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Predictors of Abdominal Pain in Depressed Pediatric Inflammatory Bowel Disease Patients

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Abstract

Background—Pediatric patients with inflammatory bowel disease (IBD) have high rates of abdominal pain. The study aims were to (1) Evaluate biological and psychological correlates of abdominal pain in depressed youth with IBD, (2) Determine predictors of abdominal pain in Crohn's disease (CD) and ulcerative colitis (UC).

Methods—765 patients ages 9–17 with IBD seen over 3 years at two sites were screened for depression. Depressed youth completed comprehensive assessments for abdominal pain, psychological (depression and anxiety), and biological (IBD-related, through disease activity indices and laboratory values) realms.

Results—217 patients with IBD (161 CD, 56 UC) were depressed. 163 (120 CD, 43 UC) patients had complete API scores. In CD, abdominal pain was associated with depression (r=0.33; p<0.001), diarrhea (r=0.34; p=0.001), ESR (r=0.22; p=0.02), low albumin (r=0.24; p=.01), weight

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loss (r=0.33; p=0.001), and abdominal tenderness (r=0.38, p=0.002). A multivariate model with these significant correlates represented 32% of the variance in pain. Only depression (p=0.03), weight loss (p=0.04), and abdominal tenderness (p=0.01) predicted pain for CD patients. In UC, pain was associated with depression (r=0.46; p=0.002) and nocturnal stools (r=.32; p=.046). In the multivariate model with these significant correlates 23% of the variance was explained, and only depression (p=0.02) predicted pain.

Conclusions—The psychological state of pediatric patients with IBD may increase the sensitivity to abdominal pain. Thus, screening for and treating comorbid depression may prevent excessive medical testing and unnecessary escalation of IBD medications.

INTRODUCTION

Abdominal pain is a common symptom in patients with inflammatory bowel disease (IBD). Pain has been traditionally thought to signify disease activity as between 50–70% of adult patients experience pain during disease flares [1–3]. However, disabling chronic abdominal pain is present in a subset of patients with inactive or mildly active IBD [4, 5]. Although there is adult data citing abdominal pain rates of 20%–50% during remission (presumed functional abdominal pain) [6], there is a paucity of pediatric data on rates of abdominal pain and functional abdominal pain (visceral hypersensitivity) in IBD [7, 8]. The largest of existing studies conducted by Zimmerman et al. [7] revealed rates of 45% in their 307 patients; with 13% meeting their criteria for functional abdominal pain (as defined by abdominal pain during disease remission). Furthermore, though adult studies have shown patients with Crohn's disease (CD) (compared to those with ulcerative colitis (UC)) have a higher degree of abdominal pain [9–11] and are more likely to be on narcotics [12], and a recent meta-analysis did note higher rates of Irritable Bowel Syndrome (IBS; which includes abdominal pain as a symptom) in CD compared to UC [13], there are no pediatric studies comparing rates of abdominal pain (or functional abdominal pain) between CD and UC. Abdominal pain itself, and even moreso functional abdominal pain often leads to invasive diagnostic testing, escalation of medical treatments, and increased medical costs. Psychological factors have been postulated to specifically play a role in functional pain [4, 7, 14, 15],

Psychological dysfunction, namely depression and anxiety, are prevalent in both adult and pediatric IBD patients [16–22]. Notably in pediatrics, Greenley et al.'s [23] meta-analysis of psychological dysfunction demonstrated higher rates of depression in pediatric patients with IBD when compared to pediatric patients with other chronic conditions (including cystic fibrosis, diabetes, functional gastrointestinal disorders, chronic headache, and cancer).

Because psychological dysfunction can influence can amplify symptom severity in chronic medical illness [24], in particular abdominal pain perception [25–27], and abdominal pain is a driving force for clinicians to embark on often invasive and costly studies to find inflammatory sources for pain, we sought to delineate if these psychological factors were stronger predictors of abdominal pain compared to biological factors (diarrhea and biochemical markers of inflammation) in a pediatric IBD cohort. Although there is overlap between biological and psychological factors, in this study, we labeled biological factors as

objectively measured markers of disease activity and psychological factors as an emotional and cognitive manifestation, which may or may not be related to disease activity.

To date, the influence these factors have on abdominal pain in pediatric patients with IBD has not been explored. The study aims were (1) To evaluate biological and psychological correlates of abdominal pain in depressed youth with IBD and (2) To determine predictors of abdominal pain in CD and UC. We hypothesize that psychological factors will be stronger predictors of abdominal pain than biological factors in depressed pediatric patients with IBD and the predictive strength of psychological factors over biological factors will be similar between the two IBD subtypes. Although we acknowledge differences between child and parent in physical symptom report [28], in this study we focused on the child's perception of abdominal pain.

MATERIALS AND METHODS

Participants ages 9–17 yrs. with biopsy-confirmed IBD (CD and UC) were recruited from the pediatric gastroenterology clinics and inpatient census at Children's Hospital of Pittsburgh and Boston Children's Hospital over a three year period as part of a large scale randomized treatment trial approved by the respective Institutional Review Boards comparing psychotherapeutic interventions for depression. Patients with indeterminate colitis (IC) were included in the UC group. Informed consent and assent were obtained from both participant and parent/guardian at the time of hospitalization or outpatient clinic visit. Patients were excluded from the study if they had (1) current/history of eating disorder severe enough to require hospitalization, bipolar disorder, or psychotic disorder according to the DSM-IV criteria [29], (2) antidepressant medications within 1 month of assessment (other than low dose antidepressants that may be used to treat visceral hypersensitivity [30]), (3) recent (within 1 month) suicide attempt or major depressive episode requiring psychiatric hospitalization within three months of study entry, (4) history of substance abuse or iatrogenic opiate use within one month of study entry and (5) current or within one year (≥12 sessions) treatment with psychotherapy for depression.

Seven hundred sixty-five (n=765) pediatric patients with IBD were screened for depressive symptoms using the Children's Depressive Inventory (CDI-C, CDI-P; [31]). Youth meeting threshold study criteria for depression (CDI-C or CDI-P score of ≥10; consistent with clinically significant depressive symptoms; [16]) completed a structured psychiatric interview (The Kiddie-Schedule for Affective Disorders and Schizophrenia for Children, Present and Lifetime Version, KSADS; [32]). Patients were included for analysis if they met criteria for major or minor depression by DSM-IV-TR criteria. Once included in the study, the subjects completed a more comprehensive assessment including both clinician-rated and self-report questionnaires assessing gastrointestinal symptoms, biochemical markers of inflammation, and psychological comorbidities.

Measures

Demographic questionnaire—The parents/guardians were asked to complete a brief demographic questionnaire. Items included their child's age, sex, race, and ethnicity.

Abdominal Pain Index (API; [33]): The API is a validated questionnaire used to assess abdominal pain over the previous two week period. The API quantifies frequency, duration, and severity of abdominal pain. Raw scores range from 0–50. Because the items on the API use difference Likert scales and no cutoff score for significant abdominal pain exists for the API, responses to the five pain ratings were standardized using Z-scores, and a mean was computed in the form of a Z-score to provide an overall index of abdominal pain, with higher scores indicating increased degree of abdominal pain perception [34, 35].

Psychological Assessments

Kiddie Schedule for Affective Disorders and Schizophrenia (KSADS) for Psychiatric Diagnoses [32]: The KSADS is a semi-structured diagnostic psychiatric interview designed to assess current Axis I psychiatric diagnoses based on the DSM-IV criteria in children and adolescents. The interview involves input from both parent/guardian and child and was used to characterize the psychopathology in the study sample. According to the DSM-IV classification [29] (which was the most recent classification when subjects were enrolled) patients were stratified by KSADS-PL into minor versus major depression. Major depression includes at least five of the following symptoms for at least two weeks: depressed mood, anhedonia, significant weight loss, sleep disturbance, psychomotor agitation or retardation, fatigue or loss of energy, feelings of worthlessness or guilt, concentration difficulties, recurrent thoughts of death. Minor depression requires the presence of two to four of the aforementioned symptoms for at least 2 weeks and does not include patients with a previous history of major depressive disorder.

The Children's Depression Inventory (CDI; [31]): The CDI is a 27-item questionnaire given separately to the child (CDI-C) and parent (CDI-P) that assesses depression symptoms that may have occurred over the previous two weeks. The questionnaire measures five components of depression – anhedonia, negative self-esteem, ineffectiveness, interpersonal problems, and negative mood. Scores ≥10 are consistent with clinically significant depressive symptoms in pediatric patients with IBD [16].

Children's Depression Rating Scale – Revised (CDRS-R; [36]): The CDRS is a validated semi-structured clinician-rated instrument consisting of 17 items probing depression. The CDRS-R score is based on input from both the patient and guardian. The total scores range from 17 to 113 with higher scores indicating higher depressive severity. CDRS scores ≤28 have typically defined remission in trials assessing pediatric depressive severity response to treatment [37, 38].

Screen for Child Anxiety and Related Emotional Disorders (SCARED; [39]): The SCARED is a 41-item self-report questionnaire using a 3-point scale that parallels the DSM-IV designed to screen for childhood anxiety disorders and anxiety severity in children and adolescents aged 9–18 years. Scores range from 0 to 82 with higher scores indicating higher anxiety severity. A score greater than 25 has been suggested as a cut off point for an anxiety disorder [39].

IBD related assessments

Pediatric Crohn's Disease Activity Index (PCDAI; [40]): CD severity was assessed using the PCDAI; which includes measures in four illness domains that are routinely collected as part of the clinical assessment: 1) self-reported pain (0=no pain, 5=mild/brief, 10=moderate/severe pain), diarrhea (0=0–1 liquid stools with no blood, 5=up to two semi-formed stools with a small amount of blood or 2–5 liquid stools per day, 10=gross rectal bleeding or greater than six liquid stools per day or nocturnal diarrhea), and well-being (0=no limitation on activities, 5=occasional difficulty with age-appropriate activities, 10=frequent limitation of activity), 2) biochemical inflammatory markers (hematocrit (graded on a scale of 0, 2.5, 5 for worsening degree of anemia per age and gender), erythrocyte sedimentation rate (ESR; mm/hr, graded on a scale of 0, 2.5, 5 for increasing ESR), and albumin (g/dl, graded on a scale of 0, 5, 10 for progressively lower values)), (3) weight (0=weight gain, stable weight, or voluntary weight loss), height (at diagnosis 0, 5, 10 for degree of height velocity decrease at diagnosis or in follow-up) and (4) physical examination findings – abdominal tenderness (0=no tenderness, 5=tenderness or mass without tenderness, 10=involuntary guarding or definite mass), perirectal disease (0=none, 5=one or two indolent fistulae with scant drainage but no tenderness, 10=active fistula with drainage, tenderness or abscess), and extraintestinal manifestations (0=none, 5=one, 10=greater than or equal to two).. The PCDAI scores range from 0–100 (0–10-inactive disease, 10–30-mild disease, and ≥31 moderate/severe disease) and are sensitive to treatment effects.

Pediatric Ulcerative Colitis Activity Index (PUCAI; [41]): The PUCAI is a six item clinical questionnaire that assesses pediatric UC severity. The questionnaire specifically assesses degree of abdominal pain (0=no pain, 5=pain can be ignored, 10=pain cannot be ignored), rectal bleeding (0=none, 10=small amount in less than 50% of stools, 20=small amount with most stools, 30=large amount (>50% of stools)), stool consistency (0=formed, 5=partially formed, 10=completely unformed), stool frequency (in terms of number of stools in twenty-four hours, 0=0–2 stools, 5=3–5 stools, 10=6–8 stools, 15=>8 stools), presence/absence of nocturnal stooling (0=none, 10=yes), and activity level (0=no limitation, 5=occasional limitation, 10=severe restricted activity). PUCAI scores range from 0–85 (0–9 inactive disease, 10–34 mild disease, 35–64 moderate disease, ≥65 severe disease) and are also sensitive to treatment effects.

Laboratory Values: Specific values for individual inflammatory markers (C-reactive protein (CRP), ESR, albumin) and hematocrit were recorded.

Data Analysis

Descriptive statistics were calculated for the sample and by IBD subtype using means and standard deviations for continuous variables and percentages for categorical variables. Those patients who had complete API-Z scores were analyzed. Differences by IBD subtype of API scores, disease activity, biochemical markers of inflammation, hematocrit, depressive severity, anxiety, were examined using Student's t-tests (continuous variables) or Chi-square tests (categorical variables). For each IBD subtype, univariate regression models were fit to determine the relationship between the total score on the API and total scores on the CDRS-R, SCARED, laboratory values (ESR, CRP, hematocrit, and albumin), the PCDAI self-

reported subcomponent degree of diarrhea (Question #2), weight change (Question #7), linear growth (Question #8), abdominal exam (Question #9), perianal exam (Question #10), and extra-intestinal manifestations (Question #11), and the PUCAI subcomponents (individually and composite score; because there are four different questions about stooling in the PUCAI) (i) rectal bleeding (Question #2), (ii) stool consistency (Question #3), (iii) stool frequency (Question #4) and (iv) presence/absence of nocturnal stooling (Question #5), and the total PCDAI and PUCAI scores minus the abdominal pain components (Questions #1 on both scales). Given literature noting other non-disease-related (for example, functional and psychosomatic) underpinnings of the patient functioning question (Question #3) in the PCDAI [5, 13, 42–45] and the fatigue question (Question #6) in the PUCAI [46] these variables were not analyzed. Because the distribution of laboratory values were not normal, log transformed values were used for regression analysis. Using the variables that were statistically significant in the univariate regression models, multivariate regression models were fit for each IBD subtype, with and without the modified disease activity scores. Age and gender were included in the final multivariate models as adjustment factors. Collinearity between the factors was not an issue in the multivariate regression model. No corrections were made for multiple comparisons given the relatively small number of comparisons made and the small sample size of this study. The individual items from the PUCAI & PCDAI that were included in regression analyses were treated as rank order variables that have increasing levels. Statistical analysis was performed using SPSS version 21.0 (SPSS Inc, Chicago, IL) and Stata version 13 (Stata, College Station, TX).

ETHICAL CONSIDERATIONS

The present study was conducted with the approval from the institutional review boards at both institutions in January 2008. Written informed assent/consent was obtained from the patients and legal guardian.

RESULTS

Participant Characteristics

Of the 765 patients screened over a three year period, 217 (28.4%) were depressed (minor or major depression). 163 (120 CD, 43 UC) of these patients had complete API scores. Table 1 shows the demographic characteristics of these 163 depressed youth who complete API scores. The mean age of both CD and UC populations was 14.32 years, slightly over half of the patients were female, and a majority of the subjects were Caucasian.

Table 2 details the general disease-related and psychological characteristics of this cohort of patients with IBD. Both disease subtypes had a relative majority of patients with even mild disease activity. A majority of both subtypes of IBD patients had major depression. Depressive severity (higher in patients with UC), daily steroid dose, and CRP were significantly different between the two IBD subtypes. Total steroid dose in the previous year, pain severity, inflammatory markers, and hematocrit were similar between the two IBD subtypes.

CD Univariate Regression Analyses for Abdominal Pain

The biological and psychological variables and their relationship with abdominal pain in patients with CD are shown in Table 3. Depression (r=0.33; p<0.001), diarrhea (r=0.34; p=.001), ESR (r=0.22; p=0.02), low albumin (r=0.24; p=.01), weight loss (r=0.33; p=0.001), abdominal tenderness (r=0.38, p=.0002), PCDAI (r=.499, p<.0001), and the modified PCDAI (r=0.43, p<.001) (r= had statistically significant associations with degree of abdominal pain. Degree of anxiety and the remaining inflammatory markers as well as hematocrit were not significantly associated with degree of abdominal pain. When disease activity was stratified into inactive, mild, and moderate-severe depression was only significantly associated with abdominal pain severity in those CD patients with moderate-severe disease (r=.40, p=.02).

UC Univariate Regression Analyses for Abdominal Pain

The biological and psychological variables and their relationship with abdominal pain in patients with UC are shown in Table 4. Depression (r=0.46, p=0.002), nocturnal stooling (r=.32, p=.046), the total PUCAI (r=.349, p=0.027), and the modified PUCAI (r=0.32, p=0.043), had statistically significant associations with degree of abdominal pain. Degree of anxiety, rectal bleeding, stool form, and the remaining inflammatory markers as well as hematocrit were not significantly associated with degree of abdominal pain. When disease activity was stratified into inactive, mild, and moderate-severe depression was only significantly associated with abdominal pain severity in those UC patients with mild severity (r=.602, p=.011).

CD Multivariate Regression Analysis

A multivariate model containing these significant correlates with abdominal pain in patients with CD represented 31% of the variance in pain and only depression (p=0.03), weight loss (p=0.04), and abdominal tenderness (p=0.01) predicted pain. In a multivariate model for CD that contained only depression, weight loss, and abdominal tenderness, all three remained statistically significant and represented 29% of the variance in pain. When adjusted for age and gender, this model predicted 32% of abdominal pain and all three predictors remained statistically significant (p<0.05).

When the modified PCDAI was incorporated into a multivariate model containing depression, ESR, albumin, the model predicted 20.4% of the variance in abdominal pain, with depression (p=0.05) and the modified PCDAI (p=0.007) being significant predictors of pain. The individual PCDAI items were excluded from this latter analysis since the modified PCDAI was a function of the specific items.

UC Multivariate Regression Analysis

A multivariate regression model was fit using the statistically significant predictors from the univariate regression models of abdominal pain (CDRS, PUCAI question#5). These variables in multivariate regression model together predicted 23%of reported abdominal pain in patients with UC (Table 5). Of these three factors, only depression was a statistically significant predictor of abdominal pain (p=0.02). When the model containing the significant predictor depression was adjusted for age and gender, it represented 16.0% of reported

abdominal pain and depression was still a statistically significant predictor ($p<0.001$) of pain.

When the modified PUCAI was incorporated into a multivariate model containing depression, the model predicted 21.3% of the variance in abdominal pain, with depression ($p=0.03$) being a significant predictors of pain. The individual PUCAI items (PUCAI question #5 specifically) were excluded from this latter analysis since the modified PUCAI was a function of the specific items.

DISCUSSION

In this study examining depressed pediatric patients with IBD, we found depressive severity, degree of diarrhea, ESR, low albumin, weight loss, and abdominal tenderness to be associated with degree of abdominal pain perception in patients with CD. Of these factors, depression, weight loss, and abdominal tenderness predicted pain; and when controlled for age and gender, all three factors continued predicted pain perception. Similarly in patients with UC we noted depression and nocturnal stooling were associated with degree of abdominal pain; and only depressive severity predicted pain perception regardless of controlling for age and gender.

Associations with and Predictors of Abdominal Pain

Overall, this study supported our hypothesis in demonstrating depression has a significant association with pain and is involved in pain perception in both IBD subtypes, perhaps moreso in UC than CD.

Comparison Between CD and UC Regression Analyses

Our hypothesis regarding the strength of association and predictive strength of psychological factors over biological factors being similar between the two IBD subtypes was refuted, though it can be argued that weight loss [47] and abdominal tenderness and potentially visceral hypersensitivity (in the CD population) may have psychosomatic underpinnings [26] and not be completely related to disease activity. Given these results, one may hypothesize that the non-transmural inflammation involved in UC does not lead to a strong enough afferent signal in comparison to psychological comorbidity affecting pain perception, given data noting enteric nervous system abnormalities that are more pronounced in CD than UC [48]. However, it must be noted that the patients with UC had significantly higher depressive severity than those with CD, which may have played a role in the predictive strength of depression.

Comparison to Previous Studies

The findings of our study corroborate those of previous studies in demonstrating abdominal pain is multi-faceted in etiology, and symptoms are not necessarily due to biological factors alone. For example, it has been shown that CD activity indices scores (on the well-validated Crohn's Disease Activity Index;[49]) did not correlate with fecal biomarkers, CRP, or endoscopic findings [50]. Furthermore, Hanauer et al.'s [51] study of patients followed for clinical and endoscopic relapse after ileocecectomy showed higher rates of clinical than

endoscopic relapse – potentially indicating a non-inflammatory cause for the patients' symptoms. Lastly, it has been postulated that the type of surgical anastomosis may influence degree of abdominal pain [52]. When depression is incorporated, Persoons et al. [24] showed non-depressed patients had higher clinical response rates than depressed patients four weeks after infliximab initiation.

In general, the presence of depression has been shown to amplify symptom severity in chronic medical illnesses [53]. Of these symptoms amplified, abdominal pain is of particular interest because it has traditionally been thought to be a harbinger of underlying inflammation and thus guided medical therapy. Furthermore, the presence of abdominal pain has been shown to be one of the most important factors to physicians when assessing patients with IBD, and not as important a symptom to pediatric patients themselves [54].

Etiology for Predictive Strengths of Psychological and Psychosocial Factors for Abdominal Pain

Given the predictive strength and statistical significance of depression with abdominal pain in the univariate analysis for both CD and UC, the entity of visceral hypersensitivity and its association with depression arises. Psychological factors may influence differences in sensory processing between those with and without perceived abdominal pain. Studies have confirmed the coexistence of visceral hypersensitivity in patients with comorbid psychiatric conditions. As stated earlier, depression has been shown to amplify symptom severity in chronic medical illnesses [53]. Elsensbruch et al. [26] also demonstrated the coexistence of psychological factors with visceral hypersensitivity by showing that in adult patients with IBS, comorbid depression and anxiety was associated with increased pain ratings to rectal balloon distension, but not to rectal sensory thresholds.

The adult study of Elsenbruch et al. [26] and our pediatric study postulate that patients with comorbid psychiatric disorders have heightened responses to visceral sensations. This effect may occur could be due to the direct effects of IBD-related cytokines on the brain, steroid use, and depressive severity. For example, Jones et al. [55] demonstrated neurobiological effects of depressive severity in IBD patients by showing increasing depressive severity in IBD patients was associated with greater constriction of pupils to negative stimuli. These results can be extrapolated to suggest that depression is associated with increased sensitivity to negative stimuli; including abdominal pain.

Strengths

This study had several strengths. No study to date has compared biological and psychological associations and predictors of abdominal pain in a depressed cohort of pediatric IBD patients alone and of this large a sample size. Furthermore, no study to date has compared the involvement of these factors in abdominal pain perception between the two subtypes of IBD. Lastly, though we assessed disease activity in these patients, we were careful not to perform correlational and regression analysis between the disease activity indices (PCDAI and PUCAI) and API scores because abdominal pain is a reported question in both disease activity indices.

Implications

Pediatric data has demonstrated high rates of abdominal pain in pediatric patients with IBD; even while they are in remission [7, 8]. This pain has the potential to impair functioning. Overall, our findings highlight the importance of psychological factors over biological factors in abdominal pain perception within a depressed pediatric cohort with IBD; particularly in UC. In comparison to adult studies, our pediatric study emphasizes the importance of depression in predicting abdominal pain in IBD over biological factors. The fact that ESR was the only significantly correlating laboratory value with abdominal pain in CD is likely due to the transmural nature of CD affecting the likelihood of rise of systemic inflammatory markers. Similarly, reasons for diarrhea (in general; and nocturnal stooling in UC) not predicting pain could be that perhaps the pathways leading to pain perception from a psychological standpoint in this depressed cohort of patients play more of a role than the degree of inflammation that diarrhea could signify. Alternatively, abdominal pain (in the form of cramping) may occur before and after diarrheal stooling, or the degree of diarrhea itself may not be due to solely inflammation; but could involve other factors such as diet [42]. Children with IBD have several unique reasons compared to adults for having psychological dysfunction – including fear of humiliation associated with disease-related factors/procedure in often stressful environments (school, peers, living with parent/guardian), fear of being a burden their caregiver, need for reliance on perceived strangers (healthcare practitioners) for care, and neurobiological changes than can occur with growth and development.

The implications of our study findings are on screening and disease management. Identification and treatment of psychiatric comorbidities that contribute to the perception of pain may lead to more appropriate treatment of pain, improve quality of life, and potentially lessen medical utilization. This notion is furthered by our previous work demonstrating that functional abdominal pain may lead to overestimation of disease activity and has psychological (depression) underpinnings [7]. Antidepressants [56, 57] and/or cognitive behavioral therapy [16] may be helpful as well.

Limitations

As this was a cross-sectional study, it is impossible to determine if depression results in increased abdominal pain sensitivity or if higher levels of abdominal pain result in higher rates of depression. Additionally, as there are a multitude of factors involved in the perception of abdominal pain it would be virtually impossible to include them all in a well-designed study. Notable factors that were not accounted for in this analysis were menstrual cycle phase (and the possibility of dysmenorrhea), medication side effects, psychosocial dysfunction, autonomic dysfunction, or general circumstances where a significant cause of pain was identified—strictures (which would not be accounted for on clinical activity indices), kidney stones, gallstones, peptic ulcer. Notably, however, the incidence of intestinal strictures in pediatric CD is low [58]. Given the potential association between duration of inflammation and hypersensitivity [59], we did secondarily exam the relationship between disease duration prior to enrollment and abdominal pain perception within IBD subtypes. The disease duration prior to enrollment was 21.10 months (standard deviation 25.95 months) and 29.45 months (standard deviation 37.27 months) for the

patients with CD and UC; respectively. However, time since diagnosis was not significantly related to abdominal pain (p=0.11 and p=0.78 for CD and UC; respectively).

Due to possible implications of depression increasing sensitivity to abdominal pain, our study raises implication for the presence of a degree of functional abdominal pain in this patient population, thereby drawing comparison to adult and pediatric studies [4, 14, 45, 60] that demonstrated psychological factor association with functional abdominal pain in patients with IBD. Further characterization of depressed and non-depressed patients with IBD (as has already by incepted by our previous work [7]) would better aid in identifying underpinnings of functional abdominal pain in larger cohorts of pediatric IBD patients. Furthermore, we did stratify disease activity across both IBD subtypes to identify if depression and disease activity had differing degrees of association. Depression was only significantly associated with abdominal pain in those CD patients with moderate-severe disease (r=0.403, p=0.022) and UC patients with mild severity (r=.602, p=.011). Additionally, the PCDAI total r=.493, p=.004) and modified scores (r=.451, p=.010) were associated with abdominal pain in patients with moderate-severe CD. These results suggest depression and pain are not independent of disease activity. However, with the small stratified sample sizes it is important to keep in mind this analysis is not sufficiently powered given the number of variables that are being examined.

It is also notable the API is only covering pain duration, severity, frequency (i.e. overall perception). There are other ways to examine pain perception – ie through suffering and disability. Various methods and scales have been employed to measure abdominal pain in the past – including the visual analog scale for current abdominal pain, self-report of symptoms, and combination scales. All of these scales have been used to assess functional pain in the pediatric literature. Specifically, Saps et al. [61] attempted to validated and differentiate between organic and nonorganic abdominal pain disorders with their combination scale which included eight questions selected for relevance from the Children's Somatization Inventory [62], five questions related to GI symptoms: abdominal pain, nausea, diarrhea, constipation, and vomiting. The other three questions addressed co-morbidities and common somatic complaints: headaches, chest pain, and limb pain. Malaty et al. [63] reviewed the existing literature and formulated a scale to measure four purported components of pain – intensity, "non pain symptoms", sense of well-being, and disability. The resulting scale was named the "Multidimension Measure for Recurrent Abdominal Pain (MM-RAP)". Although detailed, the scale doesn't directly assess abdominal pain frequency when compared to the API. Likely the most accurate scale thus far has been developed by Weinland et al. [64]; where patients electronically characterize their pain and associated physical and psychological symptoms during each pain episode – thereby eliminating recall bias. At the time of this study's inception, such a scale was not available and the API was felt to be the most optimal measure for abdominal pain.

Future Directions

The differences in strengths of association and predictors of pain between CD and UC could be due to differences in (1) overall states of inflammation (2) disease location (3) surgical history and (4) overall IBD course. The proportion of patients with CD and UC with

inactive, mild, and moderate-severe disease activity did not differ. Hence, differences in disease activity between patients with the two IBD subtypes in this cohort likely did not account for our findings. Likewise, IBD course over the previous year and surgical history did not differ between the groups. It is known that CD can affect any part of the gastrointestinal tract – either in isolated or overlapping fashion and UC typically progresses from distal to pancolonic involvement. However, no studies to date have examined the association of disease location to abdominal pain.

Further research is needed to delineate the mechanisms behind the perception of pain in this depressed pediatric cohort. Psychological, psychosocial (including parental factors such as relationship status, level of education, and employment status), neurobiological, genetic, and biological factors all likely overlap in these mechanisms and should be examined in future studies. Additionally, the differences in pain predictors between CD and UC suggest the possibility of different sources of pain in CD versus UC – such as partial obstruction in CD, differences in innervations of the small and/or large intestine and strength of nerve firing, stronger role for ischemia or vascular damage in one subtype over the other. Additionally, in UC disease location may drive disability – as distal inflammation may lead to more rectal spasms, stool frequency, and thus worse quality of life.

The question remains that these patients could have microscopic inflammation that is not captured by inflammatory markers or disease activity indices. It is well-known that depression is predisposed to increases in disease activity in both human and animal studies [24, 65–67]. Given the stronger association and predictive strength of depression over biological factors with abdominal pain in UC, the fact that UC is not transmural and therefore may not have a rise in inflammatory markers typically seen in CD, and the fact that disease activity in UC is assessed only via symptoms and not physical exam findings, the associations we found could be a manifestation of microscopic gut inflammation particularly in the patients with UC. It has been shown that microscopic gut inflammation may contribute to pain in IBD that is otherwise in clinical remission [43]. In addition, psychological stress could be mediated by the substance P – a known chemoattractant that may mediate subclinical inflammation and pain [68]. Furthermore, as mentioned above abdominal pain perception involves not only pain characteristics (duration, severity, frequency), but associated suffering and disability, in future studies we hope to identify whether or not there is a threshold on the API for poor functioning.

Additionally, there can be differences in physical symptom report by informant [28] and this report could vary with the age of the patient; future studies will examine the differences between parent and child report of abdominal pain and how that varies with the age of the child.

Lastly, future longitudinal studies will be able to differentiate and aid in delineating whether or not there is causality between depressive symptoms and increased sensitivity to abdominal pain.

Conclusions

Our study shows a child's psychological state may influence their perception or sensitivity to abdominal pain, and sheds light on future directions towards delineating mechanisms for pain in pediatric IBD. Screening and potentially treating such comorbidities while treating underlying disease may prevent medically unnecessary changes in biological treatments of IBD and lead to better concomitant therapeutic outcomes.

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Abbreviations

API	Abdominal Pain Index
CDI	Children's Depression Inventory
CDRS-R	Children's Depression Rating Scale - Revised
CRP	C-reactive protein
ESR	Erythrocyte Sedimentation Rate
KSADS	Kiddie Schedule for Affective Disorders and Schizophrenia for Psychiatric Diagnoses
PCDAI	Pediatric Crohn's Disease Activity Index
PUCAI	Pediatric Ulcerative Colitis Activity Index
SCARED	Screen for Child Anxiety and Related Emotional Disorders

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Table 1

Demographics of Depressed IBD Patients

	Total (CD and UC)	CD (n= 120)	UC (n= 43)
Age (Mean, SD)	14.32 (2.36)	14.23 (2.40)	14.60 (2.21)
Gender (% Female)	55.80%	57.50	51.20%
Race (%)	150 Caucasian (92.0%) 13 African American (8.0%) 3 Asian (1.8%) 1 American Indian/Alaska Native (0.6%) 1 Other (0.6%)	108 Caucasian (90.0%) 12 African American (10.0%) 3 Asian 2.5%) 1 American Indian/Alaska Native (0.8%) 1 Other (0.8%)	42 Caucasian (97.7%) 1 African American (2.3%) 0 Asian (0.0%) 0 American Indian/Alaska Native (0.0%) 0 Other (0.0%)

Table 2

Biopsychosocial Characteristics of Depressed IBD Patients

	Total (CD and UC)	CD (N=120)	UC (n= 43)
PCDAI [Mean (SD)][a]		21.79 (16.87)	
Diarrhea (PCDAI_2)		2.11 (3.45)	
Weight change (PCDAI_7)		2.35 (3.52)	
Height change (PCDAI_8)		2.33 (3.80)	
Abdominal exam (PCDAI_9)		1.61 (2.69)	
Perianal exam (PCDAI_10)		0.82 (2.57)	
Extraintestinal Manifestations (PCDAI_11)		0.43 (1.41)	
[+]Modified PCDAI [Mean (SD)]		17.23 (14.36)	
PUCAI [Mean (SD)][a]			25.38 (24.10)
Rectal Bleeding (PUCAI_2)			7.25 (10.61)
Diarrhea/Stool Form (PUCAI_3)			4.36 (4.32)
Diarrhea/Stool Frequency (PUCAI_4)			4.13 (4.79)
Diarrhea—Nocturnal Stools (PUCAI_5)			2.75 (4.52)
Diarrhea Total (PUCAI2-5 SUM)			17.56 (19.22)
Activity Level (PUCAI_6)			3.40 (4.25)
[+]Modified PUCAI			21.75 (22.60)
Disease severity[a] [N (%)]			
Inactive	41 (25.15)	29 (24.17)	12 (27.90)
Mild	68 (41.71)	51 (42.50)	17 (39.53)
Moderate/Severe	46 (28.22)	32 (26.67)	14 (32.55)
Daily Steroid Dose (mg)[*] [Mean (SD)]	15.07 (17.73)	12.32 (17.33)	22.59 (16.89)
Steroid dose in previous year (mg) [Mean (SD)]	1135.32 (1833.28)	986.39 (1712.96)	1514.03 (2087.68)
Current Medications[b] [N (%)]			
High Dose Steroids	43 (26.38)	25 (20.83)	18 (41.86)
Biologics	52 (31.90)	38 (31.67)	14 (25.00)
Immunomodulators	79 (48.47)	60 (50.00)	19 (33.90)
Biochemical Markers of Inflammation [Mean (SD)]			
Hematocrit	36.64 (4.05)	36.80 (3.43)	36.18 (5.50)
ESR (mm/H)	23.47 (17.68)	23.90 (17.50)	22.28 (18.34)
Albumin (g/dl)	3.77 (0.77)	3.79 (0.74)	3.68 (0.87)
CRP (g/dl)[*]	1.41 (2.60)	1.58 (2.90)	0.86 (1.47)
API Total Score [Mean (SD)]	20.89 (10.21)	20.47 (10.48)	22.36 (9.30)

	Total (CD and UC)	CD (N=120)	UC (n= 43)
API Total Z-score [Mean (SD)]	0.03 (0.85)	0.01 (0.83)	0.07 (0.91)
Psychological Parameters KSADS [N (%)]			
Minor Depression	60 (36.80)	43 (35.80)	17 (39.50)
Major Depression	103 (63.19)	77 (64.20)	26 (60.50)
CDRS-R [Mean (SD)]*	46.72 (12.80)	45.32 (12.26)	50.65 (13.50)
SCARED-C [Mean (SD)]	23.87 (12.53)	24.77 (12.36)	21.29 (12.79)
Comorbid Psychiatric Diagnoses [N (%)][c]			
GAD	33 (20.24)	25 (20.84)	8 (18.60)
Specific Phobia	21 (12.88)	16 (13.33)	5 (11.63)
ADHD	18 (11.04)	10 (8.33)	8 (18.60)
Separation Anxiety Disorder	15 (9.20)	11 (9.17)	4 (9.30)
ODD	12 (7.36)	10 (8.33)	2 (4.65)
Social Anxiety	13 (7.98)	11 (9.17)	2 (4.65)
OCD	2 (1.23)	1 (0.08)	1 (2.32)
Dysthymia	2 (1.23)	1 (0.08)	1 (2.32)
PTSD	1 (0.62)	0 (0.00)	1 (2.32)
Panic Disorder	4 (2.45)	3 (2.50)	1 (2.32)
AN	3 (1.84)	2 (1.67)	1 (2.32)
Conduct Disorder	2 (1.23)	1 (0.08)	1 (2.32)

*$p<0.05$

+Modified scores remove the individual pain item

[a]8 patients with incomplete PCDAI

[b]No patients on opiates at time of screen

[c]GAD: Generalized Anxiety Disorder; ADHD: Attention Deficit Hyperactivity Disorder; ODD: Oppositional Defiant Disorder; OCD: Obsessive Compulsive Disorder; PTSD: Post-Traumatic Stress Disorder; AN: Anorexia Nervosa

Table 3

Crohn's Disease-- Association of Abdominal Pain with Biologic & Psychological Factors

Variable	β	95% Confidence Interval	p-value	R^2
Depression (CDRS)*	0.022	0.011, 0.034	<0.0001	10.9
Anxiety (SCARED)	0.006	−0.007, 0.018	0.36	0.7
Diarrhea*				
Level 2	0.562	0.182, 0.943	0.001	11.6
Level 3	0.695	0.222, 1.168		
Ln ESR*	0.203	0.029, 0.377	0.02	4.8
Ln Albumin*	−1.078	−1.888, −0.269	0.01	6.0
Ln Hematocrit	−0.833	−2.471, 0.805	0.32	0.9
Ln CRP	0.048	−0.062, 0.158	0.39	0.9
Weight change (PCDAI _7)*				
Level 2	−0.008	−0.368, 0.351	0.001	11.1
Level 3	0.848	0.388, 1.310		
Height change (PCDAI _8)				
Level 2	−0.083	−0.613, 0.447	0.75	0.8
Level 3	−0.191	−0.702, 0.321		
Abdominal exam (PCDAI _9)*				
Level 2	0.382	0.051, 0.714	0.0002	14.1
Level 3	1.527	0.741, 2.313		
Perianal Exam (PCDAI _10)				
Level 2	−0.823	−1.654, 0.008	0.13	4.3
Level 3	0.179	−0.507, 0.865		
Extraintestinal Manifestations (PCDAI _11)	0. 100	−0.476, 0.677	0.73	0.1
Modified PCDAI*	0.025	0.015, 0.035	<0.0001	18.6
PCDAI*	0.025	0.016, 0.033	<0.0001	24.9

* $p<0.05$

Table 4

Ulcerative Colitis-- Association of Abdominal Pain with Biologic & Psychological Factors

Variable	β	95% Confidence Interval	p-value	R^2
Depression (CDRS)*	0.031	0.012, 0.050	0.002	21.5
Anxiety (SCARED)	0.010	−0.012, 0.033	0.360	2.2
Rectal Bleeding (PUCAI_2)				
Level 2	0.667	−0.061, 1.396		
Level 3	0.824	−0.269, 1.917		
Level 4	0.487	−0.390, 1.365	0.166	13.0
Diarrhea- Stool Form (PUCAI_3)				
Level 2	0.568	−0.161, 1.296		
Level 3	0.198	−0.491, 0.888	0.299	6.5
Diarrhea – Stool Frequency (PUCAI_4)				
Level 2	−0.034	−0.684, 0.616		
Level 3	0.469	−0.357, 1.295		
Level 4	1.212	0.166, 2.307	0.114	15.1
Diarrhea—Nocturnal Stools (PUCAI_5)*	0.636	0.011, 1.260	0.046	10.1
Diarrhea Total (PUCAI2-5 SUM)	0.014	−0.001, 0.029	0.071	8.5
Ln ESR	−0.188	−0.590, 0.215	0.351	2.4
Ln Albumin	0.572	−1.217, 2.361	0.521	1.2
Ln Hematocrit	−0.346	−2.198, 1.506	0.707	0.4
Ln CRP	0.011	−0.251, 0.273	0.933	0.03
Activity Level (PUCAI_6)				
Level 2	−0.147	−0.925, 0.631		
Level 3	0.560	−1.223, 1.243	0.188	8.6
Modified PUCAI*	0.013	0.0004, 0.025	0.043	10.3
PUCAI*	0.013	0.002, 0.025	0.027	12.2

* $p<0.05$

Table 5

Multivariate Models for Predicting Abdominal Pain Using Significant Biological, Psychological, and Psychosocial Factors

	β	95% Confidence Interval	p-value	R^2
Crohn's Disease (with PCDAI items)				31.5
CDRS-R	0.014	0.002, 0.027	0.03	
Diarrhea			0.16	
Level 2	0.292	−0.106, 0.690		
Level 3	0.417	−0.113, 0.946		
Ln ESR	0.014	−0.190, 0.218	0.89	
Ln Albumin	−0.039	−1.100, 1.025	0.94	
Weight change (PCDAI #7)			0.04	
Level 2	−0.221	−0.595, 0.153		
Level 3	0.509	−0.026, 1.045		
Abdominal exam (PCDAI #9)			0.009	
Level 2	0.165	−0.183, 0.514		
Level 3	1.281	0.474, 2.087		
Crohn's Disease (with modified PCDAI)				20.4
CDRS-R	0.013	0.0001, 0.026	0.05	
Ln ESR	0.057	−0.143, 0.256	0.57	
Ln Albumin	0.385	−0.757, 1.527	0.51	
Modified PCDAI	0.021	0.006, 0.036	0.007	
Ulcerative Colitis (with PUCAI items)				23.0
CDRS-R*	0.025	0.005, 0.045	0.02	
PUCAI-5	0.420	−0.191, 1.031	0.17	
Ulcerative Colitis (with modified PUCAI)				21.3
CDRS-R*	0.024	0.003, 0.045	0.03	
Modified PUCAI	0.007	−0.006, 0.020	0.31	