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Serum Biomarkers of Nociceptive and Neuropathic Pain in Chronic Pancreatitis

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Abstract

Debilitating abdominal pain is a common symptom affecting most patients with chronic pancreatitis (CP). There are multiple underlying mechanisms that contribute to pain which makes successful treatment difficult. The identification of biomarkers for subtypes of pain could provide viable targets for non-opioid interventions and the development of mechanistic approaches to pain management in CP. Nineteen inflammation- and nociception-associated proteins were measured in serum collected from 358 subjects with definite CP enrolled in PROspective Evaluation of Chronic Pancreatitis for EpidEmiologic and Translational StuDies (PROCEED), a prospective observational study of pancreatitis in US adult subjects. First, serum levels of putative biomarkers were compared between CP subjects with and without pain. Only PDGF-B stood out, with levels significantly higher in the CP pain group as compared to subjects with no pain. Subjects with pain were then stratified into four pain subtypes (Neuropathic, Nociceptive, Mixed and Unclassified). A comparison of putative biomarker concentration among five groups (No pain and 4 pain subtypes), identified unique proteins that were correlated with pain subtypes. Serum TGFβ1 level was significantly higher in the Nociceptive Pain group compared to the No Pain group, suggesting that TGFβ1 may be a biomarker for Nociceptive pain. The Neuropathic pain only group was too small to detect statistical differences. However, GP130, a co-receptor for IL-6, was significantly higher in the Mixed pain group compared to the groups lacking a neuropathic pain component. These data suggest that GP130 may be a biomarker for Neuropathic pain in CP.

Perspective—Serum TGFβ1 and GP130 may be biomarkers for nociceptive and neuropathic CP pain, respectively. Preclinical data suggest inhibiting TGFβ1 or GP130 reduces CP pain in rodent models, indicating that additional translational and clinical studies may be warranted to develop a precision medicine approach to the management of pain in CP.

Keywords

GP130; PDGF-B; TGFβ1; PROMIS; PROCEED Study; CPDPC

1. Introduction

Abdominal pain in patients with chronic pancreatitis (CP) drives morbidity, lowers quality of life and often renders patients unable to work or function normally.[21, 74] For patients whose pain is managed medically (e.g. pharmaceuticals), drugs are frequently ineffective and can cause a range of deleterious side effects.[9, 42, 45, 68] Approximately 50% of patients with CP receive an opioid treatment and less than half of those achieve complete relief.[45] Poor response rates to existing therapies are thought, in part, to stem from an inability to differentiate the multitude of mechanisms that can contribute to CP-related pain.[50] Pancreatitis-related pain is initiated by normal activation of nociceptive neurons. However, in some cases it can be associated with sensitization in one or more compartments of the nervous system (periphery, spinal cord, supraspinal). Sensitization (i.e. potentiation of nociceptive signaling) can occur in the presence or absence of nerve injury and drives increased severity of pain. Pancreatic expression of the neurotrophins NGF and BDNF is elevated in CP patients with pain relative to healthy controls.[19, 79] In cases where there is evidence of intrapancreatic nerve injury, the extent of this neuropathy also correlates with severity of CP pain.[10, 11] Indeed, upregulation of CGRP, Substance P, IL-8 and Fractalkine within intrapancreatic nerve fibers correlates with pain severity and the extent of neuritis.[8, 12, 14, 76] Unfortunately, tissue-based biomarkers are not viable options in clinical practice, so identification of circulating biomarkers are needed to improve clinicians' ability to characterize pain to predict and monitor therapeutic responses.

Circulating pro-inflammatory cytokines and chemokines have been implicated in neurogenic inflammation, nociception, and primary afferent sensitization in multiple pain conditions. Of these signaling molecules, IL-6, TNFα, fractalkine, MCP1 (CCL2), TGFβ1, and NGF are reportedly increased in serum from subjects with CP.[28, 56, 60, 76] In these studies, subjects were compared to healthy controls, but pain status was not reported. One recent study reported that high IL-1β, IL-8, and MCP1 correlate with worse quality of life, a composite score that included pain.[51] However, it is not possible to conclude from the available data whether these upregulated proteins are specifically due to pain. Because of the design of these studies, it is possible that upregulation of specific proteins is reflective of ongoing disease processes or other components of quality-of-life (QoL) measures. In the current study, we sought to validate potential pain biomarkers that have been identified in prior clinical studies (Table 1).

The pain experience is heterogenous within the CP population. We and others previously classified patients based on the distinct characteristics of their pain experience, including frequency and intensity of pain.[42, 46, 72] However, exploration of biomarkers unique to pain pattern yielded limited information.[53] Dogma in the pain field suggests that neuropathic pain in particular does not respond to anti-inflammatories or opioids. The efficacy of "neuromodulators" including anti-depressants and gabapentinoids are considered better for neuropathic pain, but their efficacy is still questionable.[23, 24, 54, 71] Thus, identification of biomarkers specific for subtypes of CP pain (i.e. neuropathic and nociceptive) would provide viable targets for non-opioid interventions and the development of mechanistic approaches to pain management in CP. Based on previous analyses, 37% of CP patients have some neuropathic component to their pain.[52] Thus, we sought to identify serum biomarkers of pain as well as to determine if unique biomarkers associate with the neuropathic and nociceptive components of pain. Evaluation of 19 inflammation- and nociception-associated proteins in serum from subjects with CP revealed unique biomarkers associated specifically with pain that does or does not have a neuropathic component.

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 (CPDPC).[55] PROCEED is a prospective observational study of US adult subjects across the pancreatitis spectrum (ranging from no pancreas disease to acute to chronic pancreatitis).[75] Detailed clinical data including sociodemographic and risk factors, disease phenotype, laboratory testing, imaging and biological specimens are collected at baseline and annual visits according to protocols approved by the a central Institutional Review Board (MD Anderson Cancer Center.[75] Informed consent was obtained from each subject prior to enrollment in the PROCEED study and included permission for use of data and biospecimens in ancillary studies. In addition, several patient-reported outcomes are acquired through the administration of validated PROMIS instruments as well as study specific questionnaires.[75] The number of subjects included in the current study is a subset of the definite CP cohort described previously.[52] All subjects in the final study cohort had definite CP, pain data and serum samples available from the PROCEED enrollment visit (Figure 1). Definite CP was defined by subjects having Cambridge 3 or 4 classification, presence of pancreatic calcification consistent with CP (by cross-sectional imaging) or a histologic diagnosis of CP.

Table 1 describes the select characteristics of 358 CP subjects who formed the study population. The median age (years) was 55 with 49% being men. This is similar to the entire PROCEED definite CP cohort (53.5% men). The cohort identified as predominantly white (85%) and non-Hispanic (97%). The median duration of pancreatitis was 5 years. A large proportion, 44%, of cases were classified as having alcohol etiology as reported by the patient's physician. Most subjects (81%) had a history of acute pancreatitis. Criteria and operational definitions for patient and clinical variables have been published previously.[75] Additionally, 43% of the study population had diabetes as defined by the American Diabetes Association (ADA) criteria. ADA criteria are abnormal values on two of the following tests or two abnormal values on the same test: a) fasting blood sugar ≥126mg/dl; b) HbA1c≥6.5%; c) Random blood glucose ≥200mg/dl OR use of anti-diabetic medications. Morphological characteristics were described by radiologists' assessment of imaging studies (e.g. CT, MRI), and 50% of the study population had a pancreatic duct stricture prior to enrollment. Exocrine pancreas insufficiency was determined by clinical history of steatorrhea or fecal elastase <100mcg/gram stool or quantitative fecal fat of >7gram/day on a 100-gram fat diet; and fecal elastase of <100mcg/gram stool during follow-up. Tobacco use was defined as cigarettes, cigars/pipes, e-cigarettes and/or tobacco chew.

2.2 Serum Analyte Assessment

Putative serum biomarkers were chosen based on previous literature implicating them as positive or negative regulators of pain (Table 2). Serum (25μl per reaction) was used to measure Substance P via a commercial ELISA assay (Cayman Chemical). The remaining analytes were measured using the Meso Scale Discovery Platform which enabled custom multiplexing to reduce the sample volume required. All assays were performed according to the manufacturers' instructions. All assays included standards to develop a calibration curve and have large detectable ranges (0.1 pg/ml-0.1 mg/ml). Positive and negative (diluent only) controls were included on each 96 well plate. All samples were run in duplicate. All research staff performing sample testing and data collection were blinded. Coded samples were randomized across plates.

2.3 Mechanism-based Pain Phenotyping In Definite CP subjects WITH Pain

CP subjects with pain completed PROMIS Pain Quality Short Forms (PROMIS-PQ) to enable stratification of pain type. Nociceptive pain quality and Neuropathic pain quality were determined as previously described.[52] A threshold of $T \geq 50$ was used as the cut-off for categorizing subjects into groups. There were four subtypes of pain, Nociceptive, Neuropathic, Mixed (both nociceptive and neuropathic) and Unclassified (could not be assigned to the other groups. During initial validation of PROMIS-PQ, a cut-off of 50 was determined to maximize both sensitivity and specificity.[4, 44] To our knowledge, the only independent study that also used PROMIS-PQ to stratify subjects into pain groups used 50 as a cut-off.[67] Therefore, we adopted the same scoring rubric to assign subjects to a pain group (Table 3).

2.4 Statistical Analysis

We used regression models to compare the 19 putative serum biomarkers among various pain subtypes. The biomarker was the outcome variable and indicators for pain subtype were covariates. Linear regression was used for continuous biomarkers and logistic regression was used for binary biomarkers. We performed log transformation on Fractalkine, MCP1, PDGF-B, NGF, NT-3, TNFα, IFNγ, IL-6, and IL-8 to reduce the skewness in their distribution when they were used in regression models. We dichotomized IL-1β (1 if >1, 0 otherwise), IL-4 (1 if > 0.06, 0 otherwise), IL-10 (1 if > 0.28, 0 otherwise), CGRP (1 if > 0, 0 if = 0), and SP (1 if > 0, 0 if = 0) because their distributions are extremely skewed and had a substantial proportion of patients with zero concentration. To reduce float point calculation error, we rescaled some continuous biomarkers by dividing TGFβ1, GP130, and resistin by 1000, 10000, and 100 respectively, and by multiplying NGF, IL-4, TNFα, IFNγ, IL-6 and IL-8 by 10 respectively. This transformation has no effect on the test statistics and was done in each biomarker's regression model. We considered models that compare pain vs. no pain, and other models that compared 5 pain phenotypes (No Pain, Neuropathic-like, Nociceptive, Mixed, and Unclassified Pain). Based on these models, we tested the null hypothesis that there was no difference in the mean biomarker among the various phenotypes, versus the alternative that there was a difference. Several subjects in the Neuropathic-like pain group had 0 pg/ml of IL-1β and/or CGRP; therefore, we used Fisher's exact test which has better justification than logistic regression when the sample size is small. To adjust for testing of multiple biomarkers, we calculated the false discovery rate (FDR) for testing the mean difference of each biomarker among the subtypes.[6] The pairwise comparison of statistically significantly different biomarkers among multiple pain groups were conducted by Tukey's Honest Significant Difference (HSD) test. Throughout this paper, we used 0.05 as the level of statistical significance, both for the raw p-values and FDR to compare multiple biomarkers.

To study whether the association between biomarkers and pain subtype is confounded by patient characteristics, we incorporated etiology, pancreatitis duration, diabetes, pancreas duct stricture, gender, body mass index (BMI), weight, age, prior acute pancreatitis and recurrent acute pancreatitis attack in the regression models as pre-specified covariates. This covariate adjusted analysis was done for putative biomarkers that had a raw p-value from the statistical analysis without covariate adjustment less than 0.2. There were rare missing values in the biomarker data (2 in TGFβ1 and TGFβ2, 1 in NT-3, 3 in CGRP and 8 in Substance P). They were imputed with mean or mode, as appropriate.

3. Results

3.1 Putative biomarkers for CP: Pain versus No Pain

Nineteen different cytokines, chemokines and neuropeptides were measured in the serum collected from subjects at enrollment. Of the 358 CP subjects, 301 (84%) reported pain in the preceding year, and the other 57 (16%) reported no pain. Descriptive statistics for the study population based on presence or absence of pain are presented in Supplementary Table S1. Of the 19 analytes studied, TGFβ1, MCP1, and PDGFB concentrations are significantly higher in CP subjects with pain compared to those with no pain at the statistical significance level of 0.05 (Table 4). However, after adjusting for multiple testing, only PDGFB remained significant with a FDR of 0.03, and TGFβ1 has a FDR of 0.07. We report the effect of pain as the coefficient for continuous biomarkers and odds ratio for dichotomized markers. Specifically, the mean level of TGFβ1, MCP1 and PDGFB are higher by 3.58, 0.15, and 0.26 for subjects with pain compared to subjects with no pain, respectively (Table 4). Pancreas duct stricture and diabetes were significantly different among pain types in a previous study of PROCEED subjects.[52] Additionally, there are covariates that may influence biomarker profile. Therefore, we reanalyzed the putative biomarkers that had a p-value less than 0.2 and included the prespecified covariates (etiology, pancreatitis duration, diabetes, pancreas duct stricture, gender, BMI, weight, age, prior acute pancreatitis and recurrent acute pancreatitis attack) in the regression model to determine if the associations between expression levels of putative biomarkers and presence of pain were confounded by the covariates (Table 5). The regression results did not change dramatically when comparing Table 4 and Table 5, suggesting that these covariates did not impact our results. Specifically, adjusted by the covariates, the mean level of TGFβ1, MCP1, and PDGFB are higher by 2.28, 0.23, 0.28 for subjects with pain compared to no pain group, respectively (Table 5).

3.3 Putative biomarkers for CP: Pain Subtypes

After the subjects were classified by presence or absence of pain, those with pain were further stratified based on their pain quality (Figure 2). Descriptive statistics of the study population stratified by pain group are presented in Supplementary Table S2. The expression of putative biomarkers was compared among the 5 subtypes, No Pain, Nociceptive, Neuropathic, Mixed and Unclassified (Table 6). Analysis of the transformed data resulted in statistically significant results in the expression of TGFβ1, GP130, and PDGF-B, based on unadjusted p-values.

However, after adjusting for multiple comparisons, only TGFβ1 (FDR = 0.046) and GP130 (FDR = 0.046) remained significantly different. Further pairwise comparisons by Tukey's HSD test among the various phenotypes within each biomarker revealed that TGFβ1 was significantly higher in the Nociceptive pain group as compared to the No Pain group (p-value = 0.0067, Figure 3A), GP130 was significantly higher in the Mixed Pain group as compared to No Pain (p-value = 0.0115), and Nociceptive and Unclassified Pain groups (p-value = 0.0226, Figure 3B). Similar to Section 3.2, we reanalyzed the putative biomarkers with an unadjusted p-value less than 0.2 by adjusting for the covariates listed in Section 3.2 (Table 5). Again, the results before and after covariate adjustment did not change dramatically, suggesting that these covariates do not impact the relationships between the biomarkers of interest and pain types (Table 6).

4. Discussion

In a large cohort of CP, we found that 84% of subjects reported abdominal pain. The pain type could be classified into four subgroups based on responses to PROMIS-PQ from most to least common (Nociceptive>Mixed>Unclassified>Neuropathic). Serum PDGF-B levels were significantly higher in CP subjects with pain compared to those with no pain. While PDGF-B levels were not different between subtypes of pain, other novel biomarkers emerged. Specifically, TGFβ1 was significantly elevated in the Nociceptive pain group as compared to the No Pain group, but not the other pain subtypes. GP130 was significantly elevated in the Mixed pain group relative to all other groups lacking a neuropathic component which suggests that GP130 may be an indicator of neuropathic pain. To our knowledge, circulating biomarkers for pancreatitis pain have not been investigated in a large cohort before. Of particular importance, is that this is the first study to identify biomarkers associated with specific subtypes of pain within the pancreatitis population. Other pain features (e.g. pain intensity and pain interference) have been previously characterized in this cohort previously.[52] Of interest, pain intensity and pain interference were statistically significantly higher in subjects in the neuropathic/mixed pain group as compared to nociceptive pain group. However, the difference was less than 1 point on the numerical rating scale, suggesting that this endpoint for analyses may not be clinically meaningful. Our study was designed to test the hypothesis that the PROMIS-PQ classification system could identify biomarkers. Based on these results serum biomarkers identified by PROMIS-PQ pain group may, in combination with other data, inform mechanism-based pain management in CP patients.

The PDGF-BB homodimer has been implicated in both angiogenesis and fibrosis. As a regulator of pancreatic fibrosis[2], it is not surprising that PDGF-B is upregulated in patients with CP compared to healthy individuals.[1, 57] PDGF-BB is also elevated in patients with other chronic pain conditions including inflammatory bowel disease, back pain, burning mouth syndrome and odontalgia.[26, 32, 33, 41] Several preclinical studies have demonstrated that PDGF-B activates nociceptive neurons and produces robust mechanical hypersensitivity [5, 37], which explains why serum PDGF-B is significantly higher in CP patients with pain compared to those with no pain. Disruption of PDGF signaling via antagonist or antibody reverses mechanical hypersensitivity in preclinical pain models.[15, 43] Importantly, morphine alone has no effect on mechanical allodynia in a rodent model in which injured nerves release PDGF-B; opioid efficacy is restored following inhibition of PDGF-B signaling.[15, 70] That PDGF-B directly activates sensory neurons and mediates opioid tolerance may explain why many CP patients do not find adequate relief from opioids. Therefore, it is biologically plausible that PDGF-B inhibitors could represent an adjunct therapy that would reduce the amount of opioids CP patients require.

GP130 is a type 1 cytokine receptor and serves as a receptor component for several cytokines including pro-nociceptive IL-6 which can act directly on sensory neurons to sensitize TRPV1, a key ion channel expressed by nociceptive neurons.[3, 34] Following deletion of neuronal GP130, another nociceptive ion channel, TRPA1 is downregulated resulting in reduced mechanonociception.[27, 39] Neuronal GP130 signaling increases excitability of nociceptive neurons[35], and GP130 is upregulated in preclinical models of visceral pain.[22] In the dibutylin dichloride model of CP, a small molecule IL-6 receptor antagonist ameliorates abdominal hypersensitivity by reducing sensitization of nociceptive neurons.[66] Furthermore, a small molecule inhibitor LMT-28 that directly targets GP130 inhibits inflammation in the cerulein model of acute pancreatits.[25] It remains unclear whether the upregulation of GP130 levels that we observed in serum are directly correlated with membrane expression of GP130. It is possible that circulating GP130 reflects shedding from damaged glial, neuronal, and immune cells given that we observed significantly higher GP130 levels in patients in the Mixed (neuropathic+nociceptive) pain group.

Elevated TGFβ1 has been detected in patients with CP as well as rodent models of spontaneous pancreatitis.[1, 28, 58, 64] The importance of TGFβ1 in CP has previously been attributed to its roles in wounding healing and promoting fibrosis.[7, 29, 69] However, application of TGFβ1 to sensory neurons increases membrane excitability which is mimicked by intrapancreatic infusion of TGFβ1.[36, 77, 78] Peripheral TGFβ1 is pro-nociceptive through downregulation of voltage-gated potassium channels and depolarizing resting membrane potential .[36, 77, 78] Further, TGFβ1 reduces rheobase, prolongs action potential duration and increases intracellular calcium in pancreas afferents. [36, 77, 78] Through Cdk5 and TAK1/PKC pathways, TGFβ1 drives sensitization of the nociceptive ion channel TRPV1.[62, 63, 73] In the TNBS model of CP, neutralizing antibodies and small molecule antagonists that target TGFβ1 reduce somatic and visceral mechanical hypersensitivity.[36, 77, 78] Given the direct actions of TGFβ1 signaling on nociceptive neuron excitability, it makes sense that elevated TGFβ1 in peripheral blood is associated with nociceptive pain. Several antibodies and small molecule inhibitors targeting TGFβ1 are in various stages of development (NCT05350371, NCT00043706, NCT00781053, NCT00574613, NCT00656825).[17, 47, 48, 65] However, whether these therapeutics ameliorate pain has yet to be investigated.

As discussed previously, the PROMIS-PQ is subjective in nature and currently there are no empirical methods to validate pain type in the context of pancreatitis.[52] However, there is biological evidence that supports the associations we detected between GP130 and TGFβ1 and Mixed and Nociceptive subtypes of pain, respectively. Unfortunately, we did not detect an association between a biomarker and the Neuropathic pain only group. This was likely due to low statistical power, a result of the small sample size and the large number of proteins we tested. The distribution of pain subtypes we observed is consistent with other complex multifactorial pain conditions including the small percentage of subjects classified as Neuropathic pain only. This makes biological sense given that pancreatitis is typically associated with inflammation and tissue injury. Regardless, the PROMIS-PQ instruments have not yet been applied to any CP populations outside of the PROCEED study so independent studies of other patient populations are needed.

In conclusion, many of the analytes assessed in the current study have been shown to be upregulated in other painful conditions as well as in preclinical pain models. We identified a potential biomarker for the presence of pain (PDGFB) as well as two potentially important biomarkers GP130 and TGFβ1 that correlate with specific subtypes of pain, Mixed and Nociceptive subtypes of pain, respectively. Importantly, targeting GP130 or TGFβ1 in animal models effectively reduces CP pain. Thus, as biologics and other pharmaceuticals are developed that target GP130 or TGFβ1, their efficacy for ameliorating CP pain should be investigated in humans. However, use of these tools in combination with biomarker assays and other things could inform selection criteria and improves chances for a successful clinical trial for CP pain management.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Disclosures

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Highlights

- Painful chronic pancreatitis is associated with higher serum PDGFB
- Serum biomarkers may dissociate subtypes of chronic pancreatitis pain
- Serum TGFβ1 is higher in those with nociceptive chronic pancreatitis pain
- Serum GP130 is higher in those with mixed-type chronic pancreatitis pain

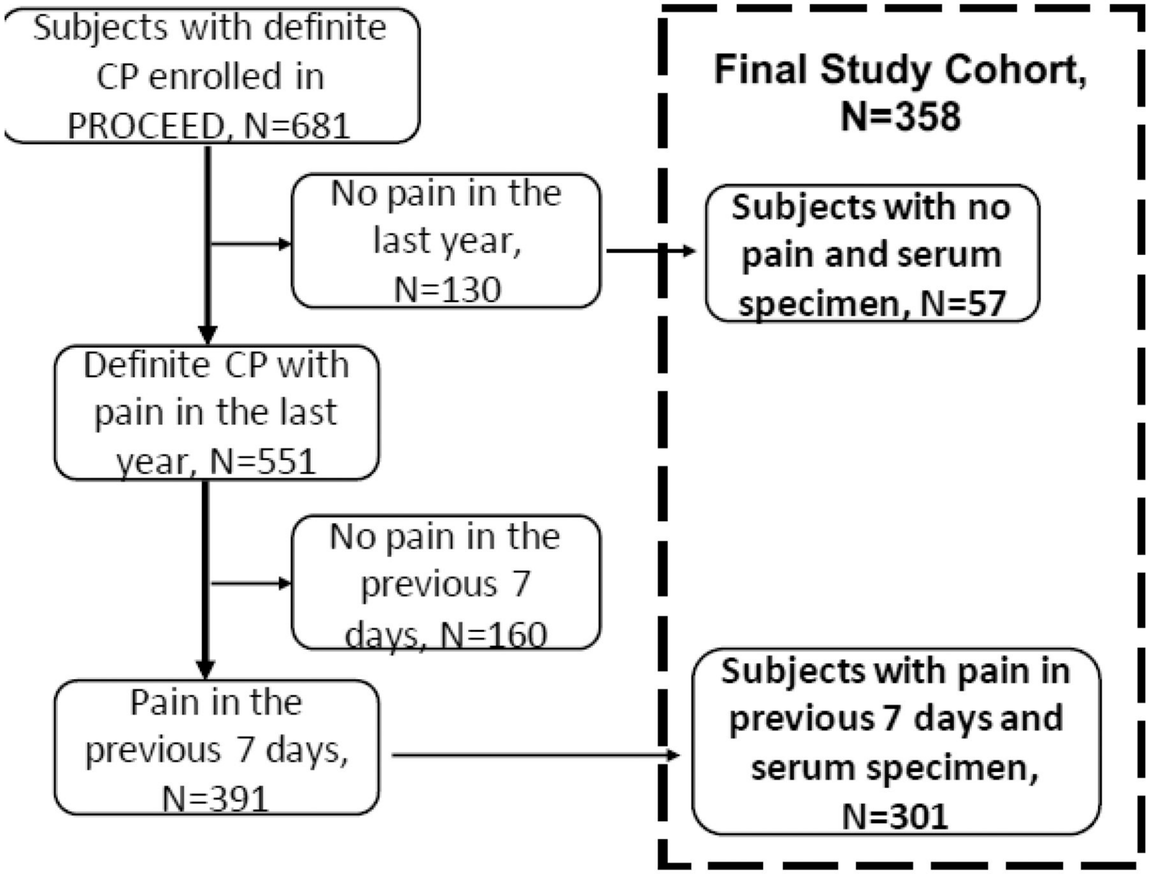

Figure 1. Subject selection.

The number of subjects were selected based on availability of serum and power analyses.

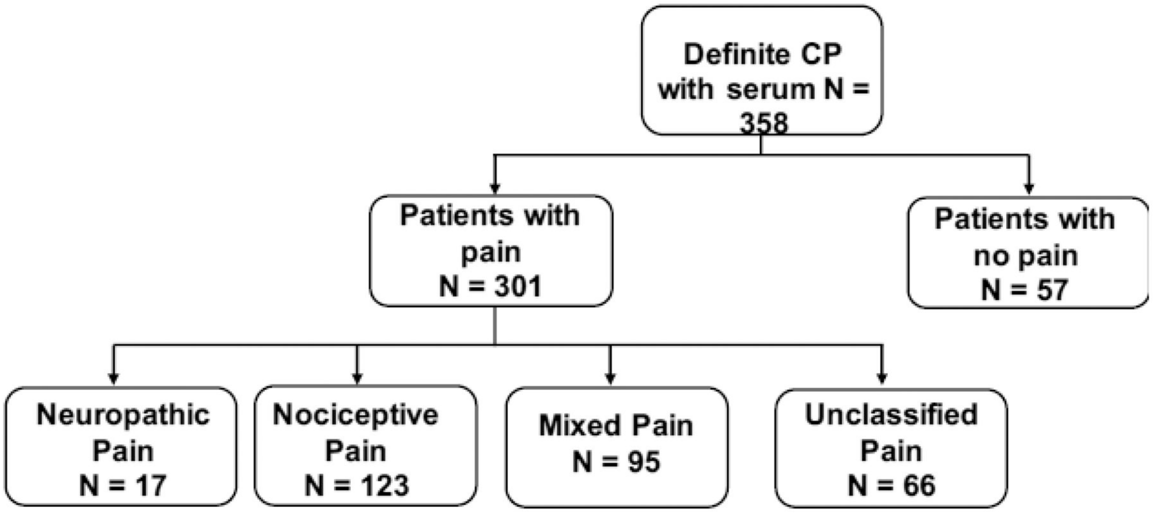

Figure 2. Final Study Cohort.

Subjects by pain group.

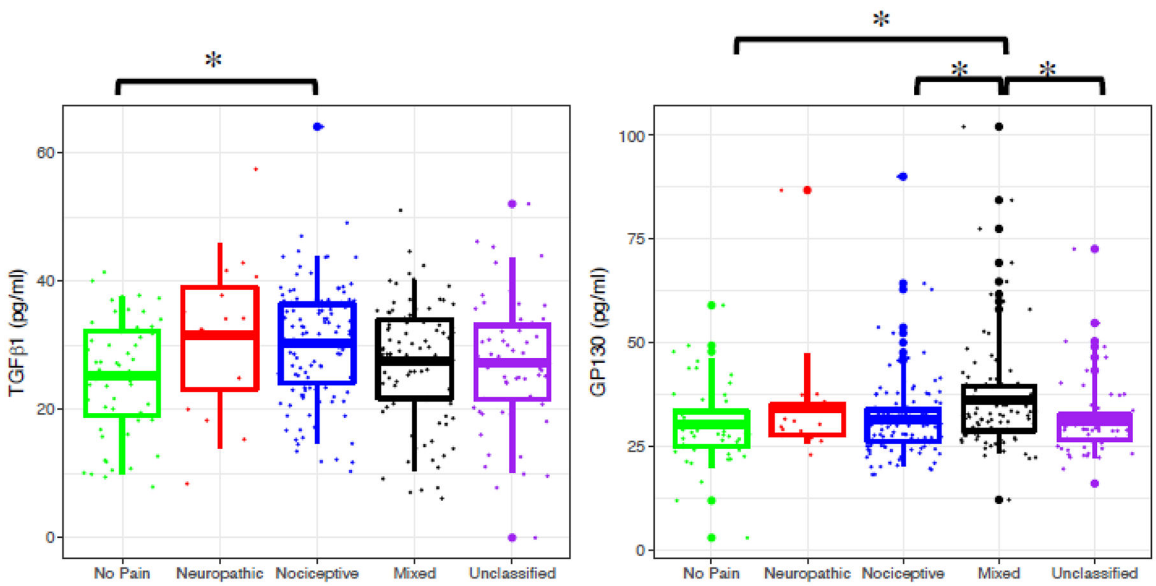

Figure 3. Serum biomarker expression by pain subtype.

A) TGFβ1 is significantly higher in the nociceptive CP group compared to the no pain CP group. B) Circulating GP130 is significantly higher than no pain or pain without a neuropathic component. The middle line of the boxplots represent mean, and the upper and lower lines of the boxes are 75% and 25% quantiles.

Table 1.

Descriptive statistics of the study population (n=358)

Age (years) – median (interquartile range)	55 (45, 63)
Gender – n (%)	
Female	183 (51)
Male	175 (49)
Race	
Black	23 (6)
Other	30 (8)
White	305 (85)
Ethnicity	
Hispanic	9 (3)
Non-Hispanic	349 (97)
BMI (kg/m^2)	24 (21, 28)
Education	
High-school or less	127 (36)
Some training after high-school, including associate degree or some college	133 (37)
Bachelor's degree, Graduate school or Other	98 (27)
Alcohol Etiology	
Yes	157 (44)
No	201(56)
Alcohol use	
Never	46 (13)
Past	233 (65)
Current	78 (22)
Tobacco use	
Never	90 (25)
Past	108 (30)
Current	160 (45)
Ever had acute pancreatitis	273 (81)[21]
Pancreatitis duration (years)	5 (2, 12)[2]
Exocrine pancreatic dysfunction present	155 (66)[123]
Diabetes present	150 (43)[11]
Prior Endoscopic therapy	216 (61)[5]
Calcification(s) present	280 (79)[2]
Pancreas size on imaging	
<7mm	51 (14)[5]
7-14mm	155 (44)
>14mm	147 (42)
Pancreatic duct dilation present	281 (80)[5]
Pancreatic duct stricture present	177 (50)[5]

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

Count (percentage) is reported for categorical variables.

Superscripts in the first row of each variable indicate the missing value counts, which are excluded from the percentage calculation.

Table 2.

Analytes Assessed In Serum from CP Patients

Analyte	Abbreviation	References
Interleukin 1beta	IL-1β	[30, 52]
Interleukin 4	IL-4	[30, 52]
Interleukin 6	IL-6	[52, 58]
Interleukin 8	IL-8	[52, 58]
Interleukin 10	IL-10	[14, 30, 52, 58]
Interferon gamma	IFNγ	[48]
Tumor necrosis factor alpha	TNFα	[40, 52, 58]
Transforming growth factor beta 1	TGFβ1	[28, 31, 40, 55, 75]
Transforming growth factor beta 2	TGFβ2	[18, 20]
Platelet Derived Growth Factor B	PDGF-B	[56]
Neurotrophin 3	NT-3	[60]
Nerve growth factor	NGF	[19, 28]
Brain derived neurotrophic factor	BDNF	[78]
Monocyte chemoattractant protein 1	MCP1 (CCL2)	[28, 52]
Fractalkine	Fractalkine (CX3CL1)	[12, 13, 31]
Resistin	Resistin	[28]
Glycoprotein 130	GP130	[3, 16, 35] *38
Calcitonin gene related peptide	CGRP	[8, 52]
Substance P	SP	[8]

*references refer to preclinical studies

Table 3.

PROMIS-PQ Scoring Rubric for Pain Group Assignment

	Nociceptive	Neuropathic	Mixed	Unclassified
PROMIS Nociceptive Pain Quality T-Score	T ≥ 50	T < 50	T ≥ 50	T < 50
PROMIS Neuropathic Pain Quality T-score	T < 50	T ≥ 50	T ≥ 50	T < 50

Table 4.

Regression models on the univariate association between each biomarker and the presence or absence of pain among CP patients.

Continuous biomarker	Coefficient	95% CI	*p*-value*	FDR
TGFβ1	3.58	0.94, 6.22	0.0079	0.0747
TGFβ2	10.45	−4.62, 25.51	0.1741	0.3307
BDNF	136.10	−54.25, 326.45	0.1611	0.3307
GP130	2.85	−0.26, 5.96	0.0727	0.3307
Resistin	6.58	−2.42, 15.59	0.1520	0.3307
Fractalkine	0.10	−0.05, 0.25	0.2122	0.3666
MCP1	0.15	0.02, 0.29	0.0259	0.1640
PDGFB	0.26	0.10, 0.43	0.0016	0.0305**
NGF	0.17	−1.58, 1.93	0.8481	0.9319
NT-3	0.19	−2.37, 2.76	0.8828	0.9319
TNFα	−0.07	−1.82, 1.67	0.9332	0.9332
IFNγ	0.57	−2.28, 3.43	0.6934	0.8783
IL-6	2.09	−0.60, 4.77	0.1277	0.3307
IL-8	0.63	−1.59, 2.85	0.5796	0.7866
Dichotomized biomarker	**Odds ratio**	**95% CI**	***p*-value***	**FDR**
IL-1β	2.53	0.32, 19.71	0.3762	0.5956
IL-4	1.59	0.90 2.81	0.1103	0.3307
IL-10	1.08	0.61, 1.90	0.7873	0.9319
CGRP	0.78	0.40, 1.51	0.4571	0.6681
SP	1.61	0.91, 2.86	0.1023	0.3307

*The *p*-value is from a test of the difference in mean biomarker between the presence and absence of pain.

**Statistically significant at a critical value of 0.05

CI: confidence interval FDR: false discovery rate adjusted p-value

Effect size is quantified as the regression coefficient for continuous biomarkers, which measures the mean difference in the biomarker between the pain groups and as the odds ratio for dichotomized biomarkers, which is the odds of having the biomarker among patients with pain divided by the odds of having the biomarker among patients without pain.

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Table 5.

Regression models on the association between putative biomarkers and presence or absence of pain adjusting for covariates

Continuous biomarker	Coefficient	95% CI	*p*-value*
TGFβ1	2.28	−0.77, 5.33	0.1427
TGFβ2	14.94	−2.36, 32.24	0.0905
BDNF	−46.44	−260.58, 167.69	0.6708
GP130	4.45	0.93, 7.97	0.0131
Resistin	7.83	−2.54, 18.20	0.1388
MCP1	0.23	0.08, 0.38	0.0032
PDGFB	0.28	0.09, 0.47	0.0044
IL-6	2.08	−0.90, 5.07	0.1708
Dichotomized biomarker	**Odds ratio**	**95% CI**	***p*-value***
IL-4	1.09	0.93, 1.28	0.3090
SP	1.08	0.92, 1.26	0.3383

* *p*-value from the regression models including covariates: etiology, pancreatitis duration, diabetes, pancreas duct stricture, gender, BMI, weight, age, prior acute pancreatitis and recurrent acute pancreatitis attacks. This analysis only includes putative biomarkers whose p-value from the regression analysis without covariate adjustment was greater than 0.2. The interpretation of the reported coefficient and odds ratio as measures of the effect size is the same as in Table 4, except that they are conditional on covariates here.

Table 6.

Putative biomarkers in various pain subtypes among CP patients

	No Pain (n = 57)	Neuropathic (n=17)	Nociceptive (n=123)	Mixed (n = 95)	Unclassified (n = 66)	Without covariate adjustment		With covariate adjustment
						p-value	FDR	*p*-value#
TGFβ1	25.22 (8.93) *	27.48 (9.17)	27.25 (9.62)	30.26 (8.84)	31.65 (12.07)	0.0041	0.0461 **	0.0416
TGFβ2	91.09 (39.64)	98.73 (57.86)	98.00 (58.08)	104.92 (53.10)	106.41 (49.21)	0.5543	0.7021	-
BDNF	786 (764)	928 (593)	786 (558)	973 (717)	1051 (809)	0.2008	0.5207	-
GP130	30.13 (9.16)	36.01 (13.56)	31.02 (8.75)	31.54 (9.64)	34.01 (14.21)	0.0048	0.0461 **	0.0007
Resistin	47.77 (24.67)	55.95 (30.99)	49.87 (28.80)	56.04 (37.33)	50.69 (24.97)	0.3865	0.5648	-
Fractalkine	9.27 (0.43)	9.37 (0.51)	9.48 (0.64)	9.29 (0.50)	9.49 (0.67)	0.1068	0.4057	0.3757
MCP1	5.80 (0.59)	5.97 (0.43)	5.94 (0.46)	5.94 (0.46)	6.04 (0.56)	0.2192	0.5207	-
PDGFB	9.92 (0.62)	10.14 (0.64)	10.18 (0.61)	10.20 (0.48)	10.36 (0.67)	0.0186	0.1180	0.2256
NGF	0.99 (5.75)	1.56 (5.45)	−0.12 (6.69)	1.66 (6.49)	0.39 (7.16)	0.3629	0.5648	-
NT-3	−1.56 (9.39)	−0.48 (9.50)	−3.36 (8.85)	−1.40 (8.77)	1.69 (7.13)	0.1927	0.5207	0.0345
TNFα	11.18 (5.27)	11.69 (5.48)	10.38 (7.70)	11.01 (6.01)	11.32 (7.13)	0.7705	0.8790	-
IFNγ	18.04 (11.67)	18.03 (8.34)	19.10 (10.78)	18.83 (9.87)	18.52 (12.45)	0.9538	0.9538	
IL-6	2.71 (7.34)	5.29 (10.80)	3.25 (10.48)	5.16 (8.65)	5.44 (9.83)	0.3342	0.5648	-
IL-8	21.39 (5.70)	23.19 (8.41)	19.63 (8.18)	22.29 (8.00)	22.83 (6.84)	0.0621	0.2949	0.0006
IL-1β (<1)	56 (98.25%)	92 (96.84%)	63 (95.45%)	117 (95.12%)	16 (94.12%)	0.7865	0.8790	-
IL-4 (<0.06)	31 (54.39%)	40 (42.11%)	34 (51.52%)	48 (39.02%)	7 (41.18%)	0.2532	0.5345	-
IL-10 (<0.28)	28 (49.12%)	48 (50.53%)	29 (43.94%)	57 (46.34%)	8 (47.06%)	0.9368	0.9538	-
CGRP (=0)	13 (22.81%)	23 (24.21%)	15 (22.73%)	39 (31.71%)	6 (35.29%)	0.4825	0.6548	-
SP (=0)	26 (45.61%)	30 (31.58%)	21 (31.82%)	44 (35.77%)	8 (47.06%)	0.3429	0.5648	-

* mean (sd)

** statistically significant at a critical value of 0.05

co-variates included in the ANOVA are etiology, pancreatitis duration, diabetes, pancreas duct stricture, gender, BMI, weight, age, prior acute pancreatitis and recurrent acute pancreatitis attacks.