Increased Risk of Depression in Patients with Crohn's Disease

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ABSTRACT

Introduction

Individuals with IBD have been shown to be at an increased risk of developing depression and anxiety. Previous work has demonstrated patients with UC were more likely to report depressive symptoms preceding their diagnosis of IBD than the general population. Young patients with CD also have a greater risk for developing anxiety disorders. One study demonstrated mental conditions are often diagnosed within one year prior to UC diagnosis. This signifies that psychiatric disorders may either be a consequence of early symptoms of the undiagnosed gastrointestinal condition or may increase an individual's susceptibility to develop IBD. Psychological disease may amplify symptom severity, particularly abdominal pain perception in adults with IBD. Previous work has demonstrated that psychological state may influence perception of abdominal pain and patients with depression were more likely to take IBD-related disability.

Methods

This was a retrospective chart review. We used a subset of Veterans charts from the national VA database. Patient charts were divided into two groups: CD with depression and CD without depression (control). From the CD with depression group, all patients with a diagnosis of Crohn's disease with depression were used, however, patients with a diagnosis of CD who did not receive treatment at the VA were excluded. Patients were considered in remission if their most recent colonoscopy showed no active disease. Patients were considered to have active disease if their most recent colonoscopy demonstrated signs of inflammation. When reported, depression severity was recorded in charts as mild, moderate or severe. From this we created a depression severity score by converting them to numerical values (mild=1, moderate=2, severe=3). Severity score is recorded as an average of these values.

Results

A total of 159 patient charts were included in this study, 122 from the Depression group and 37 from the no depression group. The odds of active Crohn's Disease increased with depression (odds ratio [OR], 2.88; 95% confidence interval [CI], 1.21-6.81; p>0.016). The odds of depression also increased with substance abuse (odds ratio [OR], 3.87; 95% confidence interval [CI], 1.28-11.7; p>0.016) and PTSD (odds ratio [OR], 6.39; 95% confidence interval [CI], 1.85-22.0; p>0.003). Mean depression severity score of remission patients was 2.00 and mean depression severity score for active Crohn's patients was 2.06. Notably, patients the odds of having more severe depression were higher for tobacco users (users: odds ratio [OR], 2.14; mean [SD], 2.14 [0.38]; 95% confidence interval [CI], 0.35-6.14; p>0.59; non-users:

mean [SD], 1.96 [0.77]) and patients with substance abuse (users: odds ratio [OR], 2.37; 95% confidence interval [CI], 0.69-8.20; mean [SD], 2.21 [0.58]; p>0.17; non-users: mean [SD], 1.88 [0.77]) .

Discussion

These findings provide additional evidence that depression is associated with increased Crohn's disease activity in the Veteran population. Based on this data, one may consider that treating an individual's depression may reduce the frequency and severity of Crohn's disease activity. There may be benefits to holistically treating a patient's IBD through also evaluating and monitoring his or her psychological health. Other studies have demonstrated the likelihood that psychiatric disorders often co-exist with inflammation, infections, and autoimmune diseases. Furthermore, our data demonstrated strong associations found between substance abuse and the likelihood of depression. Interestingly, our results indicated no association for the measured CRP and calprotectin between the Crohn's Disease with depression and the Crohn's disease without depression groups.

PAPER

Introduction

Inflammatory Bowel Disease (IBD) is a chronic condition which includes inflammation of the gastrointestinal tract and consists of Crohn's Disease (CD) and Ulcerative Colitis (UC). Only the colon is affected in patients with UC, while CD can involve anywhere from the mouth to anus.

Pain is an important manifestation of inflammation. 50-70% of patients experience chronic pain.[1] Individuals with IBD have been shown to be at an increased risk of developing depression and anxiety. Previous work has shown that over 40% of IBD patients present with mild-severe anxiety/depressive symptoms. [2] When compared to CD-free controls, young patients with CD had a significantly greater risk for developing anxiety disorders.[3] One study demonstrated mental conditions are often diagnosed within one year prior to UC diagnosis. This signifies that psychiatric disorders may either be a consequence of early symptoms of the undiagnosed gastrointestinal condition or may increase an individual's susceptibility to develop types of IBD. [4]

Psychological disease may amplify symptom severity, particularly abdominal pain perception in adults with IBD. A study of 765 IBD patients wherein 217 were determined to be depressed demonstrated that psychological state may influence their perception of abdominal pain. [5] Another study demonstrated that an Asian cohort of IBD patients with depression were more likely to take IBD-related disability.[6]

Given this background information, we hypothesized that not only would there be a strong association between depression and Crohn's Disease activity, but also that patients with CD and comorbid depression will have more frequent and severe disease activity. We aimed to measure disease activity in two main ways. Firstly, by determining the frequency of disease activity determined by colonoscopy results, which is used for both, pathologic disease surveillance and routine screening which

should occur at minimum every three years in patients with Crohn's disease. Secondly, we measured inflammatory markers, including C-Reactive Protein (CRP) and Calprotectin. CRP is an acute phase reactant produced in the liver which increases in amount in response to inflammation. Calprotectin is a specific biochemical measurement of protein in stool which indicates neutrophil activity in the intestinal mucosa. With this information we hoped to capture different Crohn's Disease activity through different modalities.

Methods

We used a subset of Veterans charts from the national VA database with a diagnosis of IBD from 1/1/2000 until 8/14/2018. Data gathered from the Veteran's Health Information Systems and Technology Architecture (VISTA) database was used for the analysis. The Veteran's Health Administration institutional review board approved the study. Patient charts were divided into two groups: CD with depression and CD without depression (control). From the CD with depression group, all patients with a diagnosis of Crohn's disease with depression were used, however, patients with a diagnosis of CD who did not receive treatment at the VA were excluded. 122 charts were reviewed from the CD with depression group. 37 patients were randomly selected from the CD without depression group.

Patients were considered in remission if their most recent colonoscopy showed no active disease. Patients were considered to have active disease if their most recent colonoscopy demonstrated signs of inflammation. Age was recorded as patient age at time of chart review, including deceased patients. Other variables included sex, diagnosis of tobacco abuse, substance abuse, schizophrenia, and PTSD. Substance abuse was defined as patients who use tobacco, cocaine, alcohol, marijuana, amphetamine or opiates. The highest CRP and calprotectin results in the chart were recorded.

When reported, depression severity was recorded in charts as mild, moderate or severe. From this we created a depression severity score by converting them to numerical values (mild=1, moderate=2, severe=3). Severity score is recorded as an average of these values.

Wilcoxon Rank Sum test was used to compare continuous variables and Chi-Squared/Fisher's Exact Test to compare categorical variables. Results reported as odds ratios (OR) with 95% CI.

Results

A total of 159 patient charts were included in this study, 122 from the Depression group and 37 from the no depression group. Colonoscopy data used to determine remission vs active Crohn's disease was available for 101 patients. Table 1 is a descriptive demographic statistic chart by IBD status, including 63 patients with active Crohn's Disease and 38 patients in remission. Of the 63 patients in active group 16 (25.4%) of patients were tobacco users, compared to 0 (0%) in the remission group ($p<0.001$). 1 (2.63%) of the patients in the remission group had alcohol use disorder compared to 12 (18.1%) of the active group ($p<0.28$). 5 (13.2%) of the remission group had substance abuse disorder compared to 24 (38.1%) of the active group ($p<0.12$).

Table 2 is a multivariable model comparing patients with depression vs no depression. From univariate standpoint, there was an association between depression status and active Crohn's Disease. The odds of active Crohn's Disease increased with depression (odds ratio [OR], 2.88; 95% confidence interval [CI], 1.21-6.81; p>0.016). The odds of depression also increased with substance abuse (odds ratio [OR], 3.87; 95% confidence interval [CI], 1.28-11.7; p>0.016) and PTSD (odds ratio [OR], 6.39; 95% confidence interval [CI], 1.85-22.0; p>0.003).

Table 3 is a univariate ordinal logistic regression. Mean depression severity score of remission patients was 2.00 and mean depression severity score for active Crohn's patients was 2.06. Notably, the odds of having more severe depression were higher for tobacco users (users: odds ratio [OR], 2.14; mean [SD], 2.14 [0.38]; 95% confidence interval [CI], 0.35-6.14; p>0.59; non-users: mean [SD], 1.96 [0.77]) and patients with substance abuse (users: odds ratio [OR], 2.37; 95% confidence interval [CI], 0.69-8.20; mean [SD], 2.21 [0.58]; p>0.17; non-users: mean [SD], 1.88 [0.77]) .

Table 1 Demographics by Crohn's disease status

Variables	Overall N=101	Remission N=38	Active N=63	p-value
Age, years (median, IQR)	64 (49, 72)	64 (55, 72)	63 (47, 71)	0.39
Sex (male, %)	92 (91.1)	33 (86.8)	59 (93.7)	0.29
CRP (median, IQR)	6.80 (3.05, 28.3)	3.8 (2.7, 16.7)	9.10 (3.30, 41.2)	0.19
Calprotectin (median, IQR)	83.5 (22.1, 347.3)	83.0 (15.6, 751.0)	84.0 (25.7, 257.2)	0.93
Alcohol (yes, %)	13 (12.9)	1 (2.63)	12 (18.1)	0.028
Tobacco (yes, %)	16 (15.8)	0 (0.00)	16 (25.4)	<0.001
Substance Abuse (yes, %)	29 (28.7)	5 (13.2)	24 (38.1)	0.012
Schizophrenia (yes, %)	3 (2.97)	3 (3.89)	0 (0.00)	0.051
PTSD (yes, %)	26 (25.7)	8 (21.1)	18 (28.6)	0.48

Wilcoxon Rank Sum test to compare continuous variables and Chi-Squared/Fisher's Exact Test to compare categorical variables.

Table 2 Multivariable model

Variables	No Depression N=37	Depression N=122	OR (95% CI)[1]	p-values	OR (95% CI)[2]	p-values
IBD severity (active, %)	15 (45.5)	48 (70.6)	2.88 (1.21, 6.81)	0.016	2.33 (0.92, 5.87)	0.072
Age, years (median, IQR)	70 (49, 75)	61.5 (51, 70)	0.97 (0.95, 1.00)	0.13		
Sex (male, %)	33 (89.2)	103 (84.4)	0.65 (0.21, 2.06)	0.47		
CRP (median, IQR)	27.7 (2.70, 80)	7.65 (3.30, 20.8)	0.98 (0.96, 1.00)	0.076		
Calprotectin (median, IQR)	394.8 (40.2, 739.4)	84 (25.7, 106.6)	0.99 (0.99, 1.00)	0.12		
Alcohol (yes, %)	2 (5.41)	18 (14.8)	3.03 (0.67, 13.7)	0.15		
Tobacco (yes, %)	2 (5.41)	21 (17.2)	3.63 (0.81, 16.3)	0.092		
Substance Abuse (yes, %)	4 (10.8)	39 (31.9)	3.87 (1.28, 11.7)	0.016	3.52 (1.05, 11.8)	0.041
Schizophrenia (yes, %)	1 (2.70)	4 (3.28)	1.22 (0.13, 11.3)	0.86		
PTSD (yes, %)	3 (8.11)	44 (36.1)	6.39 (1.85, 22.0)	0.003	5.20 (1.36, 19.8)	0.016

[1]Univariate Logistic Regression with no adjustments

[2]Multivariable Logistic Regression adjusting for substance abuse and PTSD

Table 3 Only Depression Patients

Variables	Depression Severity Score	OR (95% Ci)	p-value
	Mean (SD)		
IBD severity			
Remission	2.00 (1.0)	REF	
Active	2.06 (0.70)	1.16 (0.19, 6.77)	0.87
Age, years			
≤ 63	1.86 (0.76)	REF	
>63	2.17 (0.64)	1.03 (0.98, 1.08)	0.24
Sex			
Female	2.16 (0.75)	REF	
Male	1.97 (0.71)	0.59 (0.12, 3.05)	0.53
CRP			
<6.08	2.00 (0.87)	REF	
>6.08	2.00 (0.57)	1.03 (0.98, 1.07)	0.22
Calprotectin			
<83.5	2.00 (N/A)	REF	
>83.5	2.00 (1.41)	1.03 (0.98, 1.10)	0.26
Alcohol			
No	1.90 (0.71)	REF	
Yes	2.30 (0.67)	2.96 (0.74, 11.9)	0.13
Tobacco			
No	1.96 (0.77)	REF	
Yes	2.14 (0.38)	1.48 (0.35, 6.14)	0.59
Substance Abuse			
No	1.88 (0.77)	REF	
Yes	2.21 (0.58)	2.37 (0.69, 8.20)	0.17

Schizophrenia				
	No	2.00 (0.72)	REF	
	Yes	2.00 (N/A)	1.00 (0.04, 25.9)	1.00
PTSD				
	No	2.08 (0.71)	REF	
	Yes	1.87 (0.72)	0.57 (0.17, 1.90)	0.36

Univariate Ordinal logistic Regression

Discussion

These findings provide evidence that depression is associated with increased Crohn's disease activity in the Veteran population. Based on this data, one may consider that treating an individual's depression may reduce the frequency and severity of Crohn's disease activity and may positively impact quality of life. This insinuates that there may be benefits to holistically treating a patient's IBD through also evaluating and monitoring his or her psychological health through more frequent screening tests such as the PHQ-9.

Furthermore, there were strong associations found between substance abuse and the likelihood of depression. Tobacco use and alcohol use were also shown to be associated with increased risk of depression in this veteran population. This data indicates that there may be high rates of comorbid substance use disorder with depressive disorders.

Other studies have demonstrated the likelihood that psychiatric disorders often co-exist with inflammation, infections, and autoimmune diseases. [7-8] Interestingly, our results indicated no association for the measured CRP and calprotectin between the Crohn's Disease with depression and the Crohn's disease without depression groups. However, we recorded only the all-cause highest measured CRP and calprotectin, respectively in the patient's chart. It is possible that there is no significant difference between the range of CRP and calprotectin levels between the two groups, although it should be noted that in this study we did not capture the frequency of high CRP and calprotectin levels nor measure them exclusively.

Given our smaller sample size, a goal for future research is to replicate these findings in a larger sample size. In addition, future studies to qualify the severity of Crohn's disease in respect to patients with depression in comparison to patients without depression would help to determining the degree of effect.

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