Fatigue in inflammatory bowel disease

BACKGROUND Inflammatory bowel disease is comprised mainly of ulcerative colitis and Crohn's disease. The prevalence of fatigue and its associations with different cofactors vary between studies. The aim of this article is to describe the extent of fatigue in inflammatory bowel disease, the factors that are most commonly associated with fatigue, and its treatment. We will also discuss challenges for future research on fatigue in inflammatory bowel disease.

METHOD We conducted literature searches in the Ovid Medline and The Cochrane Library databases using combinations of the keywords «inflammatory bowel diseases», «inflammatory bowel disease*», «IBD», «crohn*», «colitis», «fatigue», «fatigue manage» and «fatigue treat». The search was limited to articles published in the period 2000–15.

RESULTS Of the 156 articles identified, 28 were included in the review. Collectively, the studies used 13 different instruments for measuring fatigue and 11 measures of disease activity. Fatigue occurs more frequently in those who suffer from inflammatory bowel disease (22–77 %) than in the general population (2–12 %). Active disease and depression are associated with higher levels of fatigue.

INTERPRETATION Fatigue is a significant problem in inflammatory bowel disease. The use of differing measures of fatigue and of disease activity in heterogeneous study populations has contributed to variability in data on prevalence and possible risk factors.

Tore Grimstad
tore.bjorn.grimstad@sus.no
Department of Gastroenterology
Stavanger University Hospital

Katrine Brække Norheim
Division of Clinical Immunology
Stavanger University Hospital

MAIN POINTS

Fatigue is more common in patients with inflammatory bowel disease than in healthy persons and represents a significant problem

Active disease and depression are often associated with fatigue

The causes and optimal treatment of fatigue in inflammatory bowel disease remain unclear

Inflammatory bowel disease is comprised mainly of ulcerative colitis and Crohn's disease – both of which are chronic inflammatory conditions that often present in early adulthood and have a relapsing-remitting course. Typical symptoms include bloody diarrhoea, abdominal pain and weight loss (1).

Many in this patient population report significant problems with fatigue (2). «Fatigue» can be defined as an overwhelming feeling of tiredness, exhaustion and lack of energy (3). It is seen commonly in a number of chronic inflammatory diseases, affecting quality of life (4) and in many cases reducing the capacity to work (5).

The pathogenesis of fatigue is only partially understood. One leading hypothesis is that it is part of an evolutionarily conserved defence mechanism triggered by acute infection or inflammation (6). The response includes fatigue, loss of initiative, anorexia and passive, withdrawn behaviour – so-called sickness behaviour. The purpose of this mechanism is to promote recovery and rehabilitation after illness (6).

Investigations into the causes of sickness behaviour have focused largely on immunological mechanisms. Pro-inflammatory signalling molecules (cytokines) such as interleukin-1β and tumour necrosis factor-α are activated upon inflammation. Interleukin-1β has been linked to fatigue in both animal experiments and human studies (7). Tumour necrosis factor-α may also be implicated in fatigue as medications that block this inflammatory factor appear to reduce fatigue in rheumatoid arthritis and possibly in inflammatory bowel disease (8). Genetic and epigenetic factors additionally contribute to the development and regulation of fatigue (7).

A number of other factors, such as pain, depression and psychosocial conditions, may modify or exacerbate fatigue (7). Depression is the strongest predictor of fatigue, but the condition also occurs in patients without additional comorbidities (7).

To date, fatigue has been studied most often in the context of rheumatic diseases, cancer and chronic fatigue syndrome/myalgic encephalomyelitis. However, in recent years, increasing numbers of studies have been published on fatigue in inflammatory bowel disease; a topic of interest to both patients and clinicians. The aim of this review is to describe the prevalence of fatigue in inflammatory bowel disease, to summarise existing knowledge on the relationship between fatigue, disease activity and other factors, and to outline the treatment strategies available. Methods of recording fatigue will also be discussed and suggestions made for improving future research in the field.

Method

We searched Ovid Medline and The Cochrane Library databases with the keywords «inflammatory bowel diseases», «inflammatory bowel disease*», «IBD», «crohn*», «colitis», «fatigue», «fatigue manage» and «fatigue treat», and combinations thereof. The search was limited to English-language articles that included adult patients and that were published between 1 January 2000 and

12 June 2015. Review articles and purely methodological papers were excluded. We obtained 164 hits after searches in Ovid Medline and 103 hits after searches in The Cochrane Library. Twenty-one articles were present in both databases, of which eight were deemed relevant. The relevance of articles was evaluated on the basis of the title and abstract.

Both authors read 35 full-text articles and their associated reference lists. Three articles were included from our own literature archives. Twenty-one articles that examined the prevalence of fatigue in inflammatory bowel disease were included in Table 1 (9–29). A further three qualitative studies and four articles on treatment were included in the review, giving 28 articles in total. Criteria for the selection of quantitative studies were the number of patients ($n \geq 50$) and the inclusion of a measure of disease activity.

Measuring fatigue in inflammatory bowel disease

Fatigue is a subjective phenomenon, and objective measures (for example, eyeblinks or stride length) correlate poorly with subjective ratings (30). Self-report measures should therefore be used for the assessment of fatigue. There are a number of such instruments available, including one recently developed scale that is specific to inflammatory bowel disease (31), as well as generic scales that can be used in several different disorders.

The instruments can be further categorised on the basis of the number of disease dimensions measured: unidimensional instruments record a single component of fatigue; multidimensional instruments divide fatigue into, for example, physical and mental or cognitive dimensions (32).

Prevalence of fatigue in inflammatory bowel disease

Twenty-one studies examined the prevalence of fatigue in inflammatory bowel disease. The study populations varied markedly, both in terms of number of patients (from 52 (33) to 10 634 (16)), the types of disease included, and whether or not patients were compared with controls (Table 1) (9–29). The majority of studies enrolled patients in a clinical context, although the study with the most participants obtained data from a patient registry and telephone interviews. Three articles were based on the same patient cohort (21, 34, 35), and therefore only one of these (21) was included in the review (Table 1).

Seven of the 21 studies reported data for ulcerative colitis and Crohn's disease separately. Fatigue seemed to be somewhat more prevalent in Crohn's disease (29–77 %) than in ulcerative colitis (22–69 %). All studies that included healthy control subjects or that made comparisons with the general population reported increased prevalence of fatigue in inflammatory bowel disease (Table 1) (9–29).

Disease activity

Eighteen studies examined the relationship between fatigue and disease activity (Table 1), including 13 cross-sectional studies. Twelve detected a (positive) association.

The majority of studies included patients with both active and inactive disease (remission), while three studies (27–29) included only patients in remission. In one study, disease activity was associated with fatigue in Crohn's disease, but not in ulcerative colitis (10).

Other factors associated with fatigue

Depression is more common in persons with inflammatory bowel disease than in the general population (36) and was the factor most frequently associated with fatigue in the current set of articles. Four studies (9, 10, 13, 28) evaluated the relationship between depression and fatigue, and all demonstrated a significant positive association. Other factors examined were closely linked to depression, such as disease-related worries, anxiety, stress and psychosocial conditions (13, 15, 19, 21, 34).

Anaemia is known to cause fatigue in other disorders, at least when severe. In the current set of articles, haemoglobin levels/anaemia were associated with fatigue in four studies (14, 18, 21, 24), whereas eight (9, 11, 15, 17, 19, 20, 26, 27) found no such association.

Quality of life and fatigue

Three qualitative studies (33, 37, 38) containing a total of 84 patients examined the impact of fatigue on quality of life, and all three concluded that quality of life was reduced.

Treatment of fatigue

No pharmaceutical studies were identified with changes in fatigue as the primary endpoint. Three studies that evaluated the efficacy of TNF inhibitors in Crohn's disease included fatigue as a secondary endpoint (8, 39, 40).

One study was single blind and included 14 patients who received placebo followed by infliximab fourteen days later. The placebo induced a transient, significant reduction in fatigue, whereas a sustained reduction was seen with the active drug (8).

Lichtenstein *et al*. found that significantly more of those who received infliximab ($n = 82$) than placebo ($n = 23$) reported increased energy levels (39).

In the third study, patients who responded to four weeks of induction therapy with adalimumab showed a significant reduction in fatigue ($n = 499$). Those who received maintenance therapy ($n = 324$) showed significantly fewer fatigue symptoms after one year of treatment than those who received induction therapy alone ($n = 168$) (40).

Psychotherapy has been used for the non-pharmacological treatment of fatigue in inflammatory bowel disease (41). This study included 98 patients who had substantial fatigue despite the fact that their Crohn's disease was in remission. The authors concluded that psychotherapy has a positive effect on fatigue in inflammatory bowel disease, but that the effect seems to disappear after discontinuation of therapy.

Discussion

There is increasing interest in fatigue in inflammatory bowel disease: four studies were published on this topic in the period 2000–10, compared with 17 in the period 2011–15.

Instruments

This review identified thirteen different instruments for measuring fatigue. One of these has been designed specifically for inflammatory bowel disease, but experience with its use is still limited (31). Some of the instruments record symptoms that may be influenced by disease activity or depression. This can give rise to spurious correlations because the same symptoms can lead to increased scores for both fatigue and disease activity. The instruments record symptoms over different timescales and using different thresholds, which makes it difficult to compare data. They are also administered in different ways. Patients will not necessarily give the same responses during a telephone interview as when using a written scale under the guidance of a healthcare professional.

Unidimensional instruments are simple to use in clinical practice, but provide limited information. Multidimensional instruments provide a more complete overall picture; however, they are more complicated to use and interpret, as well as more time-consuming. Disease-specific questionnaires for measuring fatigue will have been validated for a single condition and will take into account disease-specific factors, but their results cannot be compared across disorders.

There is no gold standard for measuring fatigue, but one generic instrument that has been used in several inflammatory diseases is the Fatigue Visual Analogue Scale (42). The Multidimensional Fatigue Inventory is validated and more comprehensive, and was the most frequently used instrument among the studies in this review (43).

Table 1 Prevalence of fatigue in inflammatory bowel disease. BFI = Brief Fatigue Inventory, D-FIS = Daily Fatigue Impact Scale, FACIT-F = Functional Assessment of Chronic Illness Therapy-Fatigue, FIS = Fatigue Impact Scale, FQ = Fatigue Questionnaire, FSS = Fatigue Severity Scale, fVAS = Fatigue Visual Analogue Scale, GSCL = Giessen Subjective Complaints List, PFS = Piper Fatigue Scale, PROMIS = Patient-Reported Outcomes Measurement Information System, n.s. = not specified

	Number of participants		Instrument	Prevalence of fatigue (%)			Increased fatigue compared with healthy controls	Fatigue associated with active inflammatory bowel disease
First author (reference)	Inflammatory bowel disease	Healthy controls		Ulcerative colitis	Crohn's disease	Inflammatory bowel disease		
Kappelman (16)	10 634		PROMIS				Yes	Yes
Lesage (23)	930	1 494	MFI-20			50		No
Romberg-Camps (24)	707		MFI-20	69/36[1]	77/38[1]			Yes
Singh (22)	704		Self-reported	33	54			Yes
Opheim (12)	428		5-item FSS	33	43			Yes
Bager (17)	425		MFI-20			44		Yes
Graff (19)	318		MFI			72/30[1]		Yes
Graff (15)	312		MFI					Yes
van Langenberg (13)	294	85	FIS	47	57		Yes	Yes
Goldenberg (11)	277		MFI			45		n.s.
Cohen (10)	220		FACIT-F	22	30			Yes (CD), no (UC)
Tinsley (18)	209		FACIT-F					Yes
Rømkens (20)	172	50	PFS			64	Yes	No
Jelsness-Jørgensen (21)	140	2 287	FQ	22	29		Yes	No
Yoo (14)	128	92	FACIT-F, BFI				Yes	No
Casellas (27)	115		D-FIS					n.s.
Grimstad (9)	81	67	FSS, fVAS	42	48		Yes	No
Banovic (29)	81		MFI			52		No
Minderhoud (26)	80	67	MFI	40			Yes	Yes
Häuser (25)	77	1 943	GSCL				Yes	n.s.
Banovic (28)	52		MFI-20					Yes

[1] Separate figures given for fatigue in active disease/remission

Fatigue and disease activity

The majority of studies found an association between fatigue and disease activity, primarily reflecting the distinction between active disease and remission (10, 12, 13, 15, 17–19, 22, 24, 26). Nevertheless, 40 % of patients in remission also reported fatigue, which means that disease activity is not the only relevant factor (20, 24).

Several of the disease activity measures are imprecise, and there is little correlation between symptom scores and endoscopic measures of inflammation (44). The use of subjective measures of disease activity (urgency of defecation, abdominal pain and general health) (45, 46) means that a comorbid functional bowel disorder (irritable bowel syndrome) may lead to overestimation of disease activity. Approximately one-third of patients with inflammatory bowel disease have comorbid irritable bowel syndrome (47).

Only four studies (9, 11, 14, 27) included an objective measure of inflammation (endoscopic grading). In our view, objective measures of intestinal inflammation, such as faecal calprotectin levels or endoscopic grading, are preferable for evaluating disease activity.

Fatigue and other factors

Physical fatigue or loss of energy are among the criteria for a major depressive episode (48). The correlation between fatigue and depressive symptoms may therefore be due in part to overlapping symptomatology.

The varying relationship between anaemia and fatigue in this review may reflect the fact that anaemia must be reasonably severe to make a measurable contribution to fatigue in inflammatory bowel disease.

Comorbid irritable bowel syndrome is associated with increased fatigue in patients in remission (47). Altered sleep patterns

may also influence fatigue. Insomnia may be related to depression or may be secondary to pain and nocturnal diarrhoea. Poor quality sleep leads to exhaustion and lack of energy, but it is important to recognise that fatigue is not the same as sleepiness.

Future studies of fatigue

There is a need for studies to examine the time course of fatigue. A two-year longitudinal study found fatigue to be an enduring problem (15). It will also be of interest to record depressive symptoms, and to examine the impact of factors besides age, psychosocial conditions and medication, for example pain and vitamin D deficiency.

In addition to the difficulty of achieving remission, a further challenge facing this patient population is the lack of therapeutic options available for fatigue. Although solution-focused psychotherapy can be effective in the short term, and biological therapy appears to be effective in some patients, many others still lack an effective treatment.

Conclusion

Fatigue is a significant problem in patients with inflammatory bowel disease, with active disease and depression the most commonly associated factors. A standardised measurement of fatigue in inflammatory bowel disease is required.

Increased understanding of the pathophysiological mechanisms underlying fatigue may lead to new treatments: this will be especially important for patients who experience high levels of fatigue in the absence of active intestinal inflammation.

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Tore Grimstad (born 1968)
specialist in internal medicine and gastroenterology, senior consultant and postdoctoral researcher.
The author has completed the ICMJE form and reports the following conflicts of interest: he has received honoraria from Abbvie, Tillotts Pharma and Ferring Pharmaceuticals.

Katrine Brække Norheim (born 1977)
specialty registrar in internal medicine, acting senior consultant and postdoctoral researcher.
The author has completed the ICMJE form and reports no conflicts of interest.

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