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Randomised clinical trial: high-dose oral thiamine versus placebo for chronic fatigue in patients with quiescent inflammatory bowel disease

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Summary

Background: Fatigue is a burdensome symptom for patients with inflammatory bowel disease (IBD). Few pharmacological interventions have documented effect on fatigue in patients with IBD. A pilot study indicated a 20-day effect with high-dose thiamine.

Aims: To investigate the effect and safety of high-dose oral thiamine (600-1800 mg/d) based on gender and weight on chronic fatigue in patients with quiescent IBD.

Methods: This was a randomised, double-blinded, placebo-controlled crossover trial. Patients had quiescent IBD, severe chronic fatigue and no other explanation for fatigue. Patients were allocated 1:1 to either 1) high-dose oral thiamine for 4 weeks, 4 weeks of washout, 4 weeks of oral placebo or 2) oral placebo for 4 weeks, 4 weeks of washout, 4 weeks of high-dose oral thiamine. Fatigue was measured using the Inflammatory Bowel Disease-Fatigue Questionnaire. The primary outcome was improvement (≥3 points) of fatigue after 4 weeks on thiamine.

Results: Forty patients were enrolled between November 2018 and October 2019. Crossover analysis showed a mean reduction of 4.5 points (95% CI 2.6-6.2) in fatigue after thiamine compared with a mean increase of 0.75 point (95% CI −1.3-2.8; $P = 0.0003$) after placebo. Furthermore, 55% of group 1 and 75% of group 2 showed an improvement ≥ 3 points while on thiamine compared with 25% of group 1 and 35% of group 2 while on placebo. Only mild side effects were detected.

Conclusion: We showed a significant beneficial effect of high-dose oral thiamine on chronic fatigue in IBD. The treatment was well tolerated.

Trial registration: NCT03634735.

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1 | INTRODUCTION

Fatigue is one of the most burdensome symptoms for patients with inflammatory bowel disease (IBD), even with IBD in remission.[1] The prevalence of fatigue in patients with quiescent IBD varies from 15% to 54%.[2] Females and patients with Crohn's disease (CD) tend to experience more fatigue than males and patients with ulcerative colitis (UC) respectively.[3] The prevalence of chronic fatigue, ie fatigue lasting more than 6 months, is estimated to range from 22% to 29% for patients with IBD compared with 11% for healthy controls.[4]

The aetiology of fatigue in patients with IBD or other diseases remains unknown. The general consensus that fatigue is multifactorial has motivated a variety of interventions.[5] Active disease, anaemia, hypothyroidism, iron, vitamin B12 or folate deficiency may induce fatigue in IBD and should be treated or corrected if possible.[2] Fatigue is measured as a patient-reported outcome (PRO) using an appropriate and validated questionnaire. If normative fatigue data have been revealed for the questionnaire used, the severity of fatigue can be compared and framed.

Only few interventions have documented effect of pharmacological interventions/measures to alleviate fatigue in patients with IBD.[5,6] Most interventions are of behavioural or psychological character. An unblinded pilot study indicated a beneficial effect of high-dose thiamine.[7] The study included 12 fatigued patients with IBD in remission: eight with UC and four with CD. The patients received high-dose thiamine in 20 days. The dosages of thiamine were gender and weight depended. Ten of the 12 included patients were women. Of the 12 patients, ten reported complete fatigue regression after treatment. None of the patients had thiamine deficiency at inclusion. Only minor side effects of thiamine were detected in the study. The suggested mechanism behind the effect was a dysfunction in thiamine transport from the blood to the mitochondria, leading to decreased cellular carbohydrate metabolism. This dysfunction was suggested to be driven by inflammatory activity.

Thiamine is essential for the human body's utilisation of carbohydrates and mitochondrial ATP production. The most common sources of thiamine are cereal products, meat, legumes and dairy products. Absorption of thiamine occurs in the small intestine. The active metabolite thiamine pyrophosphate constitutes approximately 80% of total body thiamine.[8] Because thiamine is a water-soluble vitamin with renal clearance, the risk of thiamine accumulation is limited for patients with normal kidney function. Residual thiamine can be stored in the liver for up to 18 days.[9] A high oral intake of thiamine for weeks may induce passive diffusion into the cells. Toxicity is not observed after 4 weeks of high-dose intake.[10]

The aim of this study was to test the hypothesis that high-dose oral thiamine abrogates chronic fatigue in patients with IBD in remission.

2 | METHODS

2.1 | Study design

We conducted a randomised, double-blinded, placebo-controlled, crossover trial. Patients were allocated 1:1 to either group 1 (high-dose oral thiamine for 4 weeks in epoch 1 (E1), followed by 4 weeks of washout, followed by 4 weeks of oral placebo in epoch 2 (E2)) or group 2 (oral placebo for 4 weeks in E1, followed by 4 weeks of washout, followed by 4 weeks of high-dose oral thiamine in E2). To minimise the risk of biased PROs, we applied a crossover design. Even though all the questionnaires have been validated and translated into Danish, individual variation in the responses was expected.[11] To minimise the risk of carryover, we added a 4-week washout period between E1 and E2. The duration of the washout period was based on a thiamine half-life of 1-12 hours and a thiamine storage time of less than 3 weeks.

2.2 | Participants

We studied 40 adult patients with quiescent IBD and chronic fatigue consecutively included from the outpatient clinic at Aarhus University Hospital, Denmark. Eligible patients had a diagnosis of CD or UC for more than 3 months and had disease in remission, documented by faecal calprotectin < 200 mg/kg and normal-range clinical scores. We used the Harvey–Bradshaw Activity Index (HBAI) for patients with CD and the Simple Clinical Colitis Activity Index (SCCAI) for patients with UC.[12,13] We assessed fatigue severity using the Inflammatory Bowel Disease-Fatigue Questionnaire (IBD-F) section I; patients with a fatigue score > 12 and fatigue duration > 6 months were included.[14] The cut point for fatigue was equivalent to the 95th percentile for fatigue in the background population.[15] Patients with anaemia, iron deficiency, folate acid deficiency, vitamin B12 deficiency or vitamin-D deficiency were excluded. We excluded pregnant women and patients with co-morbidity that could explain a high level of fatigue (eg cancer, chronic kidney disease, chronic heart disease, diabetes). Eligible patients gave written informed consent prior to any study procedure.

2.3 | Randomisation and masking

The included patients were randomised 1:1 to one of the two arms: group 1 or group 2. Randomisation and treatment blinding were performed by the Hospital Pharmacy at Aarhus University Hospital (using a computerised random number generator) and were monitored by the Good Clinical Practice (GCP) unit at Aarhus and Aalborg University Hospitals, Denmark. The study drugs were blinded, packed and labelled by the Hospital Pharmacy and were administered by blinded investigators.

2.4 | Procedures

All included patients received tablets for oral intake for a 4-week treatment period (thiamine or placebo), followed by a 4-week washout period and intake of the opposite tablets (placebo or thiamine) for 4 weeks. The thiamine tablets (SAD, Amgros I/S, Copenhagen) contained 300 mg thiamine hydrochloride. Similar placebo tablets were produced and delivered by Herlev Hospital Pharmacy, The Capital Region of Denmark. The daily dose depended on gender and body weight (BW) according to the following scheme: 1) Females: BW < 60 kg: 600 mg (2 tablets), BW 60-70 kg: 900 mg (3 tablets), BW 71-80 kg: 1200 mg (4 tablets), and BW > 80 kg: 1500 mg (5 tablets); 2) Males: BW < 60 kg: 900 mg (3 tablets), BW 60-70 kg: 1200 mg (4 tablets), BW 71-80 kg: 1500 mg (5 tablets), and BW > 80 kg: 1800 mg (6 tablets). The doses were inspired by the doses used in an Italian pilot study.[7] Once the individual dose was determined, the patients were asked to take the same number of tablets in both E1 and E2. Each tablet bottle was anonymised and contained the same number of tablets (n = 170), allowing treatment for 4 weeks regardless of the patient's gender and bodyweight. We counted the number of remaining tablets after a treatment period to monitor patients' compliance. Patients were advised not to take the study drug at evening or night due to the risk of temporary sleeplessness. Adherence to study medication was defined as > 80% of the study medication taken. Patients were reminded at each visit not to take any additional high-dose thiamine and were asked if they had taken any (no patients answered 'yes'). Study visits were scheduled at baseline, week 4, week 8, and week 12, with completion of PROs, blood samples, disease activity measurement, measurement of hand grip strength and safety assessments.

The IBD-F comprises three sections.[14] Section I consists of five questions exploring the frequency and severity of fatigue. Section II consists of 30 statements exploring the impact of fatigue. Both the questions and the statements are graded on a scale from 0 to 4. Section I asks about current fatigue and fatigue in the past two weeks, and yields a score between 0 and 20. Higher score indicates more fatigue. In section II, responders are asked to evaluate the impact of fatigue the past two weeks. Responses are marked on a five-point Likert scale ranging from 'None of the time' to 'All the time'. Section II yields a score between 0 and 120. A higher score indicates higher impact of fatigue. Section III of the IBD-F asks five open questions regarding fatigue and was not included in this study. The IBD-F has been translated and validated in a Danish context and was used in the study.[11] Scores were compared with normative fatigue values obtained for a random Danish background population using the Danish version of the IBD-F.[15]

The Danish version of the EQ-5D-5L was used to measure generic Health-related Quality of Life (HRQoL). The EQ-5D-5L has been validated in a variety of international settings in both general population and patient studies (see also www.euroqol.org). The EQ-5D-5L classification system comprises five dimensions (mobility, self-care, usual activities, pain/discomfort, and anxiety/depression), each of which has five levels. In addition to the five dimensions, the EQ-5D-5L instrument also yields a single overall health index score based on a visual analog scale (VAS) (0-100). Higher score indicates better health.[16]

The Danish version of the Short Health Scale (SHS) was used to measure IBD-specific HRQoL.[17,18] The SHS contains the following four items: i) bowel symptoms; ii) interference with daily life; iii) worry due to bowel disease; and iiii) general feeling of well-being. A patient's response is scored on a 10-cm VAS. A higher score indicates lower HRQoL. The HBAI and the SCCAI scores were used for disease activity measurement. Changes in muscle strength were measured by hand grip (Jamar Plus, Patterson Medical) as the highest of three attempts on right and left hand, respectively. Potential side effects were registered and reported to the Ethics Committee in Central Denmark Region and the Danish Medical Agency. A plan for dose reduction or termination of the trial drug was approved by the Danish Medical Agency.

2.5 | Outcomes

The primary endpoint was fatigue improvement after 4 weeks of thiamine treatment compared with placebo. An improvement ≥ 3 points on the IBD-F, Section I scale was defined as a clinically relevant improvement. This was based on fatigue data from a background population showing a mean fatigue score of 7 points, a standard deviation of 3.7 and an inclusion fatigue score > 12 points in this study.[15] Secondary endpoints were: to reveal possible determinants for reduced fatigue during thiamine treatment (eg gender, age, type of IBD); improvement in HRQoL during thiamine treatment; number of patients approaching normative levels of fatigue defined as the upper interquartile range for fatigue in the background population (≤ 10 points) measured on the IBD-F, Section I [15]; improvement in muscle strength; and possible side effects of thiamine treatment.

2.6 | Statistical analysis

For this 2 × 2 crossover study, we calculated a need for 17 patients in each group to detect a mean difference between thiamine and placebo. This was based on the following assumptions: (a) a decrease of ≥ 3 points on the IBD-F, section I scale, (b) a standard deviation of 3.7 points based on published data for fatigue in the background population,[15] (c) an alpha value of 0.05, and a power of 80%.[19] We anticipated that approximately 10%-15% patients could experience disease flares during participation or would drop out and therefore chose a total sample size of 40 patients (20 participants in each group).

The primary analyses were intention-to-treat (ITT) analysis on all patients included, irrespective of disease flare or other significant deviations during study participation. Secondary per protocol analysis excluded two patients with disease flare in the study period and one patient receiving intravenous iron supplement. Crossover analysis for fatigue scores and other HRQoL scores averaged the

between-treatment difference for each patient within each treatment period and then across both treatment periods, providing an estimate of treatment effect.[20,21] The estimated treatment difference, 95% confidence interval (CI) and P values were adjusted for period and sequence effects in the variance model analysis. To check for potential carryover effect, we analysed the within-subject sums of the results from both epochs and compared the two groups, using an unpaired t-test. Subsequently, we did a parallel group comparison considering group 2 as subject to delayed thiamine treatment (E2). In our primary analytical approach as per the crossover analysis, group 1 was considered to be in the thiamine treatment group at week 4 and in the control group at week 12, whereas group 2 was considered to be in the control group at week 4 and in the thiamine treatment group at week 12. Differences in fatigue between week 4 and week 12 were compared between groups, using an unpaired t-test.

Study data were collected and managed using REDCap electronic data capture tools hosted at Aarhus University.[22] REDCap (Research Electronic Data Capture) is a secure web-based application designed to support data capture for research studies, providing: (a) an intuitive interface for validated data entry; (b) audit trails for tracking data manipulation and export procedures; (c) automated export procedures for seamless data downloads to common statistical packages; and (d) procedures for importing data from external sources. Data analysis was conducted on Stata (version 16.1, StataCorp, College Station, Texas).

The protocol and consent forms were approved by the Ethics Committee in Central Denmark Region (j.no. 64207) and the Danish Medical Agency (EudraCT j.no. 2018-002324-17). The trial was conducted in accordance with the Declaration of Helsinki and the GCP principles and was monitored by the GCP unit at Aarhus and Aalborg University Hospitals. The trial was registered in ClinicalTrials.gov, study identifier NCT03634735, before initiation of patient enrolment.

3 | RESULTS

Forty of 84 patients with IBD and chronic fatigue were assessed for eligibility between 27 November 2018 and 25 October 2019, enrolled and randomly assigned to treatment. The patient flow is demonstrated in Figure 1, and baseline patient characteristics are shown in Table 1. No statistically significant baseline differences were observed between group 1 and group 2. All included patients completed the study. During the blinded high-dose treatment, two patients had a flare in IBD (one from each group), and one patient (from group 2) received intravenous iron infusion. We used data from all 40 patients in the primary ITT analysis, but the three patients mentioned above were excluded in the secondary per protocol analysis.

Both groups experienced reduced fatigue in the study period. The primary pre-specified efficacy endpoint for the trial was met at week 12 with a mean fatigue reduction (measured on the IBD-F, section I scale) of 4.7 points (95% CI 3.4-6.0; $P < 0.0001$) for the combined group 1 and group 2. The clinical effect observed for group 1

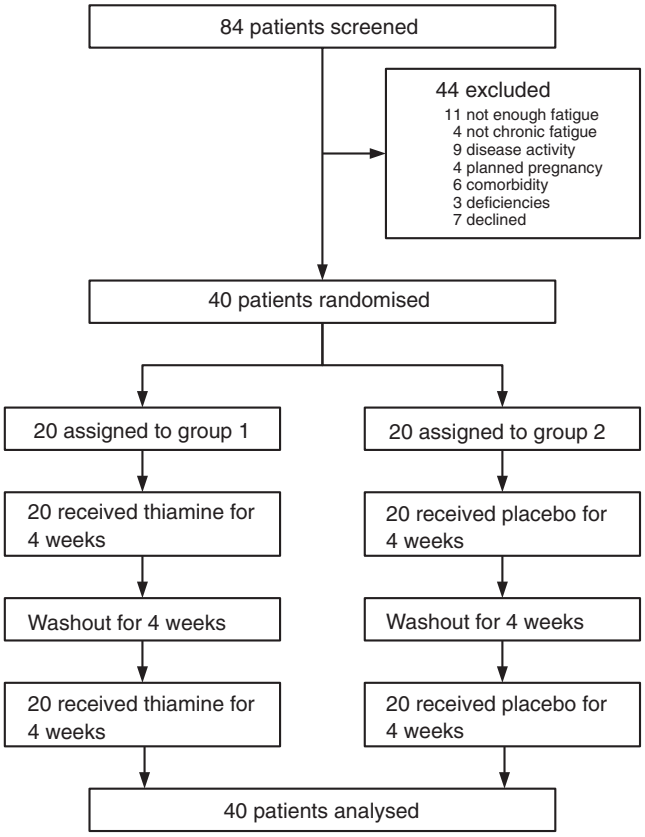

FIGURE 1 Trial profile. Group 1 received initial treatment with thiamine followed by washout and placebo. Group 2 received initial placebo followed by washout and treatment with thiamine. No participants dropped out of the study

declined in E2 (Figure 2). Furthermore, both groups experienced an increase in fatigue during the washout period. Given this and a confirmatory analysis showing a non-significant inter-group difference in the sum of fatigue at week 4 and week 12, we assumed no carryover effect. Therefore, we assessed the delayed treatment model, which showed a mean 4.5 point (95% CI 2.6-6.2 point) fatigue reduction after thiamine treatment compared with a mean 0.75 point (95% CI −1.3-2.8 point) fatigue increase after placebo ($P = 0.0003$). Furthermore, 55% (n = 11) of group 1 and 75% (n = 15) of group 2 experienced an improvement ≥ 3 points while on thiamine treatment compared with 25% (n = 5) and 35% (n = 7) while on placebo respectively (Figure 2; Table 2). This is equivalent to a number needed to treat (NNT) of 2.9. At week 12, 18 patients (45%) had reached a fatigue level comparable to that of the gender-specific background population.

Plasma thiamine levels were monitored before and during the study and were analysed after study completion by Bevital AS, Norway (http://bevital.no). Bevital AS use (2-50 nmol/L) as the normal range for thiamine.[23] At baseline, 12 patients had p-thiamine levels below 2 nmol/L. Changes in fatigue scores did not differ between patients who had thiamine levels below 2 nmol/L and those with thiamine within the reference range. Mean fatigue at baseline was 15.1 vs. 14.6 points ($P = 0.48$), mean changes in fatigue after thiamine

TABLE 1 Baseline characteristics

	Group 1: thiamine by placebo (n = 20)	Group 2: placebo followed by thiamine (n = 20)
Age (years)	38 (11)	36 (15)
Sex (male)	3 (15)	2 (10)
Body weight (kg)	73 (16)	73 (19)
Disease		
UC	8 (40)	12 (60)
SCCAI score	4.8 (2.8)	3.6 (2.8)
Classification		
E1	0	2
E2	0	2
E3	8	7
NA	0	1
CD	12 (60)	8 (40)
HBAI score	5.7 (4.1)	4.3 (4.4)
Classification		
L1	2	0
L2	3	1
L3	7	7
L4	0	0
Behaviour		
B1	7	7
B2	5	0
B3	0	1
Comorbidity		
Stoma or short bowel	0	3
Osteoporosis	4	7
RA disease	3	2
Slight depression	3	0
Medication		
5 ASA	5	9
AZA	9	8
Anti-TNF	10	11
Vedolizumab	3	3
Fatigue		
IBD-F I	14.7 (1.9)	14.9 (2.0)
IBD-F II	58.7 (18.7)	57.6 (22.8)
HRQoL		
EQ5D VAS	57.0 (20.0)	51.6 (19.0)
SHS total	14.3 (6.7)	18.1 (8.3)
Blood samples		
Haemoglobin (g/dl)	13.6 (1.3)	13.4 (0.8)
CRP (mg/l)	5.8 (3.9)	6.2 (5.9)
Albumin g/l	39.3 (3.1)	40.4 (3.5)
Thiamine (nmol/l)	4.4 (4.2)	4.5 (3.8)
Faecal calprotectin (mg/kg)	44.2 (52.9)	58.0 (53.3)

Note: Data are mean, (SD) or n, (%).

Abbreviations: CD, Crohn's disease; EQ5D, European Quality of life; HBAI, Harvey–Bradshaw Activity Index; RA, rheumatoid arthritis; IBD-F, Inflammatory Bowel Disease-Fatigue Questionnaire; SCCAI, Simple Clinical Colitis Activity Index; SHS, Short Health Scale; UC, ulcerative colitis.

treatment were 4.4 vs. 4.8 points ($P = 0.80$) and mean changes in fatigue after placebo were 2.2 vs. 1.0 points ($P = 0.33$).

For all patients (n = 40) the mean EQ5D VAS increased 10.2 points (95% CI 3.4-17.0, $P = 0.004$) from baseline to week 12. Using the crossover analysis and analysing responses to thiamine treatment, we found that HRQoL measured on the EQ5D VAS improved following thiamine treatment, with a mean increase of 13.6 point

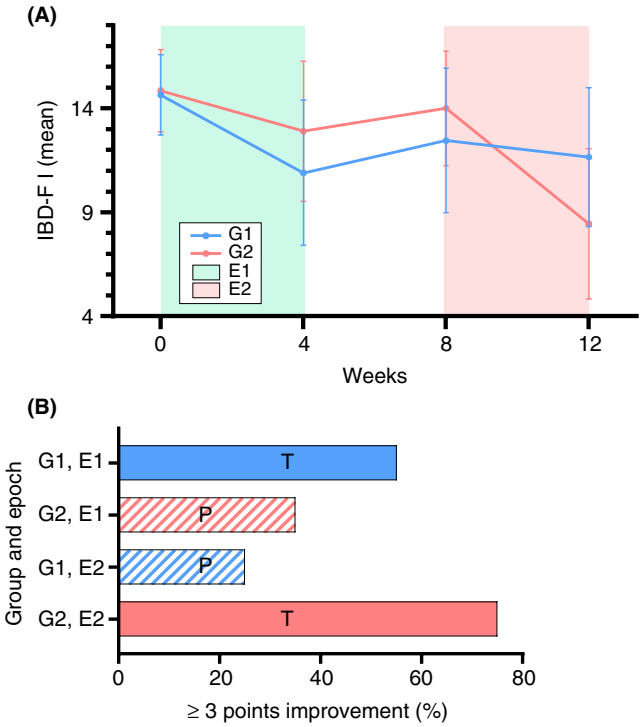

FIGURE 2 **A,**Association of thiamine treatment with fatigue in patients with IBD. Change from baseline by group and epoch (model–derived estimates of means are represented by dots with the SE from baseline represented by error bars at each relevant timepoint). Abbreviations: G1 (blue line) is group 1, thiamine–placebo; G2 (orange line) is group 2, placebo–thiamine. E1 (green shaded area) is epoch 1; E2 (pink shaded area) is epoch 2.**B,**Percentage of patients with an improvement ≥ 3 points in fatigue severity, measured on the IBD–F, section I. Abbreviations: G1,group 1 (thiamine–placebo); G2, group 2 (placebo–thiamine); E1, first epoch; E2, second epoch; T, treatment period; P, placebo period

TABLE 2 Crossover analysis of fatigue and health-related quality of life

	Group 1: thiamine followed by placebo (n = 20)			Group 2: placebo followed by thiamine (n = 20)			
	Week 4	Week 12	Difference	Week 4	Week 12	Difference	*P*-value
Fatigue							
IBD-F I, severity	10.9 (3.5)	11.7 (3.4)	0.8 (1.0)	12.9 (3.4)	8.5 (3.6)	-4.5 (0.9)	0.0003
IBD-F II, impact	38.4 (19.1)	41.7 (21.8)	3.3 (4.8)	48.6 (21.4)	25.9 (23.2)	-22.7 (4.8)	0.0005
HRQoL							
EQ5D VAS, range 0–100	59.3 (21.2)	58.1 (20.8)	−1.2 (4.2)	57.3 (19.1)	70.9 (18.0)	13.6 (4.3)	0.02
SHS, bowel symptoms	2.5 (2.6)	3.1 (2.5)	0.6 (0.4)	3.6 (2.8)	2.7 (1.7)	-0.9 (0.4)	0.012
SHS, interference with daily life	3.1 (2.7)	3.4 (2.7)	0.3 (2.7)	4.6 (2.7)	2.8 (1.8)	-1.8 (0.4)	0.0005
SHS, worry due to bowel disease	3.4 (2.5)	3.3 (1.8)	-0.1 (0.4)	4.9 (2.4)	3.2 (2.0)	-1.7 (0.5)	0.022
SHS, general feeling of well–being	3.7 (2.5)	4.0 (2.5)	0.3 (0.4)	4.9 (2.3)	3.0 (1.8)	-1.9 (0.3)	0.0001
SHS, total	12.7 (8.2)	13.7 (8.1)	1.0 (1.1)	18.0 (8.6)	11.6 (5.7)	-6.4 (1.3)	0.0001

Note: Data are mean, (SD).

Abbreviations: EQ5D VAS, European Quality of life, VAS; IBD–F, Inflammatory Bowel Disease–Fatigue Questionnaire; SHS, Short Health Scale.

(95% CI 4.4-22.8) compared with a decrease of 1.2 points (95% CI: 7.7-10.0) following placebo ($P = 0.02$) (Table 2).

When evaluating the IBD-specific HRQoL, measured as the mean total score on the SHS, we observed that the patients (n = 40) experienced an overall statistically significant improvement of 3.6 points (95% CI 1.4-5.7; $P = 0.0015$) between baseline and week 12. Comparing thiamine and placebo treatment in the crossover analysis, we observed a 6.4 point (95% CI 3.5-9.1) increase following thiamine vs. a 1.0 point decrease (95% CI −1.2-3.3) following placebo ($P = 0.0001$). Between baseline and week 12, we observed that the patients (n = 40) had significant improvements for all SHS subscales, except for the subscale measuring bowel symptoms. When comparing thiamine to placebo in crossover analysis, we found that the scores on all four subscales showed significant improvements with thiamine treatment (Table 2).

Performing stratified analysis of the effects of thiamine treatment, we found no statistically significant differences related to patient sex, patient age, concomitant anti-TNF-treatment, or moderate anxiety/depression measured on the EQ-5D-5L (Table 3).

The per protocol analysis, including 37 patients, showed an overall reduction of fatigue at week 12 (measured as mean on the IBD-F, section I scale) of 4.7 points (95% CI 3.3-6.1; $P < 0.0001$). The delayed treatment model showed a mean fatigue reduction of 4.8 point after thiamine treatment (95% CI 2.9-6.7) compared with a 1.1 point increase in fatigue after placebo (95% CI −3.1-1.2; $P < 0.0001$). Furthermore, 58% (n = 11) of group 1 and 78% (n = 14) of group 2 showed an improvement of ≥ 3 points while on thiamine treatment compared with 21% (n = 4) and 33% (n = 6) while on placebo, respectively. This is equivalent to an NNT of 2.4.

We found no significant changes in handgrip strength between patients who had thiamine or placebo. In the study population as a whole, mean hand grip strength did not change from baseline to week 12. All patients were > 80% adherent to treatment regardless if they received thiamine or placebo tablets. Adverse events related to thiamine treatment were headache (n = 2), nausea (n = 1), pyrosis

TABLE 3 Subgroup analysis of fatigue severity measured on the IBD–F, section I

	N	Change in fatigue during thiamine	Change in fatigue during placebo	*P*–value*	*P*–value**
Sex					
Female	35	4.7 (3.7)	1.3 (3.2)	0.0001	0.063
Male	5	4.2 (4.8)	1.6 (3.9)	0.5147	
IBD					
CD	20	4.0 (4.2)	1.3 (3.4)	0.0094	0.239
UC	20	5.4 (3.3)	1.5 (3.3)	0.0056	
Age group					
<40 years	21	4.5 (3.7)	1.3 (3.4)	0.0140	0.404
≥40 years	19	4.8 (4.0)	1.4 (3.3)	0.0033	
Anti–TNF treatment					
Yes	21	4.5 (4.3)	1.7 (3.7)	0.0194	0.754
No	19	4.8 (3.2)	1.0 (2.8)	0.0025	
Moderate anxiety/depression					
Yes	13	5.1 (3.9)	2.1 (3.7)	0.0814	0.351
No	27	4.4 (3.8)	1.0 (3.1)	0.0006	

Note: Data are mean, (SD).

Abbreviations: CD, Crohn's disease; IBD, Inflammatory Bowel Disease; IBD–F I, Inflammatory Bowel Disease–Fatigue Questionnaire, section I; UC, ulcerative colitis.

*Between thiamin and placebo.

**Between categories.

(n = 1), oral blisters (n = 1) and sleeplessness (n = 1). The patient who reported sleeplessness had taken the drug (thiamine) once just before going to sleep. An overview over adverse events are available in Supporting Information (Table S1).

4 | DISCUSSION

To our knowledge, this RCT is the first to provide evidence of an effect of high-dose oral thiamine on chronic fatigue in patients with IBD. We demonstrated a mean reduction in fatigue of 4.7 points after 4 weeks of treatment with high-dose oral thiamine regardless of treatment sequence. We showed significant differences in fatigue reduction between thiamine and placebo. The findings were similar in the ITT and per protocol analyses. We found no differences in fatigue when stratifying for sex, age group, anti-TNF treatment and moderate anxiety/depression. Patients with UC had improved more in terms of fatigue at week 12 than patients with CD. Likewise, both their generic HRQoL (EQ-5D VAS) and IBD-specific HRQoL (SHS) also improved. Bowel symptoms reported by the patients remained unchanged. Oral treatment with thiamine was well tolerated and associated with only mild possible side effects.

In this RCT with a robust and strong design, we demonstrated that oral thiamine abrogates chronic fatigue. Still, the study has important limitations. We included mostly females, albeit we consecutively screened all patients with IBD regardless of sex. This is not surprising as prevalence studies have revealed that females with IBD tend to report more fatigue than men.[3,24] The uneven representation of the sexes in the study sample may therefore reflect the fatigue burden in the investigated population. The crossover design could be biased by a carryover effect. We analysed this and found the magnitude of such a bias to be negligible. The dosage of thiamine and the duration of treatment were based on the results from the Italian pilot study.[7] As thiamine is a water-soluble vitamin with renal clearance, we decided to treat the patients longer than in the Italian study (20 days vs. 4 weeks) in order to optimise the chance of an effect on fatigue. The dosage was chosen pragmatically and should be divisible with 300 mg in order to be able to manufacture both thiamine and placebo tablets. We observed some degree of placebo effect. Absolute blinding is difficult to achieve because thiamine has a particular taste and smell somewhat different from placebo tablets. The tablets looked the same and were administered from uniform bottles. At week 12, we asked the patients to guess when they had received thiamine or placebo. Thirty-five patients guessed right. However, this question was asked after they had tested (and felt the effect of) both thiamine and placebo. When receiving the first blinded study drug, the patients did not know what to expect. Therefore, we believe that we have kept some kind of blinding, at least in E1. Moreover, the investigators and analyses remained blinded. A way to minimise this further could be coating of the blinded study drugs.

Our results confirm the findings in a small Italian pilot study published in 2013.[7] In addition to a significant effect of thiamine on fatigue, the authors of that study also reported that the patients' intestinal function improved after high-dose thiamine treatment. Our patients reported unchanged bowel symptoms. All 12 patients included in the Italian study had normal levels of p-thiamine at baseline. In our study 12 patients had thiamine levels below the normal range. However, we found no differences in fatigue improvement between patients with normal levels and those with low levels of p-thiamine. The findings suggest that fatigue is unlikely to be related to thiamine deficiency in patients with IBD. Thiamine status is also suggested to be measured using red cell transketolase as a predictor for the thamine status.[25] We did not measure transketolase in our study. However, it may be useful in future studies exploring the mechanisms behind the effect of thiamine on fatigue in IBD. To our knowledge, no other studies on high-dose thiamine and chronic fatigue in IBD have been published. Our findings therefore add an effective treatment option to the range of other possible interventions against chronic fatigue.[5,6]

Fatigue is multifactorial, and thiamine treatment could be combined with other interventions or initiatives.[5,6,26] The participants in this study had IBD in remission. How to treat fatigue in patients with active IBD remains unanswered and further research is needed for this topic. Because disease activity predicts fatigue, treating the underlying IBD flare is the mainstay before treating the fatigue. It is also unclear how well oral thiamine is absorbed in patients with active IBD. In patients with chronic inflammation or delayed clinical improvement, adjunctive high-dose oral thiamine could play a role as thiamine has a good safety profile and is inexpensive. Furthermore, the long-term effects of high-dose thiamine need to be investigated more. So does the possible effect of a lower maintenance dose of oral thiamine to prevent fatigue. While the effect of high-dose oral thiamine was highly significant in our study, its exact mechanisms still need to be explored and investigated. The theory of a dysfunction in thiamine transport from blood to mitochondria remains a plausible explanation. The participants in our study were exposed to high doses of thiamine which induces passive diffusion that will add thiamine to the cells and the mitochondria. Consequently, the carbohydrate metabolism can normalise, and a reduction of fatigue is likely to follow. This theory is supported by literature describing how low intracellular thiamine levels can lead to acute energy failure, a propensity to oxidative stress and mitochondrial abnormalities.[27] Furthermore, an animal study revealed high absorbability, high transformability and significant effect of oral thiamine on fatigue in rats.[28]

As fatigue is a common problem in many other conditions, further investigation of the effect of high-dose thiamine is warranted, especially in other autoimmune diseases.

In conclusion, this clinical study showed a significant effect of high-dose thiamine on severe chronic fatigue in patients with quiescent IBD. Furthermore, the treatment was safe and well tolerated by the patients. The exact mechanisms of the treatment remain to be fully clarified. Further investigations are needed, also in other groups of patients suffering from chronic fatigue.

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AUTHORSHIP

Guarantor of this article: Palle Bager.

Author contributions: PB, CH and JFD designed the study. PB wrote the manuscript. PB and CR collected the data. PB and JFD analysed the data and made the figures and tables. All authors reviewed the final manuscript and provided comments.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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SUPPORTING INFORMATION

Additional supporting information will be found online in the Supporting Information section.

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