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High prevalence of non-alcoholic fatty liver disease in patients with inflammatory bowel disease receiving anti-tumor necrosis factor therapy

Alisa Likhitsup[a,b], Jason Dundulis[a,b], Shaya Ansari[a,b], Sruthi Patibandla[a], Colleen Hutton[c], Kevin Kennedy[c], John H. Helzberg[a,b], Rajiv Chhabra[a,b]

University of Missouri Kansas City; Saint Luke's Hospital of Kansas City; Mid-America Heart Institute St. Luke's Health System, Kansas City, MO, USA

Abstract

Background Non-alcoholic fatty liver disease (NAFLD) is common in patients with inflammatory bowel disease (IBD). This study evaluated the prevalence of NAFLD and the associated risk factors among IBD patients who received anti-tumor necrosis factor (TNF) therapy.

Methods Adult IBD patients receiving anti-TNF therapy (infliximab, adalimumab, certolizumab, golimumab) were enrolled. Hepatic steatosis was assessed by abdominal ultrasound. Patients with a history of excessive alcohol or recent steroid use were excluded. Univariate and multivariate analysis were performed.

Results Eighty patients, 55% male, mean age 42±15 years, were enrolled. The sonographic prevalence of NAFLD was 54% (43/80), significantly higher than the general prevalence in the US adult population (30%) (P<0.0001). NAFLD patients had a significantly higher proportion of males, as well as greater body weight and body mass index, compared to non-NAFLD. The Crohns disease activity index (CDAI) was significantly higher among patients with NAFLD. Multivariate analysis demonstrated that a higher CDAI was independently associated with NAFLD, with an odds ratio of 1.6 (95% confidence interval 1.05-2.44; P=0.03).

Conclusions The presence of IBD is strongly associated with NAFLD. We identified a high prevalence of NAFLD among IBD patients receiving anti-TNF. CDAI was independently associated with hepatic steatosis. Further studies are still needed to evaluate the pathophysiology of NAFLD development and disease progression among IBD populations.

Keywords Hepatic steatosis, inflammatory bowel disease, non-alcoholic fatty liver disease, anti-tumor necrosis factor

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Introduction

Non-alcoholic fatty liver disease (NAFLD) is more common in the western world [1]. In the general US population, the prevalence of NAFLD has been reported to be 19-46% [2-13]. Risk factors for NAFLD include obesity, insulin resistance, diabetes mellitus, hypertension, and hypertriglyceridemia [14]. The spectrum of NAFLD is broad and ranges from benign macrovesicular steatosis to advanced steatohepatitis, cirrhosis, and liver cancer. NAFLD has become more commonly recognized among patients with inflammatory bowel disease (IBD). The prevalence of NAFLD in IBD patients has been reported to vary from 8-59%, depending on the diagnostic criteria used [15-20]. IBD, which includes Crohn's disease (CD) and ulcerative colitis (UC), is a chronic inflammatory disease of

[a]University of Missouri Kansas City (Alisa Likhitsup, Jason Dundulis, Shaya Ansari, Sruthi Patibandla, John H. Helzberg, Rajiv Chhabra); [b]Saint Luke's Hospital of Kansas City (Alisa Likhitsup, Jason Dundulis, Shaya Ansari, John H. Helzberg, Rajiv Chhabra); [c]Mid-America Heart Institute St. Luke's Health System (Colleen Hutton, Kevin Kennedy), Kansas City, MO, USA

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Correspondence to: Alisa Likhitsup, MD, 4320 Wornall Rd, Suit 240, Kansas City, MO 64111, USA, e-mail: alikhitsup@gmail.com

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the gastrointestinal tract with an estimated prevalence of 1-1.3 million in the US [21]. The pathogenesis of NAFLD among the IBD population is not well understood. Apart from metabolic syndrome, IBD-specific risk factors include malnutrition, intestinal inflammation, gut microbiota alteration, steroid exposure, and drug-induced hepatotoxicity, all of which may contribute to the pathogenesis of NAFLD [22].

The effect of anti-tumor necrosis factor (TNF) therapy on NAFLD development in IBD patients remains unclear [15,16]. The aim of this study was to evaluate the prevalence of NAFLD among IBD patients receiving anti-TNF therapy. Predictive factors associated with NAFLD among IBD patients were evaluated. The prevalence of steatohepatitis and hepatic fibrosis among IBD patients with NAFLD was assessed.

Patients and methods

The Institutional Review Board of Saint Luke's Hospital of Kansas City approved the data collection and methodology of this study. The study was performed in accordance with relevant guidelines. Informed consent was obtained from all participants. We conducted a cross-sectional study that included IBD patients, aged 18 years or older, who had been receiving anti-TNF therapy (infliximab, adalimumab, certolizumab, golimumab) through the Saint Luke's gastrointestinal specialist and Mid-America Gastrointestinal consultants ambulatory clinic for at least 6 months prior to study enrollment. Study questionnaires were completed and the following data were collected: age, body mass index (BMI), waist circumference, IBD history including disease activity, and risk factors for NAFLD (Supplementary Table 1). Blood samples were obtained for a comprehensive metabolic panel, viral hepatitis and iron studies (to exclude chronic viral hepatitis and hemochromatosis). Patients with a history of concurrent hepatitis B or C infection, elevated iron saturation >45%, excessive alcohol use (defined as >7 alcoholic drinks/week in women or >14 alcoholic drinks/week in men) or recent steroid use within the past 6 months were excluded. Abdominal ultrasound examinations were completed and reviewed by a specialized abdominal radiologist (SA) for the presence or absence of hepatic steatosis. A non-alcoholic steatohepatitis (NASH) FibroSure (LabCorp, Burlington, NC) test was completed in those patients with evidence of hepatic steatosis on abdominal ultrasound to estimate the degree of inflammation and fibrosis.

Statistical analysis

The data were presented as mean±standard deviation for continuous variables and as a total percentage for categorical variables. Student' s *t*-test and chi-square tests were used in the unadjusted analysis. The prevalence of NAFLD was compared to that of the general US population, represented by a national database [1]. Assuming a prevalence of 30%, we required 80 patients to ensure that a 95% confidence interval (95%CI) estimate of the proportion of IBD patients with NAFLD is within 10% of the true population prevalence. The prevalence of hepatic steatosis, steatohepatitis and fibrosis was assessed by NASH FibroSure (LabCorp, Burlington, NC). To assess the predictive factors associated with the presence of NAFLD in IBD patients, a multivariate logistic regression model was used, adjusted for age, sex, weight, BMI, waist circumference, presence of diabetes mellitus, and transaminase levels. SPSS version 21.0 (IBM Corp, Armonk, NY) was used for all analyses.

Results

NAFLD prevalence in IBD patients receiving anti-TNF therapy

Eighty patients were enrolled, with a mean age of 42±15 years, predominantly male (55%) and with average BMI 26±5.7 kg/m^2. Sixty-five patients (81%) had CD, with mean CD activity index (CDAI) 28±25, while 15 patients (19%) had UC, with mean simple clinical colitis activity index (SCCAI) 2±2.15 (Table 1). The mean duration of IBD since diagnosis was 14±10 years and the mean duration of anti-TNF therapy was 5±4 years. The numbers of patients receiving adalimumab, infliximab, golimumab, and certolizumab therapy were 67 (84%), 10 (13%), 2 (2.5%), and 1 (1.3%), respectively. Abdominal ultrasound detected hepatic steatosis in 43 patients, giving a prevalence of NAFLD in these patients of 54%' significantly higher than that of the general US population, assuming a prevalence of 30% (P<0.001).

Univariate comparison of IBD patients with and without NAFLD

IBD patients with hepatic steatosis had a higher percentage of male sex (67% vs. 41%; P=0.02), with greater body weight (84±20 vs. 69±18 kg; P=0.001) and BMI (30±6 vs. 24±4 kg/m^2; P=0.001). Among patients with CD, those with NAFLD had a higher mean CDAI score (35±27 vs. 22±24; P=0.01). There was no difference between the NAFLD and non-NAFLD groups in age, type of IBD (CD vs. UC), duration of IBD, duration and type of anti-TNF therapy, type of concurrent IBD medications, waist circumference, presence of diabetes, transaminase levels, or SSCCI scores (in UC patients) (Table 1).

Multivariate analysis of predictive factors for NAFLD

In the multivariate logistic regression model, age, sex, weight, BMI, waist circumference, presence of diabetes mellitus, and transaminase levels were included in the final model. An increase in CDAI score was associated with a 1.6 times higher likelihood of NAFLD development (Table 2).

Table 1 Characteristic of the study populations

Characteristics	Total	Hepatic steatosis		P-value
	(n=80)	Yes (n=43)	No (n=37)	
Age (years)	42±15	45±14	40±16	0.13
Male	44 (55%)	29 (67%)	15 (41%)	0.02*
Weight (kg)	77±20	84±20	69±18	0.001*
BMI (kg/cm^2)	26±5.7	30±6	24±4	0.001*
Waist circumference (inches)	33.4±5.4	35±5	32±5	0.17
Crohn's disease (n, %)	65 (81%)	37 (86%)	28 (76%)	0.24
History of diabetes mellitus	3 (4%)	3 (7%)	0	0.10
AST (IU/L)	35±16	36±17	33±16	0.39
ALT (IU/L)	38±22	42±25	34±18	0.12
Duration of IBD diagnosis (years)	14±10	15±10	13±11	0.69
Duration of biologic therapy (years)	5±4	5±5	4±4	0.71
Biologic therapy				0.82
Infliximab	67 (84%)	36 (84%)	31 (84%)	
Adalimumab	10 (13%)	5 (12%)	5 (14%)	
Golimumab	2 (2.5%)	1 (2.3%)	1 (2.7%)	
Certolizumab	1 (1.3%)	1 (2.3%)	0	
Concurrent IBD medications				0.46
Sulfasalazine/Mesalamine	12 (15%)	7 (16%)	5 (14%)	
AZA/6-MP	17 (21%)	10 (23%)	7 (19%)	
Methotrexate	2 (2.5%)	0	2 (5.4%)	
CDAI in CD (n=65)	28±25	35±27	22±24	0.01*
SCCAI in UC (n=15)	2±2.15	1.5±0.7	2.5±2.8	0.25

*Alpha less than 0.05 considered statistically significant

ALT, alanine aminotransferase; AST, aspartate aminotransferase; AZA, azathioprine; BMI, body mass index; CD, Crohn's disease; CDAI, Crohn's disease activity index; lbs, pounds; 6-MP, 6-mercaptopurine; SCCAI, simple clinical colitis activity index; UC, ulcerative colitis

Prevalence of NASH and hepatic fibrosis in IBD patients with NAFLD

In patients with hepatic steatosis detected on abdominal ultrasound, 31 of 43 patients (72%) completed a NASH Fibrosure test. Of these 31 patients, 21 (67%) had steatohepatitis, 19 (61%) had steatohepatitis, and 7 (22%) had hepatic fibrosis (16% with portal fibrosis, 3% with bridging fibrosis with few septa, and 3% with bridging fibrosis with many septa) (Fig. 1). No cirrhosis was detected based on NASH Fibrosure or abdominal ultrasound.

Discussion

Because of the obesity epidemic and the increasing prevalence of metabolic syndrome, the global prevalence of NAFLD has been rising to an estimated level of 24% [1]. In the general US population, the reported sonographic and biopsy-proven prevalences of NAFLD were 19-34% and 34-46%, respectively [2-13].

The prevalence of NAFLD in IBD patients has been reported to vary from 8-59%, depending on the diagnostic criteria used [15-20]. In one study, 108 of 321 IBD patients (34%) were diagnosed with NAFLD based on the hepatic steatosis index, with a reported annual incidence of 9.1% [15]. However, a serology-based diagnosis of NAFLD can lead to underreporting of its true prevalence. Ultrasonography is a widely accessible imaging technique for the detection of hepatic steatosis, with high sensitivity (85%, 95%CI 79.5-88.9%), specificity (94%, 95%CI 87.2-97%) and positive likelihood ratio (13.3, 95%CI 6.4-27.6) compared to histology [23]. The sonographic prevalence of hepatic steatosis was 26-40% in CD and 26-36% in UC patients without obesity, metabolic disorders, or underlying chronic hepatitis [18]. Another retrospective study reported only 76 of 928 (8%) IBD patients had evidence of NAFLD based on various

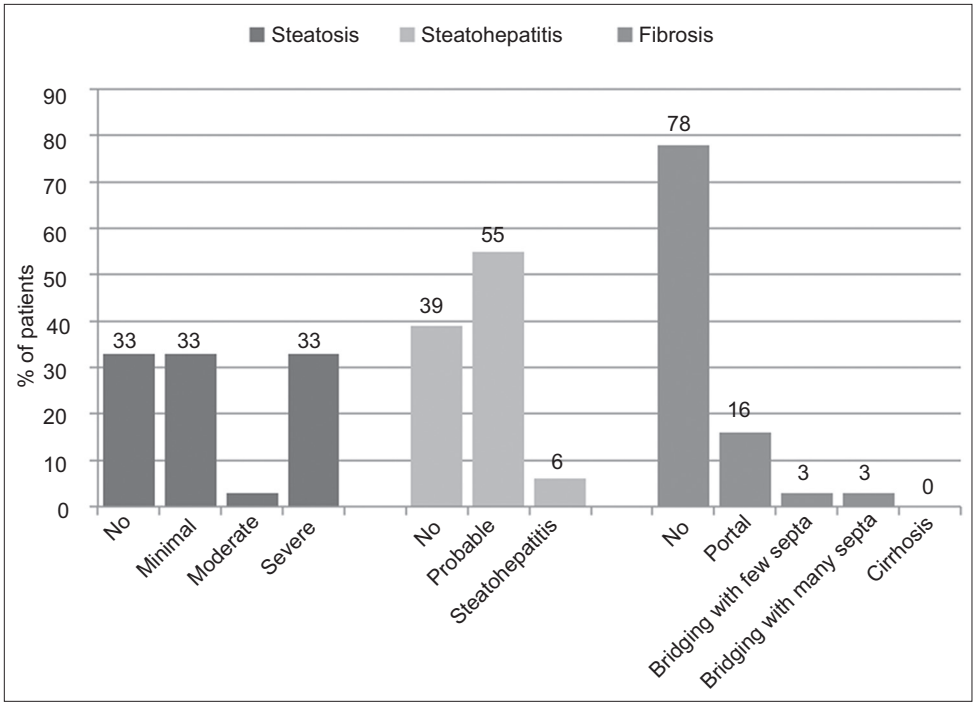

Figure 1 Non-alcoholic steatohepatitis Fibrosure in patients with the hepatic steatosis (n=31)
Steatosis score; S0=<0.3 (no steatosis), S0-1=0.3-0.4 (minimal steatosis), S1-2=0.48-0.67 (moderate steatosis), S2-3≥0.67 (severe steatosis). Steatohepatitis score; N0=0.25 (no steatohepatitis), N1=0.50 (probable steatohepatitis), N2=0.75 (steatohepatitis). Fibrosis score; F0≤0.21 (no fibrosis), F0-1=0.21-0.30 (portal fibrosis), F1-2=0.31-0.58 (bridging fibrosis with few septa), F3=0.58-0.72 (bridging fibrosis with many septa), F4≥0.72 (cirrhosis)

types of imaging studies [16]. Histological diagnosis is the gold standard, but it is invasive, as a tissue specimen is needed for the diagnosis. Fifty-nine percent of IBD patients were found to have at least grade-1 hepatic steatosis on liver histology (from liver biopsy, resection, or autopsy) [17]. In our study, the prevalence of NAFLD in IBD patients who had received anti-TNF therapy for a minimum of 6 months without steroid exposure was 54%, based on abdominal ultrasound.

Among IBD patients, 20-30% of children and 18% of adults are obese and the prevalence is rising [24]; 38% of adults with IBD were overweight [25]. Hypertension, obesity and metabolic syndrome were reportedly associated with the presence of NAFLD in IBD patients [16,19]. In our cross-sectional cohort, patients with NAFLD had higher body weight and BMI. There was no difference in waist circumference or the presence of diabetes.

Several studies have suggested that the duration of IBD is associated with the development of NAFLD [15,26]. Patients with a longer disease duration are potentially exposed to multiple risk factors associated with NAFLD, including chronic inflammation, intestinal permeability, alteration of gut microbiota, metabolic comorbidities, and hepatotoxic drugs [15]. In our study, in which the patients' mean IBD duration was 14±10 years, we did not detect any association between IBD duration and NAFLD.

A retrospective study of 321 IBD patients reported disease activity associated with NAFLD detected by the hepatic steatosis index as having a hazard ratio of 1.58 (95%CI 1-08-2.33; P=0.02) [15]. The IBD disease severity was found to be associated with elevated hepatic fat content detected on ultrasonography [27]. Another study in patients with UC reported that liver fat content might be associated with UC severity score [28]. Prior small bowel surgery, which implicitly reflects the IBD disease severity, has also been associated with NAFLD [15]. In contrast, some studies reported no such association between NAFLD and IBD status, disease activity or drugs [19,29]. In our study, the CDAI, but not the SSCCI, was found to be associated with the development of NAFLD. The multivariate logistic regression analysis showed that a high CDAI score was independently associated with a 1.6 times higher likelihood of NAFLD development. We did not detect any association between treatment duration, type of biologic therapy or concurrent IBD medication with NAFLD (Table 1).

Proinflammatory cytokines such as interleukins, TNF-α and adhesion factors, contribute to chronic inflammation and IBD exacerbation, which also have hepatic effects. TNF-α is able to trigger stellate cell activation, matrix gene expression and remodeling, important events during the onset of steatohepatitis [30]. In an experimental rat model, TNF inhibition reduced hepatic fat content, inflammation, necrosis and fibrosis, and improved insulin signal transduction in treated animals compared with placebo [31,32]. Pentoxifylline (PTX) inhibits a number of proinflammatory cytokines, including TNF-α. PTX has been studied in a NASH population and achieved an improvement in NASH histological features compared to placebo [33]. A meta-analysis showed that PTX reduced

Table 2 Predictive factors associated with the presence of non-alcoholic fatty liver disease in inflammatory bowel disease patients who received biologic treatment (n=80)

Variables	OR* (95%CI)	P-value
Male sex	3.1 (0.7-12.5)	0.11
Increased weight	0.9 (.97-1.03)	0.85
Increased BMI	1.2 (0.9-1.5)	0.17
Increased CDAI score	1.6 (1.05-2.44)	0.03**

*Adjusted for age, sex, weight, BMI, waist circumference, presence of diabetes mellitus, and transaminase levels

**Alpha less than 0.05 considered statistically significant

BMI, body mass index; CDAI, Crohn's disease activity index; OR, odd ratio; CI, confidence interval

aspartate aminotransferase and alanine aminotransferase levels and improves histological scores in patients with NAFLD and NASH, but did not affect cytokines [34]. Anti-TNF therapy has become more commonly used in IBD patients. Bessisow *et al* demonstrated that anti-TNF therapy was not associated with NAFLD in IBD patients [15]. In contrast, Sourianarayanane *et al* suggested that anti-TNF was protective against NAFLD [16]. However, these results should be interpreted cautiously, as the study included patients concurrently using steroids. Another meta-analysis showed that the pooled odds ratio [OR] for NAFLD in IBD patients using a biologic agent was 0.85 (95%CI 0.49-1.46) [35]. Another study reported that ongoing anti-TNF therapy was an independent protective factor against transaminase abnormalities (OR 0.15, 95%CI, 0-0.8; P=0.02) [27]. In our study, 54% of IBD patients who had received anti-TNF therapy for a mean duration of 5±4 years developed hepatic steatosis based on abdominal ultrasound. Hence, there may be factors other than the cytokine-mediated pathway that contribute to the pathogenesis of NAFLD in the IBD population.

The annual incidence of advanced liver fibrosis among IBD patients was 0.5% (0.2-1.1) detected by FIB-4 score [15]; 6.4% of IBD patients had elevated liver stiffness measurements (>8 kPa) detected by transient elastography and 3 patients (2.7%) had persistently elevated liver stiffness (>8 kPa) 6 months later [36]. The NASH FibroSure test (LabCorp, Burlington, NC) is a noninvasive assessment of hepatic steatosis, with a sensitivity and specificity of 46-90% and 54-88%, respectively, in the detection of hepatic steatosis and a positive predictive value of 46-63% [37]. The test performed better in the detection of steatohepatitis (sensitivity 30-88%, specificity 50-94%, positive predictive value 66-74%). The sensitivity and specificity in detecting advanced hepatic fibrosis were 25-92% and 71-97%, respectively, with a positive predictive value of 33-60% [38,39].

In our study, NASH FibroSure was applied only in patients who had hepatic steatosis based on abdominal ultrasound: 61% of the patients had hepatic steatosis (55% probable and 6% definite), while 22% of patients had hepatic fibrosis (6% with bridging fibrosis) (Fig. 1). None of our patients was diagnosed with cirrhosis.

The limitations of our study are that it was a cross-sectional cohort study, without a control population to evaluate the predictive factors associated with the development or progression of NAFLD. Given our limited resources, we did not collect C-reactive protein, fecal calprotectin or serum TNF drug levels. Furthermore, our patients were receiving anti-TNF therapy and their IBD activity was well controlled. Thus, the NAFLD prevalence yielded by our study will not apply to IBD patients with uncontrolled IBD, or to those who are not receiving anti-TNF therapy or are actively on steroids. Furthermore, the sample size was too small to perform subgroup analysis for CD and UC separately. Although the prevalence of fatty liver is known to be elevated among IBD populations, additional studies are still needed to establish the benefit of NAFLD screening, risk factors associated with NAFLD development and predictive factors associated with NAFLD progression among IBD populations.

In conclusion, the presence of IBD strongly associated with NAFLD. Our cross-sectional study identified a high prevalence of NAFLD among IBD patients receiving anti-TNF therapy. As to whether IBD disease activity is associated with NAFLD, the data are conflicting. Our study results showed that CD severity, but not UC disease severity, was independently associated with hepatic steatosis. These data suggest that, apart from changes in the prevalence of metabolic disease, there are IBD-associated factors that contribute to the pathogenesis of NAFLD among IBD population. However, further studies are still needed.

Summary Box

What is already known:

- Risk factors for non-alcoholic fatty liver disease (NAFLD) include obesity, insulin resistance, diabetes mellitus, hypertension, and hypertriglyceridemia
- The prevalence of NAFLD in patients with inflammatory bowel disease (IBD) reportedly varies from 8-59%, depending on the diagnostic criteria
- There are conflicting data regarding the effect of anti-tumor necrosis factor (TNF) therapy on NAFLD prevalence among IBD populations

What the new findings are:

- The presence of IBD is strongly associated with NAFLD
- We identified a high prevalence of NAFLD among IBD patients receiving anti-TNF therapy
- There are probably IBD-associated factors that contribute to the pathogenesis of NAFLD among IBD population, but further studies are still needed

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Supplementary Table

Supplementary Table 1 Study questionnaire

1.	Gender:	Male	Female		
2.	Age:	_____years			
3.	Type of IBD:	Crohn's Disease	Ulcerative Colitis		
	a. How long have you had this disease (or what year were you diagnosed)?_____ b. Which biologic medication are you currently on?_____ c. Have you been on this medication for more than 6 months? Yes No i. if yes, how long have you been on this medication (best estimate)_____ d. Do you CURRENTLY take other medications for your IBD? If so, please list: _____ e. Have you taken steroid to treat your IBD within the past 6 months? Yes No				
4.	Weight:	_____lbs.			
5.	Height:	_____feet	_____Inches		
6.	Waist circumference:	_____inches			
7.	Are you diabetic?	Yes No	If yes, do you require insulin?	Yes	No
8.	Do you have any personal history of liver disease?			Yes	No
	a. If yes, please explain_____				
9.	Alcohol use: ON AVERAGE, how many alcoholic drinks do you consume in a week? Note: an alcoholic drink includes a 12oz serving of beer (normal size bottle or can), a 4oz glass of wine, or a 1.5oz (or shot) of hard liquor (such as vodka, whisky, or rum):				
	0-3 4-7	8-14	15-21	22-30	> 30
10.	Crohn's Disease Activity Index (If you have ulcerative colitis, please skip to question 11).				
	a. Over the last 7 days: ON AVERAGE, how many bowel movements do you have per day?				
	b. On a scale of 0 to 3, where 0 is no pain and 3 is severe pain, please rate, ON AVERAGE, how much abdominal pain you have had daily over the past week?_____ c. Consider your general sense of well being over the past week. On a scale of 0 to 4, where 0 is feeling well and 4 is feeling terrible, rate your AVERAGE daily score:_____ d. Please check which complications of Crohn's Disease you have CURRENTLY: i. Arthritis or joint pains. Yes No ii. Iritis or uveitis (inflammation of your eyes). Yes No iii. Ulcers of other lesions in your mouth or on your skin. Yes No iv. Perirectal disease such as anal fissure, fistulas or abscesses. Yes No v. Other fistulas. Yes No vi. Body temperature greater than 37.8 C (100.0 F). Yes No e. Have you used over the counter anti-diarrheal drugs in the past 7 days? Yes No f. Have you noticed an abdominal mass recently? Yes Maybe/questionable No				
11.	Simple Clinical Colitis Activity Index (FOR ULCERATIVE COLITIS PATIENTS ONLY). Answer all questions based on your symptoms and how you have been feeling over the past ONE WEEK.				
	a. On average, how many bowel movements do you have per day (over 24 hours)?				
		0-3	4-6	7-9	10+
	b. On average, how many bowel movements do you have at night?				
		0	1-3	3+	
	c. When you need to have a bowel movement, how quickly do you need to go (urgency)?				
		No rush	Hurry	Immediately	Incontinence
	d. How frequently are you noticing blood in your stool, and how much?				
	No blood	Small traces	Occasionally bloody	Usually bloody	
	e. Please rate your general well being over the past week.				
	Very well	Slightly below par	Poor	Very poor	Terrible
	f. During the past week, have you had any of the following? i. Pyoderma gangrenosum (oozing ulcers, usually on the legs). Yes No ii. Erythema nodosum (red, swollen bumps, typically on the shins). Yes No iii. Uveitis (red, painful eyes). Yes No iv. Arthritis or Joint pains. Yes No				