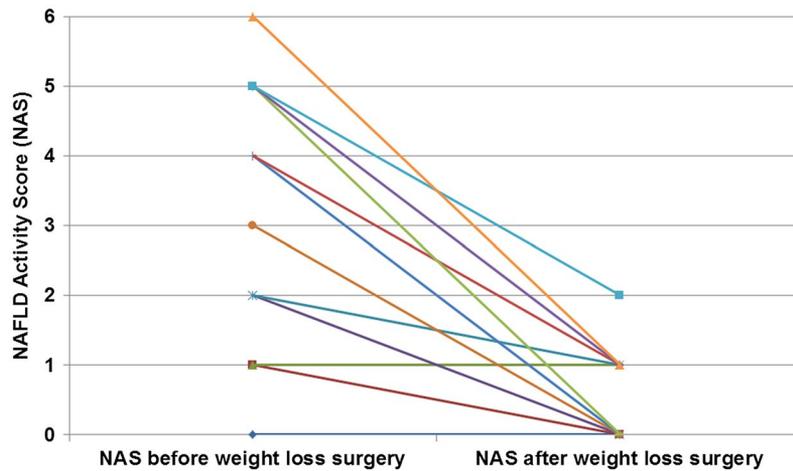


FIG. 2. Histologic NAS at the time of bariatric surgery (index) and 1 year after.

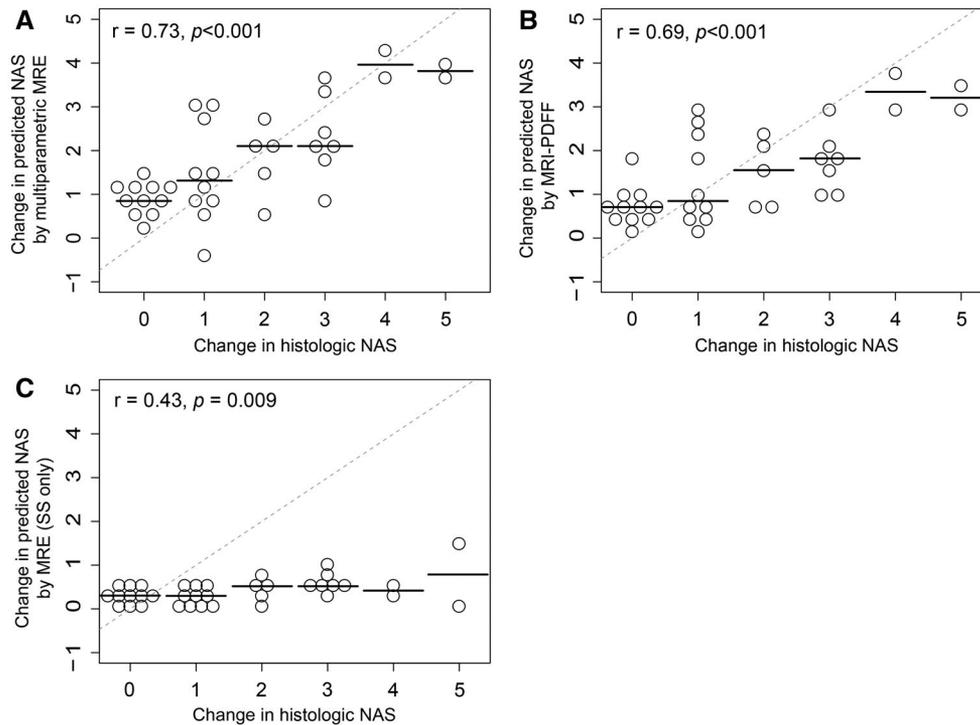


FIG. 3. Correlation between changes in NAFLD activity score by histology (x-axis) and changes predicted by imaging (y-axis). (A) Multiparametric 3D-MRE and MRI-PDFF. (B) MRI-PDFF. (C) Single-parameter 3D-MRE (shear stiffness). Change was determined by subtracting the postbariatric surgery NAS from prebariatric NAS.

NAS score (shaded area on the horizontal NAS bar). In these examples, the model predicted improvement in liver disease both in the probability of NASH and disease severity by NAS, which was confirmed by histology.

Discussion

The main conclusion of this study is that multiparametric 3D-MRE combined with MRI-PDFF is an accurate imaging biomarker in the longitudinal

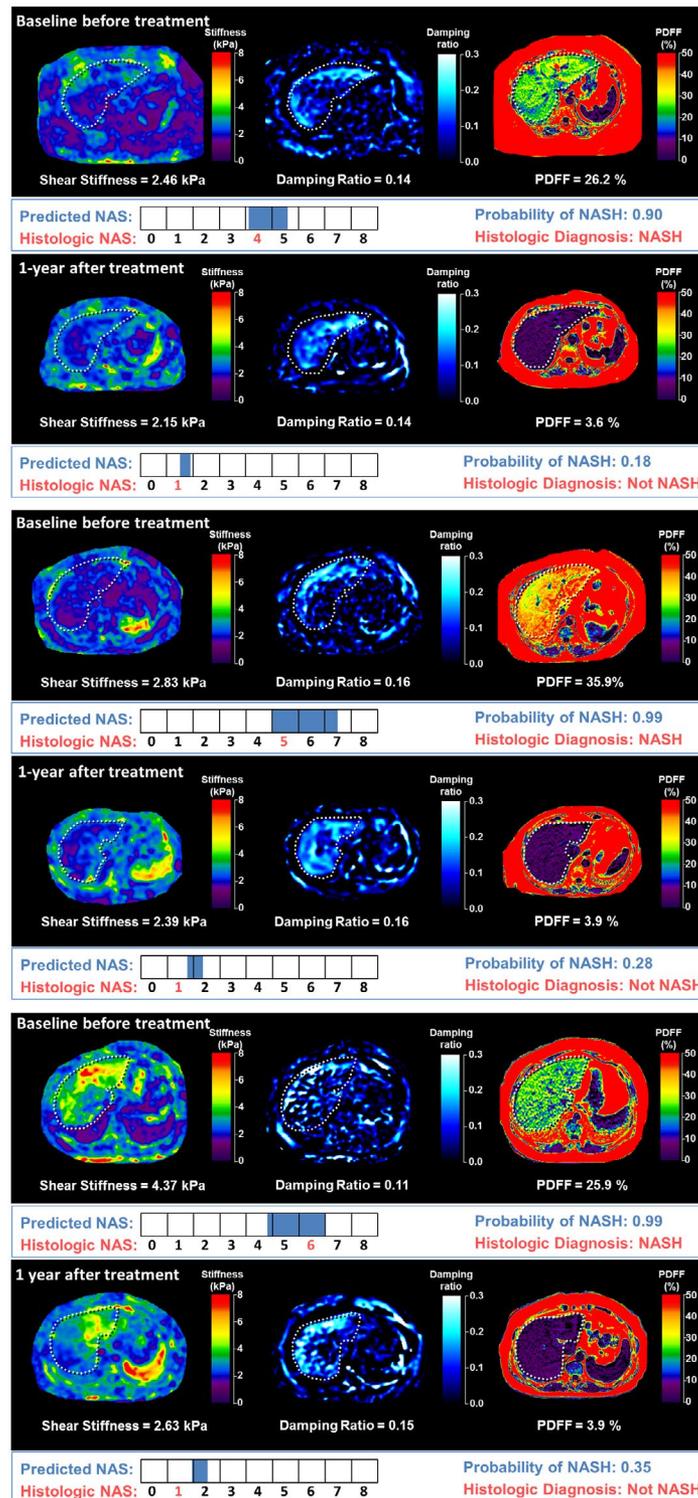


FIG. 4. Longitudinal assessment of NASH probability and NAS prediction by multiparametric 3D-MRE and MRI-PDFF in 3 study patients. The three imaging parameters included in the predictive model are shown: mf3D-MRE depiction of shear stiffness, mf3D-MRE depiction of damping ratio, and MRI-PDFF depiction of fat fraction. The horizontal boxes illustrate the predicted NAS values ranging from 0 to 8. The shaded part of the boxes represents the predicted range of NAS, which were derived from the regression model as the highest probabilities within the 68% CI.

follow-up of NASH resolution after weight-loss surgery. The decrease in NAS detected by a statistical model including three imaging parameters derived from 3D-MRE (shear stiffness at 60 Hz and damping ratio at 40 Hz) and MRI-PDFF (fat fraction) highly correlated with the change in NAS using histology as reference ($r = 0.73$, $P < 0.001$). The performance of mp3D-MRE and MRI-PDFF was superior to currently available MRI-based parameters such as MRI-PDFF ($r = 0.69$, $P < 0.001$) or shear stiffness by MRE at 60 Hz ($r = 0.43$, $P = 0.009$).

Weight-loss surgery is the most effective and sustainable treatment method for NAFLD, leading to significant improvement in steatosis, ballooning, and complete NASH resolution in approximately 75% of patients,⁽⁷⁾ with sustained effects up to 5 years.⁽⁸⁾ Because NASH resolution is not universal and transaminases have limited accuracy in NASH monitoring, noninvasive methods of longitudinal liver disease assessment are critical. Previous studies have assessed the role of imaging in longitudinal assessment of steatosis and fibrosis after bariatric surgery. These studies have shown improvement in liver stiffness measurement and steatosis by Fibroscan,⁽⁹⁻¹¹⁾ and correlations between the decrease in hepatic steatosis and the fat fraction measured by MRI.⁽¹²⁻¹⁴⁾ However, no study has been able to demonstrate correlations between imaging parameters and improvement in NASH and disease severity after bariatric surgery.

The role of imaging in the detection of longitudinal changes in NASH has been studied in several cohorts who underwent experimental drug therapies. In a secondary analysis of 54 patients with paired MRE, MRI-PDFF and liver biopsies before and after 24 weeks of treatment with selonsertib, the AUROC of MRI-PDFF in predicting a 2-point decrease in NAS was 0.70 (95% CI 0.51-0.89, $P = 0.08$), while that of shear stiffness by 2D-MRE was 0.66 (95% CI 0.48-0.83).⁽¹⁵⁾ Other studies confirmed the correlation between changes in histologic steatosis or NAS and decrease in the fat fraction by MRI-PDFF or MR spectroscopy in drug trials.^(16,17)

In keeping with the literature, our results show that changes in MRI-PDFF are associated with changes in histologic steatosis and overall NAS improvement, while the ability of liver stiffness by MRE alone to discriminate improvement in NASH is suboptimal. Additionally, we show that by combining 3D-MRE parameters of inflammation and ballooning with

MRI-PDFF assessment of steatosis, the detection of histologic changes of NASH after weight-loss interventions can be further improved. The output generated from the model combining these parameters provides the probability of NASH, as well as the predicted NAS. Individual assessment of these probabilities before and after an intervention allows estimation of the magnitude of histologic improvement. Dynamic monitoring of liver disease using objective NASH parameters allows an individualized approach to NAFLD management by providing another metric to assess whether the lifestyle changes and weight loss achieved are sufficient for NASH resolution. This technology covers a major unmet need of noninvasive diagnosis, risk assessment, and monitoring of early NASH, before progression to advanced fibrosis, when interventions have the highest impact.

These findings validate data from preclinical rodent models of NASH, in which MRE-assessed liver stiffness or storage modulus measurements at high frequencies detected ballooning and fibrosis, while the damping ratio or loss modulus at lower frequencies detected early onset of hepatic inflammation.⁽¹⁸⁾ The combination of two independent MRE parameters and MRI-PDFF predicted a virtual NAS score in diet-induced NASH progression and weight loss-induced NASH regression in mouse models.⁽¹⁹⁾

The strengths of this study include the rigorous prospective study design, contemporaneous liver histology for NASH diagnosis, and the use of innovative imaging parameters in a center with longstanding experience and investigators who have pioneered the use of MRE in liver disease. The biopsies and images were interpreted by the same study pathologist and radiologists at index and follow-up. Limitations include the small sample size, female predominance, and the mild-moderate disease severity, as demonstrated by the NAS values. By design, we targeted a population with early NASH without advanced fibrosis, in whom histologic changes after bariatric surgery would be largely related to NASH resolution and not fibrosis regression. Therefore, these results cannot be extrapolated to patients with advanced fibrosis, in whom further studies assessing the role of imaging in fibrosis regression are needed. The MRE analysis used manual selection of the ROI, leading to potential interobserver variability.⁽²⁰⁾ A confidence map calculated during the mechanical properties inversion was available to guide manual ROI selection to

mitigate interreader variation. Future studies should address the utility of automated liver elasticity calculation and its use in multiparametric technologies.⁽²¹⁾ Similarly, studies comparing the performance using different field strengths (1.5 T versus 3 T) should be performed.

In conclusion, this proof-of-concept study provides preliminary evidence of the utility of multiparametric 3D-MRE and MRI-PDFF as a longitudinal composite NASH biomarker after weight-loss surgery. These findings promise to expand the clinical applicability of conventional MRE technology beyond assessment of fibrosis, to a comprehensive evaluation of NASH severity in response to interventions. Improving the ability to monitor longitudinal changes of NASH without a liver biopsy fills one of the most important gaps in clinical practice. This is an ideal candidate biomarker for longitudinal monitoring of NASH after pharmacological therapy or lifestyle changes; therefore, further studies should explore its role and cost-effectiveness in these settings.

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