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Follow-Up of Microscopic Colitis Patients and Diarrhea Controls at 1 Year

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Abstract

BACKGROUND AND AIMS: Microscopic colitis (MC) is a common cause of chronic diarrhea; however, the clinical course of this disease is poorly understood. We aimed to investigate how patients diagnosed with MC were treated in routine clinical practice and how their symptoms compared to patients with other causes of chronic diarrhea at one year follow-up.

METHODS: We conducted a case-control study of patients undergoing outpatient colonoscopy to evaluate diarrhea. The study pathologist determined whether patients were classified as MC cases or non-MC controls. One year after colonoscopy, we interviewed cases (n = 74) and controls (n = 162) about their diagnosis, medications for diarrhea, and symptom burden.

RESULTS: At 1-year follow-up after colonoscopy, 10% of MC cases were unaware of the diagnosis, 60% had been prescribed a medication for diarrhea, 40% had fecal urgency, 32% had weight loss, and 21% had fecal incontinence. Among cases, 46% were treated with budesonide. Compared to cases, controls had worse symptoms based on the Microscopic Colitis Disease Activity Index score with a median score of 3.0 (interquartile range 1.9–4.2) vs 2.3 (interquartile

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The authors disclose no conflicts.

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The study was approved by the UNC Office of Human Research Ethics. All patients provided informed consent.

Reporting Guidelines:

STROBE.

range 1.4–3.2) at 1-year follow-up. Controls had more frequent stools, urgency, fecal incontinence, and abdominal pain.

CONCLUSION: In a cohort of patients with biopsy-confirmed MC and diarrhea controls, we found that some cases remained unaware of their diagnosis, many cases had persistent symptoms, and controls had worse symptoms than cases. These findings suggest there are opportunities to improve management of this chronic disease.

Keywords

Diarrhea; Microscopic Colitis; Colonoscopy; Communication

Introduction

Diarrhea is a common gastrointestinal symptom and leading reason for ambulatory care and emergency department visits.[1] Microscopic colitis (MC) is a common cause of chronic diarrhea and includes 2 subtypes, lymphocytic colitis (LC) and collagenous colitis.[2] The prevalence of MC is 262 cases per 100,000 person years and is most common in older women.[3] While the severity of diarrhea and other associated symptoms varies, MC is a significant detriment to quality of life.[4–6]

Despite the burden of MC, the clinical course is poorly understood. Based on data primarily from randomized controlled trials and older observational studies, persistent or recurrent gastrointestinal symptoms are thought to be common. Among patients enrolled in 4 randomized controlled trials of budesonide, 61% had symptom relapse after stopping budesonide.[7] A recent study reported the weighted proportion of patients with persistent or recurrent symptoms in prior studies to be 32%, and found that 49% of the 381 patients in their prospective cohort had chronic active or relapsing disease.[8] How the symptom burden of patients with MC compares to patients with other causes of chronic diarrhea remains unknown.

To better understand the treatment and symptoms of chronic diarrhea due to MC compared to other causes, we conducted follow-up interviews of patients 1 year after they presented with undifferentiated diarrhea and underwent diagnostic colonoscopy. We aimed to determine diagnosis recall, prescribed treatments, and changes in gastrointestinal symptoms among patients with biopsy-confirmed MC and controls with diarrhea.

Methods

The parent study has been described previously.[9–12] Briefly, we enrolled patients referred for colonoscopy for an indication of diarrhea at the University of North Carolina Hospitals. In addition to clinical biopsies to evaluate diarrhea, consented patients had research biopsies, a blood draw, and a detailed baseline interview.

All participants in the parent study were called by telephone 1 year following colonoscopy, and participants who completed the follow-up telephone interview were included in the current study. In the parent study, we excluded participants when there was a disagreement between the clinical and research pathologist. Colon biopsies from 4 participants were read

as normal by the clinical pathologist but MC by the research pathologist. One patient had biopsies that were read as possible MC by the clinical pathologist but normal by the research pathologist. These 5 patients were excluded from all analyses.

The follow-up telephone interview assessed diagnosis understanding, medication use, and symptom burden. First, patients were asked if they recalled a diagnosis of MC, LC, or collagenous colitis. They were then asked whether they were treated with prescription medications and whether they were treated with specific medications that are commonly used to treat diarrhea. The interview included the questions from the Microscopic Colitis Disease Activity Index (MCDAI). The MCDAI was developed as way to assess disease severity, and was shown to predict the physician global assessment of disease activity and correlate with quality of life.[13] The MCDAI includes questions about number of unformed stools daily, presence of nocturnal stools, abdominal pain, weight loss, fecal urgency, and fecal incontinence.[13] The minimal clinically significant difference in MCDAI score is thought to be a 2-unit decrease in MCDAI score.[13] Because these symptoms are also found in diarrhea patients without MC and part of the MCDAI index are simply questions about diarrhea, we reasoned that the index could be used as a measure of disease severity in the controls with diarrhea even though it is not specific for other etiologies of chronic diarrhea.

During our review of the survey results, we found that some patients inaccurately reported information about their diagnosis or reported unexpected prescription medications. To learn more about these responses, we performed a chart review. Referrals, clinic notes, procedure notes, pathology results, patient letters, telephone encounter notes, and medication history were reviewed and summarized.

Means and standard deviations or medians and interquartile ranges were calculated for continuous variables and proportions for categorical data. We compared recall of diagnosis, prescription medication use, and symptom questions between cases and controls using chi-square tests for categorical variables and Wilcoxon tests for continuous variables. Logistic regression was used to estimate odds ratios (ORs) and 95% confidence intervals (CIs) for being treated with budesonide for diarrhea according to baseline MCDAI score. The analysis was performed using SAS 9.4 (SAS, Cary, North Carolina).

The study was approved by the University of North Carolina Office of Human Research Ethics. All patients provided informed consent.

Results

The study enrolled patients from April 1, 2015 to December 22, 2020. Among the 362 patients included in the parent study, there were 110 cases of MC and 252 controls without MC. Of the 110 patients with MC, 74 (67%) participated in the follow-up survey 1 year after their colonoscopy. Of the 252 patients without MC, 162 (64%) participated in the follow-up survey.

Descriptive characteristics of the study participants who were interviewed 1 year after enrollment are shown in Table 1. The cases were older than the controls, mean age 63.8 vs 56.0 years. Compared to controls, cases were more likely to be White, 96% vs 88%, and

female, 86% vs 72%. Cases were more likely to have attended college or graduate school, 72% vs 44%, and have a lower mean body mass index compared to controls, 25.8 vs 29.7. There was no difference in marital status or smoking between cases and controls.

With regards to a MC diagnosis, 90% recalled the diagnosis (Table 2). There were 7 (10%) cases who either did not recall or were unsure of their diagnosis. On review of these cases, 6 had clear documentation of being diagnosed with MC. Specifically, documentation included letters with the pathology results and diagnosis listed for 4 patients, clinic encounter notes for 3 patients, and telephone encounter notes for 2 patients. For 1 patient, the clinical pathology report described patchy increase in crypt and epithelial lymphocytes with early LC in the differential. These findings might have been interpreted by physicians as nonspecific and not MC. The cases who were unaware of their diagnosis were symptomatic at baseline and follow-up, and most were prescribed medications for diarrhea (Table 3).

Among the controls, 11 (7%) reported a diagnosis of MC despite no clinical documentation to support the diagnosis and 13 (8%) controls were unsure of whether they had been diagnosed. The words “MC” were included in each of these patients’ clinical documentation, such as clinic note, colonoscopy report, or pathology report, as part of the differential diagnosis or having been excluded.

Cases were more likely to have been treated with prescription medications (60% cases vs 26% controls) (Table 2). Only 46% of all MC cases were treated with budesonide. Compared to the cases who were not treated with budesonide, the cases treated with budesonide had higher median baseline MCDAI scores (5.3 vs 4.9). Cases treated with any prescription medication had slightly higher median MCDAI scores at baseline than cases who were not prescribed medications (2.3 vs 2.0). Of the 44 cases that were prescribed medications, 18 (41%) patients reported having been prescribed more than 1 medication and 15 (34%) reported being treated with budesonide as well as at least 1 other medication.

Among patients who were prescribed medications, controls were more likely than cases to have been prescribed prednisone (20% vs 7%), diphenoxylate/atropine (27% vs 16%), loperamide (51% vs 34%), or bile salt sequestrants (24% vs 7%). Among the 3 controls who reported being treated with budesonide, 1 was treated with budesonide for potential Crohn’s disease and there was no documentation of the other 2 patients prescribed budesonide. Among the 8 controls who reported being treated with prednisone, 5 were treated with prednisone for other indications (contrast allergy, sinusitis, asthma, vasculitis, rhinosinusitis), 1 had previously been treated with prednisone for diarrhea before study enrollment, and 2 others were never treated with prednisone based on chart review. There was no documentation of the control who reported mesalamine or the control who reported azathioprine having been treated with those medications.

At 1-year follow-up, 15% of MC cases reported nocturnal stools, 28% abdominal pain, 40% fecal urgency, 32% weight loss, and 21% fecal incontinence (Table 4). Among cases, the median MCDAI score was 2.3 at 1-year follow-up. Based on MCDAI scores at baseline and follow-up, cases had similar improvement in symptoms whether or not they were treated with budesonide and there were cases who were not treated with budesonide despite

remaining symptomatic at follow-up (Table 5). For each symptom captured in our study, the severity among controls was either similar to or more severe than cases. At time of colonoscopy, cases had higher baseline MCDAI scores than controls (5.1 vs 4.5). At 1-year follow-up, cases had lower MCDAI scores compared to controls (2.3 vs 3.0) (Table 4 and Figure). Whereas 61% of cases had a clinically significant improvement in MCDAI score at 1-year follow-up (≥ 2 decrease in MCDAI score), only 37% of controls had a clinically significant improvement in MCDAI score.

Discussion

We interviewed a cohort of patients with biopsy-confirmed MC and diarrhea controls 1 year after colono-noscopy. We found that some participants were unaware they had MC and some participants reported a MC diagnosis despite normal biopies of the colon. We found that many cases and controls continued to experience ongoing gastrointestinal symptoms and only a small proportion had been offered prescription treatment for diarrhea.

Our findings demonstrate the need to improve communication after diagnostic colonoscopies. At 1 year after their procedure, 1 in 10 patients did not recall a diagnosis of MC despite having significant symptoms that were often treated with prescription medications. While most of these cases received either a letter or telephone call with the pathology results, our results suggest that patients with a new diagnosis of MC require a follow-up visit in gastroenterology clinic for education and treatment. There are limited data about how accurately patients report pathologic findings from their colonoscopy. In a 2007 study on the communication of endoscopy results, the addition of a written endoscopy report that included a verbal explanation of findings was still inadequate for the comprehension of some patients.[14] Endoscopists should also consider directly communicating with the referring provider or primary care physician about the diagnosis of this chronic disease and the potential need for ongoing treatment.

We also found that 15% of controls either thought they had MC or were unsure of their diagnosis. In each case, MC was included as part of the differential diagnosis in the medical record. Patients may have remembered the diagnosis being discussed during their evaluation, this finding further highlights the importance of clear communication and the importance of working through the differential diagnosis for chronic diarrhea in these patients.

Based on the results of randomized, placebo-controlled trials,[15–18] guidelines recommend budesonide as first-line therapy for MC.[2] Other treatments include loperamide, diphenoxylate/atropine, mesalamine, bismuth salicylate, prednisone, bile acid sequestrants, or immunomodulators in certain circumstances.[2,19] Surprisingly, only 60% of the cases in our study were prescribed medications for diarrhea and only 46% were treated with budesonide. Those cases with greater symptom burden were more likely to be prescribed budeonside. In addition to budesonide, cases were most often treated with loperamide and diphenoxylate/atropine with second-line therapies being used infrequently. Cases not treated with prescription medications may have mild symptoms, may not have been able to afford prescription therapies or have access to follow-up, or providers may not be aware of treatment options for MC.

The fact that 40% of cases were not treated with prescription medications demonstrates an opportunity to improve how often patients with MC are offered first-line therapies. There is also a need to improve adjunctive therapy as bile acid malabsorption is common in MC and only 3 cases (7%) were treated with bile acid sequestrants.[20] It is also surprising that only 26% of our diarrhea controls with significant enough symptoms to warrant diagnostic colonoscopy were offered prescription treatment. Given the several options for symptomatic treatment of diarrhea, this suggests that patients with chronic diarrhea of unclear etiology remain undertreated.

Similar to what has been described previously, many MC cases in our study had ongoing loose stools, urgency, and fecal incontinence at 1 year. Interestingly, symptoms were not more likely to improve among cases treated with budesonide as compared to those who were not treated with budesonide. The cases who improved without budesonide treatment may have been treated with other medications or had spontaneous improvement in their MC, which has been reported in a minority of patients.[8,21,22] Prior studies on symptom burden have included randomized controlled trials with relatively small numbers of patients,[17,22–24] retrospective studies,[21,25,26] prospective studies that only include patients with MC,[8,27–32] and a case-control study in which the controls were healthy patients from a background population.[5] These studies suggest that symptoms persist in 24%–50% of MC patients at follow-up.[8,25,26,29–33]

Prior studies have not compared patients with MC to patients with similar symptoms thereby limiting inferences about symptom outcomes. Our study was limited to patients with diarrhea. The cases and controls in our study were being evaluated for similar symptoms, and the controls would have been diagnosed with MC had their colonic biopsies met pathologic criteria. Although the MCDAI is only validated for the cases with MC, it evaluates relevant information about stool frequency and other symptoms that are also common in patients with other causes of chronic diarrhea like irritable bowel syndrome with diarrhea and functional diarrhea. We used the MCDAI to directly compare how patients presenting with similar symptoms progressed based on the presence or absence of MC.[13]

The finding that many patients with MC remained symptomatic 1 year after diagnosis provides further evidence that these patients should be offered follow-up to assess for sustained response to treatment.

Even though cases had worse symptoms than controls cases at baseline, controls had worse symptoms than cases 1 year after colonoscopy. Controls had more abdominal pain, fecal urgency, and fecal incontinence at follow-up. Controls also had more frequent stools. At 1-year follow-up, one-third of controls were still waking up at night to have a bowel movement. The degree to which controls were still suffering significantly from symptoms is striking.

Our finding that cases had more improvement in symptoms than controls with other diarrheal disorders underscores the importance of maintaining a high index of suspicion for MC so it can be diagnosed and treated.[2] There is such substantial symptom overlap between MC and other causes of chronic diarrhea that MC cannot be reliably distinguished

from common conditions like irritable bowel syndrome with diarrhea based on symptoms alone.[34–37] As such, the diagnosis of MC may be delayed or missed if a colonoscopy with biopsies is not performed.[37–39] A diagnostic colonoscopy should be considered for certain patients with diarrhea who fail to respond to initial antidiarrheal therapies or are at higher risk for MC, such as older female patients and patients with more severe watery diarrhea or alarm symptoms.[40]

The strengths of our study include its prospective design and the use of a standardized disease questionnaire. The slides of every patient were reviewed by an experienced research pathologist. Our study has limitations. Of the participants included in the parent study, 36 of 110 cases (33%) and 90 of the 252 controls (36%) were not included in these analyses because they did not complete the telephone interview. The outcomes patients experienced may have made them more or less likely to participate in the follow-up survey, but we would expect this to be non-differential between cases and controls because both groups had diarrhea. Loperamide and other over-the-counter medications are often used to treat diarrhea, and we may not have accurately captured the use of over-the-counter medications since we only asked about prescription medications. The MCDAI has not been validated in other etiologies of chronic diarrhea, such as irritable bowel syndrome with diarrhea and functional diarrhea, which likely caused symptoms among the controls in our study so applying it in that patient population could overestimate the severity of symptoms. We did not have data on testing for celiac disease for cases and controls so we do not know whether celiac disease had been excluded, which could have affected symptom response. The inferences that can be drawn from our findings are also limited by the lack of data on diagnoses among controls as well as lack of information about symptom progression and medication use over the course of the year.

Conclusion

In this study of patients with MC and diarrhea controls, we found that some cases and controls were unsure of a diagnosis based on their colonoscopy results, some cases and many controls were not prescribed medications, and many cases and controls remained symptomatic 1 year after colonoscopy with controls having worse symptoms than cases. Efforts to improve the communication of colonoscopy results and ensure that patients understand the implications of a new MC diagnosis would help empower patients to seek treatment when needed. This is particularly important in light of our findings that less than half of MC patients in our study were treated with first-line therapy and that many remained symptomatic at follow-up. Furthermore, only one-fourth of patients with severe enough diarrhea to warrant endoscopic evaluation who did not have MC were prescribed medications despite having an even more symptoms at follow-up. Regardless of whether MC is diagnosed, providers should monitor symptom progression in patients with chronic diarrhea, prescribe medications when symptoms persist, and refer patients to gastroenterology when necessary.

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Data Transparency Statement:

Data can be made available to other researchers upon reasonable request.

Abbreviations used in this paper:

CC	Collagenous colitis
LC	lymphocytic colitis
MC	microscopic colitis
MCDAI	Microscopic Colitis Disease Activity Index

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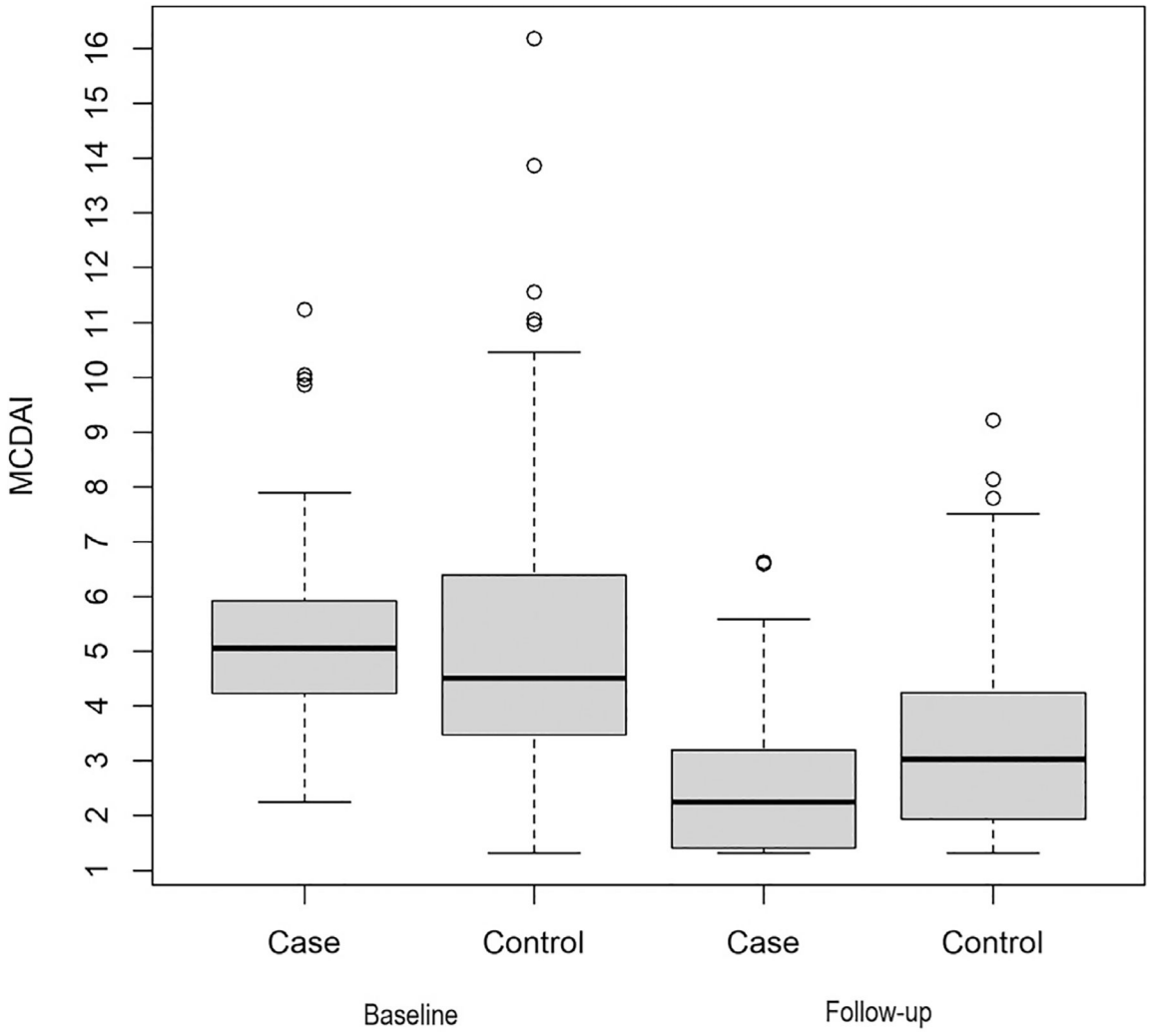

Figure.
Median Microscopic Colitis Disease Activity Index (MCDAI) for cases and controls at baseline and at 1 year follow-up.

Table 1.

Characteristics of the Study Population (n = 236)

	Cases (N = 74)		Controls (N = 162)	
Characteristics	**N or mean**	**% or standard deviation**	**N or mean**	**% or standard deviation**
Age, mean	63.8	(12.4)	56.0	(11.4)
Race, %				
White	71	96%	141	88%
Non-White	3	4%	19	12%
Sex, %				
Female	64	86%	116	72%
Male	10	14%	46	28%
Marital status, %				
Married	51	69%	109	67%
Not married	23	31%	53	33%
Education, %				
Less than college	21	28%	91	56%
College or postgrad	53	72%	71	44%
Cigarette smoking, %				
No	65	88%	134	83%
Yes	9	12%	28	17%
BMI, mean	25.6	(6.4)	29.7	(7.2)

BMI, body mass index.

Table 2.

Recall of Microscopic Colitis Diagnosis and Prescription Medication Use Among Cases and Controls at 1-y Follow-Up[a]

	Cases (N = 74)		Controls (N = 162)		
Recall of diagnosis and prescription medication use	**N**	**%**	**N**	**%**	***P***
After your colonoscopy do you recall being told that you had a condition called microscopic colitis, lymphocytic colitis or collagenous colitis?					<.001
Microscopic colitis	44	60%	11	7%	
Lymphocytic colitis	7	10%	0	0%	
Collagenous colitis	15	21%	0	0%	
No	5	7%	138	85%	
Don't know	2	3%	13	8%	
Based on your colonoscopy results were you treated with prescription medicines for diarrhea?					<.001
Yes	44	60%	41	26%	
No	29	40%	118	74%	
Prescription medications for diarrhea[b]					
Budesonide	34	77%	3	7%	
Prednisone	3	7%	8	20%	
Mesalamine	2	5%	1	2%	
Azathioprine	0	0%	1	2%	
Diphenoxylate/atropine	7	16%	11	27%	
Loperamide	15	34%	21	51%	
Alosetron	0	0%	1	2%	
Eluxadoline	0	0%	2	5%	
Bile salt sequestrants	3	7%	10	24%	

[a] Ns may not sum to total due to missing.

[b] Denominator for proportion is N who said yes to previous question about any medications. Among the 44 cases who reported prescription medications, 18 reported more than 1 medication. The following specific medication histories were reported: budesonide, loperamide: N = 7; budesonide, diphenoxylate/atropine: N = 3; budesonide, bile salt sequestrants: N = 1; budesonide, mesalamine: N = 1; budesonide, prednisone: N = 1; budesonide, prednisone, loperamide: N = 1; budesonide, prednisone, diphenoxylate/atropine, loperamide: N = 1; loperamide, bile salt sequestrants: N = 1; diphenoxylate/atropine, loperamide: N = 1; mesalamine, loperamide, bile salt sequestrants: N = 1.

Table 3.

Microscopic Colitis Disease Activity Index (MCDAI) Stratified by Proportion of Patients With Clinically Significant Improvement in MCDAI Score (≥ 2) Between Baseline and 1-y Follow-Up, and Prescription Medication Use Among Cases Who Were Unaware and Aware of Microscopic Colitis Diagnosis

	Cases unaware (N = 7)		Cases aware (N = 66)[a]	
MCDAI and prescription medication use	**N[b]**	**%**	**N[b]**	**%**
MCDAI improved by ≥2 from baseline to follow-up				
No	3	60%	21	38%
Yes	2	40%	34	62%
Based on your colonoscopy results were you treated with prescription medicines for diarrhea?				
Yes	5	71%	39	59%
No	2	29%	27	41%
Prescription medications for diarrhea				
Budesonide	3	60%	31	79%
Prednisone	0	0%	3	8%
Mesalamine	0	0%	2	5%
Azathioprine	0	0%	0	0%
Diphenoxylate/atropine	1	20%	6	15%
Loperamide	2	40%	13	33%
Alosetron	0	0%	0	0%
Eluxadoline	0	0%	0	0%
Bile salt sequestrants	0	0%	3	8%

[a] N = 66 rather than 67 due to 1 case missing the question about being aware of their diagnosis.

[b] Ns may not sum to total due to missing data.

Table 4.

Comparison of Microscopic Colitis Disease Activity Index Responses Between Cases and Controls at 1-y Follow-Up

MCDAI responses	Cases (N = 72)[a]		Controls (N = 162)		
	N[c] or median	% or IQR	N[c] or median	% or IQR	*P* [b]
During past week, average number of bowel movements per day	2	1–3.5	3	2–4	.07
During past week, average number of loose, watery or liquid bowel movements per day?	0.5	0–2	1	0–3	.09
During past week, nocturnal bowel movements?					.006
No	61	85%	109	67%	
Yes	11	15%	53	33%	
During past week, abdominal pain?					<.001
No	52	72%	73	45%	
Yes	20	28%	89	55%	
Among those with pain, severity (1 = no pain, 10 severe pain)?	4	3–5.5	5	3–7	.15
During past week, urgent bowel movement?					<.001
No	43	60%	58	36%	
Yes	29	40%	104	64%	
Compared to last year, weight change?					.18
Weight gain	13	18%	47	29%	
Weight loss	23	32%	47	29%	
No change	36	50%	66	41%	
Among those with weight change					
Average gain in pounds (N = 14)	10	5–10	10	5–20	.10
Average loss in pounds (N = 23)	10	5–15	10	5–19	.37
During the past month, fecal incontinence frequency?					.01
0	56	79%	99	62%	
1 or more times per pain	15	21%	61	38%	
Total MCDAI score	2.3	1.4–3.2	3	1.9–4.2	<.001

[a] There are 72 cases reported here because 2 of the 74 cases reported in Table 2 were missing values for all of the questions in this table.

[b] *P* value from Wilcoxon test for continuous variables, chi-square test for categorical variables.

[c] Ns may not sum to total due to missing data.

Table 5.

Median Microscopic Colitis Disease Activity Index (MCDAI) at Baseline and 1-y Follow-Up According to Treatment With Budesonide and Treatment With Any Prescription Medication for Diarrhea Among Cases

	Median MCDAI at baseline and follow-up							
	Baseline				Follow-up			
Treatment	**N**	**Median**	**IQR**	***P* value**	**N**	**Median**	**IQR**	***P* value**
Treatment with budesonide				.6				.7
No	31	4.9	4.2–5.8		37	2.3	1.4–3.2	
Yes	31	5.3	4.2–6.3		33	2.3	1.4–3.2	
Treatment with any prescription medication				.1				.3
No	22	4.8	4.1–5.6		27	2.1	1.3–2.7	
Yes	40	5.3	4.3–6.3		43	2.3	1.4–3.4	