Determination of Normal Liver Stiffness by MR Elastography in Children

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1. ABSTRACT:

MR elastography (MRE) is playing a growing role in the non-invasive diagnosis and monitoring of liver disease in the pediatric population. There is, however, little data specific to the use of this technique in children with existing data and techniques largely extrapolated from adult studies. Existing studies suggest that liver stiffness values may be different between children and adults [Etchell, Xanthakos]. As such there is an unmet need for uniquely pediatric data in both healthy and diseased cohorts. To address the need for such data, we plan a multi-site, prospective study of healthy pediatric (<18 years of age) volunteers to determine normal liver stiffness measured by MR elastography across the range of MRI equipment.

2. PURPOSE OF STUDY:

The primary purpose of this study is to determine normal liver stiffness values (and associated normal ranges) as measured by MR elastography for two pediatric age groups.

Secondary purposes of this study include:

1. To assess for cross-platform (different MRI vendors) variability in normal MRI liver stiffness values.
2. To assess for cross-field strength (1.5T vs. 3T) variability in normal MRI liver stiffness values.
3. To assess for sex-related (male vs. female) differences in normal MRI liver stiffness values.

3. BACKGROUND:

Pediatric chronic liver disease encompasses both inherited and sporadic diseases, all of which have the potential to progress to liver fibrosis and may ultimately require liver transplantation due to cirrhosis or development of hepatocellular carcinoma. Non-alcoholic fatty liver disease (NAFLD) is rapidly eclipsing other causes of liver disease in the pediatric population and is now the second most common indication for liver transplantation in the adult population [Vos].

MR elastography is becoming increasingly available, and, alongside ultrasound elastography, is playing a growing role in the non-invasive diagnosis and monitoring of liver disease. There is an increasing body of literature demonstrating the diagnostic efficacy of MR elastography in adult patients. Studies at both 1.5 and 3T have demonstrated significant positive correlation between MRI liver stiffness and pathologic grades of liver fibrosis and significant predictive accuracy for discriminating significant from little to no fibrosis in a variety of disease states [Yin, Yoshimitsu, Kim]. MR elastography currently has advantages over other tissue elastographic techniques. These advantages include the ability to evaluate the liver in its entirety, ability to characterize tissue composition in terms of fat and iron content, and standardization

across manufacturer platforms, since the vast majority elastography hardware and software currently comes from a single company (Resoundant Inc.; Rochester, MN).

While MR elastography is being used in pediatric and young adult patients and is particularly attractive in this population due to its non-invasive nature (cf biopsy), the body of literature supporting its use in this population is relatively small. To date, the only uniquely pediatric study of MR elastography that has explored diagnostic performance of the technique is a study of 35 subjects, mean age of 13 years, with suspected liver disease who underwent both MRE and liver biopsy [Xanthakos]. That study by Xanthakos et al. found that a cut-off of 2.71 kPa provided optimal sensitivity (88%) and specificity (85%) for distinguishing F0-F1 (no to little) from F2-F4 (moderate to severe) fibrosis. Of note, this cut-off is lower than the mean stiffness values previously reported for F2 fibrosis in adult studies (3.87±1.85 kPa) raising the possibility that both normal and pathologic liver stiffness may differ between pediatric and adult patients (3). Importantly, there were no subjects without liver disease in this study by Xanthakos et al. to define normal liver stiffness values.

There is one prior study of healthy pediatric patients that included 35 subjects (24 between ages 5-14 years and 11 between ages 15-18 years)[Etchell]. That study demonstrated that normal liver stiffness values were lower for healthy pediatric subjects than for healthy adult subjects (2.2 vs. 2.6 kPa). The authors also found a slight significant correlation between age and liver stiffness (r=0.38) but failed to demonstrate a difference in liver stiffness between subjects ≤14 years of age versus >14 years of age. While this prior study provides some information about normal liver stiffness in the pediatric population, it has key limitations. First, this study was performed with nonstandard multi-frequency MR elastography. One of the frequencies that was utilized (56 Hz) is close to the standard 60 Hz MR elastography utilized for clinical MRE, but differences in frequency utilized to measure tissue stiffness are known to influence liver stiffness measurements and thus normative data from this study may not apply to MR elastography performed with manufacturer standard technique. Second, the subjects imaged in this study were not fasting at the time of MR imaging. There are conflicting data regarding the effect of fasting (or lack thereof) on measured liver stiffness with some studies showing a stiffening effect of increased post-prandial splanchnic blood flow [Hines, Lemoine, Yin]. Third, while the subjects included in this study had no “known history of liver disease” MR fat fractions were not measured and serum liver function tests were not checked to confirm liver health. Finally, all examinations in this prior study were performed on a single manufacturer MR platform and at a single field strength, possibly limiting generalizability across other platforms.

MR elastography is a rapidly evolving technique and sequence improvements are constantly being developed. Additionally, new MRI techniques for assessment of diffuse liver disease are constantly being developed. At CCHMC only, additional imaging data will be acquired for exploratory aims related to these newer techniques.

4. STUDY DESIGN:

Study aims and hypotheses are as follows:

Primary aim/hypothesis – To determine normal liver stiffness values (and associated normal ranges) as measured by MR elastography for two pediatric age groups. We hypothesize that normal liver stiffness as measured by MR elastography will differ between the two pediatric age groups, increasing with increasing age.

To achieve the primary aim, MR elastography will be performed in up to 104 healthy children, somewhat evenly divided (approximately 48 each) into two age groups (7-<12years, 12-<18years). Means, standard deviations and 95% confidence intervals for normal liver stiffness will be calculated for each age group and values will be compared across groups.

Multi-site secondary aims and hypotheses are as follows:

1. To assess cross-platform variability in normal MRI liver stiffness values. We hypothesize that there will be no significant difference in mean normal liver stiffness values obtained on three different vendor platforms (GE, Philips, Siemens).
2. To assess for cross-field strength variability in normal MRI liver stiffness values. We hypothesize that there will be no significant difference in mean normal liver stiffness values obtained at 1.5T versus 3T.
3. To assess for sex-related (male vs. female) differences in normal MRI liver stiffness values. We hypothesize that there will be no sex-related differences in normal liver stiffness measured by MR elastography.

To achieve secondary aim #1, subject recruitment will be stratified across sites with approximately 32 subjects in each age group being imaged on each of the different vendor platforms (GE, Philips, Siemens). To achieve secondary aim #2, subject recruitment will be stratified across 1.5T and 3T magnets with approximately 48 subjects in each age group being imaged at each of the different field strengths. To achieve secondary aim #3, approximately equal numbers of male and female subjects will be recruited in each of the two age groups.

CCHMC exploratory aims and hypotheses are as follows:

1. To determine normal corrected T1 (cT1) values for two pediatric age groups. We hypothesize that there will be no significant difference in mean cT1 values between age groups or between field strengths.

Overall research strategy:

We propose to conduct a multi-institutional study of normal liver stiffness values in pediatric subjects with no known history of liver disease. The requirement for multiple sites relates to the need to acquire normative stiffness values on each of the three major MRI vendor platforms to assess for unexpected cross-platform variability in liver stiffness. CCHMC has Philips MRI scanners (1.5 and 3T) equipped with MR elastography but does not have access to GE or Siemens MRI scanners in a research environment. Massachusetts General Hospital (MGH) has an elastography capable GE scanner (1.5T), Children's Hospital of Philadelphia (CHOP) has elastography-capable GE and Siemens scanners (3T), and Mallinckrodt Institute of Radiology (MIR) has an

elastography-capable Siemens scanner (1.5T). This human study protocol will be submitted for approval to the Institutional Review Board at CCHMC. CCHMC will serve as the lead site. CHOP, MGH and MIR may choose to submit to their IRB or to rely on the CCHMC IRB.

Power calculation relevant to SA1: Determine normal liver stiffness values (and associated normal ranges) as measured by MR elastography for three pediatric age groups: Based on the standard deviation of normal liver stiffness measurements in the study by Etchell et al. (SD=0.3 kPa) and the confidence intervals from a study of healthy adult livers by Lee et al. (95% CI ~±0.1 kPa), we calculate that a sample size of n=18 is needed in each group to achieve 2-sided 95% confidence intervals with a distance from the mean to the limits that is equal to 0.15 kPa for each group [Etchell, Lee]. This sample size also provides 80% power to detect an effect size (Cohen's d) of 0.67 between the two age groups. Given the prior study findings of a correlation between subject age and liver stiffness, we will recruit into two subject age groups (7-<12years, 12-<18years). Based on prior published and unpublished MRI studies of "healthy volunteers" at CCHMC, we expect up to 25% of "healthy subjects" recruited for this study will have unsuspected liver disease manifest as abnormalities in liver function tests or liver fat fraction values greater than 5% by MRI proton density fat fraction (PDFF) (12). Therefore, we will increase recruitment targets by 25% over the levels required to achieve adequate statistical power. Thus, approximately 24 subjects will be recruited to each group at each field strength for a total study recruitment of n= up to 104.

MR imaging:
All imaging will be performed using multi-channel phased-array torso coil. MR elastography will be performed utilizing the manufacturer product MRE sequence (generally 2D gradient recalled echo at 1.5T and 2D spin echo echo-planar imaging at 3T) and the manufacturer standard 60 Hz frequency. For the GRE sequence, driver amplitude will be adjusted based on patient weight (no adjustment required for SE-EPI). Per standard protocol, four axial slices will be acquired through the bulk of the central liver. PDFF sequences will be performed per manufacturer recommended settings. Total imaging time will be less than 15 minutes per examination and will be accomplished with approximately six breath holds.

Sequences acquired will include:

1. 3-plane localizer
2. MR elastography (manufacturer recommended)
3. PDFF sequence
4. Axial T2-weighted single-shot fast spin-echo (anatomic sequence)

Driver amplitude will be adjusted as follows for the GRE sequence:
GRE:

Patient weight	**Amplitude**
40-49 kg	40%
50-59 kg	50%

60-69 kg	60%
70-79 kg	70%
80-89 kg	80%
90-99 kg	90%
100+ kg	100%

Additional sequences will be acquired at CCHMC only. These will extend the total imaging time to up to 30 minutes and add additional breath holds.

5. Corrected T1

MR exam post-processing:
All PDFF and MR elastography images will be processed both locally and centrally at a single site (CCHMC) by a single trained observer to ensure uniformity in post-processing technique. Post-processing will be performed as previously described with placement of single large regions of interest in the right hepatic lobe (12). Central MR elastography data will be post-processed using MRE Lab (Mayo Clinic, Rochester, MN) and PDFF data will be post-processed using Philips Intellispace (Philips Healthcare, Best, The Netherlands).

De-identified cT1 data acquired at CCHMC only will be sent to Perspectum Diagnostics for analysis.

5. DURATION:
18 months: 1 year for subject accrual, 6 months for analysis and write-up

6. SELECTION & RECRUITMENT OF PARTICIPANTS:
Healthy pediatric subjects without a known history of liver disease will be recruited via advertising through established hospital channels (e.g. email) and posted flyers and/or posters at each of the study sites. Based on prior studies of normal subjects at CCHMC, we anticipate no difficulty recruiting the required number of subjects for this study. For a prior study of pancreatic function in normal subjects that required MRI and placement of an intravenous catheter, 142 responses expressing interest in participating in the study were received within 4 days of study announcement.

For each age group, MRI vendor and field strength, approximately half the recruited subjects will be male and half will be female. CCHMC will recruit a total of 32 subjects (16 male, 16 female), CHOP will recruit up to 40 subjects (approximately 20 male, 20 female), and MIR and MGH will each recruit a total of 16 subjects (8 male, 8 female).

Inclusion criteria:

1. Age 7-less than 18 years of age
2. No documented history of liver disease
3. English speaking*

Exclusion criteria:

1. NPO less than 4 hours

2. Body mass index < 10th or > 85th percentile for age
3. Documented history of liver disease
4. Pregnancy
5. Inability to lie still for duration of the MRI
6. Inability to breath hold for the duration of the 15-20 second MR elastography sequence
7. Standard contraindication to MRI (implanted hardware, etc.)
8. Requirement of sedation or general anesthesia for MRI
9. Abnormality of any prior measured liver function test**
10. Any prior liver fat fraction > 5% by MRI PDFF**

*English speaking has been included as an inclusion criterion as successful performance of an MRE examination requires following detailed and repeated breath hold instructions. This is a multicenter study and interpreter services are not uniformly available in the imaging research environment across participating institutions.
**Research results meeting this exclusion will eliminate subjects from population analysis

7. PROCESS OF OBTAINING CONSENT:
Participants will be screened in advance of enrollment by study personnel to determine baseline eligibility for participation. Once eligibility has been confirmed, written informed consent will be obtained in person at the time of the research visit.

Written informed consent will be obtained in person from parents/guardians of subjects <18 years of age. In addition to parent/guardian informed consent, assent will be obtained from all subjects ≥11. Consent or assent may be obtained by study personnel inclusive of the PI, Co-Is or clinical research coordinator(s).

8. STUDY PROCEDURES:
To confirm “healthy status” and the absence of liver disease, subjects will be weighed and measured (height and waist circumference) prior to the research MRI.

Subjects will be surveyed about liver health using a survey created with the assistance of the study hepatologist and medical records (if available) will be reviewed to exclude documented liver disease (ATTACHMENT A).

Subjects will also undergo a research venous blood draw to confirm absence of elevation of markers of liver health inclusive of: AST, ALT, GGT, alkaline phosphatase, total and direct bilirubin. This research blood draw will require 2.5 mL of venous blood and will occur prior to or following the research MRI. At CCHMC the research blood draw will occur in the Schubert Research Center by SRC nursing staff. In addition, the research MRI will include a PDFF sequence to measure liver fat fraction in all subjects to identify previously unknown fatty liver disease.

Study visit structure (single visit):
1. Intake survey and anthropomorphic measurements

2. MRI safety screening
3. Research MRI exam
4. Research blood draw

Drugs, Devices, and Biologics:
MR elastography equipment consists of an active and a passive driver system. The passive driver is connected to the active driver in the equipment room by a wave-guide with a hollow plastic tube. The active driver generates low amplitude (60 Hz) vibrations which are passed via pneumatic pressure to the passive driver. The initiation and cessation of the vibrations are controlled by the MR pulse sequence programmed and embedded as part of the scanner software. All MRE pulse sequences and hardware to be used for this study are sold as product by the MR vendors or an aftermarket company (Resoundant, Inc.) and all are FDA approved.

The other MRI sequences to be utilized in this study (anatomic, PDFF) are FDA approved sequences sold as product by the MRI hardware vendors.

9. DATA ANALYSIS/METHODS:
All PDFF and MR elastography images will be processed both locally and centrally at a single site (CCHMC) by a single trained observer to ensure uniformity in post-processing technique. Post-processing will be performed as previously described with placement of single large regions of interest in the right hepatic lobe (12). Central MR elastography data will be post-processed using MRE Lab (Mayo Clinic, Rochester, MN) and PDFF data will be post-processed using Philips Intellispace (Philips Healthcare, Best, The Netherlands).

De-identified cT1 data acquired at CCHMC only will be sent to Perspectum Diagnostics for analysis.

Descriptive statistics will be utilized to describe the characteristics of each subject group (age, sex, scanner manufacturer, field strength). Normal liver stiffness for each age group will be summarized as mean ± std with range and 95% confidence interval also provided. Two sample t-test or one-way analysis of variance (ANOVA) will be used to assess for differences in liver stiffness between age groups and between different groups of categorical variables (sex, scanner manufacturer, field strength). The correlation between liver stiffness and continuous variables will be assessed by using Pearson on Spearman correlation coefficients as appropriate. Multiple linear regression models will be utilized to evaluate the association between liver stiffness and the predictor variables adjusting for all other covariates. Box plots will be generated to visually illustrate the results from the group comparisons mentioned above. All analyses will be performed using SAS version 9.4. A p-value less than 0.05 will be considered statistically significant for all inference testing.

10. FACILITIES and PERFORMANCE SITES:
Research blood draws will occur in the Schubert Research Clinic. All other study procedures will occur in the CCHMC Imaging Research Center (IRC).

11. POTENTIAL BENEFITS:
There are no direct benefits to study participants. This research, however, is critical for our understanding of normal MRE values in children which are relevant to the diagnosis of disease utilizing MRE. Therefore this research has potential future benefit to children with known or suspected liver disease.

12. POTENTIAL RISKS, DISCOMFORTS, INCONVENIENCES AND PRECAUTIONS:
There are no known risks from having an MRI or from use of the sequences being investigated for appropriately screened patients. However, some people are claustrophobic and may become anxious, fearful, or nervous in the scanner. Should participants become uncomfortable at any time the scan will be stopped immediately. Should any previously unknown risks related to having an MR examination be identified during the course of this study, that information will be relayed from individual site PIs to the lead PI at CCHMC and participants will be informed of those risks.

A board-certified radiologist will review the MRI exam. Any unexpected finding requiring further medical evaluation will be shared with the participant and/or the participant's physician. For any finding deemed not related to the study there will be no further follow-up by the study team. The research MRI exam will be identified by a number assigned as a part of the research study and will not become a part of the participant's permanent medical record.

There are no specific risks to pregnant patients from having the short MRI examination as part of this study.

Research blood draws may be associated with transient mild discomfort and the potential for mild bruising or fainting.

There is minimal risk of loss of confidentiality through study participation (see PRIVACY AND CONFIDENTIALITY BELOW).

13. RISK/BENEFIT ANALYSIS:
This study is minimal risk with no direct benefit to study participants. The primary risks relate to physical discomfort (blood draw, possibly MRI) and potential loss of confidentiality.

14. DATA SAFETY & MONITORING: *
No formal data safety monitoring board will be appointed for this minimal risk study. Adverse events related to study procedures will be monitored by site PIs/study coordinators, recorded and reported to the overall study PI (CCHMC).

15. PRIVACY and CONFIDENTIALITY:
Each subject will be assigned a site-specific study ID number. Password-protected tables will be maintained at each study site that link the study ID number to the medical record number. This table will be maintained on a secure server or in a locked file cabinet, as appropriate. Identifying data will be saved in a password-protected

spreadsheets at the individual study sites. Any data that are extracted from the database and used for research will be subject to standard data protection practices. Only de-identified patient data (including study ID numbers) and de-identified imaging data will be transmitted from the individual study sites to CCHMC for central analysis. Only de-identified patient data will be shared with Perspectum Diagnostics.

16. COST OF PARTICIPATION: *

There will be no cost to study participants. Study charges will be covered by grant support.

17. PAYMENT FOR PARTICIPATION:

Subjects will receive $50 for participation to cover time and expenses.

18. REFERENCES:

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