Detection of Exocrine Dysfunction by MRI in Patients with Early Chronic Pancreatitis

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ABSTRACT

PURPOSE

To determine if T1-weighted MR signal of the pancreas can be used to detect early CP.

METHODS

A retrospective analysis was performed on 51 suspected CP patients, who had both secretin enhanced magnetic resonance cholangiopancreatography (S-MRCP) and an intraductal secretin stimulation test (IDST). There were 29 patients in normal and 22 patients in the low bicarbonate group. Bicarbonate level, total pancreatic juice volume (TPJV) and excretory flow rate (EFR) were recorded during IDST. Signal intensity ratio of pancreas (SIR), fat signal fraction (FSF), pancreatograms findings and grade of duodenal filling (DF) were recorded on S-MRCP by two blinded radiologists.

RESULTS

There was a significant difference in the signal intensity ratio of the pancreas to spleen (SIR p/s) between the normal and low bicarbonate groups ($p<0.0001$). A significant positive correlation was found between pancreatic fluid bicarbonate level and SIR p/s ($p <0.0001$). SIR p/s of 1.2 yielded sensitivity of 77% and specificity of 83% for detection of pancreatic exocrine dysfunction (AUC: 0.89).

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CONCLUSION

T1-weighted MR signal of the pancreas has a high sensitivity and specificity for the detection of parenchymal abnormalities related to exocrine dysfunction and can therefore be helpful in evaluation of suspected early CP.

KEYWORDS

Chronic Pancreatitis

Secretin stimulation test

Magnetic Resonance Imaging

Exocrine Dysfunction

INTRODUCTION

The natural history of chronic pancreatitis is usually insidious. During the early stages of chronic pancreatitis (CP), the morphologic and functional changes are difficult to detect by conventional methods. [1-4]. Sensitivity of the practical non-invasive tests has been found to be inadequate [5] and ductal imaging can be normal in patients with early disease [5]. Therefore, establishing a diagnosis of CP at an early stage remains problematic [6-9]. Endoscopic ultrasound (EUS) findings can be used to predict the presence of pancreatic exocrine dysfunction in patients with chronic pancreatitis [10,11]. However, multicenter studies showed the interobserver agreement to be less than optimal using both the standard scoring and Rosemont classification [12]. Both ERCP and EUS can obtain biopsy samples however this is rarely pursued since biopsy itself can cause acute pancreatitis [13]. Therefore, validation of a widely available, less invasive imaging technique to detect early CP would have tremendous clinical benefits. Our objective was to assess the usefulness of T1-weighted signal changes in patients with suspected early CP. Specifically, we assessed whether the signal intensity ratio (SIR), can accurately differentiate individuals with and without pancreatic exocrine dysfunction when the pancreatic ductograms are normal.

MATERIALS and METHODS

Patient selection

This retrospective study was approved by the Institutional Review Board (IRB) and a HIPAA compliant retrospective analysis was performed. Electronic medical records were searched from September 2006 to December 2014 to identify 258 patients who had undergone intraductal secretin stimulation test (IDST). All of the patients presented to the gastroenterology clinic with

symptoms suspected to be of pancreatic origin and had an S-MRCP within 3 months of secretin stimulation test. This study excluded patients with an established diagnosis of acute or chronic pancreatitis (n=111), cystic fibrosis (n=2), pancreatic cystic neoplasm (n=61), pancreatic adenocarcinoma (n=27), hemochromatosis (n=1) and post splenectomy (n=3) and patients younger than 18 years old (n=2). Following applying the exclusion criteria, a total of 51 patients were eligible for the study. These patients were grouped into normal (n=29) or low bicarbonate group (n=22) based on bicarbonate concentration in the pancreatic juice. Seventy-nine percent of the patients in the normal group were female, versus 64% of patients in the low bicarbonate group. Mean age of the patients in the normal group was 43 (range 19-70) and in the low bicarbonate group it was 47 (range 32-65).

Secretin Stimulation Test

To make a diagnosis of chronic pancreatitis at the very early stages patients may require direct measurement of pancreatic exocrine function when the other diagnostic tests are normal or inconclusive. An endoscopic pancreatic function test (ePFT) shows promise for establishing a diagnosis of early CP, but its performance to date has typically been limited to tertiary referral centers. These tests may be performed at EGD, EUS or ERCP. Although there is discussion about which method is the better, IDST had gained popularity as a research tool and has been used as a reference standard to diagnose CP [14,15]. Gastroenterologists at our institution prefer the IDST; therefore this test was used in our study as the reference standard to establish the diagnosis of early CP. The technique of IDST involves cannulating the pancreatic duct during the ERCP. After an intravenous injection of 16 mcg of synthetic secretin (ChiRho Stim, ChiRhoClin Inc, Burtonsville, MD), pancreatic juice is collected in separate aliquots by continuous aspiration at 5-minute intervals for 30 minutes. The total pancreatic juice volume

(TPJV), excretory flow rate (EFR) and highest concentration of bicarbonate for each of the aliquots is recorded. Peak bicarbonate concentration of <105 mEq/L was used as indicator of decreased exocrine function [16-18].

Imaging technique

Patients fasted for at least four hours prior to the MR examination. S-MRCP was performed in all patients by acquiring images in either a 1.5 Tesla Magnetom Avanto scanner (n=35) or a 3.0 Tesla Magnetom Verio scanner (n=16) (Siemens Medical Solutions, Erlangen, Germany). Region of interest (ROI) measurements for signal intensity ratio (SIR) were performed on axial pre-contrast, T1-weighted, fat-suppressed, volume interpolated 3D gradient echo sequence (VIBE, Siemens Medical Solutions, Malvern, PA, USA) using TR 5.01 ± 0.32 ms, TE 2.52 ms, 12° flip angle, NEX 1, matrix 308 x 210 on 1.5T and TR 4.33 ± 0.32 ms, TE 1.47 ms, 9° flip angle, matrix 308 x 210 on 3.0T magnets. Same imaging parameters were used in all patients. ROI measurements for FSF were performed on axial breath-hold 2-point DIXON T1-weighted images using TR 7.47 ms, TE 4.76 ms, 10° flip angle, NEX 1, matrix 256 x 120 on 1.5 T and TR 5.45 ms, TE 2.45 ms, 9° flip angle on 3.0T units. Approximately 16 μg of secretin was administered via slow intravenous infusion over one minute and subsequently the pancreas was imaged via a coronal 2D single shot turbo spin echo sequence (HASTE, Siemens Medical Solutions, Malvern, PA), repeated every 30 seconds for 10 minutes.

Image analysis

Two experienced radiologists who were blinded to the IDST findings, performed ROI signal intensity measurements from the head, body and tail of the pancreas, also spleen and paraspinal muscle as the reference organs, on unenhanced fat-suppressed T1-weighted images using picture

archiving and communication system (Synapse, Fujifilm Medical Systems, Stamford, US). Special attention was given to making measurements using the same size (approximately 50 mm^2) circular/elliptical ROI in a homogenous region of the parenchyma avoiding volume averaging from the signal suppressed retroperitoneal fat, vessels and pancreatic duct. SIR was calculated by dividing the average pancreas signal intensity (SI) by the SI of the reference organ (spleen or muscle); $SIR = SI_{Pancreas} / SI_{Reference}$. Fat signal fraction (FSF) of the pancreas was calculated by measuring signal intensities at the same location as the T1-weigthed images on DIXON series using the formula $FSF = SI_{Fat} / [SI_{Fat} + SI_{Water}]$. The largest diameter of the main pancreatic duct and number of ectatic side branches were recorded. Duodenal filling (DF) was assessed on the last image of the post-secretin S-MRCP image as follows; grade 1, when the filling remained limited to the duodenal bulb; grade 2, when pancreatic juice filled the bulb and the duodenum up to the genu inferius; and grade 3, when the bulb and the duodenum were filled beyond the genu inferius. Grades 1 and 2 were considered decreased DF [14,19].

Statistical analysis

Pearson's correlation coefficient was calculated to assess the correlation between bicarbonate concentration and SIR. Analyses of covariance (ANCOVA) models were used to determine the differences in $SIR_{p/s}$ between normal and decreased group as well as the variability of measurements between 1.5T and 3T scanners and signal intensities between head, body and tail of the pancreas. Logistic regression was used to find the cut-off $SIR_{p/s}$ between normal and decreased exocrine function group. The Student t-test with independent samples was used to determine differences of FSF, bicarbonate, EFR, and TPJV between the normal and low bicarbonate groups. Spearman's rank correlation coefficient was used to assess relationship between the bicarbonate level and $SIR_{p/s}$ or $SIR_{p/m}$. The significance level (α) used in this study

was < 0.05 and correlation coefficients were interpreted as: weak, 0.2; moderate, 0.5; strong, 0.8; and perfect 1.0 [20]. We used multiple regression model to analyze the relationship between a dependent variable (presence of low bicarbonate) and independent variables ($SIR_{p/s}$, FSF, age, DF grade, IDST excretory rate and volume). Multiple regression model used automatic weighting to correct for heteroscedasticity and excluded independent variables from the model if the p value is higher than 0.2. Statistical analyses were performed using MedCalc version 16.8. (Medcalc, Mariakerke, Belgium).

RESULTS

The patients were categorized as normal or early CP based on peak pancreatic juice bicarbonate concentration (Table 1). There was no statistically significant difference between the age of two groups (p=0.18). T1-weighted SIR in the head, body and tail of the pancreas were statistically similar (p=0.87) therefore; average values were used in the analysis. Similar results were found on both the 1.5T and 3T scanners (p=0.62); therefore data from 1.5T and 3T were combined for each group.

Reference Organ

We compared the SIR of spleen ($SIR_{p/s}$) and paraspinal muscle ($SIR_{p/m}$) to determine which one is a better reference organ. Correlation of $SIR_{p/m}$ with bicarbonate level was less satisfactory (ρ=0.28, 95%CI: 0.01 - 0.52, p=0.04) compared to $SIR_{p/s}$ (ρ=0.70, 95%CI: 0.53-0.82, p<0.0001) as well as diagnostic performance ($SIR_{p/m}$ AUC=0.63, p=0.09 vs $SIR_{p/s}$ AUC=0.89, p =<0.0001). Therefore we used $SIR_{p/s}$ for further analysis.

T1-weighted signal (Table 1)

We found a strong positive correlation between pancreatic fluid bicarbonate level and $SIR_{p/s}$ (ρ= 0.70, p <0.0001) as shown on Figure 1. Inter-observer correlation was excellent (kappa=0.90, p <0.0001). There was a significant difference (p<0.0001) in the $SIR_{p/s}$ of the pancreas between the normal (mean 1.41, 95% CI: 1.31 - 1.51) and low bicarbonate group (mean 1.03, 95% CI: 0.97 - 1.12) as shown on Figure 2-a. Receiver operating characteristic (ROC) curve with a pancreas to splenic $SIR_{p/s}$ threshold value of 1.2 yielded a sensitivity of 77% and specificity of 83% for detection of exocrine dysfunction (AUC=0.89) (Figure 2-b).

MR pancreatogram (Cambridge Classification)

Within the normal group, S-MRCP showed 28 out of 29 pancreatograms to be normal/equivocal and only 1 was classified as mild CP according to the Cambridge classification. Within the early CP group, 20 out of 22 pancreatograms were classified as normal/equivocal according to Cambridge classification however diagnosed with early CP based on IDST results. The ductal findings on remaining 2 patients were consisted with mild CP. Based on these results, S-MRCP using the Cambridge classification yielded sensitivity of 9% (95% CI: 1-29%), specificity of 96% (95% CI: 82%-99%), positive predictive value of 67% (95% CI: 9-99%), negative predictive value of 58% (95% CI: 43-72%) for detection of early CP.

Duodenal filling after secretin stimulation

S-MRCP showed a statistically significant difference in the duodenal filling (DF) grade between the normal and low bicarbonate groups (p=0.03). Considering the DF grade 1 and 2 as abnormal; sensitivity, specificity, positive predictive value and negative predictive values were 55% (95% CI: 32-76%), 96% (95% CI: 82-99%), 92% (95% CI: 64-99%) and 74% (95% CI: 56-87%).

Fat signal fraction

In order to exclude the possibility that the relatively lower signal intensity of the pancreas was a result of partial volume effects from the voids left by signal-suppressed fat inter-digitating with parenchyma, pancreatic fat signal fraction (FSF) was calculated for both groups. Mean FSF of the normal group was 3.8% (95% CI: 3.0% - 4.7%) whereas mean of the low bicarbonate group was 4.6% (95% CI: 3.4% - 5.7%) and difference was not statistically significant (p=0.29) as depicted on Figure 3.

IDST findings (Table 2)

Two patients groups had significantly different excretory flow rate (EFR) (p= 0.01) and lower pancreatic juice volume (TPJV) (p= 0.0001). Mean EFR for normal group was 3.0 ml/min (95% CI: 2.5 - 3.5) and for the low bicarbonate group was 2.1 ml/min (95% CI: 1.7 - 2.6). Mean TPJV for the normal group was 54 mL (95% CI: 44 - 64) and for the low bicarbonate group was 30 mL (95% CI: 24 - 36).

Multiple regression analysis was performed to show correlation between the prediction of low bicarbonate and other independent variables ($SIR_{p/s}$, FSF, age, DF grade, IDST volume and rate). $SIR_{p/s}$ was the only variable that showed statistically significant correlation with the low bicarbonate ($p<0.0001$) (Table 3).

DISCUSSION

The diagnosis of CP relies on relevant symptoms and diagnostic modalities to assess pancreatic structure and function [21]. Evaluation may range from a simple and straightforward task to a tremendously challenging and intensive investigative process. Several investigations reported that the signal intensity of normal pancreatic parenchyma on T1-weighted images is typically higher than in other organs, due to the short T1 relaxation time of normal pancreatic tissue [22].

This finding is best appreciated on unenhanced, fat suppressed, T1-weighted images [23-25]. The T1-weighted signal may be decreased in many forms of pathologies including acute and subacute pancreatitis in which the parenchyma becomes edematous; in chronic pancreatitis as the normal pancreatic parenchyma containing protein-rich cytoplasm becomes replaced by fibrosis and in hemochromatosis as the iron causes paramagnetic artifacts [22,25,26].

In this study, pancreatic signal intensity was quantitatively measured in patients with upper abdominal pain suspected of pancreatic origin. These measurements were correlated with the results of a direct pancreatic function test. We found a strong positive correlation between the T1-weighted pancreatic signal and exocrine function. Our study was unique since the T1-weighted signal of the pancreas was able to detect pancreatic exocrine dysfunction in patients with no ductal abnormalities (Figure 4). Future studies comparing healthy volunteers to suspected CP patients would be helpful.

Among the prior reports [22,24-30], the most comparable study correlating the T1-weighted signal intensity of the pancreas with pancreatic function test was by Balci et.al. [28]. In that study, there was no T1 signal difference between normal and low bicarbonate groups, pancreatic juice was sampled from the duodenal lumen and there were only 12 patients in the decreased exocrine function group compared to 22 in our study. Using a larger patient population, we were able to demonstrate that T1-weighted MR signal can detect changes related to early CP with high sensitivity and specificity.

Our results concur with the previously reported poor sensitivity of the Cambridge classification for the detection of early CP [5] based on ductography. In this study, ductal imaging did not identify early CP in 91% of patients; indicating that pancreatic exocrine function precedes the ductal changes in the disease process. Our results support the idea of developing a more

comprehensive clinical diagnostic criteria for CP based on combination of clinical signs, pancreatic parenchymal changes and function [2].

Large multi-centric clinical trials have shown that utilization of secretin during MRCP improves diagnosis and clinical decision making for patients with chronic pancreatitis [31]. S-MRCP can be used to measure the volume of fluid reserves in response to secretin stimulation, giving an estimate of exocrine function with a sensitivity of 72% and specificity of 87% [14,19]. Balci et al found a significant correlation between the decreased SIR and decreased DF by S-MRCP [27]. Considering the DF grade 1 and 2 as abnormally low, we found a statistically significant difference between the two groups ($p=0.03$). Sensitivity and specificity of decreased DF for detection of exocrine dysfunction in our study population was 55% (12/22) and 96% (1/28) respectively. The reason for lower sensitivity of DF in our study can be explained by the fact that only early CP patients were included in the current study, while the former studies included all levels of severity of CP. Our results reiterate the low sensitivity of DF grade in diagnosis of early CP especially considering the limitations of this technique such as inability to suppress the fluid already present within the duodenum before secretin stimulation.

The time and cost benefit of a diagnostic and quantitative metric such as T1-weighted signal can be significant compared to other MR imaging techniques of CP. T1-weighted gradient echo imaging of the pancreas takes only 1 breath hold (20 seconds) to obtain and is routinely acquired in almost every MR study. On the other hand, secretin significantly increases the cost of S-MRCP, requires a slow intravenous injection and adds at least 12 minutes to the total examination time. For these reasons, secretin is not commonly used outside the tertiary imaging centers in the U.S. and did not become a mainstream imaging technique for CP.

The present study is limited by the sample size. This was due to our strict patient selection criteria which lowered the number of patients. Another possible limitation in patient selection is that; according to some reports, secretin stimulation tests do not always predict pancreatic exocrine dysfunction in patients with CP [32,33]. Nevertheless, it is still considered one of the best direct pancreatic function tests, at least as a research tool.

An important factor to consider when interpreting MR studies for CP is the presence of fatty infiltration and parenchymal atrophy. Since fat suppression is used for T1-weighted imaging, partial volume averaging of low signal of suppressed retroperitoneal fat inter-digitating with the pancreas could interfere with the MR signal. To control for this possibility, we ensured that the reviewers placed ROIs on relatively homogenous regions of the gland. We quantitatively measured the fat signal fraction in both groups using the chemical shift imaging technique. FSF in the mild CP group was higher, but not significantly different than the normal group ($p=0.29$).

Clinical MR studies are performed in either 1.5 or 3 Tesla strength scanners and this investigation included both. Theoretically speaking, T1-weighted properties of tissues vary with field strength and that is one of the reasons why we used signal intensity ratio, rather than the absolute signal of the pancreas alone. Statistical analysis of our data collected 1.5 and 3 Tesla yielded very similar results, and it is unlikely there would be discrepancies in our conclusions due to scanner field strength. It would also be helpful to verify our results on different MR vendors.

In summary, this study demonstrated that there is a strong positive correlation between the pancreatic exocrine function and T1-weighted signal of the pancreas. T1-weighted signal intensity can be a clinically useful and relatively cost-effective test for detection of early chronic pancreatitis when the ductal imaging is normal.

Compliance with Ethical Standards

- No funding was received for this work.
- Authors do not have any relevant conflict of interest with this study.
- All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. This article does not contain any studies with animals performed by any of the authors.
- Requirement for an informed consent was waived by the IRB.

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Table 1. S-MRCP findings in the normal and low bicarbonate groups.

Bicarbonate Level	Normal	Low	p
Cambridge Classification			
Normal/Equivocal [1]	28	1	
Mild CP [2]	20	2	
$SIR_{p/s}$	1.41 (95% CI: 1.31-1.51)	1.03 (95% CI: 0.97-1.12)	< 0.0001
FSF	3.8% (95% CI: 3.0%-4.7%)	4.6% (95% CI: 3.4%-5.7%)	0.29
Duodenal Filling			0.03
Grade 1	0	4	
Grade 2	1	8	
Grade 3	28	10	

CP= Chronic pancreatitis, $SIR_{p/s}$= Signal intensity ration of pancreas to spleen, FSF= Fat signal fraction of the pancreas.

Table 2. IDST findings in the normal and low bicarbonate groups.

	Normal	Low	p
Bicarbonate	119 mEq/L (105-135)	90 mEq/L (68-105)	
TPJV	54 mL (44-64)	30 mL (24-36)	0.0001
EFR	3.0 ml/min (2.5-3.5)	2.1 ml/min (1.7-2.6)	0.01

TPJV: Total Pancreatic Juice Volume (mL), total amount collected during IDST

EFR: Excretory Flow Rate determined during IDST, average rate

Values in parenthesis are range.

Table 3. Multiple regression analysis of the independent variables in patients with low bicarbonate.

Variables	Coefficient	Std. Error	$r_{partial}$	t	p
$SIR_{p/s}$	-0.4066	0.1648	-0.3896	-2.467	**0.02**
FSF	1.9513	1.8413	0.1788	1.060	0.30
IDST volume	-0.0079	0.0049	-0.2652	-1.604	0.12
IDST rate	0.09546	0.1108	0.1462	0.862	0.39
DF	0.2637	0.1653	0.2640	1.596	0.12
Age	0.0053	0.0038	0.2311	1.385	0.17

SIR p/s=Signal intensity ratio of pancreas to spleen, FSF=Fat signal fraction of the pancreas, IDST=Intraductal secretin test, DF=duodenal filling grade.

Figure Captions

Fig. 1. Scatter plot of the pancreatic juice bicarbonate concentration and the $SIR_{p/s}$ of the pancreas to the spleen. There is strong positive correlation between the bicarbonate concentration and the T1-weighted signal of the pancreas ($\rho = 0.70$, $p < 0.0001$). The horizontal dashed line is drawn at the bicarbonate concentration of 105 mEq/L. The vertical dashed line is drawn at the $SIR_{p/s}$ of 1.2 indicating our threshold value.

Fig. 2-a. Box and whisker plot of $SIR_{p/s}$ for the normal and decreased bicarbonate group. There was a statistically significant difference between the normal and decreased exocrine function groups. The horizontal line was drawn at our threshold $SIR_{p/s}$ value of 1.2.

Fig. 2-b. ROC curve plotted for threshold of 1.2 yielded a sensitivity of 77% and specificity of 83% for detecting pancreatic exocrine dysfunction.

Fig. 3. Box and whisker plot of the fat signal fraction (FSF) of the normal and decreased exocrine function group. Pancreatic fat fraction increased in the chronic pancreatitis group however this did not reach a statistically significant level in our study population ($p=0.29$).

Fig. 4-a. 27-year-old female with history of Crohn's disease currently in remission was referred to our institution following 2 weeks of unexplained epigastric and right upper quadrant abdominal pain. The patient was admitted to our gastroenterology service with suspicion of

pancreatitis as the etiology. A coronal thick slab image from S-MRCP acquired 10 minutes after secretin injection shows a normal appearance of the pancreatic duct (thin arrows). The main pancreatic duct diameter was 2.1 mm and there were no ectatic side branches. Excreted pancreatic juice is seen as high T2 signal filling the duodenal lumen (thick arrows) beyond the 2^{nd} portion of the duodenum. With a negative S-MRCP result, sphincter of Oddi dysfunction was suspected as the etiology of the pain and subsequently ERCP was performed.

Fig. 4-b. A fluoroscopic image obtained during ERCP following injection of contrast to the pancreatic duct, which shows no abnormalities (arrows). The sphincter pressure was within normal limits excluding possibility of sphincter of Oddi dysfunction. Following these negative findings, the gastroenterologist decided to proceed with IDST during the ERCP. Secretin was injected and pancreatic juice was collected directly from the pancreatic duct for up to 30 minutes. The peak bicarbonate concentration was 101 mEq/L and the mean EFR was 2.8 ml/min therefore the patient was deemed to have chronic pancreatitis.

Fig. 4-c. Axial fat-suppressed unenhanced T1-weighted gradient echo MR image shows the tail of the pancreas (arrow) and the spleen. ROI measurements (circle ROIs) showed average signal intensity of 245 for the pancreas and 216 for the spleen. $SIR_{p/s}$ was 1.13.