

Chronic fatigue is associated with increased disease-related worries and concerns in inflammatory bowel disease

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Abstract

AIM: To investigate the impact of chronic fatigue on disease-related worries in inflammatory bowel disease (IBD) and the potential multicollinearity between subjective questionnaires.

METHODS: Patients in remission or with mild-to-moderate disease activity completed the fatigue questionnaire (FQ), the rating form of IBD patient concerns (RFIPC), the Short-Form 36 (SF-36), and IBD question-

naire (N-IBDQ). In addition, clinical and epidemiological data were obtained.

RESULTS: In total, 140 patients were included; of which 92 were diagnosed with ulcerative colitis and 48 with Crohn's disease. The mean age of patients with chronic fatigue was 44.2 years (SD = 15.8) and for non-fatigued patients was 44.7 years (SD = 16.0). Chronic fatigued patients had clinically significantly increased levels of disease-related worries, as measured by Cohen's *d* effect size. Worries about having an ostomy bag, loss of bowel control, and energy levels were most prominent in both chronic fatigued and non-chronic fatigued IBD patients. Variance inflation factor (VIF) and tolerance indicated that there were no problematic multicollinearity among the FQ, RFIPC, SF-36 and N-IBDQ responses (VIF < 5 and tolerance > 2).

CONCLUSION: Chronic fatigue is associated with increased levels of disease-related worries and concerns in IBD. Increased levels of worries were also associated with impaired health-related quality of life.

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Key words: Fatigue; Worries; Health-related quality of life; Patient reported outcome; Inflammatory bowel disease

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INTRODUCTION

Inflammatory bowel disease (IBD) includes ulcerative colitis (UC) and Crohn's disease (CD). Both UC and CD are chronic, recurrent diseases of the gastrointestinal tract, with symptoms that include abdominal pain, frequent bowel movements, and rectal bleeding^[1,2]. Traditionally, these diseases have been defined as abnormalities in the structure and function of both organs and tissues^[3]. However, given that IBD is associated with impaired health-related quality of life (HRQoL), increased fatigue, and increased worrying regarding the potential consequences of the disease^[4-7], this definition seems too restrictive. The concept of illness might therefore be broader, embodying the subjective experiences of reduced health and bodily function^[3].

Living with chronic illness can be challenging, and individual responses to these challenges vary widely^[8]. Several HRQoL studies have found that many patients with IBD tend to do well^[9]. However, there are subgroups of patients - such as patients with more severe disease or anxiety - who seem to be particularly affected^[4,5,9]. It was recently reported that IBD patients with chronic fatigue (CF) (defined as an elevated fatigue level of a duration longer than six months) had clinically significant reductions in HRQoL, compared to patients without CF^[10]. Thus, an important aspect of measuring subjective health is to identify patients who are most severely affected.

Both generic (i.e., irrespective of illness/condition) and disease-specific HRQoL questionnaires have been developed^[11-13]. In addition, questionnaires such as the rating form of IBD patient concerns (RFIPC) and the fatigue questionnaire (FQ) are used to quantify other aspects of living with chronic illness^[7,14]. We hypothesised that measuring aspects such as worries/concerns (RFIPC) and fatigue (FQ) might help us to identify subgroups of patients that tend to have a poorer outcome. Potentially, however, there might be areas of overlap between the various questionnaires, which is often referred to as multicollinearity. Multicollinearity refers to a situation wherein predictor variables in a regression model are strongly correlated and, consequently, that variables included in the model are closely related.

The primary aim of this study was to examine the impact of chronic fatigue on disease-related worries in IBD. In addition, we wanted to investigate whether the potential association between worries, fatigue and HRQoL in IBD exhibit multicollinearity.

MATERIALS AND METHODS

Subjects

Patients, who were over the age of 18 years, had IBD that was previously verified clinically, endoscopically, or histologically, and who were either in remission or with mild-to-moderate disease activity [defined as Simple Clinical Colitis Activity Index (SCCAI)^[15] or Simple Crohn's Disease Activity Index (SCDAI)^[16] score of less than 10], were eligible for inclusion in this study. Patients

were excluded if they had cognitive impairment, were deemed unlikely to comply with the study procedures, or if they participated in another study. Participants were consecutively recruited from three outpatient clinics in South-Eastern Norway (the counties of Østfold and Hedmark) during routine follow-up visits. At each of the centre, a senior gastroenterologist was in charge of the study protocol. The inclusion period was from August 23, 2005 to January 29, 2007.

Clinical and sociodemographic data

Sociodemographic variables were gathered by interview, and data regarding clinical status and symptoms were obtained from laboratory tests, medical records and disease activity indices (SCCAI/SCDAI)^[15,16]. In addition, we asked the patients to complete a symptom-based questionnaire that graded their self-perceived IBD symptoms during the previous 14 d, using the following categories; no symptoms, mild symptoms (did not interfere with everyday activities), moderate symptoms (interfered with everyday activities and may have resulted in sick leave), and severe symptoms (unable to perform everyday activities, on sick leave, or hospitalized)^[5].

Each patient's phenotype was classified according to the Vienna Classification for CD patients, as the Montreal Classification did not exist when the study protocol was designed. The UC patients were classified into three subgroups: proctitis, left-sided colitis (with inflammation up to the splenic flexure), and extensive colitis (with inflammation beyond the splenic flexure).

The information regarding fatigue was collected with the FQ^[14], the generic HRQoL with the Short-Form 36 (SF-36)^[11], the disease specific HRQoL with the Norwegian version of the IBD questionnaire (N-IBDQ)^[17], and disease-related worries and concerns with the RFIPC^[7] (Table 1). The questionnaires were self-administered by the patients at the various centres, following a standardized procedure, which allowed the patients to fill out the questionnaires in the peace and quiet of the hospital's outpatient clinic.

Questionnaires

The RFIPC: The RFIPC is a disease-specific questionnaire that was developed by Drossman *et al.*^[7]. This questionnaire rates various important worries and concerns that are raised by IBD patients. The questionnaire consists of the 25 most frequently reported concerns reported by IBD patients, with every item framed in the same style: "Because of your condition, how concerned are you with...?" The responses were scored on a 100-mm horizontal visual analog scale. A score of 0-mm represents no worries/concerns, and a score of 100-mm represents the highest possible worries and concerns. The mean scores of all 25 items yields the "sum score". The RFIPC has been translated into Norwegian and validated (Jelsness-Jørgensen LP, Moum B, Bernklev T. Worries and concerns among inflammatory bowel disease patients followed prospectively over one year. Submitted:

Table 1 Main characteristics of the questionnaires used in this study

Questionnaire	Number of items and dimensions	Main characteristics
SF-36	36 items, divided into 8 dimensions	Measure generic HRQoL
Ware <i>et al</i> ^[11]		Scale scores from 0-100, with higher scores indicating better HRQoL
N-IBDQ	32 items, divided into 5 dimensions	Measure disease-specific HRQoL
Bernlev <i>et al</i> ^[17]		Scale scores from 32-224, with higher scores indicating better HRQoL
FQ	11 items, divided into 2 dimensions	Measure both physical and mental fatigue
Chalder <i>et al</i> ^[14]	The FQ contains 2 items asking about duration and extent of fatigue symptoms	Scale scores from 0-33 with higher scores indicating higher levels of fatigue
Jelsness-Jørgensen <i>et al</i> ^[10]		In addition scored as a dichotomized scale where original scores 0 + 1 = 0 and 2 + 3 = 1
		Chronic fatigue defined as a score of ≥ 4 on the dichotomized scale and duration of fatigue symptoms ≥ 6 mo
RFIPC	25 items, divided into 6 dimensions	Measure the 25 most frequently reported disease-related worries/concerns by IBD patients
Drossman <i>et al</i> ^[7]		

IBD: Inflammatory bowel disease; SF-36: Short-Form 36; N-IBDQ: IBD questionnaire (Norwegian version); FQ: Fatigue questionnaire; RFIPC: Rating form of IBD patient concerns; HRQoL: Health-related quality of life.

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Factor analysis of the Norwegian version of the RFIPC yielded six factors. F1: Impact of disease (e.g., financial difficulties/energy/loss of bowel control); F2: Expectancy (e.g., developing cancer/dying early); F3: Treatment (e.g., effects of medication); F4: Intimacy (e.g., ability to perform sexually); F5: Stigma (e.g., feeling dirty/smelly); and F6: Complications (e.g., undergoing surgery/ostomy bag placement).

FQ: The FQ was developed by Chalder *et al*^[14] and consists of 11 items that are divided into two main dimensions: physical fatigue (PF), which contains seven items, and mental fatigue (MF), which contains four items. The available responses included four options: 0 = better than usual, 1 = no more than usual, 2 = worse than usual, and 3 = much worse than usual. A higher score reflects a higher level of fatigue. Combining the scores of PF and MF yields the total fatigue score, with a maximum possible scale score of 33. The scale scores of the FQ were also scored on a dichotomized scale (0 = better than usual and no more than usual; 1 = worse than usual and much worse than usual). In addition to measuring episodic fatigue (irrespective of the duration of symptoms), the FQ contains two questions regarding the duration and extent of fatigue symptoms. Based on the results of the original validation study, the Norwegian validation study, and general consensus^[14,18,19], CF was defined as dichotomized scores ≥ 4 and duration > 6 mo. The FQ was recently validated for use in IBD^[6].

SF-36: The SF-36 is a generic, self-administered questionnaire containing 36 questions^[11] that are divided into eight multi-item scales consisting of: physical functioning, role limitations due to physical problems, bodily pain, general health, vitality, social functioning, role limitations due to emotional problems, and mental health (MH). For each question, the raw score was coded and transformed into a scale from 0 to 100, with 0 and 100 representing the lowest level and highest level of function, respectively. The SF-36 has been validated by others^[20]. Missing

data were treated following published recommendations: if data for half of the items within a scale or fewer were missing, they were replaced by the mean value of the respondent's completed items in the same scale in accordance with the SF-36 scoring algorithms^[21].

N-IBDQ: The IBDQ is a disease-specific questionnaire that was developed by Irvine^[12,13]. The original version consists of 32 items divided into four dimensions: bowel symptoms (e.g., loose stools or abdominal pain), systemic symptoms (e.g., fatigue or altered sleep patterns), social function (e.g., work attendance) and emotional function (e.g., anger or depression). The Norwegian validation study (N-IBDQ) revealed a five-dimensional structure: emotional function-1 (fatigue, energy), bowel function-1 (stool consistency and pattern), bowel function-2 (bowel pain and discomfort), social function (work attendance, cancelling social events) and emotional function-2 (worries)^[17]. All of the responses were scored on a 7-point Likert Scale, with a score of 7 representing no problems and a score of 1 representing severe problems. This gives a possible score range of 32-224, with a higher score reflecting improved HRQoL^[12,13,17].

Statistical analysis

To assess the characteristics of the patients, we used descriptive analyses and frequencies. A student's *t* test was used to evaluate the differences in the distribution of epidemiological and clinical variables between the diagnostic groups.

To test potential associations between the RFIPC, FQ, N-IBDQ and SF-36 questionnaires, both bivariate correlation analysis with spearman's ρ and linear regression analysis were used. In addition, the latter analysis was used to explore potential multicollinearity. A variance inflation factor (VIF) greater than 5 and a reciprocal tolerance value of less than 0.20 were defined as indicative of colinearity in accordance with published recommendations^[22,23]. We chose to analyse the RFIPC sum score, the FQ and N-IBDQ total score as dependents only, to reduce the number of dimensions tested.

Table 2 Main clinical/sociodemographic characteristics *n* (%)

	UC (<i>n</i> = 92)	CD (<i>n</i> = 48)
Age, (yr), mean ± SD	46.9 ± 5.8	40.0 ± 15.0
Age range, (yr)	20-82	19-69
Gender		
Female	43 (47)	36 (75)
Male	49 (53)	12 (25)
Disease duration, (yr), mean ± SD	8.5 ± 9.5	9.2 ± 9.6
Educational level		
Second level, first stage (lower)	16 (17.4)	5 (10.4)
Second level, second stage (medium)	42 (45.7)	22 (45.8)
Third level (university)	34 (37.0)	21 (43.8)
UC extension		
Proctitis	27 (29.3)	
Left-sided colitis	23 (25.0)	
Extensive colitis	42 (45.7)	
CD extension		
L1 terminal ileum		11 (22.9)
L2 colon		17 (35.4)
L3 ileocolon		18 (37.6)
L4 upper GI		2 (4.1)
Perceived IBD symptom score		
No symptoms	23 (25.0)	9 (18.8)
Mild symptoms	41 (44.6)	22 (45.8)
Moderate symptoms	25 (27.2)	13 (27.1)
Severe symptoms	3 (3.2)	4 (8.3)

UC: Ulcerative colitis; CD: Crohn's disease; IBD: Inflammatory bowel disease; GI: Gastrointestinal.

To control for and eliminate the effect of potential confounding factors that are known to influence RFIPC scores, age, gender, and educational level were entered as covariates through univariate analysis of variance. Perceived IBD symptoms were hypothesized to affect the RFIPC scores and we therefore additionally chose to correct for this factor as well. The effect size was calculated with Cohen's d^{24} . Operational definitions of 0.2, 0.5 and 0.8 were categorized as small, medium and large effect sizes, respectively²⁴.

All tests were 2-sided with a 5% significance level. All statistics were performed using the Predictive Analytics Software, PASW, version 18.0 (IBM Corporation, Route 100 Somers, NY 10589).

Ethical considerations

This study was performed in accordance with the principles of the Helsinki declaration and approval was obtained from the Regional Ethics committee and the Norwegian Data Inspectorate.

RESULTS

One hundred and forty-four patients who were diagnosed with either UC or CD gave their written informed consent for participation in the study. One patient was excluded due to severe disease activity at inclusion (SC-DAI > 10), one patient withdrew from the study after a few weeks, and two patients were excluded from analysis due to incomplete responses to the questionnaires. A to-

tal of 140 patients provided complete data sets and were suitable for statistical analysis.

Epidemiological and clinical characteristics

The CD patients were significantly younger than the UC patients ($P = 0.014$). There were no significant differences in the perceived IBD symptoms or the duration of disease between the two diagnostic groups. Twenty of the 92 (22%) UC patients and 14 of the 48 (29%) CD patients were judged to have CF. There were no significant differences in age, gender, disease duration or educational level between CF and non-CF patients. However, the perceived IBD symptoms were more severe in CF than in non-CF patients ($P < 0.01$). The primary characteristics of the participants are presented in Table 2.

CF and RFIPC scores

CF was associated with significantly higher RFIPC scores in one of the six dimensions in CD and in five of the six dimensions in UC. In addition, the RFIPC sum score was significantly higher in UC patients with CF compared to those without CF (Table 2). Among the individual RFIPC items, the differences between UC patients with and without CF were most pronounced in worries regarding loss of bowel control, developing cancer, dying early, energy level, being a burden to others, having surgery, or an ostomy bag ($P < 0.01$ for all items). In addition, the scores for the following RFIPC items were significantly higher in CD patients with CF compared to those without CF: ability to achieve full potential, financial difficulties, and energy level ($P < 0.05$ for all items). When comparing RFIPC dimensional scores for UC patients with CF to CD patients with CF, the analysis revealed no statistical difference. Only one of the twenty-five individual RFIPC items (worries about pain and suffering) was significantly different between UC and CD patients with CF, with CD patients reporting more worries in this item ($P < 0.01$).

Effect size (Cohen's d) is a measure of the estimated magnitude of a relationship between two variables and is calculated by subtracting the mean dimensional RFIPC scores of CF patients from non-CF patients, then dividing by the common σ of both groups. The analysis revealed that the RFIPC factors that were statistically significant in CF *vs* non-CF patients - regardless of their IBD diagnosis - also produced a large Cohen's d ($d > 0.80$) (Table 3). The analysis further revealed that although they did not reach statistical significance, the numerical differences produced small-to-medium effect sizes. Among the CD group, the differences between CF and non-CF patients resulted in a medium effect size ($d > 0.50$) in the RFIPC sum score, whereas the effect size in the remaining five out of six dimensions were small ($d > 0.20$). Among the UC group, one out of the six RFIPC factors did not differ significantly between CF and non-CF patients, producing a small Cohen's d ($d > 0.20$).

After the mean dimensional RFIPC scores (Table 4)

Table 3 Cohen's *d* effect size calculated from crude dimensional rating form of inflammatory bowel disease patient concerns scores and presence of chronic fatigue

RFIPC factors	CD no CF (<i>n</i> = 34)	CD CF (<i>n</i> = 14)	<i>P</i> value	Cohen's <i>d</i>	UC no CF (<i>n</i> = 72)	UC CF (<i>n</i> = 20)	<i>P</i> value	Cohen's <i>d</i>
Impact of disease	31.1 (20.6)	46.7 (17.7)	0.017	-0.81	25.6 (19.2)	45.7 (18.3)	< 0.001	-1.07
Expectancy	38.1 (30.5)	51.1 (23.1)	0.160	-0.48	32.6 (23.7)	55.3 (20.8)	< 0.001	-1.02
Treatment	27.5 (21.2)	38.0 (25.4)	0.146	-0.44	27.5 (22.0)	49.1 (22.5)	< 0.001	-0.97
Intimacy	20.3 (21.6)	28.3 (28.5)	0.299	-0.31	18.5 (18.9)	27.2 (20.1)	0.076	-0.44
Stigma	21.2 (24.3)	26.6 (20.2)	0.467	-0.24	17.3 (19.7)	35.0 (22.0)	0.001	-0.84
Complications	26.3 (23.6)	30.6 (18.6)	0.549	-0.20	21.2 (17.9)	35.7 (17.3)	0.002	-0.82
Sum score	29.2 (19.1)	39.6 (16.3)	0.082	-0.58	25.0 (15.9)	43.5 (14.5)	< 0.001	-1.21

Data are presented as mean (SD), calculated with independent samples *t* tests. RFIPC: Rating form of inflammatory bowel disease patient concerns; CD: Crohn's disease; UC: Ulcerative colitis; CF: Chronic fatigue. Cohen's *d* effect size: small, *d* = 0.2; medium, *d* = 0.5; large, *d* = 0.8.

Table 4 Univariate analysis of mean rating form of inflammatory bowel disease patient concerns scores in non-chronic fatigue and chronic fatigue patients

	Mean RFIPC adjusted for age, gender and education		Mean RFIPC adjusted for age, gender, education and IBD symptoms	
	No CF mean	CF mean	No CF mean	CF mean
CD (<i>n</i> = 48)	(<i>n</i> = 34)	(<i>n</i> = 14)	(<i>n</i> = 34)	(<i>n</i> = 14)
Impact of disease	30.7	47.6 ^a	32.2	44.0 ^a
Expectancy	37.3	53.0	37.8	52.0
Treatment	27.5	38.0	27.2	39.0
Intimacy	19.7	30.0	20.6	27.8
Stigma	20.9	27.3	20.8	27.6
Complications	26.4	30.3	25.9	31.8
Sum score	28.8	40.3	29.4	39.0
UC (<i>n</i> = 92)	(<i>n</i> = 72)	(<i>n</i> = 20)	(<i>n</i> = 72)	(<i>n</i> = 20)
Impact of disease	25.7	45.3 ^c	26.3	43.1 ^c
Expectancy	33.0	53.8 ^b	33.4	52.4 ^c
Treatment	27.9	47.8 ^c	28.5	45.6 ^c
Intimacy	18.7	26.7	19.0	25.6 ^a
Stigma	17.5	34.3 ^b	17.9	33.1 ^c
Complications	21.4	35.0 ^b	21.7	34.0 ^b
Sum score	25.2	42.8 ^c	25.6	41.2 ^c

RFIPC: Rating form of inflammatory bowel disease patient concerns; CD: Crohn's disease; UC: Ulcerative colitis; CF: Chronic fatigue; IBD: Inflammatory bowel disease. Significance levels are between patients reporting CF or not: ^a*P* ≤ 0.05, ^b*P* ≤ 0.01, ^c*P* ≤ 0.001.

were adjusted for the covariates age, gender and education, statistically significant differences were reproduced in the same RFIPC factors as in the raw, unadjusted analysis for both the UC and CD patients. Furthermore, when controlling for the perceived IBD symptom score, the significance level increased in two of the six factors (expectancy/stigma) for the UC group. One RFIPC factor (intimacy) in the UC group changed from non-significant to significant. Among the CD patients, controlling for perceived IBD symptoms had only a minor effect.

The correlation between RFIPC sum score, total fatigue, N-IBDQ total score and subdimensions of the SF-36 questionnaire

In both the UC and CD patient groups, increased RFIPC sum scores were associated with higher fatigue levels (measured as total fatigue) and reduced HRQoL (Table 5).

Table 5 Correlation (Spearman's ρ) between rating form of inflammatory bowel disease patient concerns sum, fatigue questionnaire sum, Norwegian inflammatory bowel disease questionnaire total and Short Form 36 dimensions

	CD (<i>n</i> = 48) RFIPC sum score	UC (<i>n</i> = 92) RFIPC sum score
FQ		
TF	0.36	0.49
N-IBDQ		
IBDQ Total	-0.53	-0.51
SF-36		
PF	-0.34	-0.40
RP	-0.28	-0.48
BP	-0.22	-0.44
GH	-0.49	-0.43
VT	-0.32	-0.48
SF	-0.40	-0.57
RE	-0.12	-0.49
MH	-0.31	-0.50

RFIPC: Rating form of inflammatory bowel disease patient concerns; CD: Crohn's disease; UC: Ulcerative colitis; FQ: Fatigue questionnaire; TF: Total fatigue; N-IBDQ: Norwegian inflammatory bowel disease questionnaire; SF-36: Short Form 36; PF: Physical functioning; RP: Role physical; BP: Bodily pain; GH: General health; VT: Vitality; SF: Social functioning; RE: Role emotional; MH: Mental health.

The latter showed a negative Spearman's ρ both for N-IBDQ and the SF-36 subdimensions. In general, these associations were stronger for the UC group than for the CD group.

Multicollinearity

Testing for multicollinearity revealed satisfactory values of both the VIF and tolerance (Table 6). The VIF was below the limit of 5 and the tolerance above the crucial threshold of 0.2 for both the UC and CD group. In the CD group, the ranges for the VIF and tolerance were 1.6-4.9 and 0.21-0.61, respectively. In the UC group, the ranges of the VIF and tolerance were 1.9-4.1 and 0.24-0.54, respectively.

DISCUSSION

The ramifications of IBD on patients subjective health has been thoroughly studied, identifying both a sub-

Table 6 Linear regression analysis of the rating form of inflammatory bowel disease patient concerns sum score, Norwegian inflammatory bowel disease questionnaire total score, total fatigue, chronic fatigue, Short Form 36 subdimensions and calculation of multicollinearity

	Dependent	Independent	β	P value	Tolerance	VIF
UC	RFIPC sum	N-IBDQ total	-0.70	< 0.001	0.24	4.1
	N-IBDQ total	RFIPC sum	0.29	< 0.001	0.58	1.7
		SF-36 BP	0.14	0.032	0.57	1.7
		SF-36 VT	0.17	0.019	0.50	2.0
		SF-36 SF	0.29	< 0.001	0.39	2.6
TF	SF-36 VT	-0.25	0.031	0.49	2.0	
	CF	RFIPC sum	0.34	0.018	0.46	2.2
CD	RFIPC sum	N-IBDQ total	-0.60	0.047	0.21	4.9
	N-IBDQ total	RFIPC sum	-0.17	0.047	0.71	1.4
		SF-36 SF	0.35	0.004	0.39	2.6
		SF-36 PF	0.22	0.033	0.49	2.0
		TF	-0.31	0.015	0.34	2.9

RFIPC: Rating form of inflammatory bowel disease patient concerns; CD: Crohn's disease; UC: Ulcerative colitis; TF: Total fatigue; CF: Chronic fatigue; N-IBDQ: Norwegian inflammatory bowel disease questionnaire; SF-36: Short Form 36; PF: Physical functioning; BP: Bodily pain; VT: Vitality; SF: Social functioning; VIF: Variance inflation factor.

group of patients with a worsening in HRQoL scores and other subgroups of patients with HRQoL scores that are comparable to the general population^[4,5,9,13]. This division of patient responses to IBD can partly be explained by demographic differences and differences in clinical variables^[4,5,9,13]. Recently, CF was reported to be at least twice as prevalent in IBD as in the general population, and CF has been reported to lead to clinically significant reductions in HRQoL^[6,10].

In the present study, we hypothesized that chronic fatigue might influence the level of disease-related concerns in IBD patients, and we found significant differences in the RFIPC scores between UC patients with CF and UC patients without CF. Although only one factor was significantly higher for CD patients with CF compared to CD patients without CF, there was a tendency of elevated scores in all RFIPC factors. In addition, we calculated effect sizes according to Cohen^[24], because statistical significant differences need not be of clinical importance and insignificant differences might be. As expected, the effect sizes were more pronounced in UC patients than in CD patients. The five RFIPC factors that were not significant in CD were, however, within Cohen's limits of small-to-medium effect sizes^[24]. This finding indicates that there are clinically important differences between IBD patients with CF and IBD patients without CF among all of the RFIPC scales.

IBD is often characterized by periods of remission and exacerbation; therefore, potentially negative consequences of the disease may become the primary focus in daily living^[1,2,5]. This has also been reported by Drossman^[7]. Worries and concerns are aspects of subjective health that can lead to decreased well-being^[7]. These worries may potentially be linked to situations in which the patient's expectations regarding physical and mental

functioning in "normal life" do not match their experienced reality^[8].

Within the published literature, there appears to be a pattern regarding which of the individual RFIPC items are rated by IBD patients as being most important^[7,25-27]. Our results concur with previous studies in this regard. However, the presence of chronic fatigue seems to further increase worries in IBD patients. To our knowledge, this association has not been previously reported for IBD. Among CD patients, we found that CF was associated with increased worries regarding pain and suffering. Research has highlighted the negative association between body pain and CD^[5] and recently it was reported that chronic fatigue further decreased body pain scores^[10]. In addition, patients with CD and CF seem to negatively relate their perceived energy capacity with their ability to achieve full potential and experience financial difficulties. The latter may be related to their ability to work and provide a household income. Indeed, studies have found that patients who are on sick-leave because of their IBD have a significant deterioration in HRQoL^[28].

The nature of worry is not clear; however, it is most often prospective and predominated by negative thinking^[29]. In IBD patients, these processes are linked to potentially negative events that may or may not occur in the future, including requiring surgery or an ostomy bag^[3,7,25-27]. IBD patients are reported to believe that stress influences the course of the disease^[30]. However, this potential link between psychological stress and inflammatory exacerbations is the subject of debate^[31-33]. Addressing the worries and concerns of patients might therefore have a potentially positive influence on both fatigue and HRQoL; on the other hand, Borgaonkar *et al*^[34] found that providing disease-related information to IBD patients worsens their short-term HRQoL.

In the present study, we found that increased levels of worrying were associated with both increased fatigue levels and reduced HRQoL. When investigating the potential association between worries, fatigue, and HRQoL in IBD patients, it is natural to wonder which is the cause and which is the effect. Is increased worrying a result of chronic fatigue or vice versa? Does impaired HRQoL increase worries and fatigue, or is HRQoL exaggerated by worries? The cross-sectional design of our study makes it difficult to reach any final conclusions. Our hypothesis, which we regard as plausible, is that both reduced HRQoL and increased fatigue are secondary effects of increased disease-related worries and concerns. This theory has also been proposed by others^[30]. Potentially, elevated levels of disease-related concerns may increase energy loss and thus manifest as increased fatigue and reduced HRQoL^[35].

The RFIPC was developed just a few years after the IBDQ, which may explain why the questionnaire has received much less attention in the literature^[7,12,36,37]. As shown by our study, employing a set of various questionnaires that measure subjective health increases the

likelihood of detecting subgroups of IBD patients who are at risk of coping less successfully^[8]. Naturally, there is the potential risk that subdimensions of different questionnaires are in fact operationalizations of the same phenomena^[22,23]. However, both the VIF and tolerance were within acceptable limits for both UC and CD patients, indicating that the questionnaires seem to measure different aspects of health perception. Given these results, we would argue that patient-reported outcome, rather than HRQoL, seems to be a more adequate definition in cases where one is interested in a wide variety of outcomes (e.g., worries, concerns, fatigue, HRQoL).

A limitation of the present study is that we did not include a specific questionnaire for measuring depression. This precludes the possibility of adjusting for depression as a potentially confounding variable for fatigue. Several reports have indicated a connection and overlap between fatigue and depression^[7,19,38]. However, the MH dimension of the SF-36 questionnaire indicated that the patients in our study did not differ from the general population in this respect. Consequently, depression does not appear to be a particular problem in this patient population. Moreover, in the CD patient group there may be type 2 statistical errors, as we were not able to obtain the strong associations between levels of worries and fatigue, as was shown for UC patients.

In conclusion, we report that chronic fatigue is associated with clinically significantly increased levels of disease-related worries in both UC and CD patients. This study provides additional information to the complex nature of understanding how IBD patients perceive their own subjective health.

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COMMENTS

Background

Fatigue is reported to be a prevalent symptom in chronic diseases. In inflammatory bowel disease (IBD), however, there has been a lack of studies with fatigue as the primary endpoint. Recent publications have revealed that the amount of patients reporting long-lasting, chronic fatigue is two to three times elevated in patients with IBD compared to the background population.

Research frontiers

Chronic fatigue has been reported to significantly reduce IBD patients' health-re-

lated quality of life. In this study, the authors demonstrate that chronic fatigue is a potential important contributor to increased disease-related worries and concerns.

Innovations and breakthroughs

Recent studies have highlighted the importance of fatigue as a subjective symptom in IBD. This is the first study to report that chronic, long-lasting fatigue symptoms is associated with increased levels of disease-related worries.

Applications

By adding further complexity to the understanding of subjective health experiences in IBD, this study might help clinicians to detect patients at risk of less successful coping, potentially enhancing the patient's quality of life, and also their course of disease.

Terminology

Chronic fatigue refers to fatigue symptoms of some intensity, which have a long-lasting duration of six months or more.

Peer review

This is a very interesting and novel original contribution analyzing the problem of chronic fatigue and its relationship with worries associated with IBD. The study is interesting, seems well done and well reported. It adds a valuable bit of information to the IBD literature.

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