EUS and secretin endoscopic pancreatic function test predict evolution to overt structural changes of chronic pancreatitis in patients with nondiagnostic baseline imaging

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ABSTRACT

Background and Objectives: The accuracy of EUS and endoscopic pancreatic function test (ePFT) for diagnosis of early or minimal-change chronic pancreatitis (MCCP) is poorly understood. We hypothesized that the natural history of the disease may be used as a “gold standard” to assess the ability of EUS and ePFT to predict the eventual development of overt chronic pancreatitis (CP) changes on computed tomography/magnetic resonance cholangiopancreatography (CT/MRCP). The aim of the study was to determine the ability of EUS and ePFT to predict disease progression in patients with suspected MCCP who had nondiagnostic baseline imaging. Methods: A retrospective cohort study was conducted. Patients who underwent EUS and ePFT for suspected CP and who had nondiagnostic CT or MRCP were included. Patients without repeat imaging performed more than 1 year after their initial EUS/ePFT were excluded. Imaging was considered diagnostic if calcifications, main duct dilation (Cambridge Class III/IV), or severe atrophy were identified. Patients lost to follow-up were contacted to complete a survey documenting current symptoms and whether patients progressed to CP based on imaging. Univariable and multivariable analyses were performed using Cox regression. Results: Two hundred and thirty patients who underwent EUS/ePFT for suspected MCCP were identified between 2006 and 2012. Of these, 90 had a non-diagnostic baseline imaging test and subsequently a follow-up imaging test greater than 1 year later. These 90 patients constituted our study population. During a mean follow-up of 7 years, 19 (21%) patients developed CP by histology and imaging. Abnormal ePFT (peak bicarbonate <80 mmol) was a significant predictor of eventual CP development. Conclusion: EUS and ePFT may be useful tests for predicting eventual MCCP progression to CP.
INTRODUCTION

Chronic pancreatitis (CP) is characterized by progressive pancreatic inflammation and scarring, irreversibly damaging the pancreas and resulting in loss of exocrine and endocrine function.[1] Classically, CP is diagnosed in the presence of morphologic changes on imaging, including pancreatic calcification, ductal dilation, and glandular atrophy. These computed tomography (CT) features are most commonly found in the end stages, and may take 10 years or more to emerge. A subset of patients pose a unique diagnostic dilemma who present with suggestive CP symptoms but lack pathognomonic abnormalities of pancreatic structure. These patients are often considered to have early or minimal-change chronic pancreatitis (MCCP).[2] Detecting this condition represents a unique opportunity for early diagnosis and intervention before extensive acinar cell destruction is obvious on cross-sectional imaging.

A growing body of literature has examined alternative tests to diagnose CP and MCCP. Two such tests are EUS and the secretin endoscopic pancreatic function test (ePFT). EUS scoring systems have been developed including criteria that correlate with histological fibrosis.[1,3] However, poor interobserver reliability[4] and lack of consensus on EUS features for CP criteria have limited its widespread use. Secretin ePFT detects mild exocrine dysfunction which has been considered a surrogate marker of early fibrosis. In one study in patients undergoing surgery for CP, a combined EUS/ePFT offered 100% sensitivity for detecting CP.[5]

Proper assessment of new tests requires a reliable gold standard. Histology is rarely available as a comparison, particularly in the early phase of this disease when patients rarely undergo surgery. In this study, we examined the ability of EUS and ePFT to predict the development of overt changes of CP over time, using the disease’s natural history as the gold standard.

METHODS

Study design

This was an institutional review board-approved single-center historical cohort study. The cohort was comprised of those undergoing EUS, ePFT, or both for evaluation of suspected CP between 2006 and 2009, and represents a subset of those from a prior study examining correlations of EUS features with ePFT results.[6] The present study is restricted to those who had nondiagnostic CT or magnetic resonance imaging (MRI) at baseline and had adequate follow-up (CT or MRI >1 year after their original endoscopic testing). Patients were excluded if they had classic imaging features of CP on cross-sectional imaging (calcifications, duct dilation, and severe atrophy) at the time of EUS/ePFT, or if they had prior pancreatic surgery or surgically altered anatomy preventing complete endoscopic assessment.

Patient charts were reviewed from April 2006 to December 2017. Relevant clinical data were obtained from patient medical records (EPIC™) and entered into REDCap electronic database. Imaging and ePFT results were abstracted from reports, and actual images re-reviewed to confirm features of CP whenever they were available. The baseline EUS results were scored based on Rosemont classification.[7] Rosemont scoring was also used at our institution on original EUS reports at the time of the initial procedure. A linear EUS scope was used for all procedures. EUS reports were available for all patients and were reviewed by two of the study authors for agreement on findings. If patients underwent additional EUS testing, results were recorded but were not used in final analysis based on the studies defined outcomes.

The baseline ePFT result was recorded as the peak bicarbonate concentration (peak bicarbonate <80 mmol is abnormal). Prior to collection, an intravenous dose of synthetic secretin (0.2 mcg/kg) was administered. A standard upper endoscope was inserted for collection
of duodenal samples. The stomach was cleared to prevent acid contamination of the duodenal samples. Duodenal samples were collected at 15, 30, and 45 min after secretin stimulation through the suction channel of the endoscope. Samples were transported on ice and analyzed for bicarbonate concentration on a hospital auto-analyzer.\(^6\)

The baseline CT and/or MRI imaging test was defined as having been performed from 1 year prior until 3 months after the EUS/ePFT assessment. Baseline imaging was reviewed for diagnostic features of CP that would require exclusion. For CT, diagnostic features included calcification, duct dilation, or severe atrophy. Additional diagnostic features from MR cholangiopancreatography (MRCP) included Cambridge Class III or IV ductal changes. The most recent CT or MRI/MRCP performed at least 1 year after EUS/ePFT was considered the “follow-up” imaging test. These were also reviewed for diagnostic CP features. Radiology reports from the time of initial patient presentation were used; radiologists at the time of patient presentation were not aware of patients’ clinical status. As such, all initial and follow-up radiology reports occurred before the time of the present study limiting any bias on interpretation. No images we reread for the present study had changes in interpretation of reporting that would affect outcomes. Follow-up clinical visit information was also collected and included current symptoms, active opioid use, use of pancreatic enzyme replacement, development of diabetes, pancreatic histology, and pancreatic surgical intervention. In the case a patient had multiple follow-up imaging tests completed, the first positive test or the last available test done if all negative was taken as the end point. Patient follow-up and interval testing was determined by the provider, and as such, there is variability in timing of testing given clinical decision making at that time.

Histopathology and surgical specimens were also reviewed for all patients if pancreatic biopsy or resection was completed. This was viewed as a gold standard for CP diagnosis when available and was correlated with imaging findings.

**Patient prospective follow-up**

Attempts were made to contact patients to obtain imaging test films that would enhance the length of follow-up and number of eligible patients. Patients were first contacted by mail with a study letter and informed consent form, followed by a phone interview conducted with questions asked based on variables for patients with no clinical follow-up (current symptoms, active opioid use, use of pancreatic enzyme replacement, development of diabetes, pancreatic histology, and pancreatic surgical intervention). Figure 1 shows the patient recruitment process.

### Statistical analysis

Data are presented as mean ± standard deviation, median (25\(^{th}\) and 75\(^{th}\) percentiles), or frequency (%). Time-to-event analysis was done to assess the risk of CP progression evident on imaging or histology. Follow-up time was defined as years from baseline imaging test to the first positive follow-up imaging test showing CP, histological confirmation of CP at the time of surgery, or the last available imaging test. Kaplan–Meier plots were constructed and log-rank tests were used to compare groups. Furthermore, unadjusted and adjusted Cox regression analysis was performed. Adjusted analysis took into account episodes of recurrent pancreatitis.

All analyses were performed using SAS (version 9.4, The SAS Institute, Cary, NC, USA), and \(P < 0.05\) was considered statistically significant.

### RESULTS

A total of 230 patients who underwent ePFT/EUS during the specified time frame were identified and reviewed. Ninety patients with nondiagnostic baseline imaging and appropriate follow-up were included in final analysis [Figure 1]. The average age was 46.2 years, and 64 (71\%) were female. The mean body mass index was 26.9. 50 (55.6\%) were identified as never-smokers and 47 (52.2\%) identified as not consuming alcohol. Patients were followed for an average of 7 years (CI: 3.5–9.5). Table 1 highlights the baseline characteristics of all patients included in the study.

Nineteen (21.1\%) patients developed overt CP during an average follow-up of 3.9 years. Overt CP was diagnosed based on imaging in 13 patients [Table 2] and surgical histology in 6 patients. CT was the most frequently used imaging modality, and severe glandular atrophy was found most frequently in 9 (69.2\%) of patients [Table 2].

The Cox univariable analysis of variables that predict progression to overt CP is summarized in Table 3.
predictive of the development of overt CP over time. The hazard ratio (HR) was 4.7 (CI: 1.8, 12.4) for an ePFT peak bicarbonate <80 mmol. The HR was 5.7 (CI: 2.1, 15.3) for an EUS Rosemont classification of “suggestive” or “most consistent.” Heavy alcohol consumption HR 5.1 (95% CI: 2.0, 13.5), and a history of >1 prior episode of acute pancreatic (AP) HR 15.1 (95% CI: 2.2, 120.8), were likewise predictors of progression. The Kaplan–Meier curves illustrating rates of progression for these predictors are shown in Figure 2. Panel A of Figure 2 shows that heavy alcohol consumption after 2 years was significantly associated with radiographic changes. Panel B shows a significantly increased detection of radiographic changes of patients with 1 and >1 episode of AP compared to patients without a history of AP. There was not a statistically significant difference between 1 episode and >1 episode of AP in terms of developing radiographic changes of CP on follow-up. Panels C and D of Figure 2 highlight the testing characteristics of interest for the study with a negative ePFT (Panel C) strongly predictive of radiographic changes and an EUS Rosemont score of consistent compared to normal (Panel D). Changes for Rosemont scoring could be seen as early as 3 years after baseline testing.

Figure 3 presents the Kaplan–Meier risk estimates for development of CP comparing positive findings on baseline EUS and ePFT testing individually and when combined. *Post hoc* comparisons showed that patients who had both tests normal had significantly lower rates of progression compared to those who had abnormal EUS only (P < 0.001), those who had abnormal ePFT only (P < 0.001), and those with both tests abnormal (P < 0.001). There were no significant differences between the three abnormal test groups.

DISCUSSION

We have shown that the results of EUS and secretin ePFT predict the eventual development of overt structural changes of CP. We reviewed 230 well-characterized patients...

Table 1. Baseline patient characteristics

| Factor                        | Total (n=90), n (%) |
|-------------------------------|---------------------|
| Demographics                  |                     |
| Age at baseline ePFT/EUS      | 46.1±14.9           |
| Male                          | 26 (28.9)           |
| Female                        | 64 (71.1)           |
| Caucasian                     | 78 (86.7)           |
| Baseline clinical characteristics|                    |
| BMI                           | 26.9±6.8            |
| Smoking status                |                     |
| Active                        | 25 (27.8)           |
| Former                        | 15 (16.7)           |
| Never                         | 50 (55.6)           |
| Alcohol consumption           |                     |
| None                          | 47 (52.2)           |
| Minimal                       | 26 (28.9)           |
| Moderate                      | 7 (7.8)             |
| Heavy                         | 10 (11.1)           |
| Diabetic                      | 10 (11.1)           |
| Previous acute pancreatitis   |                     |
| Never                         | 37 (41.1)           |
| 1 episode AP                  | 16 (17.8)           |
| >1 episode AP                 | 37 (41.1)           |
| Etiology (nonexclusive)       |                     |
| Alcohol                       | 14 (15.6)           |
| Smoking                       | 15 (16.7)           |
| Idiopathic                    | 48 (53.3)           |
| Genetic mutations             | 20 (22.2)           |
| Autoimmune pancreatitis       | 19 (21.1)           |
| Recurrent acute pancreatitis  | 24 (26.7)           |
| ePFT                          |                     |
| Peak bicarbonate              | 88.0 (75.0, 99.0)   |
| EUS                           |                     |
| Rosemont classification       |                     |
| Normal                        | 59 (66.3)           |
| Indeterminate                 | 19 (21.3)           |
| Suggestive                    | 5 (5.6)             |
| Most consistent               | 6 (6.7)             |

Statistics presented as mean±SD, median (P25, P75) or n (column %).
ePFT: Endoscopic pancreatic function test; BMI: Body mass index; SD: Standard deviation; AP: acute pancreatic
who underwent combined EUS/ePFT for suspicion of MCCP. Ninety patients have negative baseline imaging and maintained adequate follow-up and had repeat pancreatic imaging over a 10-year interval of which nineteen (21.1%) developed CP. A Rosemont score of suggestive/consistent (HR: 7.3, \(P = 0.001\)) and peak bicarbonate <80 meq (HR: 4.7, \(P = 0.009\)) were each predictive of radiographic progression.

### Table 2. Patients who developed diagnostic radiologic changes by date, modality, and findings

| Patient | Date of baseline imaging | Modality | Date of follow-up imaging | Modality | Findings |
|---------|--------------------------|----------|---------------------------|----------|----------|
| 1       | July 21, 2006            | CT       | February 20, 2012         | CT       | Calcifications, atrophy |
| 2       | July 13, 2006            | CT       | July 20, 2018             | CT       | Main duct dilation, severe atrophy |
| 3       | March 1, 2005            | CT       | April 6, 2018             | CT       | Severe atrophy |
| 4       | February 1, 2006         | CT       | February 1, 2011          | CT       | Calcifications |
| 5       | January 30, 2006         | CT       | September 9, 2018         | CT       | Severe atrophy, main duct dilation |
| 6       | December 26, 2008        | CT       | June 11, 2015             | CT       | Calcifications |
| 7       | May 23, 2009             | CT       | October 2, 2017           | CT       | Severe atrophy, calcifications |
| 8       | August 24, 2008          | MRCP     | June 30, 2009             | MRCP     | Severe atrophy, stricture |
| 9       | April 22, 2009           | CT       | July 10, 2017             | CT       | Severe atrophy |
| 10      | April 1, 2008            | CT       | March 7, 2012             | CT       | Severe atrophy |
| 11      | November 10, 2010        | CT       | February 24, 2014         | CT       | Atrophy, main duct dilation |
| 12      | March 5, 2009            | CT       | July 20, 2011             | MRCP     | Atrophy, main duct dilation, side branch changes |
| 13      | September 3, 2008        | MRCP     | March 27, 2011            | CT       | Calcifications, atrophy |

CT: Computerized tomography; MRCP: Magnetic resonance cholangiopancreatography

Figure 2. Kaplan–Meier curves for variables of interest associated with diagnostic imaging of chronic pancreatitis after baseline nondiagnostic imaging. (a) No alcohol/minimal versus moderate/heavy, (b) Episodes of acute pancreatitis; never versus 1 versus >1, (c) Peak bicarbonate on endoscopic pancreatic function test >80 mmol versus <80 mmol, (d) EUS Rosemont scores
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Table 3. Factors associated with risk of developing overt chronic pancreatitis during follow-up

| Factor | Hazard ratio (95% CI) |
|--------|----------------------|
| Age at baseline ePFT/EUS (5 years increment) | 0.94 (0.81-1.09) |
| Male versus female | 1.6 (0.68-4.0) |
| BMI (1 kg/m² increment) | 0.99 (0.92-1.05) |
| Smoking status |  |
| History of smoking (current, past) | 2.9 (1.1-7.7) |
| Current smoking versus former | 1.8 (0.74-4.3) |
| Alcohol consumption |  |
| Heavy versus none | 4.3 (1.8-13.2) |
| Moderate/heavy versus minimal/none alcohol consumption | 3.7 (1.5-9.1) |
| Heavy versus none-moderate alcohol consumption | 5.1 (2.0-13.5) |
| Diabetic | 0.40 (0.05-3.0) |
| Previous acute pancreatitis |  |
| 1 episode versus never | 10.5 (2.2-90.3) |
| >1 episode versus never | 15.8 (2.1-120.8) |
| Etiology |  |
| Heavy alcohol consumption | 3.7 (1.5-9.3) |
| Smoking | 1.4 (0.48-4.0) |
| Hypertriglyceridemia | 2.4 (0.88-6.6) |
| Idiopathic | 0.67 (0.28-1.6) |
| Genetic mutations | 2.4 (0.99-5.8) |
| Autoimmune pancreatitis | 2.0 (0.82-5.0) |
| Recurrent acute or necrotizing pancreatitis | 2.8 (1.2-6.5) |
| Family history of acute pancreatitis | 0.79 (0.11-5.9) |
| ePFT |  |
| Peak bicarbonate <80 versus ≥80 | 4.7 (1.8-12.4) |
| Rosemont classification |  |
| Suggestive/most consistent versus normal | 7.3 (2.4-22.1) |
| Suggestive/most consistent versus normal/indeterminate | 5.7 (2.1-15.3) |

Moreover, prior recurrent acute pancreatitis and heavy alcohol use were even more predictive than the EUS/ePFT results. This indicates the importance of the clinical history which informs “pretest probability” when employing these tests.

MCCP is also referred to as “early CP” in the literature, distinguishing it from “established” or “end-stage” CP. A multinational working panel statement reports that MCCP is an early disease state with usually preserved pancreatic function and potentially reversible features. However, this document abounds with questions and disagreement over the nature and natural history of early CP. No formal definitions or agreements regarding the workup and management of early CP have been reached.

Few studies have examined the natural history of patients with suspected MCCP. In one prospective study, a baseline EUS and ERCP was done in those with suspected CP and negative cross-sectional imaging. Thirty percent of patients with a normal pancreatogram had EUS features suggestive of CP, and 66% of these patients progressed to develop ductal changes of CP on subsequent ERCP after mean 18 months of follow-up. The conclusion was that EUS can detect structural changes even not initially apparent on pancreatogram. A more recent study examined the accuracy of EUS using Rosemont criteria and Japanese criteria to diagnose early stage CP. Of 40 patients, 12 (30%) progressed to overt CP within 3 years. The timing of progression observed in that study aligns with our own results, which show progression in 21% after an average of 3.9 years.

The specificity of EUS features of CP has been questioned in light of “pancreatopathy” related to age, diabetes, smoking, and other factors. Another limitation affecting the reliability of EUS diagnosis is high interobserver variability. We suspect that these issues are most problematic with regard to the “indeterminate” Rosemont category, in which there are 2 or 3 minor features. In our study, only the Rosemont strata “suggestive” and “most consistent” were found to be associated with progression. These strata require more than 5 minor features and/or major features such as parenchymal shadowing foci and honeycombing lobularity. The ability of EUS to detect lesions missed by MRI and CT is also well established. Canto et al. examined the ability to detect pancreatic lesions in asymptomatic high-risk individuals and found that CT, MRI, and EUS detected a pancreatic abnormality in 11%, 33.3%, and 42.6% of these high-risk individuals, respectively. While not examining features in CP, this study highlights the ability of EUS to detect lesions superior to CT. We believe that our study aligns with these findings, showing that EUS can better detect small lesions and early changes of CP better than CT.

Patients in our study underwent combined EUS and ePFT testing allowing for an analysis of structural and functional pancreatic status. Previous studies by Ketwaroo et al. reported a positive predictive value of pancreatic function testing of only 45%. Although the secretin ePFT may not suffice as a standalone diagnostic test, we found that a HR for peak bicarbonate was 4.7 (CI: 1.8, 12.4) for predicting future radiographic changes of CP, indicating its helpful predictive ability. We believe that combined testing may provide a more complete analysis of pancreatic function.
and degree of injury as it pertains to the MCCP disease state. In our study, only five percent of patients had concordant abnormal ePFT and EUS testing [Figure 3]. The low number of this group limited any ability to detect significant differences for prediction of CP radiological changes compared to an abnormal ePFT or EUS alone.

Additional technologies such as EUS-elastography and shear-wave measurement may provide a third layer of information when evaluating subclinical CP. These tools provide objective evidence of parenchymal fibrosis and have been correlated with Rosemont classification with high accuracy.[21,22] Their noninvasiveness and enhanced sensitivity allow for additional information to be easily obtained during EUS examination and complement pancreatic function assessment from ePFT.

Etiologic risk factors for progression of MCCP to CP in our population included heavy alcohol consumption and recurrent acute pancreatitis. Both of these are major etiologic risk factors under the TIGAR-O classification system for CP.[23] This highlights that the transition of MCCP to CP requires multiples “hits.” In our population, 27 (30.3%) patients had genetic testing, of which 6 mutations were found (5 – CFTR and 1 – SPINK1).

A strength of this study includes the use of a well-characterized group of 90 patients with reasonable suspicion of CP in spite of negative cross-sectional imaging who underwent combined EUS/ePFT testing. The length of follow-up with an average of 7 years from initial contact also allows review of the natural history of patients’ disease progression. Diligent attempts were made to contact patients who were lost in order to maximize follow-up. Imaging was obtained and reviewed whenever possible to confirm normal and abnormal findings. Rosemont scoring was used at our institution since 2013 for standardization of reports; as such, Rosemont scoring was maintained as the standard to report for this study to maintain consistency when reinterpreting EUS imaging. The study also possesses obvious limitations. The retrospective nature of the study requires a backward look at the “baseline” assessment, relying on medical notes for ascertaining symptoms and risk factors. In most cases, baseline CT scans could be viewed and confirmed as normal or nondiagnostic of CP, but in a few cases, we relied on imaging reports or “normal pancreas.” One could also argue that longer follow-up (e.g., beyond 10 years) is desirable to best understand the variable progression of this disease. The retrospective nature also limits the standardization of patient follow-up and imaging which was determined by providers’ discretion based on clinical need and not controlled for in this study. Further studies with longer follow-up and larger patient populations may eventually help validate our findings and better capture risk factors for the transformation of MCCP to established CP.

CONCLUSIONS

In summary, EUS and ePFT may be helpful tests to diagnose suspected MCCP, given that they are predictive of eventual “obvious” structural changes of CP. However, of equal importance are the presence of clinical risk factors of heavy alcohol and prior acute pancreatitis. Endoscopic test results cannot be considered in a vacuum but rather in context of the patient’s clinical predisposition. Patients who report heavy alcohol use or recurrent AP should be counseled on lifestyle modification and aggressive delineation of cause should be sought as this may provide an opportunity to intervene and slow progression. Our study also adds to understanding about the natural history of MCCP and the timeframe one can expect negative cross-sectional imaging to transform to classic diagnostic imaging.

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Conflicts of interest
There are no conflicts of interest.

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