

ANSWERING REVIEWERS

In the revised manuscript, highlighted text (green) relates to comments or changes that the authors have included in response to either the Scientific Editor or reviewers. Some explanations are also included in the Comments box where appropriate.

Scientific Editor (Yuan Qi) **COMMENTS TO AUTHORS**

For manuscripts submitted by non-native speakers of English, please provide a language certificate by professional English language editing companies mentioned in 'The Revision Policies of BPG for Review'.

Authors comments: We are native English speakers.

COMMENT 1 .The '**Conflict-of-interest**' file must be signed by the corresponding author and provided in a PDF format, and the statement must also be mentioned as a footnote in the manuscript text.

Sample wording: [Name of individual] has received fees for serving as a speaker, a [position; such as consultant and/or an advisory board member] for [name(s) of organization(s)]. [Name of individual] has received research funding from [name(s) of organization(s)]. [Name of individual] is an employee of [name(s) of organization(s)]. [Name of individual] owns stocks and/or shares in [name(s) of organization(s)]. [Name of individual] owns patent [patent identifier information (including patent number, two-letter country code, and kind code) and a brief description].

Authors comments: The '**Conflict-of-interest**' file is now included with the re-submission, as per specifications. The authors declare no conflict-of-interests. The statement '*The authors declare no conflict of interests for this article*' is also included in the footnote in the manuscript text.

COMMENT 2. Please add PubMed citation numbers and DOI citation to the reference list and list all authors. Please revise throughout. The author should provide the first page of the paper without PMID and DOI.

PMID (<http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=PubMed>)

DOI (<http://www.crossref.org/SimpleTextQuery/>) (Please begin with DOI: 10.**).

For those references that have not been indexed by PubMed, a printed copy of the first

page of the full reference should be submitted.

Authors comments: The reference listing is completely revised and includes PMID and DOI citation numbers. All of the references used are PubMed citable.

COMMENT 3. Please refer to at least 30 references. Thank you!

Authors comments: We have looked and revised at the entire reference listing.

COMMENT 4. Please provide the decomposable figure of Figures, whose parts are movable and can be edited. So please put the original picture as word or ppt or excel format so that I can edit them easily.

Authors comments: We include with the re-submission a powerpoint file that includes all the Figures in the manuscript. This includes figures which contain decomposable elements that can be moved and edited. Please note that some figures cannot be edited as it is comes this way.

Reviewer's code: 00058381

Reviewer's country: Austria

COMMENTS TO AUTHORS

Major Comment: Interesting review on an important subject. Two unimportant comments: "Limitations and future directions", first paragraph, last sentence: "...and prospective studies involving larger numbers of patients is required for validation." > ...and prospective studies involving larger numbers of patients are required for validation. Figures 5a, 5b and 9: "32-year old", "53 year old", "39-year-old" > Please use the hyphens consistently.

Authors comments:

- The sentence has been changed to "...and prospective studies involving large numbers of patients *are* required for validation."
 - In Figures 5a, 5b and 9, the hyphens are now used consistently. e.g. "32-year-old", "53-year-old", "39-year-old"
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Reviewer's code: 00289471

Reviewer's country: Italy

COMMENTS TO AUTHORS

Very good and interesting article. A few minor observations: It is not clear to me the sentence "... conventional modalities such as... may vary over a much narrower range" in "Mechanical properties of soft tissue". I don't understand well the concept of elastic modulus. Reading the article it looks that the authors speak about deformability, elasticity should be the capacity of a material to be deformed non-permanently getting back to morphology they had before the strain was applied. While it is clear there are three different ways to obtain mechanical excitation it is not clear which one is used in practice. I don't think that MRE could have a role alternative to liver biopsy since the goal of a liver biopsy is not mainly to grade fibrosis but to evaluate inflammation and parenchymal distortion, furthermore I don't think that biopsy sampling should be driven of more fibrotic areas of the liver.

Authors comments:

- The following are included in the article in regards to elastic modulus

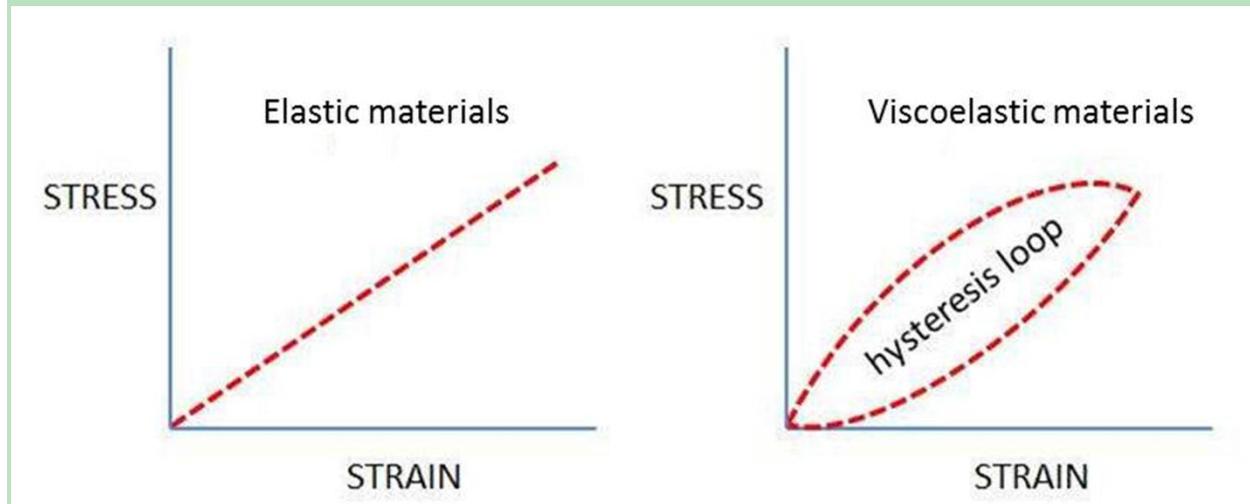
"The slope of the stress-strain curve is the '*elastic modulus*' - a physical parameter that reflects the intrinsic stiffness of the tissue [FIGURE 1]".

"Depending on the type of stress encountered, the elastic modulus is reported as Young's modulus, E ($\frac{\text{longitudinal (compressive or tensile) stress}}{\text{longitudinal strain}}$), shear modulus, μ ($\frac{\text{shear (transverse) stress}}{\text{shear strain}}$) or bulk modulus, K ($\frac{\text{volumetric stress}}{\text{volumetric strain}}$).

The SI unit for elastic modulus is expressed in kilopascals (kPa) where 1 kPa = 1 kN/m². The relationship between E , μ and K is defined mathematically as: "

$$\mu = \frac{E}{2(1+\nu)} \text{ \& } K = \frac{E}{3(1-2\nu)}$$

FIGURE 1 The schematic diagram illustrates the stress-strain relationship of elastic materials and viscoelastic materials.



- While all 3 forms of mechanical excitation may be used in practice, dynamic excitation is used for MRE as it allows for a quantitative assessment. The following are included in the text:

“MRE may be performed using either a quasi-static or dynamic excitation – while the former offers a qualitative estimation of tissue stiffness, the latter is preferred as it allows a precise quantitative assessment of this parameter [8-11]”.

The authors offer the following explanation to the reviewer’s minor comments:

- The authors believe that MRE can potentially be used as a non-invasive alternative to liver biopsy for grading liver fibrosis in well selected patients. MRE has been adopted clinically for this indication in several centres including at the Mayo Clinic. Unlike liver biopsy, MRE is non-invasive and suitable for performing repeat measurements including longitudinal patient assessment. We accept the reviewer’s point that liver biopsy may be performed to obtain information other than fibrosis such as the degree of inflammation.

REF# 12.

Venkatesh SK, Yin M, Ehman RL. Magnetic resonance elastography of liver: technique, analysis, and clinical applications. Journal of magnetic resonance imaging : JMRI 2013; 37(3): 544-555 [PMID: 23423795 DOI: 10.1002/jmri.23731]

REF#27

Park HS, Kim YJ, Yu MH, Choe WH, Jung SI, Jeon HJ. Three-Tesla magnetic resonance elastography for hepatic fibrosis: comparison with diffusion-weighted imaging and gadoxetic acid-enhanced magnetic resonance imaging. *World journal of gastroenterology* : WJG 2014; 20(46): 17558-17567 [PMID: 25516671 DOI: 10.3748/wjg.v20.i46.17558]

- A study by Perumpail RB et al. suggested the potential to use MRE to guide liver biopsy. This is motivated by the fact that fibrosis often affects the liver heterogeneously while biopsy is limited by sampling variability as it is only able to sample a small volume of the liver. The ability to target biopsy to areas in the liver where fibrosis is most severe would be of interest.

REF #41

Perumpail RB, Levitsky J, Wang Y, Lee VS, Karp J, Jin N, Yang GY, Bolster BD, Jr., Shah S, Zuehlsdorff S, Nemcek AA, Jr., Larson AC, Miller FH, Omary RA. MRI-guided biopsy to correlate tissue specimens with MR elastography stiffness readings in liver transplants. *Academic radiology* 2012; 19(9): 1121-1126 [PMID: 22877987 DOI: 10.1016/j.acra.2012.05.011]
