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Reserach Article

Eight-Weeks Individualized Exercise Program Targeted for Patients with Crohn's Disease: A Feasibility Study

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Abstract

Background: Prior work suggested a positive association between self-reported disease activity and increased fat mass in patients with Crohn's Disease on biologic therapies.

Aims: To test the feasibility of a physical activity intervention protocol aimed at reducing the severity of symptoms in patients with Crohn's Disease, including self-reported disease activity, fatigue and quality of life.

Methods: The study sample included 19 of 24 recruited, biologic-experienced, patients with Crohn's Disease with mild-to-moderate self-reported disease activity. Study participants completed patient reported outcome measures (HBI, IBD-F, EQ-5D-5L, CPSS) and body composition at baseline and after eight weeks of intervention. Intervention: In dialogue with the participant, a training consultant developed an individualized exercise program including exercise with moderate to high intensity, for the participant to follow during the course of eight weeks, including weekly phone call supervision by training consultants.

Results: Patient reported measure outcomes showed a tendency for decreased self-reported disease activity, significant decrease in stress and fatigue score along with a significant increase in general wellbeing. A decrease in fat mass ($p = 0.024$) and increase in muscle mass ($p = 0.036$) was shown.

Conclusion: Moderate to high intensive exercise was feasible and beneficial as a supplement to regular biologic therapy, in patients with Crohn's Disease. This feasibility study was limited by a small sample size, and no control group, thus the set-up and results from this study may be used in the planning of future RCT studies.

Keywords: Crohn's disease; Exercise; Inflammatory bowel disease; Disease activity; Fatigue; Body composition; Quality of life; Feasibility

Introduction

Crohn's Disease (CD) is a chronic inflammatory bowel disease, which usually manifest and is diagnosed during youth [1]. In a Danish context, approximately 7000-9000 patients are diagnosed with CD and the incidence and prevalence have increased over the last few decades [1-3]. Since the disease is chronic, patients have to live with the disease, including intense individual and socio-economic costs, throughout their lives. CD causes several symptoms such as abdominal pain, bloody stool, chronic diarrhea, weight loss and fatigue [4]. The symptoms of CD fluctuate from periods with remission having almost no symptoms, to periods with high disease activity and most symptoms present. The treatment costs vary according to the patients' disease activity where more severe symptoms and complications cost more than average [5]. Patients suffering from CD also have increased risk of developing several extra intestinal symptoms and other Comorbidity diseases such as: Arthritis, Psoriasis and the skin disease Hidradenitis Suppurativa [6]. CD affects the patients' daily lives and general wellbeing in varying degrees, as the disease, with its numerous symptoms, inhibits the functionality of daily life [7]. The symptoms of CD most often occur in the form of abdominal pain, bloody stool, diarrhea, weight loss and fatigue [4]. If the disease activity is high, the disease can affect that normal, everyday activities, such as work and social activities, are difficult, or sometimes even totally impossible, to perform [7,8]. The fact that the patients experience pain and discomfort, as a result of the disease, can adversely affect their quality of life. In addition, quality of life may be affected by periods of lacking ability to participate in social activities because of symptoms from CD [8]. Disease related fatigue is a common burden in CD – both in active disease and in remission. Prior studies show that sleep is significantly affected by the disease, and prevalence of fatigue is nearly 40% in patients with CD [9,10]. Disease related fatigue involves ongoing exhaustion that is disproportionate to exertion and not alleviated by rest [11]. CD furthermore frequently causes increased stress- and anxiety levels [7]. Smith et al. [12] suggested that although some patients with CD cope adequately, other patients do not accept the diagnosis and seem unable to adjust their lives. The symptoms affecting quality of life in many patients, hampers and decreases their ability to live their daily lives as they want due to pain, fatigue, stress, anxiety and toilet dependency [7]. The aim of any medical therapy in CD is achieving remission and thereafter maintaining remission. Optimizing the effect of biological therapy may lead to increased quality of life. However far from all patients achieve sufficient effect of biological therapy [13]. A study by Hilligsøe et al. [14] showed a positive association

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between increased fat mass and increased self-reported disease activity measured by the commonly used "Harvey Bradshaw Index" (HBI). Furthermore, a recent review of physical activity interventions as a complementary therapy for patients with inflammatory bowel disease, showed that the application of exercise interventions in IBD patients was overall safe and beneficial for overall-health, and towards the IBD symptom burden [15]. Based on the results of Hilligsøe and the review of physical activity interventions, a physical activity protocol was developed, to test if the association worked in reverse (if it is possible to reduce HBI through a reduction of fat mass). The aim of this study was to test the feasibility of a physical activity intervention protocol aimed at reducing the severity of symptoms in patients with CD. We aimed to test whether patients with increased fat mass were able to lose fat mass by a physical activity intervention only, and if these would reduce self-reported disease activity: Furthermore, in all patients, to test if a physical activity intervention protocol may reduce fatigue, stress and improve quality of life, measured by Patient Reported Outcome Measures (PROMS).

Materials and Methods

Study design and setting

The study was designed as a feasibility study. Recruitment was done by advertising on posters about the study in the reception facilities at the outpatient clinic at Department of Gastroenterology, Aalborg University Hospital, Denmark, and in CD community groups on Facebook. All participants provided written informed consent before enrolment. Recruitment took place between February 2019 and March 2019, with all follow-up data collection completed by May 2019. The study's samplings and measurements were conducted at Aalborg University Hospital, while the physical activity protocol could be performed wherever the patients preferred to exercise.

Participants

Inclusion criteria: Male and female patients above 18 years with a clinical diagnosis of CD undergoing biological therapy and be able to come to Aalborg for measuring at the beginning and end of intervention.

Safety criteria: BMI. Patients had to have a Body Mass Index above 19, not to risk patients becoming underweight during the intervention.

Disease activity: Furthermore, the patients had to have a mild to moderate self-reported disease activity as indicated by Harvey Bradshaw Index above 0 and below 16. On the first connection, where patients were informed about the study, patients were asked about their actual disease activity. If the study team found doubt that patients were well enough to participate, they were asked if we could discuss it with their primary Gastroenterologist.

Intervention

A specific physical activity protocol was developed, aiming to reduce fat mass, while being maintainable for patients with CD. The physical activity protocol was based on an initial individual start-up conversation, where the patient, in dialogue with a training consultant (with a background as either physiotherapist or bachelor in sports), tailored an individualized physical activity program. During this conversation, the patient's restrictions, barriers, motivational factors and wishes for physical activity were uncovered and implemented in their customized physical activity plan. Though the intervention is individualized, there were certain fixed criteria. Based on a literature study, existing evidence suggested that a minimum of eight weeks exercise, with three weekly exercise session of 30 minutes duration and a heart rate exceeding 80% of heart rate max is required for a fat loss to occur. Furthermore, the intervention included weekly telephone follow-up from the training consultant. This aimed at adjusting the physical exercise program with the patient, based on the patient's feedback on activities during the past week. After eight weeks, a final measurement was made including made the different measurements from the baseline test.

Behavior, fitness and health outcomes

The following outcome measures were assessed in all participants at baseline and eight weeks later at follow-up: Body composition was measured using Tanita Body Composition Analyzer BC-418MA and included body weight, fat range, fat mass, fat free mass, muscle mass and body water. Furthermore, we measured self-reported disease activity (HBI), perceived stress (measured by Cohen Perceived Stress Scale (CPSS)), health-related quality of life by EuroQol (EQ-5D-5L), and disease related fatigue by IBD-Fatigue Scale.

Statistical analysis

The statistical analyzes are performed in the Statistical Software, SAS version 9.4. As the baseline and follow-up groups were related, paired t-test was used when the assumption of normality was met, while a Wilcoxon Signed Rank test was used if data were not normally distributed. To investigate whether data were normally distributed, the Shapiro-Wilk test was used by testing whether the difference between the baseline and follow-up measurements on the different outcome variables were normally distributed. If the delta values were normally distributed, a paired t-test was used, and if the delta values were not normally distributed, a Wilcoxon Signed Rank Test was used. The level of level of significance was set to $\alpha = 0.05$.

Results

We recruited 27 patients with CD. The safety criteria regarding disease activity excluded two patients due to one being at risk of upcoming surgery and one being on high dose prednisolone. Furthermore, one patient never showed up for inclusion. Five participants were lost to follow-up - two due to insufficient mental surplus, two due to health related reasons not involving CD (knee surgery and pregnancy outside the uterus), and one for other personal reasons. Figure 1 shows inclusion and dropout flow. The final study sample included 19 (n=19), biological therapy-experienced, patients with CD who had a mild-to-moderate self-reported disease activity. Table 1 shows demographic information for the patients who completed the study. An overview of the intervention i illustrated in Figure 2. Baseline demographics and clinical characteristics of the 19 participants who completed the 8 weeks intervention and the 5 participant who dropped out are shown in Table 2. The participant who dropped out of the intervention were all female, younger, had a higher BMI and fat mass than the participants who completed the intervention. The participants who complete the study achieved an average weight loss of 0.67 kg and a fat mass loss of 1.06 kg during the intervention period. In addition, participants achieved a decrease in HBI score of 1.42, thus illustrating that on average participants experienced small improvement in the experienced disease activity, even though this was not significant. A small mean weight - and fat decrease was seen, as well as increased muscle mass from baseline to follow-up. A summary of data for the anthropometric measurements are seen in Table 3. For the PROMS, health related measures, participants achieved an average significant improvement in fatigue,

stress and quality of life on the utility scores, while HBI and quality of life measured by VAS were slightly improved, but not statistically significant. Table 4 shows the PROMS results. The values in Table 4 indicate the average changes and do not describe how many of the sample has achieved an improvement in the above parameters, or the fluctuation between levels of measures for stress and fatigue. Fluctuation between levels of measures for stress and fatigue is seen in Table 5.

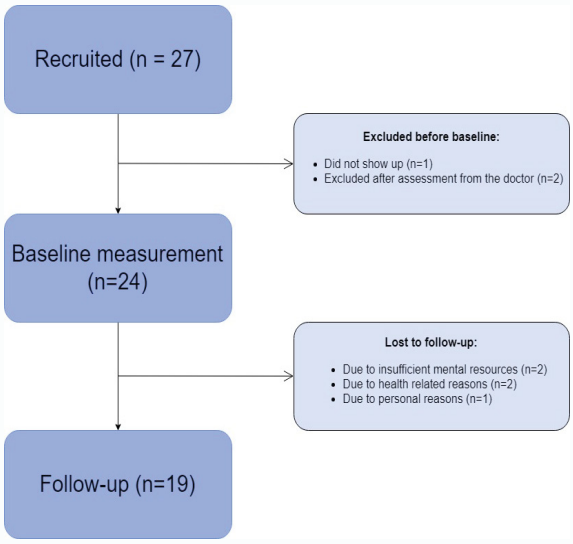

Figure 1: Participants drop-out.

Table 1: Baseline demographics and clinical characteristics of the 19 participants who completed the study.

Age, years (SD)	39 (12.8)
Sex, Female N/%	16/ 84%
Weight, kg (SD)	80.9 (4.0)
BMI kg/m2 (SD)	27.9 (6.1)
Fat mass, kg (SD)	28.4 (13.8)
Level of education	Short education: 12 Medium long / Bachelor degree: 6 Long / Master degree or above: 1

Table 2: Baseline demographics and clinical characteristics of the 19 participants who completed the 8 weeks intervention and the 5 participant who dropped out.

	Drop-out	Completed
Participants, n = 24	5	19
Age, years (SD)	28 (4.1)	39 (12.8)
Weight, kg (SD)	94.2 (5.4)	80.9 (4.0)
BMI kg/m² (SD)	33.4 (2.1)	27.9 (6.1)
Fat mass, kg (SD)	40.4 (4.5)	28.4 (13.8)
HBI-group	Remission: 2 Mild: 1 Moderate: 2 High: 0	Remission: 9 Mild: 8 Moderate: 2 High: 0

Discussion

Feasibility

The level of feasibility would normally be assessed by descriptive analysis of recruitment, attrition and compliance with the intervention. Since however, patients were sampled by being encouraged to sign up for participation by posters and on Facebook and we had no insight in the whole cohort of CD-patients treatment plans, we were not able to assess recruitment feasibility. Patients were very compliant to exercise, however these were measured only by patients' statements, and may therefore be biased by recall bias, and social desirability bias, as a well-

Table 3: Anthropometric measurements at baseline and follow-up of the 19 participants who completed the 8 weeks intervention.

	Pre (±SD)	Post (±SD)	Difference	P-value
Weight (kg)[a]	80.852 (17.324)	80.184 (15.925)	0.668	0.147
Fat range (%)[a]	33.994 (10.873)	33.142(11.581)	0.852	0.056
Fat mass (kg)[a]	28.426 (13.775)	27.368 (13.421)	1.058	0.024*
Fat free mass (kg)[b]	52.436 (10.380)	52.836 (10.757)	0.400	0.040*
Bodywater (kg)[b]	38.389 (7.595)	38.684 (7.861)	0.295	0.042*
Musclemass (kg)[b]	49.847 (9.993)	50.157 (10.213)	0.310	0.036*

[a]Lower score is better
[b]Higher score is better
*indicates significance

Table 4: Questionnaire data at baseline and follow-up of the 19 participants who completed the 8 weeks intervention.

	Pre (±SD)	Post (±SD)	Difference	P-value
HBI-score[a]	4.8 (2.2)	3.4 (3.5)	1.4	0.200
CPSS-score[a]	14.5 (7.2)	10.8 (5.9)	3.7	0.046*
IBD-Fatigue-score[a]	10.7 (3.3)	6.4 (3.4)	4.3	0.000*
EQ-5D-5L (utility)[b]	0.8 (0.1)	0.9 (0.1)	0.1	0.006*
VAS[b]	71.1 (21.5)	78.5 (20.0)	7.421	0.121

[a]Lower score is better
[b]Higher score is better
*indicatessignificance

Table 5: The fluctuation between levels of stress and fatigue measures in the 19 participants.

Level of measure N/(%)	Baseline, N (%)	Follow-up, N (%)
Level of stress		
Low	8 (42.1)	13 (68.4)
Moderate	9 (47.4)	6 (31.6)
High	2 (10.5)	0 (0)
Level of Fatigue		
No	0	0
Low to moderate	7 (36.8%)	17 (89.5%)
High	12 (63.2%)	2 (10.5%)

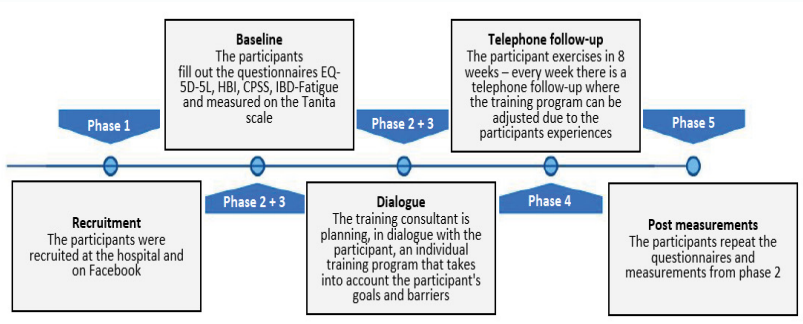

Figure 2: Phases of the physical activity intervention.

known type of response bias where the respondent may wish to please the researcher [16]. These biases are however applicable for all studies using PROMS, including the ones to which we compare our results. Five of 24 patients dropped out of the intervention before follow-up. Of these, two were for health reasons, which could not have been predicted. The remaining three dropped out for reasons that may have been foreseen, if we had made a closer inclusion interview including the participant's personal resources. The withdrawal percentage of participant in this study is 21% of the total study population. Previous studies investigating the effect of physical activity on symptoms of CD have reported a withdrawal percentage of participant on 13-30 % of the total study population [17,18], which indicates that the number of drop-outs in this study is acceptable compared to other studies. The relatively low percentage of withdrawal in this study may be due to the weekly telephone follow-up to ensure compliance and to assess the patient's progress and due to the short length of the intervention.

Study design

The health-related outcomes showed a non-significant decrease in HBI, mean difference = -1.421 ($p = 0.20$) after 8 weeks physical activity intervention. Furthermore, the result showed a significant decrease in stress score (CPSS), mean difference = -3.736 ($p = 0,046$) and fatigue score (IBD-F) mean difference = -4.316 ($p<0.000$) along with a significant increase in general wellbeing (EQ-5D-5L) with mean difference 0.080 ($p = 0.006$). EQ-5D-5L has increased by an average of 0.080. If this increase in EQ-5D-5L is converted to quality-adjusted life year (QALY), a mean increase in quality of life on 0.013 QALY is gained during the cause of eight weeks. The study is designed as a feasibility study with no control group, why it is not possible to tell if causality between fat mass and HBI occur.

With the current design of the study it is not possible to decide if the effect is due to the physical activity or other factors. Although the present study design is unable to address causality, it can indicate pair wise correlation in different variables. A randomized-controlled study design would be a more advantageous design since it would allow comparison between two or more groups with different exposure(s) and reduce the risk of confounding. The study population consists of 24 people, of whom 19 participants completed eight weeks of physical activity intervention. In a usual RCT context, a sample of 19 participants is a rather small sample - It may be advantageous to perform a power calculation, to statistically test how many participants should be recruited before the sample is representative and the design able to prove effects when effects are present.

Proms

When applying Patient Related Outcome Measures (PROMS), there may be some variations of information bias. For example, recall bias may occur, as the participants may find it difficult to remember and thus often correspond to the current situation and not to previous experiences [16]. For example, this may occur with the IDB-Fatigue questionnaire, as here there is asked about the fatigue in the last 14 days. Another type of bias that can occur in PROMS is social desirability bias; a type of bias where participants respond according to what they think is expected of them [14]. In the physical activity intervention, for example, it could be to over- or under-report outcome parameters, in relation to what they think the research managers would like to hear. In order to reduce the risk of bias and understanding difficulties in the questionnaires, only questionnaires validated in a Danish context have been used.

The intervention

Furthermore, the physical activity intervention is designed to cater for all participants' living condition and manual skill – therefore exercise form, frequency, intensity and duration varies. This can cause divergent results, which can affect the study's internal and external validity as well as the reliability, since energy consumption varies in different exercise forms [15]. Furthermore, the metabolism for each person can vary, which results in that some patients burn more calories than other patients at the same activity, intensity and duration.

Conclusion

In conclusion, moderate to high intensity physical activity are feasible and acceptable exercise strategies in patients with quiescent or mildly active CD. physical activity seems feasible to recommend patients with CD as a supplement to their regular treatment, as physical activity does have certain benefits and effects regarding CD. This study was limited by a small sample size, no control group and no follow-up, thus the results from this study could be used in the planning of future RCT studies. Larger-scale trials are needed to provide precise estimates of the benefits and harms of different physical activity programs, and our findings suggest that a multi-centre trial of supervised physical activity training is feasible. Physical activity remains a potentially useful adjunct therapy and lifestyle behavior in patients with CD.

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