MRCP: A Reliable, Non Invasive Method for Staging Chronic Pancreatitis in Pediatrics

Protocol Document

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STUDY TITLE: Magnetic Resonance Cholangiopancreatography (MRCP) A Reliable, Non Invasive Method for Staging Chronic pancreatitis from Minimal Change Disease to the Advanced Stages in Pediatrics

ABSTRACT:

Introduction/Methods: Pancreatic fibrosis is the end stage of chronic pancreatitis (CP), which leads to loss of acinar volume and secretory capacity, and ultimately pancreatic insufficiency (PI). CP and congenital PI affect the pediatric population, and are both increasingly recognized in children. PI has serious negative implications on a child's growth and health but, if diagnosed early, PI can be treated, minimizing the detrimental effects of PI. Currently, direct pancreatic function testing (PFT) via collection of pancreatic fluid is the "gold standard" for diagnosis of PI but it is an invasive testing that may require sedation or general anesthesia. Magnetic resonance cholangiopancreatography (MRCP) with secretin administration (MR-PFT) and MR elastography (MRE) may allow non-invasive, and potentially early diagnosis of CP and PI. Currently, however, normative data with which to compare MR-PFT and MRE results in pediatric patients with suspected CP/PI is not available. **Aims:** Herein, we propose to determine the normal range for secreted pancreatic fluid volume in response to secretin administration and determine the normal range for pancreatic parenchymal stiffness in a pediatric population that is not affected by pancreatic disease. Additionally, we will assess visibility of the pancreatic duct pre and post administration of secretin. To date, we have validated our MRCP technique and have successfully performed both MR-PFT and MRE in CP patients; however normative data is essential for validation of our non-invasive technique. **Conclusion:** Normative pediatric data derived from this study will provide a baseline against which future studies of pediatric patients with suspected CP and PI can be assessed. Additionally, the techniques described herein might also be leveraged in the future in the adult population.

PURPOSE OF STUDY:

Collect normative data for pancreatic state (the size, volume, anatomy, biliary and vascular structures) as well as the volume of secreted fluid in response to secretin administration in a representative sample of healthy pediatric controls.

Determine secreted volumes: *Hypothesis 1.* Total secreted fluid volume as measured by MR-PFT will correlate with subject size and age. *Exp 1.* MR-PFT will be performed in 50 healthy pediatric subjects including 25 subjects ages 6-11.9 years and 25 subjects 12-15.9 years. Secreted volumes will be correlated with subject age and height, weight, body mass index and body surface area.

Collect normative data for pancreatic stiffness as measured by MR elastography. *Hypothesis 2.* Pancreatic parenchymal stiffness in the pediatric population will fall in a normative range similar to adult norms and will not depend on subject age or size. *Exp 2.* Pancreatic parenchymal stiffness will be measured in the same healthy cohort of 50 healthy pediatric subjects including 25 subjects ages 6-11.9 years and 25 subjects 12-15.9 years.

Assess the relationship between pancreatic exocrine function, pancreatic stiffness and pancreatic parenchymal volume. *Hypothesis 3.* Pancreatic exocrine function as measured by MR-PFT and pancreatic stiffness as measured by MRE will be dependent on pancreatic parenchymal volume. *Exp 3.* Secreted fluid volumes as measured by MR-PFT and pancreatic

stiffness as measured by MRE will be correlated with volumetric measurements of pancreatic parenchymal volume.

Assess the effect of secretin on the visibility of the pancreatic duct. *Hypothesis 4***.** A subjective, blinded assessment of pancreatic duct visibility pre-and post-secretin will show an increase in visibility on post-secretin images.

We will also store this data to identify normative values in controls for pancreatic and any other gastrointestinal parameters in MRCP.

Significance and Innovation:
Our study will add significant information to the existing literature regarding diagnosis and staging of CP, and will set the foundation for using MR as a non-invasive biomarker for CP/PI in pediatrics. Our study is novel because it will investigate the use of MRI for assessing pancreatic anatomy, function, and stiffness in the pediatric population. It will also shed light on gastrointestinal anatomy and function in pediatric healthy controls which has not yet been described in the literature. Moreover, the results of our study will fill a knowledge gap regarding normal secretory function of the pancreas in children.

BACKGROUND:

Chronic pancreatitis (CP) is a morbid condition with poor quality of life, significant pain, and negative impact on growth, health and overall wellbeing [1-4]. Late stages of the disease, manifest as parenchymal fibrosis and loss of function (pancreatic insufficiency (PI)), are easier to diagnose than mild and early stages (minimal change disease). If CP is recognized early, therapies to treat mild disease and halt the progression to PI could be applied [5-8]. As such, studies geared toward early detection are needed to identify minimal change disease and allow early therapeutic intervention. Once PI is suspected, direct pancreatic function testing (PFT) is the gold standard for assessment of pancreatic exocrine function. PFTs, as currently performed, are invasive and require sedation/anesthesia [9, 10]. Potential non-invasive means of assessing pancreatic structure and function include magnetic resonance cholangiopancreatography (MRCP) and MR elastography (MRE)[11, 12]. In adult patients, MRCP with secretin stimulation has been demonstrated to allow non-invasive assessment of pancreatic exocrine function [13]. MRCP for assessment of pancreatic exocrine function (MR-PFT), however, has not been validated in children and normative data are not available, limiting the utility of this test in the pediatric population. MR Elastography uses transmitted vibrations to assess tissue stiffness and early studies have shown efficacy in measuring pancreatic stiffness in adult patients [14, 15]. By measuring pancreatic stiffness, MRE might be utilized as a non-invasive assessment measure of developing pancreatic fibrosis which may serve as a biomarker of minimal change CP [14].

In preparation for this study, we developed a protocol to measure pancreatic fluid volume secreted in response to secretin administration, confirmed feasibility of pancreatic stiffness measurements by MRE and analyzed our experience with MR in pediatric patients with pancreatic disease, primarily CP. We have a cohort of CP patients that have undergone MRCP with the proposed study protocol and we will continue to collect data on CP patients that undergo MR studies. The overall aim of this pilot-study is to collect MR-PFT and MRE data in a small group of normal pediatric subjects (with no history of pancreatic disease, CP/PI, or intestinal disease) to serve as a preliminary data set for a subsequent comparative study of MR-PFT and MRE in children with CP. The ultimate aim is to provide results that would position non-invasive MR studies as an accurate, sensitive, and specific alternative to standard modalities of CP diagnosis and therapy monitoring (endoscopic PFT (ePFT), endoscopic

retrograde cholangiopancreatography (ERCP), endoscopic ultrasound (EUS), and biopsy). **Our overall hypothesis is that normative ranges can be established for total secreted pancreatic fluid volume as measured by MR-PFT and for pancreatic stiffness as measured by MRE and that secreted volumes but *not* pancreatic stiffness will depend on subject age and size.**

STUDY DESIGN:

This will be a single center prospective study of children with no history of pancreatic disease to quantify normal pancreatic volumes and secreted fluid volume (SV) in response to secretin administration as measured by MR-PFT. We will also assess the pancreatic stiffness by MR elastography as well as pancreatic duct visibility (pre-and post-secretin) in the same cohort.

MR elastography:

MRE 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 which is placed on the patient's abdomen. The initiation and cessation of the vibrations are controlled by the MR pulse sequence programmed and embedded as part of the scanner software. The MRE pulse sequence does not bypass any scanner safety standards as specified by the manufacturer. The MRE sequence will produce magnitude and phase images at multiple levels in the pancreas. After the MRE magnitude and phase images are obtained, the data is converted into quantitative images displaying the stiffness of the pancreatic parenchyma. Stiffness and quantitative mean stiffness values are generated from the phase images. The MRE sequence being used as part of this study is an investigational sequence with which we have experience in both the clinical and research environment. The investigational sequence will be performed in such a way that the Food and Drug Administration (FDA) general MR safety guidelines cannot be overridden and/or exceeded.

Secretin:

Synthetic human secretin is a peptide hormone with an amino acid sequence identical to naturally occurring secretin. The main action is to increase the secretion of pancreatic juice, including bicarbonate by stimulating the exocrine pancreas thereby assisting in the diagnosis of exocrine pancreatic dysfunction. Secretin is FDA approved for pancreatic stimulation use in adults. We regularly use secretin in clinical practice at CCHMC. A limited MRCP with secretin stimulation with a dose of 0.2 mcg/kg (maximum of 16 mcg) will be performed and post-processed as detailed below.

MR imaging:

All studies will be performed on a 1.5T GE HDx MRI scanner (General Electric; Milwaukee, WI) using the 8-channel Torso coil. The following sequences will be obtained through the upper abdomen:

Pre-Secretin:
Axial 3D T1 GRE (LAVA)
Axial fat saturated T2 fast spin echo (FSE)
Axial 3D GRE magnetic resonance elastography (MRE)
Axial T2 map
Coronal 3D fast relaxation fast spin echo (FrFSE)
Coronal fat saturated T2 SSFSE

Post-Secretin:
Coronal fat saturated T2 SSFSE at 1, 5, 10 and 15 minutes after Secretin injection
Coronal 3D FrFSE

MR post-processing:
MR-PFT:
Total secreted fluid volume in response to secretin will be determined from the pre- and post-secretin coronal T2 SSFSE using commercially available software (ImageJ, MatLab) by selecting a signal intensity threshold which isolates intraluminal fluid in the duodenum and proximal jejunum. A region of interest will then be drawn on each image inclusive of thresholded pixels, to determine the area (mm^2) of fluid signal. The area of fluid signal on each image will then be multiplied by the image slice thickness and all slice values will be summed to determine a fluid volume over the entire imaged volume.

MRE:
MR elastography images will be post-processed using software leased from Resoundant (Rochester, MN) with pancreatic parenchymal stiffness expressed as a mean stiffness (kPa) for the pancreatic neck, body, and tail.

Parenchymal volume:
Pancreatic parenchymal volume will be measured by manual segmentation of the pancreas using commercially available software (MIM, MIM Software Inc.; Cleveland, OH).

DURATION:

This initial pilot study is anticipated to take approximately 12 months but we will continue up to 24 months if we are not able to meet the recruitment target the first year.

RECRUITMENT & CONSENT OF PARTICIPANTS:

Subject Recruitment:
Recruited subjects will have no history of pancreatic disease and will be identified through review of patients presenting for non-abdominal imaging examinations. Patients presenting for musculoskeletal MRI examinations will likely be the major source for recruited patients. In the last 2 years, 1297 musculoskeletal MR examinations have been done in pediatric patients, ages 6 -15 years, at our institution, providing a ready source for recruitment. Subjects may additionally be recruited through public recruitment using existing clinical trial recruitment services at CCHMC, including advertising within our institution to raise awareness of the study. CCHMC employees may be invited to enroll their children in the study; they would be invited by the research coordinator. Subject charts will be reviewed for evidence of pancreatitis or other pancreatic disease prior to/during enrollment. Following initial screening, subjects will be contacted by the study coordinator or an investigator and enrolled after informed consent is obtained. During enrollment, absence of exclusion criteria will be confirmed with a questionnaire completed prior to imaging.

50 evaluable subjects will be recruited evenly divided as follows:
25 subjects age 6-11.9 years
25 subjects age 12-15.9 years

Inclusion Criteria:

1. Subjects between the ages of 6 and 15.9 years.
2. Subjects without a documented history of (or suggestive of) pancreatic disease.

Exclusion Criteria:

1. History of pancreatic disease, liver disease, intra-abdominal neoplasm, abdominal inflammatory process such as inflammatory bowel disease (IBD), or systemic illness that may affect pancreatic state (e.g. cystic fibrosis).
2. Subjects with surgical hardware/implanted devices making them ineligible for MRI (e.g. pacemaker or other implanted medical device not approved for MRI).
3. Subjects who require any form of sedation or general anesthesia for MRI.
4. Subjects unable to breath-hold for the required 15-20 second imaging sequence.
5. Subjects who are pregnant or less than 12 months post-partum.

Process of obtaining Consent:
In accordance with the International Conference on Harmonization – Good Clinical Practices (ICH-GCP) and local legislation, all participants/families will be fully informed about the study, and the parents will give written informed consent prior to enrollment in the study and prior to any study specific procedures being performed. Participants ≥11 years of age will be asked to sign an assent form prior to participating in the study.

All participants will be asked to complete a metal screening form prior to participation in the study, regardless of whether or not they have done so in the past. This will ensure the MR screening information is up-to-date for anyone who participates in this protocol.

Females who are able to get pregnant will be screened with a urine pregnancy test prior to imaging. Results will be shared with subject and parent, if applicable.

Subjects will be reminded that participation in research is completely voluntary. Coercion is eliminated by having the subjects sign an assent document and the parent/guardian signs the consent document. Time will be given for families to read the consent documents and for any questions to be answered.

STUDY PROCEDURES:

We will contact each family prior to the MRI visit to provide information about the study. Written consent will be obtained on the day of the exam. At that time, absence of exclusion criteria will be confirmed with a questionnaire and pregnancy testing for all females of child bearing potential will be completed prior to imaging.

MR-PFT (Exp 1) and MRE (Exp 2) exams will each be performed once per subject on a 1.5T GE HDx MRI scanner (General Electric; Milwaukee, WI). Subjects will be required to fast (NPO) for four hours prior to MR imaging. Subjects will be weighed and measured immediately prior to imaging. The IV will be placed by the MRI technologist at the beginning of the imaging examination. The patient will then be placed into the scanner and the MRE passive driver will be placed on their abdomen. The patient will be provided with standard hearing protection and entertainment options (video goggles). All pre-secretin imaging will then be performed. A study team physician or a Radiology Department nurse will then inject the secretin through the IV and all post-secretin imaging will be performed. Once imaging is completed, the patient will be removed from the scanner and the IV will be removed.

Anticipated duration of MR imaging is approximately 35 minutes scan time (total 50 min in room time). Scan time pre-secretin (5 sequences, including MRE) is approximately 20 minutes. Scan time post-secretin (sequences for MR-PFT) is approximately 15 minutes. The additional time is required for positioning, localization, sequence planning, and secretin injection. The MRI examinations can be terminated at any time upon request of the participant. All MR imaging will be done as scheduled appointments.

All images will be maintained in the research PACS environment. Data that will be saved will include participant number, age at time of examination, and MR data. Identifying data will be saved in a password-protected database.

Facilities:
Visits will be conducted within the main clinical CCHMC Radiology Department. The MR scanner being used is owned and operated by the CCHMC Department of Radiology.

Radiologist Review of Images:
The imaging protocol used in this study includes only the minimum scanning needed to achieve the research objective outlined by the study investigator. No report will be generated or supplied to the research participants. However, all scans performed for this project will be reviewed for gross abnormalities by a board-certified or board-eligible radiologist. Although no diagnosis will be made, in the event that abnormal findings are identified, the PI will be informed and will assume responsibility for notifying the participant. In this case written documentation that an abnormal finding has been identified will be provided to the participant.

DATA ANALYSIS/METHODS:

Statistical analysis:
Statistical analyses will be tailored to our study purposes as follows:

Collect normative data for volume of secreted fluid in response to secretin administration in a representative sample of healthy pediatric controls.
Means, standard deviations and 95% confidence intervals will be used to summarize study population secreted volumes. Linear regression will be used to assess for significant correlation between subject age and secreted volume. Similar regression models will be used to test other body-size covariates such as BSA, BMI, etc. If feasible, a quantile regression will be performed of secreted volume or BSA normalized secreted value to attempt to quantify normal range as a function of age, BMI, etc.

Collect normative data for pancreatic stiffness as measured by MR elastography.
Means, standard deviations and 95% confidence intervals will be used to summarize study population pancreatic parenchymal stiffness. Linear regression will be used to assess for significant correlation between subject age and parenchymal stiffness. Similar regression models will be used to test other body-size covariates such as BSA, BMI, etc.

Assess the relationship between pancreatic exocrine function, pancreatic stiffness and pancreatic parenchymal volume.
Linear regression will be used to define correlation between pancreatic parenchymal volume and secreted fluid volume in response to secretin administration.

For the stored anatomy and other gastrointestinal functional data from the controls, we will conduct statistical analyses according to the purpose of the question that is asked from this data, for instance for pancreatic volume measurements, we will conduct a comparison analysis

by t test, ANOVA, Wilcoxon test and other measures to fit the purpose of the other future studies.

Assess the effect of secretin on the visibility of the pancreatic duct.
Frequencies and rankings will be compared with Fischer exact test and Wilcoxon rank sum tests to compare visualization of the pancreatic duct pre- and post-secretin.

Power calculation:
To establish relationship between secreted fluid volume and subject body size or age, we base a power calculation on analysis of MR-PFT data in 19 CP patients and the assumption that secreted volume is correlated with age in this sample of patients. In a linear regression analysis of these patients, the observed residual standard error is approximately 39, with an R^2 ~ 0.40. The observed regression coefficient is 5.274, and standard deviation of predictor age is ~5.816. If this holds in a general population, we require at least 15 normal subjects to have a significant regression coefficient at 0.05 level, and 80% power.

Additionally, from the previously reported study of normal adult patients by Mensel et al. [25], the coefficient of variation (CV) of secreted volume (TEV in the paper) at various time points from secretin injection ranged from 0.30 to 0.51. Given that we plan to enroll subjects in two age groups (6-11.9 and 12-15.9 years old), 25 subjects in each age group will provide 80% chance that the 95% confidence interval of mean secreted volume will be within 12% to 20% of the mean value, depending on the actual CV observed.

Therefore, we plan to enroll a total of 50 evaluable subjects in the study to meet both needs above.

POTENTIAL RISKS & BENEFITS:

Potential Risks:
The risk category for all subjects who choose to participate in the study will fall into the minimal risk category.

MR: There are no known risks from having an MRI. 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 risks related to having an MR examination be identified during the course of this study, participants will be informed of those risks.

Secretin: The administration of secretin will involve placement of an intravenous catheter (IV), which may cause some pain, bleeding, or bruising at the site and in rare instances can result in infection. Secretin is associated with some minimal and temporary side effects, such as abdominal pain, nausea, or flushing. These effects are minor (if they happen at all) and can be easily monitored in patients undergoing MRCP.

Data Safety Monitoring Plan:
This study is a non-intervention study. Therefore, no formal data safety monitoring board will be appointed. Adverse events related to the study procedures will be monitored by the study coordinator and reported to the PI and the Division Director. The PI will then report any adverse

events in writing to the CCHMC IRB within the time frame specified in the IRB guidelines. These procedures should be highly effective in minimizing risk to study participants.

Potential Benefits:
There will be no direct benefits to participants in this study other than potential knowledge of the results from the scans that may be shared with them by the clinical staff. This research, however, may have generalized benefits in terms of providing a preliminary data set for a subsequent comparative study of MR-PFT and MRE in children with CP.

PRIVACY & CONFIDENTIALITY:
Each subject will be assigned a study ID number. A password-protected table will be maintained that links the study ID number to the medical record number. This table will be maintained on a secure server and/or in a locked file cabinet, as appropriate. The password-protected database containing the MRE and MRCP data will be maintained on a secure server with access limited to study personnel. Identifying data will be saved in a password-protected database. We plan to keep the de-identified data for future studies. Any data that are extracted from the database and used for research will be subject to standard anonymization and data protection practices.

COST OF PARTICIPATION:
There is no cost to participate in this study.

PAYMENT FOR PARTICIPATION:
We will provide each participant/family with a $100 gift card (Clincard) for the reimbursement of time and trouble to participate in the study. Compensation will be given at the end of the study visit upon completion of the MRI exam.

REFERENCES:

1. Amann ST, Yadav D, Barmada MM, et al. Physical and mental quality of life in chronic pancreatitis: a case-control study from the North American Pancreatitis Study 2 cohort. Pancreas 2013;42:293-300.
2. Schwarzenberg SJ, Bellin M, Husain SZ, et al. Pediatric chronic pancreatitis is associated with genetic risk factors and substantial disease burden. J Pediatr 2015;166:890-6 e1.
3. Somaraju UR, Solis-Moya A. Pancreatic enzyme replacement therapy for people with cystic fibrosis. Cochrane Database Syst Rev 2014;10:CD008227.
4. Arya VB, Senniappan S, Demirbilek H, et al. Pancreatic endocrine and exocrine function in children following near-total pancreatectomy for diffuse congenital hyperinsulinism. PLoS One 2014;9:e98054.
5. Conwell DL, Zuccaro G, Jr., Vargo JJ, et al. An endoscopic pancreatic function test with cholecystokinin-octapeptide for the diagnosis of chronic pancreatitis. Clin Gastroenterol Hepatol 2003;1:189-94.
6. Abu Dayyeh BK, Conwell D, Buttar NS, et al. Pancreatic juice prostaglandin e2 concentrations are elevated in chronic pancreatitis and improve detection of early disease. Clin Transl Gastroenterol 2015;6:e72.
7. Pelley JR, Gordon SR, Gardner TB. Abnormal duodenal [HCO3-] following secretin stimulation develops sooner than endocrine insufficiency in minimal change chronic pancreatitis. Pancreas 2012;41:481-4.
8. Sendler M, Beyer G, Mahajan UM, et al. Complement Component 5 Mediates Development of Fibrosis, via Activation of Stellate Cells, in 2 Mouse Models of Chronic Pancreatitis. Gastroenterology 2015;149:765-76 e10.
9. Conwell DL, Zuccaro G, Purich E, et al. The effect of moderate sedation on exocrine pancreas function in normal healthy subjects: a prospective, randomized, cross-over trial using the synthetic porcine secretin stimulated Endoscopic Pancreatic Function Test (ePFT). Am J Gastroenterol 2005;100:1161-6.
10. Conwell DL, Zuccaro G, Purich E, et al. Comparison of endoscopic ultrasound chronic pancreatitis criteria to the endoscopic secretin-stimulated pancreatic function test. Dig Dis Sci 2007;52:1206-10.
11. Zuccaro P, Stevens T, Repas K, et al. Magnetic resonance cholangiopancreatography reports in the evaluation of chronic pancreatitis: a need for quality improvement. Pancreatology 2009;9:764-9.
12. Sainani NI, Kadiyala V, Mortele K, et al. Evaluation of Qualitative Magnetic Resonance Imaging Features for Diagnosis of Chronic Pancreatitis. Pancreas 2015;44:1280-9.
13. Balci NC, Smith A, Momtahen AJ, et al. MRI and S-MRCP findings in patients with suspected chronic pancreatitis: correlation with endoscopic pancreatic function testing (ePFT). J Magn Reson Imaging 2010;31:601-6.

14. Shi Y, Glaser KJ, Venkatesh SK, et al. Feasibility of using 3D MR elastography to determine pancreatic stiffness in healthy volunteers. J Magn Reson Imaging 2015;41:369-75.
15. Itoh Y, Takehara Y, Kawase T, et al. Feasibility of magnetic resonance elastography for the pancreas at 3T. J Magn Reson Imaging 2015.