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SHORT REPORT

Association of Serum Endocannabinoid Levels with Pancreatitis and Pancreatitis-Related Pain

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on behalf of the Consortium for the Study of Chronic Pancreatitis, Diabetes, and Pancreatic Cancer (CPDPC)

Abstract

Background and Aims: This investigation examined the association of pancreatitis and pancreatitis-related pain with serum levels of two endocannabinoid molecules such as anandamide (AEA) and 2-arachidonoylglycerol (2-AG) and two paracannabinoid molecules such as oleoylethanolamide (OEA) and palmitoylethanolamide (PEA).

Methods: A case–control study was conducted within the Prospective Evaluation of Chronic Pancreatitis for Epidemiological and Translational Studies, including participants with no pancreas disease ($N = 56$), chronic abdominal pain of suspected pancreatic origin or indeterminate chronic pancreatitis (CP) ($N = 22$), acute pancreatitis ($N = 33$), recurrent acute pancreatitis ($N = 57$), and definite CP ($N = 63$).

Results: Circulating AEA concentrations were higher in women than in men ($p = 0.0499$), and PEA concentrations were higher in obese participants than those who were underweight/normal or overweight ($p = 0.003$). Asymptomatic controls with no pancreatic disease had significantly ($p = 0.03$) lower concentrations of AEA compared with all disease groups combined. The highest concentrations of AEA were observed in participants with acute pancreatitis, followed by those with recurrent acute pancreatitis, chronic abdominal pain/indeterminant CP, and definite CP. Participants with pancreatitis reporting abdominal pain in the past year had significantly ($p = 0.04$) higher concentrations of AEA compared with asymptomatic controls. Levels of 2-AG were significantly lower ($p = 0.02$) among participants reporting abdominal pain in the past week, and pain intensity was inversely associated with concentrations of 2-AG and OEA.

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Conclusions: Endocannabinoid levels may be associated with stage of pancreatitis, perhaps through activation of the CB1 receptor. Validation of our findings would support the investigation of novel therapeutics, including cannabinoid receptor-1 antagonists, in this patient population.

Keywords: cannabis; endocannabinoids; pancreatitis; pain

Introduction

Pancreatitis is a multifactorial and progressive fibroinflammatory disease in which repeated episodes of pancreatic inflammation lead to recurrent acute pancreatitis characterized by cellular injury, deposition of fibrotic tissue, and risk for exocrine and endocrine insufficiency.[1] Chronic pancreatitis (CP) occurs in more than a third of those with recurrent acute pancreatitis and is associated with abdominal pain, reduced quality of life and life expectancy, and increased risk of pancreatic cancer. Endoscopic and surgical options for pain are often not effective, and treatment recommendations are based on an incomplete understanding of the neuropathology of pain.[2] Societal costs include increased hospitalizations, high rates of opioid dependence, lost employment, and reduced educational achievement.[3] Strategies are needed to slow the progression of pancreatitis and improve pancreatitis associated quality of life.

The rising pancreatitis burden, particularly in African Americans and Hispanics, has been attributed to the changing etiological landscape for pancreatitis.[4] Aside from alcohol and tobacco use, diabetes, and gallstones, diseases that disproportionately affect groups that have been historically underrepresented in biomedical research are among the leading risk factors for acute pancreatitis (Fig. 1).[5] The management of pancreatitis is challenging, focused mainly on complications and symptom alleviation.[6,7] Common complications include progression to CP, exocrine pancreatic insufficiency, diabetes mellitus, duct strictures, pseudocysts, and cancer. These complications are due to the progressive fibro-inflammatory response generating the disease pathogenesis. Unfortunately, the treatment of pain in pancreatitis has not been uniformly effective. Invasive procedures, such as surgery, are avoided until other options have been exhausted, and many patients resort to analgesics, such as opioids, for

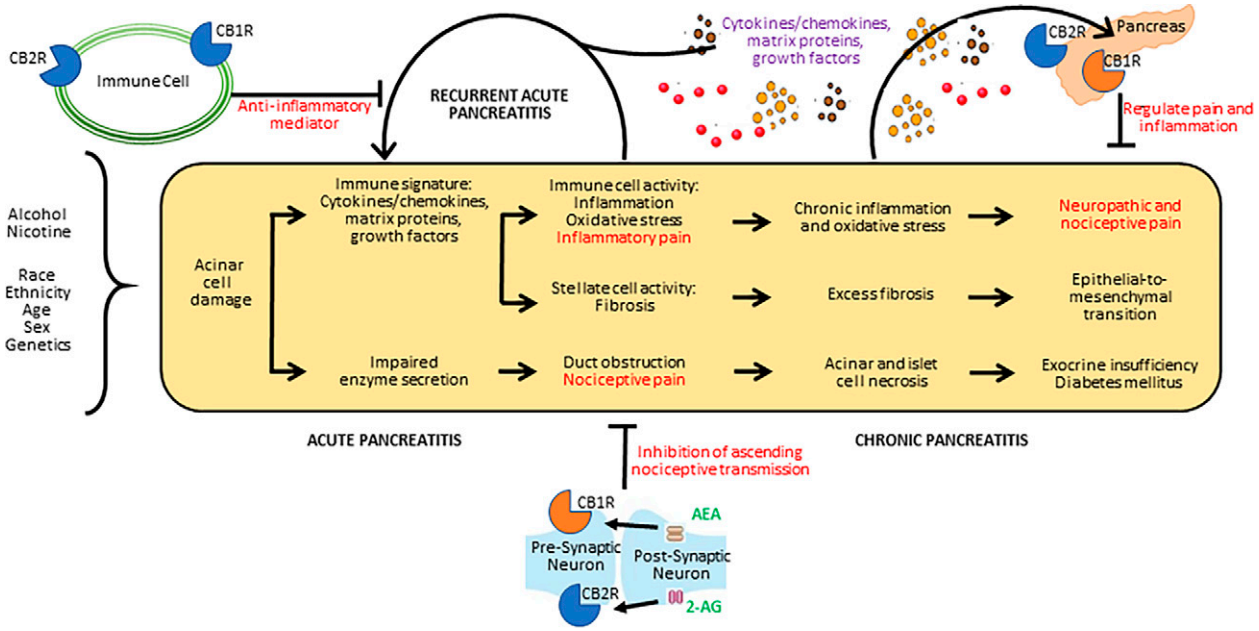

FIG. 1. Hypothetical role of the endocannabinoid system in pain control among individuals with pancreatitis.

pain management. It is important to mitigate pain in pancreatitis patients to better manage complications and to develop treatment options that have improved safety profiles.

Biological correlates of pain in pancreatitis are poorly understood, but they are likely a consequence of tissue damage resulting from fibrosis and inflammation (Fig. 1). Cannabis use has been reported as a potential cause of acute pancreatitis,[8–10] but evidence is based primarily on case reports and animal studies. Activation of cannabinoid receptors, CB1R and CB2R, has been associated with a reduction in systemic inflammation and immune activation. These receptors are activated by both exogenous compounds, such D^9-tetrahydrocannabinol (THC) in cannabis, and by endogenous fatty acid derivatives, the endocannabinoids. CB1R is found in brain and peripheral organs, including the pancreas and liver.[11] CB2R is mainly expressed in cells of the immune system and peripheral nerves.

A recent report concluded that substantial evidence exists regarding the benefits of cannabis and cannabinoids for treating chronic pain in adults.[12] Cannabinoids activate CB1R and CB2R, which regulate neurotransmitter release in the brain and influence the immune response in the pancreas and other organs. The endocannabinoids, including the fatty acid-derivatives anandamide (AEA) and 2-arachidonoylglycerol (2-AG), are released in response to pain stimuli and inflammation. AEA has a pharmacology similar to THC, binding to the CB1R and, to a lesser extent, CB2R, where it acts as a partial agonist. AEA deactivation is mediated by the intracellular serine hydrolase, fatty-acid amide hydrolase.[13]

2-AG binds to CB1R and CB2R with similar affinity, acting as a full agonist at both receptors and is deactivated by the intracellular serine hydrolase, monoacylglycerol lipase.[14] The paracannabinoids, oleoylethanolamide (OEA), and palmitoylethanolamide (PEA) are similar in structure to AEA but do not productively bind to cannabinoid receptors. Rather, they activate the ligand-operated transcription factor, peroxisome proliferator-activated receptor-α to regulate feeding,[15,16] energy metabolism,[17] inflammation,[18] and pain.[19]

While little is presently known about the association of endocannabinoids with the etiology of pancreatitis or chronic pain, cannabis consumption is increasing in the United States,[20] and there is great interest in the potential therapeutic role of cannabinoids in the regulation of inflammation and pain.[21] Increased CB1R activity contributes to tissue fibrosis in the pancreas and liver;[22] and a rat model of type-2 diabetes showed enhanced activity of proinflammatory macrophages, which generated AEA and CB1R leading to β-cell death.[23] Based on these preclinical data, we hypothesized that circulating levels of endocannabinoids and paracannabinoids would be positively associated with pain and pancreatitis. Banked specimens and data at baseline were used to characterize the association of disease status, pain, and health-related quality of life indicators with four endocannabinoid and paracannabinoid molecules using a case–control study that leveraged existing clinical, biological, and epidemiological measures in the ongoing Prospective Evaluation of Chronic Pancreatitis for Epidemiological and Translational Studies (PROCEED) study.[24]

Methods

Study population

PROCEED is an ongoing multicenter prospective cohort study (NCT03099850) implemented in 2017 to define disease progression, test the predictive capability of candidate biomarkers, and develop a platform to conduct translational and mechanistic studies in pancreatitis. As previously described, participants are currently being enrolled at nine clinical centers including men and women of all race/ethnic groups, 18–75 years of age, across the spectrum of pancreatitis, including asymptomatic and symptomatic controls.[24] In this analysis, we selected 231 PROCEED participants for analysis from the following disease groups: no pancreas disease or "negative control (N = 56)," chronic abdominal pain of suspected pancreatic origin and indeterminate CP or "positive control (N = 22)," acute pancreatitis (N = 33), recurrent acute pancreatitis (N = 57), and definite CP (N = 63). The no pancreas disease controls were recruited through advertisements (i.e., brochures university or medical center wide advertisements, records reviews, and searches), as well as approaching patients who come in for preventative services (screening colonoscopy, breast cancer screening, or influenza vaccination), and those being recruited as volunteers to other studies.

In this discovery study, we targeted a sample size of 56 participants per group to achieve 90% statistical

power to detect an effect size of 0.75. Participants with abdominal pain, acute pancreatitis, and recurrent pancreatitis were combined in some analyses to increase sample size.

Study assessments

As previously described, participants completed questionnaires and donated blood specimens at study enrollment.[24] A Patient Case Report Form was self-administered with a trained coordinator available to answer questions and to verify participant responses. The interview included demographics, socioeconomic status, diet and lifestyle, tobacco, and alcohol use, as well as three Patient-Reported Outcomes Measurement Information System (PROMIS) instruments. The Global Health Instrument assesses quality of life and general and mental (emotional) health. The PROMIS-29, a quality-of-life instrument, was used to evaluate seven domains including satisfaction with social and physical activities, fatigue, pain interference, and pain intensity in the past week.[25] In this analysis, we focused on the pain interference items, Q25–Q28 covering pain during daily activities, work at home, social activities, and chores using a five-category scale from "not at all" to "very much." Average pain (Q29) in the past week was assessed using an 11-point scale (0 [no pain]–10 [worst imaginable pain]). Raw scores were tabulated and converted to a normalized T scores according to the published PROMIS scoring manual (http://www.healthmeasures.net). In addition to PROMIS-29, participants who reported having abdominal pain in the past year were asked to choose from five predefined patterns that describe the severity and frequency of their pain.

The PROMIS Nociceptive and Neuropathic Pain Quality Instruments evaluate neuropathic pain quality ("pins and needles," "numb," "electrical") and nociceptive pain quality ("sore," "tender," "achy," "deep") in the subset of participants reporting pain in the 7 days preceding enrollment. Nociceptive pain was defined as a T score ≥50 on the nociceptive short form, and neuropathic pain was defined as a T score ≥50 on the neuropathic short form. Participant pain was considered unclassifiable if the score was <50 on both the nociceptive and neuropathic short forms.[26]

The Physician Case Report Form queries about serum pancreatic enzyme levels, information about episodes of acute pancreatitis, recurrent acute pancreatitis and CP, and medications including use of narcotics, nonsteroidal anti-inflammatory drugs, neuromodulators, and pancreatic enzyme replacement therapy for pain management.

Sample processing and analysis of endocannabinoid levels

Blood samples were collected at the study sites using standardized operating procedures, and time from blood draw to end of processing was noted.[27] In general, biospecimens were frozen at −80°C in <4 h from the time of collection and were kept on wet ice until frozen. Frozen samples were subsequently sent on dry ice to a central Consortium biorepository. For the current analysis, frozen samples were shipped to the Piomelli lab for batch analysis. Laboratory staff were blinded to participant data. Samples were thawed and serum (0.1 mL) was processed as described by Ahmed et al.[28] Briefly, liquid chromatography/mass spectrometry analyses were carried out using a 1200 series LC system (Agilent Technologies), consisting of a binary pump, degasser, temperature-controlled autosampler, and column compartment coupled to a 6410B triple quadrupole mass spectrometric detector (Agilent). The MassHunter software (Agilent Technologies) was used for instrument control, data acquisition, and data analysis.

Data analysis

Participant characteristics were compared using χ^2 tests for categorical variables, t-tests for normally distributed continuous variables, and the nonparametric Wilcoxon rank-sum test for non-normally distributed variables. Continuous variables were summarized using median and interquartile ranges. Generalized linear models were used to assess between-group differences in biomarker levels and pain scores after log-transformation and adjustment for sex and/or body mass index (BMI) where indicated. We performed all analyses to covary for processing time.[29] All tests were two-sided. A p-value <0.05 was considered statistically significant. Data analyses were performed using SAS Version 9.4.

Institutional Review Board approval for the study was obtained from all participating institutions. Written informed consent was obtained from all participants prior to data collection.

Results

The final study population included 109 women and 122 men. Among participants with CP, 52% were current tobacco smokers, 27% were current alcohol

drinkers, and 16% were obese (BMI ≥ 30 kg/m^2) (Table 1). Alcohol, tobacco, and cannabis use were more common among participants with chronic abdominal pain, indeterminate CP, acute pancreatitis or recurrent acute pancreatitis, and those with definite CP than among those with no pancreas disease.

Few differences were found for the association of the four target analytes and patient characteristics, although AEA concentrations were higher in women than in men ($p = 0.0499$) and varied by processing time ($p < 0.0001$) (Table 2). PEA concentrations were higher in obese participants than those who were

Table 1. Characteristics of Disease Groups and Controls

	No pancreas disease *n* = 56	Chronic abdominal pain, indeterminate CP, AP, RAP *n* = 112		Definite chronic pancreatitis *n* = 63	
	n (%)	*n* (%)	*p*-value[a]	*n* (%)	*p*-value[a]
Sex					
Female	26 (46%)	57 (51%)	0.59	26 (41%)	0.57
Male	30 (54%)	55 (49%)		37 (59%)	
Age					
18–39	11 (20%)	33 (29%)	0.20	5 (8%)	0.17
40–59	28 (50%)	57 (51%)		37 (59%)	
60–75	17 (30%)	22 (20%)		21 (33%)	
Race					
White	40 (71%)	87 (78%)	0.28	53 (84%)	0.24
Black	9 (16%)	9 (8%)		5 (8%)	
Other	7 (13%)	16 (14%)		5 (8%)	
BMI					
Underweight/Normal weight	19 (34%)	45 (40%)	0.64	38 (60%)	0.01
Overweight	24 (43%)	40 (36%)		15 (24%)	
Obese	13 (23%)	27 (24%)		10 (16%)	
Pancreatitis Etiology					
Alcohol	~	19 (19%)	~	31 (49%)	~
Idiopathic	~	60 (59%)		23 (37%)	
Other	~	22 (22%)		9 (14%)	
Diabetes at baseline					
Yes	2 (4%)	22 (20%)	<0.0001	27 (43%)	<0.0001
No	0 (0%)	84 (75%)		36 (57%)	
Unknown	54 (96%)	6 (5%)		0 (0%)	
Drinking status					
Current	41 (73%)	27 (24%)	<0.0001	17 (27%)	<0.0001
Past	5 (9%)	64 (57%)		43 (68%)	
Never	10 (18%)	20 (18%)		3 (5%)	
Don't know/decline to answer	0 (0%)	1 (1%)		0 (0%)	
Heaviest alcohol use—lifetime[b]					
Abstainers	10 (18%)	20 (18%)	0.48	3 (5%)	0.001
Light/moderate drinkers	28 (50%)	46 (41%)		20 (32%)	
Heavy/very heavy drinkers	13 (23%)	38 (34%)		37 (59%)	
Don't know/decline to answer	5 (9%)	7 (6%)		3 (5%)	
Tobacco use					
Never	42 (75%)	60 (54%)	0.003	11 (17%)	<0.0001
Current	2 (4%)	26 (23%)		33 (52%)	
Past	12 (21%)	25 (23%)		19 (30%)	
Cannabis use					
Never	47 (84%)	57 (51%)	0.0001	31 (49%)	0.0002
Current	1 (2%)	20 (18%)		12 (19%)	
Past	8 (14%)	34 (31%)		20 (32%)	
Serum processing time (h)					
0–<1	18 (32%)	22 (20%)	0.03	18 (29%)	0.88
1–<2	33 (59%)	61 (54%)		40 (63%)	
2–<3	3 (5%)	25 (22%)		2 (3%)	
3–<4	2 (4%)	4 (4%)		3 (5%)	

[a]*p*-values calculated for chi-square are for each disease group compared with the "No pancreas disease" controls.
[b]Light: 1–3 drinks/week. Moderate: 4–7 drinks/week for females and 4–11 drinks/week for males. Heavy: 8–24 drinks/week for females and 15–34 drinks/week for males. Very Heavy: >34 drinks/week.

Table 2. Endocannabinoid Levels by Patient Characteristics

		AEA		2-AG		PEA		OEA	
	N	Median (IQR)	*p*-value	Median (IQR)	*p*-value	Median (IQR)	*p*-value	Median (IQR)	*p*-value
Smoking status									
Never	113	43.5 (33.5, 51.4)	0.38[a]	5426 (2016, 29586)	0.92[a]	4018 (2457, 17687)	0.53[a]	2193 (1535, 15563)	0.42[a]
Past	56	45.1 (36.3, 55.6)		4418 (2282, 33996)		4884 (2664, 17204)		2351 (1670, 17672)	
Current	61	43.6 (36.2, 61.2)		6711 (2322, 37805)		4191 (2694, 17991)		2619 (1815, 18191)	
Drinking Status									
Current	85	46.9 (36.2, 52.7)	0.81[a]	5667 (2090, 35223)	0.94[a]	4544 (2638, 19280)	0.53[a]	2308 (1679, 17188)	0.41[a]
Past	112	43.4 (34.5, 53.4)		4776 (2389, 26927)		4259 (2408, 15355)		2198 (1606, 14957)	
Never	33	43.3 (32.1, 53.0)		4969 (1443, 28792)		4572 (2484, 19866)		2531 (1524, 15553)	
Heaviest alcohol use (drinks per week)—lifetime[e]									
Abstain	33	43.3 (32.1, 53.0)	0.32[a]	4969 (1443, 28792)	0.48[a]	4572 (2484, 19866)	0.58[a]	2531 (1523, 15552)	0.70[a]
Heavy	43	45.0 (38.2, 55.8)		3687 (2022, 13805)		3806 (2472, 13453)		2193 (1707, 4081)	
Light	43	48.5 (37.1, 54.3)		4605 (2272, 25142)		3617 (2457, 19032)		2231 (1598, 19724)	
Moderate	51	43.0 (34.1, 50.0)		8752 (2282, 45332)		4380 (2310, 17602)		2219 (1519, 15562)	
Very Heavy	45	40.8 (32.9, 47.2)		5167 (2641, 36484)		6127 (3045, 17461)		2308 (1675, 17796)	
Cannabis Use									
Current	33	43.4 (33.0, 53.2)	0.12[a]	5323 (2322, 26620)	0.80[a]	4517 (2950, 14404)	0.92[a]	2723 (1637, 14453)	0.91[a]
Past	62	44.8 (37.9, 56.9)		4179 (2239, 32138)		4298 (2638, 16654)		2389 (1878, 16472)	
Never	135	43.5 (33.3, 52.7)		6179 (2138, 34223)		4459 (2465, 18053)		2121 (1510, 17033)	
BMI									
Underweight/Normal	102	43.6 (33.9, 53.7)	0.16[a]	4451 (2108, 30589)	0.49[a]	3922 (2336, 15775)	0.0028[a]	2465.8 (1606, 16701)	0.27[a]
Overweight	79	43.0 (33.6, 52.5)		4968 (2485, 31167)		4035 (2583, 15829)		2021.9 (1596, 15102)	
Obese	50	47.4 (39.3, 54.2)		9137 (2282, 47880)		12019[d](3679, 25007)		2626.8 (1743, 17796)	
Gender									
Female	109	45.0[d] (39.3, 54.5)	0.0499[b]	6689 (2138, 33996)	0.86[b]	4002 (2472, 19866)	0.82[b]	2530.6 (1806, 16860)	0.25[b]
Male	122	43.1 (33.3, 51.4)		4771 (2283, 31854)		4880 (2691, 16049)		2103 (1535, 16472)	
Correlations	N	r_S	*p*-value	r_S	*p*-value	r_S	*p*-value	r_S	*p*-value
Age	231	−0.06	0.33[c]	−0.03	0.71[c]	0.03	0.62[c]	<0.01	0.94[c]
Processing time	231	0.30	<0.0001[c]	0.10	0.18[c]	0.03	0.61[c]	0.06	0.36[c]

All *p* values computed from log-transformed data using
[a]ANOVA,
[b]Student's *t-test*, or
[c]Spearman's Rank Correlation.
[d]Value significantly higher than all other groups.
[e]Light: 1–3 drinks/week. Moderate: 4–7 drinks/week for females and 4–11 drinks/week for males. Heavy: 8–24 drinks/week for females and 15–34 drinks/week for males. Very Heavy: >34 drinks/week.
AEA, anandamide; 2-AG, 2-arachidonoylglycerol; OEA, oleoylethanolamide; PEA, palmitoylethanolamide.

underweight/normal or overweight (p = 0.003). We found no association of smoking status, alcohol consumption, or cannabis use with target analyte levels; nor did levels of endocannabinoids vary by medication use, including pain medications (data not shown).

Concentrations of AEA, but not 2-AG, PEA, or OEA, varied by disease group after adjustment for processing time, sex (for AEA), and obesity (PEA). Those with no pancreas disease had significantly (p = 0.047) lower levels of AEA compared with participants with chronic abdominal pain/indeterminate CP, acute pancreatitis, or recurrent acute pancreatitis (Fig. 2).

We found neither an association of endocannabinoid levels and pain type (nociceptive versus neuropathic reported in the past week) nor an association of abdominal pain reported in the past year among participants with pancreas disease compared with participants with no pancreas disease (Figs. 3a,3b). Levels of 2-AG were significantly lower (p = 0.02) among participants reporting abdominal pain in the past week after adjustment for disease group and processing time (Fig. 3c). However, no association was found for pain severity in the past week and concentrations of any of the endocannabinoids (Fig. 3d).

Analyte levels were not associated with pain during daily activities, work at home, social activities, or chores in the past week after adjustment for potential confounders (Supplementary Table S1). Although pain intensity was inversely associated with concentrations of 2-AG, PEA, and OEA, the pain scores were nonlinear and the fit of the regression models was poor, suggesting the need for caution in interpretation of this result (Figs. 3e,3f).

Discussion

We found that higher serum concentrations of AEA, but not serum levels of three other endocannabinoid or paracannabinoid substances, were associated with pancreatitis. Several inflammatory conditions have been associated with high circulating levels of endocannabinoids. For example, AEA, but not 2-AG, was upregulated in cirrhotic participants and positively correlated with a model of end-stage liver disease score.[30] Matsuda et al.[31] reported that rats with acute pancreatitis had elevated circulating AEA concentrations compared with controls, and Dembinski et al.[32] found that AEA levels were positively associated with the severity of cerulein-induced pancreatitis. In a rat model of type-2 diabetes, proinflammatory macrophages generate AEA, which binds to CB1R, leading to β-cell death.[23]

The mechanisms of pain and fibro-inflammatory response in pancreatitis are likely interconnected by shared pathways (Fig. 1). In normal pancreas, pancreatic stellate cells are in a quiescent state; however, in the environment of inflamed pancreatic tissue, pancreatic stellate cells become activated producing abundant extracellular matrix proteins leading to fibrosis as well as inflammatory cytokines.[33,34] As shown in Figure 1, we postulate that higher levels of AEA activate the CB1R leading to fibrosis, tissue damage, and enhanced pain. By contrast, inhibition of CB1R results in decreased stellate cell fibroinflammatory response, supporting an inverse association of AEA with pancreatitis and concomitant nociceptive and neuropathic pain. The inhibition of CB1R has been used in the past for treatment of cirrhosis and pulmonary fibrosis, but side effects stopped the trials early.[22]

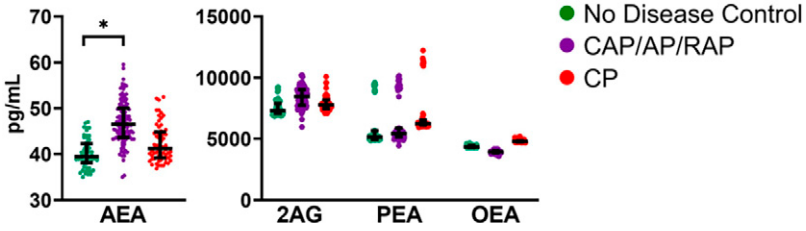

FIG. 2. Adjusted median endocannaboid levels by pancreatic disease status. All analyses performed by generalized linear regression modeling on log-transformed data and adjusted for processing time (log-transformed). AEA was additionally adjusted for sex. PEA was additionally adjusted for BMI group. CAP: Chronic abdominal pain of suspected pancreatic origin and indeterminate chronic pancreatitis; AP: Acute pancreatitis; RAP: Recurrent acute pancreatitis; CP: Chronic pancreatitis * p = 0.047

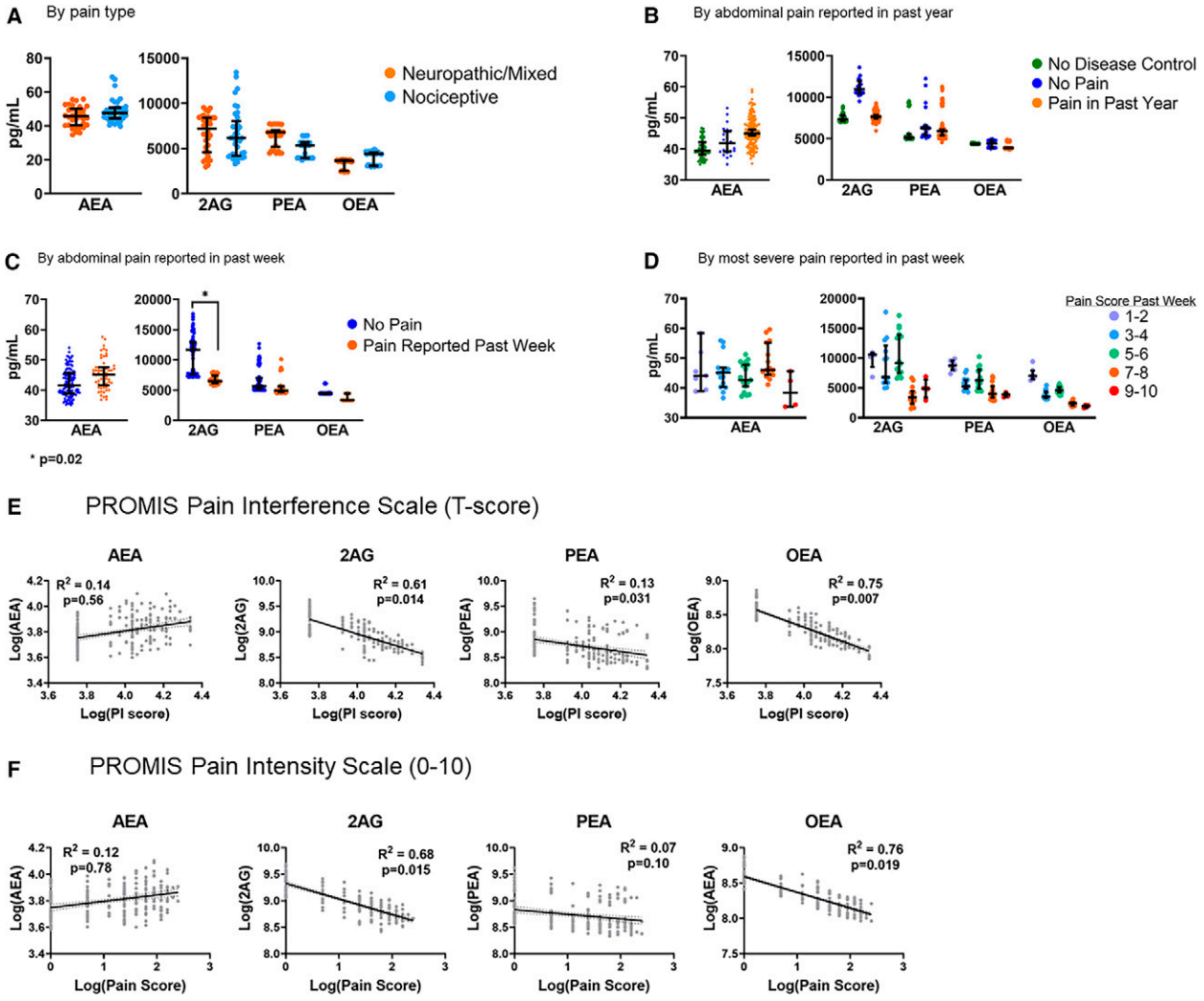

FIG. 3. Serum endocannabinoid levels by pain type and PROMIS pain scores. **(A)** By pain type. **(B)** By abdominal pain reported in past year. **(C)** By abdominal pain reported in past week. **(D)** By most severe pain reported in past week. **(E)** PROMIS Pain Interference Scale (T-score). **(F)**. PROMIS Pain Intensity Scale (0–10). PROMIS, Patient-Reported Outcomes Measurement Information System. All analyses performed by generalized linear regression modeling on log-transformed data and adjusted for processing time (log-transformed) and disease group. AEA was additionally adjusted for sex. PEA was additionally adjusted for BMI group. Cases: Chronic abdominal pain of suspected pancreatic origin and indeterminate chronic pancreatitis; Acute pancreatitis; Recurrent acute pancreatitis; Chronic pancreatitis.

Observational studies in humans suggest that cannabis use is a potential cause of acute pancreatitis.[35] Although there is no direct evidence that cannabis use legalization has influenced pancreatitis hospitalizations in the United States,[36] a prospective study reported that 13% of acute pancreatitis participants under the age of 35 were cannabis users.[37] Both CB1R and CB2R are expressed in pancreatic tissues where they are bound by THC, which activates endocannabinoid production.[35] It is possible that the activation of CB1R through cannabis use may induce fibrotic changes in the pancreas leading to acute pancreatitis.

Abdominal pain is the chief complaint in pancreatitis with 85%–97% of CP participants reporting pain

after initial diagnosis.[38] Not surprisingly, pain has the most important influence on diminished health-related quality of life and increased resource utilization in pancreatitis participants.[2,39] Our studies have shown that pain in pancreatitis patients is not only debilitating but also associated with decreased life expectancy.[40] Although an association of AEA with abdominal pain is intriguing, the relation may be related to disease status as participants reporting no pain also had (nonsignificantly) higher circulating levels of AEA. Levels of 2-AG were lower among participants reporting abdominal pain in the past week, but no association was found for recent pain severity and concentrations of any of the other endocannabinoids. While circulating concentrations of 2-AG and OEA were inversely correlated with PROMIS pain intensity scores measured during the past week, beta-values for the regression modeling were small, even after log transformation, so the clinical relevance is questionable.

The use of cannabis for pain control has a long history, and its scientific benefits are under intense evaluation. Promising studies suggest that cannabis in various forms provides beneficial physical and mental effects that may be useful in treating chronic pain. A meta-analysis of clinical trials examining the effects of cannabis-based preparations on neuropathic pain reported significant pain reduction of 30% or more among the cannabinoid intervention group compared with the placebo group.[41] Unfortunately, the treatment of pain in pancreatitis has not been uniformly effective, and many patients use analgesics, such as opioids, chronically for pain management. While the precise number of such patients is unknown, the opioid overdose epidemic continues to worsen with more than 75,000 deaths linked to opioid use in 2021.[42] It is important to identify markers for pain in pancreatitis patients to better manage complaints and to develop treatment options with improved safety profiles.

This study had several strengths, including the case–control design within a prospective cohort study that allowed for the assessment of endocannabinoid and paracannabinoid levels, the geographic diversity of the study sample enhancing the generalizability of results, and the availability of three well-phenotyped subcohorts representing different stages of the natural history of pancreatitis. Moreover, PROCEED is designed according to the prospective specimen collection, retrospective blinded evaluation principles[43,44] to support phase I and II biomarker discovery, and validation studies.[24]

Potential limitations of this study include the modest sample sizes for subgroup comparisons and the potential influence of blood processing time on analyte levels. Our results may not be generalizable to the broader population with pancreatitis or at risk for developing the disease. In addition, those participants with acute pancreatitis may have had residual inflammation, which would have influenced the results. This possibility was reduced by enrolling participants with acute pancreatitis at least 30 days after hospitalization.

In conclusion, we demonstrated that higher levels of circulating AEA are found in individuals with chronic abdominal pain of suspected pancreatic origin, acute pancreatitis, or recurrent acute pancreatitis compared with healthy controls. Independent validation and evaluation of chronological trends are needed to confirm these findings in larger populations and to establish long-term relations between the endocannabinoids. Future studies focused on investigating whether circulating AEA may influence the risk of pancreatitis through oxidative stress pathways or through immune function may provide further insights. Finally, the development of safe next-generation CB1R antagonists should be tested for therapeutic efficacy in pancreatitis.

Data Transparency Statement

Datasets generated during this study are available at the Coordinating and Data Management Center (CDMC) at MD Anderson Cancer, which is responsible for the coordination and data management for the PROCEED Study, which is part of the NIH funded (1U01DK108328). Contact Li Liang, PhD, 713-563-4276, lli15@mdanderson.org for more information.

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Authors' Contributions

M.T.G.: Conceptualization, methodology, validation, writing—original draft, visualization, project administration, and funding acquisition. C.L.: Conceptualization, methodology, validation, writing—original draft, and visualization. A.T.: Formal analysis. C.B.: Formal analysis. J.L.S.: Writing—review and editing. L.L.: Methodology,

validation, and writing—review and editing. Y.Y.: Methodology and validation. W.E.F.: Resources and funding acquisition. E.L.F.: Resources and funding acquisition. C.E.F.: Resources and funding acquisition. D.L.C.: Resources and funding acquisition. P.A.H.: Resources, writing—review and editing, and funding acquisition. W.G.P.: Resources and funding acquisition. M.T.: Resources and funding acquisition. S.S.V.: Resources and funding acquisition. S.K.V.E.: Resources and funding acquisition. M.D.B.: Resources and funding acquisition. D.K.A.: Resources and funding acquisition. J.S.: Resources and funding acquisition. D.Y.: Resources, writing—review and editing, and funding acquisition. S.J.P.: Conceptualization, resources, writing—original draft, and funding acquisition. D.P.: Methodology, resources, writing—original draft, and funding acquisition.

Author Disclosure Statement

The authors have no conflicts of interest to declare.

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Supplementary Material

Supplementary Table S1

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Abbreviations Used

2-AG = 2-arachidonoylglycerol
AEA = anandamide
BMI = body mass index
CB1R = cannabinoid receptor-1
CB2R = cannabinoid receptor-2
OEA = oleoylethanolamide
PEA = palmitoylethanolamide
PROCEED = Prospective Evaluation of Chronic Pancreatitis for Epidemiologic and Translational Studies
PROMIS = Patient-Reported Outcomes Measurement Information System
THC = D^9-tetrahydrocannabinol