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Validation of the Functional Assessment of Chronic Illness Therapy-Fatigue (FACIT-F) in patients with inflammatory bowel disease

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SUMMARY

Background
Many patients with ulcerative colitis (UC) and Crohn's disease (CD) complain of significant fatigue. To date, no instrument to measure fatigue has been validated in a US inflammatory bowel disease (IBD) population.

Aim
To determine the reliability and validity of the Functional Assessment of Chronic Illness Therapy-Fatigue (FACIT-F) scale in IBD.

Methods
A total of 209 patients with IBD completed the 13 items of the FACIT-F, alongside laboratory testing and disease activity assessment. Internal consistency was measured by Cronbach's alpha; test–retest reliability by the intraclass correlation coefficient (ICC); validity by the correlation of the FACIT-F score with C-reactive protein (CRP) erythrocyte sedimentation rate (ESR), haematocrit (HCT) and disease activity as measured by the Harvey-Bradshaw Index (HBI; CD) and Simple Clinical Colitis Activity Index (SCCAI; UC).

Results
The mean ± SD FACIT-F score was 38.9 ± 11.0 overall (CD 38.6 ± 11.3; UC 39.4 ± 10.6). Cronbach's alpha was 0.94. The ICC for first and repeat FACIT-F scores assessed within 180 days without change in disease state was 0.81 (CD 0.78; UC 0.87). FACIT-F scores were lower in patients with active symptoms (CD 4.6 points, 95% CI 2.4–6.9, $P < 0.001$; UC 8.5 points, 95% CI 5.5–11.4, $P < 0.001$). In UC, FACIT-F scores were correlated with ESR (−0.76, 95% CI −0.89 to −0.50), CRP (−0.72, 95% CI −0.88 to −0.43) and HCT (0.53, 95% CI 0.22–0.74).

Conclusion
The FACIT-F scale is a reliable and valid instrument for measuring fatigue in IBD.

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INTRODUCTION

The inflammatory bowel diseases (IBD) are chronic inflammatory conditions of the gastrointestinal tract and comprise two major forms: Crohn's disease (CD) and ulcerative colitis (UC). Although the predominant clinical manifestation of CD and UC involves intestinal inflammation often resulting in abdominal pain and diarrhoea, many patients suffer from systemic symptoms that negatively affect their physical well-being, functional status and quality of life. One such symptom is fatigue.[1] IBD-associated fatigue can be severe and, for some patients, is the most debilitating part of their disease.[2–4]

Fatigue can be difficult to define. One definition that has been used in the literature states that fatigue represents an overwhelming, sustained sense of exhaustion and decreased capacity for physical and mental work.[1, 5]

Despite the overall paucity of research in IBD-associated fatigue, accumulating data suggest that patients with IBD experience greater fatigue than the general population.[6] While there appears to be an association between IBD disease activity and fatigue, some studies have also demonstrated significant levels of fatigue in patients with quiescent disease.[7, 8] The impact of fatigue on patients' quality of life has also been evaluated. In both CD and UC, fatigue was shown to be associated with a significant reduction in health-related quality of life (HRQOL).[8, 9]

Fatigue has been found to be an important symptom in patients with several other chronic diseases such as primary billiary cirrhosis, rheumatoid arthritis, ankylosing spondylitis, systemic lupus, sclerosing cholangitis, psoriatic arthritis and multiple sclerosis.[10–17] Many of these diseases, like IBD, are thought to involve an abnormal immune response. In other diseases, fatigue has been measured by various scales that attempt to determine the patient's perception and severity of fatigue. Some of these scales have been validated.[15, 18, 19] Chaldler's fatigue scale was recently validated in a Norwegian population of IBD patients.[20] To be considered valid, a scale must possess certain properties. These include content, construct and criterion validity, as well as internal consistency, stability, sensitivity to change and feasibility.[21]

The Functional Assessment of chronic Illness Therapy (FACIT) instrument is a comprehensive compilation of questions that measure health-related quality of life in patients with chronic illnesses. The FACIT-fatigue (FACIT-F) is a subscale of the general questionnaire, the FACIT-G. It was developed to assess fatigue associated with anaemia with item content established by combined expert and patient input.[22] To date, the FACIT-F scale has been validated in the general population as well as in patients with cancer, psoriatic arthritis, rheumatoid arthritis, systemic lupus erthematosus, paroxysmal nocturnal haemoglobinuria and Parkinson's disease.[6, 10, 15, 23–25] It comprises 13 questions, the responses to which are each recorded on a 5-point Likert scale (Appendix A). Scores range from 0 to 52, with lower scores representing greater fatigue. Like other FACIT-subscales, it is written at the 6th-grade level, can be completed quickly and is easily scored and interpreted. The English version of the FACIT-F questionnaire can be downloaded free-of-charge (http://www.facit.org/FACITOrg/Questionnaires) and is also available in many other languages. Overall, the FACIT-F questionnaire appears to be an excellent candidate scale for assessing fatigue in IBD patients.

The goal of this study was to validate the FACIT-F, a previously developed fatigue-scale, for use in patients with inflammatory bowel disease.

MATERIALS AND METHODS

Inflammatory bowel disease patients seen at the Massachusetts General Hospital Crohn's and Colitis Center between Jan 2005 and Feb 2009 were identified. Patients aged 18 and older with a diagnosis of Crohn's disease or ulcerative colitis, based upon standard endoscopic, radiographic and histological criteria, were included in the study. Exclusion criteria included patients diagnosed with cancer, a history of other immune-mediated diseases, or who were pregnant. At each visit, patients were further characterised as having active disease, defined as having a Harvey-Bradshaw Index (HBI) of 5 or higher for Crohn's disease, or a Simple Clinical Colitis Activity Index (SCCAI) score of 5 or higher for ulcerative colitis.[26, 27] Patients with inactive disease were those on stable therapy and with a HBI of 4 or less (CD) or a SCCAI (UC) of 4 or less.

Patients were asked to fill out the 13-point FACIT-F questionnaire at each visit while physicians recorded a Physician's Global Assessment (PGA) of disease activity (Appendix B). Laboratory testing included the erythrocyte sedimentation rate (ESR), C-reactive protein (CRP) and haematocrit (HCT).

Statistical analysis

The internal consistency of the 13 items on the FACIT-F questionnaire was measured using the Cronbach's alpha. Test–retest reliability was determined using the intraclass correlation coefficient (ICC) between FACIT-F assessments completed within 180 days of each other in patients with stable health. Stable health was defined as Physician's Global Assessment of a patient's health status

as 'same' on question 2 (Appendix B). Construct validity was tested by correlation of baseline FACIT-F assessments with commonly used clinical disease indices (HBI for CD and SCCAI in UC) along with the serum inflammatory biomarkers ESR and CRP. We also determined the correlation of the FACIT-F with patients' haematocrit (HCT). Confidence intervals for the observed Pearson correlation coefficients were estimated using Fisher's z-transformation with bias adjustment. The sensitivity of FACIT-F to change was assessed in two ways. Serial FACIT-F assessments were analysed in a linear mixed model with fixed effect indicators for disease (CD vs. UC), disease activity (active vs. inactive), and their interaction and random participant-specific intercepts. Serial changes in FACIT-F scores were also analysed in a linear mixed model with fixed effects for disease, the 5-level PGA score measuring change from the previous visit, and their interaction and assuming first-order autoregressive covariance among residuals.

Ethical requirements

The study was approved by the Massachusetts General Hospital Institutional Review Board and all patients provided informed consent.

RESULTS

A total of 209 patients were included in the study. Table 1 describes the demographic, disease characteristics and FACIT-F scores.

Table 1 | Patient demographics, disease characteristics and mean FACIT-F scores at baseline (n = 209)

	Ulcerative colitis (UC)	Crohn's disease (CD)	Overall
Men/women	37/40	61/71	98/111
Mean (SD) age (years)	39.5 (13.3)	38.2 (12.2)	38.6 (12.6)
Active disease (%)	19.5	15.2	16.7
ESR (SD) mm/h	18.7 (21.6)	22.6 (18.0)	21.4 (19.1)
CRP (SD) mg/L	3.2 (5.9)	8.3 (11.8)	6.7 (10.6)
HCT (SD) %	40.3 (5.0)	40.9 (3.9)	40.7 (4.3)
HBI (SD)	n.a.	2.93 (3.3)	n.a.
SCCAI (SD)	2.64 (3.3)	n.a.	n.a.
FACIT-F (SD)	39.4 (10.6)	38.6 (11.3)	38.9 (11.0)

CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; FACIT-F, Functional Assessment of Chronic Illness Therapy-Fatigue; HBI, Harvey-Bradshaw Index; HCT, haematocrit; n.a., not applicable; SCCAI, Simple Clinical Colitis Activity Index.

Internal consistency

The internal consistency of the 13 items of the FACIT-F questionnaire measured by Cronbach's alpha was 0.94 for UC and 0.95 for CD.

Test–retest reliability

The intraclass correlation coefficient (ICC) between FACIT-F assessments was 0.81 (Figure 1) for all IBD patients with FACIT-F assessments completed within 180 days of each other in patients in stable health

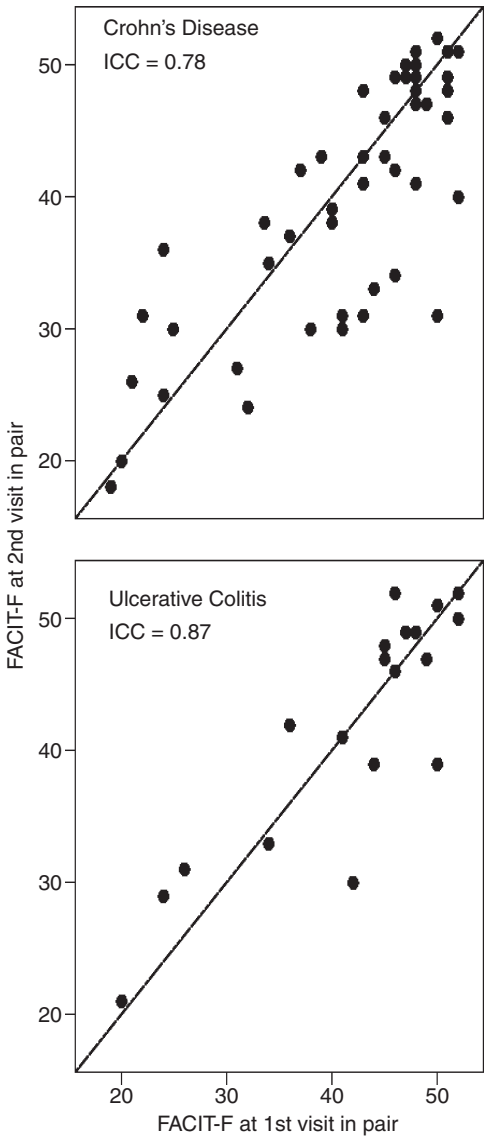

Figure 1 | Intraclass Correlation Coefficient (ICC) between FACIT-F assessments for CD (n = 47) and UC (n = 19) patients with FACIT-F assessments completed within 180 days of each other in patients in stable health.

(n = 66). The ICC was 0.78 for patients with CD (n = 47) and 0.87 for those with UC (n = 19).

Construct validity

The mean FACIT-F scores obtained from all IBD patients in this study was 38.9 [11.0], which was lower than what has been reported in the general population (43.6 [9.4], n = 1010, $P < 0.001$).[6] In CD, the FACIT-F correlated with the HBI at −0.49 (95% CI −0.61 to −0.35, $P \leq 0.001$). In UC, the correlation of the FACIT-F with the SCCAI was −0.59 (−0.72 to −0.41, $P \leq 0.001$).

In UC, FACIT-F scores correlated with ESR at −0.77 (95% CI −0.89 to −0.50, $P \leq 0.001$), CRP at −0.73 (95% CI −0.88 to −0.43, $P \leq 0.001$) and Haematocrit at 0.53 (95% CI 0.22–0.74, P = 0.001). In contrast, in Crohn's disease, there was no significant correlation with ESR (−0.02 95% CI −0.29 to 0.26, P = 0.92), CRP (−0.07 95% CI −0.33 to 0.22, P = 0.65) or with HCT (0.20 95% CI −0.04 to 0.41, P = 0.10) (Table 2).

Sensitivity to change

FACIT-F scores were lower in patients with active CD (−4.6 points, 95% CI −6.9 to −2.4, $P \leq 0.001$) and UC (−8.5 points, 95% CI −11.4 to −5.5, $P \leq 0.001$). Physician's assessments of change in patients' health corresponded closely to changes in FACIT-F scores (adjusted mean [95% CI], P-value: Much better = −11.8 [−15.9, −7.8] $P \leq 0001$, slightly better = −2.6 [−4.5, −0.7] P = 0.007, same = 0.7 [−0.3, 1.6] P = 0.17, slightly worse = +2.4 [0.9, 3.9] P = 0.002, much worse = +5.2 [3.2, 7.1] $P \leq 0001$). There was no difference between disease groups in the association between change in FACIT-F scores and PGA assessments (interaction P = 0.73).

DISCUSSION

In this study, we have demonstrated that a fatigue scale (FACIT-F) used in other disease populations is a reliable and valid instrument to measure fatigue in patients with CD and UC. In 2008, a study involving patients with CD used the FACIT-F to measure fatigue as a HRQOL outcome following biological therapy.[28] However, until now, the FACIT-F has not been validated in an IBD population.

We demonstrated that patients with UC and CD have lower FACIT-F scores and therefore experience more fatigue than the general population (38.9 vs. 43.6, $P < 0.001$).[6] A difference of 3–4 units is considered a minimal clinically important difference.[10, 29] The mean FACIT-F score in our outpatient population was higher than the FACIT-F score previously reported in patients with severe Crohn's disease receiving adalimumab as part of a clinical trial.[28] In addition, IBD patients in our study had higher FACIT-F scores (38.9 overall) than values reported in SLE (19.1), psoriatic arthritis (35.8) and anaemic patients with cancer (36.8).[6, 15, 25] While it remains possible that fatigue is more pronounced in these other conditions, some differences probably result from heterogeneity in disease severity at the time of evaluation, as only 16.7% of our study patients had active disease at their initial visit.

Internal consistency of the FACIT-F was excellent, with a Crohnbach alpha of 0.94 for UC and 0.95 for CD. This is similar to what has been reported in psoriatic arthritis and other chronic diseases in which the FACIT-F has been validated.[17, 22, 30, 31]

The FACIT-F scale was also stable, with an intraclass correlation coefficient (ICC) of 0.81 for all IBD patients. The ICC was lower than reported among patients with psoriatic arthritis (0.95) and cancer patients (0.90),

Table 2 | Correlations between the FACIT-F and ESR, CRP and HCT and disease activity (n = 209)

	UC (n = 77)	P-value	CD (n = 132)	P-value	Overall (n = 209)	P-value
ESR (mm/h)	−0.759 (−0.894 to −0.496)*	<0.001	−0.015 (−0.290 to 0.261)	0.915	−0.285 (−0.482 to −0.057)	0.014
CRP (mg/L)	−0.720 (−0.876 to −0.429)	<0.001	−0.065 (−0.334 to 0.215)	0.650	−0.189 (−0.401 to 0.044)	0.109
HCT (%)	0.525 (0.736 to 0.221)	<0.001	0.198 (−0.043 to 0.414)	0.104	0.327 (0.140–0.489)	<0.001
HBI	n.a.	n.a.	−0.494 (−0.614 to −0.349)	<0.001	n.a.	n.a.
SCCAI	−0.585 (−0.715 to −0.410)	<0.001	n.a.	n.a.	n.a.	n.a.

ESR, erythrocyte sedimentation rate; CRP, C-reactive protein; FACIT-F, Functional Assessment of Chronic Illness Therapy-Fatigue; HCT, haematocrit; HBI, Harvey-Bradshaw Index; n.a., not applicable; SCCAI, Simple Clinical Colitis Activity Index.

* 95% Confidence interval.

although this seems likely due to the much shorter test–retest interval in these samples (7 days vs. 180 in our sample).[6, 15] Interestingly, the ICC was higher for UC patients than for CD patients (0.87 vs. 0.78).

When their disease was active, as measured by clinical disease activity indices, the IBD patients in our study were more fatigued as evidenced by lower FACIT-F scores. This suggests that the FACIT-F is sensitive to clinical changes, an important component of construct validity. Although we addressed the issue using disease activity in a cross-sectional design, Loftus *et al.* previously evaluated this property of the scale as part of a longitudinal study on the effects of adalimumab on HRQOL in Crohn's disease patients.[28] Following induction therapy, mean FACIT-F scores increased by 11.9 points. While not the primary aim of their study, these findings do support the idea that this fatigue scale is sensitive to change following an intervention. Future studies designed to administer the FACIT-F before and after initiation of various treatments, with fatigue scores as the primary outcome are needed.

In our patients with inactive disease, the mean FACIT-F scores were 40.2 (95% CI 38.9–41.5) among CD patients and 42.2 (95% CI 40.4–44.1) among UC patients. For CD, this finding is consistent with other studies that have reported significantly higher levels of fatigue in IBD patients with quiescent disease than the general population[7] This may be the result of ongoing subclinical inflammatory activity and the limitations of IBD indices to accurately measure disease activity. It is also possible that, even in the absence of ongoing inflammation, persistent fatigue may remain in a subgroup of IBD patients.

ESR, CRP and HCT, serum blood tests that are often used as surrogate markers of disease activity were also shown to correlate with fatigue in ulcerative colitis. Surprisingly, in CD, there was no significant correlation between FACIT-F scores and ESR, CRP or HCT. This lack of correlation may reflect the inadequacy of these markers as indicators of active disease. However, it may suggest that in Crohn's disease, fatigue may be attributable to factors other than inflammation and anaemia such as depression, sleep disturbances or sarcopenia.[30, 31–34]

Overall, given our findings, we believe that FACIT-F is an ideal tool to assess fatigue in an IBD population. Although various fatigue scales have been used to evaluate patients with IBD before, this is the first time one has been specifically validated in a US IBD population. Ideally, instruments designed to measure HRQOL should be validated for a particular study population prior to their use. Compared with the validation of a different fatigue questionnaire in Norwegian IBD patients, the internal consistency of the FACIT-F scale was found to be slightly higher in our study (Cronbach's alpha of 0.96 vs. 0.89).[35] Both this fatigue questionnaire, developed by Chalder *et al.*, and the FACIT-F demonstrate good construct validity.[20, 35] However, the test–retest reliability of the fatigue questionnaire in IBD patients was not addressed in the study by Jelsness-Jørgensen and colleagues.[35]

While multiple other fatigue scales (both unidimensional and multidimensional) exist, the FACIT-F offers several advantages over other available measurement tools. As demonstrated in this study, it appears to be valid in an IBD population. To date, the FACIT-F questionnaire has been successfully translated into 48 languages (http://www.facit.org) according to rigorous methodology, permitting cross-cultural comparisons of fatigue in patients of diverse backgrounds.[36, 37] In addition, as the result of its use in over 70 published studies with over 20,000 people, the FACIT-F scale has now been incorporated into the US National Institutes of Health (NIH) initiative Patient Reported Outcomes Measurement Information System (PROMIS; http://www.nihpromis.org).[25] PROMIS is a questionnaire that contains item banks measuring various domains commonly seen in patients with chronic illness. A link between PROMIS and FACIT-F has been created, which allows FACIT-F scores to be converted to scores on the PROMIS. Ultimately, this allows clinicians to compare a patient's fatigue with that of the general population, as well as with patients with other chronic diseases.[38] The ability to carry out this type of comparison between patient groups argues strongly for the need to validate fatigue scales separately in individual disease states.

A limitation of our study is the inherent difficulty in measuring such a complex and subjective entity as fatigue. An important aspect of the validation process – assessing criterion validity – is severely limited by the lack of an accepted gold standard measure of fatigue. As such, we did not address this component of validity in our study. Some investigators have attempted to evaluate the criterion validity of particular fatigue scales by simply correlating scores with those obtained on other fatigue scales.[15] Finally, a potential drawback of using the FACIT-F questionnaire exclusively in future studies of IBD-associated fatigue relates to the unidimensional nature of the tool. We acknowledge that

well-constructed and appropriately validated multidimensional scales may offer additional insights into the various underlying components of IBD-associated fatigue. However, given its many strengths, we believe that the FACIT-F is an important instrument that can serve as a foundation for improving our understanding of fatigue in IBD patients.

IBD-associated fatigue continues to be extremely distressing to many patients. Although measuring fatigue in IBD patients is certainly improved with the utilisation of disease-specific validated scales, elucidating the key drivers of fatigue in UC and CD remains a considerable challenge. A pro-inflammatory state, anaemia, nutritional deficiencies, abnormalities in the hypothalamic-pituitary-axis (HPA), sleep abnormalities, depression, and medication side-effects have all been suggested as potential contributors.[20, 30, 35, 39] Future studies are needed to determine the potential and relative contributions of these and other factors to IBD-associated fatigue.

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APPENDIX A

FACIT fatigue scale (FACIT-F) Version 4

Below is a list of statements that other people with your illness have said are important**. Please circle or mark one number per line to indicate your response as it applies to the past 7 days.**

		Not at all	A little bit	Some-what	Quite a bit	Very much
HI7	I feel fatigued	0	1	2	3	4
HI12	I feel weak all over	0	1	2	3	4
An1	I feel listless ('washed out')	0	1	2	3	4
An2	I feel tired	0	1	2	3	4
An3	I have trouble starting things because I am tired	0	1	2	3	4
An4	I have trouble finishing things because I am tired	0	1	2	3	4
An5	I have energy	0	1	2	3	4
An7	I am able to do my usual activities	0	1	2	3	4
An8	I need to sleep during the day	0	1	2	3	4

APPENDIX A (CONTINUED)

		Not at all	A little bit	Some-what	Quite a bit	Very much
An12	I am too tired to eat	0	1	2	3	4
An14	I need help doing my usual activities	0	1	2	3	4
An15	I am frustrated by being too tired to do the things I want to do	0	1	2	3	4
An16	I have to limit my social activity because I am tired	0	1	2	3	4

FACIT-F scoring guidelines (Version 4)

Subscale	Item code	Reverse item?		Item response	Item score
FATIGUE SUBSCALE (FS)	HI7	4	–	_____	=_____
	HI12	4	–	_____	=_____
	An1	4	–	_____	=_____
	An2	4	–	_____	=_____
Score range: 0–52	An3	4	–	_____	=_____
	An4	4	–	_____	=_____
	An5	0	+	_____	=_____
	An7	0	+	_____	=_____
	An8	4	–	_____	=_____
	An12	4	–	_____	=_____
	An14	4	–	_____	=_____
	An15	4	–	_____	=_____
	An16	4	–	_____	=_____
				Sum individual item scores: _____	
				Multiply by 13: _____	
				Divide by number of items answered: _____**=F Subscale score**	

APPENDIX B

Physician's Global Assessment (PGA)

Question 1:	How would you rate your patient's health today with regard to their Crohn's disease or ulcerative colitis?
Very Well	0
Fair to Good	1
Poor	2
Very Poor	3
Question 2:	How would you rate your patient's health today with regard to their Crohn's disease or ulcerative colitis in comparison with their previous visit?
Much better	+2
Slightly better	+1
Same	0
Slightly worse	–1
Much worse	–2

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