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## Chronic abdominal pain, fatigue and inflammatory bowel disease in children

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# **CHAPTER 6**

## **THE RELATIONSHIP BETWEEN SELF-REPORTED FATIGUE IN CHILDREN WITH INFLAMMATORY BOWEL DISEASE AND HAEMOGLOBIN LEVELS AND DISEASE ACTIVITY: A MULTICENTRE CROSS-SECTIONAL STUDY**

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**ABSTRACT**

**OBJECTIVES AND STUDY:** Inflammatory bowel diseases (IBD) are known to affect the patient's energy level. Although children and adolescents report fatigue as their most distressing symptom, even at times of disease remission, it has hardly been studied. We aimed to obtain a better understanding of the nature of fatigue in paediatric patients with IBD. We compared biological and functional parameters in fatigued and non-fatigued paediatric patients with IBD to assess possible (non-)correlations.

**METHODS:** We conducted a cross-sectional observational study of 106 children and adolescents with quiescent to moderately active IBD (defined as having Paediatric Ulcerative Colitis Activity Index (PUCAI) scores below 65 or Paediatric Crohn's Disease Activity Index (PCDAI) scores below 37.5). Participants were recruited from five tertiary care and six secondary care centers in Belgium and the Netherlands. Patients were considered fatigued when the PedsQL™ fatigue was  $< -2.0$  Z for age, while non-fatigued patients had scores above this cut-off point. We measured haemoglobin concentration, iron indicators, faecal calprotectin, six-minute walking distance (6MWD) and disease specific quality-of-life (IMPACT-III).

**RESULTS:** The study cohort's mean PedsQL™ fatigue Z-score was  $-1.0$ . Twenty-three of 106 (22%) patients were fatigued. Fatigued and non-fatigued IBD patients were not significantly different in IBD disease phenotype. Fatigued IBD patients had a significant lower IMPACT-III score than non-fatigued patients (respectively 120 vs. 146,  $p < 0.0001$ ), and a larger proportion was not in clinical remission (26% vs. 63%,  $p = 0.003$ ). Mean haemoglobin Z-scores ( $-1.7$  vs  $-1.5$ ,  $p = 0.589$ ), ferritin concentration (14 vs 23  $\mu\text{g/L}$ ,  $p = 0.206$ ) and faecal calprotectin concentrations (414 vs 355  $\mu\text{g/g}$ ,  $p = 0.928$ ) were not significantly different between fatigued and non-fatigued IBD patients.

**CONCLUSION:** Our data indicate that neither haemoglobin levels nor faecal calprotectin levels are strongly correlated with the self-rating of fatigue. Further investigations are needed to identify practical treatment targets.

## **INTRODUCTION**

Inflammatory bowel disease (IBD) is a chronic illness of the gastrointestinal tract characterized by episodes of inflammation and remission and has significant impact on psychological and social functioning.(1-3) Fatigue is a common feature during active inflammation as well as during disease remission, which further decreases quality-of-life and hinders participation in daily activities.(5) Fatigue is defined as a 'subjectively overwhelming sense of tiredness, lack of energy, and feeling of exhaustion that decreases one's capacity for physical and mental activity'.(4) Though fatigue is considered a patient-relevant outcome measure, (5) studies on fatigue are limited.

We recently explored the paediatric literature about fatigue in IBD and concluded that biological, functional, as well as behavioral factors contribute to fatigue.(6) Several studies suggest that disease activity and anaemia in particular affect the physical functioning of paediatric IBD patients.(7-10)

### **Disease activity and fatigue**

Persisting mucosal inflammation may go unnoticed when response to therapy is only monitored by clinical parameters such as the paediatric Crohn's disease activity index (PCDAI). The decision to escalate therapy may then be seriously delayed with consequently lower exercise capacity, quality of life and fatigue. Elevated faecal calprotectin levels correlate with endoscopic active disease and thus better reflect ongoing disease activity than clinical parameters.(11)

### **Anaemia and fatigue**

Anaemia is a common systemic complication in IBD and significantly impacts on physical performance, quality of life, and absenteeism from school and extracurricular activities.(12-14) In adult IBD patients normalisation of haemoglobin levels improves general well-being, physical ability and quality of life.(15)

To improve our understanding of fatigue in paediatric IBD, we conducted a cross-sectional observational study to assess the relationship between biological and functional factors. We hypothesize that patients with IBD who have elevated faecal calprotectin levels (>250 µg/g) (16, 17), anaemia (Hb < -2SD) (18) or low iron stores (ferritin < 30 µg/L) (19) have a

significant lower exercise capacity, more fatigue and poorer quality of life than IBD-patients with normal parameters.

## **METHODS**

### **Patients**

Patients aged between 8 and 18 years were recruited at the outpatient clinics of five tertiary care centers and six large teaching hospitals in Belgium and the Netherlands. Patients were eligible for inclusion when they had a Paediatric Ulcerative Colitis Activity Index (PUCAI) score below 65 (20) or a Paediatric Crohn's Disease Activity Index (PCDAI) score below 37.5.(21) Patients were asked to complete two questionnaires, including the PedsQL™ multidimensional fatigue score and the disease specific quality-of-life score IMPACT III, to provide a blood and stool sample, and to perform a 6-minute walking test(6MWT).

### **PedsQL™ Multidimensional Fatigue Scale**

The PedsQL™ Multidimensional Fatigue Scale consists of a child and parent report and is a commonly used fatigue questionnaire with good reliability.(22) The scale comprises the General Fatigue Scale (GFS, 6 items), Sleep/Rest Fatigue Scale (S/RFS, 6 items), and Cognitive Fatigue Scale (CFS, 6 items).(22) The GFS contains questions regarding the subjective feeling of fatigue and the energy to execute activities, the S/RFS contains questions about the quantity and quality of sleep and rest and the CFS contains questions regarding attention and memory.(23) We used the Dutch version of the Child Self Report, which has been validated for children (8 to 12 years) and adolescents (12 to 18 years).(24) Several studies on fatigue have reported imperfect agreement between child self-reports and parent proxy reports (25) and the child and adolescent self-report questionnaires have a strict factorial invariance across gender and age subpopulations.(26) Participants were asked to rate how often a particular problem occurred in the past month, using a 5-point Likert scale. Scores were transformed on a scale from 0 to 100, in which higher scores indicated fewer symptoms of fatigue. PedsQL™ scores were expressed as z-scores derived from published normative data.(11)

### **IMPACT-III questionnaire**

The IMPACT-III questionnaire is a disease-specific quality-of-life questionnaire, that comprises 35 items in 6 domains: IBD-related symptoms (7 items), systemic symptoms (3), emotional functioning (7), social functioning (12), body image (3) and treatment/intervention-related concerns (3).(27) Each item is scored on a 5-point Likert scale, coded from 1 to 5 points. The maximum score is 175, higher scores indicate better quality-of-life. The Impact-III (NL) is a translated and modified version of the original Canadian Impact questionnaire (77) and has been validated for use in children of 8 years and older.(37)

### **Laboratory tests**

Anaemia was defined as a haemoglobin (Hb) concentration more than two standard deviations below the mean of similarly aged children and adolescents from an iron supplemented USA reference population.(18) Hb Z-scores were calculated by subtracting the reference population mean ( $\mu$ ) from the individual score ( $x$ ) and then dividing the difference by the reference population standard deviation ( $\sigma$ ):  $z = \frac{x-\mu}{\sigma}$ .

Iron deficiency was defined as a ferritin concentration below 30  $\mu\text{g/L}$ .(19) Iron deficiency anaemia was defined as a combination of Hb  $< -2$  Z-scores in combination with ferritin concentration  $< 30 \mu\text{g/L}$ . Intestinal inflammation was assessed by measuring faecal calprotectin. We used three commonly used categories:  $<250 \mu\text{g/g}$  for disease remission,  $>500 \mu\text{g/g}$  for disease flare, and  $250-500 \mu\text{g/g}$  for the indecisive range.(29)

### **6-minute walking test**

Exercise capacity was assessed with the 6-minute walking test, and was expressed as the distance (in meters) a person can walk at a constant, uninterrupted pace in 6 minutes.(30) The 6-minute walking distance (6MWD) is age and sex dependent.(30, 31) Z-scores were calculated by subtracting the reference population mean ( $\mu$ ) from the individual score ( $x$ ) and then dividing the difference by the reference population standard deviation ( $\sigma$ ).(32)

### **Ethical considerations**

This study was conducted according to the principles of the Declaration of Helsinki (59th version, October 2008). The independent Medical Ethical Committees of the Zuyderland Medical Center (Heerlen, the Netherlands) and the University of Antwerp (Antwerp, Belgium) approved the study (NL42995.096.12; BE17/50/56). Secondary approval was obtained from the boards of the other participating centers. All parents or legal guardians and participants aged 12–18 years gave informed consent.

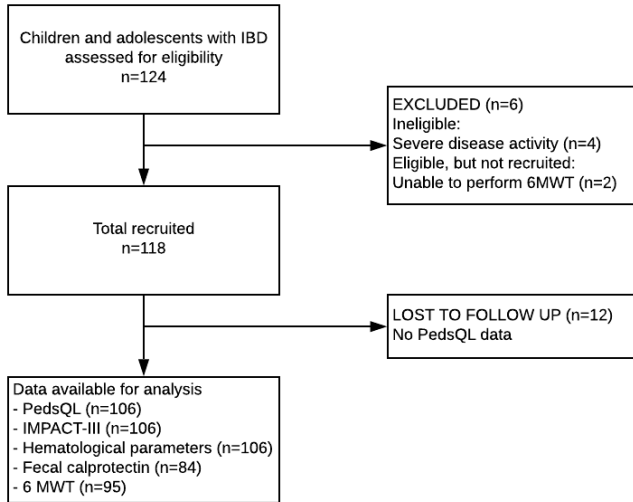
### **Statistical analysis**

Patients were considered fatigued when the PedsQL™ fatigue was below -2.0 Z for age, while non-fatigued patients had scores above this cut-off point. Baseline characteristics were compared between fatigued and non-fatigued patients using a Chi-square test for categorical variables and an independent-samples t-test for continuous variables. In case of non-normal distribution, we used non-parametric alternatives (Fischer's exact test and Mann-Whitney test, respectively; median and IQR are reported). Distributions of PedsQL™ and 6MWD Z-scores among IBD patients were compared with the healthy reference population using the Kolmogorov Smirnov test.

## **RESULTS**

### **Baseline characteristics of the study population**

Patients were recruited between June 2014 and January 2019. Of 124 patients who were assessed for eligibility, 18 were excluded for reasons listed in **Figure 1**. A total of 106 patients were included in the final analysis.



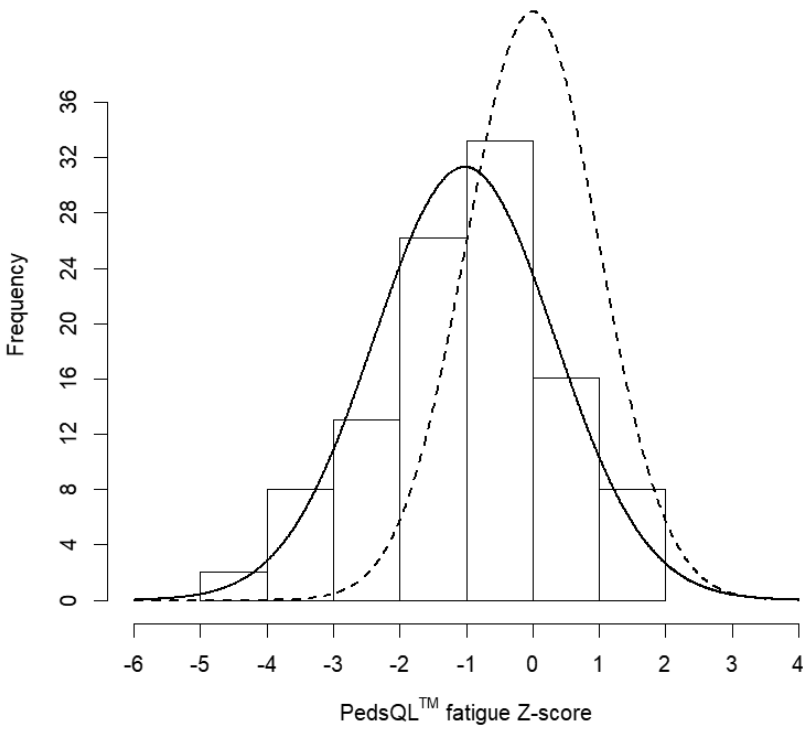
**Figure 1 |** Study flow diagram

Forty-five percent (48/106) of participants were female. Thirty-nine percent (41/106) were aged 8 to 12 years, and 61% (65/106) were aged 13 to 18 years. Twenty-four percent (25/106) of the participants had ulcerative colitis, 73% (77/106) had Crohn’s disease, and 4% (4/106) had IBD-unclassified. Fifty-four percent (53/98) had disease activity scores indicating clinical remission, 45% (44/98) had mild disease activity and one participant had moderate disease activity.

### Fatigue prevalence

The distribution of PedsQL™ total fatigue scores in patients with IBD was significantly lower compared to healthy peers ( $p < 0.0001$ ). In patients aged 8 to 12 years the mean fatigue Z-score was -0.9 (SD 1.3). In patients aged 12 to 18 years the mean fatigue Z-score was -1.1 (SD 1.4). IBD patients scored lower than healthy peers on all dimensions of the PedsQL™ fatigue scale. [Figure 2] Twenty-three patients (22%) had Z-scores below -2.0 and were considered fatigued.





**Figure 2 |** Distribution of PedsQL™ fatigue Z-scores in IBD patients (solid line) vs. the healthy reference population (dashed line) for children

**Table 1** shows that females were overrepresented in the fatigued category ( $p=0.008$ ). Age distribution, disease phenotype and disease duration were not significantly different between fatigued and non-fatigued patients. A significant larger proportion of fatigued patients had higher disease activity scores compared to non-fatigued patients (74% vs. 37%,  $p=0.003$ ). Fatigued and non-fatigued IBD patients did not differ in haemoglobin Z-score nor in ferritin concentration and had similar proportions with high faecal calprotectin values ( $>500 \mu\text{g/g}$ ).

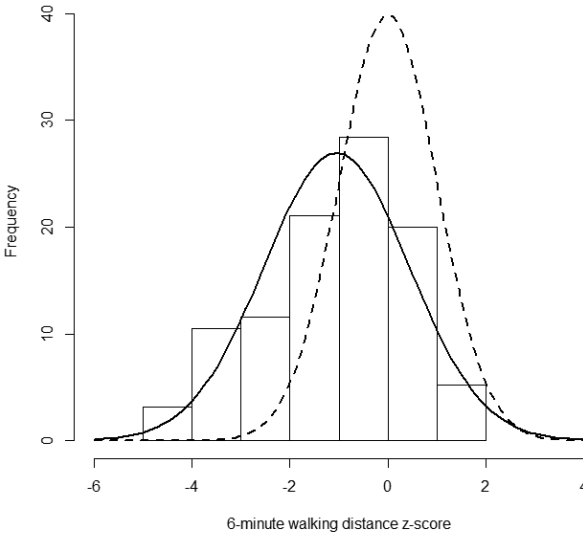
**Table 1** | Demographic, clinical and laboratory characteristics of fatigued and non-fatigued patients

	Fatigued patients (n=23)	Non-fatigued patients (n=83)	p-value
<b>Female gender</b>	16 (70%)	32 (39%)	0.008
<b>Age category</b>			0.359
8-12 years	7 (30%)	34 (41%)	
13-18 years	16 (70%)	49 (59%)	
<b>IBD phenotype</b>			0.821
M Crohn	18 (78%)	59 (71%)	
CU	5 (22%)	20 (24%)	
IBDU	0 (0%)	4 (5%)	
<b>Disease activity score</b>		*	0.003
Remission	6 (26%)	47 (63%)	
Mild	17 (74%)	27 (36%)	
Moderate		1 (1%)	
<b>Disease duration in years</b>	2 (1-3)	1 (0-3) **	0.768
<b>Mean haemoglobin Z-score (SD)</b>	-1.7 (1.2)	-1.5 (1.7)	0.589
<b>Number (proportion) of patients with anaemia (Hb &lt; -2.0 SD)</b>	12 (52%)	31 (37%)	0.200
<b>Number (proportion) of patients with anaemia (HB&lt;-1.5 SD)</b>	13 (57%)	40 (48 %)	0.238
<b>Mean ferritin (SD) in µg/l</b>	14 (7-31)	23 (12-43) #	0.206
<b>Number (proportion) of patients with iron deficiency anaemia</b>	11 (50%)	24 (32.4%)	0.133
<b>Faecal calprotectin in µg/g mean (SD)</b>	1085.5 (1608.4)**	833.9 (1280.1)	
Faecal calprotectin (≥ 250 µg/g)	10 (53%)**	36 (55%)	0.832

\*8 missing values, \*\*4 missing values, #17 missing values, ##18 missing values

**6-minute walking distance**

The distribution of 6MWDs of patients with IBD children was significantly lower compared to age and sex matched healthy peers [Figure 3], but the mean 6MWD and 6MWD Z-scores between fatigued and non-fatigued patients were not significantly different (respectively 581 meters (-1.1 Z) and 594 meters (-1.0 Z))[Table 2].



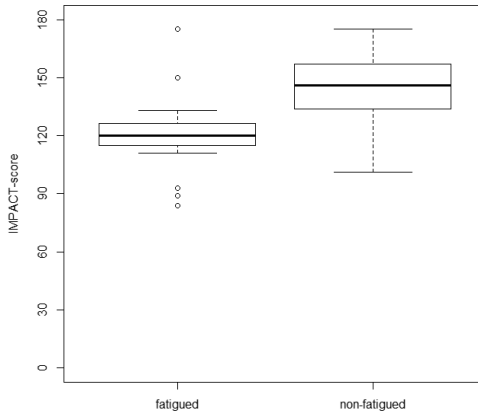
**Figure 3 |** Distribution of 6-minute walking distance Z-scores in IBD patients (solid line) vs. the healthy reference population (dashed line).

**Table 2 |** 6-minute walking distance in fatigued and non-fatigued participants.

	Fatigued patients (n=22)	Non-fatigued patients (n=73)	p-value
Mean 6MWD in m (SD)	581 (86)	594 (91)	0.533
Mean 6MWD Z-score (SD)	-1.1 (1.5)	-1.0 (1.5)	0.863

## Quality-of-life

Fatigued patients had lower median quality-of-life scores compared to non-fatigued IBD patients (120 (IQR 115 to 127) vs. 146 (IQR 134 to 157);  $p < 0.0001$ ) [Figure 4].



**Figure 4 |** IMPACT-III quality-of-life scores in fatigued and non-fatigued patients. Central boxes span 25th and 75th centiles (or the interquartile range). Horizontal line within box represents median.

## DISCUSSION

### Key findings

In this multicenter study we found that approximately a quarter of paediatric patients with quiescent to moderately active IBD qualified as fatigued. Interestingly, neither haemoglobin parameters nor faecal calprotectin nor the exercise capacity, expressed as the 6MWD, was significantly different between fatigued and non-fatigued IBD patients. Fatigued patients had a significantly lower quality-of-life scores and higher clinical activity indices, but otherwise this group did not differ in any respect from the non-fatigued patients.

The mean total Z-score of the Child Self Report PedsQL™ Multidimensional Fatigue Scale in our study cohort (-1.0) was comparable with the total Z-score (-0.7) in a similarly aged American cohort of IBD patients described by Marcus and colleagues.(12) In this single center case-control study, IBD patients completed questionnaires about fatigue, quality-

of-life (IMPACT III) and depression (PedsQL Depression inventory), and were compared to healthy controls. This is the only other cohort in which fatigue was assessed with the PedsQL™ fatigue scale. Like us, they concluded that adolescents with IBD are significantly more fatigued than healthy controls, even when clinical remission was reached.

The 6MWD as a proxy of exercise capacity has been used in many other chronic conditions, including congenital heart disease (33), cystic fibrosis (34) and juvenile idiopathic arthritis (35), but not yet in IBD. A German case-control study evaluated exercise capacity in adolescents with IBD with a wearable device (Sensewear Pro 2) to plot spontaneous physical activity over time.(36) Contrary to our observations, the exercise capacity was not different between patients with IBD and healthy controls. Werkstetter and colleagues included 39 IBD patients only, which may have been a too small sample size to detect a group difference.

Recently published adult studies on fatigue and IBD show results that are similar to ours.(37-39) These studies also suggest that fatigue negatively impacts on quality-of-life and is not associated with biological factors such as anaemia or persistent mucosal inflammation. Fatigue was rather associated with behavioural factors such as anxiety, depression and sleep disturbances.(37-39)

### **Methodological strengths and limitations**

The cross-sectional design of this study does not allow to evaluate causality between fatigue and biological parameters. A prospective intervention study to evaluate whether iron supplementation reduces fatigue, improves exercise capacity and quality of life in paediatric patients, is currently underway.[toetsingonline NL42995.096.12] Also, the use of self-report questionnaires may have underestimated the prevalence of fatigue, as patients with low exercise capacity and anaemia may tend to adapt to a lower level of activity and accept this as is.

### **Implications for clinical practice and future research**

The impact of fatigue on quality-of-life justifies a thorough evaluation of possible causal factors, including behavioural factors such as psychological distress and sleep disturbances. Cognitive Behavioural Therapy has recently been shown to be an effective

treatment against fatigue in another autoimmune inflammatory condition (systemic lupus erythematosus), and may also be of use in improving psychological distress-associated fatigue in IBD.(40) Further research is needed to identify practical treatment targets.

## **CONCLUSION**

This study shows that fatigue is a rather common feature in children and adolescents with IBD, irrespective of the presence of mucosal inflammation and anaemia. Our findings confirm that fatigue negatively impacts on the quality-of-life. We found no association between self-reported fatigue and exercise capacity. In order to get a full picture of the possible causes of fatigue, we suggest that future studies measure functional as well as behavioral factors.

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