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TITLE PAGE

Title: Fatigue in Inflammatory Bowel Disease Reflects Mood and Symptom-reporting Behavior Rather than Biochemical Activity or Anemia.

Short Title: Fatigue in IBD: Influencing factors.

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Abbreviations:

CD	Crohn's disease
FC	fecal calprotectin
IBD	inflammatory bowel disease
IBS	irritable bowel syndrome
UC	ulcerative colitis

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INTRODUCTION

Fatigue is common and debilitating, reported by over 80% of patients with active inflammatory bowel disease (IBD) and 40% with quiescent disease. [1-2] The etiology is complex and incompletely understood. Studies suggest links between fatigue, IBD activity, and various psychological factors. [3-6] We assessed the relationship between fatigue and clinical and biochemical disease activity, as well as factors including mood, somatization, and presence of irritable bowel syndrome (IBS)-type symptoms. We hypothesized there would be no correlation between fatigue and objective markers of disease activity, rather that fatigue would be associated with low mood, somatoform behavior, and symptom-reporting in general.

METHODS

We performed a cross-sectional study of outpatients with IBD at Leeds Teaching Hospitals NHS Trust, UK, between December 2016 and April 2017. All patients received study information and gave written informed consent. They provided blood for hemoglobin and stool for fecal calprotectin (FC) (Immundiagnostik, Bensheim, Germany). Patient demographics and disease characteristics were collected. Fatigue was assessed using the IBD fatigue self-assessment scale, [7] consisting of two sections. Section one assesses frequency and severity of fatigue, and section two impact of fatigue on daily activities. Higher scores represent higher fatigue severity, and greater impact on daily life. We used validated questionnaires assessing co-existent IBS-type symptoms (Rome III), clinical disease activity (Harvey-Bradshaw index for Crohn's disease (CD) and simple clinical colitis activity index for ulcerative colitis (UC)), mood (hospital

anxiety and depression scale), and somatization-type behavior (patient health questionnaire-15). The study was approved by the local research ethics committee (Reference Number: 16/YH/0235).

The student's t-test was used to compare mean fatigue severity and impact scores across various clinical and psychological factors. Correlation between fatigue scores and both hemoglobin and FC levels, as continuous variables, was analyzed using Pearson's correlation co-efficient. P values <0.05 were considered statistically significant. All analyses were performed using SPSS for Windows version 23.0 (SPSS Inc, Chicago, Illinois, USA).

RESULTS

Seventy-one IBD patients were recruited (mean age 37.4 years, 49 (69.0%) female). Fifty-two (73.2%) had CD, 19 (26.8%) had UC, and 43 (60.6%) had quiescent disease according to clinical disease activity indices. Mean fatigue scores according to patient characteristics are summarized in Table 1. Patients with clinically active disease reported higher fatigue severity and impact compared with patients in clinical remission ($P = 0.047$ and $P = 0.01$, respectively). However, there was no correlation between fatigue severity ($r = 0.16$, $P = 0.28$) or impact ($r = 0.10$, $P = 0.49$) and FC levels, and no difference according to normal or abnormal FC.

Patients with abnormal anxiety scores reported higher fatigue severity ($P = 0.001$) and impact ($P < 0.001$). There was no difference in fatigue severity between patients with normal and abnormal depression scores ($P = 0.28$). However, fatigue impact scores were higher in those with abnormal depression scores ($P = 0.004$). Patients reporting IBS-type

symptoms had greater fatigue severity (P = 0.01), but there was no difference in fatigue impact (P = 0.08). High levels of somatization were strongly associated with both greater fatigue severity and impact scores (P < 0.001 for both). Fatigue scores did not differ in those with or without anemia, or according to hemoglobin levels (fatigue severity r = -0.167, P = 0.18, and fatigue impact r = -0.129, P = 0.30).

DISCUSSION

This study demonstrates patients with IBD with clinically active disease report greater fatigue severity and impact. However, there was no correlation between fatigue and FC levels. In addition, abnormal anxiety scores, and high levels of somatization were strongly associated with greater levels of fatigue severity and impact. Patients with abnormal depression scores reported greater impact of fatigue on daily activities, and those with IBS-type symptoms reported higher fatigue severity. Finally, fatigue scores did not differ according to hemoglobin level or presence of anemia.

These findings confirm the multifactorial etiology of fatigue, and the significant impact of psychological factors. The fact that higher fatigue scores were associated with clinical disease activity scores, mood scores, high levels of somatization, and presence of IBS-type symptoms, but not biochemical evidence of IBD activity, supports previous observations that disease activity scores do not always reflect genuine mucosal inflammation, but rather are influenced by psychological co-morbidities that may also be prevalent in IBD patients [8]. Our results also suggest fatigue-reporting may relate more to poor psychological health, and willingness to endorse symptoms referable to multiple body systems, rather than arising as a direct consequence of mucosal inflammation or

anemia. In order to improve fatigue in IBD, interventional studies focusing on improving psychological wellbeing are required.

Table 1. Association Between Fatigue in IBD and Various Patient Characteristics.

	Mean Fatigue Severity Score (SD)	P Value	Mean Fatigue Impact Score (SD)	P Value
Type of Inflammatory Bowel Disease				
Crohn's disease	12.9 (3.6)		52.0 (28.7)	
Ulcerative colitis	11.5 (3.0)	0.12	53.5 (22.9)	0.84
Clinically Active Disease				
Present	14.1 (3.4)		66.0 (25.8)	
Absent	12.2 (3.4)	0.047	47.8 (25.5)	0.01
Biochemically Active Disease*				
Present	13.0 (3.4)		51.4 (23.5)	
Absent	13.7 (3.7)	0.49	51.3 (30.3)	0.99
Abnormal Anxiety Scores				
Present	15.3 (2.0)		77.8 (16.1)	
Absent	12.0 (3.5)	0.001	46.0 (25.2)	<0.001
Abnormal Depression Scores				
Present	13.2 (2.8)		63.9 (21.8)	
Absent	12.3 (3.8)	0.28	45.0 (27.5)	0.004
Rome III IBS-type Symptoms				
Present	13.4 (3.4)		57.1 (25.1)	
Absent	11.3 (3.0)	0.01	45.5 (28.5)	0.08

High Levels of somatization				
Present	14.3 (2.6)		76.5 (27.8)	
Absent	11.9 (3.6)	<0.001	40.9 (17.8)	<0.001
Anemia†				
Present	12.0 (3.7)		50.3 (22.4)	
Absent	12.8 (3.5)	0.60	52.8 (27.7)	0.78

*FC ≥100μg/g

†<13.5g/dL in males and <11.5g/dL in females

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