ORIGINAL ARTICLE

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The Rosemont Criteria Can Predict the Pain Response to Pancreatic Enzyme Supplementation in Patients with Suspected Chronic Pancreatitis Undergoing Endoscopic Ultrasound

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Background/Aims: The Rosemont classification system was designed to standardize the endosonographic assessment of chronic pancreatitis. To determine whether the Rosemont classification system can predict the response to pancreatic enzyme supplementation in patients undergoing endoscopic ultrasound (EUS) evaluation of suspected chronic pancreatitis. **Methods:** Sixty-five patients were included with abdominal pain undergoing endosonography for suspected chronic pancreatitis were included. Patients completed a questionnaire for evaluation of their abdominal pain. Group 1 (n=13) had EUS findings consistent with or suggestive of chronic pancreatitis. Group 2 (n=45) had EUS findings that were normal or indeterminate in the Rosemont classification system. Patients were given pancreatic enzyme supplementation and then given a follow-up pain questionnaire for a mean of 37 days subsequent to EUS regarding the change in pain. **Results:** Group 1 patients were more likely to have a response to pancreatic enzymes (62% vs 24%, p= 0.012) and a decrease in their pain scale ratings (2.62 vs 0.29, p=0.01). Computed tomography findings of chronic pancreatitis and narcotic use did not predict the response to pancreatic enzyme supplementation. The individual Rosemont criteria of hyperechoic foci with shadowing (p=0.03), lobularity (p=0.02), and stranding (p=0.001) were associated with improvement of pain after treatment. **Conclusions:** The Rosemont classification system can identify patients who are more likely to have improvement in abdominal pain after treatment with pancreatic enzyme supplementation. **(Gut Liver 2012;6:521-526)**

Key Words: Endoscopic ultrasound; Chronic pancreatitis; Rosemont criteria

INTRODUCTION

Chronic pancreatitis is a fibro-inflammatory disease of the pancreas characterized by irreversible morphologic changes that typically cause pain and/or loss of function.[1] Pain occurs in 80% to 90% of patients, and is considered the most important factor affecting quality of life.[2] Despite this, the pathophysiology of pain in chronic pancreatitis is poorly understood.[3] Clinically it is usually difficult to determine if abdominal pain is related to chronic pancreatitis or some other cause, such as a functional disorder. One of the goals of this trial was to determine if endoscopic ultrasound (EUS) criteria for chronic pancreatitis can help determine which patients' abdominal pain will be responsive to pancreatic enzyme supplementation in the absence of any gold standard that can reliably identify chronic pancreatitis as the cause of any particular patients' abdominal pain.

Pancreatic enzyme replacement therapy is often initiated for the treatment of pain in chronic pancreatitis. In animal studies,[4,5] the presence of intraluminal exogenous pancreatic enzymes appear to regulate pancreatic enzyme secretion through a negative feedback loop. Theoretically, this may reduce pancreatic duct pressure and improve abdominal pain in those with chronic pancreatitis. Some randomized trials,[6,7] but not all,[8-10] have shown that abdominal pain in patients with chronic pancreatitis improves with pancreatic enzyme supplementation therapy. None of these trials used endoscopic ultrasound to assess the presence and severity of chronic pancreatitis. Therefore, there is no guidance as to which patients undergoing EUS for abdominal pain with potential chronic pancreatitis may benefit from pancreatic enzyme replacement therapy.

EUS is thought to be the most sensitive procedure to detect chronic pancreatitis.[11] Criteria which suggest chronic pancreati-

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tis are divided into parenchymal and ductal findings.[12] Recently a group of experts in the field of endosonography convened in Rosemont, Illinois to attempt to standardize the endosonographic diagnosis of chronic pancreatitis.[13] The Rosemont classification system categorizes patients undergoing endosonography by their likelihood of having chronic pancreatitis based on defined EUS criteria. The utility of these criteria at predicting prognosis and outcome of therapy in patients with chronic pancreatitis is unknown. The hypothesis of this study was that patients with abdominal pain and clinical concern for chronic pancreatitis were more likely to have a pain response to pancreatic enzyme supplementation if they met Rosemont criteria for chronic pancreatitis at the time of EUS. We also sought to determine which endosonographic criteria for chronic pancreatitis can best predict a reduction in pain with pancreatic enzyme supplementation therapy.

MATERIALS AND METHODS

This study was conducted from October 2008 to March 2010. It was approved by the Institutional Review Board at the University of Vermont. The procedures followed were in accordance with the Helsinki Declaration of the World Medical Association. Patients referred for endosonography with suspected chronic pancreatitis and abdominal discomfort were considered for enrollment. For inclusion into the study patients had to: 1) have intermittent or persistent abdominal pain for at least 3 months prior to the EUS exam, and 2) have abdominal discomfort at the time of EUS. Patients with an alternative diagnosis of abdominal pain (pancreatic cancer, peptic ulcer disease, choledocholithiasis, duodenal obstruction) or who had undergone a previous trial of pancreatic enzymes were excluded. Patients younger than 18 years old, those who could not fill out a questionnaire, or those who could not provide informed consent were also excluded. Patients with clinical symptoms of advanced chronic pancreatitis (steatorrhea, and weight loss) were included. This study was approved by the Committee for Human Research at the University of Vermont.

Included patients completed a questionnaire regarding their pain, bowel habits and weight prior to endosonography. The questionnaire evaluated the presence, duration, frequency and severity of abdominal pain. An 11-point linear analogue scale (0-10) was used to assess abdominal pain severity, as has been used previously to evaluate pain response to pancreatic enzymes in patients with chronic pancreatitis.[8] Patients were asked to report the worst pain they had in the preceding 24 hours. Patients characterized the frequency of their abdominal pain as "monthly", "weekly", "daily", or "constantly." They were considered to have intermittent pain if the pain occurred less frequently than daily. Medication usage, including narcotics and proton pump inhibitors, history of depression, alcohol consumption, abdominal computed tomography (CT) exams and the presence of abnormalities in serum levels of amylase and lipase were recorded. Patients were classified as alcohol users if they reported drinking alcohol on the initial questionnaire. Patients were classified as alcohol abusers if they had a history of alcoholism as identified in the electronic medical record. CT exams were considered consistent with chronic pancreatitis if this was the impression of the reading radiologist.

EUS was performed by one of 2 experienced endosonographers (R.Z., E.G.) using a radial (UCT 160) echoendoscope (Olympus America, Melville, NY, USA) with the Prosound α10 Premier processor (ALOKA America, Wallingford, CT, USA). The linear array echoendoscope (UCT 140) was also used if a fine needle aspiration was performed. Sedation for procedures was left to the discretion of the endosonographer. Endosonographic criteria for chronic pancreatitis were recorded at the time of EUS. Parenchymal endosonographic criteria for chronic pancreatitis included hyperechoic foci (with or without shadowing), lobularity (with or without honeycombing), cysts and stranding. Ductal features included dilation, hyperechogenicity or irregularity of the main pancreatic duct, calculi within the main pancreatic duct or dilation of side branches. The presence or absence of each of these criteria was recorded for each patient. Patients were then classified according to the likelihood of having chronic pancreatitis as per the Rosemont Classification System.[13] This system classifies findings as consistent with chronic pancreatitis, suggestive of chronic pancreatitis, indeterminate for chronic pancreatitis or normal. We segregated our patients into 2 groups. Group 1 had EUS findings that were consistent with or suggestive of chronic pancreatitis. Group 2 had EUS findings that were indeterminate for chronic pancreatitis or normal.

All included patients were started on pancreatic enzyme supplementation (Viokase®-16; 4 tablets with meals and 2 with snacks) subsequent to their EUS exam. Viokase®-16 contains 16,000 units of lipase, 60,000 units of protease, and 60,000 units of amylase per tablet. A follow-up visit was then conducted 1 month after initiation of therapy. Patients were queried regarding their response to pancreas enzyme supplementation. A follow-up questionnaire identical to the one completed prior to performance of the EUS exam was completed. Patients were again asked to report the worst abdominal pain they had in the preceding 24 hours. Medication usage, including narcotic intake, alcohol intake, and compliance with pancreatic enzyme supplementation, was assessed. Compliance with pancreatic enzyme supplementation was defined as ingestion of at least half of one month's supply of enzyme supplementation as reported by the patient. Patients who felt better with pancreatic enzyme supplementation and had an improved abdominal pain scale were classified as responders. Patients that had resolution of abdominal pain on pancreatic enzyme supplementation were considered complete responders.

Statistical analysis was performed using SPSS software (SPSS Inc., Chicago, IL, USA). Two-sided p-values of less than 0.05

were used to determine significance. The entire cohort was analyzed with descriptive statistics for demographic data (age, gender), pain characteristics (severity duration, and frequency) medication usage (narcotics, proton pump inhibitors), alcohol consumption, CT evidence of pancreatitis, history of depression, prior elevation in serum pancreatic enzymes, and compliance with pancreatic enzyme supplementation. Univariate analysis was performed between the 2 groups using the chi-squared test for qualitative variables, and the independent samples t-test for numeric data. Patients who were not compliant with pancreatic enzymes were included in the analysis. The primary question was whether patients having an EUS exam consistent with or suggestive of chronic pancreatitis (group 1) were more likely to respond to pancreatic enzyme supplementation than patients with a normal exam or one that was indeterminate for chronic pancreatitis (group 2). This question was analyzed in 2 ways. First, it was assessed in a binary fashion with respect to response to pancreatic enzymes. The chi-squared test was used for this analysis. Second, changes in the linear analogue scale for abdominal pain were compared between the 2 groups. The Independent samples t-test was used for this analysis. The chi-squared test was used to analyze which individual EUS characteristics best predicted response to pancreatic enzyme supplementation. Accuracy of the individual Rosemont criteria was defined as true positives+true negatives divided by the true positives+true negatives+false positives+false negatives.

Table 1. Patient Characteristics for the Sample and by Group

Characteristic	Total cohort (n=58)	Group 1 (n=13)	Group 2 (n=45)	p-value (group 1 vs group 2)
Mean age±SD	52 ±12.5	56±11.7	51±12.7	0.26
Gender (% female)	62%	39%	69%	0.05
Mean yr of pain duration±SD	3.1±4.5	2.4±2.8	3.4±4.9	0.52
Pain constant or daily	85%	85%	85%	0.99
Mean initial pain±SD	5.3±2.4	5.7±2.9	5.2±2.3	0.51
History of depression	51%	62%	48%	0.38
Current alcohol use	25%	46%	18%	0.04
History of alcohol abuse	29%	46%	24%	0.12
CT consistent with chronic pancreatitis	29%	69%	15%	0.001
Elevated serum pancreatic enzyme	55%	83%	49%	0.03
Narcotic use	25%	38%	21%	0.19
Proton pump inhibitor use	48%	67%	43%	0.15

SD, standard deviation.

RESULTS

There were a total of 65 patients enrolled in this study. Seven patients were excluded, 4 due to lack of follow-up, 1 who underwent cholecystectomy, and 2 with pancreaticobiliary cancer. There were 13 patients (22.4%) with EUS findings consistent with or suggestive of chronic pancreatitis as per the Rosemont classification system (group 1). There were 45 patients (77.6%) with EUS findings that were normal or indeterminate for chronic pancreatitis (group 2). The mean age of the cohort was 52 and 62% were female. The presumed etiologies of chronic pancreatitis of patients in group 1 included alcohol (n=6), idiopathic (n=5), autoimmune (n=1), and medications (n=1). Table 1 illustrates the characteristics of patients in the total cohort, as well as differences between patients in group 1 and group 2. The mean duration, frequency, and initial severity of pain were not significantly different between groups. Males, current alcohol users, patients with an elevated serum pancreatic enzyme prior to endoscopic ultrasound and patients with an abdominal CT scan consistent with chronic pancreatitis were significantly more likely to have EUS findings consistent with or suggestive of chronic pancreatitis.

The mean duration of time between the EUS and the follow-up visit was 37 days (standard deviation, ±12). Seventy-eight percent of patients were compliant with pancreatic enzyme supplementation. A response to pancreatic enzyme supplementation was defined as patient reported improvement in abdominal pain at follow-up in addition to improvement of pain as assessed by an 11-point linear analogue scale. A complete response to enzyme supplementation was defined as complete resolution of abdominal pain at one month. Overall, 33% of patients had a response to pancreatic enzyme supplementation, and 22% of patients had a complete response to treatment.

Table 2. The Rosemont Classification and Prediction of Response to the Pancreatic Enzyme Supplementation

	Total cohort	Group 1	Group 2	p-value (group 1 vs group 2)	OR	95% CI
Response	33%	62%	24%	0.012	4.9	1.3-18.3
Complete response	22%	46%	16%	0.02	4.7	1.2-18.1

Group 1 had endoscopic ultrasound (EUS) findings consistent with or suggestive of chronic pancreatitis. Group 2 had EUS findings that were normal or indeterminate for chronic pancreatitis.
OR, odds ratio; CI, confidence interval.

Patients who had EUS findings consistent with or suggestive of chronic pancreatitis (group 1) were significantly more likely to respond to pancreatic enzyme supplementation therapy (62% vs 24%; p=0.012; odds ratio [OR], 4.9; 95% confidence interval [CI], 1.3 to 18.3) (Table 2). These patients were also significantly more likely to have a complete response to pancreatic enzyme supplementation (46% vs 16%; p=0.02; OR, 4.7; 95% CI, 1.2 to 18.1). The average decline in abdominal pain with pancreatic enzyme supplementation was significantly greater in group 1 patients than in group 2 patients (2.62 vs 0.29, p=0.01). Having pain intermittently (less than daily), and the duration of pain did not predict a response to pancreas enzymes.

CT findings consistent with chronic pancreatitis, narcotic use, age, gender, history of depression, and elevation in serum pancreatic enzymes did not predict a response to pancreatic enzyme supplementation (Table 3). Patients who drank alcohol were more likely to respond to therapy (57% vs 26%, p=0.03) in the overall group. Alcohol use did not predict response to pancreatic enzyme therapy on subgroup analysis of group 1 or group 2 separately (group 1, p=1.0; group 2, p=0.09). A history of alcohol abuse was borderline statistically significantly associated with improvement with pancreatic enzyme supplementation in the overall group (50% vs 23%, p=0.05). A history of alcohol abuse did not predict response to pancreatic enzyme therapy on subgroup analysis of group 1 or group 2 separately (group 1, p=1.0; group 2, p=0.18). Patients who took proton pump inhibitors in conjunction with enzyme supplementation were more likely to respond to supplementation in the overall group (48% vs 17%, p=0.01). Proton pump inhibition did not predict response to pancreatic enzyme therapy on subgroup analysis of group 1 (p=1.0), but patients in group 2 who took proton pump inhibitors were more likely to improve with pancreatic enzyme therapy (p=0.02).

Individual parenchymal (hyperechoic foci with shadowing, lobularity, hyperechoic foci without shadowing, cysts and stranding), and ductal (main pancreatic duct calculi, irregular main pancreatic duct contour, dilated side branches, main pancreatic duct dilation, hyperechoic main pancreatic duct margin) EUS Rosemont criteria for chronic pancreatitis were evaluated for their ability to predict a response to pancreatic enzyme supplementation (Table 4). The parenchymal findings of hyperechoic foci with shadowing, lobularity and stranding were predictive of a response to pancreatic enzyme supplementation. None of the ductal findings were predictive of improvement with enzyme therapy.

Table 3. Predictors of a Pain Response to Pancreatic Enzyme Supplementation

Characteristic	p-value	OR	95% CI
CT consistent with chronic pancreatitis	0.11	0.4	0.1-1.2
Gender	0.11	2.5	0.8-7.7
Age	0.79	NA	-8-6.1
History of depression	0.17	0.4	0.1-1.4
Pain duration	0.69	NA	-3.2-2.1
Alcohol use	0.03	3.9	1.1-13.7
Alcohol abuse	0.05	0.3	0.1-1.0
Narcotic use	0.66	0.8	0.2-2.8
Elevated serum pancreatic enzyme	0.11	0.4	0.1-1.3
Proton pump inhibitor use	0.01	0.2	0.1-0.8

OR, odds ratio; CI, confidence interval; NA, not applicable.

DISCUSSION

The use of pancreatic enzyme supplementation is controversial for the treatment of pain in patients with chronic pancreatitis.14 While abdominal pain improved in only 33% of our cohort that were given pancreatic enzyme supplementation, patients whose EUS findings were consistent with, or suggestive of, chronic pancreatitis, as per the Rosemont classification system, were significantly more likely to respond to pancreatic enzyme supplementation (62% vs 24%, p=0.012), and had a greater reduction in pain scales (2.62 vs 0.29, p=0.01) than those who had a normal EUS or indeterminate findings. Also, 46% of patients with EUS findings consistent with or suggest of chronic pancreatitis had complete resolution of abdominal pain at the time of follow-up, and this was significantly different from patients whose EUS findings were indeterminate or normal.

This is the first trial to evaluate whether endoscopic ultrasound can predict a pain response to pancreatic enzymes in patients suspected of having chronic pancreatitis. EUS is increasingly used to evaluate chronic pancreatitis. It is the most

Table 4. The Accuracy of the Individual Rosemont Criteria in Predicting a Pain Response to Pancreatic Enzyme Supplementation

Rosemont criteria	Accuracy, %	p-value
Parenchymal findings		
Hyperechoic foci with shadowing	72	0.03
Lobularity	71	0.02
Hyperechoic foci without shadowing	55	0.15
Cysts	67	0.32
Stranding	74	0.001
Ductal findings		
MPD calculi	67	0.59
Irregular MPD contour	66	0.32
Dilated side branches	71	0.08
MPD dilation	69	0.15
Hyperechoic MPD margin	67	0.38

p-values indicate whether the individual criteria were associated with a pain response to pancreatic enzyme supplementation.
MDP, main pancreatic duct.

sensitive imaging modality for detecting pancreatic parenchymal changes.[3,15] However, it can sometimes be difficult to distinguish EUS findings of chronic pancreatitis from normal variation in echogenicity of the pancreas, and it is not always clear how these findings should change patient management. Also, EUS exams for chronic pancreatitis are subject to interobserver variability.[16,17] Ideally The Rosemont classification system could improve identification of patients with chronic pancreatitis, and help guide therapy. Our study suggests that this classification system can identify patients more likely to respond to pancreatic enzyme supplementation. The parenchymal EUS criteria of hyperechoic foci with shadowing, lobularity and stranding were best at predicting a response to pancreatic enzyme supplementation in our study. Ductal criteria were not able to predict a response to therapy. It is possible that pancreatic enzyme supplementation is more effective in milder chronic pancreatitis prior to the development of ductal changes. Prior randomized controlled trials evaluating the utility of pancreatic enzyme supplementation in chronic pancreatitis used CT and/or endoscopic retrograde cholangiopancreatography to identify patients.[6-10] In our study CT findings consistent with chronic pancreatitis could not predict a response to pancreatic enzyme supplementation. It may be that EUS is better at detecting a population of patients with chronic pancreatitis that will benefit from pancreatic enzyme supplementation because it is the best imaging test to detect subtle changes in the pancreatic parenchyma.

There are limitations to our study. First, medication use, and the clinical manifestations and pattern of pain, vary greatly amongst patients with suspected chronic pancreatitis. This complicates analysis of change in discomfort over a given time interval. In our study we queried patients as to the worst pain they had experienced in the 24 hours prior to filling out the questionnaire in order to minimize problems with diurnal variation in pain, and asked them to grade the frequency of their pain. Variation of pain at intervals greater than one day may have impacted our results; however this seems unlikely because only a minority of patients had pain less frequently than daily (15%), there was no differences between groups in the variation of pain, and the frequency of pain could not predict a response to enzyme therapy. Second, there is no widely accepted and well validated questionnaire to evaluate pain in patients with suspected chronic pancreatitis. We therefore decided to use a simple linear analogue pain scale as has been used in previous studies to evaluate a response to pancreatic enzyme therapy in patients with chronic pancreatitis.[6-8] Third, the limited sample size of this study makes it difficult to reliably evaluate subgroups (i.e., gender, substance abuse, psychiatric history, or cause of chronic pancreatitis and response to pancreatic enzyme supplementation). Fourth, our follow-up was relatively short. Although the study shows that EUS criteria can predict pain response to pancreatic enzyme supplementation in patients with suspected chronic pancreatitis at 1 month, long-term follow-up data is needed. Finally, the design of our trial allows us to assert only that EUS findings of chronic pancreatitis are associated with a short-term improvement of pain when patients are given pancreatic enzyme supplementation. An alternative explanation to our findings could be that the natural course of pain is different between patients with EUS defined chronic pancreatitis and those with unexplained abdominal pain and a normal or indeterminate EUS. The fact that there was no difference in the frequency, duration or initial severity of pain between the two groups; however, would argue against this alternative explanation of our findings. A randomized controlled trial of pancreatic enzyme supplementation in patients with EUS findings of chronic pancreatitis would help resolve this question. Even if pancreatic enzyme supplementation is not responsible for the difference in improvement of abdominal pain between the 2 groups, our study still demonstrates that EUS can identify patients that will have a different clinical course of abdominal pain.

In conclusion, when EUS is performed for abdominal pain with concern for chronic pancreatitis, the Rosemont classification system can identify patients that are more likely to have improvement in abdominal pain after treatment with pancreatic enzyme supplementation. The parenchymal EUS findings of hyperechoic foci with shadowing, lobularity and stranding were able to predict improvement in abdominal pain with pancreatic enzyme supplementation, and could potentially be used to guide therapy in this patient population.

CONFLICTS OF INTEREST

No potential conflict of interest relevant to this article was reported.

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