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ORIGINAL RESEARCH—CLINICAL

Pain Sensitivity and Psychiatric Comorbidities in Chronic Pancreatitis Patients With and Without Pain: Past Experience Matters

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BACKGROUND AND AIMS: Pain is the primary symptom of chronic pancreatitis (CP) and has been associated with abnormal pain processing and psychologic distress. Little is known about these phenomena in patients with painless disease. The aim of this study was to characterize patterns of pain processing and psychologic distress in patients with primary painless vs painful CP. **METHODS:** This was a cross-sectional multicenter study of 235 patients with definitive CP. Patients were categorized based on current and past pain history; current pain (79%), no current (but prior) pain (11%), and painless CP (10%). Demographic information and clinical data including symptoms of anxiety and depression using the Hospital Anxiety and Depression Scale were collected. All patients underwent quantitative sensory testing to assess patterns of pain processing. **RESULTS:** A total of 235 patients (57% males, mean age 53.9 ± 14.0 years, 41% alcohol etiology) were included. Compared to patients with painless CP, enhanced pain sensitivity was observed in both patients with current pain (odds ratio [OR] 3.29; 95% confidence interval [CI] [1.11–9.77], $P = .032$) and no current pain (OR 4.07; 95% CI [1.10–15.03], $P = .035$). Patients with current pain also had increased depression prevalence compared to patients with painless CP (OR 6.15; 95% CI [1.28–29.41], $P = .023$), while no difference was seen for patients with no current pain (OR 1.24; 95% CI [0.19–8.26], $P = .824$). **CONCLUSION:** Total absence of pain in CP is associated with normal pain processing and low prevalence of psychologic distress, whereas patients with prior pain experience appear to have persistent and enhanced pain sensitivity even in the absence of clinical pain and psychologic distress.

Keywords: Chronic Pancreatitis; Pain; Psychiatric Comorbidities; Hyperalgesia

Introduction

Chronic pancreatitis (CP) is a fibroinflammatory disease of the pancreas, which manifests with abdominal pain in the majority of patients during their disease course.[1,2] There is a subset of patients, however, between 10% and 15%, who have "painless CP." This develops silently and is often either an incidental finding or is diagnosed in the workup of CP sequelae including exocrine pancreatic insufficiency or diabetes mellitus.[3,4] Such patients with painless CP typically have pancreatic morphology indistinguishable from that of those with painful CP, and therefore, other mediators of pain than those directly affecting the pancreatic gland must be of importance.

Sustained pancreatic inflammation and fibrosis have been associated with sensitization of pancreatic nerves and central nociceptive pathways.[5–7] These changes manifest clinically as allodynia (pain to stimuli that are not normally painful) and hyperalgesia (increased pain sensitivity to painful stimuli) and are thought to be key pain mediators in a subset of CP patients. However, it is largely unknown how or whether such alterations in pain processing manifest as alterations in pain experience. In addition, psychologic distress, including anxiety and depression, are highly prevalent in CP patients with pain and have previously been seen to associate with increased pain intensity scores and reduced quality of life, but the prevalence of psychologic distress is also largely unknown in patients with painless CP.[5]

Taken together, the connection between pain, pain processing, and psychologic distress in CP patients in relation to

Abbreviations used in this paper: **CI, confidence interval; CP, chronic pancreatitis; OR, odds ratio; P-QST, pancreatic quantitative sensory testing.**

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changes in pain experience remains little investigated. This information is important for clinical management, as pain is a dynamic process in CP, and many patients experience changes in their pain intensity and pain pattern over time.[2,6,8] Hence, when pain is successfully treated, it is unknown what occurs with either pain sensitivity or symptoms of psychologic distress experienced by patients. In other disorders such as recurrent low back pain and fibromyalgia, abnormal patterns of pain processing have been shown to change with dynamic pain experience, even returning to normal in some cases in the absence of pain.[7,9]

In this cross-sectional evaluation of CP patients, we hypothesized that increased pain sensitivity as identified by pancreatic quantitative sensory testing (P-QST) and increased prevalence of psychologic distress are present in a large proportion of patients with current pain, whereas in patients in whom the pain resolved, the prevalence of these phenomena will be closer to that of those observed in patients with primary painless CP. Hence, the aims of this study were to characterize pain processing and psychologic distress in patients with CP stratified according to current and prior pain experience.

Methods

Study Design and Patient Population

This was a cross-sectional, multicenter study conducted at 4 tertiary referral hospitals in Denmark and the United States. Patients were enrolled between October 2016 and March 2021. The protocol was approved by the institutional review board for all sites individually (University of Pittsburgh IRB PRO17060648, Johns Hopkins IRB 00143375, Indiana University IRB 1909843967, and Aalborg University Hospital N-20090008). All patients provided written informed consent prior to enrollment. The study is registered with Clinicaltrials.gov (NCT03434392).

The study cohort comprised adult CP patients ($\geq$18 years) scheduled for P-QST with a definitive diagnosis of CP (Cambridge III or IV or pancreatic calcifications on cross-sectional imaging).[1] Patients were excluded if they had previously undergone an abdominal surgery interfering with the dermatomes used for P-QST assessment, if they had an attack of acute pancreatic inflammation at the time of P-QST, or if they had a painful condition, symptoms of which they were unable to distinguish from pancreatic pain. This study is an extension of a prior cross-sectional study evaluating the distribution of P-QST phenotypes in patients with CP[10] and is a secondary analysis of partially overlapping cohorts. A subgroup of these subjects including those enrolled at the University of Pittsburgh, Johns Hopkins University, and some of those enrolled at the Aalborg University were included in the prior cross-sectional study.

Patient Characteristics

We obtained information on patient pancreatic pain history, demographics, etiology of CP, history of prior invasive therapies (endotherapy or pancreatic surgery) from patient interviews, and review of medical charts. Information was registered in a standardized case report form. We classified etiology as alcohol, genetic, obstructive, idiopathic, or "other." The presence of exocrine pancreatic insufficiency was determined by cutoff thresholds of fecal elastase at each institution or by a previous clinical diagnosis of steatorrhea and/or prescription of pancreatic enzyme replacement therapy. Information on diabetes status was obtained from patient reports and verified with the medical chart. Smoking status was registered according to past and current tobacco use and organized into never smoker vs past or current smoker. Information on current alcohol consumption was registered as alcohol units consumed per week and organized into the following categories: abstainers, light-to-moderate, and heavy-or-very-heavy use.[2]

Classification of Clinical Pain Phenotypes

Patients were categorized into 3 mutually exclusive subgroups based on prior and current history of pancreatic pain elicited through interview and consistent with our prior publication.[10] The categories included (1) painful CP defined as patients with a history of abdominal pain due to CP and average abdominal pain $\geq$3 on visual analog scale (0–10) within 7 days of testing; (2) no current pain defined as patients with a history of pancreatic pain but with no current pain within 7 days of testing (heretofore described as subjects with no current pain); and (3) painless CP defined as patients with no history of abdominal pain or acute pancreatitis but with unequivocal morphologic changes of CP as per the M-ANNHEIM criteria.[11] Hence, group 1 and 2 comprised patients with painful CP as opposed to the patients with painless CP in group 3.

Experimental Pain Sensitivity

We used a previously published P-QST protocol for assessment of experimental pain sensitivity and pain processing.[12] This consists of 2 stimulation modalities (repetitive pinprick and pressure stimulation) applied at different dermatomes and a cold pressor test where the hand was immersed in ice water for 2 minutes. Each patient underwent P-QST testing in the following order: repetitive pinprick stimulation (temporal summation), in the upper abdominal area (T10 ventral dermatome [equals pancreatic viscerotome]) and dominant forearm (control area); followed by pressure stimulation to determine the pressure pain detection threshold at C5 (clavicula), T10 back and T10 ventral (pancreatic viscerotome), L1 (anterior superior iliac crest), and L4 (the quadriceps 15 cm above the patella) on the patient's dominant side. This was followed by assessment of conditioned pain modulation, which was induced by a conditioning stimulus (the cold pressor test) and quantified by applying a painful pressure stimulation (pain tolerance threshold assessed on the quadriceps musculature) before and after the conditioning stimulus. Based on a previously published algorithm and diagnostic thresholds derived from a reference population, we categorized patients into 3 mutual exclusive subgroups based on the pattern of pain sensitivity and pain processing: (1) normal responses to experimental pain stimuli, (2) segmental changes (ie, abnormal P-QST responses confined to the T10 dermatome), and (3) widespread changes (ie, changes in pain sensitivity beyond the T10 dermatomes and abnormal patterns of pain processing).[8] Segmental changes are believed to be associated with increased excitability of second-order neurons in the spinal

cord sharing spinal innervation with the pancreatic gland, while widespread changes are associated with more generalized changes in pain processing including both spinal and supraspinal pathways. Patients with either segmental or widespread P-QST changes were combined in analysis to represent an overall group of patients with enhanced pain sensitivity.

Psychologic Distress

We used the Hospital Anxiety and Depression Scale to test for the presence of anxiety and depression. The Hospital Anxiety and Depression Scale is a self-rating scale developed to evaluate symptoms indicative of anxiety and depression in patients without a known underlying psychiatric disease. We used a validated cutoff score of >7 on either the anxiety or depression subscale to define abnormality.[13,14]

Statistical Analyses

Data are reported as means with standard deviations or numbers (%) unless otherwise specified. The data analysis followed a 2-step procedure. We first compared demographic and clinical characteristics of patients with painful vs painless CP using binary logistic regression analysis. Parameters independently associated with clinical pain phenotypes and parameters known to influence P-QST assessment parameters or psychiatric comorbidities were included as covariates in subsequent analysis to adjust for putative confounding effects. We next compared the proportion of patients with enhanced pain sensitivity, depression, and anxiety across subgroups of clinical pain phenotypes (ie, current pain vs prior pain vs painless CP) using Fisher's exact test as well as unadjusted and adjusted binary logistic regression analysis. Results are presented as odds ratios (ORs) with 95% confidence intervals (CIs). We used Stata 16.1 (College Station, TX) for all data management and statistical analyses.

Results

In total, 235 patients were included in the study, of whom 23 (10%) had painless CP. In the group of patients with painful CP, 185 (79%) had current pain, and 27 (11%) reported no current pain. Demographic and clinical characteristics are reported in Table 1. The mean age of patients was 53.9 ± 14.0 years, and 133 (57%) were male. The most frequent etiology was alcohol (41%), followed by idiopathic (32%) and genetic (22%) etiologies.

Demographic and Clinical Characteristics of Painful vs Painless CP

Compared to patients with painless CP, patients with painful CP were more likely to be current or past smokers ($P = .003$), while patients of older age were less likely to have painful CP ($P < .001$). Also, patients with painful CP used more antidepressants ($P = .02$) and opioids ($P < .001$) and had more frequently undergone an endoscopic pancreatic duct decompression procedure ($P < .001$) (Table 1).

On multivariate analysis, independent and significant associations were confirmed for smoking (OR 4.88; 95% CI [1.60–14.86], $P = .005$), age (OR 0.37; 95% CI [0.21–0.65], $P < .001$) per decade, opioid use (OR 5.02; 95% CI [1.02–24.57], $P = .046$), and endoscopic decompression (OR 6.03; 95% CI [1.57–25.42], $P = .009$).

Experimental Pain Sensitivity

The proportion of patients with enhanced pain sensitivity (segmental or widespread) was 54% among those with current pain vs 56% among those with no current pain vs 22% in the painless CP group ($P = .012$) (Figure 1). Compared to patients with painless CP, enhanced pain sensitivity was observed in both patients with current pain (OR 3.29; 95% CI [1.11–9.77], $P = .032$) and no current pain (OR 4.07; 95% CI [1.10–15.03], $P = .035$) in multivariate analysis (Table 2).

Psychologic Distress

The proportion of patients with anxiety was 54% among those with current pain vs 26% among those with no current pain vs 23% in the painless CP group ($P = .001$) (Figure 2). There were no differences between groups in relation to prevalence of anxiety in multivariate analysis after adjustment for relevant confounders (Table 2).

The proportion of patients with depression was 48% among those with current pain vs 15% among those with no current pain vs 9% in the painless CP group ($P < .001$) (Figure 2). Compared to patients with painless CP, patients with current pain had an increased depression prevalence (OR 6.15; 95% CI [1.28–29.41], $P = .023$), while no difference was seen for patients with no current pain (OR 1.24; 95% CI [0.19–8.26], $P = .856$) in multivariate analysis (Table 2).

Discussion

In this multicenter cohort of patients with CP separated by pain experience, enhanced pain sensitivity was seen to be present in both patients with current pain and those patients who had previously had pain but were currently pain-free. Symptoms of depression were most prevalent in patients with current pain, while those patients who had become pain-free showed a much lower prevalence of psychologic distress close to that of patients with painless CP. Taken together, these findings suggest that effective treatment (or resolution) of pain in CP may be likely to resolve depression, a frequent complication to pain, or that the lack of pain forestalls the development of concomitant depressive symptoms. On the other hand, enhanced pain sensitivity appears to persist beyond the resolution of clinical pain symptoms. The latter has important clinical implications as patients in a "hyperalgesic state" will probably respond with supranormal responses to recurrent

Table 1. Demographic and Clinical Characteristics of the Study Cohort

Demographic characteristics	All patients n = 235	Painful CP		Painless CP n = 23	*P* value[a]
		Current pain n = 185	No current pain n = 27		
Male gender, n (%)	133 (57)	98 (53)	20 (74)	15 (65)	.51
Age, mean y (SD)	53.9 (14.0)	51.7 (13.2)	53.4 (15.9)	66.9 (10.1)	<.001
Age category, n (%)					
<40 y	40 (17)	34 (18)	6 (22)	0 (0)	<.001
40–60 y	106 (45)	99 (54)	3 (11)	4 (17)	
>60 y	89 (38)	52 (28)	18 (67)	19 (83)	
Race, n (%)					
Caucasian	202 (87)	159 (86)	21 (81)	22 (96)	.49
Afro-American	19 (8)	17 (9)	2 (8)	0 (0)	
Other	12 (5)	9 (5)	4 (15)	1 (4)	
Aetiologies, n (%)					
Alcohol	96 (41)	75 (41)	12 (44)	9 (39)	.49
Genetic	52 (22)	42 (23)	5 (19)	5 (22)	
Obstructive	9 (4)	6 (3)	3 (11)	0 (0)	
Others	3 (1)	2 (1)	1 (4)	0 (0)	
Idiopathic	75 (32)	60 (32)	6 (22)	9 (39)	
Smoking, n (%)					
Never smoker	90 (38)	64 (35)	10 (37)	16 (70)	.003
Past or current smoker	145 (62)	121 (65)	17 (63)	7 (30)	
Alcohol, n (%)					
Abstainer	170 (72)	134 (72)	20 (74)	16 (70)	.47
Light-to-moderate use	42 (18)	31 (17)	5 (19)	6 (26)	
Heavy-or-very-heavy use	23 (10)	20 (11)	2 (7)	1 (4)	
Exocrine insufficiency, n (%)	143 (61)	110 (59)	18 (67)	15 (65)	.82
Diabetes mellitus, n (%)	88 (37)	62 (34)	13 (48)	13 (57)	.07
Endoscopic pancreatic duct decompression, n (%)	125 (53)	96 (52)	18 (67)	3 (13)[b]	<.001
Pancreatic surgery, n (%)	24 (10)	19 (10)	4 (15)	1 (4)	.48
Opioid use, n (%)	103 (44)	94 (51)	7 (26)	2 (9)[c]	<.001
Gabapentinoid use, n (%)	60 (25)	55 (30)	3 (11)	2 (9)	.08
Antidepressant use, n (%)	71 (30)	57 (31)	12 (44)	2 (9)	.02

[a]Painful vs painless CP.
[b]All patients underwent pancreatic duct compression for a pancreatic stone located in the pancreatic head in an attempt to restore pancreatic exocrine function.
[c]One patient was treated intermittently with opioids for headaches, and 1 patient was maintained on suboxone for a history of opioid use disorder.

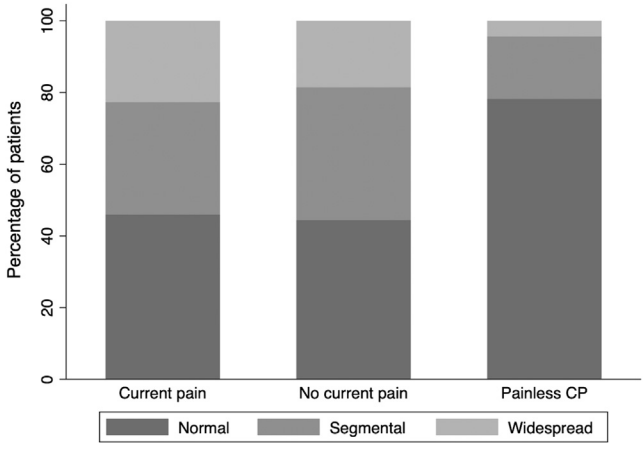

Figure 1. Proportion of patients with enhanced pain sensitivity (segmental or widespread) in patients separated by pain pattern. CP, chronic pancreatitis.

bouts of pancreatic inflammation and/or ductal hypertension.

Characteristics of Painless vs Painful CP

Smoking and younger age were independently associated with painful CP as opposed to painless CP, which is in keeping with past observations. Hence, patients with CP who are active or past smokers have previously been reported to have higher rates of constant pain and require higher doses of daily pain medication than their nonsmoking counterparts.[15–17] Also, CP patients with a smoking history more frequently used opioids as opposed to other medications for pain control.[18,19] Older patients have previously been seen to report lower pain levels.[20] Adding to this finding is that the mean age of painless CP patients in our study is higher than that of those with current or no

Table 2. Multivariate Analysis of Hyperalgesia as Assessed by P-QST and Psychiatric Comorbidities Across Chronic Pancreatitis Subgroups

	Current pain		No current pain	
	Odds ratio (95% CI)	*P*	Odds ratio (95% CI)	*P*
Hyperalgesia				
Unadjusted	4.24 (1.51–11.89)	.006	4.50 (1.29–15.68)	.018
Adjusted[a]	3.29 (1.11–9.77)	.032	4.07 (1.10–15.03)	.035
Anxiety				
Unadjusted	3.97 (1.40–11.21)	.009	1.19 (0.32–4.44)	.796
Adjusted[b]	2.19 (0.70–6.89)	.178	0.75 (0.18–3.10)	.695
Depression				
Unadjusted	9.36 (2.13–41.22)	.003	1.74 (0.29–10.52)	.547
Adjusted[b]	6.15 (1.28–29.41)	.023	1.24 (0.19–8.26)	.824

The painless CP group was set as the reference.
[a]Smoking, past endoscopic treatment, opioid and antidepressant use adjusted.
[b]Age, sex, smoking, past endoscopic treatment, opioid and antidepressant use adjusted.

current pain, also consistent with prior clinical findings in cohorts of painless CP patients.[3,4]

Experimental Pain Sensitivity

In the studied patient population, 56% of patients with no current pain and 54% of patients with current pain both exhibited enhanced pain sensitivity to experimental stimuli. Although the sensory testing does not directly assess the neuronal changes, evidence from previous studies in patients with somatic and visceral pain suggests that probing of the sensory system is able to indirectly assess central neuronal hyperalgesia and neuroplasticy.[21–23] Our findings indicate that the sensitization of nociceptive pathways—once altered by the severe pain of CP—still persists even after clinical pain has subsided or in the absence of pain. This has previously been seen in experimental animal models of joint inflammation, where mice exhibit post-inflammatory tactile allodynia and signs of new neuropathic pain long after acute inflammation has subsided.[24–26] In human studies of painful CP, patients with evidence of central sensitization and pronociceptive descending modulation have shown poorer pain outcomes in response to pain-relieving surgical intervention than their counterparts without these changes or healthy controls.[27,28] This phenomenon may help to explain the persistence of pain in a large subset of the population following, for example, a technically successful therapy for pancreatic ductal obstruction.[29,30] The findings from this study may have important clinical implications for patients with painful CP, as according to these figures, at least half are in a "hyperalgesic state" and probably respond with supranormal responses to recurrent bouts of pancreatic inflammation and/or ductal hypertension, as well as extrapancreatic stimulations of the sensory system. This again may explain the discordance between imaging findings and subjective pain reports often seen in the CP population.[31]

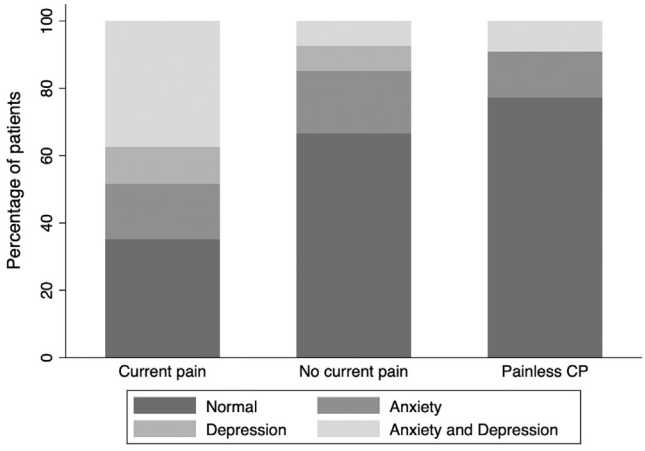

Figure 2. Proportion of patients with anxiety, depression, or both among those separated by pain pattern. CP, chronic pancreatitis.

Psychologic Distress

There exists a high prevalence of psychologic distress—both anxiety and depression—in patients with painful CP, and a correlation between psychologic distress and diagnosis of painful CP has been previously established.[5,32] In a prior cross-sectional analysis, the presence of anxiety or depression was associated with a higher pain prevalence, pain severity, and pain interference scores.[5] The direction of any causality in the relationship remains unclear partially due to its complexity: It has been postulated that not only neural mechanisms but also underlying immunomodulatory mechanisms and genetics may play mediating roles.[33,34] In fact, constant severe pain in CP has been associated with genetic loci for both anxiety and depression in a large North-American cohort of patients.[35] It remains unclear how the successful treatment of pain may influence the prevalence of symptoms of anxiety and depression. The findings of this study suggest a tight link

between pain and psychiatric comorbidity such that resolution of pain symptoms may result in the simultaneous resolution of symptoms of depression.

Strengths and Limitations

The study is a multicenter study with a large cohort of definite CP patients. The findings related to enhanced experimental pain sensitivity and its relationship to both clinical pain symptoms and psychiatric comorbidities are novel and establish the foundation for future research that will be needed in larger cohorts of well-phenotyped CP patients. Several limitations of this study should however be acknowledged. It is a cross-sectional evaluation of CP patients, limiting any longitudinal assessment and causal inference from the data collected. Opioid use is assessed and controlled for; however, it is not used as a factor in categorizing subjects. The effective treatment of pain with opioids or other agents may have also resulted in some classification bias. In addition, the cohort of painless CP patients is relatively small ($n = 23$) despite the size of the overall cohort, limiting extrapolation of the data seen here to a wider cohort: Additional studies will need to be done with larger cohorts of painless CP patients to validate these findings. As is mentioned above, the complex causal relationship among pain, pain sensitivity, and psychologic distress makes directionality difficult to assess in a cross-sectional cohort, and so limited conclusions may be drawn regarding the reasons underlying the correlations (or lack thereof) seen in these data.

Conclusions

In patients with CP, total absence of pain is associated with normal sensory processing and low prevalence of psychologic distress, whereas patients with prior pain experience appear to have persistent pain hypersensitivity even as clinical pain and psychologic distress resolve.

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