Original Contribution

A PRELIMINARY STUDY OF LIVER FAT QUANTIFICATION USING REPORTED ULTRASOUND SPEED OF SOUND AND ATTENUATION PARAMETERS

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Abstract—The quantification of liver fat as a diagnostic assessment of steatosis remains an important priority for non-invasive imaging systems. We derive a framework in which the unknown fat volume percentage can be estimated from a pair of ultrasound measurements. The precise estimation of ultrasound speed of sound and attenuation within the liver is found to be sufficient for estimating fat volume assuming a classic model of the properties of a composite elastic material. In this model, steatosis is represented as a random dispersion of spherical fat

ultrasound compression wave measures for their predictive value in our model of steatosis. To accomplish that goal, this article reviews first the key equations and assumptions leading to a quantitative model of steatosis and the solutions to two equations with two unknowns. Next, a group of reported measurements of speed of sound (SoS) and attenuation are collected from the literature with a focus on ultrasound around 3.5 MHz, which is common in human abdominal studies. Then, these measurements or their median values are paired and assessed in both the forward model, by way of a nomogram, and the inverse model, by way of regularized optimization of the model equations. The results exhibit reasonable agreement against magnetic resonance imaging (MRI) steatosis estimates and steatosis stages across a number of studies. These preliminary results highlight the potential for routine ultrasound quantification of liver steatosis using scanners capable of accurate speed of sound and attenuation measurements.

THEORY

Composite inclusion model

The accumulation of fat in a liver is generally in the form of small spherical vesicles within the liver hepatocytes. As the vesicles grow in number, our biophysical models predict changes in scattering (Baek et al. 2020b) and biomechanical properties (Parker et al. 2018; Parker and Ormachea 2021). Recently we found (Parker and Ormachea 2021) that the complex (elastic and lossy) hepatic viscoelastic properties could be quantitatively related to the volume percentage of fat. The steatotic liver is modeled as a composite material where the baseline properties are set by normal lean liver. We assume the normal lean liver has a fat content near zero and has well-defined viscoelastic properties (Zhang et al. 2007; Parker et al. 2018). A strong viscous or loss term is linked to fat volume fraction V. The general model of composite medium was originally derived in a landmark paper by Christensen (1969). By imposing the principle of minimum strain energy in a deformed elastic medium, and assuming the inhomogeneities are spherical inclusions, Christensen derived bounds for the effective bulk and shear moduli for the limiting cases of the volume fraction V

This can be separated into two equations, one real part and another imaginary part. By separating these terms, the real part of the composite $\mathrm{Re}\{B_c\}$ and the imaginary part $\mathrm{Im}\{B_c\}$ can be identified:

$$\mathrm{Re}\{B_c\} = \frac{B_{1_{Re}}\left(B_{2_{Re}}^2 + B_{2_{Im}}^2\right)(1-V) + \left(B_{1_{Re}}^2 B_{2_{Re}} + B_{1_{Im}}^2 B_{2_{Re}}\right)V}{B_{2_{Re}}^2 + B_{2_{Im}}^2 - 2\left(B_{2_{Re}}^2 - B_{1_{Re}}B_{2_{Re}} + B_{2_{Im}}(B_{2_{Im}} - B_{1_{Im}})\right)V + \left((B_{1_{Re}} - B_{2_{Re}})^2 + (B_{1_{Im}} - B_{2_{Im}})^2\right)V^2}$$

$$\mathrm{Im}\{B_c\} = \frac{B_{1_{Im}}\left(B_{2_{Re}}^2 + B_{2_{Im}}^2\right)(1-V) + \left(B_{1_{Re}}^2 B_{2_{Im}} + B_{1_{Im}}^2 B_{2_{Im}}\right)V}{B_{2_{Re}}^2 + B_{2_{Im}}^2 - 2\left(B_{2_{Re}}^2 - B_{1_{Re}}B_{2_{Re}} + B_{2_{Im}}(B_{2_{Im}} - B_{1_{Im}})\right)V + \left((B_{1_{Re}} - B_{2_{Re}})^2 + (B_{1_{Im}} - B_{2_{Im}})^2\right)V^2} \quad (7)$$

Let us assume that the parameters for the lossy part of the normal liver and the fat vesicles are known, $B_{1_{\mathrm{Im}}}$ and B_{fat}, respectively. In addition, B_c is assumed to be accurately estimated from experimental measurements at a specific frequency ω as in eqn (4). In this particular case we then have two equations in two unknowns, $B_{1_{\mathrm{Re}}}$ (real part of B_{liver}) and V (fat volume percentage), that can be solved using numerical methods. In practice, regularization methods are employed to minimize problems

spectral shift, spectral difference, spectral log difference and hybrid methods (Bigelow and Labyed 2013). Thus, the AC has been used as a surrogate parameter for hepatic fat quantification. In this work, we report AC results for *in vivo* liver patients using commercial implementations of SoS and AC estimation in different ultrasound clinical systems. The numbers of reviewed articles were: 4 using the 2-D attenuation imaging (ATI) system (Aplio i800, Canon Medical Systems, Otawara, Japan), 3 applying the attenuation parameter (ATT) system (Aloka-Arietta, Fujifilm, previously Hitachi Ltd., Japan), 2 using the ultrasound-guided attenuation parameter (UGAP) system (LOGIQ E9, General Electric, Schenectady, NY, USA), 1 using the diagnostic system (EPIQ-7G, Philips, Bothell, WA, USA) and 1 using the tissue attenuation imaging (TAI) system (RS85, Samsung Medison, Seoul, Korea). We were not able to extract the AC parameter from the ultrasound-derived fat fraction (UDFF) system (Acuson S3000, Siemens Healthineers, Erlangen, Germany) as this product directly reports its estimated fat fraction percentage. Table 2 gives more details on the reviewed references for AC measurements. For the study using the Samsung system, Jeon et al. (2021) reported TAI values based on visual steatosis grades and the controlled attenuation parameter. Thus, we included the mean and standard deviation of TAI values, in Table 2, based on both grades.

Solution b nomogram

A nomogram can be employed as a simplified graphical solution approach. To generate a nomogram, the forward solution is calculated from eqns (2)□(4), and the resulting theoretical values of c_l and α are plotted on a graph, with contours representing regular increments of $\{V, B_{1_{\mathrm{Re}}}\}$ values. Then, any measured pair of $\{c_l, \alpha\}$ can specify a unique point location within the contours, which provides an immediate graphical estimate of the corresponding $\{V, B_{1_{\mathrm{Re}}}\}$. As an example, see Figure 1

allowed to have a few percent variations from the measured modulus B_{m} (because of the imprecision of measurements), as indicated in the lower two lines of eqn (8). In these expressions, the two unknowns are $B_{1_{\mathrm{Re}}}$ (the real part of the liver's bulk modulus) and V (the volume fraction of fat vesicles), which are linked to the composite modulus. The simulated annealing algorithm searches

measurements of SoS and AC for *in vivo* liver patients that are properly bounded by clinical studies reported in the literature, as entry values for the nomogram and the numerical inverse solution.

RESULTS

Speed of sound

Overall, hepatic SoS varied from 1470 to 1590 m/s depending on the underlying pathology. Normal liver SoS was approximately 1570 m/s, while fatty livers had lower SoS values. While Bamber and Hill (1981), Chen

Inverse solution

Figure 5 illustrates the numerical estimates from the 40 selected pairs of SoS and AC within the literature review indicating the estimated volume percentage V of fat as a function steatosis stages S0 to S3. A steady

these V values agree and correlate with the similar MRI-PDFF steatosis grades used in these two studies: S0 $\square$6.5%, S1 $<$ 16.5%, S2 $<$ 22% and S3 $\square$22%.

DISCUSSION

Both the nomogram approach and the inverse numerical solution approach produce reasonable agreement with independent assessments of hepatic fat. In particular, MRI-PDFF assesses the concentration of mobile triglycerides within the hepatic tissue (Caussy et al. 2018). It is an imaging biomarker that has excellent diag-

of bulk moduli used in the model. The variability of the bulk moduli of the fat/oil component between individuals is an area requiring further research. Furthermore, the model predicts that fibrosis within a steatotic liver is an important cofactor by means of changing the bulk modulus of the liver; however, this requires further study with independent confirmation of the degree of influence. The studies included in Tables 1 and 2 did not quantify fibrosis and so this remains a parameter requiring additional research for comparison against the predictions of the model. Also, the effects of other cofactors such as inflammation and high blood pressure have not been incorporated. Furthermore, we have centered our study around the common abdominal scanning frequency of 3.5 MHz; however, lower and higher center frequencies are available for obese and thin or small patients, respectively. The results will be strongly dependent on frequency as attenuation in liver is commonly expressed in terms of decibels per centimeter per megahertz (dB/cm/MHz); thus, a factor of 2 change in frequency will result in an (approximately) factor of 2 change in attenuation. In our model this is directly reflected in eqns (3) and (4) and the *a priori* estimate of the bulk modulus of fat in eqn (5). These will require further verification.

It is interesting to compare these results using ultrasound waves and bulk moduli against those obtained recently using shear waves and shear moduli (Ormachea and Parker 2021). The composite model and nomograms for each case have some similarities, but the precision required to accurately determine fat volume percentage V from the measured parameters differs. This is a larger subject that will require further refinement, but it is possible to speculate that a clinical scanner capable of four measurements (speed and attenuation from both ultrasound and shear waves) would be able to improve the final estimation of fat content by using both sets of solutions. This remains for future work as measurement capabilities increase in clinical scanners.

CONCLUSIONS

An analysis of the composite model of hepatic steatosis was performed, and a fat quantification of liver was achieved using the longitudinal (compressional) speed of sound and attenuation coefficient, with results in good

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