EXPLORING *FATIGUE* IN INFLAMMATORY BOWEL DISEASE PATIENTS

Associated factors and management

Lauran Vogelaar

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Vermoeidheid bij patiënten met inflammatoire darmziekten:

Oorzaken en behandeling

PROEFSCHRIFT

ter verkrijging van de graad van doctor
aan de Erasmus Universiteit Rotterdam
op gezag van de rector magnificus Prof.dr. H.A.P. Pols
en volgens besluit van het College voor Promoties.

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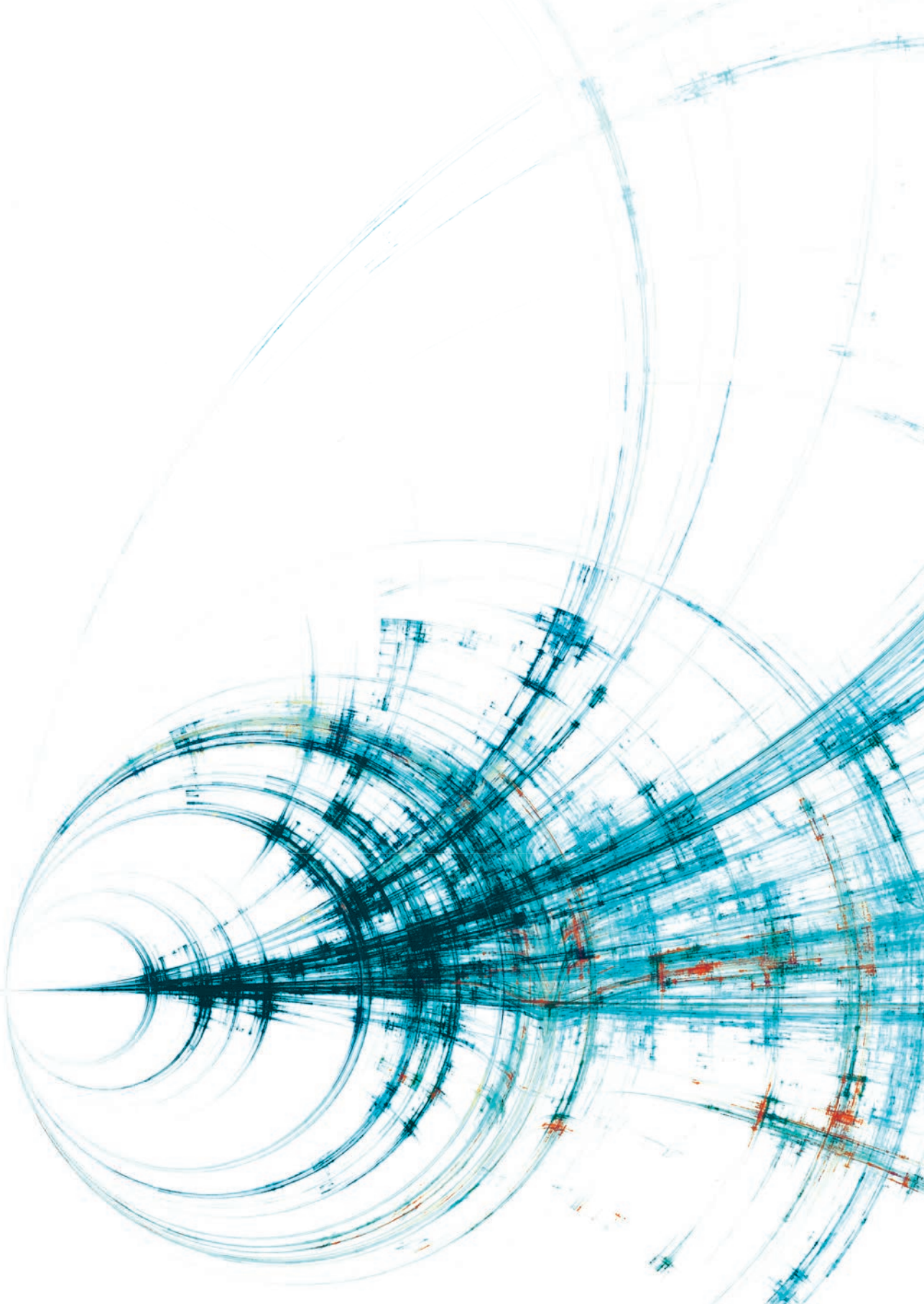

CHAPTER 1

General introduction

INTRODUCTION

Inflammatory bowel disease (IBD) is characterized by a chronic relapsing inflammation of the gastrointestinal tract. IBD comprises two major disorders: ulcerative colitis (UC) and Crohn's disease (CD). These two conditions differ in the localisation and extent of mucosal inflammation. Whereas UC is defined by inflammation limited to the mucosal layer of the colon, CD is characterized by transmural inflammation which may be localised at any part of the gastrointestinal tract.

The clinical manifestations of IBD are variable, but typical symptoms are diarrhoea, abdominal pain, weight loss, and rectal blood loss.[1] In addition, about 50% of IBD patients present with extra-intestinal manifestations, such as arthritis, ocular involvement (uveitis, iritis, episcleritis), skin disorders (erythema nodosum, pyoderma gangrenosum), and liver disease (primary sclerosing cholangitis).[2]

At present, no curative treatment is available for IBD. Current therapy for IBD consists mainly of immune suppressive medication. Despite treatment, a significant proportion of patients progress to structural or penetrating complications of the disease.[3]

IBD is known to interfere with quality of life (QoL) and even patients with quiescent IBD report significant disease-related concerns which impair their QoL.[4-6] Several factors have been identified to relate to impaired QoL in IBD patients, including: severity of symptoms, disease activity, female sex, extra-intestinal manifestations, and short bowel syndrome.[7-13]

In addition to somatic-related factors, a variety of psychosocial factors may influence the burden of IBD.[4-6]

Fatigue is one of the most frequently reported complaints affecting QoL in IBD patients.[4, 14-18] Approximately 40% of patients with quiescent IBD suffer from severe fatigue.[17, 18] Factors known to contribute to fatigue in IBD are disease activity, female sex, psychological distress (e.g. anxiety and depression), perceived stress, medication use, anemia, and sleep difficulties.[15, 18-21]

Fatigue in IBD patients is typically chronic, irreversible, not related to exertion, and not alleviated by rest. In addition, compensatory mechanisms that are useful in reducing acute fatigue are not effective in IBD-related fatigue.[22] Knowledge on the mechanisms underlying fatigue in IBD patients is limited.

The aetiology of fatigue in other diseases is also largely unknown. There is insufficient evidence for either a purely somatic or psychological origin. A multifactorial model to understand fatigue seems more plausible. The bio-psycho-social model was proposed by Engel, in which both biological and psychological factors are proposed.[23]

The bio-psycho-sociological model is currently the most comprehensive approach of chronic fatigue syndrome (CFS). Previous literature indicate that it is helpful to distinguish between predisposing, precipitating and perpetuating factors at both a biological and psychosocial

level.[24, 25] Research into predisposing factors has shown different items that make patients more vulnerable to the development of CFS, including: female sex, physical inactivity, somatic diseases, personality disorders, anxiety, depression, family members with somatic or mental diseases, somatisation of the parents, and early adverse experiences (i.e. physical or emotional neglect or abuse).[26-29]

Distinct somatic and psychological stressors, such as surgery, Epstein-Barr virus infection, life events, physical overload, can precipitate CFS.[28, 30]

Psychological processes seem to be involved in perpetuating CFS symptoms, including: anxiety, depression, unhelpful coping thoughts and focusing on bodily symptoms. Also different biological factors are known to play a role in perpetuating CFS symptoms, including: disturbed sleep-wake cycle, physical inactivity, pain, overactive or underactive lifestyle.[25, 26]

Bio-psycho-sociological factors of fatigue were also proposed in fatigued cancer patients, including: lower levels of physical activity, depressive mood, sleep difficulties, deficiency of social support, and stimulation of the immune system by cancer cells or by psychological distress.[31-33]

Nevertheless, fatigue in cancer patients need further exploration to unravel the aetiology and to develop management strategies.

Although knowledge about fatigue in other diseases could be useful to understand fatigue in IBD patients, fatigue in IBD patients is probably more complicated because of the chronic inflammatory character of IBD and the potential influence of inflammation on fatigue.

AIMS AND OUTLINE OF THE THESIS

Despite its high prevalence and negative impact on QoL, data on mechanisms underlying fatigue in IBD patients are limited and management strategies to improve fatigue are lacking.

The main aims of this thesis were therefore to identify factors associated with IBD-related fatigue and to evaluate the effect of management strategies on fatigue and QoL in IBD patients.

Chapter 1. General introduction

Chapter 2. The prevalence of fatigue in quiescent Crohn's disease (CD) is approximately 40% according to previous literature. However, based on a survey conducted in our referral hospital, the prevalence in quiescent CD patients was even higher.[34] Differences in the prevalence of IBD-related fatigue might relate to the heterogeneity of the evaluated patient populations. The aim of **chapter 2** was therefore to compare the prevalence of IBD-related fatigue and associated factors between a general hospital and a referral hospital.

Chapter 3. Fatigue is known to be associated with impaired physical fitness and reduced physical activity in cancer patients as well as in liver transplant recipients. Such data are not available

for IBD-related fatigue. In this chapter, we studied whether fatigue was associated with physical fitness and physical activity in IBD patients.

Chapter 4. Although several factors influencing fatigue have been recognized, the pathogenesis of fatigue in IBD patients is still unknown. Several immunological variables have been suggested to be involved in the pathogenesis of fatigue in chronic diseases. In chapter 4 the association between immune parameters and fatigue was explored by comparing the distribution of leukocyte subsets and the expression of various cytokines between fatigued and non-fatigued IBD patients.

Chapter 5. Since disease activity has been recognized as a significant factor in reduced quality of life and fatigue, remission is an important goal in the treatment of IBD patients. Treatment strategies consisting of corticosteroids, 5-aminosalicylates and immunnosuppressants did, however, not show significant long-term improvement on fatigue and QoL in previous studies. **Chapter 5** provides a literature review of the effect of biologics on fatigue and QoL.

Chapter 6. Although fatigue is reported as one of the most debilitating complaints of patients with IBD, adequate management strategies are lacking. This chapter presents the results of a pilot study assessing the feasibility of two types of psychological intervention, i.e. problem solving therapy and solution focused therapy, to manage fatigue in IBD patients.

Chapter 7. Based on the pilot study described in chapter 6, proposing solution focused therapy as a feasible and effective intervention, the focus of chapter 7 was to evaluate the effectiveness of solution focused therapy in a randomized controlled trial.

Chapter 8. Summary and conclusions.

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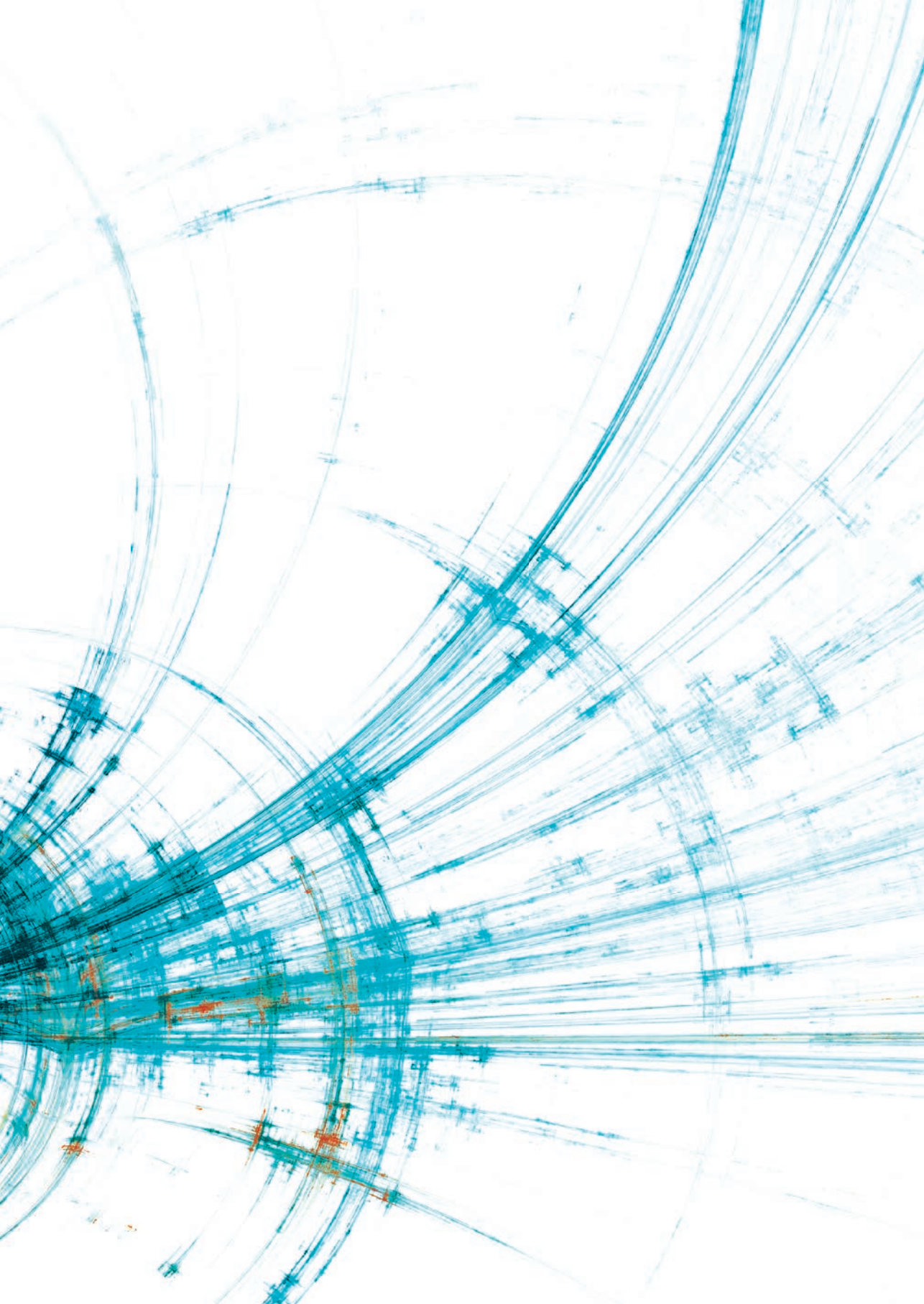
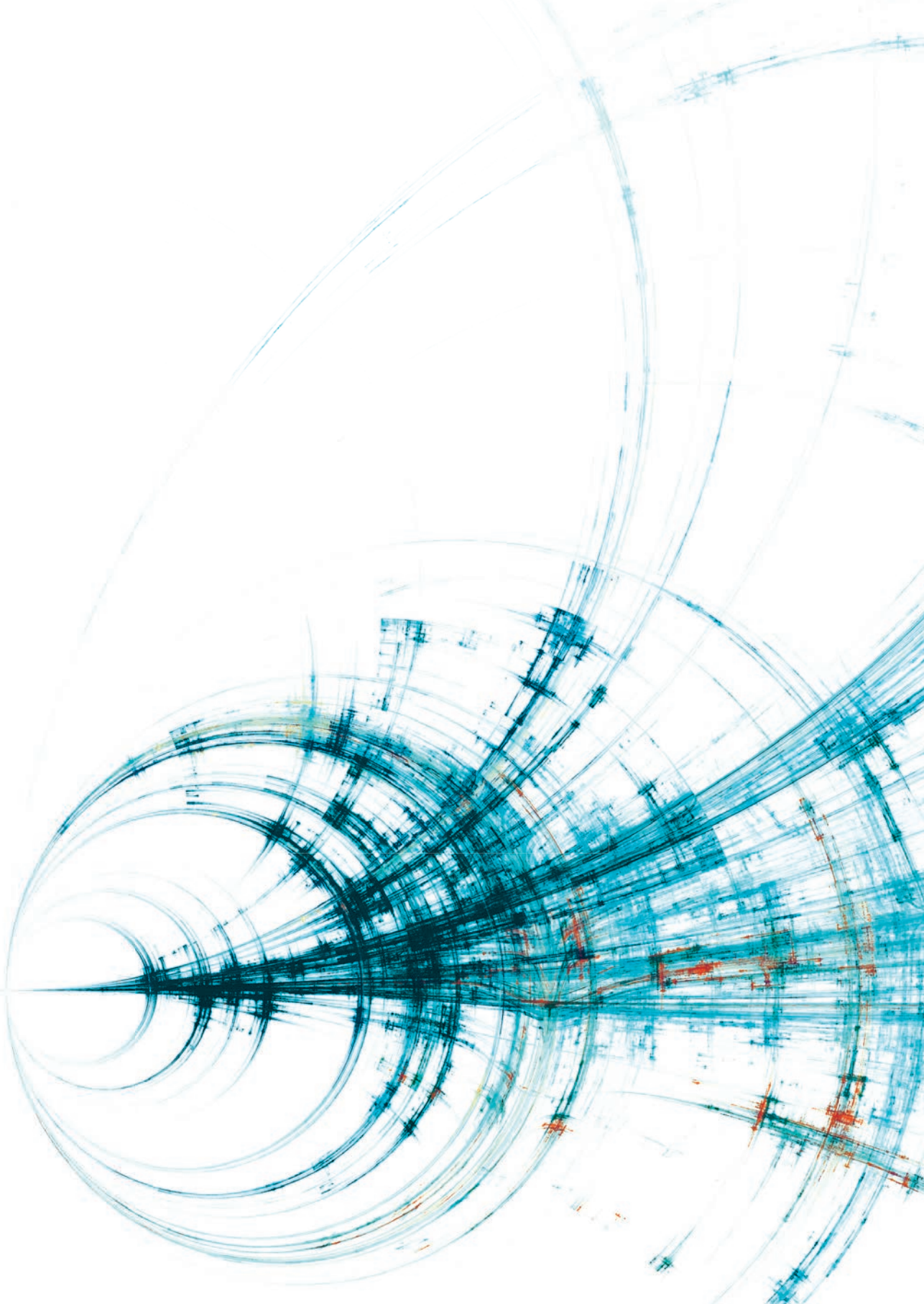
PART I

Factors associated with fatigue in IBD patients





CHAPTER 2

Determinants of fatigue in Crohn's disease patients

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Antonie J.P. van Tilburg, Ernst J. Kuipers, Reinier Timman,
C. Janneke van der Woude

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ABSTRACT

Objective

Crohn's disease (CD) is often associated with severe fatigue. Little is known about patients who may be at the highest risk for fatigue. Therefore, we assessed the disease phenotype and factors related to fatigue in the presence of CD in two different populations.

Methods

Patients presenting at the clinic of a referral hospital and a general hospital were included in the study. They completed questionnaires including the Checklist Individual Strength, the Hospital Anxiety and Depression Scale, a questionnaire on disease activity, and one on medication use. The Montreal classification and sociodemographics were obtained from medical records. Hemoglobin and C-reactive protein levels were measured at baseline.

Results

In total, 425 patients were included (276 women, mean age: 42 years). Compared with patients from the general hospital, patients at the referral hospital had worse disease activity, worse disease behavior, more bowel resections, and a higher percentage of side-effects to medication and use of anti-tumor necrosis factor (TNF).

The prevalence of fatigue was significantly higher in the referral patients compared with the general patients (65.7 vs. 51.7% respectively; $p = 0.01$). Similar results were found in patients in remission (53.3 vs. 40.5%; $p = 0.061$).

Factors related to fatigue were the use of anti-TNF at baseline, side-effects to 5-aminosalicylic acid, disease activity, female sex, and shorter disease duration. Furthermore, we found improvement in fatigue and a trend toward lower disease activity after 1 year of anti-TNF use.

Conclusion

A high percentage of CD patients suffer from fatigue. As a more aggressive phenotype seems to be associated with more severe fatigue and patients in remission still suffer from fatigue, a multidimensional approach for fatigue is warranted in these patients.

INTRODUCTION

Patients with Crohn's disease (CD) have a chronic relapsing condition that significantly impairs their health-related quality of life. An important factor that contributes toward the health-related quality of life in CD patients is fatigue.[1] Fatigue is a common complication in various chronic diseases, ranging from inflammatory conditions such as rheumatic disease and multiple sclerosis to oncological conditions, as well as in chronic infectious diseases.[2, 3] The prevalence of fatigue in patients with quiescent CD ranged in previous series from 40 to 41%.[1, 4] Factors that contribute toward the severity of fatigue in CD patients are disease activity, sex, psychological well-being, medication use, anemia, and sleep difficulties.[1, 5, 6]

We observed a high prevalence of fatigue among the CD patients in our referral hospital (66%)[7], even higher compared with that in other published studies.[1, 4, 8] This might be because of the heterogeneity of the populations included in these previous studies.

To explore this difference, we investigated the frequency of fatigue in two different hospitals, searched for factors related to the risk for fatigue, and investigated differences between disease phenotype in CD patients of a referral hospital and a general hospital.

METHODS

This study was approved by the ethical review board of the Erasmus MC University Medical Center. All patients provided informed consent.

Patients

All adult CD patients visiting the outpatient clinics of the Department of Gastroenterology and Hepatology of two different hospitals in Rotterdam, the Netherlands, between October 2008 and January 2009 were asked to complete a set of questionnaires. The two hospitals were the Erasmus MC University Medical Center (EMC: referral hospital) and the Sint Franciscus Hospital (SFG: general hospital). In the EMC, the questionnaires were part of an ongoing fatigue study. Therefore, patients of the EMC completed the questionnaires twice: at baseline and after 1 year.

Questionnaires

The following questionnaires were used: the Checklist Individual Strength (CIS)[9], the Hospital Anxiety and Depression Scale (HADS)[10], the Harvey Bradshaw Index (HBI)[11], and a questionnaire focusing on current medication use and side-effects.

The medication questionnaire was a list with all possible inflammatory bowel disease (IBD) medications used for IBD in the Netherlands according to the Dutch guidelines for the

treatment of IBD patients; patients could mark their drugs in this list and state whether they experienced side-effects. The questionnaires were verified from medical records and in the case of missing values by telephone by the principal investigator.

The CIS is a 20-item self-reporting instrument measuring the severity of fatigue, motivation, activity level, and concentration as a mean of the levels over the past 14 days. Patients with a score of 35 or higher on the subscale fatigue were considered to be fatigued. The severity of fatigue was used as an outcome measure.

The HADS is a 14-item self-reporting questionnaire, measuring anxiety and depression. Scores between 8 and 10 are considered to reflect subclinical anxiety or depression, whereas scores of 10 or higher are considered to reflect a clinical level of anxiety and/or depression.

The HBI is a five-item self-reporting questionnaire measuring disease activity in CD patients. An HBI score below 5 indicates disease remission. As patients were not examined physically, the item of 'abdominal mass' was scored as zero (no abdominal mass).[12]

Sociodemographic variables and clinical status included the following: sex, age, disease type, disease phenotype (Montreal classification)[13], year of diagnosis, number and type of previous surgical interventions, presence of a stoma, C-reactive protein level (reference value: 0-9 mg/l) and hemoglobin level (reference value: women, 7.5-10 mmol/l; men, 8.5-11 mmol/l).

Statistical analysis

Differences between samples from the two hospitals were evaluated using the Chi-square test and Student's t-test for independent samples.

Follow-up measurements were taken 1 year after baseline for about one-third of the participants. To deal with the dependency between these baseline and follow-up measures, we applied multilevel modeling, also known as mixed modeling. Follow-up measures were only taken at the referral hospital, which could have led to a difference between patients who were subject to follow-up measurements and those who were not. When such a difference influences the outcome variable, multilevel modeling corrects for the absence or presence of the measures, also referred to as missing at random.[14] Although there was no intervention between the two measures, the effects of time were included in the model to determine a possible effect of using medication at both time points. First, a saturated model was postulated with the CIS fatigue subscale as a dependent variable. The saturated model included age; sex; duration of disease; disease activity (HBI); use of anti-tumor necrosis factor (TNF), 5-aminosalicylic acid (5-ASA), immunosuppressives, and corticosteroids; the occurrence of side-effects of these medicines; time point; and all interactions with time point. We did not include depression and anxiety as covariates which are found to be general correlates of fatigue, because this study is more focused on medicines related to fatigue and differences in disease phenotype.

The deviance statistic using restricted maximum likelihood was applied to determine whether

a random slope was required in addition to a random intercept.[15] The saturated model was reduced by eliminating insignificant effects, considering that interaction effects must be nested under their respective main effects. The significance of the difference between the saturated model and the parsimonious final model was determined with the deviance statistic using ordinary likelihood. Statistical analyses were carried out with SPSS (version 17.0; SPSS Inc., Chicago, Illinois, USA). Two-sided p-values less than 0.05 were considered significant.

RESULTS

Characteristics of patients

Five hundred EMC patients and 241 SFG patients were invited to participate. In total, 425 CD patients were included [309 EMC patients (62%) and 116 SFG patients (48%); see Table 1 for patient characteristics]. For four (0.9%) of these 425 patients, data on disease phenotype were missing.

Comparison of Crohn's disease patients in the Erasmus MC University Medical Center and the Sint Franciscus Hospital

For a comparison between the two patient groups, see Table 1. Patients in the EMC were younger at diagnosis (41 vs. 44; p = 0.029). Further, EMC patients had a higher disease activity score (4.7 vs. 3.7; p = 0.025), disease behavior differed significantly among them, and they were significantly more often treated with anti-TNF compared with the SFG patients (24.5 vs. 13.8%; p = 0.017).

In addition, more side-effects to medication were reported in the EMC group (38.0 vs. 20.9%, respectively; p = 0.003). Significantly more EMC patients had a previous history of bowel resection compared with SFG patients (52.8 vs. 32.5%w, respectively; p = 0.0001) and also the number of resections differed (mean 0.8 vs. 0.5, respectively; p = 0.003).

Fatigue scores and Hospital Anxiety and Depression Scale scores

Table 2 lists the mean CIS-20 and HADS scores. The prevalence of fatigue (CIS fatigue ≥ 35) was significantly higher in the EMC compared with the SFG (65.7 vs. 51.7% respectively; p = 0.01). As expected, patients with disease remission (HBI < 5) were less fatigued compared with patients with active disease (CIS fatigue score: 33 vs. 45 respectively; p = 0.0001). The prevalence of fatigue in patients in remission in the EMC compared with the SFG was similar (53.3 vs. 40.5% respectively; p = 0.061).

Patients in the EMC and SFG had similar scores for anxiety and depression (mean: 7.2 vs. 6.9 for anxiety and mean: 5.8 vs. 5.1 for depression, respectively). In the EMC and the SFG, 28.4 and 27.6%, respectively, of the patients showed clinically relevant anxiety (p = 0.904). This was 19.9 and 12.9% respectively for depression (p = 0.118).

Table 1: Patient characteristics

Patient characteristics	SFG	EMC	p - value
Age in years (SD)	44 (11)	41 (14)	0.029
Female gender (%)	69.8	63.4	0.216
Crohn's disease (n)	107	261	
Crohn's disease with stoma (n)	9	48	0.038
Current medication use			
5-ASA (%)	21.6	25.8	0.364
Immunosuppressives (%)	32.8	41.8	0.089
Corticosteroids (%)	13.8	21.9	0.062
Biologicals (anti-TNF) (%)	13.8	24.5	0.017
Side-effects to medication (%)	20.9	38.0	0.003
5-ASA (%)	8.0	21.5	0.127
Corticosteroids (%)	12.5	49.3	0.007
Immunosuppressives (%)	18.4	35.9	0.042
Biologicals (anti-TNF) (%)	50.0	30.7	0.139
Disease activity			
Mean HBI (SD)	3.7 (3.7)	4.7 (4.2)	0.025
Montreal classification			
Age at diagnosis (%)			
A1	6.2	5.3	0.013
A2	68.1	70.4	0.631
A3	25.7	14.3	0.005
Mean age at diagnosis (SD) in yr	32 (11)	27 (12)	0.0001
Location (%)			
L1	21.1	27.8	0.170
L2	38.6	33.0	0.298
L3	38.6	38.8	1.00
L4	1.8	0.4	0.180
+L4	3.5	8.1	0.128
Behaviour (%)			
B1	76.3	64.1	0.019
B2	17.5	20.7	0.582
B3	6.2	15.2	0.013
p	16.7	34.3	0.0001
Surgery			
Bowel resection (%)	32.5	52.8	0.0001
Number of resections; mean (SD)	0.5 (0.9)	0.8 (1.0)	0.003
Age at first resection; mean (SD)	31 (10.6)	30 (10.7)	0.419
Stoma (%)	7.8	15.5	0.038
Rectum amputation (%)	3.5	7.1	0.253
CRP (mg/l)	5.5 (5.3)	5.3 (12.1)	0.890
haemoglobin (mmol/l) - female	8.2 (0.7)	8.0 (0.8)	0.244
haemoglobin (mmol/l) - male	9.0 (0.7)	9.0 (0.9)	0.793

SD: standard deviation

Corticosteroids: prednisone, budesonide

Immunosuppressives: azathioprine, methotrexate, cyclosporine

5-ASA: 5-aminosalicylic acid; CRP: C-reactive protein; EMC: Erasmus MC University Medical Center (referral hospital); HBI: Harvey–Bradshaw Index; SFG: Sint Franciscus Hospital (general hospital); TNF: tumor necrosis factor.

Factors related to fatigue at baseline and during follow-up

CIS-20 scores as well as anxiety and depression scores remained stable over 12 months of follow-up (Table 2). Furthermore, there was no difference in the baseline fatigue scores of patients with or without follow-up data.

Table 2: Mean scores of Checklist Individual Strength and Hospital Anxiety and Depression Scale (SD).

	SFG	EMC	p-value*	EMC follow-up	p-value**
CIS Fatigue	35.1 (13.9)	38.7 (14.2)	0.018	37.5 (14.1)	0.123
CIS Concentration	15.5 (8.5)	18.0 (8.8)	0.009	17.6 (9.1)	0.409
CIS Motivation	14.6 (6.3)	14.4 (6.6)	0.793	14.6 (6.6)	0.592
CIS Physical Activity	12.4 (5.3)	13.0 (5.6)	0.373	12.4 (5.6)	0.112
CIS Total	77.6 (28.2)	84.0 (30.2)	0.047	82.2 (30.8)	0.154
HADS – Anxiety	6.9 (4.2)	7.2 (4.3)	0.489	7.3 (4.5)	0.171
HADS – Depression	5.1 (4.3)	5.8 (4.3)	0.161	5.9 (4.4)	0.571

SD: standard deviation

CIS: Checklist Individual Strength; EMC: Erasmus MC University Medical Center (referral hospital); HADS: Hospital Anxiety and Depression Scale; SFG: Sint Franciscus Hospital (general hospital).

* Difference between SFG baseline and EMC baseline

** Difference between EMC baseline and EMC – follow-up

Fatigue

The fixed parameters (follow-up, sex, disease duration, disease activity, 5-ASA, side-effects of 5-ASA, anti-TNF, and follow-up*anti-TNF), standard errors and 95% confidence intervals, and significances of the effects on the CIS fatigue subscale in the final mixed model are presented in Table 3. Women were on average more severely fatigued than men (+2.81). A longer duration of

Table 3: Final multilevel model.

CIS fatigue	B	SE	95% CI	p-value
Intercept	31.19	2.30	23.85–32.91	< 0.001
Follow-up	0.39	0.94	-1.47–2.25	0.68
Sex*	2.81	1.23	0.39–5.24	0.02
Disease duration	-0.14	0.06	-0.25–0.03	0.02
Disease activity	1.33	0.13	1.09–1.58	< 0.001
5-ASA	-2.04	1.26	-4.51–0.44	0.11
Side effects 5-ASA	7.65	2.35	3.04–12.27	0.001
Anti-TNF	4.01	1.28	1.50–6.52	0.002
Follow-up * anti-TNF	-3.55	1.72	-6.95–0.14	0.04

Follow-up, 1 year. Disease activity: Harvey–Bradshaw score.

5-ASA: use at baseline. Side-effects 5-ASA: side-effects at baseline. Anti-TNF: use at baseline.

Follow-up*anti-TNF: anti-TNF use during 1 year of follow-up.

ASA: 5-aminosalicylic acid; B: regression coefficient; CIS: Checklist Individual Strength; SE: standard error; TNF: tumor necrosis factor, CI: confidence interval

*Male =0, female =1.

disease was associated with less fatigue (-0.14 for each disease year); more disease activity was associated with more fatigue (+ 1.33 for each point on the HBI). Patients using 5-ASA at baseline showed less fatigue (-2.04), but when 5-ASA caused side-effects, fatigue levels were higher (-2.04 + 7.65 = + 5.61) at baseline. Anti-TNF use at baseline resulted in a higher fatigue level (+ 4.01); maintaining anti-TNF through the follow-up year resulted in a decreased fatigue level (+0.39 - 3.55 = -3.16); however, this level was still increased compared with that in non-anti-TNF users (0.39 + 4.01 - 3.55 = 0.85).

DISCUSSION

Our study underlines fatigue as an important contributing factor toward the burden of disease in CD patients. In both patients from a referral and a general hospital, the prevalence of fatigue was high. This high rate of fatigue among CD patients is in agreement with previous reports; however, the prevalence in the different studies ranges between 40 and 41%.[1, 4] The prevalence of fatigue in the CD patients (in remission) from the general hospital was 41%, which is within the range reported earlier; however, in CD patients (in remission) from our referral hospital, a higher rate of fatigue was reported (53%). These contrasting results could be explained by the heterogeneity of the populations included in previous studies. These studies did not discriminate between populations from referral hospitals and general hospitals. We clearly defined a general CD population and a referral CD population and showed that the Montreal classification differed significantly within these two populations, with a higher percentage of patients with severe disease (e.g. penetrating disease, perianal disease) in the referral population. Earlier studies have shown penetrating disease and perianal disease as factors associated with lower quality of life.[16, 17] As quality of life is highly associated with fatigue, a more severe form of disease seems to be an important factor in the severity of fatigue.[18]

In addition, we found disease activity to contribute toward the severity of fatigue, and this activity was significantly higher in the referral patients compared with the general patients. This was not supported by the significantly higher levels of C-reactive protein or by anemia in the referral patients. However, it is known that C-reactive protein is not reliable for the identification of remission. Therefore, endoscopy is the most reliable tool for identifying disease activity.

Disease activity has been associated with higher fatigue levels, whereas inducing remission has been associated with improvement in fatigue and quality of life.[1, 19]

Different drugs are effective in inducing remission in CD patients and improving quality of life, but some of these treatments cause side-effects during prolonged use, which negatively affect the quality of life.[20-22]

In addition to these published studies[20-22], we show that the use of anti-TNF at baseline and

side-effects to 5-ASA are related to a higher fatigue score at baseline.

Our study reports a high percentage of side-effects, even higher than that in previous reports. This may be because our study reports on more subjective side-effects reported by our patients. The higher fatigue levels at baseline in patients using anti-TNF might be because of recent disease activity; however, this was not investigated in this study. The use of anti-TNF for a longer period, for 1 year of follow-up in our study, was predictive of less fatigue at follow-up. However, fatigue scores higher than that reported in patients without anti-TNF were obtained. Patients using 5-ASA at baseline showed less fatigue. These results may imply that patients who need anti-TNF fail to respond to other medication and are more fatigued at baseline. In addition to this outcome, patients who started with anti-TNF during follow-up showed higher disease activity at baseline compared with patients who did not need anti-TNF therapy during follow-up. During follow-up, there was a trend toward lower disease activity in patients who used anti-TNF compared with those who did not use anti-TNF. Therefore, during follow-up anti-TNF seems to contribute toward reducing fatigue, probably by induction and maintenance of remission.

Although patients in the referral population had a more severe form of the disease and higher disease activity, the difference in the prevalence of fatigue remained significant even when comparing this only in quiescent patients. Therefore, it is important to recognize other factors that contribute to fatigue. Similar to earlier studies we found longer disease duration to be significantly associated with less fatigue.[23] This finding could be related to the adaptive coping style of CD patients with their chronic disease. It is known that CD patients have less effective coping styles compared with healthy individuals, which is associated with lower quality of life, which in turn could lead to more severe fatigue. However, patients seem to be adaptive to their disease over time.[24]

It has been reported previously that factors such as perceived stress, low sleep quality, female sex, hemoglobin, anxiety and depression are also associated with fatigue in CD patients.[1, 6, 8, 25] In our study we found a higher prevalence of concomitant depression among CD patients than among the general population in the Netherlands.[26] Because of multicollinearity it was statistically not possible to relate depression to more fatigue. Furthermore, we confirmed female sex as a predictor of fatigue in CD patients. Although women are known to report more psychological distress than men, the finding that women are more fatigued than men may reflect a statistical side-effect of the fact that women tend to have a more complicated form of the disease.[27, 28] In our study, female patients also had significantly higher disease activity measured by the HBI both at baseline and at follow-up compared with men.

The limitations of this study were the measurement of disease activity with the HBI. Endoscopy and biomarkers are more sensitive tools to measure disease activity, but are expensive and time-consuming. Another limitation is the high percentage of female patients, because women suffer more commonly from Irritable bowel syndrome (IBS) which is associated with fatigue. However,

the number of women did not differ between the two populations.
Overall, the fatigue scores did not change during the 1-year follow-up. However, as we mentioned earlier, patients treated with anti-TNF during follow-up showed improvement in fatigue. This might indicate that fatigue in CD patients should be targeted with effective medical treatment. In addition, it has been reported that additional psychological treatment could play a role in improving fatigue, as psychological factors affect fatigue. [1, 8, 25, 29] For CD patients in remission, independent solution-focused therapy also seems to be effective in the treatment of fatigue.[30]

CONCLUSION

Fatigue is common among patients with CD. It is related to disease activity and seems to be related to the severity of the disease. During follow-up, we found an improvement in fatigue in patients using anti-TNF. These patients also showed improvement in disease activity. However, a high percentage of patients in remission still suffer from fatigue, which implies that a multidimensional approach to treatment of CD patients suffering from fatigue is required. Currently, we are examining the role of an additional psychological approach in decreasing fatigue in CD patients. Further research should also include more sensitive tools such as fecal biomarkers and endoscopy to measure disease activity.

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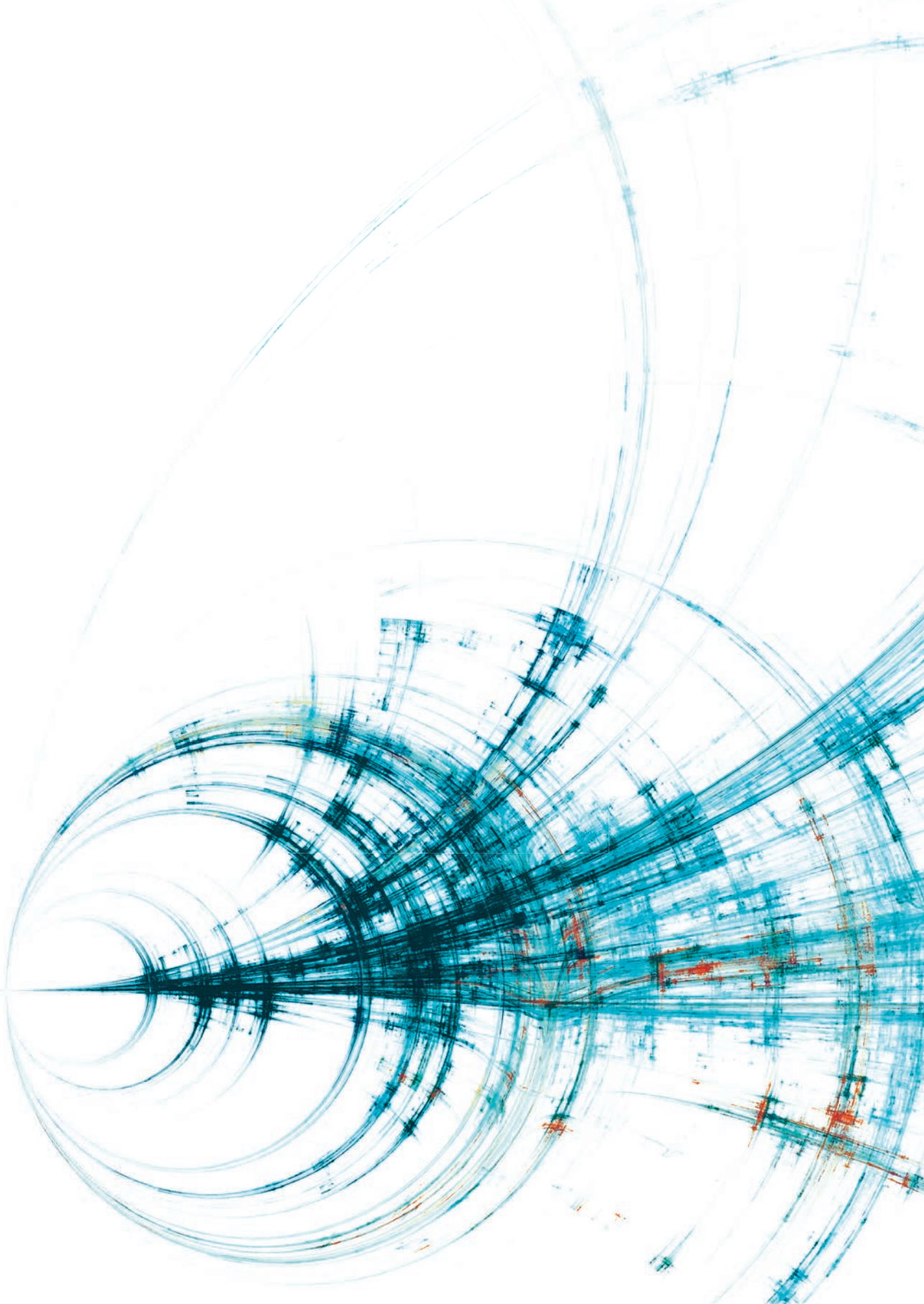

CHAPTER 3

Physical fitness and physical activity in fatigued and non-fatigued IBD patients

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ABSTRACT

Objective

To assess physical fitness and physical activity in inflammatory bowel disease (IBD) patients and whether fatigue is associated with impaired physical fitness and impaired physical activity.

Materials and Methods

Ten patients with quiescent IBD and fatigue (fatigue-group: [FG]) based on the Checklist Individual Strength-fatigue score ≥ 35 were matched for age (± 5 years) and sex with a non-fatigue group (NFG) with IBD.

Physical fitness was measured with a cyclo-ergometric based maximal exercise test, a submaximal 6-min walk test, and a dynamometer test to quantify the isokinetic muscle strength of the knee extensors and flexors. Level of physical activity was measured with an accelerometer-based activity monitor.

Results

The patients in both groups did not differ in regard to medication use, clinical characteristics, and body composition. However, medium-to-large effect sizes for impaired physical fitness (both cardiorespiratory fitness and muscle strength) and physical activity were seen between the patients in the FG and the NFG. Especially, intensity of physical activity was significantly lower in the FG patients compared with the NFG patients (effect size: 1.02; $p = 0.037$). Similar results were seen when outcomes of the FG and NFG were compared with reference values of the normal population.

Conclusion

Fatigued IBD patients show an impaired physical fitness and physical activity compared with non-fatigued IBD patients. This gives directions for a physical component in fatigue in IBD patients. Therefore, these new insights into fatigue indicate that these patients might benefit from an exercise program to improve physical fitness and physical activity.

INTRODUCTION

Despite more effective treatments for patients with inflammatory bowel disease (IBD), many patients still suffer from disabling fatigue, which is associated with decreased quality of life (QoL).[1-5] Several factors such as disease activity, perceived stress, depressive coping, female sex, and psychological well-being contribute to fatigue in IBD patients. Moreover, we showed in a previous study that solution-focused therapy, a psychological intervention, is effective in reducing fatigue and subsequently in increasing QoL.[5-13] However, although effective in the majority, there are still patients who suffer from invalidating fatigue.

Previous studies among cancer patients and liver transplant recipients showed evidence for a relationship between fatigue, impaired physical fitness and impaired physical activity.[14-16]

Cardiorespiratory fitness (VO_2peak) in liver transplant recipients was related with severity of fatigue and QoL, but no indications of impaired muscle strength was observed.[17] Furthermore, the level of daily physical activity measured with an accelerometer was related with fatigue in liver transplant recipients.[18] In cancer patients the etiology of fatigue is poorly understood, and literature on fatigue and objective physical components is scarce. However, literature suggests associations between impaired muscle strength, impaired physical activity and fatigue.[15, 19]

Moreover, most research on fatigue in cancer patients focused on exercise interventions and showed reduction of fatigue by these interventions.[16, 20-25]

Therefore, we hypothesize that fatigue in IBD patients might be partly related to impaired physical fitness and impaired physical activity. However, data on the association between physical activity and physical fitness and fatigue in IBD patients is lacking. For the development of an exercise intervention to reduce fatigue, more objective knowledge of these associations is necessary.

The aim of this study was to assess the level of physical fitness (cardiorespiratory fitness and muscle strength) and daily physical activity in IBD patients and whether fatigue is associated with impaired physical fitness and impaired physical activity.

METHODS

Study design

We performed a matched cross-sectional study in fatigued and non-fatigued IBD patients. This study was conducted in accordance with the protocol International Conference on Harmonization Guidelines for Good Clinical Practice, the Declaration of Helsinki, and local national regulations governing clinical study conduct. The protocol was approved by the medical ethics committee of the Erasmus Medical Center (Erasmus MC, registration number: MEC-2010-249; NL33396.078.10). The study was not designed for an interim analysis and no Data Safety Monitoring Board was

assigned. All patients gave written informed consent. Patients were enrolled at the Erasmus MC in The Netherlands from November 2010 to October 2011. Patients were randomly selected from the IBD outpatient population.

Sample size

For the sample size calculation, we applied data from the study of van den Berg-Emons et al.[18.] They reported correlation between -0.81 and -0.84 between severity of fatigue and daily physical activity within a group of liver transplant recipients. Applying a two-sided alpha level of 0.05, power 0.80, nine cases are needed for a correlation of 0.80. In a study of van Ginneken et al. correlations between -0.50 and -0.61 were reported between cardiorespiratory fitness and severity of fatigue within a group of liver transplant recipients.[17] Again applying a two-sided alpha level of 0.05, power 0.80, 28 cases are needed for a correlation of 0.50, and 18 cases for a correlation of 0.60. Combining these results we felt confident in applying a sample size of 20. Therefore we decided to include 10 patients in the fatigue group (FG) and 10 patients in the non-fatigue group (NFG). Patients were matched for sex and age (maximal difference: ± 5 years).

Patients and fatigue measurement

Men and women aged ≥18 years, diagnosed with IBD which was radiologically or endoscopically/ histologically confirmed, were included. Patients had to be in remission of the disease, defined as Harvey Bradshaw Index score <5 or Clinical Activity Index score <10 and C-reactive protein < 10 mg/L (reference value: 0-9 mg/L). Fatigue was defined as a Checklist Individual Strength-fatigue (CIS-fatigue) score of ≥35 and non-fatigue as a CIS-fatigue score of <35.[26]

Pregnant women or breastfeeding women, surgery within 12 weeks prior to the screening visit, short bowel syndrome, a history of lymphoproliferative disease or cancer, other than skin basocellular carcinoma, gastrointestinal disease other than IBD, and contraindication for maximal exercise testing according to the Physical Activity Readiness Questionnaire (PAR-Q) were not included.[27]

Measurements Physical fitness

Cardiorespiratory fitness - cyclo-ergometric exercise test

Cardiorespiratory fitness was measured with a progressive maximal cyclo-ergometric exercise test (ER800, Jaeger Toennies, Breda, The Netherlands) (Figure 1).

The test was preceded by a 4-min warm-up period (20 Watt [W]). The test started at 20 W, followed by an increase in resistance of 15 or 20 W/min, depending on the ability of the patients. Individual test protocols were chosen aimed for a test duration of 8-12 min according to the

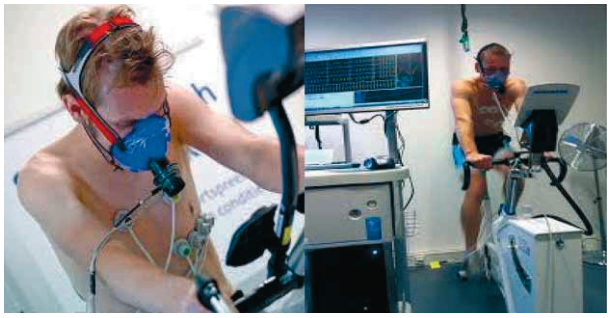

Figure 1. Cardiorespiratory fitness: cyclo-ergometric exercise test.

American College of Sports Medicine criteria.[28] Subjects were instructed to use a pedal rate of 60 rpm and were encouraged to achieve maximal effort.

The test was terminated when the subject was subjectively exhausted, or when the patient was unable to maintain the instructed pedal rate. Breathing gas exchange and heart rate (HR) were monitored continuously using a breath-by-breath gas analysis system (Oxycon Pro, Jaeger Toennies, Breda, The Netherlands).

The respiratory exchange ratio (RER) was calculated during the test. An RER of ≥1.1 indicates maximal exercise.[29-31] The predicted maximum HR was calculated with the formula of Tanaka: 208 – (0.7 x age).[32]

Subjective strain was measured immediately after the final stage by the Borg Category Ratio Scale (Borg-CR10 scale).[33, 34] Patients were asked to indicate how strenuous they had experienced the test by giving a number from 0 (no effort at all) to 10 (maximal effort). Cardiorespiratory fitness was defined as the highest mean oxygen uptake during 30 seconds of exercise (VO2peak L min^{-1}). Ventilatory threshold (VT) was defined as an increase in VE/$\dot{V}O_2$ without a concomitant increase in VE/$\dot{V}CO_2$.[35, 36]

Cardiorespiratory fitness: 6-minute walk test

Furthermore, cardiorespiratory fitness was also measured with the submaximal 6-min walk test (6MWT).[37] Patients were instructed to walk, n ot run, as far as they could along a 30-meter marked track during a 6-min period. Standardized encouragement was provided with the following phrases: "you are doing well" and "keep up the good work". Patients were allowed to stop and rest during the test but were instructed to resume walking as soon as they felt able to do so. The 6-min walk distance (6MWD) was recorded.

Muscle strength

Isokinetic muscle strength of the knee extensors and flexors was assessed in both legs using a Biodex® dynamometer (Shirley, New York, USA), recording strength as torque in Newton meters. The patients were seated against a backrest, firmly strapped at the hip and thigh. The rotational

axis was aligned with the lateral femoral epicondyle. After three familiarization repetitions, isokinetic strength was measured at 60°/second (60°/s) with 5 maximal contractions and at 180°/second (180°/s) with 15 maximal contractions. Maximal effort was encouraged. Peak torque (PT) was defined as the maximum torque generated by the patients throughout a series of repetitions at each velocity. The mean PTs were separately calculated from all torques of both legs at each velocity.

Physical activity

For assessment of the level of daily physical activity an activity monitor (AM) (Temec Instruments BV, Kerkrade, The Netherlands) was used. The AM is based on long-term ambulatory monitoring of signals from body-fixed accelerometers and consists of four accelerometers, a portable data recorder and a computer with analysis software.[38]

After the measurement, data were downloaded onto a computer for analysis by the Kinematic Analysis part of the Vitagraph Software.[39] A detailed description of the activity detection procedure has been described previously.[38, 40]

Data were calculated for 1 day (24-h period) and the following variables were assessed: duration of dynamic activities (walking, including climbing/descending stairs and running, cycling, general non-cyclic movement) as percentage of a 24-hour period; number of transitions (contains all transitions except the lying transitions such as the transition from lying prone to lying supine); and number of walking periods (> 10 s). In addition, body motility was assessed, addressing mean motility over a 24-h period (representing intensity of daily physical activity) and motility during walking (representing walking speed).[38, 41, 42]

The AM system was set up at each participant's home to minimize influence on the normal physical activity pattern. To avoid measurement bias, we instructed the participants to continue their ordinary daily life activities. The principles of the AM were explained to the participants after all measurements had been made.

Descriptive parameters

Body composition

Height (cm) and body mass (kg) were measured without shoes. Body mass index (BMI, kg m^{-2}) was calculated from height and body mass. Body fat was estimated using skinfold measurements with a Harpenden Skin-Fold Caliper (Burgess Hill, UK). The mean of the two measurements was used as representative for each site. Percentage body fat was predicted from skinfold thickness according to the method of Durnin and Womersley.[43, 44] Fat-free mass was calculated as total body mass minus body fat.

Questionnaires

The Harvey Bradshaw Index (HBI)[45] or Clinical Activity Index (CAI)[46], a questionnaire focusing on current medication use and side-effects, were filled in.

A HBI score <5 or a CAI score <10 in addition to a C-reactive protein value of <10 mg/L are considered to reflect remission of the disease.

Demographics, disease phenotype (Montreal Classification) were collected from medical records.[47]

Measurement protocol

Before inclusion, the CIS, HBI, or CAI, a questionnaire focusing on current medication use and side effects to medication were filled in. After inclusion, the level of daily physical activity with an AM was measured. Maximal 1 week thereafter, the fitness measurements were performed. During the day of the fitness measurements, patients refrained from heavy exercise (running, walking/climbing briskly up a hill, fast cycling, aerobics, fast swimming, competitive sports and games, heavy shoveling or digging ditches, carrying/moving heavy loads [>20kg]).

The order of the tests was standardized: patients started with the 6MWT, body composition measurements and the isokinetic muscle strength test, followed by a questionnaire (PAR-Q) [27] and finally the progressive maximal cyclo-ergometric exercise test. Exercise tests were performed under supervision of a physician.

Statistical analysis

Data of the FG and NFG are given in frequencies and percentages for binary data (gender, disease type, Montreal Classification) and in means and standard deviations for continuous data (age, disease activity, outcome variables). Group differences were analyzed with Chi-square tests for categorical variables and t-tests for independent groups for continuous variables. Differences between the FG and NFG are expressed in effect sizes (Cohen's d) where appropriate. Effect sizes were calculated by dividing the difference between the means of the FG and NFG by their pooled standard deviations.

Effect sizes of 0.20 are considered a small effect, 0.50 a medium effect, and 0.80 a large effect.[48]

Reference values for VO2peak were calculated by subtracting the age, sex, height and weight corrected norms, presented by Fairbarn et al., from the observed values and dividing these by the respective normed standard deviations.[49]

For the 6MWD, corrections for age and gender were made by subtracting the expected values based on the reference values presented by Gibbons et al.[50]

For isokinetic muscle strength (peak torque), corrections for age and gender were made by subtracting the expected values based on the reference values presented by Akima et al.[51]

For normalization of physical activity data, we applied norm scores of 52 healthy, age-range-

matched participants recruited at the Erasmus MC, measured with the same AM system and protocol.[38, 52]

Data were analyzed with SPSS Software for Windows, version 20 (SPSS Inc, Chicago, IL, USA). Results were considered significant when two-sided p-values were <0.05.

RESULTS

Baseline characteristics

Baseline characteristics according to type of disease, body composition, medication use, and side effects to medication were not significantly different between the FG and NFG (Table 1). Mean age was 37.3 (11.4 standard deviation [SD]). Table 1 also shows the baseline fatigue scores. No differences were observed in clinical characteristics of the disease between the FG and NFG (Table 2). Moreover, there were no differences in co-morbidity between the FG and NFG.

Outcomes

Table 3 shows the results of the maximal cyclo-ergometric exercise tests. The outcomes were indicative for maximal performed tests in both groups. The mean modified Borg-CR10 score of

Table 1: Baseline characteristics.

Patient characteristics	**fatigue n=10**	**non-fatigue n=10**	**p-value**
Age; mean (SD)	36.4 (12.3)	38.2 (11.0)	
Female (frequency)	5	5	
Crohn's disease (frequency)	7	8	1.00
Ulcerative colitis (frequency)	3	2	1.00
Body composition	**mean (SD)**	**mean (SD)**	
Height (cm)	175 (11)	176 (11)	0.80
body mass (kg)	72 (12)	80 (13)	0.16
body mass index (kg/m2)	23 (2)	26 (5)	0.15
body fat (%)	27 (9)	30 (10)	0.44
fat free mass (kg)	52 (10)	56 (10)	0.49
Medication	**frequency**	**frequency**	
5-ASA	2	2	1.00
Immunosuppressives	7	3	0.074
Corticosteroids	1	0	0.305
Biologicals (anti-TNF)	0	2	0.136
Side-effects to medication	4	1	0.139
	mean (SD)	**mean (SD)**	
CIS-fatigue	44.8 (8.6)	18.2 (6.9)	< 0.001

Chi-square test for dichotomous variables, independent samples t-test for continuous variables.
5-ASA = 5-aminosalicylic acid; CIS = Checklist Individual Strength; SD = standard deviation.

the FG was 5.3 (2.2 SD) and 5.5 (1.9 SD) for the NFG (p = 0.831), which indicates that patients experienced the maximal cyclo-ergometric exercise test on average as heavy (= Borg-CR10 score ≥ 5).

Table 2: Clinical characteristics

Montreal classification	**fatigue**	**non-fatigue**	**p-value**
Montreal classification - CD	**n=7**	**n=8**	
Age at diagnosis (%)			
A1	14.3	12.5	0.379
A2	42.8	75.0	
A3	42.9	12.5	
Location (%)			
L1	71.4	75.0	0.988
L2	14.3	12.5	
L3	14.3	12.5	
L4	100	100	1.00
+L4	0	0	
Behaviour (%)			
B1	57.1	62.5	0.535
B2	42.9	25.0	
B3	0	12.5	
p	42.9	25.0	0.464
Disease activity			
Mean HBI (SD)	3.4 (1.0)	2.4 (1.4)	0.114
Montreal classification - UC	**n=3**	**n=2**	
Age at diagnosis (%)			
A1	33.3	50.0	0.233
A2	66.7	0	
A3	0	50.0	
Location (%)			
E1	0	0	1.00
E2	0	0	
E3	100	100	
Severity (%)			
S0	100	100	1.00
S1	0	0	
S2	0	0	
S3	0	0	
Disease activity			
Mean CAI (SD)	2.7 (0.6)	2.0 (0.0)	0.184
Surgery			
Bowel resection (%)	50	60	0.653
Stoma (%)	10	0	0.305

Chi-square test for dichotomous variables, independent samples t-test for continuous variables.
CD = Crohn's disease; UC = ulcerative colitis; HBI = Harvey Bradshaw Index; CAI = Clinical Activity Index;
SD = standard deviation.

The effect sizes of the different variables were medium to large comparing the FG with the NFG, except from number of transitions. Especially, the FG showed a significantly lower intensity of daily physical activity (motility) compared with the NFG (mean: FG: 0.022, NFG: 0.028) (effect size: 1.02; p = 0.037) (Table 4).

Between the FG and NFG, both related to their normed reference values, medium to large effect sizes for physical fitness and physical activity were seen. Details of these results are presented in Table 5. Intensity of daily physical activity (motility) was also significantly lower for the FG compared with the NFG, when the results of the FG and NFG were compared with reference values (mean: FG: -0.77, NFG: 0.04) (effect size: 1.02; p = 0.037) (Table 5).

Table 3: Results on cyclo-ergometric exercise test

	fatigue	**non-fatigue**	**p-value**
	mean (SD)	mean (SD)	
Max. RER	1.14 (0.1)	1.14 (0.1)	0.986
Max.HR % of predicted*	89 (10.1)	96 (7.1)	0.084

Independent samples t-test for continuous variables.

*Maximal HR as percentage of predicted maximum heart rate (calculated with the formula of Tanaka: 208 – (0.7x age)) [32]

Abbreviations: SD = standard deviation; Max. = maximal; HR = heart rate; RER = respiratory exchange ratio.

Table 4: Means and effect sizes for fatigued patients compared with non-fatigue patients.

	fatigue	**non-fatigue**	**fatigue vs. non-fatigue**
	mean (SD)	mean (SD)	Cohen's d (p-value)
VO2peak (L kg^{-1} min^{-1})	1.99 (0.44)	2.43 (0.75)	0.76 (0.130)
VT	1.19 (0.33)	1.43 (0.40)	0.68 (0.152)
6MWD in meters	538.40 (72.32)	597.70 (80.5)	0.78 (0.100)
PT extension 60°/s (Nm)	107.05 (25.41)	123.73 (37.96)	0.54 (0.263)
PT extension 180°/s (Nm)	60.73 (12.30)	73.45 (21.42)	0.78 (0.125)
PT flexion 60°/s (Nm)	51.74 (14.25)	62.99 (20.13)	0.66 (0.166)
PT flexion 180°/s (Nm)	31.06 (7.96)	38.89 (14.22)	0.73 (0.147)
Dynamic activity (% 24h)*	9.65 (3.38)	12.00 (3.34)	0.70 (0.134)
Mean motility (g)‡	0.022 (0.005)	0.028 (0.007)	1.02 (0.037)
Motility during walking (g)#	0.155 (0.037)	0.184 (0.050)	0.67 (0.159)
Transitions (number)§	121.90 (40.16)	123.4 (31.83)	0.04 (0.927)
Walking periods > 10 seconds (number)	148.60 (67.44)	194.00 (93.96)	0.57 (0.232)

Abbreviations: Cohen's d = effect size; SD = standard deviation; VO2peak (L min^{-1}) = peak oxygen uptake; VT = ventilatory threshold (an increase in $\dot{V}E/\dot{V}O2$ without a concomitant increase in $\dot{V}E/\dot{V}CO2$); 6MWD = 6-min walk distance; PT = peak torque; g = gravitational acceleration (1 g = 9.81 m/s^2).

*Composite measure (walking, cycling, general (non-cyclic) movement) expressed as percentage of a 24-h period.

‡Intensity of daily physical activity (1 g =/9.81 m/s^2).

#Walking speed.

§Contains all transitions except the lying transitions such as the transition from lying prone to lying supine.

Table 5: Means and effect sizes of reference values for fatigued patients compared with non-fatigued patients.

	fatigue	non-fatigue	fatigue vs. non-fatigue
	mean (SD)	mean (SD)	Cohen's d (p-value)
VO2peak (L min^{-1}) vs. references values of Fairbarn[49]	-1.09 (0.47)	-0.74 (0.51)	0.72 (0.126)
6MWD in meters vs. reference values of Gibbons[50]	-184.21 (69.77)	-119.53 (51.57)	0.80 (0.030)
PT extension 60°/s (Nm) vs. reference values of Akima[51]	13.59 (29.44)	32.22 (39.76)	0.57 (0.249)
PT extension 180°/s (Nm) vs. reference values of Akima[51]	-32.50 (17.19)	-17.75 (22.48)	0.81 (0.117)
PT flexion 60°/s (Nm) vs. reference values of Akima[51]	-45.20 (15.31)	-32.29 (21.53)	0.72 (0.140)
PT flexion 180°/s (Nm) vs. reference values of Akima[51]	-64.03 (12.59)	-54.40 (18.96)	0.81 (0.197)
Dynamic activity (% 24h)* vs. reference values of the ErasmusMC[38, 52]	-0.35 (0.98)	0.35 (0.97)	0.70 (0.134)
Mean motility (g)‡ vs. reference values of the ErasmusMC[38, 52]	-0.77 (0.71)	0.04 (0.89)	1.02 (0.037)
Motility during walking (g)# vs. reference values of the ErasmusMC[38, 52]	-0.31 (1.26)	0.67 (1.69)	0.67 (0.159)
Transitions (number)§ vs. reference values of the ErasmusMC[38, 52]	-0.65 (0.88)	-0.62 (0.70)	0.04 (0.927)
Walking periods > 10 seconds (number) vs. reference values of the ErasmusMC[38, 52]	-0.64 (0.97)	-0.02 (1.35)	0.57 (0.232)

6MWD = 6-min walk distance; VO2peak (L min^{-1}) = peak oxygen uptake; Cohen's d: effect size;
SD = standard deviation; PT = peak torque; g = gravitational acceleration (1 g = 9.81 m/s^2); MC = medical center.
*Composite measure (walking, cycling, general (non-cyclic) movement) expressed as percentage of a 24-h period
‡Intensity of daily physical activity (1 g =/9.81 m/s^2).
#Walking speed.
§Contains all transitions except the lying transitions such as the transition from lying prone to lying supine.

DISCUSSION

This study showed an impaired physical fitness (cardiorespiratory fitness and muscle strength) and physical activity in fatigued IBD patients compared with non-fatigued IBD patients. The same was seen when outcomes of both fatigued and non-fatigued IBD patients were compared to reference values of non-IBD healthy persons.

To our knowledge, this is the first study which shows a medium effect size for lower cardiorespiratory fitness (VO2peak, VT, and 6MWD) in fatigued IBD patients compared with

non-fatigued IBD patients. This finding is consistent with literature on cancer patients and liver transplant recipients, which demonstrated a relationship between impaired cardiorespiratory fitness and severity of fatigue.[17, 22] The origin of the impaired cardiorespiratory fitness is possibly a less active behavior, as part of sickness behavior.[53-56] Since we know that disease activity is an important determinant of fatigue complaints, this sickness behavior may be induced by circulating cytokines (IL-1, IL-6 and TNF-α) during active disease.[3, 5, 7, 57-60] Therefore, it can be hypothesized that sickness behavior, and the direct negative effect of the cytokines IL-6 and TNF-α on muscle performance induce lowering of physical activity. Lowering of physical activity could result in impaired physical fitness, thereby leading to further deteriorating of fatigue complaints (Figure 2).[17, 54, 57, 61-68] Because physical exercise lowers pro-inflammatory cytokines, physical exercise could interfere in this cascade.[65, 66, 69]

Impaired cardiorespiratory fitness is known to be related to lower muscle strength.[70, 71] Our study found a medium effect size for lower muscle strength (PT extension 60°/s, PT flexion 60°/s, PT flexion 180°/s) and a large effect size for lower PT extension 180°/s in fatigued IBD patients compared with non-fatigued IBD patients. Previous studies in IBD also showed impaired muscle strength in these patients, but fatigue was not investigated in these studies.[72-74] Only one study showed an association between impaired muscle strength and fatigue severity in IBD patients.[61] Because we measured the muscle strength both at 60°/s and 180°/s, combined with flexion and extension of both lower limbs, we were able to show a broader spectrum of muscle performance. The etiology of the impaired muscle strength seems multifactorial. The use of corticosteroids is one of the factors associated with impaired muscle strength.[75-77] However, in our study only one patient in the fatigue group used corticosteroids at the time of participation. Although we are unaware of the former corticosteroid use in these patients, it is unlikely that impaired muscle strength in fatigue patients was induced by corticosteroid use.

Nutritional status, in a previous study defined as lower BMI, was found as a factor of impaired muscle strength.[78] We could not confirm this, because no differences were found in BMI and fat free mass between fatigued and non-fatigued patients. It might be that cytokines negatively influence muscle strength in IBD patients.[61, 67, 68] Beside the negative effect of cytokines on muscle strength, reduced physical activity is associated with lower muscle strength.[79, 80] We showed medium effect sizes for reduced physical activity in fatigued IBD patients compared with non-fatigued IBD patients. This is in line with a previous reported relationship between lower physical activity and severity of fatigue in liver transplant recipients.[18]

This finding is in contrast with a previous study which showed no difference in physical activity between fatigued IBD patients and a healthy control group.[61] However, this latter study did not report on the intensity of physical activity, which was significantly lower in our fatigued IBD patients.

Our results of impaired physical fitness and physical activity in fatigued IBD patients are

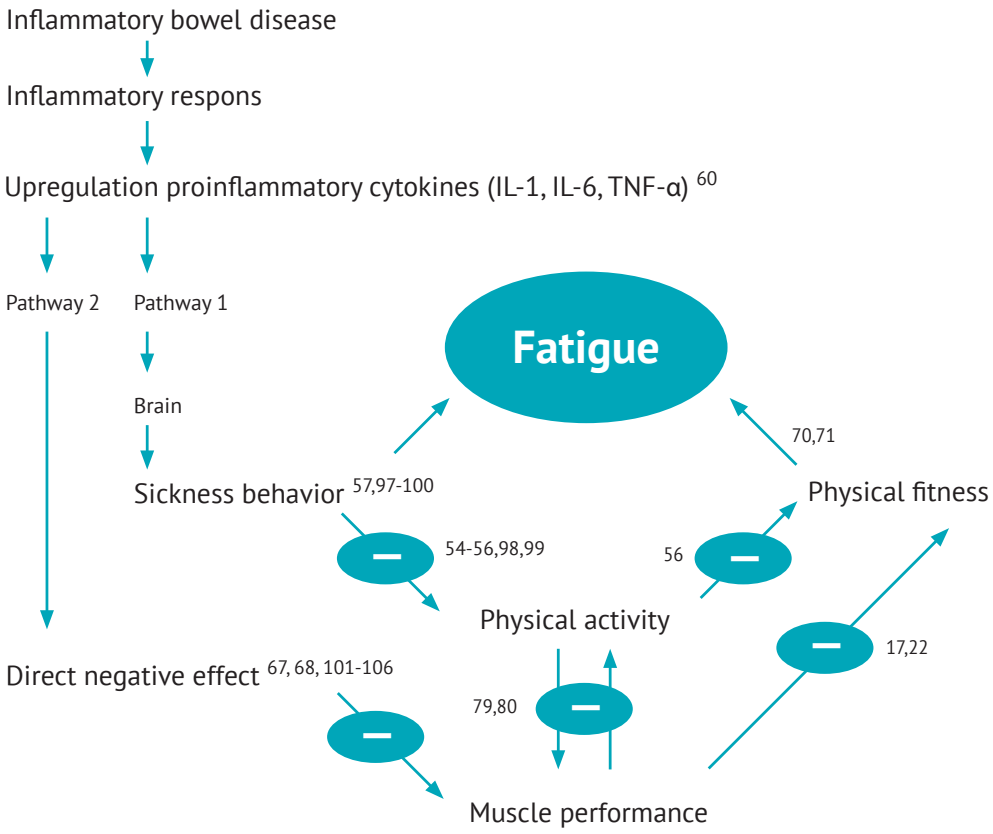

Figure 2: Conceptual model of action of proinflammatory cytokines on the induction of fatigue.
Profinflammatory cytokines (IL-1, IL-6, TNF-α) are upregulated as an inflammatory response due to inflammatory bowel disease.[60] These cytokines may induce sickness behaviour via several immune-to-brain communication pathways.[57, 97-100]

We hypothesize that proinflammatory cytokines act via two additional pathways:
Pathway 1: proinflammatory cytokines may induce sickness behaviour. Sickness behaviour results in less active behaviour (=impaired physical activity), thereby leading to impaired physical fitness.[54-56, 98, 99] Impaired physical activity also induces impaired muscle performance.[79, 80] Impaired muscle performance result in impaired physical fitness leading to further deteriorating fatigue.[17, 22, 70, 71]
Pathway 2: proinflammatory cytokines (particular TNF-α and IL-6) negatively affects on muscle performance.[67, 68, 101-106] Impaired muscle performance results in impaired physical fitness leading to further deteriorating fatigue.[17, 22, 70, 71]

important for optimization of fatigue management and must be regarded in addition to fatigue associated factors, such as disease activity, perceived stress, and depressive coping. Previously it was shown that optimal management of disease activity, stress, and coping is effective to reduce fatigue.[13, 81-84] Despite that these aforementioned interventions are effective in the majority of IBD patients, there are still patients suffering from severe fatigue. As previous studies showed positive effects of exercise interventions on QoL in IBD patients and also on fatigue in other patients with chronic disorders.[16, 20, 21, 85-95,] we suppose that a multidisciplinary approach to reduce the fatigue burden is needed.

This study has some limitations: first, patients were not screened for disease activity using calprotectin at inclusion.[96] For measuring disease activity we used the HBI and CAI. Although these questionnaires are validated and widely used in trials, they are more prone to subjective results of disease activity.

Second, no data on cytokines were obtained. Although it is difficult to draw a conclusion in regard to cytokines in a small sample size, it is worth investigating the possible influence of cytokines on muscle performance and physical activity.

CONCLUSION

Fatigued IBD patients showed impaired physical fitness and physical activity compared with non-fatigued IBD patients. These results offer new possibilities to optimize fatigue management for IBD patients. Further research is warranted using exercise interventions, to confirm whether exercise reduces fatigue complaints in IBD patients.

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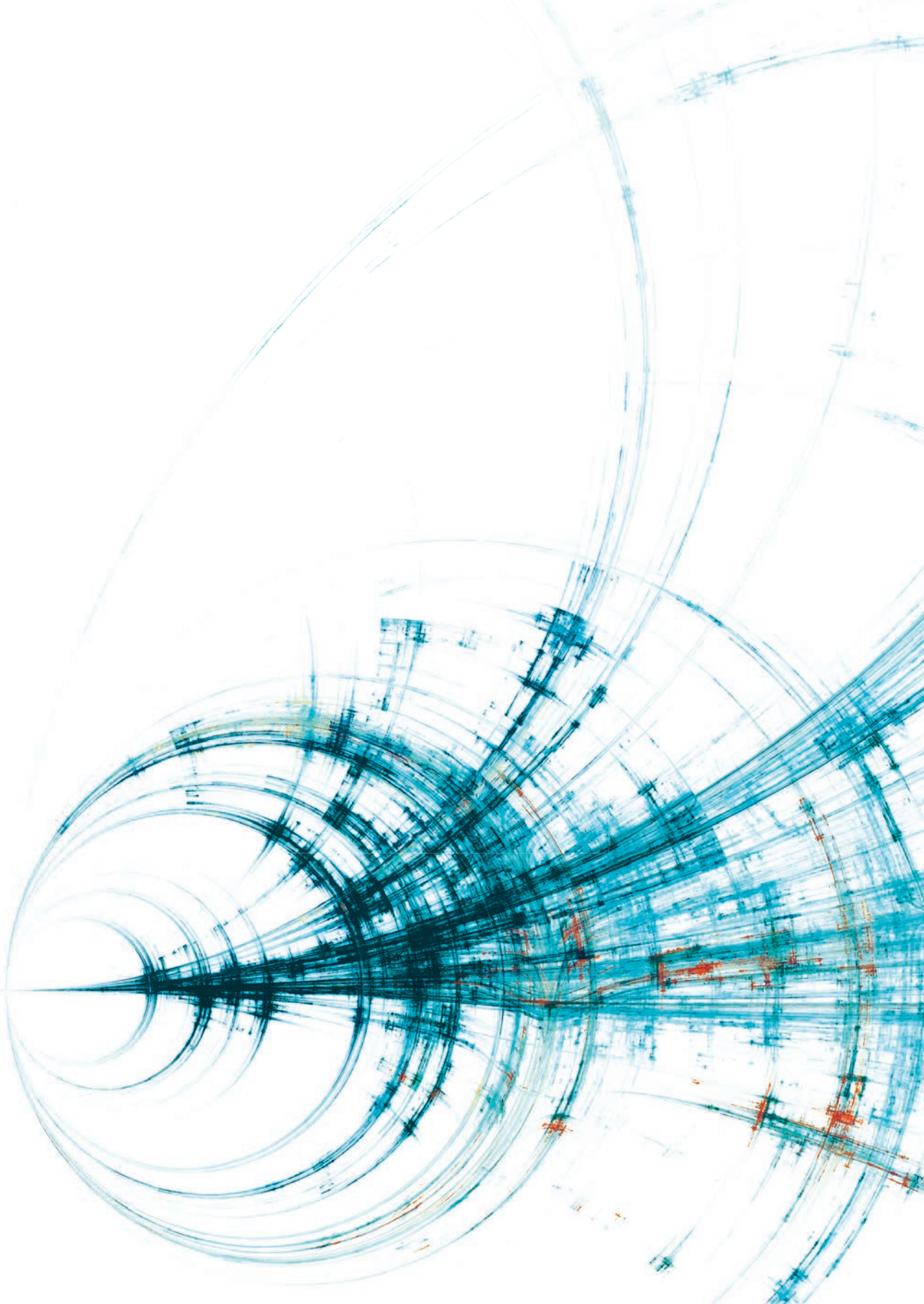

CHAPTER 4

Fatigue in IBD patients is associated with distinct differences in immune parameters

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ABSTRACT

Background

Although it is well recognized that fatigue is an important problem in a large fraction of quiescent inflammatory bowel disease (IBD) patients, it is unknown whether immunopathology is different in fatigued versus non-fatigued patients. Here we contrasted the characteristics of the immune system in fatigued against non-fatigued IBD patients in clinical remission.

Methods

IBD patients in clinical remission were phenotyped according to the montreal classification and the checklist individual strength-fatigue (CIS-fatigue) was used to assess fatigue (CIS-fatigue ≥ 35). Flow cytometry on peripheral blood samples was used to investigate differences in leukocyte subsets. The expression of various cytokines was determined in stimulated whole blood and serum samples using ELISA. Differences between fatigued and non-fatigued IBD patients were assessed.

Results

In total, 55 patients were included in the fatigue group (FG) and 29 patients in the non-fatigue group (NFG). No differences in demographic and clinical characteristics were observed between the groups.

Flow cytometry data showed a significant lower percentage of monocytes (5% vs. 7%; p = 0.013), and naive T-cells (36% vs. 47%; p = 0.048), higher percentage of memory T-cells (44% vs. 34%; p = 0.005) and neutrophils (77% vs. 69%; p = 0.033) in the FG compared with the NFG. Median serum level of IL-12 (4.8 pg/ml, 3.3 pg/ml; p = < 0.001) was significantly higher in the FG, while IL-8 (2.6 pg/ml, 5.7 pg/ml; p = 0.048) was significantly lower in the FG compared with NFG.

Conclusion

A dichotomy exists between fatigued and non-fatigued patients in that the fatigued patients show signs of immune stimulation. This upregulation of the immune system could maintain fatigue complaints via immune-to-brain communication pathways. Further exploration of the underlying immune effects associated with fatigue is warranted to determine potential treatment options.

INTRODUCTION

Patients with inflammatory bowel disease (IBD) suffer from an immune-mediated chronic relapsing disease. This disease significantly impairs the health-related quality of life of patients. Fatigue is an important factor negatively affecting the health-related quality of life in these patients.[1-4] With more than 40% of IBD patients suffering from fatigue, even when the disease is in remission, further understanding of the etiology of fatigue in IBD is warranted.[1, 3, 5] There is bidirectional communication between the brain and the immune system. As such fatigue can affect the immune system and vice versa. If fatigue influences the immune system in IBD it is well possible that stratification for pharmacological treatment based on fatigue status may improve clinical outcome. If fatigue merely reflects ongoing immune activation in IBD patients it might also implicate the potential usefulness of targeted therapy for IBD related fatigue.

A variety of factors, including disease activity, sex, psychological well-being, medication use, anemia, and sleep difficulties are influencing the severity of fatigue in IBD patients, and interestingly many of these factors may in turn also affect immune parameters.[3, 4, 6] Indeed in other diseases, especially chronic fatigue syndrome (CFS), fatigue and immunity show important correlations.[7-13] The mechanisms by which fatigue status is linked to the immune system remain largely obscure, but in view of the increasing evidence for the existence of a gut-brain axis it is well possible that also in IBD, fatigue-related effect of the immune system may exist.[14-16] This effect of the immune system was also proposed in fatigued MS and cancer patients, where higher levels of pro-inflammatory cytokines were seen in fatigued patients.[17, 18] Nevertheless, the relation between fatigue status and immune status in IBD remains unexplored and thus studies on this aspect of IBD are urgently called for. The above-mentioned considerations prompted us to investigate whether the fatigued IBD patients differ from non-fatigued IBD patients with respect to immunity.

MATERIALS AND METHODS

Study design

For this study we exploited an earlier-published study cohort in which the effects of solution focused therapy on fatigue in IBD patients was characterized.[19]

Use of this cohort allowed us to include patients with well-characterized fatigue status. Patients from this cohort were asked to participate in this study.

The checklist individual strength (CIS) was used to determine whether a patient suffered from fatigue (CIS-fatigue subscale score ≥ 35).[20] As described in our earlier-published study cohort, faecal calprotectin concentration was measured in the fatigue patients. Levels of <200 ug/g

were regarded as compatible with disease remission.[19] The Harvey Bradshaw index (HBI) < 5 for Crohn's disease or the colitis activity index (CAI) < 10 for ulcerative colitis was used to determine clinical remission of the disease in the non-fatigue patients.[21, 22]
Demographics, disease phenotype (Montreal classification) were collected from medical records and concomitant medication use was investigated with a questionnaire focusing on current medication use and subjective side-effects to medication.[23]
After these baseline measurements and measurements on blood samples, the fatigue patients (FG) were enrolled in a clinical trial to study the effect of psychotherapy, especially solution-focused therapy on fatigue of which the results have been described.[19] Consecutive IBD patients from the same hospitals as the fatigue cohort, with a CIS-fatigue score < 35 were enrolled in the non-fatigue group (NFG) for this study. As in the FG, patients of the NFG were aged ≥ 18 years, and the diagnosis of IBD was radiologically or endoscopically/histologically confirmed. Exclusion criteria, as described in the clinical trial, were equal for the FG and NFG.
Differences in baseline measurements between the FG and the NGF, included laboratory values. In the NFG patients only CRP and leukocytes were measured.

This study was conducted in accordance with the protocol International Conference on Harmonization Guidelines for Good Clinical Practice, the Declaration of Helsinki and local national regulations governing clinical study conduct, and was registered at the medical ethical committee (MEC) of the Erasmus Medical Center (registration number: MEC-2010-107; NL32020.078.10). The protocol was approved by the institutional review board. All patients gave written informed consent. Patients were enrolled in The Netherlands from January 2010 to January 2011 by the principal investigator.

Blood collection and stimulation

Following blood drawing, serum was obtained using a coagulation tube and stored at -80 °C until further analysis. Serum was collected from both fatigue and non-fatigue IBD patients and immune assays were conducted at the same location for all blood samples.
Heparinized whole blood samples were diluted 1:10 with RMPI 1640 (Lonza, Basel, Switzerland) were stimulated with 25 ug/ml PHA (phytohaemagglutinin) (Remel, Lenexa, KS, USA) or 100 ng/ml LPS (lipopolysaccharide) (Sigma-Aldrich, Zwijndrecht, The Netherlands). Supernatants of the LPS and PHA stimulated cultures were obtained at 24 and 72 hours respectively and stored at -80 °C till further analysis.

Leukocyte subsets analysis

After removal of erythrocytes using ery-lysis buffer, the heparinized whole blood samples were

stained using antibodies against CD16 (Pacific Blue), CD14 (PerCP/Cy5.5), CD56 (PE/Cy7), CD62-L (Alexa Fluor 647) purchased from BioLegend (San Diego, CA, USA); CD3 (AmCyan) and CD4 (APC-H7) from BD (Franklin Lakes, NJ, USA); CD45RA (FITC) from eBioscience (San Diego, Ca, USA) and CD19 (PE) from Beckman Coulter (Brea, CA, USA) to analyse the different leukocyte subsets using the FACS-Canto II flow cytometer with BD FACSDiva software from BD biosciences (Franklin Lakes, NJ, USA). The different leukocyte subsets were identified and counted using Flowjo software (TreeStar Incorporation, Ashland, OR, USA).

The leukocytes were subdivided into 3 main populations based on FSC-SSC: lymphocytes, granulocytes, and monocytes. The different leukocyte subsets were subdivided into lymphocytes (T-cells, B-cells, Cytotoxic T-cells, T-helper cells, Memory T-cells, Effector T-cells, Naïve T-cells and NK-cells), monocytes (CD14+CD16+, CD14-CD16+ and CD14+CD16-) and granulocytes (eosinophils and neutrophils) as shown in Table 3.

Cytokine levels

Serum and supernatant levels of IL-4, IL-5, IL-6, IL-8, IL-10, IL-12, TNF-α and IFNγ were assessed using Ready-Set-Go!® ELISA sets from eBioscience (San Diego, Ca, USA) according to the manufacturers' instructions and using Maxisorp 96 wells plates (Nunc, Waltham, MA, USA) and a model 680 Microplate Reader from Bio Rad (Hercules, CA, USA). When levels were below detection limit the concentration was put at 2.0, the lowest levels that was accurately measurable.

Statistical analysis

For differences in characteristics and disease phenotype between the fatigue and non-fatigue groups, χ^2 tests were used for dichotomous variables and t-tests for continuous variables.

Normality of laboratory parameters, leucokyte subsets and cytokines were determined with Shapiro-Wilks tests. All outcomes, except lymphocytes, granulocytes, monocytes, naive T-cells and memory T-cells, were not normally distributed. Differences between the FG and NFG were analyzed with t-tests for normally distributed outcomes and with Mann-Whitney U-tests for abnormal distributed outcomes. Medians, interquartile ranges and differences are presented in Table 3.

Data was analyzed with SPSS Software for Windows, V.20 (SPSS, Chicago, IL).

Results were considered significant when two-sided p - values were less than 0.05.

RESULTS

Patient characteristics

In total, 55 fatigued IBD patients (FG) of the earlier-published study cohort agreed to participate

in this study, and 29 patients in the non-fatigue group (NFG) were included.

Before analyzing the differences in immune parameters, the demographic and clinical characteristics of the groups were analyzed (FG vs. NFG, see Tables 1 and 2). No differences were observed between the two groups. With regard to remission of the disease, the NFG showed a mean CAI score of 2.3 (SD 0.6) and a HBI score of 1.2 (SD 1.1). The mean calprotectin level in the FG was 66 ug/g. Based on these scores both groups were in clinical remission.

Table 1: Patient characteristics.

Patient characteristics	**fatigue n=55**	**non-fatigue n=29**	**p-value**
Age in years; mean (SD)	40.1 (10.4)	40.7 (14.4)	0.861
Females (%)	65.5	44.8	0.068
Crohn's disease (%)	76.4	89.7	
Ulcerative Colitis (%)	23.6	10.3	0.140
Current medication use (n)			
5-ASA	20	10	
Immunosuppressives	20	13	0.954
Corticosteroids	10	5	0.376
Biologicals (anti-TNF)	13	9	0.971
Side-effects to medication (n)			
5-ASA	3	1	0.484
Immunosuppressives	11	7	0.402
Corticosteroids	3	3	0.876
Biologicals (anti-TNF)	8	3	0.066

Chi-square test for dichotomous variables, and t-test for continuous variables.
SD: standard deviation
Corticosteroids: prednisone, budesonide
Immunosuppressives: azathioprine, methotrexate, cyclosporine

Whole blood leukocytes

As a first crude indicator of a link between fatigue status and the immune system in IBD patients, the composition of the leukocyte system was investigated using flow cytometry. No differences were detected in total leukocyte numbers (Table 3) between the groups. Within the major leukocyte subpopulations (lymphocytes, granulocytes and monocytes) a significant lower percentage of monocytes (median: FG: 5.3, NFG: 7.2; p = 0.013) was detected in the FG compared with the NFG. When monocytes were further subphenotyped, we found a significant lower percentage of the non-classical CD14dim CD16+ monocytes in the FG compared with the NFG (median: FG: 7.9, NFG: 11.9; p = 0.017).

Within the lymphocyte subsets no differences were detected, only within the CD4+ (helper) T-cell population, a significant higher percentage of central memory CD4+ T cells (median: FG: 43.7, NFG: 33.7; p = 0.005) in the FG compared with the NFG was found. Further analysis of the granulocyte

population showed a significant higher percentage of neutrophils (median: FG: 77.0, NFG: 68.8; p = 0.033) in the FG compared with the NFG. Thus analysis of the composition of the leukocyte compartment supports the idea that there is a difference in immunity between fatigued and non-fatigued IBD patients.

Whole blood cytokine production

In addition to the leukocyte subset analysis, we also determined the production of cytokines by the leukocytes after stimulation with PHA or LPS, in which PHA stimulates mostly lymphocytes and LPS is more prone to trigger de innate granulocytes and monocytes to produce cytokines (Table 3). PHA stimulation induced higher median cytokine levels in whole blood from the FG for all cytokines measured except for IL-6. Of these cytokines, the levels of TNF-α (median: FG: 224, NFG: 125; p = 0.022) and IFN-y (median: FG: 28875, NFG: 9536; p = 0.047) were significantly higher in the FG compared with the NFG. LPS stimulation induced significantly higher median IL-6 levels in the NFG compared with the FG (median: FG: 3114, NFG: 5064; p = 0.046)

Serum cytokine levels

We also investigated the serum levels of a variety of cytokines (Table 3). The levels of IL-12 (median: FG: 4.8, NFG: 3.3; p = < 0.001) were significantly higher in the FG serum samples, whereas the levels of IL-8 were significantly reduced in the FG serum compared with the NFG (median: FG: 2.6, NFG: 5.7; p = 0.048). Although the difference in IL-6 was also significantly reduced, the cytokine levels were very low or not detectable in the serum, making this parameter less reliable.

DISCUSSION

A large part of patients with IBD suffer from fatigue even when the disease is in clinical remission. The intricate bidirectional relation between the immune system and the brain justifies the search for possible difference in immune parameters in these patients.

We compared a large variety of immune parameters between fatigued and non-fatigued IBD patients to determine whether there were parameters that were discriminative between the groups. Since we are the first to compare a large variety of immune parameters between IBD patients with fatigue and without fatigue, we can only mirror our data to those studies that assessed immune parameters in patients suffering from fatigue in different disease settings like cancer, chronic fatigue syndrome (CFS) or chronic viral infections.[7-13, 24-30]

With regard to the differences in leukocyte subsets the reduced naïve CD4 population (CD45RA+ and CD62L+) was in contrast to data observed in patients with CFS, in these patients no or the opposite differences have been reported.[31,32] Since viral infections are a popular proposed cause of CFS, it

Table 2 (part 1): Disease phenotype

Patient characteristics	fatigue n=55	non-fatigue n=29	p-value
Montreal classification - CD			
Age at diagnosis (%)			
A1	9.8	26.9	0.065
A2	75.6	69.2	0.566
A3	14.6	3.8	0.159
Mean age at diagnosis in years (SD)	27.4 (9.2)	24.0 (9.0)	0.135
Location (%)			
L1	9.8	11.5	0.816
L2	41.5	34.6	0.575
L3	48.8	50.0	0.922
L4	2.4	3.8	0.742
+L4	2.4	11.5	0.126
Behaviour (%)			
B1	68.3	57.7	0.378
B2	14.6	23.1	0.380
B3	14.6	19.2	0.621
p	26.8	34.6	0.497
Surgery CD			
Bowel resection (%)	46.3	61.5	0.225
Number of resections; mean (SD)	1 (0.9)	1.5 (1.1)	0.122
Age at first resection; mean (SD)	29.8 (9.7)	29.5 (13.1)	0.930
Stoma (%)	14.6	15.4	0.933
Rectum amputation (%)	7.3	7.7	0.955

was interesting to notice that naïve CD4 cells and enhanced memory cells are a sign of chronic adaptive immune activation and have been previously reported in patients with chronic hepatitis C infection and was associated with CMV and H. Pylori titers.[33-35] As such, these data support the idea that there may still be some ongoing immune activation of unknown origin involved in the fatigue complaints. As with the T-cell changes, differences in neutrophils and monocytes between fatigued and non-fatigued patients could all be pointing towards an ongoing infection in the fatigued IBD patients.

Both the significant enhanced TNF-α and IFN-γ release upon stimulation with PHA are in line with observations in CFS patients where PBMC (peripheral blood mononuclear cells) instead of whole blood was stimulated.[36] Both of them are also supportive of a Th1-skewed immunity driving the fatigue complaints in IBD patients.

With regard to the serum pro-inflammatory cytokine levels, no significant difference in the levels of TNF-α was observed as often reported in CFS.[37, 38] However, anti-TNF treatment could influence these results.

The enhanced IL-12 and reduced IL-8 serum levels in fatigued IBD patients was also in line with data previously reported on plasma of CFS patients compared to healthy controls.[8, 39]

Table 2 (part 2): Disease phenotype

Patient characteristics	fatigue n=55	non-fatigue n=29	p-value
Montreal classification - UC			
Age at diagnosis (%)			
A1	0	0	
A2	92.3	66.7	0.226
A3	7.7	33.3	0.226
Mean age at diagnosis (SD)	29.2 (8.1)	35.7 (6.0)	0.215
Location (%)			
E1	7.7	0	0.620
E2	53.8	100	0.137
E3	38.5	0	0.195
Severity (%)			
S0	46.2	0	0.137
S1	53.8	66.7	0.687
S2	0	33.3	0.032
S3	0	0	
Surgery UC			
Bowel resection (%)	7.1	0	0.633
Number of resections; mean (SD)	1	0	-
Age at first resection; mean (SD)	22	-	-
Stoma (%)	0	0	-
Rectum amputation (%)	0	0	-
Laboratory CD and UC			
CRP; median (interquartile range) – baseline	1.0 (0.0-2.0)	2.0 (1.0-3.0)	0.140
Leukocytes; median (interquartile range) – baseline	6.0 (5.1-7.6)	5.4 (4.5-7.2)	0.188

Chi-square test for dichotomous variables, Mann-Whitney U-test for the continuous variables CRP and leukocytes, t-test for all other continuous variables.
CD: crohn's disease, UC: ulcerative colitis; SD: standard deviation; CRP: C-reactive protein

The differences in immune parameters between the fatigued and non-fatigued IBD patients suggest that there is a link between the immune system and the brain in IBD-associated fatigue. Whether this is a direct link cannot be concluded from our data.

Most of our data support the idea that there is an ongoing low level of immune activation in the IBD patients that present fatigue complaints while in clinical remission. Because of the multifactorial origins of fatigue there could be a variety of causes of the observed immune activation that may even differ between patients presenting similar immune parameters. Viral infections either acute or chronic may be involved in the IBD associated fatigue.[34, 40] Since serology status for different viral infections was not obtained during this study, we cannot rule out their possible role in at least subsets of the fatigued patients. Another possible cause may be the occurrence of microscopic relapses, at the level of the lamina propria, without affecting clinical disease

Table 3: Leucocyte subsets and cytokines.

Patient characteristics	Fatigue		Non-fatigue		p - value
	median	(interquartile range) n=55	median	(interquartile range) n=29	
Baseline					
Leukocytes	6.0	(5.1-7.6)	5.4	(4.5-7.2)	0.188
Lymfocytes	33.2	(22.8-46.0)	35.0	(28.7-50.7)	0.202
NK-cells	2.7	(0.4-6.6)	4.7	(0.9-8.2)	0.158
B-cells	8.5	(4.7-11.2)	8.6	(4.4-12.4)	0.963
T-cells	78.3	(59.5-82.4)	77.8	(66.2-82.7)	0.862
T-helper cells	64.4	(57.4-71.3)	67.6	(54.3-74.8)	0.519
Naive T-cells	36.1	(26.5-43.0)	47.0	(29.2-58.1)	**0.048**
Memory T-cells	43.7	(36.4-49.9)	33.7	(27.9-39.6)	**0.005**
Effector T-cells	16.5	(10.3-23.6)	12.8	(8.2-23.0)	0.263
Cytotoxic T-cells	35.6	(28.7-42.6)	32.4	(25.2-45.7)	0.527
Granulocytes	46.6	(34.2-58.6)	40.5	(28.5-52.6)	0.390
Eosinophils	3.6	(2.5-6.7)	4.9	(2.7-11.8)	0.097
Neutrophils	77.0	(64.6-83.6)	68.8	(58.9-78.2)	**0.033**
Monocytes	5.3	(3.5-7.5)	7.2	(4.7-9.1)	**0.013**
CD14- CD16+	7.9	(5.7-11.5)	11.9	(7.9-15.3)	**0.017**
CD14+ CD16+	3.5	(2.8-6.6)	2.6	(2.1-4.0)	**0.010**
CD14+ CD16-	86.9	(82.2-91.3)	84.6	(80.8-90.5)	0.361
PHA-stimulated WB					
IL-5	118.1	(86.5-211.2)	85.6	(62.3-148.7)	0.078
IL-6	2452.4	(1628.6-13758.0)	3464.3	(1223.7-15217.8)	0.982
IL-8	57142.7	(41053.9-94130.1)	46236.6	(23678.6-85122.2)	0.156
IL-10	657.7	(325.8-1108.2)	276.3	(154.2-1133.5)	0.132
TNF-α	223.7	(111.8-677.8)	125.0	(48.0-438.3)	**0.022**
IFN-y	28875.3	(17486.9-51397.7)	9536.2	(2525.3-75475.8)	**0.047**
LPS-stimulated WB					
IL-6	3114.5	(2394.2-5276.4)	5064.6	(3286.7-7268.3)	**0.046**
IL-8	5843.9	(2815.9-9539.2)	4760.1	(3067.1-10641.3)	0.777
IL-10	199.5	(107.3-304.3)	135.5	(96.3-275.5)	0.651
TNF-α	559.5	(173.7-1207.6)	206.0	(65.7-709.4)	0.073
Serum cytokines					
IL-4	2.0	(2.0-3.2)	2.0	(2.0-2.4)	0.583
IL-5	14.7	(3.2-54.0)	10.0	(2.0-27.6)	0.248
IL-6	2.0	(2.0-2.0)	2.3	(2.0-4.7)	**0.001**
IL-8	2.6	(2.0-4.8)	5.7	(2.0-50.7)	**0.048**
IL-10	2.2	(2.0-3.1)	2.0	(2.0-2.4)	0.067
IL-12	4.8	(3.8-9.0)	3.3	(2.0-4.4)	**< 0.001**
TNF-α	49.5	(11.9-94.1)	45.1	(13.5-174.2)	0.660
IFN-y	4.6	(2.8-7.3)	3.3	(2.0-10.8)	0.377

symptoms.[41] Since our patients were in clinical remission, no biopsies are available to rule out this possibility. Microscopic disease activity may enable enhanced translocation of bacteria, described as 'leaky gut' a phenomenon that has been associated with CFS as well.[42, 43]
Since microbes are well known to influence the immune system, it will be interesting to include characterization of the microbiome in future studies focusing on fatigue in IBD, or even consider testing therapeutic microbes for treatment of IBD related fatigue.[37, 44]

CONCLUSION

We show for the first time that differences in immune parameters are associated with fatigue symptoms in IBD patients without clinically active disease. These data warrant further investigation into the possible causal relations between these parameters and the fatigue symptoms since this may lead to an effective resolution in part of the IBD patients with fatigue.

t-test for normally distributed variables (lymphocytes, granulocytes, monocytes, naive T-cells and memory T-cells), Mann-Whitney U-test for not normally distributed variables.
Cytokine concentrations in pg/ml. WB: whole blood
- Lymphocytes, Granulocytes, Mononcytes: percentage of whole blood
- T-helper cells, Cytotoxic T-cells: percentage of T-cells
- Naive T-cells, Memory T-cells, Effector T-cells: percentage of T-helper cells
- Eosinophils, Neutrophils: percentage of granulocytes
- CD14- CD16+, CD14+ CD16+ and CD14+ CD16- monocytes: percentage of total monocytes

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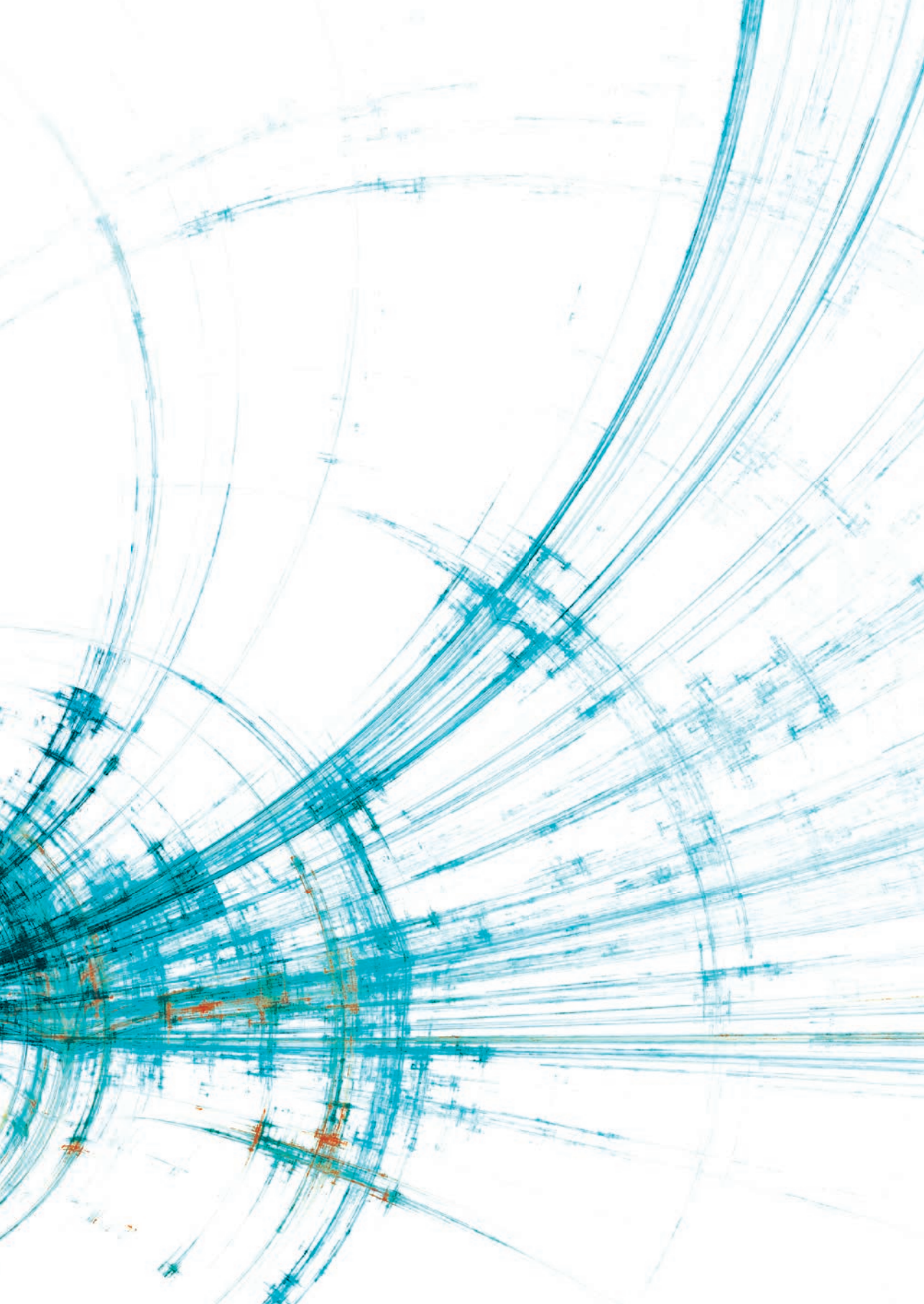
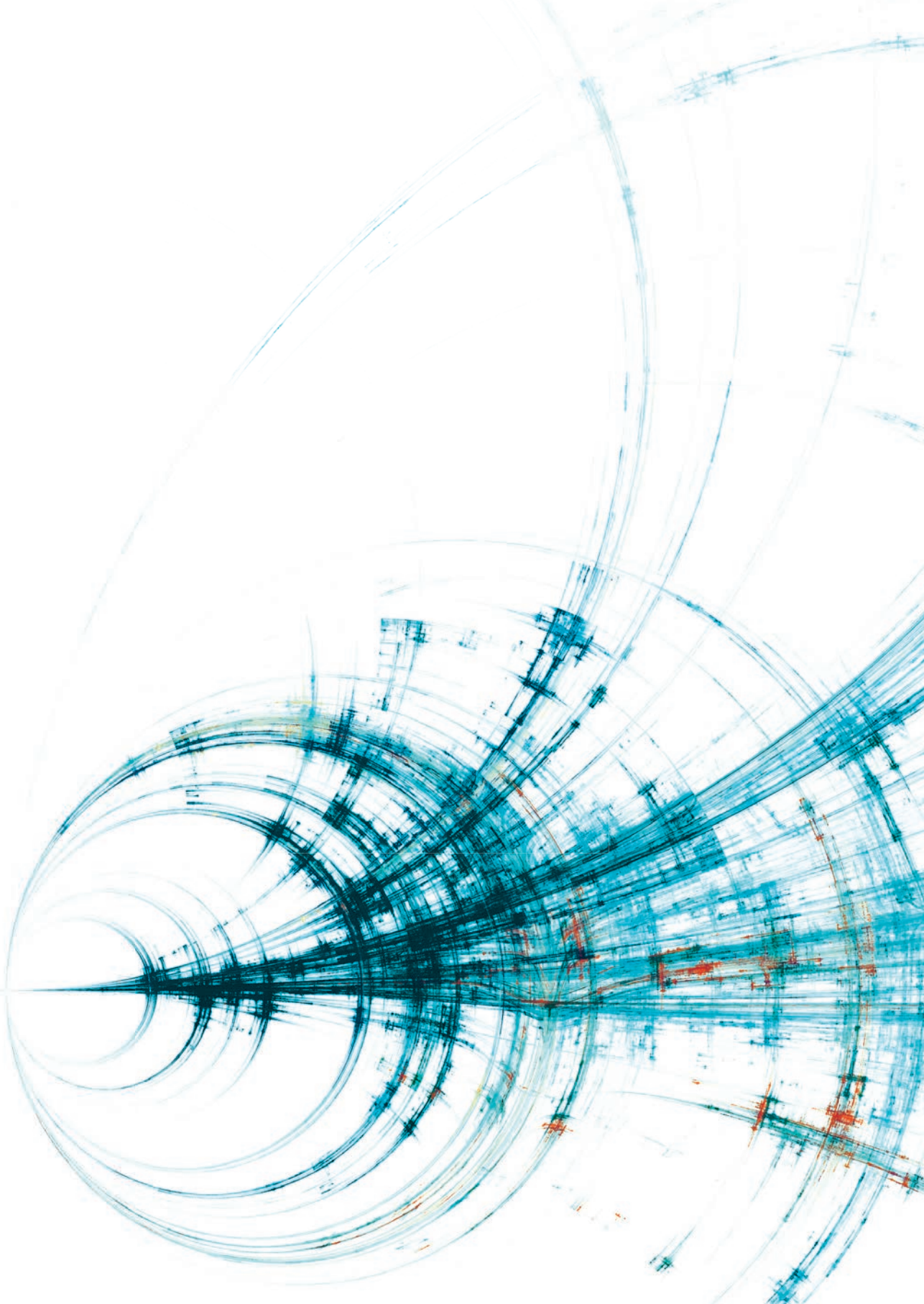
PART II

Fatigue management in IBD patients





CHAPTER 5

The impact of biologics on health-related quality of life in patients with IBD

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ABSTRACT

Background

Inflammatory bowel disease (IBD) is characterized by a chronic relapsing inflammation of the gastrointestinal tract. Adult IBD patients suffer from a disabling disease which greatly affects health-related quality of life (HRQoL). A worse HRQoL in these patients may result in a defensive and ineffective use of medical attention and thus higher medical costs. Because of its chronic nature, IBD may also cause psychological problems in many patients which may also influence HRQoL and care-seeking behavior. An important factor reducing HRQoL is disease activity. Induction of remission and long-term remission are important goals for improving HRQoL. Furthermore, remission is associated with a decreased need for hospitalization and surgery and increased employment, which in turn improve HRQoL. Treatment strategies available for many years are corticosteroids, 5-aminosalicylates and immunnosup- pressants, but these treatments did not show significant long-term improvement on HRQoL. The biologics, which induce rapid and sustained remission, may improve HRQoL.

Objective

To review and evaluate the current literature on the effect of biologics on HRQoL of IBD patients.

Methods

We performed a MEDLINE search and reviewed the effect of different biologics on HRQoL. The following subjects and synonyms of these terms were used: inflammatory bowel disease, Crohn's disease, ulcerative colitis, quality of life, health-related quality of life, fatigue, different anti-TNF medication, and biologicals/biologics (MESH). Studies included were limited to English-language, adult population, full-text, randomized, double-blind, placebo-controlled in which HRQoL was measured.

Results

Out of 202 identified articles, 8 randomized controlled trials (RCT) met the inclusion criteria.
Two RCTs on infliximab showed significant improvement of HRQoL compared to placebo which was sustained over the long term. One RCT on adalimumab showed a significant and sustained improvement of HRQoL compared to placebo. This study showed also significant decrease of fatigue in the adalimumabtreated patients. Three RCTs on certolizumab showed a significant improvement of HRQoL in the intervention group compared to placebo. Two RCTs of natalizumab treatment were found. One study showed significant and sustained improvement compared to placebo, and also scores of HRQoL comparable to that in the general population, but in the other no significant results were found.

Conclusion

The biologics infliximab, adalimumab, certolizumab, and natalizumab demon- strated significant improvement of HRQoL of IBD patients compared with placebo. However, we found differences in improvement of HRQoL between the different biologics.

INTRODUCTION

Inflammatory bowel disease (IBD) is characterized by a chronic relapsing inflammation of the gastrointestinal tract. Although IBD is a chronic disease with a normal life expectancy, the disease decreases health-related quality of life (HRQoL). Adult IBD patients have a lower HRQoL than the general population. A reduction of HRQoL can be predicted by symptom severity, disease severity, rheumatic symptoms, female gender and higher need for hospitalization. The chronic nature of the disease also affects HRQoL. The long period of time needed to adapt to the disease may cause psychological symptoms which negatively influence HRQoL and care-seeking behavior.[1–7]

IBD patients frequently complain of fatigue. Approxi- mately 41% patients with quiescent IBD are known to suffer from fatigue,[8] which is frequently associated with a decreased HRQoL.

In a substantial group of IBD patients HRQoL may impaired because of prolonged treatment and the adverse effects associated with such treatment, the need for surgery and hospitalization.[9–15] Another important factor influencing HRQoL is disease activity.[16–20] Improvement of HRQoL can therefore be achieved by inducing remission.[21] Furthermore, remission is associated with less medical care, increased employment, and thus improved HRQoL.[22]

For decades, 5-aminosalicylates (5-ASA), corticosteroids and immunosuppressants comprised the cornerstone of treatment for IBD patients. Despite their effectiveness in active disease, these drugs cannot prevent progression to a more complicated disease.[23] Although IBD patients showed significant improvement of HRQoL on the short term, during prolonged treatment no significant improvement of HRQoL has been shown with these drugs,[9,24–31] partly because of side effects that also negatively affect HRQoL.[11–13,32]

Because current treatments fail to prevent progression to more complicated disease stages, and because of the negative influence of the disease and its treatment on HRQoL, a more effective treatment is needed.[5,9,15,16,19,32,33] Biologics, which induce rapid and sustained disease remission, may provide effective treatment.[34]

However, biologics are more expensive than 5-ASA, corticosteroids and immunosuppressants used for treating IBD. IBD has high direct and indirect costs for patients and society. The direct costs (±50%) comprise inpatient care, outpatient care, self-care, medications and tests/procedures. The indirect costs comprise work absenteeism, decreased incomes, decreased HRQoL and fatigue. The direct costs vary between €6,000 and €40,000 per patient year.[35,36–38] In the near future, the

costs for IBD will increase, largely because of the increased incidence rates of IBD over recent decades in developed countries together with the early onset of the disease.[38–42]
Treatment with expensive biologics will increase the up front health care costs for IBD, however they can be cost- effective due to rapid induction and long-term remission.[22] In order to reduce indirect costs, biologics must improve HRQoL. We therefore focus our review on the effect of these drugs on HRQoL.

METHODS

Search

In MEDLINE we searched (from 1980 up to January 2009) for the following subjects and synonyms: inflammatory bowel disease (MESH), Crohn's disease (MESH), ulcerative colitis (MESH), quality of life (MESH), health related quality of life, fatigue (MESH), infliximab, adalimumab, certolizumab and natalizumab, and biologicals/biologics (MESH). We also hand-searched the reference lists of the relevant articles for titles which included a biologic and quality of life.
The search was limited to English-language, adult population and full-text publications. Studies were included for review if they were randomized, double blind, placebo- controlled trials (RCTs) of biologics (ie: infliximab, adalimumab, certolizumab or natalizumab) maintenance treatment in IBD and if HRQoL was measured by the Inflam- matory Bowel Disease Questionnaire (IBDQ) and/or the Short Form Health Survey (SF-36) as a primary or secondary outcome measurement. Only studies using these question- naires were included, because in current research these are the most commonly used validated questionnaires, enabling reliable comparison of the study outcomes.[43–46] We included only randomized, double blind, placebo-controlled trials, to rule out confounding of the results by placebo effects or physician preference for biologics.

Questionnaires

The IBDQ is a disease-specific HRQoL questionnaire containing 4 subscales: bowel symptoms, systemic symptoms, emotional functioning, and social functioning.[43] The total IBDQ score is the sum of the responses to each of the IBDQ questions. Total IBDQ score can range from 32 (very poor HRQoL) to 224 (perfect HRQoL). Patients in symptomatic remission usually have a score of 170 or greater.[43] An absolute change of 16 points in the total IBDQ score has been used to define a minimum clinically relevant improvement.[43,47,48]
The SF-36 is a generic HRQoL assessment and is also much used in IBD studies. The SF-36 consists of 8 scales (physical functioning, role-physical, bodily pain, general health, vitality, social functioning, role-emotional, and mental health). The SF-36 comprises two summary components, the physical component summary (PCS) and the mental com- ponent summary (MCS) which are

derived from individual scale scores.[44–46] The 8 scales are scored on a scale of 0 to 100, higher scores indicating better health.[49] For the PCS and the MCS the mean score is 50 and the SD 10 for the general population in the US.[50] An absolute increase of 3 to 5 points in the PCS or MCS scale is generally accepted as a meaningful change.[51,52]

RESULTS

The literature search identified 202 potentially eligible articles. Of these, 143 were not focused on HRQoL. Fifty studies were excluded because they were not RCTs. Of the 9 remaining studies, we excluded 1 RCT which reported results from only a single infusion of infliximab.[53] The first author determined which studies were excluded and an inter-rater agreement check of 10% of the articles was done by the last author. A perfect agreement was reached in this random sample. Table 1 summarizes the studies, which are discussed below.

Infliximab and HRQoL

Two studies, the Active Ulcerative Colitis Trials 1 and 2 (ACT 1 and 2) and the ACCENT 1 study (Crohn's disease), investigated the effect of infliximab on the HRQoL.[54,55]

The ACT 1 and 2 compared infliximab 5 mg/kg with 10 mg/kg and a placebo-controlled group. Both the ACT 1 and ACT 2 studies showed a significant improvement of total IBDQ and SF-36 scores at week 8 compared with baseline in both the infliximab 5 mg/kg and 10 mg/kg groups. There were no differences in HRQoL between the 2 treatment groups. The improvement in HRQoL was significantly greater in the treatment groups than in the placebo-control group for the IBDQ ($p < 0.05$) and the SF-36 ($p < 0.01$). Also, the percentage of patients achieving clinically relevant improve- ment on the IBDQ and SF-36 was significantly greater in the treatment groups than in the placebo-controlled group ($p < 0.05$). The bowel and social domain scores seemed to be responsible for the improvement of the IBDQ, whereas both PCS and MCS of the SF-36 scores were responsible for the improvement. At 30 and 54 weeks the improvement in the treatment groups was still significantly greater than in the placebo-controlled group ($p < 0.001$).

The ACCENT I study compared 3 treatment modalities (single infusion of 5 mg/kg with placebo maintenance; 5 mg/kg single infusion with 5 mg/kg maintenance; 5 mg/kg single infusion with 10 mg/kg maintenance). In all 3 treatment groups, all 4 IBDQ dimensional scores (emotional functioning, social functioning, systemic symptoms and bowel symptoms dimensions) improved from baseline throughout the study. However, the improvement in total IBDQ score at week 10, 30, and 54 was consistently larger ($p < 0.05$) in both infliximab maintenance groups compared with the placebo maintenance group. The IBDQ subscales for bowel and systemic symptoms showed the largest improvement. The SF-36 scores improved from baseline to week 54 in all treatment

Table 1 Demographic and baseline characteristics

Study	n	Crohn's disease/ ulcerative colitits	Age, years (mean ± SD)	Sex male, number (%)
Feagan 2007[54]	728	Ulcerative colitis	Placebo: 40.3 ± 13.6 Infliximab (5 mg/kg): 41.5 ± 13.7 Infliximab (10 mg/kg): 41.0 ± 41.1	291 (40)
Feagan 2007[61] (ENACT-2)	339	Crohn's disease	Natalizumab: 37 ± 13 Placebo: 37 ± 12	Natalizumab: 77 (46) Placebo: 59 (35)
Feagan 2003[55]	573	Crohn's disease	37 ± 12 (all patients)	239 (41.7)
Loftus 2008[56]	499	Crohn's disease	Group 1: 36.9 ± 11.9 Group 2: 36.4 ± 11.1 Group 3: 36.9 ± 11.8	Group 1: 65 (38) Group 2: 61 (36) Group 3: 62 (39)
Rutgeerts 2008[57]	292	Crohn's disease	Placebo: 35.8 (range 19–64) Certolizumab 100 mg: 33.5 (range 18– 56)/200 mg: 40.1 (range 19–71)/400 mg: 35.9 (18–67)	Placebo: 24 (32.9) Certolizumab 100 mg: 35 (47.3)/200 mg: 22 (30.6)/400 mg: 32 (44.4)
Sands 2007[62]	79	Crohn's disease	Natalizumab + Infliximab: 39.9 ± 12.6 Placebo + Infliximab: 38.9 ± 13.2	Natalizumab + Infliximab: 24 (46) Placebo + Infliximab: 17 (63)
Sanborn 2007[58] (PRECISE)	662	Crohn's disease	Certolizumab: 37 ± 12 Placebo: 38 ± 12	Certolizumab: 157 (47) Placebo: 131 (40)
Sanborn 2007[58] (PRECISE 2)	668	Crohn's disease	Certolizumab: 38 ± 11 Placebo: 38 ± 12	Certolizumab: 92 (43) Placebo: 109 (52)

CDAI, Crohn's Disease Activity Index; IBDQ, Inflammatory Bowel Disease Questionnaire; MCS, mental component summary; PCS, physical component summary; SF-36, Short-Form Health Survey; SD standard deviation

CDAI (mean ± SD) baseline	Total IBDQ score (mean ± SD) baseline	Total SF-36 score (mean ± SD) baseline	Intervention	Control group
	126 ± 31.7	PCS: 38.4 ± 8.5 MCS: 40.3 ± 11.5	Group 1: Infliximab: 5 mg/kg wk 0, 2, 6; maintenance every 8 wk Group 2: Infliximab: 10 mg/kg wk 0, 2, 6; maintenance every 8 wk	Placebo
Natalizumab: 296 ± 56 Placebo: 302 ± 58	123.6 ± 29.7	PCS: 33.7 ± 8.0 MCS: 38.4 ± 10.9	Natalizumab induction (300 mg) or placebo wk 0, 4, 8 Responders: Natalizumab (300 mg/4 wk)	Placebo
302 ± 54	128 ± 27	PCS: 34 ± 8 MCS: 39 ± 11	Infliximab induction (5 mg/kg wk 0 Responders: Group 1: Infliximab (5 mg/kg) wk 2,6; maintenance every 8 wk Group 2: Infliximab(5 mg/kg) wk 2, 6; maintenance (10 mg/kg) every 8 wk	Placebo
Group 1: 321.1 ± 67.1 Group 2: 315.7 ± 61.5 Group 3: 312.6 ± 58.3	124.6 ± 28.7	PCS: 36.9 ± 7.6 MCS: 37.6 ± 10.8	Adalimumab induction (80 mg) wk 0, 2 Responders: Group 1: Adalimumab (40 mg/every other wk) Group 2: Adalimumab (40 mg/wk)	Placebo
Placebo: 291.5 (206–448)/ Certolizumab 100 mg: 299.2 (194–520)/200 mg: 310.7 (184–446)/400 mg: 304.5 (204–461)	126.1 ± 27.4		Group 1: Certolizumab (100 mg) wk 0, 4, 8 Group 2: Certolizumab (200 mg) wk 0, 4, 8 Group 3: Certolizumab (400 mg) wk 0, 4, 8	Placebo
Natalizumab + Infliximab: 263.8 ± 89.3 Placebo + Infliximab: 243.6 ± 57.1	Not mentioned		Natalizumab (300 mg) wk 0, 4, 8 + Infliximab (5 mg/kg) single doses at wk 6	Placebo + infliximab (5 mg/kg) single doses at wk 6
Certolizumab: 301 ± 62 Placebo: 306 ± 61	Not mentioned		Certolizumab 400 mg) wk 0, 2, 4; maintenance (400 mg) every 4 wk Placebo: wk 0, 2, 4; maintenance every 4 wk	Placebo
Certolizumab: 300 ± 64 Placebo: 297 ± 62	Not mentioned		Certolizumab induction (400 mg) wk 0, 2, 4 Responders: maintenance (400 mg) every 4 wk or Placebo: maintenance every 4 wk	Placebo

groups. The summary scale PCS improved significantly in both infliximab groups ($p < 0.05$). The summary scale MCS improved significantly in the 10 mg/kg infliximab group ($p < 0.05$). The PCS scale improved more than the MCS scale.

Adalimumab and HRQoL

The CHARM study investigated the effect of adalimumab on HRQoL and fatigue.[56] This study compared 3 arms. Every treatment arm started with 80 mg induction of adalimumab followed by 40 mg at week 2. At week 4, patients followed the treatment arm for which they were randomized: 40 mg adalimumab every other week (eow) for 1 year, 40 mg adalimumab every week for 1 year, or placebo injections. The analyses included only the 499 patients responding to treatment at week 4. Induction therapy of adalimumab significantly improved HRQoL ($p < 0.0001$). The IBDQ significantly improved in the adalimumab groups up to 1 year later ($p < 0.001$ for adalimumab eow and $p < 0.05$ for adalimumab weekly).

No differences were found between both maintenance groups. The systemic and social domains were particularly responsible for the improvement of the IBDQ. On the SF-36, patients in the 40 mg every other week group showed signifi- cantly more improvement on PCS and MCS at 1 year than the induction-only group ($p < 0.05$). The 40-mg-every-week group did not show a significantly greater improvement than the induction-only group. The 2 maintenance groups did not differ significantly. Finally, both maintenance groups reported fewer fatigue symptoms than the placebo group ($0.05 > p < 0.001$).

Certolizumab and HRQoL

Three studies investigated the effect of certolizumab pegol on HRQoL (Table 1).[57–59]

In the first study patients received either 100 mg, 200 mg, 400 mg, or placebo at weeks 0, 4, and 8. HRQoL was mea- sured with the IBDQ for 3 months.[57] Analyses focused on the 400 mg group, because this dose was identified in another study as the most effective dose.[60] HRQoL improved sig- nificantly from baseline to 12 weeks follow-up ($p < 0.05$), and significantly more than in the placebo group at all time points ($p < 0.05$). On the subscales of the IBDQ , at 12 weeks patients receiving 400 mg certolizumab reported significantly more improvement on emotional functioning and systemic functioning compared with the placebo group. No significant differences were found at 12 weeks for bowel functioning and social functioning.

The PRECISE 1 and 2 studies investigated the efficacy of certolizumab pegol treatment and the efficacy of the maintenance of this treatment, respectively. The studies included also measurements of the HRQoL with the IBDQ.[58,59]

The PRECISE 1 study patients received either 400 mg certolizumab pegol or placebo at weeks −0, −2, and 4 followed by every 4 weeks through week 26.[58] The HRQoL increased from baseline to week 26, and in the certolizumab group significantly more than in the placebo

group (p = 0.03).[58]

The PRECISE 2 study patients received induction therapy of certolizumab pegol 400 mg at weeks -0, -2, and 4. Patients with a clinical response at week 6 were included in the intervention group (certolizumab 400 mg every 4 weeks) or the placebo group (placebo every 4 weeks) and received injections through week 24. The IBDQ was measured at weeks 0, -6, -16, and 26. The scores of the IBDQ were significantly higher in the intervention group (certolizumab 400 mg) than the control group (p = 0.007) at week 26.[59]

Natalizumab and HRQoL

For the effect of natalizumab on HRQoL, which is registered for the treatment of Crohn's disease in the US only, 2 studies were included (Table 1).[61,62] The first study investigated the combination therapy of infliximab (5 mg/kg) at weeks –10, –2, and 6 and natalizumab (300 mg) at weeks 0, 4 and 8 compared with infliximab (5 mg/kg) and placebo. The combination therapy of natali- zumab and infliximab showed a similar increase of the IBDQ compared with the combination of infliximab and placebo in CD patients (p = 0.811).[62]

Another study (ENACT-2) followed up on patients responding to natalizumab with continued treatment (300 mg infusions every 4 weeks up to 48 weeks) or placebo. HRQoL was not reported in the ENACT-1 study. In the follow-up study, it was reported that the scores of patients had already improved from baseline to inclusion in the ENACT-2 study. From inclusion in the follow-up study to 60 weeks, patients in the intervention group showed significantly greater increase in IBDQ total score and subscale scores at all time points than the placebo group (0.05 > p < 0.001). The highest percentages of patients who exceeded the minimally impor- tant difference on the 4 subscales of the IBDQ were seen in the bowel and social domains.

The SF-36, PCS and MCS scores improved significantly more in the intervention group than the placebo group at weeks 48 and 60 (P , 0.01). Of particular note in this study is that the SF-36 profile of the natalizumab group was similar to the profile of the general population.[61]

Disease activity and HRQoL

HRQoL appears to be related to disease activity in the articles that studied this relationship. ACT 1 and 2 (infliximab) showed that response or remission (Mayo subscore) was correlated with improvement of IBDQ and SF-36.[54,63] ACCENT 1 (infliximab) showed significant correlations between the IBDQ scores and Crohn's disease activity index (CDAI) scores at week 54.[54,63]

For certolizumab, CDAI score was correlated positively with IBDQ score.[57] This study showed that the clinical efficacy of certolizumab pegol in patients with moderate-to-severe Crohn's disease is paralleled by improvement in HRQoL.

DISCUSSION

Adult IBD patients suffer from a chronic disease with an impaired HRQoL. Impairment of HRQoL and in particular fatigue in patients may result in a defensive and ineffective use of medical resources. Therefore impaired HRQoL may lead to more frequent visits, more tests and often variable treatment, and thus higher medical costs.[8,64–66] It is expected that improvement of HRQoL will redirect medical attention- seeking behavior of patients, resulting in a more cost-effective way of treating these patients. Therapeutic strategies that have been available for many years include corticosteroids, 5-aminosalicylates and immunnosuppressants. However, no significant long-term improvement has been seen on HRQoL with these therapies. More recently, biologics have been introduced in the treatment of IBD. Individual studies report favorable results of biologics on HRQoL.

This present review showed that 7 studies report a significant improvement of HRQoL (IBDQ and/or SF-36) in patients treated with a variety of biologics compared to placebo. One study reported on the use of 2 biologics. This study found no incremental effect on HRQoL of natalizumab over infliximab.

Although all biologics improve HRQoL, we found differences in the effect on HRQL between different biologics. On the IBDQ, adalimumab, natalizumab and certolizumab all improved HRQoL to a level of patients in remission (>170 points). Infliximab showed improvement on total IBDQ score (improvement with ≥16 points), but not to a total score above 170 points. Further differences were shown in the SF-36 profiles. Patients using natalizumab had a profile comparable with that of the general population. Patients using infliximab, adalimumab or certolizumab did not have such a profile.

The reason for the differences in effect on HRQoL between the biologics is unclear. One hypothesis is that the differences found may be due to the route of administration of these drugs. Infliximab is given in the outpatient setting or in the hospital intravenously, while certolizumab and adalimumab is administered subcutaneously at home. However, natalizumab, which is also administered intravenously, demonstrated the greatest improvement on HRQoL.

Another explanation for the differences found could be that the patients included in the different studies are not comparable. For instance, CDAI scores at baseline were lower in the intervention group of the natalizumab study (ENACT 2) than in the intervention groups of the infliximab, adalimumab and certolizumab studies. Baseline IBDQ and SF-36 scores were also lower in the natalizumab study (ENACT 2) than in the infliximab, adalimumab and certolizumab studies (except MCS score of the SF-36 in the adalimumab study) (Table 1). These differences are in contrast of what is expected, because natalizumab increased IBDQ scores up to a level of patients in remission.

Although fatigue is one of the factors that alter HRQoL in IBD patients, leading to increased costs and occurring in a high percentage of IBD patients, only one study reported the effects of treatment on fatigue.[8,56] In the CHARM study adalimumab significantly decreased fatigue.[56] Further research is needed to investigate the long-term effects of other biologics on fatigue.

Although all drugs appeared to have beneficial effects on HRQoL, a limitation of our review is that the number of studies included in this review is low. Therefore no definitive conclusions on the influence of biologics on the different dimensions of the IBDQ can be made yet.

With that caveat in mind, it appears that treatment with biologics particularly improves the bowel, systemic and social domains of the IBDQ. Emotional functioning seems to be less responsive to biologics.

Another limit is that the studies included in this review included only patients with active disease and most studies included only patients with moderate-to-severe disease. This could bias the outcome, since more improvement is feasible in patients with a low HRQoL than in patients with a high HRQoL. Whether biologics have comparable favorable results in patients with limited disease needs to be studied separately.

EXPERT OPINION

In recent years awareness of the importance of HRQoL has increased, not only for the benefit of the patients but also for reducing health care costs in IBD. However, research on the magnitude of fatigue, which is an important factor in altering HRQoL and the health care costs, is limited in IBD patients.

Biologics increase health care costs and in the near future newer expensive biologics will be introduced. Because biologics can induce and sustain remission and therefore improve HRQoL, these strategies are expected to be cost-effective despite the high costs of treatment with biologics.

For future therapeutic strategies more research is needed on HRQoL and fatigue and the influence of newer therapeutic agents on different domains of HRQoL. Furthermore, studies must increase the duration of follow-up to investigate whether the new biologics are capable of sustaining the short-term benefits on HRQoL in IBD patients.

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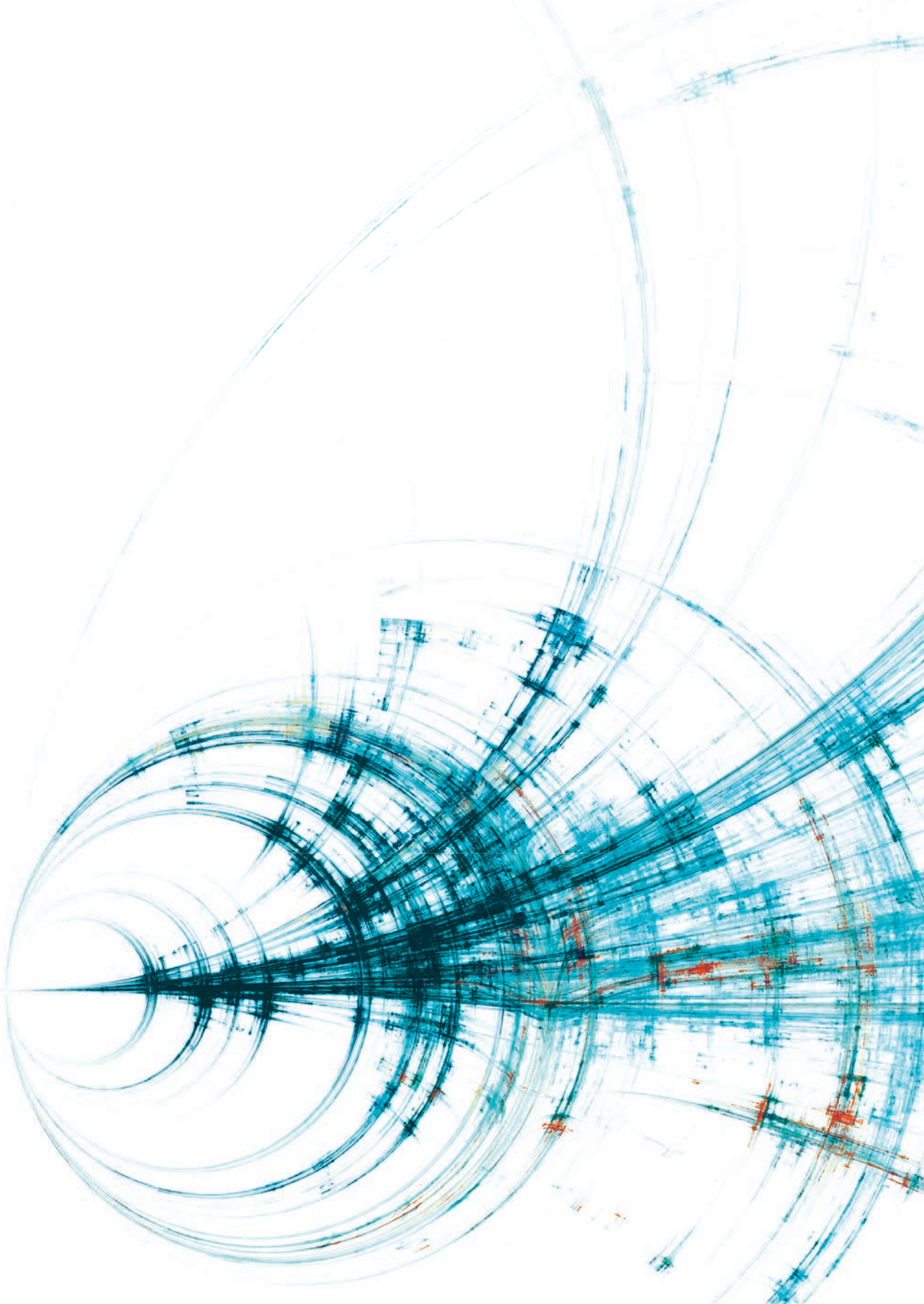

CHAPTER 6

Solution focused therapy: A promising new tool in the management of fatigue in Crohn's disease patients

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ABSTRACT

Background

Crohn's disease patients have a decreased Quality of Life (QoL) which is in part due to extreme fatigue. In a pilot study we prospectively assessed the feasibility and effect of psychological interventions in the management of fatigue.

Methods

Patients with quiescent Crohn's disease and a high fatigue score according to the Checklist Individual Strength were randomized to Problem Solving Therapy (PST), Solution Focused Therapy (SFT) or to a control group (treatment as usual, TAU). Patients completed the Inflammatory Bowel Disease Questionnaire, the EuroQol-5D, and the Trimbos questionnaire for Costs.

Results

Twenty-nine patients were included (12 TAU, 9 PST, 8 SFT), of these 72% were female, mean age was 31 years (range 20-50). The SFT group improved on the fatigue scale in 85.7% of the patients, in the PST group 60% showed improved fatigue scores and in the TAU group 45.5%.
Although not significant, in both intervention groups the QoL increased. Medical costs lowered in 57.1% of the patients in the SFT group, in the TAU 45.5% and the in PST group 20%. The drop out rate was highest in the PST group (44%; SFT 12.5%; TAU 8.3%).

Conclusion

PST and SFT both positively affect the fatigue and QoL scores in patients with Crohn's disease. SFT seems most feasible with fewer dropouts and is therefore a promising new tool in the management of fatigue in Crohn's disease patients.

INTRODUCTION

Inflammatory Bowel Disease (IBD) patients suffer from a chronic relapsing disease with significant impairment of Quality of Life (QoL) which may lead to the development of psychological symptoms such as depression. This impacts the care-seeking behaviour of these patients.[1-8]

Fatigue contributes to the impairment of QoL in IBD patients.[9, 10] One of the factors negatively influencing fatigue is disease activity and therefore induction of disease remission is a first requirement in the management of fatigue.[11, 12] However a large proportion of IBD patients in remission still suffer from disabling fatigue (41%).[10, 13]

Besides the impact on QoL, fatigue may also lead to low employment and high disability rates.[14] Additionally, it can be hypothesised that fatigue has a negative influence on the medical consumption[15, 16] and therefore higher costs. The overall costs that are directly related to IBD consist of direct costs (15-44% e.g. inpatient care, outpatient care, self-care, medications and tests/procedures) and indirect costs (e.g. work absenteeism, decreased incomes).[17-19] The direct costs vary between 1871 euro and 18,000 dollar per patient annually[19-21], the indirect costs are estimated between 842 euro and 7260 dollar.[20, 22] Although fatigue is one of the most important complaints of IBD patients management strategies are lacking.[23] Psychological interventions are used in IBD care for multiple goals (e.g. improving QoL, decreasing depression, decreasing flares). The conclusions from several studies show inconsistent results for these interventions.[24-28]

In order to find out whether psychological interventions can improve fatigue, we performed a pilot study. We assessed the feasibility and a first impression of the effect of 2 different psychological interventions (Problem Solving Therapy (PST) and Solution Focused Therapy (SFT)), designed to manage fatigue. In PST, patients learn to solve problems in a structured way, using five steps (i.e. problem definition and goal setting, brain storm about solutions, weighting pro's and con's for each solution, choosing a solution and trying the solution and evaluation of the effectiveness).[29-33] SFT has as a starting point that no problem exists always. The solution to a problem is thus finding the exception when the problem is not present. Once the exception is found, patients learn to do more what they do at that moment, so the problem disappears.[34, 35] Furthermore, SFT is shorter than PST (5 versus 10 sessions).

METHODS

Patients

This study was approved by the ethical review board of the Erasmus MC Rotterdam, The Netherlands. Adult non-pregnant patients with proven Crohns's disease (CD) visiting the outpatient clinic of the Department of Gastroenterology and Hepatology at the Erasmus MC were asked

to participate and to fill in the Checklist Individual Strength (CIS).[36] This questionnaire is the validated Dutch Checklist Individual Strength (CIS-20) consisting of 20-items that are answered on a 7 point Likert scale. The CIS-20 is designed to measure five dimensions of fatigue: (1) subjective experience of fatigue (8 items): 8-56; (2) concentration (5 items): 5-35; (3) motivation (4 items): 4-28; (4) physical activity level (3 items): 3-21; (5) total score (20 items): 20-140. A higher score indicates more fatigue. Furthermore clinical disease activity was measured by the Harvey Bradshaw index (HBI).[37] Consecutive patients with a high score on the fatigue scale (≥ 35 on the CIS dimension 1) and in clinical remission (HBI< 5) were asked to participate in the study. After written informed consent participants filled out different questionnaires. The QoL was estimated with the Inflammatory Bowel Disease Questionnaire (IBDQ) and the EuroQol-5D (EQ-5D).[38, 39] Furthermore patients filled in the Hospital Anxiety and Depression Scale (HADS).[40] Patients with a HADS score of more than 10 on one or both of the two subscales were excluded. Other exclusion criteria included: breastfeading; surgery 3 months prior or intended during the study period; short bowel syndrome, cancer, and underlying psychiatric disorders. Sociodemographic variables and clinical status were collected during history taking and from the medical record. These included gender, age, employment status and concomitant drugs. Phenotype was classified according to the Montreal classification.[41, 42] Blood samples were taken for regular blood screening of CRP (reference value: 0-9 mg/l), hemoglobin (reference value: females 7.5-10 mmol/l; males 8.5-11 mmol/l) and ferritin (reference value: females 10-150 ug/l; males 20-300 ug/l).

Randomization process

Eligible patients were randomized either to serve as a treatment as usual (TAU) group (n=20) or to participate in one of the psychological interventions (n=20). After baseline assessment, patients were randomized to treatment or not in blocks of 20 subjects using randomization lists drawn from a computer-generated series of random numbers. We randomised 20 patients for the intervention groups and 20 TAU patients.

Patient inclusion

Overall, 60 patients were assessed for eligibility. Twenty patients were excluded, because they did not meet the inclusion criteria (Fig. 1).

In total 40 patients intended to participate: 10 in the PST group, 10 in the SFT and 20 in the TAU group. During the screening period 5 patients dropped out because of pregnancy (2) or relapse of disease (3). Six patients refused further continuation for unknown reasons.

The PST group started with 9 patients, the SFT group with 8 patients, and 12 patients were included in the TAU group. During follow up 6 patients refused to fill in the questionnaires for various reasons (i.e. lack of time, lack of concentration to fill in questionnaires).

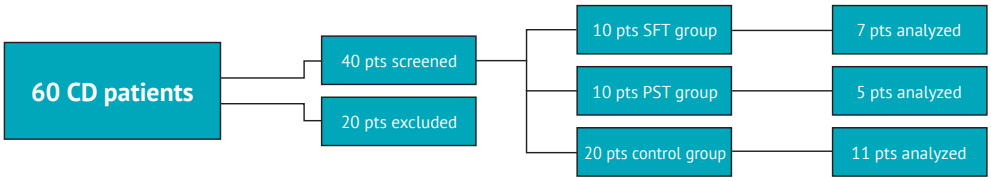

Figure 1. Patient inclusion.

Psychological interventions

The interventions were given by an experienced psychotherapist specifically trained to give PST and SFT courses.

Problem Solving Therapy group

The treatment goal of PST is to increase the capabilities of the patients to deal with the daily stressful problems caused by CD.[43] This is a 10 session's course during 3 months and based on a general model of problem solving, adjusted for the purpose of this patient population.

Solution Focused Therapy group

This is a 5 session's course during 3 months. It includes a brief psychological intervention based on the solution focused model of solving problems.[34, 44, 45]

The solution-focused model offers a wide range of interventions that channel the attention of patients towards constructing possible solutions. The method has been empirically validated and shown to be successful in other patient groups with chronic diseases. For the purpose of this study the SFT was modified to focus on fatigue management in IBD patients.

Treatment as usual

The TAU received standard medical care and no additional psychological interventions. This group was chosen in this setting to rule out any intervention effect.

Cost – effectiveness

The cost-effectiveness of fatigue management was evaluated by the Trimbos institute for Medical Technology Assessment (iMTA) questionnaire for Costs associated with Psychiatric Illness (TiC-P) at baseline and at month 6. The TiC-P is a questionnaire for collecting data on

health care utilisation and productivity losses.[46, 47] The TiC-P questionnaire collects data about medical consumption and productivity losses for the previous 3 months. Medical consumption includes the costs of outpatient clinic visits of specialists, psychological care, visits of the general practitioner, the company doctor, paramedical care (e.g. physiotherapist), hospital admissions and costs of medication. Data for the TAU patients were collected at similar time-points.

Questionnaires during follow-up

Participants filled in the CIS, IBDQ, EQ-5D, HADS, HBI and Tic-P questionnaires at inclusion (at week 0, pre – study) and at month 6 (3 months after the last session of the intervention).

Statistical analysis

Because of the pilot design of this study a power calculation was not possible. Studies in this field and with similar design often start with 10 patients in both the intervention and control group. Therefore we decided to include 10 patients in each intervention group and 20 patients in the control group.
Statistical analyses were performed using descriptive statistics (means, SD). Statistical analyses of questionnaire results were carried out using the Chi-square test. The laboratory results were analyzed using non-parametric tests (i.e. Kruskal Wallis and Wilcoxon test), the HBI was analyzed using the Kruskal Wallis test.
The cost data is presented as the percentage of the patients, of which their costs have risen or fallen, based on medication costs, the costs of outpatient clinic visits and admissions of the last 3 months. Statistical analyses were performed with SPSS for Windows software (version 17.0). A two-sided p value of < 0.05 was considered significant. The data analyses were performed on the most recent samples at the end of the study (see Figure 1).

RESULTS

Patient characteristics
Patient characteristics are presented in Table 1. No significant differences were found between the groups with respect to mean age or medication use, disease activity (HBI) and Montreal classification (Table 1). CRP, hemoglobin and ferritin levels remained stable during follow-up and were similar between the different groups (Table 2).

Table 1: Patient characteristics of the SFT, PST, TAU group

Patient characteristics	TAU		SFT		PST		Dropouts	
Age in years, mean (SD)	32	(8.9)	29.9	(6.9)	30.9	(8.1)	28	(9.3)
Female gender (%)		65%		75%		78%		100%
Immunosuppressives (%)		17%		50%		56%		66.7%
Corticosteroids (%)		0%		0%		22%		0%
Biologicals (anti-TNF) (%)		42%		50%		22%		33.3%
Antidepressant (%)		0%		14%		20%		0%
Mean HBI, (SD)	2.9	(2.1)	4.4	(2.7)	2.0	(2.5)	2.7	(1.5)
Working/student (%)		100%		100%		80%		100%
Unemployement (%)		0%		0%		20%		0%
Ileostomy (%)		27%		0%		20%		17%
Ileocaecal resection (%)		0%		43%		40%		17%
Subtotal colectomy (%)		36%		0%		0%		17%
Short bowel syndrome (%)		0%		0%		0%		0%
Montreal classification		(%)		(%)		(%)		(%)
Age at diagnosis								
A1		25.0		0		0		0
A2		75.0		100		100		100
A3		0		0		0		0
Location								
L1		25.0		12.5		44.4		33.3
L2		33.3		12.5		22.2		16.7
L3		41.7		75.0		22.2		50.0
L4		0		0		11.1		0
Behaviour								
B1		66.7		75.0		66.7		66.7
B2		0		0		0		0
B3		33.3		25.0		33.3		33.3
p		16.7		25.0		33.3		16.7

HBI: Harvey Bradshaw Index; SD: standard deviation
TAU: treatment as usual, SFT: solution focused therapy, PST: problem solving therapy

Influence on fatigue

In the SFT group, the CIS subscale fatigue and CIS total score showed a decrease in 85.7% of patients from baseline to 3 months follow up (Table 3). The PST group showed a decreased CIS subscale fatigue and CIS total score in 60% of patients. The control group showed in 45.5% of patients a decreased score on both CIS scales. No significant differences were observed between the groups.

Costs

The SFT treated group showed a decrease in total direct costs 3 months after finishing therapy in 57.1% of patients, which was 20% of the PST patients and 45.5% of the control patients (not

significant). Contributing factors for the higher score in SFT were fewer visits to the outpatient clinic, lower medication costs and less hospital admissions during follow-up. Compared to the other groups this decrease was not significant. In the intervention groups there were no differences in the costs of medication, costs of outpatient clinic visits and admissions compared with the control group (Table 4).

Quality of life

The IBDQ total score of the intervention groups showed more patients with improved scores than the control patients from baseline to follow up (SFT: 71.4%; PST: 60%; TAU: 50% of the patients). When comparing the intervention groups with the control group; no significant differences were observed.

The EQ-5D VAS scores ranged from 72 to 67 at baseline. The SFT group showed an increased mean VAS score in 71.4% of patients whereas the mean VAS scores of the PST increased in 25% of patients and in 54.5% of control patients. The EQ-5D Index showed similar results. No significant differences of the EQ-5D scores were seen between the intervention groups and the control group.

Anxiety and depression

All patients remained under the score of 10 points, meaning that no clinical significant depression or anxiety occurred during the 6-months study period.

Table 2: Means of laboratory parameters.

Patient characteristics	CRP (mg/l)	Hemoglobin (mmol/l)	Ferritin (µg/l) Female	Ferritin (µg/l) Male
TAU				
Baseline (SD)	4.8 (4.7)	8.5 (0.9)	43.5 (44.0)	70.2 (59.3)
Follow up (SD)	4.0 (3.5)	8.5 (1.1)	65.0 (103.8)	79.3 (57.1)
SFT				
Baseline (SD)	1.4 (0.9)	8.5 (0.8)	31.2 (5.2)	117.5 (64.3)
Follow up (SD)	2.3 (0.7)	8.9 (0.7)	43.3 (23.3)	132.0 (38.2)
PST				
Baseline (SD)	3.0 (2.9)	8.7 (1.0)	28.0 (11.8)	110.0 (32.5)
Follow up (SD)	2.8 (2.4)	8.3 (1.2)	33.0 (16.6)	76.0 (0)

SD: standard deviation
CRP: C-reactive protein,
mg/l: milligrams per liter
mmol/l: millimoles per liter
ug/l: microgram per liter
TAU: treatment as usual, SFT: solution focused therapy, PST: problem solving therapy

Table 3: Checklist Individual Strength scores between baseline and follow up.

Patient characteristics	TAU (%)	SFT (%)	PST (%)
CIS Fatigue			
increase	54.5	14.3	40.0
decrease	45.5	85.7	60.0
CIS Concentration			
increase	40.0	50.0	60.0
decrease	60.0	50.0	40.0
CIS Motivation			
increase	50.0	33.3	50.0
decrease	50.0	66.7	50.0
CIS Physical Activity			
increase	54.5	14.3	60.0
decrease	45.5	85.7	40.0
CIS Total			
increase	54.5	14.3	40.0
decrease	45.5	85.7	60.0

Increase: a higher score from baseline to follow up = impairment of this domain
Decrease: a lower score from baseline to follow up = improvement of this domain
TAU: treatment as usual, SFT: solution focused therapy, PST: problem solving therapy

Table 4: Percentages of increased and decreased total direct costs.

Patient characteristics	TAU (%)	SFT (%)	PST (%)
Decreased costs	45.5	20.0	57.1
Increased costs	45.5	60.0	28.6
Equal costs	9.0	20.0	14.3

Decreased and increased total direct costs in euro: difference from baseline to follow up.
TAU: treatment as usual; SFT: solution focused therapy; PST: problem solving therapy

Dropouts

The dropout rate during the intervention period was highest in the PST group (44%, 4pts), 1 patient in the SFT group (12.5%) and 1 patient in the control group (8.3%). Reasons for stopping: 3 patients had other responsibilities (work or study) and 3 patients stopped because the scope of the intervention did not meet their expectations. There were no significant different baseline characteristics between the dropouts and patients who finished the study period (see Table 1).

DISCUSSION

We present the first study in which two different psychological interventions focusing on fatigue management in CD patients were compared with a TAU group. Although this was a small sized pilot study, we were able to demonstrate that these interventions have a positive effect on fatigue and health care costs. Comparing a longer term intervention (PST) and a short term intervention (SFT), the SFT showed more patients with less fatigue and better quality of life. In the TAU group the fatigue worsened in a high percentage during follow up. SFT intervention seems most feasible due to lesser dropout rate.

Similar to our results, in conditions like cancer-related fatigue, cognitive therapy already showed to improve fatigue.[48-50]Additional to lowering fatigue, SFT seems also to lower health care costs more often when compared with the costs for patients in the TAU and PST group. Costs of medication are the main factor contributing to the health care costs and was not related to the activity of disease, but less outpatient clinic visits were noted in the SFT group.

During the intervention period an unexpected high dropout rate occurred, especially in the PST group. One of the factors contributing to the dropout rate could be that patients at the start of the intervention did not fully comprehend the impact of psychotherapy and were reluctant to further participation after the first session. Furthermore, other factors such as age and accompanying lifestyle could influence the group process and potentially lead to dropout. Additionally, PST is a time-consuming intervention which could be a factor accountable for the higher dropout rate in this group. Hypothetically, the relatively large number of extra visits to the hospital for the PST intervention could interfere with work rhythms and thus result in a lower adherence.

This study is hampered by its small sample size. Therefore no firm conclusions can be drawn, but it gives rise to further research to confirm the results of this pilot study.

CONCLUSION

We believe that SFT is a promising new tool to manage fatigue in quiescent CD patients. A larger randomized controlled trial is needed to further investigate this fatigue management strategy.

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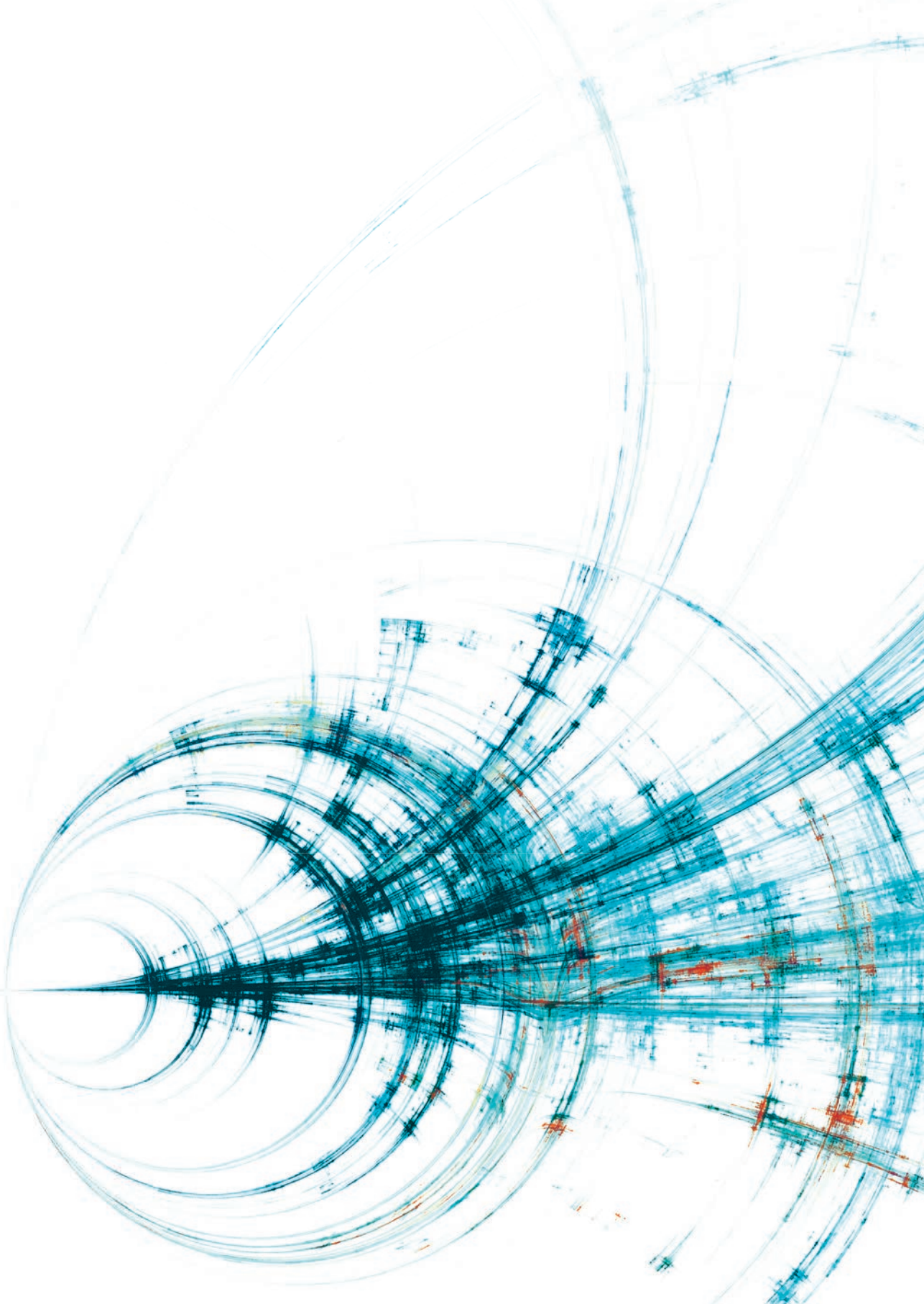

CHAPTER 7

Fatigue management in patients with IBD:

A randomised controlled trial

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ABSTRACT

Objective

To assess the effectiveness of solution-focused therapy (SFT) on fatigue and quality of life (QoL) in inflammatory bowel disease (IBD) patients with fatigue.

Design

Randomised controlled trial in two Dutch hospitals. Patients with IBD with quiescent IBD and with a Checklist Individual Strength-fatigue (CIS-fatigue) score of ⩾ 35 were enrolled. Patients were 1:1 randomised to receive SFT or care as usual (CAU) for 3 months. Patients were followed for a further 6 months after the SFT. Primary endpoint was defined as changes in fatigue and QoL during follow-up. Secondary endpoints included change in anxiety and depression, medication use, side effects to medication, disease activity, laboratory parameters (C-reactive protein, leukocytes and haemoglobin) and sleep quality.

Results

Ninety-eight patients were included, of whom 63% were women, mean age was 40.1 years. After the SFT course, 17 (39%) patients in the SFT group had a CIS-fatigue score below 35 compared with eight (18%) of patients in the CAU group ($p = 0.03$). The SFT group also showed a greater reduction in fatigue across the first 6 months compared with the CAU group (CIS-fatigue: $p < 0.001$ and CIS-total: $p = 0.001$).

SFT was associated with a significant higher mean IBD questionnaire change at 3 months ($p = 0.020$). At 9 months, no significant differences between the two groups were observed.

Conclusion

SFT has a significant beneficial effect on the severity of fatigue and QoL in patients with quiescent IBD. However, this effect diminished during follow-up.

INTRODUCTION

Inflammatory bowel disease (IBD) can lead to severe, debilitating fatigue which may significantly impair the quality of life (QoL).[1-6] Over 40% of IBD patients suffer from severe fatigue, even during disease remission.[1, 3, 7] Although most patients have persistent fatigue, and psychological factors are known to be associated with fatigue, management strategies focussing on fatigue are lacking and intervention studies are scarce.[5-18] Psychological interventions for patients with IBD have previously been applied for multiple goals such as improving QoL, decreasing depression, and decreasing flares. However, none of these studies investigated the effect on fatigue. Furthermore, due to heterogeneity between studies, it is difficult to draw conclusions on the effectiveness of these interventions on QoL.[10-18]

Fatigue is also seen in other chronic conditions, such as disease remission after treatment for cancer, rheumatic disease, multiple sclerosis and chronic infectious diseases.[19, 20]

Especially in former cancer patients, in patients with rheumatic disease and in patients with multiple sclerosis, psychotherapy showed to be effective in reducing fatigue.[21-24] We earlier reported in a pilot study with a small sample size that psychotherapy, especially solution-focused therapy (SFT) in patients with IBD is feasible and reduced fatigue.[25] Therefore, we assessed in a randomised controlled trial whether SFT is more effective in improving fatigue and Qol than care as usual (CAU).

METHODS

Study design and sample size

This randomised controlled trial was designed to evaluate the efficacy of SFT in comparison to CAU in quiescent patients with IBD with severe fatigue. This trial was conducted in accordance with the protocol International Conference on Harmonisation Guidelines for Good Clinical Practice, the Declaration of Helsinki and local national regulations governing clinical study conduct and was registered at the medical ethical committee (MEC) of the Erasmus MC (Registration number: MEC-2010-107; NL32020.078.10). The protocol was approved by the institutional review board or by the ethics committee at each centre. The study was not designed for an interim analysis and no Data Safety Monitoring Board was assigned. All patients gave written informed consent. Patients were enrolled at two sites in The Netherlands from January 2010 to January 2011 by the principal investigator.

The sample size calculation was based on results from a small open-label study, reporting that SFT might reduce fatigue in patients with IBD.[25] A power analysis was performed using α=0.05

and β=0.80. Assuming an expected decrease of three points on the Checklist Individual Strength (CIS)-fatigue score in the intervention group versus no effect in the CAU group, the required sample size was 42 patients in each group. Assuming a dropout rate of approximately 15%, we determined to include 98 patients in the study.

Intervention and randomisation

Patients randomised for the intervention arm participated in a 7-session solution-focused course, focussing on coping styles for fatigue. Control subjects received CAU.

The course consisted of six group sessions during 3 months, and was completed by a booster session at month 6. Duration of each session was 1.5 h. Each group consisted of seven patients. In the fifth session a partner, family member or close relative participated. The course consisted of psychoeducation about IBD and fatigue and SFT. SFT is a brief form of psychotherapy. The focus is on the existing adequate coping abilities of patients, rather than on their problems. For the purpose of this study the SFT was modified to focus on fatigue management.[25]

Patients were randomised to the treatment or control arm in blocks of 14 subjects using randomisation lists drawn from a computer-generated series of random numbers. Randomisation was conducted by the second author. The randomisation lists were anonymised for the randomization process.

Patients

Men and women aged ⩾ 18 years and diagnosed with IBD with a CIS-fatigue score of ⩾ 35 were eligible for inclusion. Patients had to be in remission defined as a Crohn's Disease Index (CDAI) < 150 or Clinical Activity Index (CAI) (ulcerative colitis index) < 10 and a C-reactive protein (CRP) < 10. Demographic and baseline IBD severity data, concomitant medication use were collected.

The diagnosis of IBD (at least 6 months in duration) was radiologically or endoscopically / histologically confirmed. Pregnant or breastfeeding women were not included. Patients were also excluded if they had a history of lymphoproliferative disease or cancer, other than skin basocellular carcinoma; other gastrointestinal disease than IBD; listeriosis; HIV infection; immunodeficiency syndrome; central nervous system (CNS) demyelinating disease; chronic hepatitis B or C virus infection or untreated tuberculosis. Patients were excluded if they had poorly controlled medical conditions, including anaemia, low iron levels, diabetes mellitus, kidney disease, liver disease and unstable ischaemic heart disease; a known pre-existing condition that could interfere with the patient's participation such as psychiatric conditions or CNS trauma or active seizure disorders. Additionally, patients were excluded if they had undergone surgery in the past 12 weeks prior to the screening visit. Patients with a history of clinically significant drug or alcohol abuse in the last 2 years were not allowed to participate in this study.

Study endpoints

At baseline, routine laboratory values were assessed including CRP (reference value: 0-9 mg/L), leukocytes (reference value: 3.5-10x109/L), trombocytes (reference value: 150-370x109/L), haemoglobin (reference value: women 7.5-10 mmol/L; men 8.5-11 mmol/L), aspartate aminotransferase (reference value: women < 31 U/L; men < 35 U/L), alanine aminotransferase (reference value: women < 34 U/L; men < 45 U/L), alkaline phosphatase (reference value: women < 98 U/L; men < 115 U/L), gamma-glutamyl transferase (reference value: women <38 U/L; men < 55 U/L), amylase (reference value: < 107 U/L), iron (reference value: 10-30 µmol/L), ferritin (reference value: women 10-140 µg/L; men 30-240 µg/L), creatinine (reference value: 55-90 µmol/L), glomerular filtration rate (reference value: >60 ml/min/1,73m^2), thyroid stimulating hormone (TSH) (reference value: 0.4-4.3 mU/L), vitamin B12 (reference value: 145-637 pmol/L), 25(OH)vitamin D (reference value: >50 nmol/L) and folic acid (reference value: 8-28 nmol/L).
Furthermore, faecal calprotectin concentration was measured using the Bühlmann calprotectin test (calprotectin ELISA test). Levels < 200µg/g were regarded as compatible with disease remission.[26, 27]

The primary objective of the study was to assess the effect of SFT on fatigue and QoL at month 6. This was measured with the CIS[28], Fatigue Severity Scale-9 (FSS-9)[29-31], Inflammatory Bowel Disease Questionnaire (IBDQ)[32, 33], Short Form-36 (SF-36)[34, 35] and EuroQol (EQ-5D)[36] at baseline, month 3, month 6 and month 9.
The secondary objective was to investigate the effect of SFT on anxiety and depression, sleep quality, disease activity, medication use, side effects to medication and laboratory parameters (CRP, leukocytes and haemoglobin). Measurements of these items were performed at baseline, month 3, month 6 and month 9 with the Hospital Anxiety and Depression Scale (HADS)[37], Pittsburgh Sleep Quality Index (PSQI)[38], CDAI[39, 40] or Clinical Activity Index (CAI)[41], a questionnaire focusing on current medication use and side effects and laboratory parameters on full blood.

The CIS is a 20-item patient-reported validated instrument, measuring severity of fatigue, motivation, activity level, and concentration. The severity of fatigue, measured with the subscale 'fatigue', was used as an outcome measure. Patients with a score of 35 or higher on this subscale were considered to be fatigued. The CIS is a renewed format of the Multifactorial Fatigue Index (MFI), 5 questions are different formulated, all other questions are the same. The CIS is standardised and uses a cut-off score for fatigue by contrast with the MFI.
The FSS-9 is a self-administered questionnaire. A total score of ⩾ 4 is considered as indicative of chronic fatigue. Furthermore, the FSS-9 is sensitive to different gradations of fatigue severity.
The HADS is a self-assessment questionnaire, measuring anxiety and depression. Scores of 10 or higher are considered to reflect a clinical level of anxiety and/or depression.

The PSQI was developed to measure sleep quality during the previous month. A PSQI global score >5 is considered to indicate significant sleep disturbance.
The medication questionnaire listed all possible IBD medications registered in The Netherlands. Patients could mark their drugs in this list and state whether they experienced side effects.
The questionnaires were verified by medical records and in case of missing values by enquiries from the principal investigator.

Data and statistical analysis

Mixed modelling, also known as random effect modelling, multilevel or hierarchical linear regression analysis was applied for longitudinal analysis of the data. At first, saturated models were postulated with the CIS-fatigue, CIS-total, FFS-total, EQ-5D, IBDQ-total, SF-36 physical and mental scales, PSQI, HADS, CDAI/CAI, medication and side-effects to medication, CRP, leukocytes and haemoglobin as dependent variables. The saturated models included age, gender, linear time, quadratic time, the logarithm of time and their interaction with treatment and age and gender as fixed effects. The deviance statistic[42] using restricted maximum likelihood[43] was applied to determine the covariance structure, that is whether a random slope and intercept-time covariance was needed in addition to a random intercept. Then the saturated models were reduced by eliminating insignificant fixed effects, respecting that interaction effects must be nested under their respective main time effect. The significance of the difference between the saturated models and the parsimonious final models were determined with the deviance statistic using ordinary likelihood. Potential gender differences and differences between Crohn's disease (CD) and ulcerative colitis (UC) were analysed by adding these effects and interactions with time to the parsimonious models.
For baseline characteristics, the Chi-square test was used for dichotomous variables and the independent samples t-test for continuous variables. Frequencies of response at months 3, 6 and 9 were compared between groups by using the Chi–square test.
Data were analysed with SPSS Software for Windows, version 20 (SPSS Inc, Chicago, IL).
Results were considered significant when two-sided p values were less than 0.05. Effect sizes were calculated by dividing the effects by the estimated SD's at baseline.[44] The data was anonymised for the investigators conducting data analysis.

RESULTS

Patient flow diagram

Overall, 98 patients were enrolled in the study, 49 in the SFT group and 49 in the CAU group (Figure 1). One patient declined further participation after randomisation.

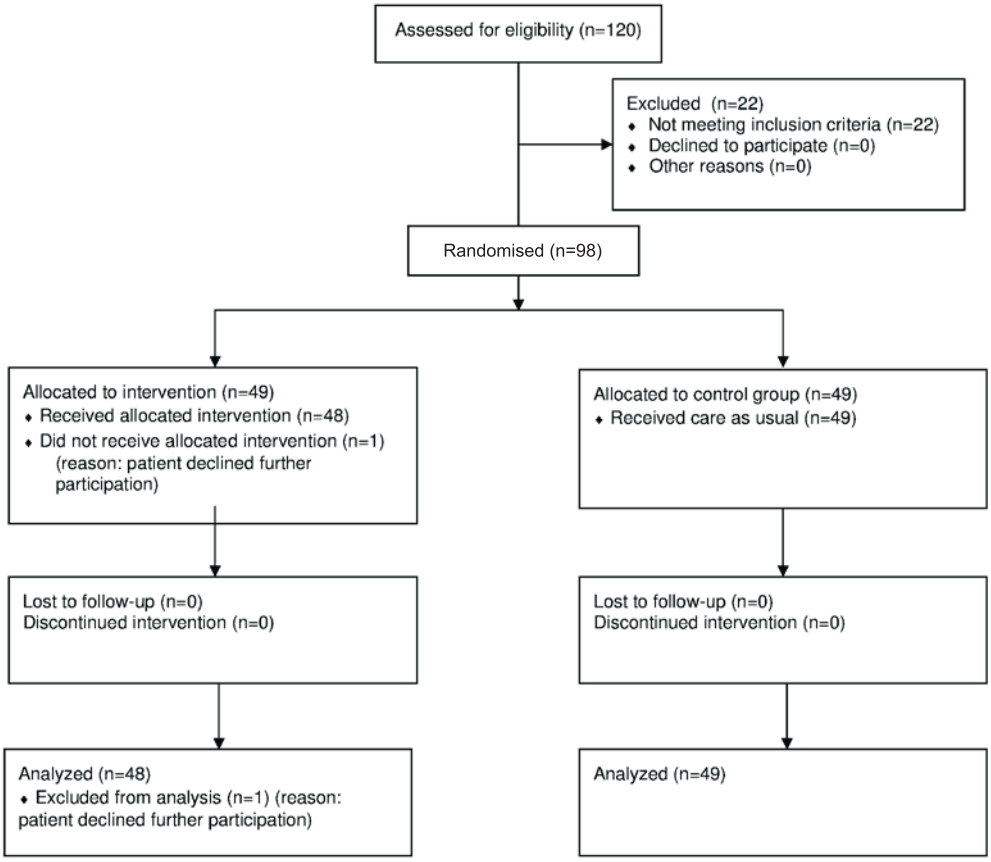

Figure 1. CONSORT 2010 Flow Diagram

7

Baseline characteristics

Tables 1 and 2 show the clinical characteristics of each group. Baseline characteristics were similar between the two groups, indicative of successful randomisation. The mean age of the patients was 40.1 years (10.3 SD), 37% was male, 58 (59%) patients were diagnosed with CD, and 40 (41%) with UC. Means (SD) of baseline questionnaire scores are shown in table 3. For fatigue scores no differences were observed for gender or age.

Outcomes

Tables 4 and 5, and Figures 2 and 3 show the main endpoints.

Table 1: Disease phenotype.

Montreal classification	SFT n = 48	CAU n = 49
Montreal classification - CD		
Age at diagnosis (%)		
A1	17.2	3.4
A2	75.9	82.8
A3	6.9	13.8
Mean age at diagnosis (SD)	26.6 (9.6)	28.0 (7.8)
Location (%)		
L1	17.2	10.3
L2	41.4	39.3
L3	41.4	44.8
L4	0.0	3.4
+L4	0.0	3.4
Behaviour (%)		
B1	75.9	62.1
B2	10.3	17.2
B3	13.8	20.7
p	24.1	27.6
Disease activity		
Mean CDAI (SD)	89.36 (49.05)	99.96 (38.02)
Montreal classification - UC		
Age at diagnosis (%)		
A1	10.5	0.0
A2	68.4	70.0
A3	21.1	30.0
Mean age at diagnosis (SD)	31.1 (11.8)	34.8 (10.5)
Location (%)		
E1	38.9	25.0
E2	22.2	35.0
E3	38.9	40.0
Severity (%)		
S0	27.8	50.0
S1	72.2	50.0
S2	0.0	0.0
S3	0.0	0.0
Disease activity		
Mean CAI (SD)	4.05 (1.84)	3.86 (1.06)
Surgery		
Bowel resection (%)	22.9	24.5
Number of resections; mean (SD)	1.7 (1.5)	1.3 (0.7)
Number of resections; mean (SD)	1.7 (1.5)	1.3 (0.7)
Age at first resection; mean (SD)	29.5 (9.1)	29.1 (9.9)
Stoma (%)	4.2	6.1
Rectum amputation (%)	2.1	2.0

$\chi 2$ test for dichotomous variables, independent samples t test for continuous variables.
SD: standard deviation; CAI: Clinical Activity Index; CAU: care as usual group; CD: Crohn's disease; CDAI: Crohn's Disease Activity Index; SFT: solution-focused therapy group; UC: ulcerative colitis.

Table 2: Laboratory parameters at baseline

Laboratory parameter	SFT n=48		CAU n=49	
	Mean	(SD)	Mean	(SD)
CRP	1.8	(2.3)	3.0	(3.9)
Leucocytes	6.3	(2.3)	6.9	(1.8)
Haemoglobin (female)	8.3	(0.6)	8.0	(0.4)
Haemoglobin (male)	9.2	(0.6)	9.4	(0.6)
Haemoglobin (overall)	8.6	(0.7)	8.6	(0.8)
TSH	1.5	(1.6)	1.4	(0.7)
Vitamin B12	428.1	(298.8)	438.6	(334.5)
Vitamin D	70.3	(32.0)	67.2	(29.8)
Folic acid	21.5	(11.2)	22.7	(12.0)
Iron	19.2	(9.1)	17.8	(8.1)
Ferritin	97.5	(151.1)	88.0	(136.9)
Calprotectin	56	(61)	87	(84)

Independent samples t test for continuous variables.
CAU: care as usual group; CRP: C-reactive protein;
SFT: solution-focused therapy group;
TSH: thyroid stimulating hormone; SD: standard deviation
SFT: solution focused therapy; PST: problem solving therapy

Table 3: Baseline questionnaire scores.

Questionnaire	SFT n=48		CAU n=49	
	Mean	(SD)	Mean	(SD)
CIS				
fatigue	46.6	(5.6)	46.3	(5.9)
total	100.0	(15.3)	101.5	(19.2)
FSS total	5.6	(0.07)	5.4	(0.73)
EQ-5D	0.84	(0.12)	0.80	(0.12)
IBDQ total	168.9	(22.2)	162.0	(22.7)
SF-36				
physical	38.6	(8.4)	40.0	(8.3)
mental	45.2	(10.0)	41.0	(13.2)
HADS				
depression	5.7	(3.9)	6.5	(3.3)
anxiety	7.0	(2.9)	7.7	(4.3)
PSQI	6.0	(3.3)	6.2	(3.1)

χ2 test for dichotomous variables, independent samples t test for continuous variables.
CAU: care as usual group; CIS: Checklist Individual Strength; EQ-5D: EuroQol; FSS: Fatigue Severity Scale; HADS: Hospital Anxiety and Depression Scale; IBDQ: Inflammatory Bowel Disease Questionnaire; PSQI: Pittsburgh Sleep Quality Index; SF-36: Short Form-36; SFT: solution-focused therapy group. SD: standard deviation

Table 4: Final mixed models.

Outcome effect	Estimate	Standard error	p-value
CIS-Fatigue			
Intercept	46.42	0.76	< 0.001
Time linear	- 0.37	0.44	0.449
Time logarithmic	-2.05	1.59	0.199
Treatment * time linear	1.69	0.61	0.006
Treatment * time logarithmic	- 7.01	2.12	0.001
Age	0.02	0.07	0.742
Age * time linear	0.03	0.01	0.015
CIS-Total			
Intercept	100.70	1.80	< 0.001
Time linear	-1.03	0.98	0.296
Time logarithmic	-3.03	3.57	0.397
Treatment * time linear	3.52	1.35	0.010
Treatment * time logarithmic	-14.78	4.78	0.002
FSS-Total			
Intercept	5.51	0.071	< 0.001
Time logarithmic	-0.29	0.037	< 0.001
EQ-5D			
Intercept	0.83	0.01	< 0.001
IBDQ-Total			
Intercept	165.47	2.33	< 0.001
Time linear	2.11	0.86	0.015
Time logarithmic	- 3.65	3.06	0.234
Treatment * time linear	-3.17	1.96	0.009
Treatment * time logarithmic	11.58	4.20	0.006
SF-36 Physical			
Intercept	39.29	0.84	< 0.001
Time linear	0.47	0.41	0.255
Time logarithmic	0.45	1.51	0.763
Treatment * time linear	-1.20	0.57	0.036
Treatment * time logarithmic	4.32	2.04	0.035
Age	0.02	0.08	0.823
Age * time linear	-0.09	0.04	0.009
SF-36 Mental			
Intercept	41.9	1.44	< 0.001
Treatment	4.0	2.04	0.054
Pittsburg Sleep Quaility Index			
Intercept	6.01	0.30	<0.001
Time logarithmic	-0.27	0.10	0.006

CIS: Checklist Individual Strength; FSS: Fatigue Severity Scale; IBDQ: Inflammatory Bowel Disease Questionnaire.

Table 5: Estimates and effects sizes for SFT group and care as usual group.

	SFT (n=48)		CAU (n=49)		SFT vs. CAU	
Outcome effect	**Estimate**	**Effect size**	**Estimate**	**Effect size**	**Estimate**	**p-value**
CIS-Fatigue*						
baseline	46.4		46.4			
3 months	37.9	-1.13	42.6	-0.51	-0.62	< 0.001
6 months	36.9	-1.26	40.4	-0.80	-0.46	0.010
9 months	37.8	-1.15	38.7	-1.03	-0.12	0.610
CIS-Total						
baseline	100.7		100.7			
3 months	83.5	-0.97	93.4	-0.41	-0.56	0.001
6 months	81.0	-1.11	88.6	-0.68	-0.43	0.010
9 months	82.1	-1.05	84.4	-0.91	-0.13	0.531
FSS-Total						
baseline	5.51		5.51			
3 months	5.11	-0.54	5.11	-0.54		
6 months	4.95	-0.75	4.95	-0.75		
9 months	4.85	-0.89	4.85	-0.89		
EQ-5D						
All time points	0.83			0.83		
IBDQ-Total						
baseline	165.5		165.5			
3 months	173.3	0.34	166.7	0.06	0.29	0.020
6 months	174.6	0.40	171.0	0.24	0.15	0.241
9 months	174.2	0.38	176.1	0.46	-0.08	0.635
SF-36 Physical*						
baseline	39.1		39.1			
3 months	44.8	0.69	42.5	0.40	0.29	0.070
6 months	45.9	0.82	44.7	0.67	0.15	0.351
9 months	45.7	0.80	46.6	0.90	-0.10	0.605
SF-36 Mental						
All time points	45.9		41.9			
PSQI						
baseline	6.01		6.01			
3 months	5.63	-0.13	5.63	-0.13		
6 months	5.48	-0.18	5.48	-0.18		
9 months	5.38	-0.21	5.38	-0.21		

CIS: Checklist Individual Strength; FSS: Fatigue Severity Scale; IBDQ: Inflammatory Bowel Disease Questionnaire; PSQI: Pittsburgh Sleep Quality Index; SFT: solution-focused therapy group; CAU: care as usual group.
*Estimates at the mean of covariate age (40.12 years).

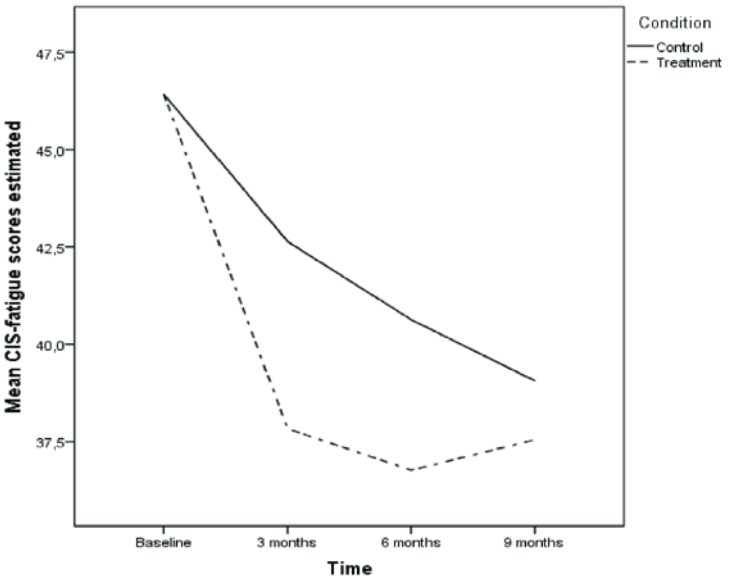

Figure 2. Mean Checklist Individual Strenght-Fatigues scores.

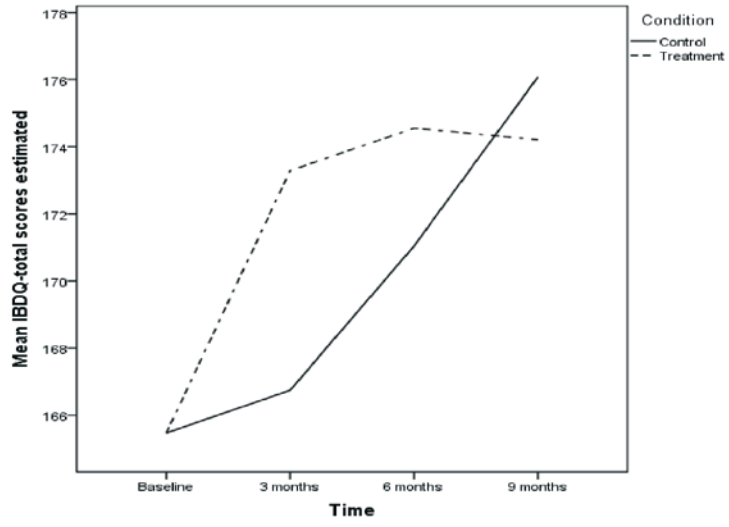

Figure 3. Mean Inflammatory Bowel Disease Questionnaire-total scores.

Primary outcomes

Random effects

The EQ-5D model only needed a random intercept, no random slope. In all other models a random slope was significant. The FFS-total and IBDQ-total models also needed a random covariance between intercept and slope, for these models an unstructured covariance structure was postulated.

Fixed effects

The final models for CIS-fatigue, CIS-total, IBDQ-total and SF-36 physical all included linear and logarithmic time effects and interactions with the treatment (table 4). Quadratic time effects were not significant and were dropped from the models.

At 3 months, scores were significantly better in the SFT group than in the CAU group. This effect was medium for CIS-fatigue and for CIS-total, and small for IBDQ-total. For CIS-fatigue and CIS-total this effect was maintained at 6 months. At 9 months the effects were not significant any more (table 5, Figures 2 and 3).

At 3 months, significantly more patients of the SFT group (39%) compared with the CAU group (18%) scored below the cut-off score of 35 on the CIS-fatigue ($p = 0.03$). At 6 months, this was 34% and 21% respectively ($p = 0.19$). At 9 months, 30% of the SFT group and 26% of the CAU group showed lower scores than 35 on the CIS-fatigue scale ($p = 0.66$).

In the EQ-5D model, only the intercept showed a significant fixed effect. The FSS-total model also included a logarithmic time effect but no treatment effect. The SF-36 mental scale included an intercept and a treatment main effect, but no time effects, which is in accordance with the nearly significant difference at baseline. The final models are presented in table 4. The estimates at the time points are given in table 5.

Secondary outcomes

Hospital Anxiety and Depression Scale

During follow-up both groups showed a similar decrease in HADS-anxiety without differences between the two groups (estimated at baseline for both groups: 7.35 and at 9 months 5.93; decrease: 1.42; $p < 0.001$). HADS-depression showed at baseline (SFT: 6.1; CAU: 6.1), at 3 months (SFT: 5.0; CAU: 5.9; $p = 0.03$) and at 9 months (SFT: 5.5, CAU: 5.3, $p = 0.70$).

Medication use and side effects

Overall, no significant differences were seen over time with respect to medication use and side

effects to medication in the groups separately or between the two groups.
However, the use of corticosteroids decreased over time in both groups (SFT: 19-4.3%, CAU: 16-9.3%), but this was not significantly different between the two groups (p = 0.41).

Disease activity
During follow-up the CDAI and CAI showed no significant differences between the groups or in the two groups separately.

Laboratory parameters
Laboratory parameters (CRP, leukocytes and haemoglobin) remained stable during the study period and no differences were observed between the SFT group and the CAU group.

DISCUSSION

With this randomised controlled trial we demonstrate that SFT for fatigued IBD patients is effective in reducing fatigue and improving QoL. A significant proportion of SFT treated patients returned to fatigue levels seen in the normal population (CIS-fatigue < 35).
Lowering fatigue and thereby improving QoL is important in managing IBD, because fatigue and impaired QoL are related to an increased risk for relapse or symptoms of the disease 9, [45-55] and it was shown that psychological intervention to improve QoL results in a significant drop in healthcare usage.[56-58]
Importantly, at 3 months, a significant lower depression score was seen in the SFT group compared with the CAU group. During follow-up, no differences were seen with respect to sleep quality, anxiety, medication use and disease activity.
Of interest is that during follow-up, fatigue levels in the CAU group improved. This was not completely expected, because previous longitudinal studies showed no improvement on fatigue and QoL over time.[8, 9] However, regression to the mean is a well known phenomenon which could explain the improvement in the CAU group.
Several other factors might explain our results. First, both groups were examined at baseline by a physician, and were informed about the study and the design of the treatment. This direct medical attention may have reduced fatigue levels and, thereby, improved their QoL. Attention effect was earlier described in previous studies that showed lowering of stress, increased QoL or decreased fatigue in control patients on the waiting list.[12, 14, 15, 59-61] Previously, it was reported that hope is related to patients' well-being.[62-64] Therefore, the hope for future fatigue treatment may have reduced fatigue levels.
Second, patients completed questionnaires with a focus on fatigue and QoL. Some patients stated

that filling in the questionnaires made them think about the relationship between their illness and fatigue. This may have started a cognitive reappraisal of their fatigue, reducing the perceived impact of the fatigue. And third, last SFT session was at 6 months without follow-up plans. It may be that patients felt left without support after treatment and this may result in increased fatigue and decreased QoL. The phenomenon of diminished treatment effect during follow-up was also seen in previous studies evaluating psychotherapy to improve QoL or to reduce fatigue.[14, 60] This suggests that a booster session a couple of months after the last treatment session might increase the long-term effectiveness of the treatment. [65]

The effect of the treatment on fatigue and QoL was most pronounced at month 3 and remained significant during the first 6 months of the study. After finishing the SFT, the fatigue levels seemed to incline again, although they remained lower than before the SFT was started. It is known that psychotherapy necessitates repeated treatment sessions in the long term. [66] Therefore, it seems that a longer period of treatment with more follow-up sessions is needed for a more sustained effect on fatigue and QoL. This was shown in a previous study which included two booster sessions after the intervention that resulted in a more sustained effect on QoL. Additionally, a longer follow up showed a further diminished effect in the control group.[12]

Earlier studies investigating the effects of psychotherapy on stress, QoL or fatigue showed that the intervention group improved on psychological distress, QoL or fatigue during the intervention, but this improvement often ended after treatment.[14, 15, 17, 18, 67, 68]

By contrast with our study, these studies had a small sample size, and did not include validated fatigue questionnaires. Our study had a greater sample size and included validated QoL questionnaires and also validated fatigue questionnaires, which give a more evident outcome on these parameters.

This study has a number of limitations. At inclusion, we screened for disease activity using calprotectin, however, we do not have follow-up results for this measurement. For measuring disease activity during follow-up we used the CDAI and CAI. Although these questionnaires are validated and used widely in trials, they are more prone to subjective results of disease activity and therefore we were not able to answer the question whether SFT reduces the number of relapses, which was demonstrated earlier.[69]

Another limitation is that the results of the CAU group may be affected by attention. This probably influenced outcomes of the CAU group.

Although it is difficult to exclude all attention to the patients, it is worth to investigating this possible influence with a control group not receiving information about the intervention.

Another limitation of our study is the follow-up time of 6 months, because it was previously demonstrated that a longer follow-up period of 18 months leads to a decrease of QoL in the CAU group, while QoL increased in the intervention group during that follow-up.[12]

CONCLUSION

SFT has a significant positive effect on fatigue and quality of life in patients with IBD, and offers a management strategy for these patients. Although very effective, this effect declined during follow-up. Because of the burden of fatigue in patients with IBD, we argue that this fatigue management, especially in groups, should be part of the IBD treatment.

Further research should focus on when and for how long fatigue management should be implemented. This includes a cost-effectiveness analysis of this intervention.

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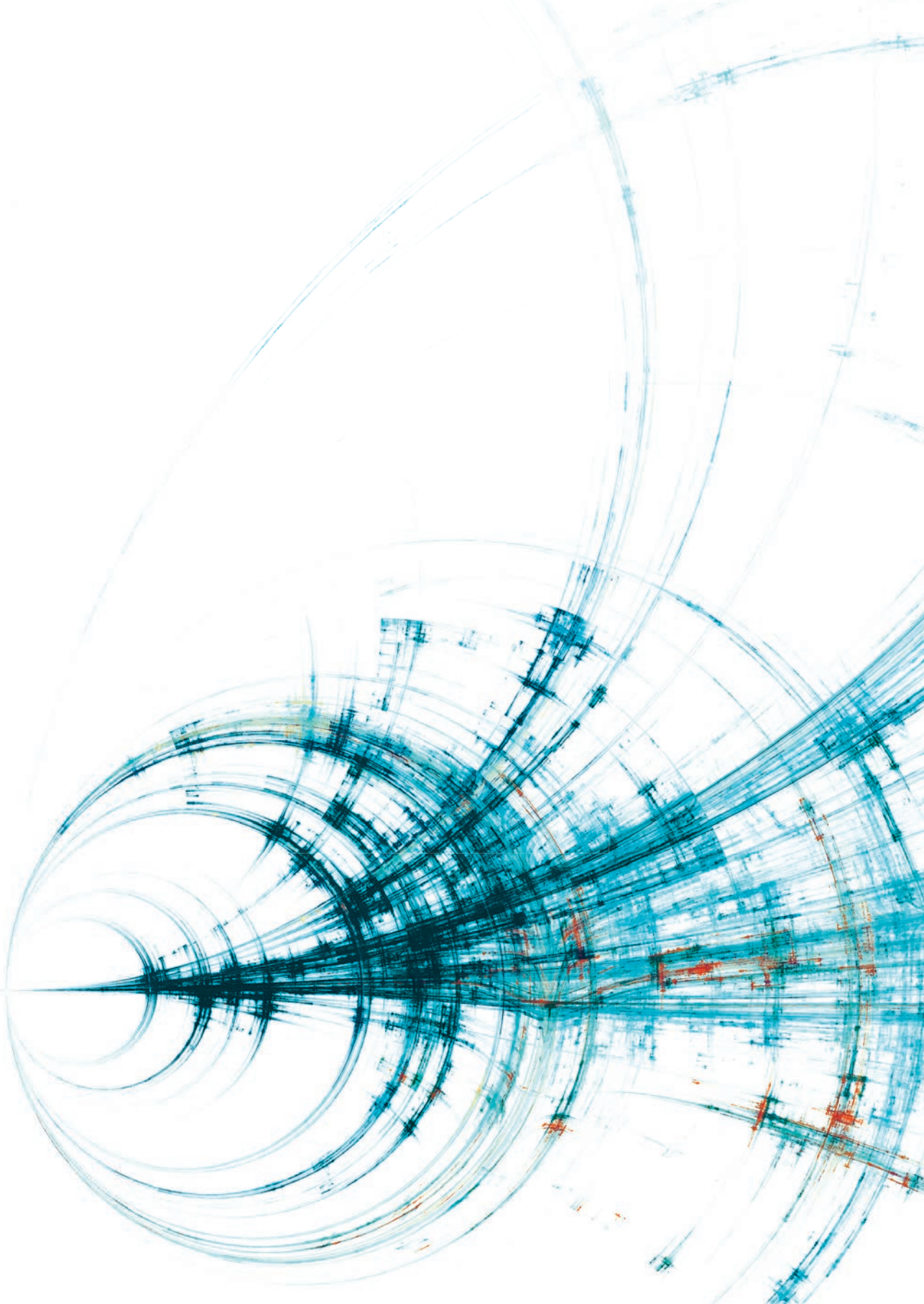

CHAPTER 8

Summary and conclusions

Nederlandse samenvatting

EPIDEMIOLOGY

Fatigue in inflammatory bowel disease (IBD) patients contributes significantly to the burden of the disease. Approximately 40% of patients with quiescent IBD suffer from severe fatigue. [1, 2] According to a survey conducted at our referral hospital we observed an even higher prevalence of fatigue in IBD patients.3 Differences in the reported prevalence of IBD-related fatigue most likely relate to the heterogeneity of the evaluated patient populations.
To evaluate this hypothesis, the distribution of IBD-related fatigue and associated factors was compared between a general hospital and a referral hospital in **Chapter 2**.
As was to be expected, a higher prevalence of fatigue was observed in the referral IBD population compared with the general IBD population (66% vs. 53%, respectively; p=0.01). A similar trend in the distribution of fatigue was noticed when exclusively considering patients with quiescent IBD (53% vs. 41%, respectively; p=0.06).

ASSOCIATED FACTORS OF FATIGUE IN IBD PATIENTS

Factors associated with fatigue in both populations were: female sex, disease activity, and shorter disease duration, use of anti-TNF α, and side-effects to 5-aminosalicylic acid.
Several factors may have contributed to the higher prevalence of fatigue in the referral IBD population. Compared to IBD patients at the general hospital, referral IBD patients demonstrated an increased disease activity, worse disease behaviour, with a need for more bowel resections, a higher rate of side-effects to medication and a higher rate of anti-tumor necrosis factor α (TNF-α) use.

Follow-up data were available for the referral IBD population and demonstrated improvement of fatigue and a trend towards reduced disease activity after one year of treatment with anti-TNF α.
In general, **Chapter 2** supports the hypothesis that a more aggressive IBD phenotype is associated with more severe fatigue. However, also patients with quiescent disease suffer from fatigue. Therefore, we proposed in chapter 3 that additional factors are involved in IBD-related fatigue.

Physical fitness and physical activity in fatigued IBD patients
Chapter 3 provides evidence that physical fitness and physical activity are related to fatigue in IBD patients. Compared to non-fatigued IBD patients, fatigued IBD patients demonstrated impaired physical fitness with a reduction in both cardiorespiratory fitness and muscle strength. The level of physical activity was also decreased in fatigued IBD patients; particularly the intensity of daily physical activity was found to be reduced. From these data, we cannot conclude whether physical fitness and physical activity are involved in the causal pathway of fatigue in IBD patients or are

merely a consequence of the fatigue itself or fatigue related factors.
Previous data have illustrated that physical exercise reduces levels of proinflammatory cytokines, which are supposed to be involved in the induction of sickness behaviour and thereby fatigue (**Chapter 4**).[4-6] We therefore hypothesize that, based on the findings of **Chapter 3**, fatigued IBD patients may benefit from an exercise program focused at improving physical activity and physical fitness.

IBD-related fatigue and the immune system
Fatigue is considered one of the features of sickness behaviour. Evidence is emerging that sickness behaviour is induced by a variety of cytokines.
Since cytokines are known to be involved in the pathophysiology of IBD, it seems reasonable that cytokines are also involved in the induction of sickness behaviour and thereby fatigue in IBD patients. In **Chapter 4** the association between several immune parameters, including leukocyte subsets and cytokines, and IBD related fatigue was explored. Reduced percentages of monocytes, and naive T-cells, and increased percentages of memory T-cells and neutrophils were found in fatigued IBD patients compared with non-fatigued IBD patients. The median serum level of IL-12 was significantly higher in the fatigued patients, whereas IL-8 was significantly lower in the fatigued IBD patients. Although we were not able to demonstrate altered levels of the cytokines IL-1, IL-6 and TNF-α as proposed in figure 1, a dichotomy was observed between fatigued and non-fatigued patients in that the fatigued patients showed signs of immune stimulation. Upregulation of the immune system may both induce and maintain fatigue complaints via immune-to-brain communication pathways.
To gain more insight into the complex interaction between the immune system, endoscopic and histological objectified disease activity and fatigue in IBD patients, prospective studies are recommended.

FATIGUE MANAGEMENT IN IBD PATIENTS

Despite the high prevalence of fatigue and the significantly contribution to the disease burden, management strategies to alleviate fatigue are lacking.
Since disease activity is a significant factor related to fatigue, remission of the disease is considered an important goal in the treatment of fatigued IBD patients. Biologics can induce rapid and sustained disease remission. **Chapter 5** provides a literature review on the effect of several biologics on fatigue and quality of life (QoL) in IBD patients. Compared with placebo, biologics significantly reduced fatigue and improved QoL. This is in line with our observation of a reduction in fatigue severity after one year of treatment with anti-TNF α (**Chapter 2**).

Although induction of disease remission is considered an important requirement in the management of IBD-related fatigue, a large proportion of IBD patients with quiescent disease still suffer from disabling fatigue. This suggests other factors to be involved in addition to parameters related to disease activity.

Chapter 6 reports on a pilot study assessing the feasibility and effectiveness of two psychological interventions, i.e. problem solving therapy (PST) and solution focused therapy (SFT), in the management of fatigue in patients with quiescent Crohn's disease. Both PST and SFT demonstrated beneficial effects on fatigue. SFT appeared to be the most feasible psychological intervention.

Based on these results, we investigated the effect of six months SFT in a randomized controlled trial (**Chapter 7**). Patients randomized to SFT reported a significant reduction in fatigue severity during the course of treatment compared with the control group, who received care as usual (CAU). After the SFT course, 39% of the SFT group demonstrated fatigue levels similar to the general population, compared with 18% of the CAU group ($p = 0.03$). At 9 months from baseline, the differences in reported fatigue scores between the SFT and CAU groups diminished because the CAU group also showed a reduction in fatigue severity during the follow-up. Because patients randomized to the CAU group were also examined by a physician and received information about the treatment design, the phenomenon of reduced fatigue in the CAU group might be relate to attentional and educational effects. Future studies should take these potential effects into account. In addition, a longer period of SFT with booster sessions might further improve and consolidate the observed beneficial effects of SFT.

CONCLUSIONS

Fatigue is a common phenomenon in IBD patients, which contributes significantly to the burden of the disease. The pathophysiology of IBD-related fatigue is considered multifactorial, but at present the underlying mechanisms are largely unknown. Based on the literature and the data presented in this thesis, we propose a multifactorial conceptual model in which both somatic and psychological factors are accounted for fatigue (Figure 1).

FUTURE DIRECTIONS

Expanding the knowledge of etiologic and prognostic factors associated with fatigue in IBD patients will likely form the cornerstone of future initiatives for effective and patient-tailored interventions to mitigate the adverse effects of fatigue.

Based on previous studies and data presented in this thesis, ongoing activation of the immune

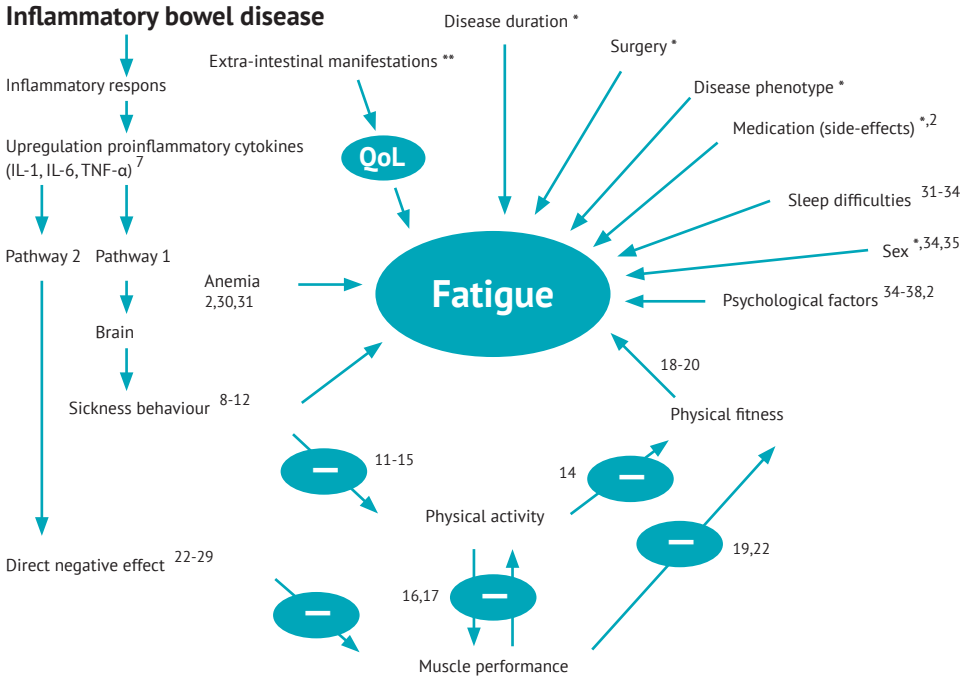

Figure 1: Multifactorial conceptual model of fatigue in IBD
Profinflammatory cytokines (IL-1, IL-6, TNF-α) are upregulated in inflammatory bowel disease.[7] These cytokines may induce sickness behaviour via several immune-to-brain communication pathways.[8-12]

We hypothesize that proinflammatory cytokines act via two additional pathways:
Pathway 1: Proinflammatory cytokines may induce sickness behaviour, which interferes with physical activity. A sustained reduction in physical activity will lead to impaired physical fitness, affecting both the cardiorespiratory fitness and muscle performance.[11-17] Impaired physical fitness may result in a further deterioration of fatigue.[18-21]
Pathway 2: Proinflammatory cytokines, particularly TNF-α and IL-6, adversely affect muscle performance.[22-29] Impaired muscle performance may results in impaired physical fitness and subsequent deterioration of fatigue.[18-21]

* = this thesis
** = related to quality of life (QoL) in IBD, no data about direct relation to IBD-related fatigue

system might serve as an important intermediate in chronic fatigue in IBD patients.[9, 39-45] Therefore, further exploration of the immunological mechanisms underlying IBD-related fatigue is needed.

Since disease activity is a substantial factor associated with IBD-related fatigue, an effective treatment to induce sustained remission of IBD is crucial. In addition to induction of remission,

it seems essential to include coping strategies in the management of fatigued IBD patients. According to the data presented in **Chapter 6** and **Chapter 7**, SFT is effective in the reduction of fatigue in patients with quiescent IBD. Further optimization of the frequency and duration of SFT, might further improve its beneficial effects. Besides treatment with medication and psychological interventions, it seems reasonable to include exercise intervention in future studies, aimed to improve both the physical fitness and physical activity and thereby diminishing of fatigue in IBD patients. Currently it is unknown, if an exercise intervention could have an additional effect on the effects of a psychological intervention or that only an exercise intervention has potential effects on fatigue.

An appropriate study design to define the most effective non-pharmacological treatment strategy would be a randomized controlled trial with four arms, i.e. 1) psychological intervention, 2) psychological intervention + exercise intervention, 3) exercise intervention, and 4) control group. Because previous literature demonstrated immunological effects of exercise interventions and possibly also of psychological interventions, immunological parameters should be included in this study. With this study discrimination whether mainly psychological or mainly somatic aspects play a substantial role or that both aspects need attention in fatigued IBD patients could be possible. Further exploration of the involvement of the immune system in fatigued IBD patients is needed to develop novel non-pharmacological treatments or pharmacological treatments to mitigate fatigue

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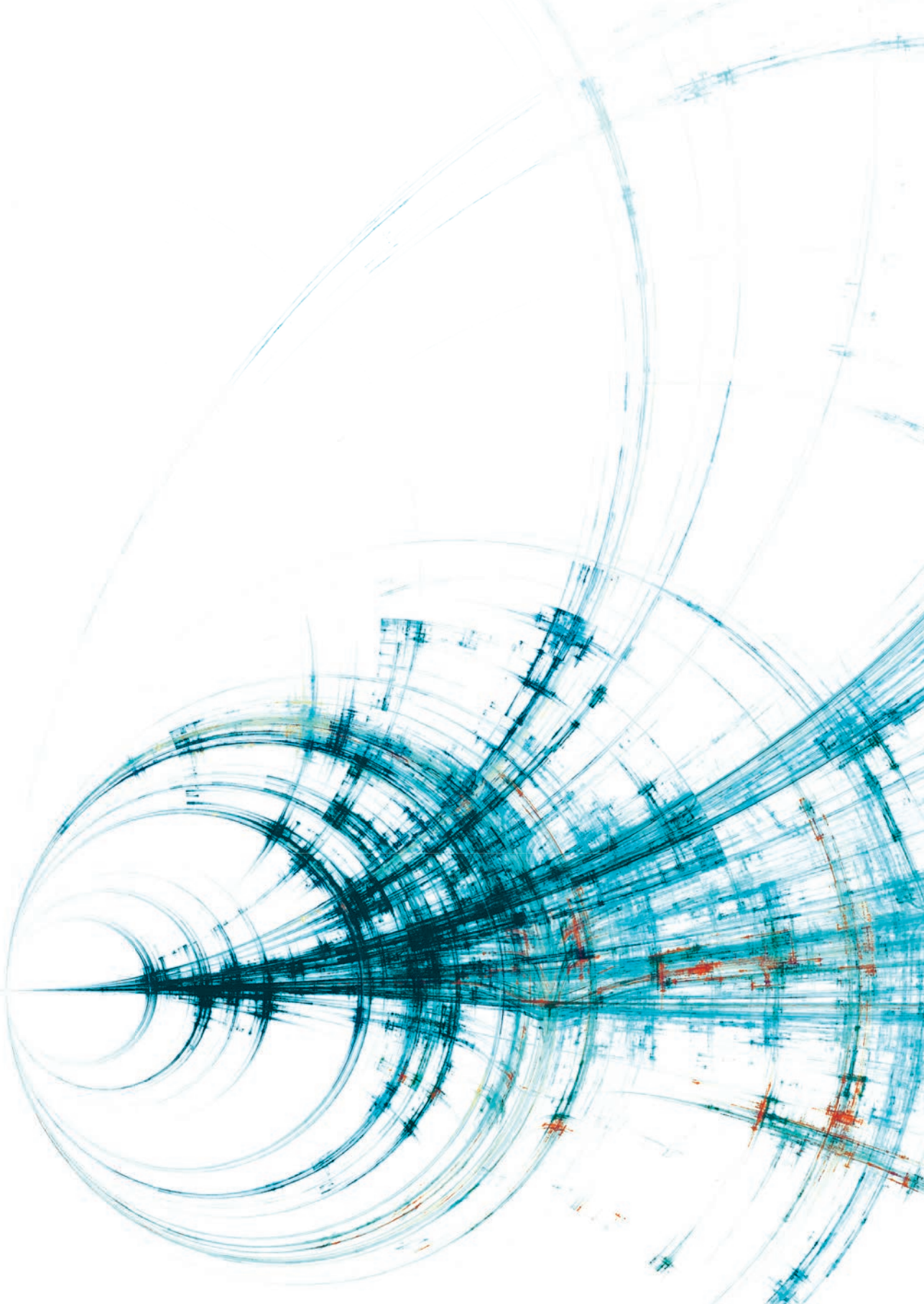

Nederlandse samenvatting

EPIDEMIOLOGIE

Vermoeidheid bij patiënten met inflammatoire darmziekten (IBD) draagt significant bij aan de ziektelast van deze patiënten. Ongeveer 40% van de IBD patiënten waarbij de ziekte in remissie is lijden aan ernstige vermoeidheid.[1, 2] Een enquête in het Erasmus MC liet echter een nog hoger percentage van vermoeidheid onder IBD patiënten zien.[3] Dit verschil komt waarschijnlijk doordat de onderzochte populaties heterogeen zijn.
Om deze hypothese te evalueren, hebben we in **hoofdstuk 2** onderzocht of er verschillen bestaan in het percentage vermoeide IBD patiënten tussen een IBD populatie van een perifeer en een academisch ziekenhuis.
Er werd inderdaad een hoger percentage vermoeide patiënten gevonden in de academische IBD populatie vergeleken met de perifere IBD populatie (66% vs. 53%, respectievelijk; p=0.01). Een vergelijkbare trend was zichtbaar wanneer uitsluitend patiënten met IBD in remissie werden vergeleken (53% vs. 41%, respectievelijk; p=0.06).

FACTOREN GEASSOCIEERD MET VERMOEIDHEID BIJ IBD PATIËNTEN

In **hoofdstuk 2** is tevens geëvalueerd welke factoren geassocieerd zijn met vermoeidheid bij IBD patiënten. Factoren die gerelateerd bleken te zijn aan vermoeidheid in beide IBD populaties waren: vrouwelijk geslacht, een hogere ziekte activiteit, kortere ziekteduur, behandeling met anti-TNF α, en bijwerkingen van 5-aminosalicylzuur.
Verschillen in de distributie van deze factoren zouden een verklaring kunnen bieden voor het hogere percentage vermoeidheid onder academische IBD patiënten. Vergeleken met de perifere IBD populatie werd in de academische IBD populatie een hogere ziekte activiteit, ernstiger IBD fenotype, meer darmoperaties, vaker bijwerkingen van medicatie, en frequentere behandeling met anti-TNF α gevonden.
Follow up van de academische IBD populatie toonde een afname van vermoeidheid na een jaar behandeling middels anti-TNF α.
Bovengenoemde data illustreren dat een ernstiger IBD fenotype geassocieerd is met de mate van vermoeidheid. Echter, ook een aanzienlijk deel van de IBD patiënten waarbij de ziekte in remissie is lijden aan vermoeidheid. Daarom is het aannemelijk dat er ook andere factoren een rol spelen bij IBD gerelateerde vermoeidheid. Dit werd onderzocht in **hoofdstuk 3 en 4**.

Fysieke fitheid en fysieke activiteit in vermoeide IBD patiënten
Hoofdstuk 3 laat zien dat fysieke fitheid en fysieke activiteit gerelateerd zijn aan vermoeidheid bij IBD patiënten. Vergeleken met niet-vermoeide IBD patiënten hadden vermoeide IBD patiënten

een verlaagde fysieke fitheid, waarbij zowel de cardiorespiratoire fitheid als de spierkracht verminderd was. Ook de fysieke activiteit bleek verminderd in vermoeide IBD patiënten, waarbij met name de intensiteit van de fysieke activiteit gereduceerd was.
Op basis van de uitkomsten van deze studie kunnen we niet concluderen of er een causaal verband is tussen fysieke fitheid, fysieke activiteit en vermoeidheid of dat deze factoren een gevolg zijn van vermoeidheid.
Wel laten verschillende studies zien dat fysieke inspanning een afname kan induceren van proinflammatoire cytokines, die waarschijnlijk betrokken zijn bij vermoeidheid.[4-6] Deze studies suggereren, in aanvulling op de uitkomsten van **hoofdstuk 3**, dat vermoeide IBD patiënten baat zouden kunnen hebben bij fysieke inspanning

IBD gerelateerde vermoeidheid en het immuun systeem
Vermoeidheid wordt beschouwd als één van de kenmerken van 'sickness behaviour'. Daarnaast is er steeds meer bewijs dat 'sickness behaviour' wordt geïnduceerd door verschillende cytokines.
Aangezien cytokines een belangrijke rol spelen in de pathofysiologie van IBD, lijkt het aannemelijk dat cytokines ook betrokken zijn bij de inductie van 'sickness behaviour' en daarmee van vermoeidheid bij IBD patiënten.
In **hoofdstuk 4** is de associatie tussen verschillende immuun parameters, waaronder leukocyten subtypes en verschillende cytokines, en IBD gerelateerde vermoeidheid verder onderzocht.
Er werden verminderde percentages monocyten en naïeve T-cellen en verhoogde percentages geheugen T-cellen en neutrofiele granulocyten gevonden in vermoeide IBD patiënten ten opzichte van niet-vermoeide IBD patiënten.
Verder waren de mediane IL-12 serum levels significant hoger in vermoeide IBD patiënten, terwijl IL-8 serum levels significant lager waren in vermoeide IBD patiënten vergeleken met niet-vermoeide IBD patiënten. Hoewel deze studie geen verschillen liet zien in de cytokines IL-1, IL-6 en anti-TNF α, waarvan bekend is dat ze 'sickness behaviour' induceren, werden er aanwijzingen gevonden voor verhoogde activiteit van het immuunsysteem in vermoeide IBD patiënten. Een verhoogde activiteit van het immuunsysteem kan bijdragen aan het induceren en onderhouden van vermoeidheid via interacties tussen het immuun systeem en het centraal zenuwstelsel.
Om meer inzicht in deze complexe interacties tussen het immuunsysteem, ziekte activiteit (endoscopisch en histologisch bevestigd), en vermoeidheid bij IBD patiënten te verkrijgen, zijn echter meer prospectieve studies nodig.

BEHANDELING VAN VERMOEIDHEID BIJ IBD PATIËNTEN

Ondanks de hoge prevalentie van vermoeidheid onder IBD patiënten en de significante bijdrage

hiervan aan de ervaren ziektelast, zijn er geen evidente behandelstrategieën ter vermindering van vermoeidheid.

Inductie van ziekteremissie

Aangezien ziekte activiteit gerelateerd is aan vermoeidheid, is het bereiken van ziekte remissie een belangrijk doel van de behandeling van vermoeidheid bij IBD patiënten. Biologics zijn geschikt in het induceren en onderhouden van ziekteremissie. **Hoofdstuk 5** beschrijft de resultaten van een literatuur review over het effect van verschillende biologics op vermoeidheid en kwaliteit van leven bij IBD patiënten. Vergeleken met placebo zijn biologics geassocieerd met een significante reductie van vermoeidheid en een verbetering in kwaliteit van leven. Dit is conform onze bevinding in hoofdstuk 2 dat vermoeidheid vermindert na één jaar behandeling met anti-TNF α.

Psychologische interventie

Hoewel het induceren van ziekte remissie een belangrijk doel is in de behandeling van IBD gerelateerde vermoeidheid, blijft er een hoog percentage IBD patiënten ernstig vermoeid ondanks remissie van de ziekte. Dit wekt de suggestie dat er ook andere factoren belangrijk zijn in de behandeling van vermoeidheid bij IBD patiënten.

Hoofdstuk 6 beschrijft de resultaten van een pilot studie naar de haalbaarheid en effectiviteit van twee psychologische interventies, namelijk problem solving therapy (PST) en solution focused therapy (SFT), als behandeling van vermoeidheid bij IBD patiënten waarbij de ziekte in remissie is. Deze studie liet zien dat zowel PST als SFT gunstige effecten hebben op vermoeidheid. Echter, SFT was beter uitvoerbaar in de klinische praktijk.

Gebaseerd op de resultaten van hoofdstuk 6, is in **hoofdstuk 7** het effect van zes maanden SFT onderzocht in een gerandomiseerde studie. Patiënten die werden gerandomiseerd voor de SFT groep lieten een significante reductie van vermoeidheid zien gedurende de therapie vergeleken met de controle groep. Na zes maanden SFT, lieten 39% van de patiënten in de SFT groep en 18% van de patiënten in de controle groep, vermoeidheidsscores zien vergelijkbaar met die van gezonde personen ($p = 0.03$).

Drie maanden na het afronden van de SFT (negen maanden vanaf de baseline) verminderde het verschil in vermoeidheidsscores tussen de SFT en controle groep. Dit werd veroorzaakt doordat ook de controle groep gedurende de studie een afname in vermoeidheidsklachten liet zien. Aangezien de controle groep eveneens werd gezien door een arts en geïnformeerd werd over SFT, zou vermindering van vermoeidheid in de controle groep gerelateerd kunnen zijn aan gerichte aandacht en educatie. Toekomstige studies zullen rekening moeten houden met dit effect. Op basis van de resultaten van **hoofdstuk 7** lijkt het verder waarschijnlijk dat een langere duur van psychologische interventie en enkele 'booster sessies' nodig zal zijn om langduriger effect op vermoeidheidsklachten te bewerkstelligen bij IBD patiënten.

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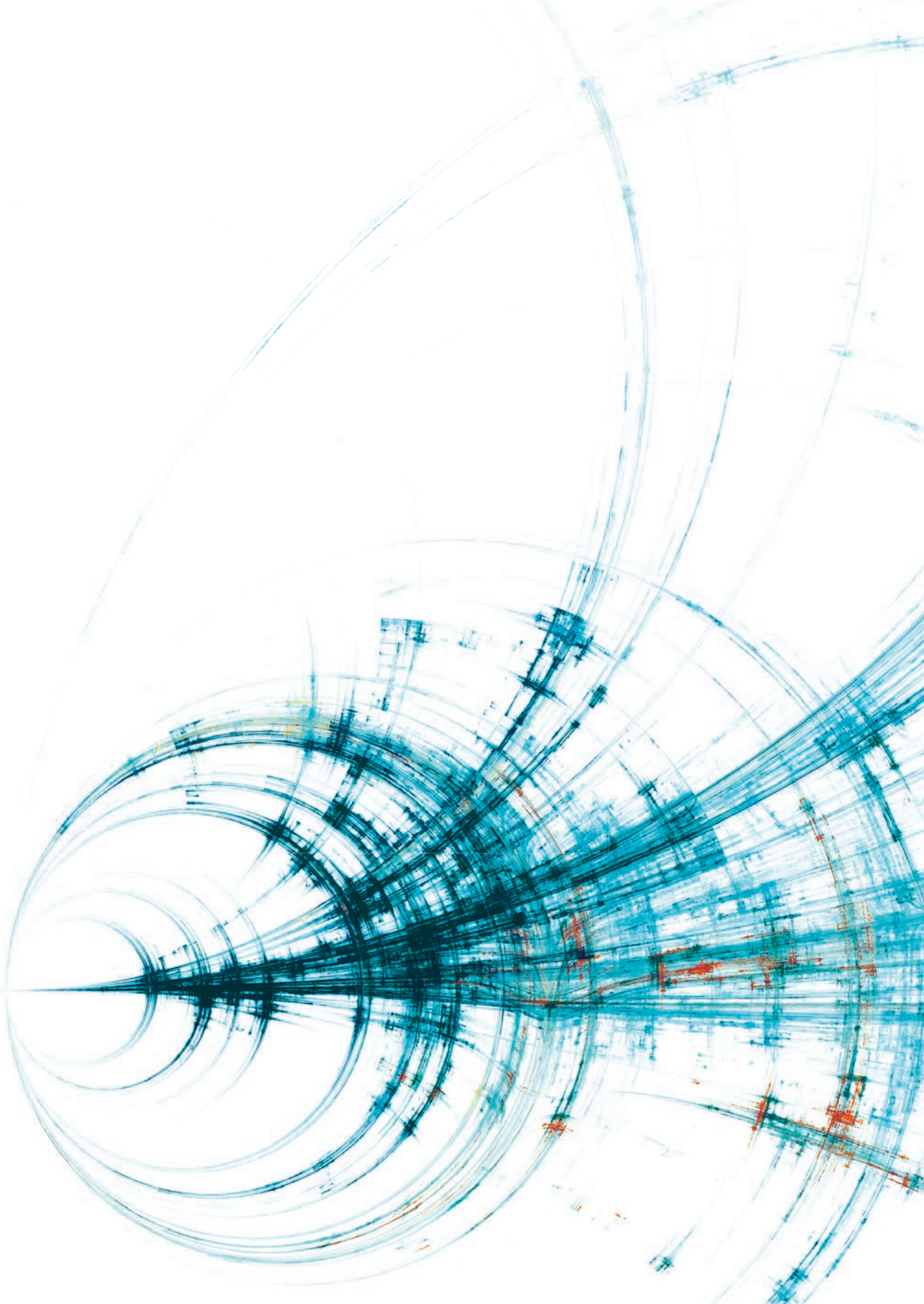

List of publications

LIST OF PUBLICATIONS

1. **Vogelaar L**, van 't Spijker A, van der Woude CJ. The impact of biologics on health-related quality of life in patients with inflammatory bowel disease. Clin Exp Gastroenterol 2009;24;101-109
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3. **Vogelaar L**, van den Berg-Emons RJ, Bussmann H, Rozenberg R, Timman R, van der Woude CJ. Physical fitness and physical activity in fatigued and non-fatigued inflammatory bowel disease patients. Scand J of Gastroenterology 2015;50:1357-1367
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1. Baars JE, **Vogelaar L**, Wolfhagen FH, Biermann K, Kuipers EJ, van der Woude CJ. A short course of corticosteroids prior to surveillance colonoscopy to decrease mucosal inflammation in inflammatory bowel disease patients: results from a randomized controlled trial. J Crohns Colitis. 2010;4:661-668
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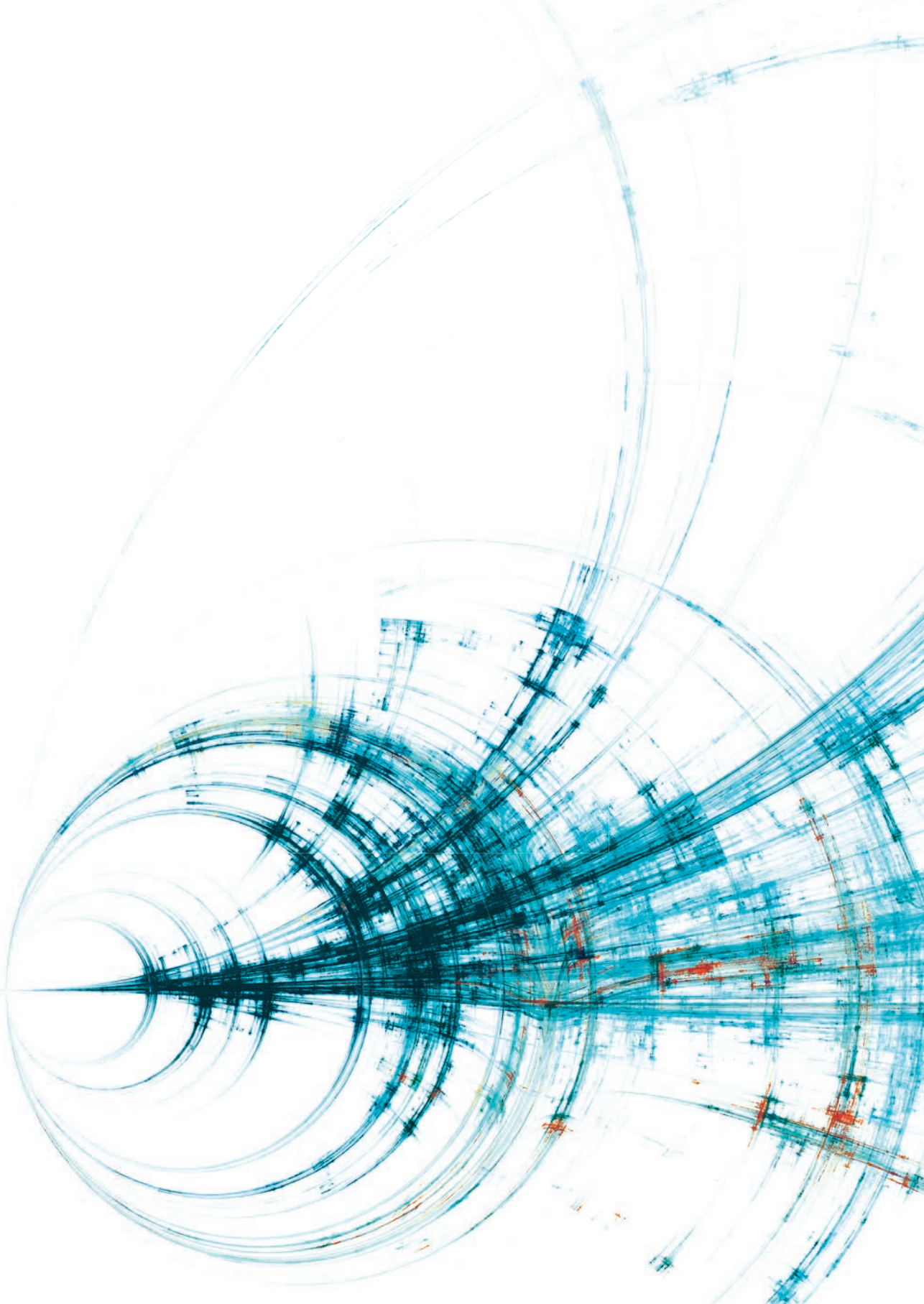


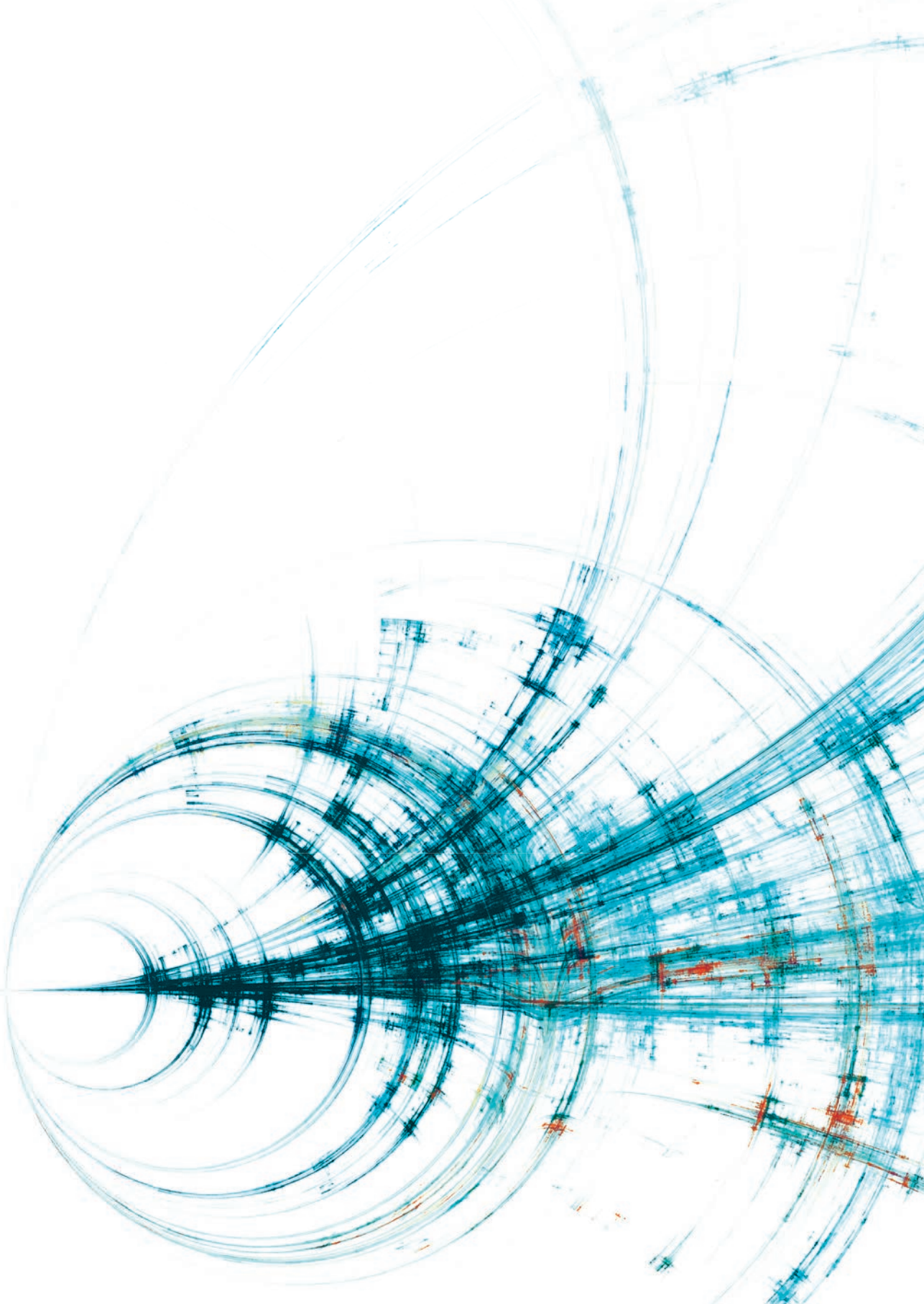
PhD Portfolio

PhD PORTFOLIO

Summary of PhD training and teaching

Name PhD student: Laurens Vogelaar Erasmus MC Department: Gastroenterology and Hepatology	PhD period: 2009-2015 Promotor(s): Prof.Dr.C.J. van der Woude Co-promotor: Dr. A. van't Spijker	
1. PhD training		
	Year	**Workload**
General courses		
- Biomedical English Writing and Communication Course	2008	56 hours
- Nihes Biostatistics for Clinicians	2010	28 hours
- CPO course: 'methodologie van patient gebonden onderzoek'	2008	8 hours
- Presentation course	2009	8 hours
Specific courses		
- Liver transplantation course	2009	8 hours
Oral presentations		
- NVGE	2009	28 hours
- VNTO Chrover	2009	12 hours
- CCUVN	2009	12 hours
- Regional meeting IBD and fatigue	2010	12 hours
- Broad Foundation, Los Angeles	2010	28 hours
- ECCO, Barcelona	2012	28 hours
Poster presentations		
- UEGW	2009	28 hours
- DDW	2010	28 hours
- DDW	2011	28 hours
- DDW	2012	28 hours
- ECCO	2012	28 hours
(Inter)national conferences		
- Symposium 'Cognitie of Conditie'	2008	10 hours
- Symposium IBD and immune diseases	2008	8 hours
- Symposium Quality of life	2008	8 hours
- Endoscopy Days	2008	8 hours
- Endoscopy Days	2009	8 hours
- Symposium 'effectiviteit en therapie tegen welke prijs'	2009	8 hours
- Broad Foundation, Los Angeles	2010	28 hours
- Chronic fatigue and treatment	2011	8 hours
- DDW	2010	28 hours
- DDW	2011	28 hours
- ECCO	2012	28 hours
- ECCO	2013	28 hours

- NVGE	2009	28 hours
- UEGW	2009	28 hours
2. Teaching		
Lecturing		
- Quality of life and IBD. Lectures for 4th year medical students.	2011	28 hours
Supervising practicals and excursions, Tutoring		
- Inflammatory bowel disease practical, 1st year medical student	2010	8 hours
- Inflammatory bowel disease practical, 4th year medical student	2010	8 hours
Supervising Master's theses		
- Quality of life in IBD, Annemarie Edel	2010	60 hours
- Immunological parameters associated with fatigue in IBD, Bas Aerts	2011	60 hours
- Fitness and physical activity in IBD patients, Badr Nouhaili	2011	60 hours
- Physical fitness and physical activity in IBD patients, Silvie-An de Schipper	2011	60 hours
Other		
- Design of minor 'Gastroenterology and Quality of life'	2011	56 hours



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dank daarvoor. Zwagertjes uit Lieren, het was niet altijd makkelijk voor jullie afgelopen jaren: wat zijn er veel schalen vol heerlijks aan jullie neus voorbij gegaan. Maar jullie hebben nooit geklaagd: ik ben trots op jullie.

Lieve oma's, ondanks dat de families steeds groter worden, blijven jullie altijd even geïnteresseerd. Dank voor jullie warmte en betrokkenheid. Hopelijk kunnen jullie mijn promotie meevieren.

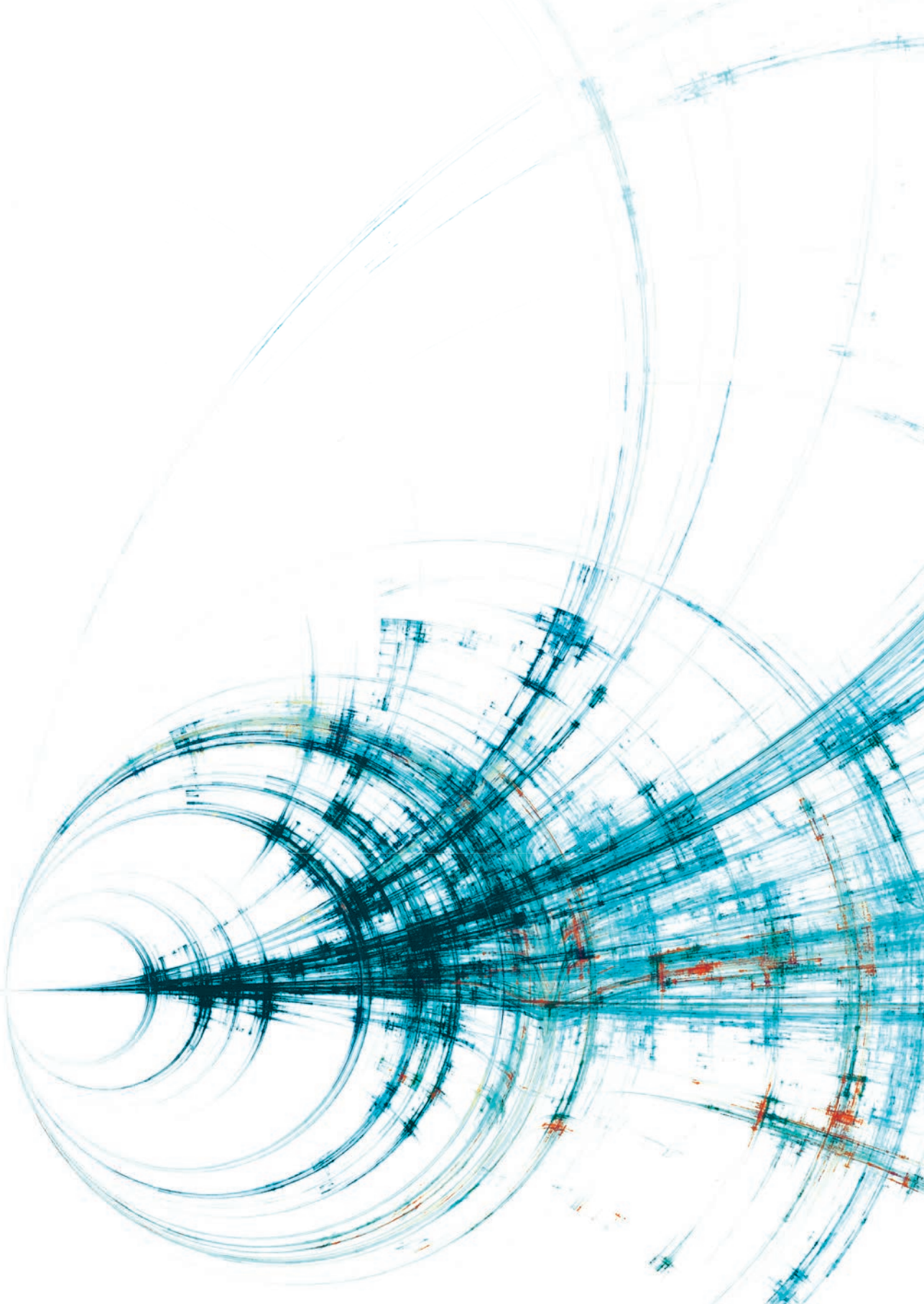
Lieve pa's en ma's, het is niet goed in woorden te vatten wat jullie voor mij en voor ons hebben betekend de achterliggende jaren. Jullie waren altijd geïnteresseerd en hebben ons altijd gesteund. Dank voor jullie onvoorwaardelijke liefde die jullie op een eigen manier laten zien. Ik ben er trots op zulke (schoon)ouders te hebben. We kijken er naar uit om de route naar Lieren en Veenendaal vanaf nu zonder laptop af te leggen.

Pa en mede auteur, in het bijzonder wil ik jou bedanken. Jij kwam met het idee om vermoeide IBD patiënten met SFT te behandelen, wat succesvol bleek te zijn. Wat heb je er ontzettend veel vrije tijd in gestoken. Elke week naar Rotterdam om de onderzoeksgroepen therapie te geven. Ik moest er niet aan denken dat je trein vertraging zou hebben en ik er alleen voor zou staan. Het was een bijzondere ervaring om als professional met je samen te werken. Ik waardeer het enorm dat je dit voor me hebt gedaan. Maar we moeten wel eerlijk bekennen, zonder de gevulde koeken van ma, waren we nergens geweest.

Lieve Mar en Gitte, wat hebben we uitgezien naar dit moment, terugkijkend waren het pittige jaren, maar gelukkig is het nu afgerond. Onze laptops kunnen aan de wilgen. Mar, dank dat je er altijd voor me was. Gelukkig wist jij altijd aan te sturen op tijd voor ons samen. Ik ben trots op je! En de rest……dat vertel ik je wel onder 4 ogen.

Lieve Gitte, jij kan nog niet lezen, maar jij was ongetwijfeld een hele belangrijke reden om af en toe niet aan dit proefschrift te werken. Ik geniet elke woensdag weer van samen het 'paad eten geven', samen 'kossie' drinken en om te ontdekken wie de lekkerste appeltaart van Amersfoort kan maken. Dat gaan we de komende tijd wat vaker doen, goed?

Naast alle mensen die bijgedragen hebben aan mijn proefschrift, is het God die mij alles gegeven heeft wat nodig was om dit proefschrift af te ronden. Hem komt de eer toe. 'Wat zal ik de HEERE vergelden voor al Zijn weldaden, aan mij bewezen?' (Psalm 116:12, de Bijbel).



Curriculum Vitae

CURRICULUM VITAE

Lauran Vogelaar werd geboren op 20 oktober 1980 te Dirksland. Na het behalen van zijn propedeuse Bewegingstechnologie, startte hij in 2002 met de studie Geneeskunde aan de Erasmus Universiteit te Rotterdam. Na het verrichten van zijn afstudeeronderzoek met als onderwerp 'Sex related differences in inflammatory bowel disease', behaalde hij in september 2008 zijn artsexamen. Aansluitend begon hij zijn promotieonderzoek op de afdeling Maag- Darm- en Leverziekten van het Erasmus MC te Rotterdam, onder supervisie van prof. dr. C.J. van der Woude en dr. A. van 't Spijker. Sinds december 2011 is hij in opleiding tot Maag- Darm- Leverarts (opleider dr. R.A. de Man). De tweejarige vooropleiding Interne Geneeskunde volgde hij in het Deventer ziekenhuis (opleider dr. C.J. Vermeij) en continueerde zijn opleiding op de afdeling Maag- Darm- en Leverziekten van het Deventer ziekenhuis (opleider dr. F. ter Borg). Lauran is getrouwd met Margaretha Brouwer en samen met hun dochter Gitte (2013) wonen ze in Amersfoort.