Research Paper

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Characterizing mechanism-based pain phenotypes in patients with chronic pancreatitis: a cross-sectional analysis of the PROspective Evaluation of Chronic Pancreatitis for EpidEmiologic and Translational StuDies

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Abstract

Pain is common in chronic pancreatitis (CP) and profoundly reduces quality of life (QoL). Multiple underlying mechanisms contribute to a heterogenous pain experience and reduce efficacy of pain management. This study was designed to characterize the distribution of mechanism-based pain phenotypes in painful CP. The data analyzed were collected as part of the PROspective Evaluation of Chronic Pancreatitis for EpidEmiologic and Translational StuDies, an NCI/NIDDK-funded longitudinal study of the natural history of CP. The PROspective Evaluation of Chronic pancreatitis for EpidEmiologic and translational stuDies includes patient-reported outcome (PRO) measures of pain, medication use, global health, and QoL. Of subjects (N = 681) with CP, 80% experienced abdominal pain within the year before enrollment. Subjects who experienced pain in the week before enrollment (N = 391) completed PROMIS Neuropathic and Nociceptive Pain Quality instruments which were then used to classify them by pain type: 40% had nociceptive, 5% had neuropathic-like, and 32% had both types of pain. The prevalence of having both types of pain was higher among women and subjects with diabetes mellitus, whereas nociceptive-only pain was more prevalent among men and those with pancreatic duct stricture. Other factors, including pain medication use and healthcare utilization, did not differ between groups based on pain type. Subjects in the Both group had significantly worse health and QoL scores relative to those with nociceptive-only pain, suggesting that using psychosocial pain surveys may be useful for understanding pain subtypes in patients with CP. Additional research is needed to identify biochemical and biophysical signatures that may associate with and predict responses to mechanism-specific interventions.

Keywords: Neuropathic pain, Nociceptive pain, PROMIS instruments, Chronic pain

1. Introduction

Chronic pancreatitis (CP) is defined as "a fibroinflammatory syndrome of the pancreas in individuals with genetic, environmental, and/or other risk factors who develop persistent pathologic responses to parenchymal injury or stress."[39] Some patients exhibit advanced structural changes, but interestingly,

Sponsorships or competing interests that may be relevant to content are disclosed at the end of this article.

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PAIN 164 (2023) 375–384

http://dx.doi.org/10.1097/j.pain.0000000000002710

they do not correlate with pain intensity.[34,41] Chronic pain is a cardinal symptom, but based on the new *ICD-11* classification scheme, pancreatitis pain is classified as chronic secondary visceral pain because its origin can be attributed to a disease-related mechanism.[2] There are pain management guidelines that offer an array of interventions including pharmacologic, psychosocial, endoscopic and/or surgical strategies.[8] However, only half of the patients with CP achieve satisfactory and enduring pain relief.[5,26,38] Poor response rates to existing therapies are believed, in part, to stem from our inability to differentiate the multitude of mechanisms that can contribute to CP-related pain. To begin to address this, researchers have previously stratified patients by pain patterns. In painful CP, 5 patterns based on intensity and frequency have been identified.[24,28,41] Using this classification system, it has been shown that a pain pattern directly correlates with quality of life (QoL) and disability.[24] However, severity and/or frequency of pain are not predictive of therapeutic responses, and this approach to characterizing CP pain has yielded no improvements in clinical management.

Canonically, the efficacy of different analgesics (eg, nonsteroidal anti-inflammatory drugs [NSAIDs], narcotics, or neuromodulators) is believed to depend on the underlying mechanism. For instance, NSAIDs are more efficacious for inflammatory pain, whereas neuromodulators such as gabapentinoids are considered better for treatment of neuropathic pain and central nervous system changes.[4,7,40,43] Current guidelines recommend the use of an analgesic ladder that has been adapted for chronic noncancer pain.[8] Analgesic therapy is often rapidly escalated in an attempt to achieve pain relief that has resulted in opioids becoming a mainstay for many patients with CP. The challenges of pain management in gastrointestinal diseases have contributed to increasing rates of opioid prescriptions in the United States, with prescriptions for CP being the highest.[21] Although opioids can be effective in some cases, they have a number of deleterious consequences including opioid-induced hyperalgesia, gastrointestinal dysfunction, tolerance, and addiction.

In an effort to improve pain management and reduce opioid prescriptions (and dependence), researchers of other chronic pain conditions have begun to explore mechanism-based pain phenotyping (nociceptive vs neuropathic) as a way to classify patients.[1,18] The expectation is that this classification schema will better inform therapeutic decision-making. The pain experience varies widely among patients with CP, with some patients using "neuropathic" descriptors (eg, stinging or electrical) and others reporting "nociceptive" descriptors when characterizing their pain (eg, achy or sore). Therefore, we sought to investigate the contribution of nociceptive and neuropathic pain components in the context of CP. Specifically, the current study was designed to (1) characterize the distribution of mechanism-based pain categories in CP, (2) examine patient or disease-related factors associated with the mechanism-based pain subtypes, and (3) compare pain-related outcomes among patients with different pain subtypes.

2. Methods

2.1. Study subjects and participating sites

PROspective Evaluation of Chronic pancreatitis for EpidEmiologic and translational stuDies (PROCEED) is funded through the NCI/NIDDK-sponsored Consortium for the Study of Chronic Pancreatitis, Diabetes, and Pancreatic Cancer.[33] PROspective Evaluation of Chronic Pancreatitis for EpidEmiologic and Translational StuDies is a prospective observational study of U.S. adult subjects within the spectrum of CP (healthy to acute to CP).[42] Clinical data including laboratory testing, imaging, and biological specimens are collected at baseline and annual visits according to protocols approved by the MD Anderson Institutional Review Board. In addition, several patient-reported outcomes are acquired through the administration of validated PROMIS instruments as well as study-specific questionnaires (refer to case report forms [CRFs]). Subjects in the current study were 18 years or older at the time of enrollment (June 27, 2017-August 25, 2021) and had definite CP. Definite CP was defined by subjects having Cambridge 3 or 4 classification, presence of pancreatic calcification consistent with CP (by CT, MRI, or MRCP), or a histologic diagnosis of CP.

2.2. Case report forms

Detailed data are collected using structured CRFs completed by the study participants, research coordinators, and study physicians as previously described.[42] A variety of information is collected including demographics, family history, lifestyle (alcohol, tobacco, cannabis, and other substance use), pancreas-related symptoms including pain and disability, presence of exocrine or endocrine insufficiency, medication use, and treatments including endoscopic and surgical interventions.

2.3. Mechanism-based pain phenotyping

Mechanism-based pain type was determined using PROMIS Pain Quality Short Forms for measuring nociceptive pain quality and neuropathic pain quality.[1,25] Both of these instruments consist of 5 multiple choice items asking, "In the past 7 days, did your pain feel (sic)?." Raw scores are tabulated and converted to a normalized T score according to the published PROMIS scoring manual (http://www.healthmeasures.net). The PROMIS Pain Quality instruments focus on pain in the previous 7 days. A clarifying question, "Have you had pain in the previous 7 days?" was added to the PROCEED study on March 16, 2018. If subjects answered yes, they were instructed to complete the PROMIS Pain Quality instruments. For the cases in which enrollment occurred before the addition of the question, numerical pain intensity ratings (refer to PROMIS-29) were used to determine whether the subject had pain in the previous 7 days. In the current study, a threshold of $T \geq 50$ was used as the cutoff for categorizing subjects into groups. This classification system was previously used in a study examining a variety of painful conditions including osteoarthritis, rheumatoid arthritis, diabetic neuropathy, and chemotherapy-induced neuropathy.[1] However, this study is the first time it is being applied to subjects with CP. "Nociceptive only" was defined as a T score ≥ 50 on the nociceptive short form and <50 on the neuropathic short form. "Neuropathic-like only" was defined as a T score ≥ 50 on the neuropathic short form and <50 on the nociceptive short form. The "Both" group was defined by a T score ≥ 50 on both the nociceptive and neuropathic short forms. If the subject scored <50 on both the nociceptive and neuropathic short forms, they were considered to have "unclassifiable" pain.

2.4. Outcomes of interest

2.4.1. Global health

The PROMIS Global Health instrument is designed to assess both physical and mental health. Subjects are asked to consider the previous 7 days when answering the questions. Raw scores are

determined and converted to a T score (http://www.healthmeasures.net). A T score above 50 indicates the subject is healthier than the general U.S. population.

2.4.2. Hospital utilization

The research coordinator administered CRFs including questions related to hospitalization for pancreatitis or upper abdominal pain before enrollment (lifetime and the preceding 12 months). The number of emergency department visits in the preceding 12 months for pancreatitis or upper abdominal pain that did not result in hospitalization was also ascertained.

2.4.3. Pain and quality of life

2.4.3.1. Pain medication use

Information about medications the subject was taking as well as the indication (eg, pain vs other) was recorded. Four classes of medication were included in the current analysis—narcotics, NSAIDs, neuromodulators (eg, gabapentinoids or antidepressants), and pancreatic enzyme replacement therapy.

2.4.3.2. Pain pattern

The research coordinator asked subjects to indicate whether they have had upper abdominal pain or pancreatitis-related abdominal pain within the past year. If yes, the subject was asked to identify the pattern from the following options—episodes of mild to moderate pain, episodes of severe pain, constant mild to moderate pain, constant mild to moderate pain plus episodes of severe pain, or constant severe pain. Frequency and severity of pain within the previous year were extrapolated as categorical variables to investigate whether they are independently affected by mechanism-based pain types. Frequency was defined as intermittent or constant. Severity was defined as mild-moderate or severe. Subjects who reported having both episodic and constant pain were included in the constant pain group. Subjects were also asked to report pain intensity in the previous 7 days using a numerical rating scale from 0 to 10, where 0 = no pain and 10 = worst pain imaginable.

2.4.3.3. Overall quality of life

To analyze QoL, the PROMIS-29 instrument was administered. PROMIS-29 assesses 7 domains of health and well-being: physical function, anxiety, depression, fatigue, sleep disturbance, satisfaction with participation in social roles, and pain interference. With the exception of physical function that does not indicate a period, all other domains are assessed over the previous 7 days. Raw scores for each domain are calculated and converted to T scores as described above. For all domains except social roles and sleep disturbance, a T score of 50 indicates the subject is similar to the U.S. general population. For social roles and sleep disturbance, the calibration sample was enriched for chronic illness, so a T score of 50 suggests the subject is sicker than the general U.S. population. Higher scores for negatively worded concepts (eg, anxiety) are considered worse than average, and higher scores for positively worded concepts are considered better than average (eg, physical function).

2.5. Statistical analysis

Categorical variables were summarized by frequencies and percentages (based on the effective sample size without missing data) and compared between groups with Fisher exact tests. Continuous variables were summarized using median and interquartile ranges and compared between groups by the Kruskal–Wallis test. Generalized linear models were used to assess between-group differences in PROMIS scores. All statistical tests used a significance level of 5%. All statistical analyses were performed using SAS version 9.4.

3. Results

3.1. Study cohort and prevalence of pain

Overall, 681 subjects with definite CP were enrolled in the PROCEED study from 9 clinical centers. At the time of enrollment, 80.9% (551/681) reported experiencing pain in the previous year, with 71.0% (391/551) of those reporting pain within the 7 days preceding their study visit (**Fig. 1**). The mean age (years) of these subjects was 51 ± 12 years, with 179 subjects (45.8%) being men. The cohort was predominantly White (321, 82.1%) and non-Hispanic (377, 96.4%). A large proportion of cases were classified has having alcoholic etiology (174, 44.5%). Most subjects (317, 81.1%) have had acute pancreatitis (AP) with about one-third (139, 35.5%) having had attack(s) within the previous 3 years and two-thirds (256, 65.5%) had a history of recurrent AP.

3.2. Classification and distribution of mechanism-based pain subtypes

Subjects with painful CP were classified into 4 different pain categories based on their Nociceptive and Neuropathic Pain Quality T scores (**Fig. 2**). The Unclassifiable group (n = 92) was excluded from further analyses to enable direct comparisons between groups with or without neuropathic pain. The initial analyses compared 2 groups, Nociceptive only (n = 156) and Both (n = 123), because the Neuropathic-like only group was too small (n = 20) resulting in insufficient statistical power to analyze it as an independent group. In a second parallel set of analyses, the Neuropathic-like only group was combined with the Both group. This combined group was then compared directly to the Nociceptive-only group. The *P* values for both analyses are presented.

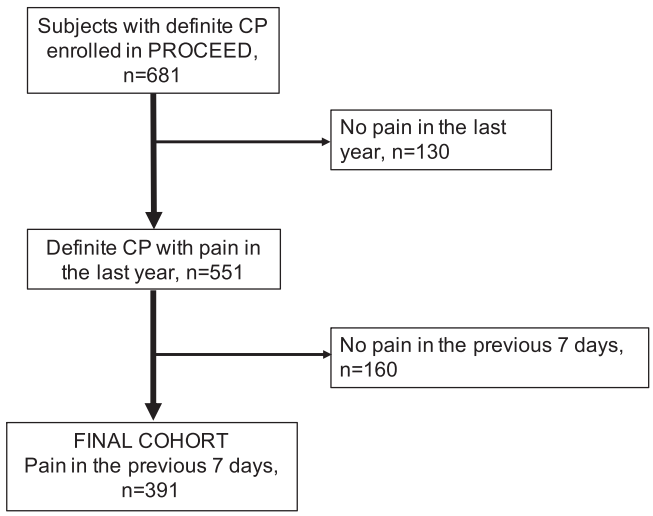

Figure 1. Study participant flowchart. CP, chronic pancreatitis.

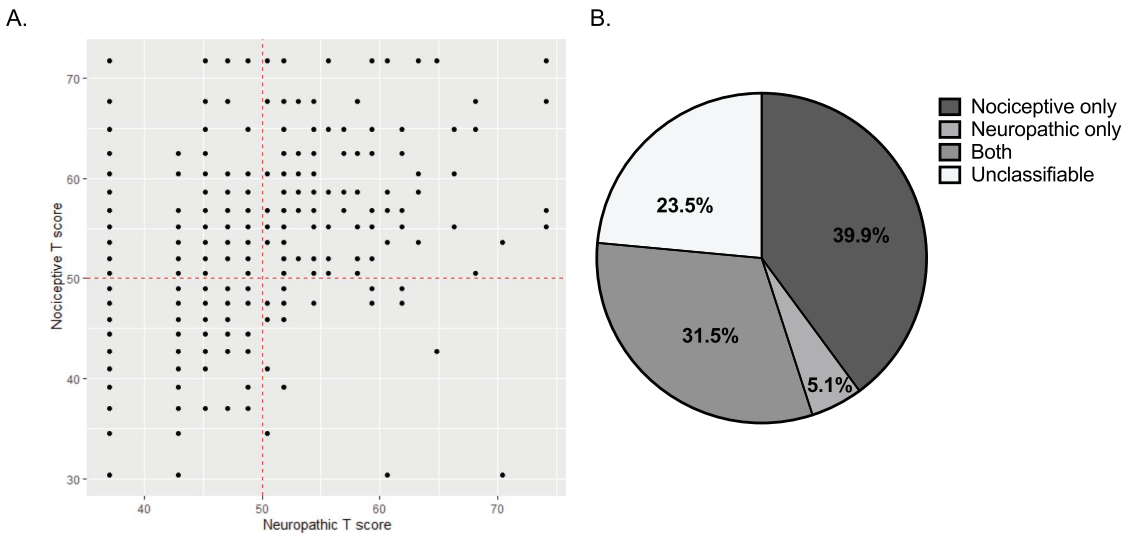

Figure 2. Distribution of pain phenotypes. (A) Scatterplot of neuropathic T score vs nociceptive T score (N = 391). Dashed line indicates T = 50, the chosen cutoff. (B) Percentages of subjects identified has having neuropathic-like pain, nociceptive pain, both, or unclassifiable pain.

3.3. Patient-related and disease-related factors based on the pain group

Analysis of patient-related and disease-related characteristics revealed a few differences between the pain groups (**Table 1**). Compared with the Both group, the Nociceptive-only group had a smaller proportion of men (49% vs 35%) and was less likely to be a high-school graduate, GED or less (45% vs 32%). Surprisingly, factors related to natural history of pancreatitis, comorbidity, exocrine dysfunction, endoscopic or surgical intervention, and substance use did not differ between subtypes of pain. Most morphological features (eg, atrophy, stones, and duct dilation) were similar across groups. However, compared with the Both group, the Nociceptive-only group was less likely to have diabetes mellitus at baseline (34% vs 49%) and more likely to have a pancreatic duct stricture (57% vs 43%). The trends were the same and significant when comparing the Nociceptive group with the combined group (Both + Neuropathic-like only) (**Table 1**).

3.4. Global health and hospital utilization between pain groups

Global physical and mental health were assessed with the PROMIS Global Health scales (**Table 2**). Physical health was lower than that of the general population for all groups ($T < 50$), but the Nociceptive-only group had significantly better physical health than the Both group. Global mental health scores were also lower than those of the general population for all pain groups ($T < 50$). Mental health scores significantly differed between pain groups, with the Nociceptive-only group having scores 3.62 units higher than the Both group. However, the number of hospitalizations or emergency department visits (lifetime or 12 months before enrollment) did not differ between pain subtypes (**Table 3**).

3.5. Pain patterns between pain groups

Pain severity was reported in 2 forms, categorical (**Table 4**) and continuous (refer to intensity, **Table 2**). Subjects in the Nociceptive-only group were more likely to have mild to moderate abdominal pain (25%) than subjects with both types of pain (15%). When comparing the Nociceptive-only group with the combined group (Both and Neuropathic-like only), the *P* value became a statistical trend ($P = 0.05$) and was no longer statistically significant. Subjects also rated their pain on a numerical rating scale, where 0 = none and 10 = worst pain imaginable. The average numerical pain rating for the Both group (6.6 ± 1.9) was significantly higher than that of the Nociceptive-only group (5.7 ± 2.0). The difference in numerical pain rating remained significant when comparing the Nociceptive-only group with the combined group (Both + Neuropathic-like only) (**Table 2**).

The temporal nature of pain was also assessed as an independent feature (**Table 4**). The proportion of subjects in the Nociceptive-only group who experienced constant abdominal pain related to pancreas/pancreatitis within the past year was significantly lower than that in the Both group (73% vs 84%). The trend was no longer significant when comparing the Nociceptive-only group with the combined group (Both + Neuropathic-like only).

There are 5 pain patterns based on a combination of severity and frequency of pain that patients with CP commonly identify (refer to the Methods section). This is an important feature to consider given that it is unknown whether severity and temporality are entirely independent features. In addition, there are some patients who report experiencing both intermittent and constant pain. **Table 4** illustrates that the proportion of patients with this experience is similar between Nociceptive and Both groups (53% vs 59%, respectively). There is a significantly larger proportion of patients with both types of pain who report constant severe pain compared with the Nociceptive-only group (16% vs 7%). However, the trend was no longer significant when comparing the Nociceptive-only group with the combined group (Both + Neuropathic-like only). About half of the patients in the Nociceptive-only and Both groups identify as constant mild to moderate pain plus episodes of severe pain, whereas 55% of patients in the Neuropathic-like only pain group are usually free of abdominal pain, with episodes of severe pain (**Table 4**).

3.6. Pain medication use

Overall use of pain medications and 4 classes of pain medications (NSAIDs, narcotics, neuromodulators, and pancreatic enzyme

Table 1

Comparison of patient-related and disease-related characteristics among the different mechanism-based pain phenotypes in participants with chronic pancreatitis.

	Nociceptive pain only (N = 156)	Both (nociceptive + neuropathic) (N = 123)	Neuropathic pain only (N = 20)	*P** nociceptive pain only vs both	*P** nociceptive vs (both + neuropathic only)
Age (y)—median(IQR)*	52.0 (43.0, 61.0)	51.0 (43.0, 57.0)	50.0 (45.0, 58.5)	0.26	0.28
Male gender	54(35)	60(49)	16(80)	0.002	0.02
Race				0.0001	0.0001
Black	5(3)	19(15)	2(10)		
Other	13(8)	17(14)	2(10)		
White	138(88)	87(71)	16(80)		
Ethnicity				0.34	0.36
Hispanic	4(3)	6(5)	1(5)		
Non-Hispanic	152(97)	117(95)	19(95)		
Education				0.006	0.005
High-school graduate/GED or less	50(32)	56(45)	11(55)		
Some training after high-school, including associate degree or some college	19(12)	15(12)	2(10)		
	45(29)	28(23)	4(20)		
Bachelor's degree	28(18)	17(14)	2(10)		
Graduate school	13(8)	2(2)	1(5)		
Other/do not know/missing	1(1)	5(4)	0		
Body mass index (kg/m^2)	23.7 (20.7, 27.9)	24.3 (20.5, 29.5)	24.3 (22.0, 28.2)	0.81	0.77
Charlson comorbidity index				0.27	0.38
0-1	113(72)	78(63)	15(75)		
2-3	30(19)	33(27)	1(5)		
>3	13(8)	12(19)	4(20)		
Alcohol use				0.15	0.30
Never	16(10)	20(16)[1]	1(5)		
Past	111(71)	87(71)	15(75)		
Current	29(19)	15(12)	4(20)		
Any tobacco exposure (cigar, tobacco chew, or cigarette)				0.55	0.54
Never	112(72)[1]	90(73)[1]	11(55)		
Past	33(21)	21(17)	6(30)		
Current	11(7)	12(10)	3(15)		
Cigarette packs per day (current or historical)				0.48	0.18
<1	72(61)[37]	50(56)[33]	4(25)[4]		
≥1	47(39)	40(44)	12(75)		
Marijuana use				0.74	0.60
Never	74(48)[2]	63(52)[2]	13(65)		
Past	44(29)	34(28)	3(15)		
Current	36(23)	24(20)	4(20)		
Ever had acute pancreatitis	133(90)[8]	97(89)[14]	16(80)	0.84	0.57
Recurrent acute pancreatitis	111(85)[3]	78(82)[2]	11(69)	0.58	0.31
# acute pancreatitis attacks in the past 3 years				0.39	0.23
0	36(38)[38]	24(35)[28]	1(9)[5]		
1-2	39(41)	24(35)	5(45)		
3 or more	20(21)	21(30)	5(45)		
Duration (in y) from earliest signs of pancreatitis to enrollment	5.0 (2.0, 12.0)[1]	6.0 (3.0, 11.0)[2]	3.5 (1.5, 9.5)	0.53	0.79
Duration (in y) from earliest documentation of chronic pancreatitis	2.0 (1.0, 5.0)[19]	3.0 (1.0, 6.5)[15]	1.0 (0.0, 4.0)[1]	0.19	0.45

(*continued on next page*)

Table 1 (*continued*)

	Nociceptive pain only (N = 156)	Both (nociceptive + neuropathic) (N = 123)	Neuropathic pain only (N = 20)	*P** nociceptive pain only vs both	*P** nociceptive vs (both + neuropathic only)
Primary etiologic classification is alcoholic pancreatitis	77(49)	56(46)	9(45)	0.55	0.56
Exocrine pancreatic insufficiency				0.18	0.20
Not tested†	58(37)	58(47)	9(45)		
No	38(24)	18(15)	4(20)		
Yes	60(38)	47(38)	7(35)		
Diabetes present	51(34)[4]	57(49)[7]	9(45)	0.01	0.01
History of endoscopic treatment	109(70)[1]	74(62)[3]	11(55)	0.16	0.09
History of surgical treatment	17(11)	12(10)[5]	2(10)	1.00	0.85
Calcification(s) present	119(77)[1]	96(78)	12(60)	0.88	0.89
Pancreas atrophy				0.76	0.74
>14 mm	71(46)[1]	51(42)[1]	8(40)		
7-14 mm	69(45)	57(47)	10(50)		
<7 mm	15(10)	14(11)	2(10)		
Pancreatic duct stricture	88(57)[1]	53(43)[1]	9(45)	0.03	0.03
Pancreatic duct dilation	119(77)[1]	93(76)[1]	14(70)	1.00	0.79
Intraductal stone	62(40)[1]	54(44)[1]	8(40)	0.54	0.56

Count (column percentage) is reported for categorical variables.
Superscripts in the first row of each variable, if present, indicate the missing value counts, which are excluded from the percentage calculation.
* Median (25th and 75th quantiles) is reported for continuous variables.
† Subjects did not have insufficiency at enrollment and did not have a fecal elastase test.
IQR, interquartile range.

replacement therapy) were assessed (**Table 4**). There was no statistical difference in use of pain medication. There were also no significant differences between pain groups in the use of specific types of pain medications.

3.7. Quality of life (PROMIS-29) between pain groups

Quality of life was assessed across 7 domains of well-being (**Table 2**). Subjects in the Nociceptive-only and Both pain groups reported worse physical function and ability to participate in social roles as compared to the general population (T score <50). However, the Nociceptive-only group had significantly improved physical function compared with the Both group (43.6 vs 38.3). Similarly, the Nociceptive-only group had improved ability to participate in social roles (46.2 vs 42.2) than the Both group. All pain groups had worse anxiety, depression, fatigue, sleep disturbance, and pain interference relative to the general population (T score >50), but the Both group was significantly worse than the Nociceptive-only group in all these categories. The trends were the same and significant when comparing the Nociceptive-only group with the combined (Both+Neuropathic-like only) group.

4. Discussion

In this study, we characterized pain in a large, multicenter cohort of patients with definite CP. Similar to the multicenter NAPS cohort (46%),[6] 44.5% of the cohort was assigned alcoholic etiology. In our cohort, the history of RAP was 65.5%, which is also similar to the NAPS cohort (66%).[32] Importantly, the prevalence of pain (80.9%) is in range with other CP cohorts (72%-93%).[16,24,36,41] To the best of our knowledge, this is the first study to use the PROMIS Pain instruments in CP. Over two-thirds of patients in the cohort could be classified as having nociceptive-only (~40%), neuropathic-like only (~5%), or both (~32%) types of pain, but a subset had unclassifiable pain (~24%). This distribution is similar to other complex diseases.[1,18] It should be noted that the PROMIS Pain Quality forms were initially designed and validated for somatic, not visceral, pain conditions. However, pancreatitis has a somatic component in addition to visceral; this enables the use of quantitative sensory testing to predict therapeutic responses.[10,19,29] Although it is often assumed that pancreatitis-related somatic pain is referred pain, the parietal peritoneum that covers the pancreas is directly innervated by somatic afferents.[35] Thus, chemicals released by injured pancreas as well as mechanical changes induced by edema and fibrosis can directly drive somatic nociception and pain.

There was no difference between pain groups with respect to most patient-related and disease-related factors. However, the proportion of women was significantly higher in the Nociceptive-only pain group. In a study of musculoskeletal pain, women also had significantly higher nociceptive pain T scores compared with men.[37] Regarding disease factors, only diabetes status and presence of pancreatic duct stricture were significantly different. Diabetes is associated with neuropathy in the peripheral somatosensory system.[11] The current study did not specifically assess for diabetic neuropathy, but it is not surprising that there is a larger proportion of subjects with diabetes in the Neuropathic-like pain only group. Pancreatic duct stricture involves mechanical stimulation of the nerve endings innervating duct cells which drives nociceptor activation and may explain why there is a higher proportion of subjects having a stricture in the Nociceptive-only pain group.

Previous studies used severity and frequency of CP pain as a means to stratify the population into subtypes of pain. Here, subjects with both types of pain are more likely to have constant and severe pain when they are considered as independent

Table 2

Univariate analysis of health and quality of life: PROMIS instruments.

Domain	Nociceptive pain only (N = 156), T score	Both (nociceptive + neuropathic) (N = 123), T score	Neuropathic pain only (N = 20), T score	*P** nociceptive pain only vs Both	*P** nociceptive pain only vs (both + neuropathic only)
PROMIS Global Health					
Physical component	39.2 (7.4)	35.1 (6.6)	36.2 (7.2)	<0.001	<0.001
Mental component	44.6 (8.9)	40.9 (7.4)	41.9 (8.1)	0.0002	0.0062
PROMIS-29					
Physical function	43.6 (8.9)	38.3 (7.4)	39.5 (8.1)	<0.001	<0.001
Anxiety	55.1 (8.6)	59.3 (8.6)	58.6 (9.0)	<0.001	0.0005
Depression	53.7 (8.6)	57.3 (9.8)	56.3 (10.0)	<0.001	0.0246
Fatigue	57.2 (8.7)	61.9 (8.5)	60.7 (9.3)	<0.001	0.0011
Sleep disturbance	55.9 (8.4)	60.3 (8.2)	59.3 (8.6)	<0.001	0.0007
Social roles	46.2 (9.3)	42.2 (7.5)	43.4 (8.1)	<0.001	0.006
Pain interference	63.5 (7.7)	67.0 (6.2)	65.6 (7.1)	<0.001	0.015
Pain intensity	5.7 (2.0)	6.6 (1.9)	6.2 (2.2)	0.0003	0.03

Mean (SD) is reported for PROMIS continuous variables.

variables. Furthermore, subjects in the Both pain group had worse QoL on all domains of the PROMIS instruments. This is consistent with observations in other CP cohorts in which those with constant pain have poorer QoL.[16,22] When considering the pain pattern, which incorporates severity and frequency into a single variable, more than half of the subjects in the Both pain group did not experience constant severe pain but actually have constant mild pain with episodes of severe pain. Half of the Neuropathic-like only subjects are pain free with only episodes of severe pain. Taken together, this may suggest that in the Both pain group, neuropathic pain is responsible for pancreatitis-related episodic pain and nociceptive pain is responsible for the constant pain. This is consistent with somatic peripheral neuropathies that commonly feature spontaneous or evoked attacks or flare-ups of severe pain.[20,23,30]

Using our classification system, approximately one-quarter of patients did not have a strong neuropathic or nociceptive pain component. There are multiple potential explanations for this, including that they suffer from another type of pain. Nociplastic pain is a somewhat controversial concept that is defined as "altered nociception despite no clear evidence of actual or threatened tissue damage causing activation of peripheral nociceptors or evidence for disease or lesion of the somatosensory system causing the pain."[17] Given that CP by definition is associated with tissue damage, it could

Table 3

Univariate analyses of outcome: Hospital utilization.

	Nociceptive pain only (N = 156)	Both nociceptive and neuropathic pain (N = 123)	Neuropathic pain only (N = 20)	*P** nociceptive pain only vs both	*P** nociceptive pain only vs (both + neuropathic only)
# Hospitalization before enrollment (lifetime)				0.50	0.55
0	21(14)[2]	16(13)[1]	2(10)		
1-2	22(14)	18(15)	7(35)		
3-5	39(25)	22(18)	5(25)		
≥ 6	72(47)	66(54)	6(30)		
# Hospitalization before enrollment (past 12 months)				0.50	0.45
0	58(37)[1]	41(34)[1]	9(45)		
1-2	44(28)	43(35)	8(40)		
3-5	41(26)	26(21)	3(15)		
≥ 6	12(8)	12(10)	0(0)		
# ED visits before enrollment (past 12 months)				0.13	0.26
0	87(56)[1]	53(44)[2]	15(75)		
1-2	31(20)	29(24)	1(5)		
3-5	15(10)	21(17)	3(15)		
≥ 6	22(14)	18(15)	1(5)		

Median (25th and 75th quantiles) is reported for continuous variables.

Count (column percentage) is reported for categorical variables.

Superscripts indicate the missing value counts, which are excluded from the percentage calculation, similar to Table 1.

Table 4

Univariate analyses of outcome: Pain.

	Nociceptive pain only (N = 156)	Both nociceptive and neuropathic pain (N = 123)	Neuropathic pain only (N = 20)	*P** nociceptive pain only vs both	*P** nociceptive pain only vs (both + neuropathic only)
Using any pain medication	111(72)[1]	88(72)[1]	7(37)[1]	1	0.45
PERT	32(21)	16(13)	1(5)	0.11	0.06
NSAIDs	15(10)	14(11)	1(5)	0.69	0.85
Narcotics	90(58)	68(56)	6(32)	0.71	0.35
Neuromodulators	36(23)	32(26)	2(11)	0.58	0.89
Pain severity				0.04	0.05
Mild to moderate	39(25)	18(15)[1]	4(20)		
Severe	117(75)	104(85)	16(80)		
Pain temporality				0.04	0.60
Intermittent	42(27)	20(16)[1]	14(70)		
Constant	114(73)	102(84)	6(30)		
Pain pattern				0.03	0.11
I am usually free of abdominal pain, but I have episodes of severe pain	24(15)	12(10)[1]	11(55)		
I am usually pain free but have episodes of mild to moderate pain	18(12)	8(7)	3(15)		
I have constant mild to moderate pain	21(13)	10(8)	1(5)		
I have constant mild to moderate pain plus episodes of severe pain	82(53)	72(59)	4(20)		
I have constant severe pain that does not change	11(7)	20(16)	1(5)		

Median (25th and 75th quantiles) is reported for continuous variables.
Count (column percentage) is reported for categorical variables.
Superscripts indicate the missing value counts, which are excluded from the percentage calculation, similar to Table 1.

be difficult to measure nociplastic pain in this population. However, it is possible that some of the patients in our study who had unclassifiable pain fall into this category. It is also possible that the subjects in the Unclassifiable group have a more robust response to interventions for unknown reasons, and this resulted in lower scores on the PROMIS instruments. When the PROMIS Neuropathic Pain Quality instrument was validated in cohorts with osteoarthritis, rheumatoid arthritis, diabetes, and chemotherapy-induced neuropathy, the cutoff T score of 50 (used in the study) had a specificity of 0.77 and a sensitivity of 0.70.[1] Thus, it is likely that some of the patients in the Unclassifiable group have neuropathic or nociceptive pain components, but the instrument was not able to detect it with our chosen cutoff score.

Despite taking medication or undergoing medical intervention for pain, many patients with CP report a lack of sufficient relief. Chronic CP pain arises from neuroplasticity in the peripheral nervous system where inflammation in combination with tissue or nerve injury contributes to nociceptive or neuropathic pain, respectively. In our study, the duration of disease was not correlated with pain severity or mechanism-based phenotype. Patients may develop nociceptive and/or neuropathic pain at different times during the course of disease, which could help explain why some patients may or may not respond to a particular pain management strategy. Furthermore, for unknown reasons, some patients develop sensitization of the central nervous system that causes widespread systemic hypersensitivity explaining why local peripherally targeted interventions fail.[10] Adoption of tools that can identify different peripheral and central pain mechanisms is likely to improve clinical decision-making and subsequently patients' perceived effectiveness of interventions.

In-depth analysis of biopsychosocial features including quantitative sensory testing has been used successfully in other chronic pain conditions to cluster patients into clinically meaningful subgroups. The ultimate goal being to develop classification systems that can predict incidence of first onset of disease as well as response to interventions. In the context of temporomandibular disorders (TMDs), a validated algorithm based on 4 psychosocial measures (anxiety, depression, pain pressure threshold (PPT), and somatization) can reliably cluster patients.[3,13] Pain pressure threshold is the lowest pressure a subject experiences as painful, and it is determined through quantitative sensory testing. Pain pressure threshold has been used successfully to characterize CP pain and predict response to the neuromodulator pregabalin.[27] Somatization is the manifestation of psychological distress as bodily symptoms such as pain can be measured using the PHQ-15. Patients with TMD in the cluster with worst anxiety, depression, and somatization also had the highest sensitivity to pain. Although somatization and PPT were not assessed in the current study, subjects in the Both pain group had the worst physical health as well as mental health, including anxiety and depression. Future studies should add the psychophysical measures of somatization and PPT to determine whether, in combination with anxiety and depression, they are sufficient to categorize patients with CP in a similar manner as shown for TMD and breast mastectomy pain.[3,12,13]

The identification of specific pain mechanisms is key for identifying the intervention most likely to provide relief. Pharmacologic (prescribed or nonprescribed) interventions function through different mechanisms of action and are

therefore predicted to have differing efficacy depending on the underlying mechanism driving an individual patient's pain. For instance, patients with multiple sclerosis with nociceptive-only pain report NSAIDs are more effective than patients with both types of pain.[18] In the same study, patients with multiple sclerosis in the Both group reported significantly better relief ratings for cannabinoid use as compared to the Neuropathic-like only group. Unfortunately, the current study did not assess relief ratings, but we detected no statistical differences in NSAID or marijuana use. Pain dogma suggests that neuropathic pain is more likely to respond to neuromodulators such as gabapentinoids than nociceptive pain. Furthermore, anxiety and depression exacerbate the pain experience.[9] Given that the Both and Neuropathic-like only pain groups had worse anxiety and depression, we expected that these groups would have higher neuromodulator use. However, there was no significant difference in the prevalence of neuromodulator (eg, gabapentin or antidepressant) use between pain groups. The efficacy of gabapentinoids and antidepressants for many confirmed neuropathic conditions is quite variable.[14,15,31] This makes interpreting the lack of association with neuromodulator use difficult, neither supporting nor refuting assignation to the Neuropathic-like pain group. The lack of a higher percentage of neuromodulator use in the Both and Neuropathic-like pain groups might also be dependent on the prescription patterns of the physicians that was not assessed in the PROCEED study.

In conclusion, this study demonstrates that subjects with definite CP can be stratified by a mechanism-based pain phenotype. Given that clinical data, including duration of disease, are not sufficient to predict a patient's pain type, it is important to add tools that can identify a mechanistic pain type to inform therapeutic decision-making. The incorporation of PROMIS Pain instruments and other tools (eg, quantitative sensory testing) is necessary to move CP pain management forward and make a difference in patient's QoL. If phenotype-specific biomarkers can be identified, it could move the field toward a more personalized medicine approach. The discovery of biochemical signatures related to a specific mechanism-based pain component (ie, neuropathic or nociceptive) may uncover novel targets for therapeutic intervention or provide insight into predicting response to currently available therapies.

Conflict of interest statement

The authors have no conflicts of interest to declare.

Acknowledgments

This work was supported by grants from the National Institute of Diabetes and Digestive and Kidney Diseases: R21 DK122293 and K01 DK120737 (JLS). Research reported in this publication was supported by the National Cancer Institute (NCI) and National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) under award numbers: U01DK108288 (S.S.V. and M.T.), U01DK108300 (W.G.P.), U01DK108306 (A.E.P. and D.Y.), U01DK108314 (S.J.P.), U01DK108323 (E.L.F.), U01DK108326 (W.E.F.), U01DK108327 (P.A.H. and D.L.C.), U01DK108332 (S.K.V.), UO1DK108320 (C.E.F.), and U01DK108328 (S.L., L.L.). The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health.

Article history:
Received 16 March 2022
Received in revised form 19 May 2022
Accepted 31 May 2022
Available online 7 June 2022

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