Gastrointestinal hypoalgesia in inflammatory bowel disease

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Abstract	
	Background Pain perception is critical for detection of noxious bodily insults. Gastrointestinal hypoalgesia in inflammatory bowel disease (IBD) is a poorly understood phenomenon previously linked to poor patient outcomes. We aimed to evaluate the risk factors associated with this condition and to discern characteristics that might differentiate these patients from pain-free quiescent counterparts.

Methods We performed a retrospective analysis using an IBD natural history registry based in a single tertiary care referral center. We compared demographic and clinical features in 3 patient cohorts defined using data from simultaneous pain surveys and ileocolonoscopy: a) active IBD without pain (hypoalgesic IBD); b) active IBD with pain; and c) inactive IBD without pain.

Results One hundred fifty-three IBD patients had active disease and 43 (28.1%) exhibited hypoalgesia. Hypoalgesic IBD patients were more likely to develop non-perianal fistulae (P=0.03). On logistic regression analysis, hypoalgesic IBD was independently associated with male sex, advancing age and mesalamine use, and inversely associated with anxious/depressed state and opiate use. Hypoalgesic IBD patients were demographically and clinically similar to the pain-free quiescent IBD cohort (n=59). Platelet count and C-reactive protein were more likely to be pathologically elevated in hypoalgesic IBD (P=0.03), though >25% did not exhibit elevated inflammatory markers.

Conclusions Hypoalgesia is common in IBD, particularly in male and older individuals, and is associated with an increased incidence of fistulae and corticosteroid use. Novel noninvasive diagnostic tools are needed to screen for this population, as inflammatory markers are not always elevated.

Keywords Abdominal pain, hypoalgesia, hyposensitivity, inflammatory bowel disease, Crohn's disease

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Introduction

Abdominal pain is one of the most common symptoms associated with gastrointestinal disorders. It is a major driver behind the deterioration of patients' quality of life and increased healthcare resource utilization in inflammatory bowel disease (IBD), including both Crohn's disease (CD) and ulcerative colitis (UC) [1-4]. While there is little doubt that abdominal pain can have a detrimental impact on the lives of IBD patients, it also serves an indispensable physiological service. The ability to properly perceive pain is critical for the detection of noxious insults that have the potential to cause damage to the body. This is true even in the gastrointestinal tract, where perception of noxious exposures may be vaguer and poorly localized [5], and it is particularly relevant when considering IBD. If IBD patients with clinically significant disease activity do not simultaneously

experience and/or report symptoms commensurate with the degree of inflammation, including abdominal pain, they are described as having silent IBD. Silent IBD is important because it has been associated with the development of more frequent and serious complications, including strictures, fistulae, and abscesses [6,7], as well as increased hospitalization [8]. As abdominal pain is one of the most frequently described and consequential symptoms in the setting of IBD [9], it is not difficult to imagine that a lack of or reduction in abdominal pain by itself during periods of significant disease activity, or "hypoalgesic IBD", can impart a tremendous risk of poor outcomes over time.

Unfortunately, hypoalgesic IBD is a poorly understood condition and little is known about its pathophysiology or epidemiology. Investigators have gleaned some idea of the prevalence of this condition from the findings of prior studies evaluating silent IBD. Unfortunately, these studies were: a) not specifically designed to evaluate silent or hypoalgesic IBD; b) focused primarily on one form of IBD; and/or c) utilized less reliable symptom-based disease activity scores (e.g., CD activity index) [10] to make determinations about intestinal inflammatory status. Other clinical features, including disease location (e.g., upper gastrointestinal tract CD) [11], a variety of extraintestinal manifestations (EIMs) [12-16], and IBD-associated complications [17-20] have previously been implicated as potential signs of silent disease, but it is not clear how effective they are for screening.

Several endoscopic, radiologic and laboratory tests have been proposed as screening options for silent IBD [11,21-25], but their clinical practicality and cost-effectiveness are still uncertain, particularly when the scale of this issue remains incompletely understood. To this point, no studies have specifically evaluated for reduced abdominal pain perception in IBD patients while simultaneously evaluating disease activity using the most reliable assessment methods (e.g., direct endoscopic visualization). Thus, prior estimates as to the actual incidence of silent and/or hypoalgesic IBD may be inaccurate. Just as importantly, no prior investigation has been undertaken to identify risk factors for hypoalgesic IBD. To provide appropriate screening and care for these patients, it is imperative for IBD providers not only to recognize that this condition exists, but also to gain an improved understanding of the risk factors associated with it and how to screen for it.

Our primary aim in undertaking this study was to determine the incidence of abdominal hypoalgesia in both CD and UC, as well as to evaluate for demographic and clinical factors associated with the presence of this condition. Secondly, we sought to identify patient characteristics and test findings that could help differentiate hypoalgesic IBD patients from pain-free IBD patients with inactive disease.

Patients and methods

Study population

We performed a retrospective analysis using information derived from consecutive patients enrolled in the Intestinal Diseases Natural History Database at Pennsylvania State University Hershey Medical Center (PSHMC) between January 1, 2015, and August 31, 2018. This database includes clinical and research information related to the encounters of IBD patients undergoing clinical management at PSHMC, a tertiary care referral hospital with a dedicated IBD center that cares for over 5000 patients with these disorders. This work was performed in accordance with the rules and regulations set forth by the Pennsylvania State University College of Medicine Institutional Review Board and carried out under protocol PRAMSHY98-057.

To be included in this study, participants had to be adults (i.e., older than 17 years) and have an established diagnosis of CD, UC or IBD colitis of indeterminate nature (IC), based on standard clinical criteria routinely used to identify IBD. They also needed to have undergone an ileocolonoscopy and completed contemporaneous surveys on abdominal pain experience (including the Short Inflammatory Bowel Disease Questionnaire [SIBDQ] and Harvey-Bradshaw Index [HBI]). UC patients were excluded if they had undergone previous colonic surgery.

Definitions and data abstraction

Presence of "significant inflammation" was defined as moderate to severe activity based on findings during ileocolonoscopic evaluation, while quiescent disease was defined as the lack of any gross inflammation within the ileum or colon. Endoscopic activity in UC was determined using the Mayo endoscopy sub-score, which ranges from 0-3, with 0=no disease ("quiescent") and 3=severe disease. Thus, "significant" UC-related inflammation was defined as a Mayo endoscopy subscore of 2-3. In CD, we used the Simple Endoscopic Score for CD (SES-CD), where scores of 7-15 indicated moderate disease and those >15 were representative of severe disease. Using this system, "significant" CD-related inflammation was defined as an SES-CD greater than or equal to 7. Pain ratings were obtained contemporaneously with each ileocolonoscopy and were based on responses to 2 separate items: 1) the fourth question in the SIBDQ ("How often over the past 2 weeks have you experienced abdominal pain?", where patients respond using a frequency-based inverse Likert scale, with 1 representing pain "all of the time" and 7 representing pain "none of the time"); and 2) the second question from the HBI, which included potential responses of 0 ("no abdominal pain"), 1 ("mild"), 2 ("moderate") and 3 ("severe"). For the purposes of this study, clinically relevant abdominal pain was defined as a numeric rating of <6 on the SIBDQ pain score and/or a score of 1 or greater on the HBI pain score. To qualify as having "hypoalgesic IBD" (see below), a patient could not have described clinically significant pain on either of these 2 measures. Age, sex, IBD duration, IBD extent/location (e.g., organ involvement, using the Montreal classification system), disease complications (including stricture, intra-abdominal fistula, abscess, and cancer development), EIMs (including inflammatory arthritides), IBD-associated dermatopathies (including pyoderma gangrenosum, erythema nodosum, uveitis, episcleritis, and primary sclerosing cholangitis), physician global assessment, endoscopic severity

(defined by the Mayo Index endoscopy sub-score or the SES-CD as appropriate), medication use (including antidepressant/anxiolytic, corticosteroid, mesalamine, immunomodulator such as azathioprine, 6-mercaptopurine and/or methotrexate) and biologic therapy (infliximab, adalimumab, certolizumab, golimumab, vedolizumab and/or ustekinumab), surgical history, laboratory values (white blood cell count [WBC], erythrocyte sedimentation rate [ESR], C-reactive protein [CRP]), opiate, "other" pain medications (acetaminophen, nonsteroidal anti-inflammatory drugs [NSAIDs], dicyclomine and/or tricyclic agents), and tobacco use were obtained from the record. The presence of anxiety or depression symptoms was determined based upon responses to the Hospital Anxiety and Depression Scale completed at the time of the clinical encounter, using anxiety or depression subscores of 8 or greater to indicate the clinically significant presence of each.

Statistical analysis

Data were extracted and analyzed using GraphPad Prism version 8 (San Diego, CA) or SAS version 9.4 (Cary,NC). Initially, demographic and clinical variables were compared using univariate analysis (e.g., Student's t-test, chi-square test or Fisher's exact test, as appropriate) between 2 distinct cohorts: 1) IBD patients with active disease without abdominal pain (hereafter referred to as "hypoalgesic IBD"); and 2) IBD patients with active disease with abdominal pain (hereafter referred to as "active IBD with pain"). A multivariate logistic regression model was then created incorporating each significant variable identified during the univariate analysis to examine the odds of developing hypoalgesic IBD. A binary logistic regression was used for optimization. Univariate analysis was also used to compare demographic and clinical variables between: 1) hypoalgesic IBD patients; and 2) IBD patients with inactive disease without abdominal pain (hereafter referred to as "quiescent IBD without pain") in order to evaluate for clinical factors that might be used to differentiate between these 2 groups. The primary endpoint for each of these analyses was hypoalgesic IBD (as defined above). Values listed represent means ± standard error of the mean (SEM) or odds ratio (OR), with 95% confidence interval (CI) in brackets as appropriate.

Results

Prevalence and clinical characteristics of hypoalgesic IBD

To assess the prevalence of hypoalgesic IBD, we evaluated consecutive patients who had undergone an ileocolonoscopy and completed concurrent validated pain-related surveys at our center. One hundred fifty-three individuals (71 female, 82 male) were found to have moderate-to-severe disease on gross endoscopic evaluation (i.e., Mayo endoscopy subscore of 2-3 or SES-CD of 7 or greater) during the study period (Table 1).

Ninety-three individuals had CD (24.7% ileal CD [L1], 22.6% colonic CD [L2], 52.7% ileocolonic CD [L3]), 55 had UC (1.8% had proctitis, 30.9% L-sided UC, 67.3% pan-UC), and 5 individuals had IC. Of this cohort, 43 patients (28.1%) were found to have hypoalgesic IBD. Similar rates of hypoalgesic IBD (26.1% vs. 30.9% respectively, P=0.57) were exhibited in CD and UC. In view of the latter finding, we chose not to evaluate for other differences between IBD subtypes in this setting.

Though disease duration (10.8 vs. 9.9 years, P=0.63) and location (CD: L1 16.7% vs. 26.5%, L2 29.2% vs. 20.6%, L3 54.1% vs. 52.9%, P=0.52; UC: E1 0.0% vs. 2.5%, E2 23.5% vs. 32.5%, E3 76.5% vs. 65.0%, P=0.61) were similar between the hypoalgesic and pain-perceptive sub-cohorts respectively, hypoalgesic IBD patients were older (47.7 vs. 41.8 years, P=0.03) and were more likely to be male (72.1% vs. 46.4%, P=0.004). While hypoalgesic IBD patients had a statistically similar proportion of severe endoscopic scores (34.9% vs. 39.1%, P=0.71) and inflammatory laboratory values with regard to WBC (8300 vs. 9300 cells/mm^3, P=0.15), CRP (1.7 vs. 2.4 mg/dL, P=0.55) and ESR (23.8 vs. 26.2 mm/hour, P=0.30), they were less likely to exhibit extraintestinal manifestations (16.3% vs. 41.8%, P=0.003) compared to pain-perceiving active IBD patients. Hypoalgesic IBD patients were also less likely to exhibit clinically significant symptoms of anxiety or depression (20.9% vs. 61.8%, P<0.0001). Notably, hypoalgesic CD patients had a significantly higher rate of non-perianal fistulae than their pain-reporting counterparts (54.2% vs. 29.4%, P=0.03).

Utilization of IBD-directed therapies and other medications in the active IBD cohorts

Hypoalgesic IBD patients used mesalamine products more frequently (30.2% vs. 10%, P=0.005) and corticosteroids less frequently (4.7% vs. 22.7%, P=0.008) compared to active IBD patients with pain. They exhibited very similar use of immunomodulator (30.2% vs. 31.8%, P=>0.99) and biologic therapies (67.4% vs. 56.7%, P=0.27) (Table 1). The two sub-cohorts also had statistically similar rates of having prior surgery (18.6% vs. 24.6%, P=0.52). Notably, hypoalgesic IBD patients were less likely to use opiates (2.3% vs. 14.6%, P=0.04) or to use antidepressants or anxiolytics (7.0% vs. 26.4%, P=0.008), and they exhibited a statistically insignificant difference in the use of other pain medications (including acetaminophen, NSAIDs, dicyclomine and tricyclic agents) at a similar frequency as pain-perceiving IBD patients (18.6% vs. 34.6%, P=0.12). Reported use of tobacco (4.7% vs. 16.4%, P=0.06) and marijuana (0% vs. 4.5%, P=0.32) was also not significantly different in hypoalgesic IBD. No other significant difference in demographics, disease characterization or medication use was found.

Employing a multivariate logistic regression analysis to evaluate the 153-patient study cohort described above, we found that hypoalgesic IBD was independently associated with male sex (OR 3.23, 95%CI 1.29-8.1; P=0.006), advancing age (>50 years of age) (OR 3.47, 95%CI 1.36-8.87; P=0.004) and mesalamine use (OR 4.12, 95%CI 1.28-13.24; P=0.02), but inversely associated with anxious and/or depressed state

Table 1 Demographic and clinical characteristics of the hypoalgesic and pain-perceiving active IBD cohorts

Variable	Cohort	Hypoalgesic IBD	Active IBD with pain	P-value
Sample (% women)	153 (46.4%)	43 (27.9%)	110 (53.6%)	0.0044
Age (years)	43.5±1.3	47.7±2.7	41.8±1.4	0.0327
BMI	30.2±2.0	26.2±1.0	31.8±2.8	0.2208
Disease type	CD-93	24 (55.8%)	69 (62.7%)	0.6679
	UC-55	17 (39.5%)	38 (34.5%)	
	Indet-5	2 (4.7%)	3 (2.7%)	
Disease location (Montreal)	CD UC	CD UC	CD UC	CD UC
	L1-23 E1-1	L1-4 E1-0	L1-18 E1-1	0.52 0.61
	L2-21 E2-17	L2-7 E2-4	L2-14 E2-12	
	L3-49 E3-37	L3-13 E3-13	L3-37 E3-25	
	L4-0 ---	L4-0 ---	L4-0 ---	
Crohn's disease behavior (Montreal)				
Non-stricturing/non-penetrating (B1)	32	5 (20.8%)	27 (39.1%)	0.1041
Stricturing (B2)	61	19 (79.2%)	42 (60.9%)	0.1041
Penetrating (B3)	33	13 (54.2%)	20 (29.0%)	0.0264
Disease duration (years)	10.1±0.8	10.8±1.8	9.9±0.9	0.8523
Severe inflammation (MES=3 or SES-CD>15)	58	15 (34.9%)	43 (39.1%)	0.7123
Cancer	0	0	0	1.000
Active EIM	53	7 (16.3%)	46 (41.8%)	0.0026
Short inflammatory bowel disease Questionnaire	43.9±1.2	55.3±1.8	39.5±1.2	<0.0001
Harvey–Bradshaw index	7.6±0.6	5.1±1.5	8.6±0.6	0.0108
Short clinical colitis activity index	4.6±0.3	2.5±0.4	5.5±0.4	<0.0001
Laboratory studies				
WBC (10^3 cells/mm^3)	9.0±0.3	8.3±0.4	9.3±0.4	0.1532
Platelet count (10^3/mm^3)	328.4±10.4	316.6±16.7	333.5±13.1	0.5760
ESR (mm/h)	25.5±1.8	23.8±3.2	26.2±2.0	0.5521
CRP (mg/dL)	2.2±0.3	2.2±0.3	2.4±0.3	0.7023
Current IBD medications				
Corticosteroid	27	2 (4.7%)	25 (22.7%)	0.0084
Mesalamine	24	13 (30.2%)	11 (10.0%)	0.0052
Immunomodulator	48	13 (30.2%)	35 (31.8%)	>0.9999
Biologic	91	29 (67.4%)	62 (56.9%)	0.2719
Active pain medication/substance use				
Tobacco use	20	2 (4.7%)	18 (16.4%)	0.0632
Marijuana use	5	0 (0.0%)	5 (4.5%)	0.3225
Opiate use	17	1 (2.3%)	16 (14.6%)	0.0419
Other pain medications	46	8 (18.6%)	38 (34.6%)	0.1206
Symptoms of anxiety/depression	77	9 (20.9%)	68 (61.8%)	<0.0001
Antidepressant/anxiolytic use	32	3 (7.0%)	29 (26.4%)	0.0076
Prior IBD-related surgery	35	8 (18.6%)	27 (24.6%)	0.5236

IBD, inflammatory bowel disease; BMI, body mass index; MES, Mayo Endoscopy Subscore; SES-CD, Simple Endoscopic Score for CD; CD, Crohn's disease; EIM, extraintestinal

(OR 0.23, 95%CI 0.09-0.58; P=0.008), and opiate use (OR 0.10, 95%CI 0.01-0.98; P=0.04) (Table 2).

Differentiating hypoalgesic IBD from quiescent IBD without abdominal pain

To find potential characteristics that might differentiate hypoalgesic IBD patients, we also used endoscopic and pain-related survey data to identify a cohort of asymptomatic quiescent IBD patients to compare to the hypoalgesic IBD group described above. Using this approach, we identified 59 individuals who qualified as having quiescent IBD without abdominal pain. The quiescent IBD without abdominal pain cohort was composed of mostly Crohn's disease patients (45 CD: 13 ileal [L1], 7 colonic [L2], 25 ileocolonic [L3]; 12 UC: 4 left-sided [E2], 8 pan-colonic [E3]; 2 IC) and was predominantly male (24 female, 35 male), exhibiting disease

Table 2 Multivariate analysis of factors associated with hypoalgesic IBD

Variable	Odds Ratio (95% Confidence Interval)	P-value
Sex (male)	3.23 (1.29-8.1)	0.0055
Age (>50 years old)	3.47 (1.36-8.87)	0.0043
Anxiety/depression symptoms	0.23 (0.09-0.58)	0.0077
Antidepressant/anxiolytic use	0.20 (0.04-1.05)	0.0649
Extra-intestinal manifestations	0.47 (0.19-1.17)	0.2108
Opiate use	0.10 (0.01-0.98)	0.0402
Mesalamine use	4.12 (1.28-13.24)	0.0227

IBD, inflammatory bowel disease; CD, Crohn's disease; UC, ulcerative colitis

distributions that were similar for both CD (P=0.30) and UC (P>0.99). It shared a similar demographic and clinical profile with the hypoalgesic IBD group, with the exception that individuals with quiescent IBD without pain trended toward being more likely to have CD (P=0.07) and have a longer mean disease duration (P=0.07). Hypoalgesic patients also trended toward utilizing antidepressants or anxiolytics (P=0.05) less frequently than the quiescent pain-free cohort (Table 3).

However, several laboratory values differed significantly between these two sub-cohorts. Specifically, hypoalgesic IBD patients exhibited a higher mean WBC (8300 vs. 6700 cells/mm^3, P=0.04), ESR (23.8 vs. 14.9 mm/h, P=0.03) and platelet count (316.6 × 10^3 vs. 259.1 × 10^3/mm^3, P=0.03) and trended toward having a higher CRP (P=0.09) (Table 3). Using the laboratory-associated upper limit of normal (ULN) for each of these tests, we also found that hypoalgesic IBD patients more frequently had a significantly elevated ESR (50.0% vs. 25.7%, P=0.05), CRP (66.7% vs. 28.6%, P=0.02) and platelet count (40.0% vs. 12.5%, P=0.008). When we looked for a significant elevation in any one of these tests, we found that hypoalgesic IBD patients had exceeded the ULN for at least one of these tests at least 71.4% of the time, compared to 34.8% for the quiescent IBD group without pain (P=0.001).

Finally, we evaluated for gastrointestinal symptoms other than abdominal pain that are commonly experienced by IBD patients and might provide a clue to discriminating between these two cohorts. Recent or current symptoms of diarrhea (62.8% vs. 69.5%, P=0.52), nocturnal stooling (25.6% vs. 25.4%, P=0.99), blood in stools (32.6% vs. 17.0%, P=0.10), fecal urgency (55.8% vs. 49.2%, P=0.55), and sensation of an abdominal mass (4.7% vs. 3.4%, P=0.99) were statistically similar between the cohorts. Even when these symptoms were combined (86.1% vs. 79.7%, P=0.44), there was no significant difference.

Discussion

We demonstrated that hypoalgesic IBD is relatively common in both CD and UC, affecting over one-quarter of patients with moderate-to-severe disease activity in this study. We also found that hypoalgesic CD patients were at increased risk of

developing IBD-associated complications (e.g., fistulae). Each of these findings was comparable to what has been reported in other studies that attempted to evaluate silent IBD [6-8,10]. These results reinforce the clinical relevance of hypoalgesic IBD and the importance of improving our understanding of this condition.

Our study is the first to characterize several key aspects of hypoalgesic IBD. We demonstrated that hypoalgesic IBD patients exhibit similar inflammatory severity and distribution of disease, and similar use of most IBD-associated therapies (with the exception of mesalamine), as well as pain-modifying prescription medications or illicit substances, compared to their pain-reporting counterparts. In fact, hypoalgesic patients use opiate medications less frequently and opiate use was inversely associated with this condition on multivariate analysis. These results suggest that our findings, and the differences in abdominal pain perception demonstrated by hypoalgesic IBD patients, are not related to disease type, severity or differences in analgesic use. Coupling this with the demonstration that male sex and advanced age are independently associated with hypoalgesic IBD and that symptoms of anxiety and/or depression and opiate use, were both inversely associated with hypoalgesic IBD, these findings each provide potential clues to the pathophysiological underpinnings of hypoalgesic IBD. For example, could differences in pain perception be explained by alterations in gonadal hormone signaling factors? Are there age-related effects on visceral sensory signaling pathways that diminish abdominal pain perception? These questions warrant further consideration in future studies of this condition.

Additionally, when comparing active and inactive IBD cohorts reporting little to no pain, we found that several inflammatory markers (including WBC, platelet count, ESR and CRP) may be elevated in hypoalgesic IBD, supporting the findings of previous studies [8,25]. However, a quarter or more of these patients will demonstrate normal inflammatory markers, demonstrating the potential limitation of this type of testing. Interestingly, when we compared the presence of EIMs between these cohorts, we found a potential trend but no significant difference in their incidence, suggesting that these clinical features may not be particularly sensitive for screening hypoalgesic IBD. Finally, when comparing the presence of other major gastrointestinal symptoms between these cohorts, there were no significant differences. Clearly endoscopy, radiological testing, laboratory testing and patient symptom history are critically important aspects of monitoring IBD disease activity. They all have limitations, however, in regard to cost, time, and/or efficacy. Our study highlights some of these potential deficiencies and reinforces the need to develop alternative approaches for identifying individuals at risk for this condition. To this end, our group has identified a genetic marker that could help risk-stratify patients for hypoalgesic IBD [7]. However, further investigation is required in this regard to clarify the potential utility of this approach for screening out hypoalgesic IBD patients.

Beyond the implications described above, there is also a great deal that could be learned from the hypoalgesic IBD patient. There are undoubtedly critical insights related to improving our understanding of human gastrointestinal pain perception and finding novel approaches to manage any condition associated with chronic visceral pain. There is still a lack of safe,

Table 3 Demographic and clinical characteristics of the cohorts with hypoalgesic IBD and quiescent IBD without abdominal pain

Variable	Cohort	Hypoalgesic IBD	Quiescent IBD without pain	P-value
Sample (% women)	102 (46.4%)	43 (27.9%)	59 (40.7%)	0.2961
Age (years)	46.1±1.8	47.7±2.7	45.0±2.4	0.4634
BMI	26.8±0.8	26.2±1.0	27.0±1.1	0.5948
Disease type	CD-69 UC-29 Indet-4	24 (55.8%) 17 (39.5%) 2 (4.7%)	45 (76.2%) 12 (20.3%) 2 (3.5%)	0.0879
Disease location (Montreal)	CD UC L1-17 E1-0 L2-14 E2-8 L3-38 E3-21 L4-0 --	CD UC L1-4 E1-0 L2-7 E2-4 L3-13 E3-13 L4-0 --	CD UC L1-13 E1-0 L2-7 E2-4 L3-25 E3-8 L4-0 --	CD UC 0.30 0.99
Crohn's disease behavior (Montreal)				
Non-stricturing/non-penetrating (B1)	25	5 (20.8%)	20 (44.4%)	0.0002
Stricturing (B2)	44	19 (79.2%)	25 (55.6%)	0.0033
Penetrating (B3)	24	13 (54.2%)	11 (24.4%)	0.0026
Disease duration (years)	14.0±1.4	10.8±1.8	16.2±2.1	0.0712
Cancer	0	0	0	1.000
Active EIM	24	7 (16.3%)	17 (28.8%)	0.1626
Short inflammatory bowel disease questionnaire	55.4±1.2	55.3±1.8	55.6±1.6	0.8961
Harvey–Bradshaw Index	4.4±0.7	5.1±1.5	3.9±0.5	0.3960
Short Colitis Clinical Activity Index	4.6±0.3	2.5±0.4	2.1±0.3	0.3742
Laboratory Studies				
WBC (10^3 cells/mm³)	7.4±0.4	8.3±0.4	6.7±0.5	0.0435
Platelet count (10^3/mm³)	285.3±13.3	316.6±16.6	259.1±19.3	0.0305
ESR (mm/h)	18.9±2.0	23.8±3.2	14.9±2.0	0.0298
CRP (mg/dL)	1.3±0.3	1.7±0.4	0.9±0.2	0.0729
Current IBD Medications				
Corticosteroid	12	2 (4.7%)	10 (16.9%)	0.2003
Mesalamine	31	13 (30.2%)	18 (30.5%)	>0.9999
Immunomodulator	24	13 (30.2%)	11 (18.6%)	0.2374
Biologic	59	29 (67.4%)	30 (50.8%)	0.1078
Pain medication/substance use				
Tobacco use	4	2 (4.7%)	2 (3.3%)	>0.9999
Marijuana use	3	0 (0.0%)	3 (5.1%)	0.2612
Opiate use	3	1 (2.3%)	2 (3.3%)	>0.9999
Other pain medications	18	8 (18.6%)	10 (16.9%)	>0.9999
Symptoms of anxiety/depression	25	9 (20.9%)	16 (27.1%)	0.4963
Antidepressant/anxiolytic use	16	3 (7.0%)	13 (22.0%)	0.0532
Prior IBD-related surgery	28	8 (18.6%)	20 (33.9%)	0.1164

IBD, inflammatory bowel disease; BMI, body mass index; CD, Crohn's disease; EIM, extraintestinal manifestation; SIBDQ, Short Inflammatory Bowel Disease Questionnaire; ESR, sedimentation rate; CRP, C-reactive protein

efficacious analgesic options for abdominal pain in this setting. As evidenced above, hypoalgesic IBD patients demonstrate significantly better quality of life scores than their symptomatic counterparts with active disease, and exhibit symptom profiles that are similar to their quiescent counterparts. Although there are clearly consequences to the lack of appropriate symptomatology in the setting of IBD, conditions defined more by the presence of symptoms such as abdominal pain rather than an overt inflammatory process, including irritable bowel syndrome (IBS), might benefit from alternative approaches to pain management, particularly when we consider the lack of efficacy and/or toxicity of the available analgesics frequently utilized to manage disorders associated with chronic abdominal pain, including NSAIDs and opiates [26-29]. Notably, our study demonstrated an independent association between hypoalgesic IBD and mesalamine. This was somewhat surprising, considering that the bulk of mesalamine use was associated with the UC sub-cohort in this study. Although recent trials have suggested that mesalamine does not improve abdominal pain in IBS patients [30,31], perhaps there are

benefits specifically for IBD populations, particularly those suffering from colitis. Additionally, there may be other novel diagnostic and therapeutic targets for pain management that could be identified with a more complete understanding of the underlying pathophysiology associated with hypoalgesic IBD.

This study had several limitations. First, it was undertaken in a single tertiary care center and evaluated a predominantly Caucasian population. Thus, these findings may not be relevant to every patient subtype. It is also a relatively small study, evaluating even smaller sub-cohorts of CD and UC, potentially limiting our ability to identify otherwise significant clinical and/ or demographic associations, including sex differences within each disease subtype. There are several reasons that patients with CD and UC could exhibit gastrointestinal hypoalgesia in widely varying ways, including differing use of certain medications (e.g., mesalamine), anatomic disease distribution, disease complication impact (e.g., decompression related to fistula formation) and even variable impact on visceral sensory physiology. A large part of the data was also collected in a retrospective manner, so relevant clinical information may have been missed and there was the potential for selection bias. We also excluded UC patients who had undergone surgery, limiting our ability to compare surgical rates as well as potential complication rates (e.g., involving strictures and/or prior pre-cancerous or cancerous lesions) among UC-related cohorts. Although this was the most comprehensive study of hypoalgesic IBD to date, there are other potential factors worth investigating, including stool-based markers of intestinal inflammation (e.g., fecal calprotectin), concurrent radiological findings (e.g., computed tomography or magnetic resonance enterography), laboratory and clinical markers of nutritional status and lifestyle choices (e.g., exercise), that we were not able to evaluate consistently as part of this work. This study design also limited our ability to assess for potential cause and effect relationships. In order to verify the findings reported in this study and to determine if other relevant factors impact the development of hypoalgesic IBD, it will be important to undertake larger, prospectively designed investigations that evaluate each subtype separately.

However, the findings reported here are important, as they demonstrate how common hypoalgesic IBD is, reinforce the danger of reduced abdominal pain perception in IBD, and identify potential risk factors associated with this condition. This study emphasizes the importance of educating IBD providers to ensure that they are screening for this condition and the necessity of incorporating regular clinical evaluations into the care of IBD patients. The need for employing more objective determinants of disease activity, such as endoscopy, on an ongoing basis is reinforced. Given the time and expense associated with these interventions, however, our findings also highlight the need to develop quicker, cheaper and more tolerable methods for identifying patients at risk for this condition and its associated complications. This study also helps to answer questions about the nature of hypoalgesic IBD. Given the lack of evidence for any association with IBD disease type, activity, inflammatory or pain therapy, our data suggest that this condition is more likely related to other factors inherent to the patient. We demonstrated that age-related phenomena and sex-based differences probably play a role, but the exact mechanisms underlying these relationships are unclear. Given how common hypoalgesic IBD is, and the persistent questions that exist regarding its pathophysiology, as well as the great potential for learning more about human gastrointestinal pain perception and finding new methods for addressing conditions associated with chronic visceral pain, further larger scale natural history studies and more refined mechanistic investigations would be appropriate.

Acknowledgments

Summary Box

What is already known:

- Lack of symptomatology during active phases of inflammatory bowel disease (IBD), also known as silent IBD, has previously been associated with poor patient outcomes, including increased rates of complications and hospitalizations
- Reduced or absent abdominal pain perception (or gastrointestinal hypoalgesia) is a major aspect of silent IBD but it is not clear how common or impactful this condition is
- Further study on this topic is important to understand how this phenomenon develops and to identify more effective means of screening and identifying patients at risk for it

What the new findings are:

- We demonstrated that gastrointestinal hypoalgesia is common in IBD and is associated with an increased frequency of complications, including non-perianal fistulae
- Gastrointestinal hypoalgesia is also independently associated with male sex, advancing age and mesalamine use
- While inflammatory markers may be helpful in differentiating some patients, at least a quarter of patients with gastrointestinal hypoalgesia and active IBD demonstrated no elevation in these tests

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