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Fatigue in Newly Diagnosed Inflammatory Bowel Disease

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Abstract

Background and Aims: The present study investigated the prevalence and severity of fatigue in patients with newly diagnosed and untreated ulcerative colitis (UC) and Crohn's disease (CD) and examined relevant disease variables that may influence the severity of fatigue.
Methods: Eighty-one patients with inflammatory bowel disease (IBD) (60 with UC and 21 with CD) were assessed for fatigue using two fatigue instruments: the Fatigue Severity Scale (FSS) and a fatigue visual analogue scale (fVAS). Cut-off for fatigue was defined as ≥4 for FSS and ≥50 for fVAS. Results were compared with fatigue scores from age-and gender-matched healthy individuals. Disease activity was assessed by symptom scores using the Mayo score in UC patients and the Harvey–Bradshaw index for CD patients, as well as C-reactive protein (CRP) and faecal calprotectin.
Results: The prevalence of fatigue based on FSS and fVAS was 47 and 42%, respectively, in UC and 62 and 48% in CD. In multivariate regression models, disease activity markers were not associated with fatigue, while a significant relationship was found with age and depression for both fatigue measures.
Conclusions: Close to 50% of patients with IBD reported fatigue at the time of diagnosis. In newly diagnosed patients with active disease, the severity of fatigue was not associated with measures of disease activity.

Key Words: Fatigue; IBD

1. Introduction

Fatigue is increasingly recognized as a substantial phenomenon in many chronic inflammatory diseases, including inflammatory bowel disease (IBD), rheumatoid arthritis and primary Sjøgren's syndrome.[1] Fatigue can be described as an overwhelming sense of tiredness, lack of energy and feeling of exhaustion that is unaffected by prolonged rest.[2] Fatigue is a non-specific, subjective phenomenon that may interfere with emotional, physical and social functions, often leading to social withdrawal and decreased ability to work.[3]

Recent reviews point to chronic fatigue as being highly overlooked in IBD, and only a few published studies have included fatigue as a primary outcome.[4,5] Fatigue is a major concern for IBD patients,[6] with some data indicating that 40–80%[7,8] of patients with active intestinal inflammation experience fatigue. Notably, 20–40%[9,10] still report fatigue when in remission from IBD, despite the absence of signs of intestinal inflammation.

Physical and psychological factors have been reported in relation to fatigue in IBD. The most frequently discussed associations are disease activity, anaemia, anxiety and depression, but the mechanisms

underlying these relationships are still unknown. Also, the management of fatigue in IBD is far from clear.[5]

The aim of the present study was to describe the prevalence and degree of fatigue in a cohort of newly diagnosed and untreated UC and CD patients compared with matched healthy subjects. In addition, we wanted to explore the possible associations between fatigue and depression and/or markers of disease activity.

2. Methods

2.1. Patients

Patients newly diagnosed with IBD were recruited consecutively from the Department of Gastroenterology at Stavanger University Hospital from 1 April 2012 until 31 December 2013. The inclusion criteria were age >16 years and newly diagnosed IBD. Diagnosis of IBD was made after combined clinical, laboratory, endoscopic, histological and radiological evaluation according to international criteria (ECCO guidelines).[11,12] The exclusion criteria were previously diagnosed IBD, receiving specific treatment within the last 10 years and inability to adhere to the treatment protocol. Patients were included at the time of the index colonoscopy and all study data were collected and recorded within 3 days of the colonoscopy. A total of 81 patients (46 males, 35 females) were included in the study, which was registered at ClinicalTrials.gov (NCT01551563).

2.2. Healthy subjects

The control group consisted of 67 subjects with no medical complaints who volunteered to fill out the fatigue visual analogue scale (fVAS) and Fatigue Severity Scale (FSS) questionnaires. The healthy subjects were age- and gender-matched with the patients. To reduce the number of control subjects, some individuals served as controls for both UC and CD cases.

2.3. Fatigue assessment

We used the generic fVAS and the FSS instruments[13] to assess fatigue severity. The FSS is a unidimensional fatigue instrument in which the patient responds to nine items, each with a score of 1–7. The FSS score is the mean score of the nine items, and a higher FSS score indicates more fatigue. An FSS score of 3 or 4 has previously been used as cut-off for fatigue, and ≥4 was used in this study as a conservative approach.[14] The fatigue VAS was a 100-mm horizontal line with vertical anchors. The wording on the left end (0 mm) was 'No fatigue' and that on the right end (100 mm) was 'Fatigue as bad as it can be'. The presence of fatigue was defined as an fVAS score ≥50 mm.[15] To assess a concomitant depressive state we applied the Hospital Anxiety and Depression Scale (HADS).[16] The HADS consists of 14 items, seven each for depression (HADS-D) and anxiety (HADS-A). The patients give each item a number from 0 to 3, and the scores are summed to obtain the anxiety and depression subscales. An HADS-D score ≥8 was previously found to be adequate as a cut-off for depression and was used in this study.[17]

2.4. Evaluation of disease activity

For the symptomatic assessment of IBD disease activity at the time of diagnosis, we used the Mayo score (MS) for UC patients. This score evaluates four items: stool frequency, blood content, the physician's estimate of disease activity and endoscopic inflammation.[18] An MS of >2 and/or an endoscopic subscore of >1 was regarded as active disease. The Harvey–Bradshaw index (HBI) was applied to evaluate symptoms in CD patients. The index incorporates an assessment of general well-being, abdominal pain, and the number of loose stools the previous day, in addition to the presence of a palpable mass in the abdomen and extra-intestinal manifestations, such as arthralgia, fistula and abscesses.[19] An HBI of ≥5 was regarded as active disease.

2.5. Inflammatory markers

At the time of diagnosis, serum C-reactive protein (CRP) (±3 days) and faecal calprotectin (until 4 weeks before and 3 days after diagnosis) were measured in all patients. A CRP level ≥ 5 μg/mL and faecal calprotectin ≥50 mg/kg were regarded as abnormal and suggestive of inflammatory activity.

2.6. Other blood variables

Haemoglobin and ferritin were measured at the time of diagnosis ±3 days and analysed at the hospital's routine laboratory. Iron deficiency was defined as ferritin <30 μg/L if CRP was <5 mg/L or ferritin <100 μg/L if CRP was ≥5 mg/L.[20] As ferritin is an acute-phase protein, cut-off levels for iron deficiency were adjusted in relation to CRP values.

2.7. Outcome measures

Fatigue scores were compared between patients and healthy controls. The prevalence of fatigue, as measured by fVAS and FSS, in the IBD population was calculated using the designated cut-offs for the respective scales. A conservative overall prevalence of fatigue is reported based on the number of patients with results above the cut-off values for fVAS or FSS.

2.8. Statistical analysis

The normality of the data was tested using the Shapiro–Wilk test. To compare UC and CD patients with healthy subjects, continuous, normally distributed data were analysed by the paired *t*-test and non-normally distributed data by the Wilcoxon rank test. To compare the total IBD group with healthy subjects, the Mann–Whitney rank test for unpaired samples was used. For discrete data, Spearman's χ^2 test was applied. When establishing regression models for fatigue, variables presumed to influence fatigue were used for UC (MS, CRP, faecal calprotectin), CD (HBI, CRP, faecal calprotectin) and total IBD (CRP, faecal calprotectin, ferritin, HADS-D) and tested by age- and sex-adjusted linear regression. Based on the results of these regression analyses, a fully adjusted model was established for fatigue in the total IBD group. Variables with $p \leq 0.25$ in age- and sex-adjusted analyses were included in the fully adjusted model. We considered $p < 0.05$ as significant. Analyses were performed using IBM SPSS statistical software version 21.

2.9. Ethical considerations

The study was approved by the regional ethics committee and carried out in compliance with the principles expressed in the Declaration of Helsinki. All patients provided written informed consent to participate in the study.

3. Results

3.1. Patient characteristics

Ninety-four patients were potentially eligible for study. Ten patients were not included due to lack of personnel, and thus 84 patients were examined for eligibility. One patient was excluded due to psychiatric illness and inability to adhere to the treatment protocol, and two were excluded due to treatment for IBD within the last 10 years.

A total of 81 consecutive patients (46 males, 35 females) were thus included in the study, 60 with UC and 21 with CD. Sixty-seven age- and gender-matched controls with a median (range) age of 34 (15–73) years were included.

The patient characteristics are given in Table 1. There were no missing data. Twenty-nine (48%) of the UC patients and 12 (57%) of the CD patients were iron-deficient. Anaemia was defined as haemoglobin ≤13.4 g/L in males and ≤11.7 g/L in females. Fourteen (23%) of the UC patients and 4 (19%) of the CD patients were anaemic. Fifteen (19%) of the IBD patients were depressed.

3.2. Fatigue

Patients with UC and CD had significantly higher fatigue scores than age- and gender-matched healthy subjects based on both fVAS and FSS (Figures 1 and 2).

Similarly, when comparing all IBD patients with all control subjects, a significantly higher degree of fatigue was found in IBD patients, as measured by both fVAS and FSS (Figure 3A, B). The prevalence of fatigue is given in Table 2.

3.3. Associations between fatigue and disease activity

Age- and sex-adjusted analyses revealed no significant associations between fVAS or FSS scores and MS, CRP or faecal calprotectin in UC patients. Also, no significant associations were found between fVAS or FSS scores and HBI, CRP or faecal calprotectin in the age- and gender-adjusted model for CD (Table 1, Supplementary Data). However, for both UC and CD the FSS increased with elevated symptom scores and faecal calprotectin, although not reaching significance (data not shown).

In the age- and gender-adjusted analyses for the total IBD cohort, fVAS scores from the initial analyses were associated with CRP, ferritin and HADS-D, whereas FSS scores were associated with faecal calprotectin and HADS-D (Table 3). Five patients (three with UC, two with CD) were considered as outliers based on the scatterplot of standard residuals and were excluded from further analyses.

The fully adjusted model for the total IBD group revealed that neither CRP (p = 0.372) nor ferritin (p = 0.101) influenced the fVAS scores. Also, FSS scores were not influenced by faecal calprotectin (p = 0.525) (Table 4). As expected, HADS-D and age were significantly associated with fVAS (p < 0.001 and p = 0.001, respectively) and FSS scores (p < 0.001 and p = 0.02, respectively). Higher HADS-D scores and decreased age were associated with higher fatigue levels (Table 4).

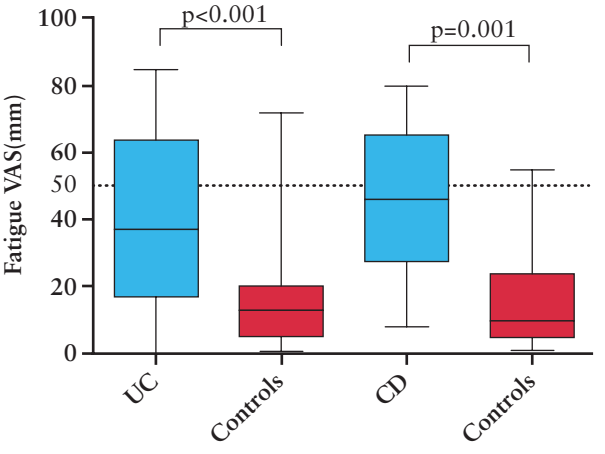

Figure 1. Fatigue VAS measured in 60 UC and 21 CD patients compared with equal numbers of age- and gender-matched healthy subjects. Medians and the 25th and 75th percentiles are shown. Whiskers indicate range. The dotted line indicates the cut-off for significant fatigue. VAS, visual analogue scale; UC, ulcerative colitis; CD, Crohn's disease.

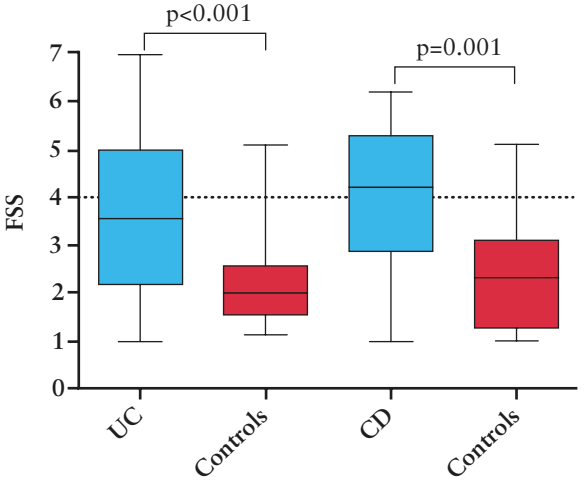

Figure 2. FSS measured in 60 UC and 21 CD patients compared with equal numbers of age- and gender-matched healthy subjects. Medians and 25th and 75th percentiles are shown. Whiskers indicate range. The dotted line indicates the cut-off for significant fatigue. FSS, Fatigue Severity Scale; UC, ulcerative colitis; CD, Crohn's disease.

Table 1. Demographic and clinical characteristics of 81 patients with ulcerative colitis (UC) and Crohn's disease (CD).

	UC (n = 60)	CD (n = 21)	Total (n = 81)
Age, years	34 (17–71)	22 (17–72)	31 (17–72)
Males	37 (62)	9 (43)	46 (57)
Ferritin, µg/L	82 (7–667)	56 (7–1382)	71 (7–1382)
Haemoglobin, g/L	13.6 (1.6)	13.9 (1.6)	13.5 (1.6)
C-reactive protein, mg/L	9.5 (1–130)	9.1 (1–139)	9.4 (1–139)
Faecal calprotectin, mg/kg	634 (21–3216)	400 (45–1409)	615 (21–3216)
HBI	NA	5 (1–16)	NA
MS	7 (1–11)	NA	NA

Results are presented as n (%) for males, mean (SD) for haemoglobin, and median and range for other variables.
HBI, Harvey–Bradshaw index; MS, Mayo score; NA, not applicable.

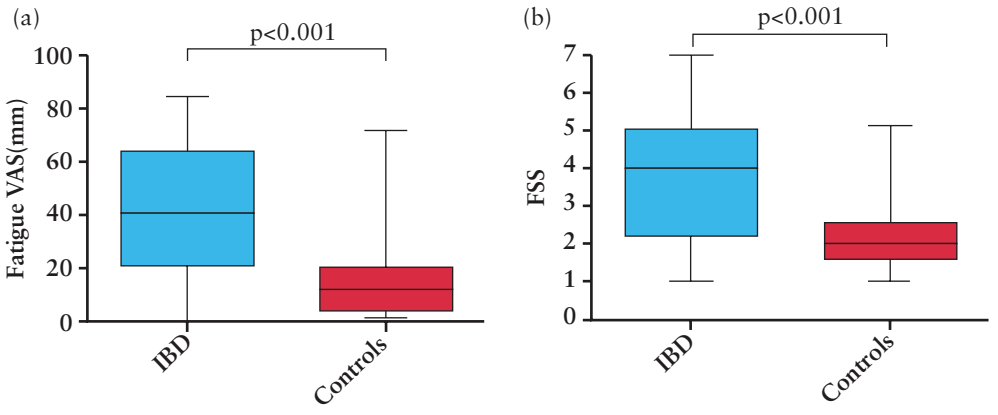

Figure 3. Fatigue VAS (A) and FSS (B) measured in the total IBD group (UC and CD; $n = 81$) compared to 67 age- and gender-matched healthy subjects. Medians and 25th and 75th percentiles are shown. Whiskers indicate range. VAS, visual analogue scale; FSS, Fatigue Severity Scale; IBD, inflammatory bowel disease; UC, ulcerative colitis; CD, Crohn's disease.

Table 2. Prevalence of fatigue[a] in UC ($n = 60$) and CD ($n = 21$) patients compared with age- and gender-matched healthy controls ($n = 67$).

	FSS score		*p*-value[b]	fVAS score		*p*-value[b]
	≥4	<4		≥50 mm	<50 mm	
UC	28 (46.7)	32 (53.3)	<0.001	25 (41.7)	35 (58.3)	<0.001
Healthy subjects	4 (6.7)	56 (93.3)		1 (1.7)	59 (98.3)	
CD	13 (61.9)	8 (38.1)	<0.001	10 (47.6)	11 (52.4)	0.002
Healthy subjects	2 (9.5)	19 (90.5)		1 (4.8)	20 (95.2)	
All IBD patients	41 (50.6)	40 (49.4)	<0.001	35 (43.2.)	46 (56.8)	<0.001
Healthy subjects	4 (6.0)	63 (94)		2 (3.0)	65 (97)	

Data are *n* (%).

Some healthy individuals were used as controls for both UC and CD patients.

[a]Defined as FSS score ≥4 or fVAS ≥ 50 mm.

[b]Differences between patients and controls were analysed by the Pearson χ^2 test.

FSS, Fatigue Severity Scale; fVAS, fatigue visual analogue scale; IBD, inflammatory bowel disease.

Table 3. Age- and sex-adjusted regression analyses for the total IBD group ($n = 76$).[a]

	fVAS			FSS		
	β	R^2	*p*-value	β	R^2	*p*-value
CRP	0.15	0.06	0.24	<0.01	0.04	0.27
Faecal calprotectin	<0.01	0.06	0.27	<0.01	0.05	0.15
Ferritin	0.05	0.07	0.13	<0.01	0.02	0.89
HADS-D	4.56	0.44	<0.001	0.32	0.46	<0.001

[a]Five patients were excluded as outliers.

IBD, inflammatory bowel disease; fVAS, fatigue visual analogue scale; FSS, Fatigue Severity Scale; CRP, C-reactive protein; HADS-D, Hospital Anxiety and Depression Scale depression subscale.

4. Discussion

The main finding in this study is that approximately 50% of patients with IBD suffer from fatigue at the time of diagnosis and that traditional disease activity measures are not associated with this phenomenon. Using conservative cut-offs, the prevalence of fatigue in UC patients is 47% based on the FSS and 42% based on the fVAS. In patients with CD, fatigue is reported by 62% and 48% of patients on the FSS and fVAS, respectively. The percentages are considerably higher than in the healthy subjects, as fatigue was reported by 10% at the most. This difference demonstrates that fatigue is a prevalent and serious problem for patients suffering from IBD. The severity and prevalence of fatigue in newly diagnosed IBD is comparable to that of primary Sjøgren's syndrome and rheumatoid arthritis, and considerably more effort has been put into exploring these issues.[21,22]

A higher prevalence of fatigue in IBD patients compared with healthy individuals has previously been reported,[10] but the use of fatigue as a primary outcome has not been widely investigated. This is the first report of fatigue in an IBD cohort consisting of only newly diagnosed patients not receiving anti-inflammatory or immune-modulating medication.

The reported prevalence of fatigue in previous studies has varied from 41% in patients in remission to 86% in CD patients with active disease,[8,23] and from 44 to 64% in patients with different disease activity.[7,24] In the current study, disease activity ranged from mild to severe, and the reported fatigue was in line with studies in cohorts involving various grades of disease activity.

The disease activity of IBD (active disease as opposed to remission) has been reported to influence fatigue in the majority of previous studies,[8,10,25,26] but we could not confirm these observations. This might be expected, as all patients had active disease. Although the FSS increased with increased signs of inflammation, as measured by symptom scores and faecal calprotectin, these differences did not reach statistical significance (data not shown). Fatigue may be markedly different between patients in remission and those with active disease, but in newly diagnosed patients with active inflammatory disease the association between disease activity and fatigue could be

Table 4. Final and optimal multiple regression model for the total IBD group ($n = 76$)[a]

	fVAS		FSS	
	β	p-value	β	p-value
CRP	0.09	0.37	NA	NA
Calprotectin	NA	NA	<0.01	053
Ferritin	0.04	0.1	NA	NA
HADS-D	4.5	<0.001	4.52	<0.001
Age	–0.47	0.001	–0.34	0.02
Gender	4.66	0.32	0.95	0.84

Adjusted R^2 0.47 for fVAS and 0.433 for FSS.

[a]Five patients were excluded as outliers.

IBD, inflammatory bowel disease; fVAS, fatigue visual analogue scale; FSS, Fatigue Severity Scale; CRP, C-reactive protein; HADS-D, Hospital Anxiety and Depression scale depression subscale; NA, not applicable.

less distinct. Studies showing that patients devoid of IBD activity still experience fatigue, as well as a number of studies in other inflammatory diseases, also suggest that disease activity alone cannot explain fatigue.[27–29] In addition, the use of generic versus disease-specific fatigue instruments, different patient cohorts and different settings may have influenced the results. Thus, we deliberately employed generic and unidimensional fatigue instruments (FSS and fVAS) that could not be influenced by disease-specific symptoms, clinical findings or laboratory variables.

The biological mechanism of fatigue remains unclear, but increasing evidence indicates that fatigue is a preserved behavioural response to inflammation and immunological danger.[30] Activation of the immune system induces the production of pro-inflammatory cytokines, as well as protective molecules, which trigger an adaptive and evolutionarily conserved behavioural response (i.e. sickness behaviour). Traditional measures of disease activity are likely not to be sensitive enough to capture the fine balance between pro-inflammatory and protective molecules that signal sickness behaviour and, ultimately, fatigue development. Based on the results from our study, the fatigue response is independent of the grade of intestinal inflammation and may be signalled through other pathways.

Other factors that may contribute to fatigue are anaemia and iron deficiency,[31,32] but we did not reveal any association between fatigue and haemoglobin or ferritin levels in this study, which is in line with other recent studies.[7,33]

The relationship between fatigue and depression is well known, but it is a complicated issue. Instruments and methods used for fatigue and depression often have similarities in wording and probably overlap in comprehension, tapping shared dimensions or domains. This may lead to circular reasoning and false conclusions regarding relationships. In addition, elements of depression and sickness behaviour/fatigue are signalled in the brain through shared biological pathways, such as the interleukin-1 system.[34,35] Age was negatively associated with both measures for fatigue. This is in line with recent findings,[36] although the results in that study were from IBD patients in remission.

The choice of a fVAS cut-off of ≥50 mm could be debated. Although this cut-off has been used in previous studies, the dichotomization of *fatigue* and *no fatigue* is artificial. Complex biological phenomena such as fatigue cannot easily be divided into a yes/no response. However, the prevalence obtained with the fVAS matches the results from FSS well.

This study has some limitations. The CD cohort consisted of only 21 patients, which reduces the statistical power. We used the generic and unidimensional FSS and fVAS to measure fatigue, which makes it impossible to directly compare our results with previous IBD studies that employed other fatigue instruments. Further testing of cut-off points for fatigue is recommended in future studies.

On the other hand, the choice of newly diagnosed and untreated patients strengthens the conclusions, as treatment with biologicals is reported to influence fatigue.[8] Therefore, to the best of our knowledge, this is the first report of fatigue prevalence in a newly diagnosed, untreated IBD cohort.

In summary, fatigue was found in nearly 50% of patients with newly diagnosed, active and untreated IBD, significantly more than among healthy individuals. In this population, significant associations were not detected between fatigue and markers of disease activity, haemoglobin or ferritin.

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Conflict of Interest

The authors report no conflicts of interest.

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Author Contributions

Study concept and design: TG, LA, RO, LNK. Acquisition of data: TG, KI, KL, AC, AKH, LNK, IMS, LG, EH, LA. Analysis and interpretation of data: TG, KBN, RO. Drafting the manuscript: TG, KBN, LA, RO, KI, KL. Critical revision of the manuscript and approval of final manuscript: all authors.

References

1. Parrish BP, Zautra AJ, Davis MC. The role of positive and negative interpersonal events on daily fatigue in women with fibromyalgia, rheumatoid arthritis, and osteoarthritis. *Health Psychol* 2008;**27**:694–702.
2. Krupp LB, Pollina DA. Mechanisms and management of fatigue in progressive neurological disorders. *Curr Opin Neurol* 1996;**9**:456–60.
3. Norheim KB, Jonsson G, Omdal R. Biological mechanisms of chronic fatigue. *Rheumatology (Oxford)* 2011;**50**:1009–18.
4. van Langenberg DR, Gibson PR. Systematic review: fatigue in inflammatory bowel disease. *Aliment Pharmacol Ther* 2010;**32**:131–43.
5. Czuber-Dochan W, Ream E, Norton C. Review article: Description and management of fatigue in inflammatory bowel disease. *Aliment Pharmacol Ther* 2013;**37**:505–16.
6. Casati J, Toner BB, de Rooy EC, *et al*. Concerns of patients with inflammatory bowel disease: a review of emerging themes. *Dig Dis Sci* 2000;**45**:26–31.
7. Bager P, Befrits R, Wikman O, *et al*. Fatigue in out-patients with inflammatory bowel disease is common and multifactorial. *Aliment Pharmacol Ther* 2012;**35**:133–41.
8. Minderhoud IM, Samsom M, Oldenburg B. Crohn's disease, fatigue, and infliximab: is there a role for cytokines in the pathogenesis of fatigue? *World J Gastroenterol* 2007;**13**:2089–93.

9. Minderhoud IM, Oldenburg B, van Dam PS, *et al*. High prevalence of fatigue in quiescent inflammatory bowel disease is not related to adrenocortical insufficiency. *Am J Gastroenterol* 2003;**98**:1088–93.
10. Jelsness-Jorgensen LP, Bernklev T, Henriksen M, *et al*. Chronic fatigue is more prevalent in patients with inflammatory bowel disease than in healthy controls. *Inflamm Bowel Dis* 2011;**17**:1564–72.
11. Dignass A, Eliakim R, Magro F, *et al*. Second European evidence-based consensus on the diagnosis and management of ulcerative colitis. Part 1: definitions and diagnosis. *J Crohns Colitis* 2012;**6**:965–90.
12. Van Assche G, Dignass A, Panes J, *et al*. The second European evidence-based Consensus on the diagnosis and management of Crohn's disease: definitions and diagnosis. *J Crohns Colitis* 2010;**4**:7–27.
13. Krupp LB, LaRocca NG, Muir-Nash J, *et al*. The fatigue severity scale. Application to patients with multiple sclerosis and systemic lupus erythematosus. *Arch Neurol* 1989;**46**:1121–3.
14. Keyser RE, Rus V, Cade WT, *et al*. Evidence for aerobic insufficiency in women with systemic lupus erythematosus. *Arthritis Rheum* 2003;**49**:16–22.
15. Pollard LC, Choy EH, Gonzalez J, *et al*. Fatigue in rheumatoid arthritis reflects pain, not disease activity. *Rheumatology (Oxford)* 2006;**45**:885–9.
16. Zigmond AS, Snaith RP. The hospital anxiety and depression scale. *Acta Psychiatr Scand* 1983;**67**:361–70.
17. Olsson I, Mykletun A, Dahl AA. The Hospital Anxiety and Depression Rating Scale: a cross-sectional study of psychometrics and case finding abilities in general practice. *BMC Psychiatry* 2005;**5**:46.
18. Schroeder KW, Tremaine WJ, Ilstrup DM. Coated oral 5-aminosalicylic acid therapy for mildly to moderately active ulcerative colitis. A randomized study. *N Engl J Med* 1987;**317**:1625–9.
19. Harvey RF, Bradshaw JM. A simple index of Crohn's-disease activity. *Lancet* 1980;**1**:514.
20. Gasche C, Berstad A, Befrits R, *et al*. Guidelines on the diagnosis and management of iron deficiency and anemia in inflammatory bowel diseases. *Inflamm Bowel Dis* 2007;**13**:1545–53.
21. Haldorsen K, Bjelland I, Bolstad AI, *et al*. A five-year prospective study of fatigue in primary Sjogren's syndrome. *Arthritis Res Ther 20* 11;**13**:R167.
22. Wolfe F, Hawley DJ, Wilson K. The prevalence and meaning of fatigue in rheumatic disease. *J Rheumatol* 1996;**23**:1407–17.
23. Bjornsson E, Simren M, Olsson R, *et al*. Fatigue in patients with primary sclerosing cholangitis. *Scand J Gastroenterol* 2004;**39**:961–8.
24. Romkens TE, van Vugt-van Pinxteren MW, Nagengast FM, *et al*. High prevalence of fatigue in inflammatory bowel disease: A case control study. *J Crohns Colitis* 2011;**5**:332–7.
25. Graff LA, Clara I, Walker JR, *et al*. Changes in fatigue over 2 years are associated with activity of inflammatory bowel disease and psychological factors. *Clin Gastroenterol Hepatol* 2013;**11**:1140–6.
26. Romberg-Camps MJ, Bol Y, Dagnelie PC, *et al*. Fatigue and health-related quality of life in inflammatory bowel disease: results from a population-based study in the Netherlands: the IBD-South Limburg cohort. *Inflamm Bowel Dis* 2010;**16**:2137–47.
27. van Hoogmoed D, Fransen J, Bleijenberg G, *et al*. Physical and psychosocial correlates of severe fatigue in rheumatoid arthritis. *Rheumatology (Oxford)* 2010;**49**:1294–1302.
28. Ng WF, Bowman SJ. Primary Sjogren's syndrome: too dry and too tired. *Rheumatology (Oxford)* 2010;**49**:844–53.
29. Wang B, Gladman DD, Urowitz MB. Fatigue in lupus is not correlated with disease activity. *J Rheumatol* 1998;**25**:892–95.
30. Dantzer R, O'Connor JC, Freund GG, *et al*. From inflammation to sickness and depression: when the immune system subjugates the brain. *Nat Rev Neurosci* 2008;**9**:46–56.
31. Gasche C, Lomer MC, Cavill I, *et al*. Iron, anaemia, and inflammatory bowel diseases. *Gut* 2004;**53**:1190–7.
32. Stein J, Dignass AU. Management of iron deficiency anemia in inflammatory bowel disease - a practical approach. *Ann Gastroenterol* 2013;**26**:104–113.
33. Goldenberg BA, Graff LA, Clara I, *et al*. Is iron deficiency in the absence of anemia associated with fatigue in inflammatory bowel disease? *Am J Gastroenterol* 2013;**108**:1392–7.
34. Goshen I, Kreisel T, Ben-Menachem-Zidon O, *et al*. Brain interleukin-1 mediates chronic stress-induced depression in mice via adrenocortical activation and hippocampal neurogenesis suppression. *Mol Psychiatry* 2008;**13**:717–28.
35. Lawson MA, McCusker RH, Kelley KW. Interleukin-1 beta converting enzyme is necessary for development of depression-like behavior following intracerebroventricular administration of lipopolysaccharide to mice. *J Neuroinflammation* 2013;**10**:54.
36. Pellino G, Sciaudone G, Caserta V, *et al*. Fatigue in inflammatory bowel diseases: relationship with age and disease activity. *International Journal of Surgery* 2014;**12** Suppl 2:S60–63