Title

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Magnetic resonance elastography biomarkers for detection of histologic alterations in nonalcoholic fatty liver disease in the absence of fibrosis

Abstract

Objectives: To investigate associations between histology and hepatic mechanical properties measured using multiparametric magnetic resonance elastography (MRE) in adults with known or suspected nonalcoholic fatty liver disease (NAFLD) without histologic fibrosis.

Methods: This was a retrospective analysis of 88 adults who underwent 3T MR exams including hepatic MRE and MR imaging to estimate proton density fat fraction (MRI-PDFF) within 180 days of liver biopsy. Associations between MRE mechanical properties (mean shear stiffness (|G*|) by 2D and 3D MRE, and storage modulus (G'), loss modulus (G"), wave attenuation (α), and damping ratio (ζ) by 3D MRE) and histology, demographic and anthropometric data were assessed.

Results: In univariate analyses, patients with lobular inflammation grade ≥ 2 had higher 2D |G*| and 3D G″ than those with grade ≤ 1 (P=0.04). |G*| (both 2D and 3D), G′ and G″ increased with age (rho = 0.25 to 0.31; $P \leq 0.03$). In multivariable regression analyses, the association between inflammation grade ≥ 2 remained significant for 2D |G*| ($P = 0.01$) but not for 3D G″ ($P = 0.06$); age, sex or BMI did not affect the MRE-inflammation relationship ($P > 0.20$).

Conclusions: 2D |G*| and 3D G″ were weakly associated with moderate or severe lobular inflammation in patients with known or suspected NAFLD without fibrosis. With further validation and refinement, these properties might become useful biomarkers of inflammation. Age adjustment may help MRE interpretation, at least in patients with early-stage disease.

Keywords

Magnetic resonance imaging; Elasticity imaging techniques; Non-alcoholic fatty liver disease; Inflammation

Introduction

The prevalence of nonalcoholic fatty liver disease (NAFLD) is increasing worldwide [1]. An estimated 25% of patients with NAFLD are thought to have nonalcoholic steatohepatitis (NASH), a more aggressive phenotype [2] that can progress to advanced fibrosis and cirrhosis [3–6] and that is associated with higher rates of morbidity and all-cause mortality [7]. Early detection of NASH would permit early therapeutic intervention that could reduce morbidity and mortality [8].

Currently, reliable assessment of NAFLD/NASH requires liver biopsy and histologic interpretation [9]. NASH is defined as the presence of hepatic steatosis, inflammation and ballooning injury with or without fibrosis [10]. However, biopsy is invasive, prone

to sampling variability, observer dependent, impractical for repeated measurements, and inappropriate for population-based studies [11]. For this reason, noninvasive biomarkers for the evaluation of NAFLD are needed [12]. Hepatic proton density fat fraction (PDFF) estimated by confounder-corrected chemical-shift-encoded magnetic resonance imaging (MRI) has been established as a reliable biomarker to quantify hepatic steatosis cross-sectionally and to measure its change longitudinally [13].

MR elastography (MRE) is an advanced technique that estimates liver shear stiffness [14] and other viscoelastic properties [15] based on the analysis of shear wave propagation through the liver. Shear stiffness, also called the magnitude of the complex shear modulus $\left(|G^*| = \sqrt{\left((G')^2 + (G'')^2\right)}\right)$, is the most commonly used MRE parameter; it reflects both elastic and viscous (or damping) elements of tissue stiffness [15; 16] (Table 1). Other MRE parameters – such as storage modulus (G′), loss modulus (G″), wave attenuation (α) and damping ratio (ζ) [15–17] (Table 1) – have been studied more recently. In patients with NASH and other chronic liver diseases, it has been shown that liver fibrosis increases stiffness and related mechanical properties [15; 18; 19]. Fibrosis is just one component of the pathology of NASH, and other factors like lobular inflammation and hepatocellular ballooning play important roles in the progression of disease. However, the ability of MRE to measure these other histological alterations through their impact on mechanical properties remains elusive. Some NAFLD animal models and human studies have suggested that hepatic steatosis, lobular inflammation, and hepatocellular ballooning can affect hepatic mechanical properties [15; 20–23]. One study, for example, reported that the loss modulus (G″) may be sensitive to inflammation, and that G″ and damping ratio (ζ) were elevated in early NASH [15], while other human studies have found no significant associations [24; 25]. A plausible explanation for the inconsistent results in human NAFLD studies is that liver fibrosis may dominate the impact on the hepatic mechanical properties measured using MRE, obscuring potential weaker associations with other histologic features [26]. One way to better understand the association between mechanical properties and histologic features other than liver fibrosis in human NAFLD would be to eliminate the dominant effect of fibrosis by assembling a cohort with histologically-verified absence of fibrosis.

To this end the purpose of this study was to investigate the association between histology and hepatic mechanical properties measured using MRE in adults with known or suspected NAFLD and with histologically-verified absence of fibrosis. We secondarily sought to assess the inter-relationship and impact of demographic and anthropometric data on mechanical properties.

Materials and Methods

Study design

This was a retrospective, cross-sectional, single-center, secondary analysis of adults who participated in one or more parent NAFLD prospective studies at our institution between October 2010 and January 2017. All subjects in this secondary analysis have been previously reported [27–30]. The prior articles included patients with fibrosis and so differed in their population cohorts. Also, the prior articles either did not report MRE results [27;

29] or reported only a single MRE-measured parameter (shear stiffness) [28; 30]. In this analysis, we examine multiple MRE-measured parameters and we focus on adults with histologically-verified absence of fibrosis.

Inclusion criteria for the parent studies included: age ≥ 18 years; research MR exams performed with acquisition of MRI-PDFF as well as either 2D, or both 2D and 3D MRE; and liver biopsy performed to assess known or suspected NAFLD. Exclusion criteria for the parent studies were excess alcohol consumption; evidence of secondary NAFLD or of other forms of liver disease; contraindication(s) to MR examination; or pregnancy or trying to become pregnant. Two additional exclusion criteria for this secondary analysis were that liver biopsy showed any fibrosis and that the time interval between the MR examinations and biopsy was 180 days or more.

This analysis and the parent studies were approved by our Institutional Review Board and are compliant with the Health Insurance Portability and Accountability Act. All subjects provided written informed consent for the parent studies from which cases were selected for inclusion in this analysis.

MR examinations

Noncontrast MR examinations were performed at 3T (GE Signa EXCITE HDxt, GE Healthcare) and are further described in the Supplementary Material. MRE examinations were performed using a 60-Hz paddle vibration frequency, as previously described [31].

MRE sequences and analysis

Axial breath-hold 2D and 3D MRE images were acquired. In this study, 3D MRE refers to acquisition of the shear wave field in 3 spatial dimensions and with separate motion encoding in the x, y, and z directions, at 3 timepoints in the wave cycle, using a multislice sequence. These vector MRE data are then processed with a full 3D MRE inversion algorithm. Acquisition parameters for MRE are listed in Table 2. Wave images were processed with a 2D multimodel direct-inversion (MMDI) algorithm for 2D MRE, and a 3D direct-inversion algorithm for 3D MRE. Quantitative parametric maps of mechanical properties were generated, including the magnitude of complex shear modulus (|G*|) for both 2D and 3D MRE, as well as the storage modulus (G'), loss modulus (G''), wave attenuation (α), and damping ratio ($\zeta = G''/2G'$) for 3D MRE [15; 32; 33].

MRE images were analyzed offline by two trained image analysts (K.J.G. and J.C., each with ≥ 10 yrs experience) blinded to the clinical and histologic data. (Each MRE exam was analyzed by a different reader.) A free-form region-of-interest (ROI) was drawn on portions of the right hepatic lobe on wave images. The analysis of hepatic MRE properties is further described in the Supplementary Material.

MRI-PDFF sequence and analysis

Hepatic PDFF images were acquired according to previously reported methods [27–30]. Acquisition parameters are listed in Table 2. The analysis of hepatic MRI-PDFF is described further in the Supplementary Material.

Demographic, anthropometric, laboratory and histologic data

Demographic, anthropometric and laboratory data were collected. Histologic scoring was performed by an experienced hepatopathologist (M.A.V., > 10 yrs experience) blinded to the clinical and imaging data. Histologic measures were scored according to the NASH Clinical Research Network histologic scoring system [34]. This scoring system is described further in the Supplementary Material.

Statistical analyses

Statistical analyses were performed by a biostatistical analyst under the supervision of a faculty statistician (T.W. and A.C.G., both with > 20 yrs experience) using statistical computing software (R version 2.15.1; R Foundation for Statistical Computing). Demographic, anthropometric, laboratory, histologic data, and hepatic mechanical properties measured using MRE were summarized descriptively. Continuous variables were expressed as mean ± standard deviation or median with interquartile range, and categorical variables were expressed as number and percentage. A 2-tailed *P*-value < .05 was considered statistically significant. Correction for multiple comparisons was not applied.

Given that it is a secondary analysis of parent studies, age and sex were compared between patients who were included and those who were excluded in this analysis using a t-test and a chi-squared test of proportions, respectively. Steatosis grade and NAFLD activity score (NAS) were treated as ordinal. All other histologic variables were dichotomized and are further described in the Supplementary Material.

In univariate analyses, the relationship between MRE mechanical properties and dichotomized histologic variables were assessed using Wilcoxon-Mann-Whitney tests. Additionally, Spearman's correlation coefficients (rho) were calculated to explore the association between MRE mechanical properties and continuous (age, body mass index (BMI), MRI-PDFF) or ordinal (histology-determined steatosis, NAS) variables. Relationships that showed significant differences in univariate analyses were then further examined using multivariable logistic regression analyses. In each regression, the predictors consisted of one MRE property as well as the covariates of age (continuous), sex and BMI (continuous).

Results

Cohort characteristics

Of 203 participants in the parent studies, 88 adults (mean age, 48.7 years; range, 18.5 to 75.8 years) were selected for this analysis. 114 participants were excluded because they had biopsy-proven liver fibrosis. One participant was excluded because the MR-biopsy interval exceeded 180 days. Included and excluded patients did not differ on age (p = 0.57) or sex (p = 0.87).

All 88 included subjects had undergone 2D MRE, and 77/88 (87.5%) also had undergone 3D MRE in the parent studies. The majority (79/88 for 2D MRE, 72/77 for 3D MRE) had biopsy-proven NAFLD; 57/88 for 2D MRE and 49/77 for 3D MRE had grade 2 or 3 lobular

inflammation, while all other included patients had grade 1 or no lobular inflammation. The mean and median time interval between MR imaging and biopsy was 33 and 19 days (range, 1 to 173 days), respectively. The mean shear stiffness (|G*|) from 2D and 3D MRE were 2.38 kPa and 2.04 kPa, respectively. The mean storage modulus (G′) and loss modulus (G″) from 3D MRE were 1.98 kPa and 0.38 kPa, respectively. Demographics, anthropometry, laboratory, histology, and cohort 2D and 3D MRE mechanical properties are summarized in Table 3.

Univariate associations between histologic measures and MRE mechanical properties

Mean hepatic shear stiffness (|G*|) measured using 2D MRE and loss modulus (G″) measured using 3D MRE were significantly higher for participants with lobular inflammation grade ≥ 2 vs. ≤ 1 (2.58 ± 0.61 vs. 2.27 ± 0.29 kPa, $P = 0.04$ and 0.42 ± 0.12 vs. 0.36 ± 0.11 kPa, $P = 0.04$, respectively) (Figures 1, 2). For participants with lobular inflammation grade ≥ 2 vs. ≤ 1, the difference in hepatic shear stiffness (|G*|) or storage modulus (G′) measured by 3D MRE did not reach statistical significance ($P = 0.08$ and 0.09, 2.16 ± 0.46 vs. 1.97 ± 0.26 kPa and 2.10 ± 0.46 vs. 1.91 ± 0.25 kPa, respectively) (Figure 2). Hepatic wave attenuation (α) and damping ratio (ζ) showed no differences between lobular inflammation grade ≥ 2 and grade ≤ 1 ($P = 0.84$ and 0.31, respectively) (Figure 2).

No MRE mechanical property showed any significant association with steatosis, hepatocellular ballooning, NAS, or diagnosis of NASH ($P > 0.10$). Results of univariate associations between MRE histologic measures and mechanical properties are summarized in Table 4.

Univariate associations between MRE mechanical properties and age, BMI, MRI-PDFF

Hepatic shear stiffness (|G*|) (both 2D and 3D), storage modulus (G′) and loss modulus (G′) increased significantly with age; the Spearman's coefficients ranged from 0.25 to 0.31 (all $P \leq 0.03$) (Table 4; Figure 1). There was no significant association between any MRE mechanical property and BMI or MRI-PDFF (rho = −0.15 to 0.06, all $P \geq 0.20$ for BMI; rho = −0.19 to 0.10, all $P \geq 0.10$ for MRI-PDFF) (Table 4).

Multivariable regression analysis

After adjusting for age, sex, and BMI in multivariable regression analysis, the association between grade ≥ 2 inflammation remained significant for |G*| measured using 2D MRE ($P = 0.01$) but not for G″ measured using 3D MRE ($P = 0.06$); age, sex or BMI did not affect the MRE-inflammation relationship ($P > 0.20$). Results of multivariable analyses are summarized in Table 5.

Discussion

In this study, we performed a secondary analysis of prospectively acquired data in adults with known or suspected NAFLD without histologic fibrosis to determine the possible association of pathological features with MRE-determined tissue mechanical properties. Hepatic inflammation is one of the responses to injury and considered an important pathogenic component of NAFLD/NASH. When the liver is injured, lymphocytes and

macrophages in the parenchyma release chemokines, which attract and promote retention of additional immune cells in the tissue; the infiltration into the liver of immune cells and the release of adhesion factors are thought to increase the viscosity of liver tissue [17]. We therefore postulated that inflammation might impact MRE measurements. We found that there were relationships between elevated mean hepatic shear stiffness (measured using 2D MRE) and elevated mean hepatic loss modulus (measured using 3D MRE) with moderate to severe lobular inflammation, and the relationship with elevated mean hepatic shear stiffness (measured using 2D MRE) remained significant after adjusting for age, sex, and BMI. These findings suggest that with further refinement, MRE-based assessments of hepatic mechanical properties may permit detection of early alterations of histopathology prior to the development of fibrosis. Further studies are needed to verify our results.

Other authors have attempted to explore the relationship of inflammation and MRE measures. Chen et al. [21] found that hepatic stiffness measured using 2D MRE correlated with inflammation grade in NAFLD patients. Although the authors did not exclude patients with fibrosis, they adjusted for the effects of fibrosis in a multivariable analysis. Similarly, Shi et al. [35] found that hepatic stiffness measured using 2D MRE was significantly higher in patients with moderate or severe inflammation compared with no or mild inflammation in HBV patients without fibrosis. Others have not demonstrated this same correlation. Leitão et al. [25] found that in patients with mixed chronic liver disease, inflammation was not independently associated with hepatic viscoelastic properties measured using MRE, possibly because patients in their study had various etiologies, and patients with fibrosis were not excluded. While not the first to attempt to measure inflammation using MRE, our study has some advantages: 1) we attempted to isolate the possible effect of inflammation by focusing on patients with early stage NAFLD and excluding patients with more advanced disease (i.e. those with fibrosis) and 2) we performed all MRE examinations under controlled protocols as all participants were enrolled in parent research studies.

Our finding that the mean loss modulus measured using 3D MRE is significantly higher in subjects with moderate to severe lobular inflammation compared to subjects with no or mild lobular inflammation in univariate analyses provides a possible positive signal for future research. After adjusting for other covariates, loss modulus measured using 3D MRE almost reached significance with a p-values of 0.06. This suggests that studies with larger sample sizes might find a statistically significant contribution, help to verify the incremental benefit of 3D MRE in assessing inflammation, and support the eventual clinical adoption of 3D MRE, which currently is used mainly in the research domain. Moreover, although 3D MRE and 2D MRE ended up with p-values on different sides of the significance threshold of 0.05 in a multivariable model, they were both close to that threshold, and it is possible that the two methods provide complementary information. Future studies are warranted.

The storage modulus reflects the elasticity of tissue and is thought to be sensitive mainly to fibrosis [15]. Thus, the small, nonsignificant ($P = 0.09$) difference in storage modulus between patients with lobular inflammation grade ≥ 2 vs. ≤ 1 is not surprising, given that our analysis included only subjects with no fibrosis.

As our secondary aim, we evaluated the relationship of age, MRI-PDFF and BMI with MRE measurements. We found that mean hepatic shear stiffness, and storage and loss moduli increased with age (all $P \leq 0.03$). A prior individual participant data pooled analysis reported similar observations in NAFLD patients with no or varying stages of fibrosis [36], finding a modest positive correlation between age and liver stiffness measured using MRE. To the best of our knowledge, our findings are the first report of associations between age and hepatic mechanical properties measured using multiparametric MRE in NAFLD patients without fibrosis. Our findings suggest that age adjustment may help interpret MRE results, at least in patients with early-stage disease.

Prior studies have reported no association between MRI-determined hepatic signal fat fraction [21] or PDFF [37] and 2D MRE-determined shear stiffness in NAFLD patients, the majority of whom had fibrosis. Our study helps to verify these findings in a NAFLD cohort without fibrosis, and we also add to those findings by showing that other MRE-assessed mechanical properties were not associated with hepatic histologic steatosis or MRI-PDFF (all $P \geq 0.10$). No hepatic MRE mechanical property had a significant association with BMI, hepatocellular ballooning grade, NAS, or diagnosis of NASH score (all $P > 0.10$).

Our study has several limitations. First, this is a retrospective, single-center and cross-sectional study, and reproducibility of multiparametric MRE was not evaluated. We do provide potential positive signal to explore in future prospective work that may aim to establish the repeatability/reproducibility of and refine and validate these MRE parameters as biomarkers of inflammation. Second, given the continuous spectrum of histological alterations of NAFLD, our sample size is relatively small. Histologic data were not uniformly distributed across grades/stages; we had more cases with mild or moderate inflammation than cases without NAFLD or severe inflammation, which prevented a comprehensive analysis of MRE mechanical properties grading inflammation across its entire biological range. A larger study population with sufficient subjects in each grade/stage is required to more completely assess the association between histologic features and MRE parameters in the future. Third, all of the MRE mechanical parameters reported in this study are frequency-dependent properties [15; 19]. MRE data in our study were acquired at only one frequency (60 Hz). Yin et al. [38] found that loss modulus measured using 3D MRE at 80 Hz had significant positive effects in predicting lobular inflammation in a NAFLD mouse model. Future studies are necessary to determine the frequency or frequencies with the best multiparametric MRE diagnostic performance for the assessment of histologic measures of NAFLD, as well as the possible role of measuring frequency dispersion (how the parameters change with frequency) [39; 40]. Finally, the interval between the MR examinations and biopsy within 180 days is relatively large although acceptable [23; 41]. Moreover, the mean MR-biopsy interval was only 33 days, reducing the risk of interim biological change.

In conclusion, moderate to severe inflammation was associated with elevated mean hepatic shear stiffness (measured using 2D MRE) and elevated mean hepatic loss modulus (measured using 3D MRE) in patients with known or suspected NAFLD, but with histology-confirmed absence of liver fibrosis, and the relationship of 2D MRE-stiffness with inflammation grade remained significant after adjusting for age, sex, and BMI. Our results suggest that with further technical refinement these MRE-assessed mechanical properties

may permit detection of inflammation before the onset of fibrosis in NAFLD. In addition, increasing age was found to be associated with higher mean hepatic shear stiffness, and storage and loss moduli, suggesting that age adjustment may help interpret MRE results, at least in patients with early-stage disease.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Abbreviations

BMI	body mass index
MMDI	multimodel direct inversion
MRE	magnetic resonance elastography
MRI	magnetic resonance imaging
NAFLD	nonalcoholic fatty liver disease
NAS	nonalcoholic fatty liver disease activity score
NASH	nonalcoholic steatohepatitis
PDFF	proton density fat fraction
ROI	region of interest

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Key points:

1. Moderate to severe lobular inflammation was associated with hepatic elevated shear stiffness and elevated loss modulus (P=0.04) in patients with known or suspected NAFLD without liver fibrosis; this suggests that with further technical refinement these MRE-assessed mechanical properties may permit detection of inflammation before the onset of fibrosis in NAFLD.
2. Increasing age is associated with higher hepatic shear stiffness, and storage and loss moduli (rho = 0.25 to 0.31; $P \leq 0.03$). this suggests that age adjustment may help interpret MRE results, at least in patients with early-stage NAFLD.

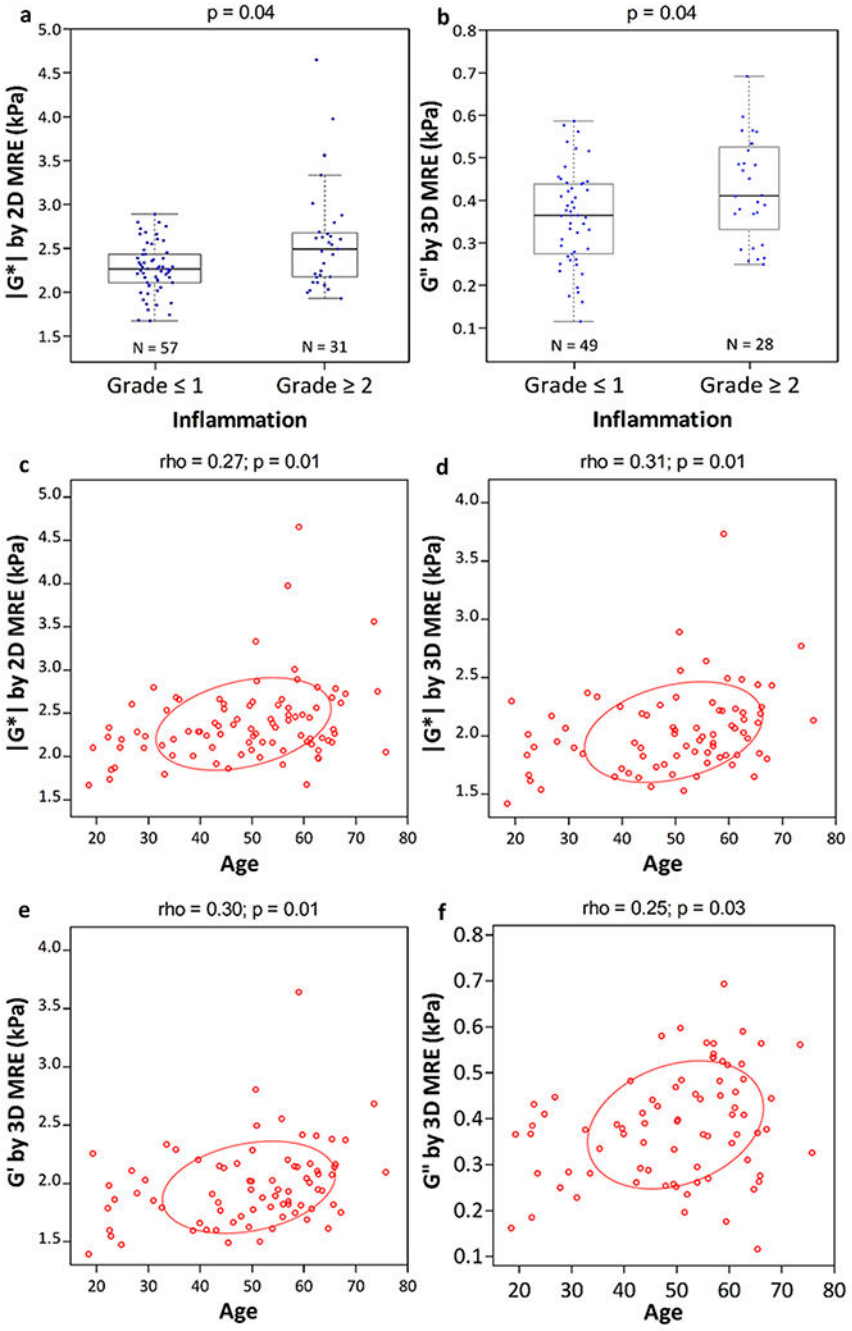

Figure 1.

Boxplots show that in patients without liver fibrosis, the presence of inflammation is associated with significantly higher shear stiffness |G*| measured using 2D MR elastography (MRE) (A) and loss modulus G″ measured using 3D MRE (B). Scatterplots show that MRE-derived biomarkers including shear stiffness |G*| (both 2D and 3D) (C)-(D), storage modulus G′ (E) and loss modulus G″ (F) tended to increase with age. The ellipses in the plots, computed based on the variance and covariance of the X and Y measures being

plotted, are visual representations of the strength and direction of the relationship between the X and Y.

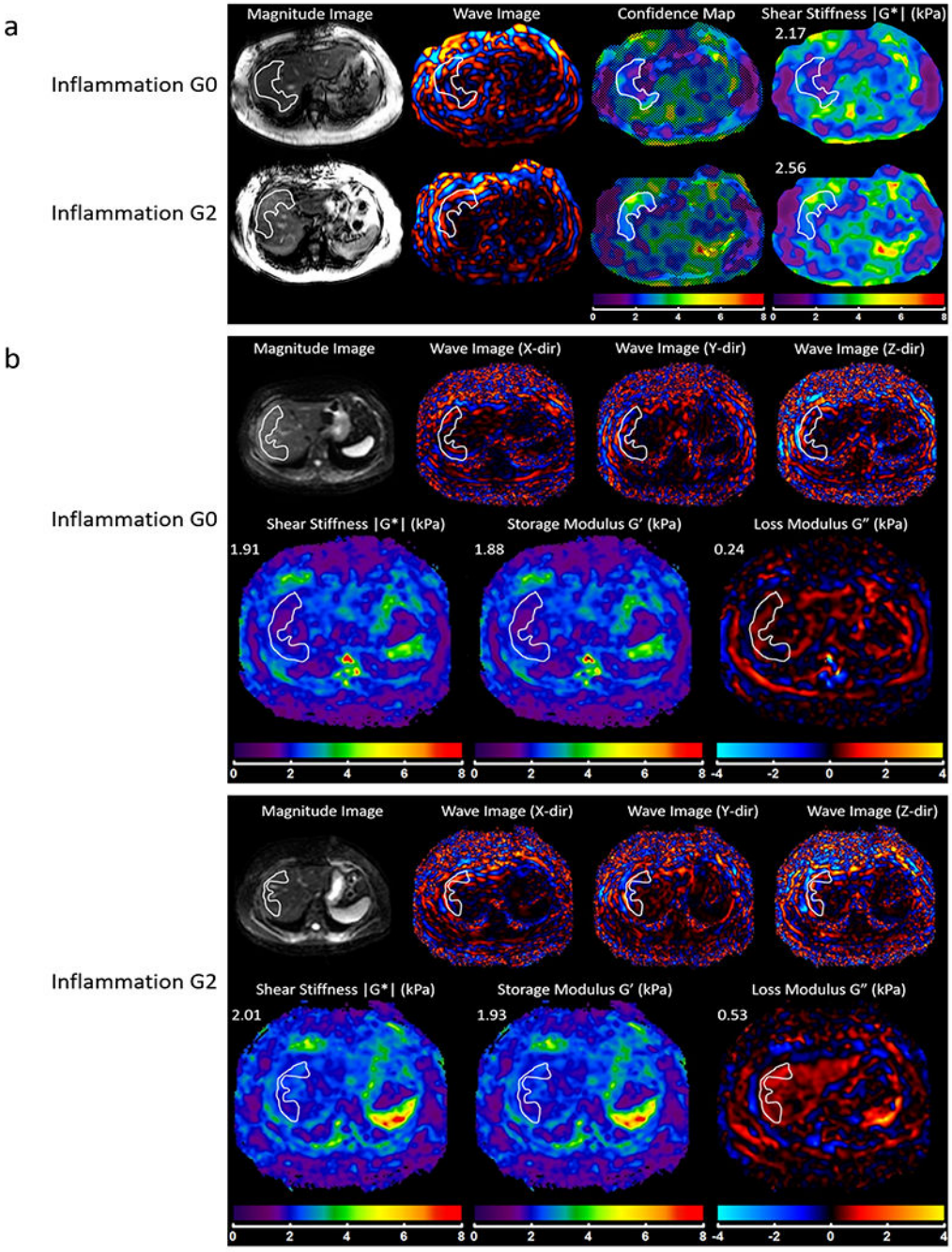

Figure 2.

Examples of 2D (A) and 3D (B) MRE images in a 52-year-old woman with no lobular inflammation, and in a 57-year-old woman with lobular inflammation grade 2. The white line depicts the manually traced region of interest (ROI). It should be noted that the ROIs on the shear stiffness (|G*|), storage modulus (G′) and loss modulus (G″) maps are copies of the ROI drawn using the magnitude and wave information for display purposes, but

the values of |G*|, G′, G″ and wave attenuation (α) were derived from ROI-based mean complex shear modulus values mathematically.

Table 1.

Multiparametric MRE Mechanical Properties (15-17)

MRE Mechanical Property	Shear Stiffness |G*| (kPa)	Storage Modulus G′ (kPa)	Loss Modulus G″ (kPa)	Wave Attenuation α (m^{-1})	Damping Ratio ζ
Definition/formula	$\left\|G^*\right\| = \sqrt{(G')^2 + (G'')^2}$	Re (G*)	Im (G*)	α = -Im(sqrt(ρω²/G*))	G″/2 G′
Physical correlate	Reflects both the elastic and viscous (or damping) elements of stiffness	Elastic element of complex stiffness	Viscous element of complex stiffness	The energy or amplitude loss of the wave as a function of depth and is related to viscosity	Relative contribution of damping or viscous elements to overall tissue stiffness

MRE magnetic resonance elastography; *Re (G*)* real part of the complex shear modulus (G*); *Im (G*)* imaginary part of the complex shear modulus (G*); ρ material density (assumed to be equal to the density of water); ω circular frequency of the vibration.

Table 2.

Parameters for MR Techniques

Acquisition Parameters	2D GRE MRE	3D SE-EPI MRE	MRI-PDFF
TR (ms)	50	1167 or 1333.8	≥ 150
TE (ms)	20.2	51.0	1.15, 2.3, 3.45, 4.6, 5.75, 6.9
FA (degrees)	30	90	10
Slice thickness (mm)	10	3.5	8
Number of slices	4	28-32	17-33
Inter-slice gap (mm)	0	0	0
Matrix	256 × 64	72 × 72	224 x 128 –160
FOV (cm)	38-48 × 38-48	38-48 × 38-48	38-44 × 38-44
BW (kHz)	± 31.25	± 250	± 142
Number of averages	1	1	1
Parallel imaging acceleration factor	2	3	1.25

2D two-dimensional; *3D* three-dimensional; *BW* Bandwidth; *FA* Flip angle; *FOV* Field of view; *GRE* gradient-recalled echo; *MRE* magnetic resonance elastography; *MRI-PDFF* magnetic resonance imaging-proton density fat fraction; *SE-EPI* spin-echo echo-planar imaging; *TR* repetition time; *TE* echo time

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Table 3.

Demographics, Anthropometry, Laboratory, Histology and Cohort 2D and 3D MRE Mechanical Properties of Study Cohort

Characteristic	Values
Demographic and anthropometric data (n=88)	
Age at biopsy, *y*, mean ± SD	48.7 ± 14.3
Female, n (*%*)	52 (59.1)
Male, n (*%*)	36 (40.9)
BMI, kg/m^2, mean ± SD	31.4 ± 5.3
Laboratory data (n=88)	
AST, *U/L*, median (IQR)	28.0 (10)
ALT, *U/L*, median (IQR)	42.0 (32)
Platelet count, $10^9/L$, median (IQR)	248,500 (95,500)
Histologic data (n=88)	
Steatosis, n (*%*)	
0	10 (11.4)
1	31 (35.2)
2	32 (36.4)
3	15 (17.0)
Lobular inflammation, n (*%*)	
0	10 (11.4)
1	47 (53.4)
2	30 (34.1)
3	1 (1.1)
Ballooning, n (*%*)	
0	50 (56.8)
1	34 (38.6)
2	4 (4.6)
Diagnosis of NASH, n (*%*)	
0 No NAFLD	9 (10.2)
1 NAFLD, not NASH	35 (39.8)
2 Borderline NASH	13 (14.8)

Characteristic	Values
3 Definite NASH	31 (35.2)
NAS, mean ± SD	3.3 ± 1.7
2D MRE (n=88)	
Shear stiffness |G*|, *kPa*, mean ± SD	2.38 ± 0.45
3D MRE (n=77)	
Shear stiffness |G*|, *kPa*, mean ± SD	2.04 ± 0.36
Storage modulus G', *kPa*, mean ± SD	1.98 ± 0.35
Loss modulus G", *kPa*, mean ± SD	0.38 ± 0.12
Wave attenuation α, m^{-1}, mean ± SD	28.5 ± 6
Damping ratio ζ, mean ± SD	0.1 ± 0.03
Interval between MR and biopsy, *day*, mean ± SD (median; range) (n=88)	33 ± 37 (19; 1-173)

ALT alanine aminotransferase; *AST* aspartate aminotransferase; *BMI* body mass index; *IQR* interquartile range; *MRE* magnetic resonance elastography; *NAFLD* nonalcoholic fatty liver disease; *NAS* NAFLD activity score; *NASH* nonalcoholic steatohepatitis; *SD* standard deviation.

Table 4.

Results of Associations between MRE Mechanical Properties and Histologic Features, Age, BMI and MRI-PDFF using Wilcoxon Mann-Whitney or Spearman's Correlation Tests

Characteristics	Scores	2D MRE	3D MRE				
		Shear Stiffness |G*| (kPa)	**Shear Stiffness |G*| (kPa)**	**Storage Modulus G′ (kPa)**	**Loss Modulus G″ (kPa)**	**Wave Attenuation α (m^{-1})**	**Damping Ratio ζ (G″/2G′)**
Steatosis	Grade 0-3	Rho = 0.11, *P* = 0.32	Rho = −0.16, *P* = 0.17	Rho = −0.17, *P* = 0.15	Rho = 0.05, *P* = 0.70	Rho = 0.18, *P* = 0.12	Rho = 0.09, *P* = 0.41
Lobular Inflammation	Grade ≥ 2 vs. ≤ 1	**2.58 ± 0.61 vs. 2.27 ± 0.29, *P* = 0.04***	2.16 ± 0.46 vs. 1.97 ± 0.26, *P* = 0.08	2.10±0.46 vs. 1.91 ± 0.25, *P* = 0.09	**0.42 ± 0.12 vs. 0.36 ± 0.11, *P* = 0.04***	28.50± 6.42 vs. 28.48 ± 6.56, *P* = 0.84	0.10 ± 0.02 vs. 0.10 ± 0.03, *P* = 0.31
Hepatocellular Ballooning	Grade ≥ 1 vs. 0	2.39 ± 0.46 vs. 2.37 ± 0.45, *P* = 0.92	2.04 ± 0.41 vs. 2.03 ± 0.31, *P* = 0.80	1.99 ± 0.40 vs. 1.97 ± 0.31, *P* = 0.86	0.39 ± 0.11 vs. 0.38 ± 0.13, *P* = 0.91	28.39± 6.37 vs. 28.56 ± 6.61, *P* = 0.94	0.10 ± 0.02 vs. 0.10 ± 0.03, *P* = 0.82
NAS	Score 0-8	Rho = 0.15, *P* = 0.18	Rho = −0.04, *P* = 0.73	Rho = −0.04, *P* = 0.73	Rho = 0.12, *P* = 0.29	Rho = 0.12, *P* = 0.29	Rho = 0.12, *P* = 0.31
Diagnosis of NASH	Definite/ borderline NASH vs. no NASH (Grade ≥ 2 vs. ≤ 1)	2.44 ± 0.49 vs. 2.33 ± 0.41, *P* = 0.46	2.08 ± 0.42 vs. 1.99 ± 0.27, *P* = 0.61	2.02 ± 0.41 vs. 1.94 ± 0.27, *P* = 0.62	0.41 ± 0.12 vs. 0.36 ± 0.12, *P* = 0.11	28.84± 6.36 vs. 28.13 ± 6.64, *P* = 0.50	0.10 ± 0.03 vs. 0.09 ± 0.03, *P* = 0.17
	Definite NASH vs. not definite NASH (Grade 3 vs. ≤ 2)	2.50 ± 0.55 vs. 2.32 ± 0.38, *P* = 0.17	2.10 ± 0.47 vs. 2.00 ± 0.26, *P* = 0.76	2.04 ± 0.46 vs. 1.94 ± 0.25, *P* = 0.76	0.41 ± 0.11 vs. 0.37 ± 0.12, *P* = 0.22	28.60± 6.92 vs. 28.42 ± 6.25, *P* = 1.00	0.10 ± 0.02 vs. 0.10 ± 0.03, *P* = 0.39
Age	Continuous	**Rho = 0.27, *P* = 0.01***	**Rho = 0.31, *P* = 0.01***	**Rho = 0.30, *P* = 0.01***	**Rho = 0.25, *P* = 0.03***	Rho = −0.03, *P* = 0.78	Rho = 0.09, *P* = 0.44
BMI	Continuous	Rho = 0.06, *P* = 0.58	Rho = 0.01, *P* = 0.91	Rho = 0.01, *P* = 0.90	Rho = −0.08, *P* = 0.48	Rho = −0.15, *P* = 0.20	Rho = −0.06, *P* = 0.58
MRI-PDFF	Continuous	Rho = 0.08, *P* = 0.44	Rho = −0.19, *P* = 0.10	Rho = −0.19, *P* = 0.10	Rho = −0.05, *P* = 0.68	Rho = 0.10, *P* = 0.38	Rho = 0.01, *P* = 0.95

*The results were significant at a significance level of 0.05. Significant results are in bold. *BMI* body mass index; *MRE* magnetic resonance elastography; *MRI-PDFF* magnetic resonance imaging-proton density fat fraction; *NAS* NAFLD activity score; *NASH* nonalcoholic steatohepatitis.

Table 5.

Odds Ratios and P-values from the Multivariable Regression Analysis with Lobular Inflammation Grade ≥ 2 vs. ≤ 1 as Outcome

Model	Predictors	Odds Ratio	P
1	Shear Stiffness (|G*|) by 2D MRE	**6.29**	**0.01** *
	Age	1.00	0.88
	Sex	1.24	0.67
	BMI	0.97	0.46
2	Shear Stiffness (|G*|) by 3D MRE	4.58	0.06
	Age	1.01	0.62
	Sex	1.01	0.98
	BMI	0.97	0.58
3	Storage Modulus (G′) by 3D MRE	4.50	0.07
	Age	1.01	0.59
	Sex	1.02	0.98
	BMI	0.97	0.58
4	Loss Modulus (G′) by 3D MRE	72.47	0.06
	Age	1.01	0.52
	Sex	1.20	0.72
	BMI	0.98	0.65
5	Wave Attenuation (α) by 3D MRE	1.01	0.89
	Age	1.02	0.22
	Sex	1.28	0.62
	BMI	0.98	0.71
6	Damping Ratio (ζ) by 3D MRE	8407.67	0.31
	Age	1.02	0.24
	Sex	1.33	0.57
	BMI	0.98	0.72

* The results were significant at a significance level of 0.05. Significant results are in bold. *BMI* body mass index; *MRE* magnetic resonance elastography