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PANCREAS

3D MR elastography of the pancreas in children

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Abstract

Purpose Early diagnosis of chronic pancreatitis (CP) remains elusive. Preliminary data suggest that MR elastography (MRE) may have diagnostic value in the identification of CP. We sought to measure pancreas stiffness by MRE in healthy children and to compare measured values to stiffness values in pediatric patients with acute recurrent pancreatitis (ARP) or CP.

Methods Under IRB approval, 49 healthy controls volunteered to be included, and 14 patients with ARP or CP that underwent 3D MRE on a 1.5T MR scanner were included in the study. A soft passive driver was utilized and vibrated at 40 Hz. Regions of interest for measurement of pancreatic stiffness were drawn by two blinded readers and statistical analysis were performed for comparisons between the two groups.

Results Mean age of the healthy controls was 11 ± 2.7 years and mean pancreas stiffness was 1.7 ± 0.3 (Reader 1) and 1.7 ± 0.3 (Reader 2) kPa. For patients with ARP or CP, mean age was 12.6 ± 4.4 years and mean pancreas stiffness was 0.9 ± 0.2 (Reader 1) and 1.1 ± 0.3 (Reader 2) kPa. Pancreas stiffness was significantly lower in patients with ARP and CP as compared to healthy controls ($p < 0.001$). Between readers, there was a strong and statistically significant agreement on measured pancreas stiffness ($r = 0.81$; $p < 0.001$). Bland–Altman difference analysis showed a mean bias of only 0.05 kPa (95% limits of agreement: -0.49 to $+0.58$)

Conclusion MRE of the pancreas can be performed in pediatric patients. Through this study, we have defined normal pancreas stiffness for children and have shown decreases in measured stiffness in patients with ARP or CP compared to healthy controls.

Clinical relevance 3D MRE of the pancreas offers a novel approach for detecting pancreatic disease based on changes in tissue mechanical properties.

Keywords Magnetic resonance imaging · MR elastography · Pancreas · MRE · 3D MRE · Pancreas MRE · Pancreas stiffness · MR elastography of pancreas · Pediatric · Children adolescents

Introduction

Chronic pancreatitis (CP) and acute recurrent pancreatitis (ARP) reflect repeated episodes of inflammation of the pancreas, ultimately leading to end organ damage representing parenchymal loss, fibrosis, and decreased exocrine and/or endocrine pancreatic function [1]. Exocrine pancreatic insufficiency (EPI) can have serious sequelae including malnutrition, bone disease, and growth failure if not promptly diagnosed and treated [2]. Unfortunately, diagnosing CP and EPI early and accurately remains a challenge but is critical to allow early intervention with medications, endoscopic therapies, or surgery. Imaging findings of CP including parenchymal loss/atrophy, parenchymal changes including T1 signal loss and calcification, and duct dilation and irregularity/strictures are typically late findings. Similarly, diagnosis of

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EPI is typically a late finding in the CP course when patients present with symptoms including malabsorption and failure to thrive.

Biomarkers of early CP and EPI are actively being sought and non-invasive biomarkers are of particularly interest given that the reference standard testing for EPI as a marker of CP with endoscopic pancreatic function testing [3]. Magnetic resonance elastography (MRE) is a non-invasive means of measuring tissue stiffness, which has been correlated to fibrosis, and is thus an attractive potential biomarker for CP [4, 5].

There are a few initial reports describing use of MRE in the assessment of the pancreas in adults [6–8]. One study has shown some predictive accuracy of MRE for detecting and classifying CP [8]. Notably, there is some suggestion that pancreatic stiffness as measured by MRE depends on patient age, at least in adults [9]. To our knowledge, there has been no exploration of the use of pancreatic MRE in the pediatric population, in whom non-invasive assessment of pancreatic disease would be particularly needed.

The purpose of this study was to define normal pancreatic stiffness as measured by MRE in a pediatric population with no known history of pancreatic disease ('healthy controls') and to describe early application of the technique in pediatric patients with ARP or CP.

Methods

Institutional review board (IRB) approval was obtained for both the healthy control and pancreatitis arms of this study. The healthy control arm was conducted prospectively with written informed consent obtained from parents/guardians and assent obtained from all participants ≥ 11 years of age. The pancreatic disease arm of this study was a retrospective review of clinically indicated imaging with a waiver of informed consent granted as part of IRB approval. All study activities were performed in a Health Insurance Portability and Accountability Act-compliant manner.

Experimental set up

The healthy controls described in this study were ages 6 to less than 16 years and also underwent secretin-stimulated magnetic resonance cholangiopancreatography (MRCP) which has previously been reported [10]. The patients with pancreatitis in this study were undergoing clinically indicated MR examinations with MRE performed as part of that examination. ARP was defined as the presence of at least two episodes of pancreatitis. All clinically indicated MR examinations were performed between May 2016 and March 2018.

All MR examinations for both arms of this study were performed on a 1.5T MR scanner (HDx, GE Healthcare, WI, USA). All study participants fasted for ≥ 4 h prior to their imaging examination. Participants were scanned in supine position, typically positioned feet first. A soft pillow-like passive driver, different from the standard MRE passive driver was positioned at the level of the subxyphoid abdomen and was secured in place by a 20-cm wide elastic band (Fig. 1). Pediatric subjects were prepared in advance for the sensation of paddle vibrations [11]. An external, eight channel phased-array cardiac/abdomen radiofrequency (RF) coil was used for signal reception. Low amplitude mechanical waves at 40 Hz frequency were generated in the upper abdomen using an active acoustic driver placed outside the scanner room (Resoundant Inc., Rochester, MN). 40 Hz was utilized based on the study by Shi et al. [6] in which the authors reported that reproducible measurements of pancreas stiffness could be acquired at 40 Hz.

Image acquisition

An accurate and reproducible stiffness measurement of the pancreas, given its small size, and deeply seated location, requires 3D analysis of wave field data [6]. For this reason, 3D MRE was utilized for all study imaging. In 3D MRE, the propagating shear waves are imaged with a 2D multi-slice spin-echo echo planar imaging (SE-EPI) pulse sequence modified to include the motion encoding gradients (MEG) in the X, Y and Z directions. This is different from the 2D MRE typically utilized for liver imaging in which motion is encoded only in a single direction [11]. Imaging protocol details are listed in Table 1.

For the purpose of this study, axial slices through the pancreas were prescribed on the coronal localizer images. Motion encoding gradients (MEG) were applied to spatially encode in-plane and through plane components of motion in separate breath holds. The acquisition time for each encoding direction was about 8 to 10 s. Immediately after acquisition, stiffness maps were automatically generated on the scanner by an in-line post-processing script. Confidence maps were also automatically generated and overlaid on the elastograms. The confidence map is a standardized estimate of data quality based on a statistical measure of model fit performance that is provided in all commercial versions of MRE.

Image analysis

Images were visually evaluated for presence of any artifacts. Guided by side by side comparison of slice-matched anatomic images, regions of interest (ROI) were drawn on the elastograms by two independent readers blinded to each other (One reader with 8+ years of experience processing MRE images and other a board certified pediatric body radiologist with 5+ years of pediatric radiology experience).

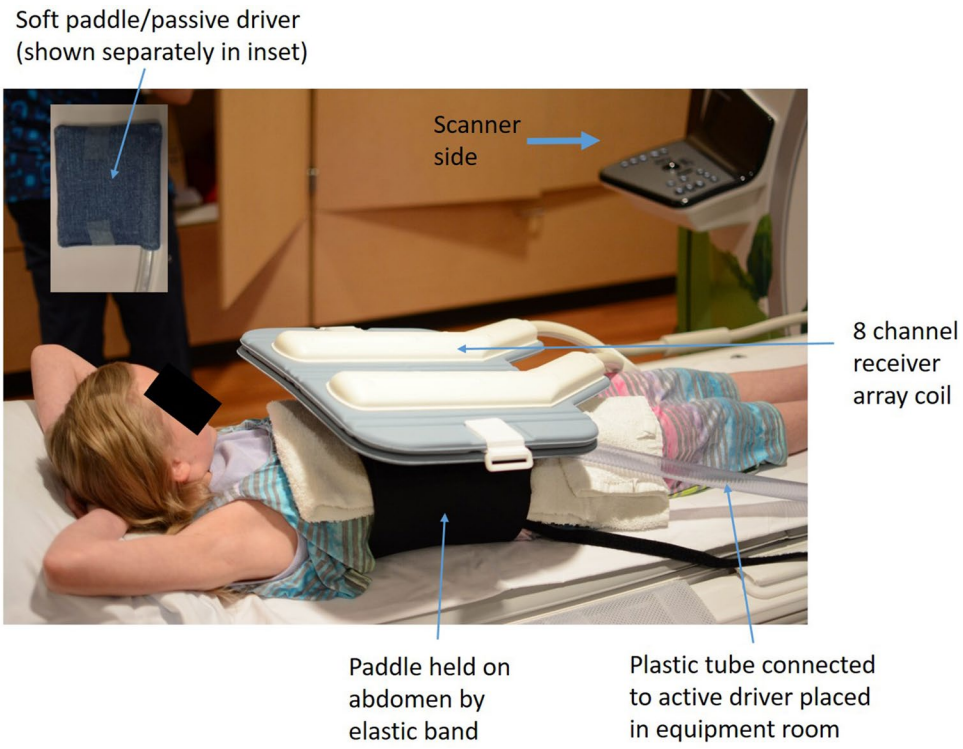

Fig. 1 MRE of the Pancreas–patient setup up to scan supine, feet first. A soft passive driver (shown in insert) is placed on the abdomen centered at the epigastrium region, close to the pancreas and was secured in place by a 20-cm wide elastic band wrapped around it. The passive driver is connected to the active driver placed in the equipment room via a plastic tube. The active driver transmits low-frequency sound waves via an audio subwoofer. A multi-channel recieving radiofrequency coil is placed on top

Table 1 Imaging protocol parameters

Parameter	3D MRE of pancreas
Pulse sequence type	2D SE-EPI
Matrix	96 × 96
No. of averages	1
No. of EPI shots	1
TR (ms)	2400
TE (ms)	Minimum
No. of slices	42
Slice thickness (mm)	3.6
Gap (mm)	0, Interleave
No. of phases	3
MEG frequency (Hz)	120
Wave frequency (Hz)	40
No. of breath holds	6
Acceleration factor	3
Driver amplitude range	30–50%

Technical failure of MRE was defined as the absence of visualized wave propagation on the wave images and/or no pixel value with a confidence index higher than 95% on the confidence map. ROIs were drawn to include as much of the pancreas as possible while staying 1 mm or more inside the margins of the pancreas and while also staying in areas demarcated by the scanner-produced confidence maps as "good" data [12]. The corresponding magnitude image and wave images were used as a guide. The average of the value in the ROIs was recorded. For statistical comparisons, stiffness was expressed as a mean of mean stiffness values measured on each section (in kilopascals, kPa).

Statistical analysis

Pancreas shear stiffness values were expressed as means and standard deviations (SD) in kilopascals. T-tests were used for comparisons of means, Pearson correlation was used for correlation analysis and Bland–Altman analysis was used for comparison of stiffness values measured by the two readers. Data analysis was performed using Medcalc (Medcalc, Ostend, Belgium). A p value of less than 0.05 was considered statistically significant for all inference testing.

Results

Patient characteristics

Of the 50 healthy controls recruited, complete MRE data were available for 49 subjects. Mean age was 11 ± 2.7 years and 28 were female. For the 14 patients with ARP or CP, mean age was 12.6 ± 4.4 years and 8 were female.

MR elastography

Mean pancreas shear stiffness measured by readers 1 and 2 in both the healthy controls and patients with pancreatitis

are presented in Table 2. Among the healthy controls, age ($r = 0.07$, $p = 0.54$) and gender ($p = 0.73$) were not significantly associated with pancreas stiffness. Representative images of a 10 year old healthy control and a 11 year old patient with history of CP are shown in Fig. 2. Compared to the healthy controls, pancreas stiffness was significantly lower in patients with ARP or CP ($p < 0.0001$) (Fig. 3).

Table 2 Patient demographics and pancreas stiffness values measured by two readers

	Healthy controls	Patients with pancreatitis
Number of individuals	49	19
Age range (years)	6.3–15.9	5.5–19.6
Gender (male/female)	21 boys, 28 girls	11 boys, 8 girls
Reader 1		
Mean pancreas stiffness (kPa) ± SD	1.7 ± 0.3	0.9 ± 0.2
Median pancreas stiffness (kPa)	1.7	0.8
Range of pancreas stiffness (kPa)	1.1–2.5	0.5–1.7
Reader 2		
Mean pancreas stiffness (kPa) ± SD	1.7 ± 0.3	1.1 ± 0.3
Median pancreas stiffness (kPa)	1.7	1.1
Range of pancreas stiffness (kPa)	1.0–2.6	0.9–2.4

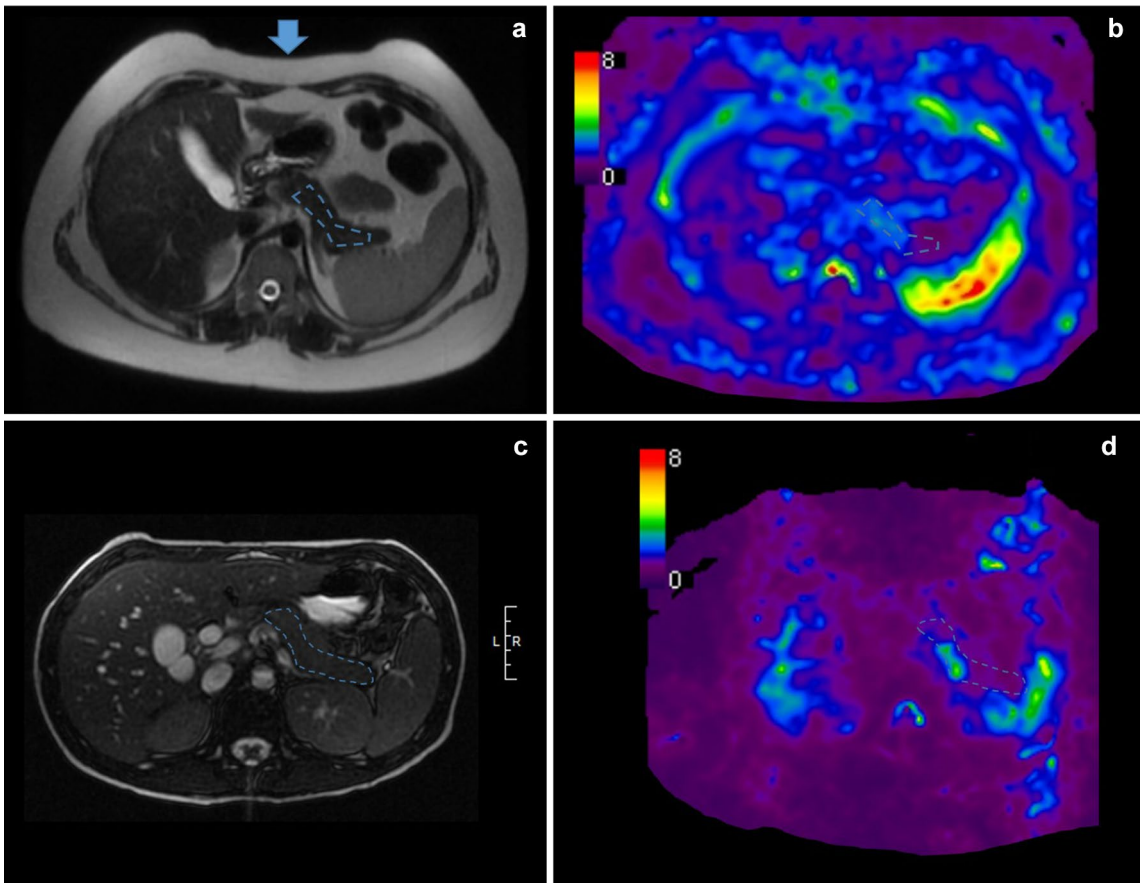

Fig. 2 Interpretation of elastograms from representative cases, a 10 year old 'healthy control' (pancreas stiffness = 2.5 kPa). **a** Axial T2 W single shot. **b** Shear stiffness map demonstrating shear stiffness maps from MRE; and representative images of a 11 year old patient presented with history of patient with CP from our cohort demonstrating regressing mean stiffness value (pancreas stiffness = 1.1 kPa). **c** Axial SSFP image, and **d** Shear stiffness map. Arrow shows indentation due to placement of passive driver and dotted lines show closely matched ROI locations

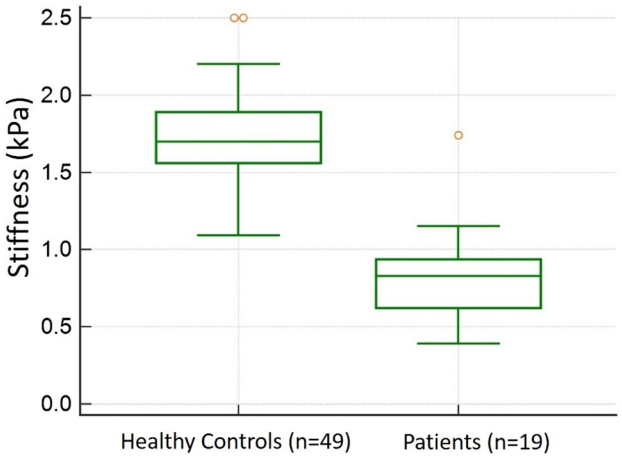

Fig. 3 Box plots showing relationship between MRE derived pancreas stiffness values measured in 'healthy controls' ($n=49$) vs patients with pancreatitis ($n=19$). Horizontal lines within boxes represent medians, and vertical lines and whiskers represent lowest and highest observations within 1.5 interquartile ranges of lower and upper quartiles, respectively. Pancreas stiffness was significantly lower in patients with pancreatitis vs controls ($p<0.0001$). The data points with the circles are values that fall outside the 1.5 interquartile range but within 3 interquartile range

Between readers, there was a strong agreement on measured pancreas stiffness ($r=0.81$; $p<0.001$) (Fig. 4). Bland–Altman difference analysis (Fig. 5) showed a mean bias of only 0.05 kPa (95% limits of agreement: − 0.49 to + 0.58) between readers.

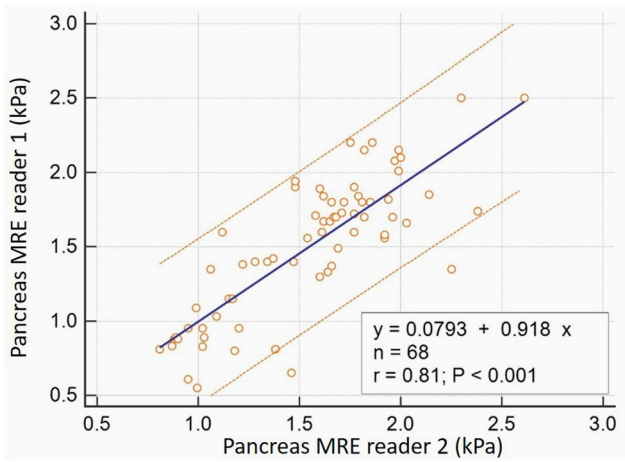

Fig. 4 Scatterplot of pancreas stiffness measurements by two independent readers ($r=0.81$; $p<0.001$)

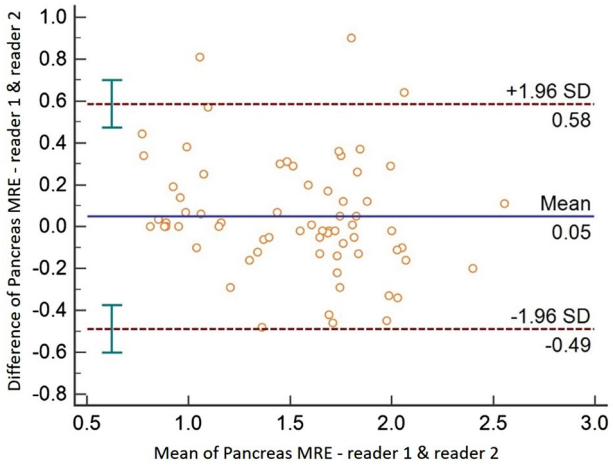

Fig. 5 Bland-Altman difference plot of pancreas stiffness measurements made by two blinded readers. Mean bias between readers was 0.05 kPa (95% limits of agreement: − 0.49 to + 0.58 kPa)

Discussion

CP is increasingly being recognized in the pediatric population [13]. CP ultimately leads to irreversible damage to the pancreas with resultant loss of digestive function EPI or diabetes [14]. If diagnosed early, however, effective treatment options may be considered to slow the progression of disease or even prevent irreversible damage. The problem is, currently available non-invasive diagnostic modalities, including imaging, typically can only make a diagnosis late in the progression CP when irreversible damage has taken place [1]. Consequently, there is a significant need for non-invasive means of diagnosing earlier stage CP.

MRE has been demonstrated to detect hepatic fibrosis in a screening capacity and thus might be leveraged to detect pancreatic fibrosis, as a component of CP [11, 15]. 3D MRE of the pancreas has previously been demonstrated to be feasible and has been shown to have high test–retest reliability in adults [6, 7]. To our knowledge, MRE of the pancreas has not been described in a pediatric population in whom non-invasive diagnostic modalities would be particularly valuable. In this study we have shown a high rate of technical success for MRE of the pancreas in children.

In our population of healthy volunteers we have defined normal stiffness values for children and we have shown that age and sex do not significantly impact pancreas stiffness. This is in contrast to a study by Kolipaka et al. of 22 healthy adult volunteers (age range 22–64 years) in which the authors reported a significant association between pancreatic shear stiffness, measured at 60 Hz, and age with stiffness increasing by up to 0.8 kPa with increasing age [9]. Scatter plots from that study show appreciable increases in pancreas stiffness from age 30 onward. In our data we did not observe any relation

of pancreas stiffness vs age. The cause of this discrepancy is uncertain given limited data at this time. It may be the case that increasing stiffness reflects senescent changes of the pancreas that do not manifest until older age.

The stiffness values seen in our healthy control population are somewhat higher than those reported by Shi et al. [6] who reported a mean pancreas stiffness of 1.1 kPa at 40 Hz in 20 healthy adults (mean age: 34 years). A subsequent study of 35 healthy adults by Wang et al., reported mean pancreas stiffness to be 1.2 kPa [8]. Mean stiffness value in our healthy and dedicated pediatric population is slightly greater but in the same range as reported in these prior studies (1.7 kPa).

Further, we have shown statistically significantly lower pancreas stiffness values in patients with a history of CP as compared to healthy controls (1 kPa vs. 1.7 kPa). This result conflicts with a study by H. An et al., that included five healthy adult volunteers and five adult patients with CP (mean age of 55.6 years) [7]. In that study, a mean stiffness value of 1.1 kPa was reported for healthy controls, slightly lower than the value seen in our population, compared to a mean stiffness of 1.5 kPa in the five patients with CP [7]. Further in the study by Wang et al. the authors reported mean stiffness values of 1.5 and 1.9 kPa in 30 and 16 adults with mild and moderate to severe CP as classified by the Cambridge Criteria [8]. Both of these studies in adult subjects reported stiffness values in patients with CP higher than the values in healthy patients in the same study (1.2 kPa). In our dedicated pediatric study, we observed patients with CP or ARP had stiffness values that were lower than healthy controls. The cause for the discrepant results between our pediatric study and these prior adult studies is uncertain.

In this study we also looked at agreement between readers on measured pancreas stiffness by MRE. In our population, with two blinded readers, we found strong agreement ($r = 0.81$; $p < 0.001$) between measurements showing high reproducibility between readers.

While our study adds to the body of literature regarding MRE of the pancreas, particularly in younger patients, it does have limitations. First, the patient arm of the study was retrospective and included only a small number of patients. Second, diagnosis ARP and CP was based on a chart review. Finally, the MRE data were acquired using more than one breath hold to allow for motion encoding in three directions, multiple breatholds may be a limiting factor for wide application of this technique, particularly in patients that are unable to perform or maintain consistent breath holds.

Conclusion

Our data suggest that it is feasible to perform MRE of the pancreas in the pediatric population, including those with ARP and CP. We have defined what can likely be considered a normal stiffness value for the pediatric pancreas and have shown, that in children, measured stiffness is lower in ARP and CP compared to healthy controls. Further studies to validate our findings in a large population will be needed in future.

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