ORIGINAL ARTICLE
COPD

A double-blind randomised controlled trial of protein supplementation to enhance exercise capacity in COPD during pulmonary rehabilitation: a pilot study

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ABSTRACT

Background: Pulmonary rehabilitation is a cost-effective management strategy in chronic obstructive pulmonary disease (COPD) which improves exercise performance and health-related quality of life. Nutritional supplementation may counter malnutrition and enhance pulmonary rehabilitation outcomes but rigorous evidence is absent. We aimed to investigate the effect of high-protein supplementation (Fortisip Compact Protein (FCP)) during pulmonary rehabilitation on exercise capacity.

Methods: This was a double-blind randomised controlled trial comparing FCP (intervention) with PreOp (a carbohydrate control supplement) in COPD patients participating in a pulmonary rehabilitation programme. Participants consumed the supplement twice a day during pulmonary rehabilitation and attended twice-weekly pulmonary rehabilitation sessions, with pre- and post-pulmonary rehabilitation measurements, including the incremental shuttle walk test (ISWT) distance at 6 weeks as the primary outcome. Participants' experience using supplements was assessed.

Results: 68 patients were recruited (intervention n=36 and control n=32). The trial was stopped early due to the COVID-19 pandemic. Although statistical significance was not reached, there was the suggestion of a clinically meaningful difference in the ISWT distance at 6 weeks favouring the intervention group (intervention 342±149 m (n=22) *versus* control 305±148 m (n=22); p=0.1). Individuals who achieved an improvement in the ISWT had a larger mid-thigh circumference at baseline (responders 62±4 cm *versus* nonresponders 55±6 cm; p=0.006). 79% of the patients were satisfied with the taste and 43% would continue taking the FCP.

Conclusions: Although the data did not demonstrate a statistically significant difference in the ISWT, high-protein supplementation in COPD during pulmonary rehabilitation may result in a clinically meaningful improvement in exercise capacity and was acceptable to patients. Large, adequately powered studies are justified.

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High-protein supplementation combined with pulmonary rehabilitation in COPD did not statistically improve exercise capacity but may be associated with a clinically meaningful improvement. Larger trials are needed to confirm this. https://bit.ly/3tMtX9O

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This study is registered at ClinicalTrials.gov with identifier number NCT04027413. Data sharing: Participants' data, the trial protocol and the statistical plan are available upon reasonable request from the corresponding author.

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Introduction

Patients with chronic obstructive pulmonary disease (COPD) often have daily symptoms and reduced exercise capacity, both of which result in an impaired health-related quality of life (HRQoL) [1, 2]. COPD patients may lose skeletal muscle mass, which leads to muscle weakness, dysfunction and disuse, thus negatively affecting activity, mobility and overall strength [3, 4]. Muscle disuse can result from a sedentary lifestyle such that voluntary immobilisation leads to further muscle deconditioning and reduced muscle strength/endurance [4]. Pulmonary rehabilitation is a multiprofessional education and exercise programme that is a fundamental management strategy in COPD, resulting in improved exercise performance and HRQoL, promoting self-dependency in relation to activities of daily living while reducing dyspnoea and the risk of exacerbation [5, 6]. Maximising the value and response to pulmonary rehabilitation is of great interest to clinicians and patients alike.

Malnutrition is common in COPD, and may adversely affect the ability to undertake and maximally benefit from pulmonary rehabilitation. Several studies, summarised in a recent systematic review by Aldhahir *et al.* [7], have investigated the benefit of using nutritional supplementation during pulmonary rehabilitation, but yielded conflicting results with diversity in supplements, study design and outcome measures. There is a clear need for further research. In particular, COPD patients may require a higher intake of protein, as recommended by the British Association for Parenteral and Enteral Nutrition, due to a higher protein requirement to preserve lean mass [8].

An integrated approach of exercise training and nutritional support may offer the greatest potential benefit. We hypothesised that a low-volume, high-protein oral nutritional supplement taken by COPD patients over the course of pulmonary rehabilitation would enhance benefits in terms of exercise capacity.

Material and methods

Trial design

This double-blind, parallel group randomised control superiority trial was registered at ClinicalTrials.gov with identifier number NCT04027413. The study was approved by a local ethics committee and the UK Health Research Authority (approval 18/LO/1842).

Participants

Participants with confirmed COPD (post-bronchodilator forced expiratory volume in 1 s (FEV_1)/forced vital capacity (FVC) ratio <0.7) and an appropriate exposure history, enrolling on a pulmonary rehabilitation programme, were recruited from the Central and North West London NHS Foundation Trust (London, UK) between 7 January 2019 and 31 January 2020, with the last visit for the last participant completed on 20 March 2020. At this point the study had to be suspended; a national "lockdown" for the COVID-19 pandemic meant that the pulmonary rehabilitation service was stopped.

Before starting pulmonary rehabilitation, all participants were required to attend an assessment visit conducted by physiotherapists. The physiotherapist approached participants regarding the study. Patients who agreed to participate were consented and enrolled into the study by the researcher (A.M.A.). A full medical history with demographic information was collected.

Patients with any physical or mental health disorders preventing compliance with the trial protocol, or those unable to communicate in English, with malabsorption syndrome, who were unable to perform the incremental shuttle walk test (ISWT), who were already using other oral dietary supplements under the care of a dietician, had galactosaemia, had cow's milk protein allergy or lactose intolerance, or who had a body mass index (BMI) >30 $kg \cdot m^{-2}$ without recent weight loss of >5% were excluded from the study.

Randomising and blinding

Participants were randomised (1:1) using a web-based service (Sealed Envelope; www.sealedenvelope.com) with equal allocation concealment, block size 4, stratified based on BMI $\geqslant$20 or <20 $kg \cdot m^{-2}$, given that oral nutritional supplementation is recommended in COPD patients with a BMI <20 $kg \cdot m^{-2}$ or those who

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are at medium to high risk of malnutrition. Patients were randomly assigned to the intervention or control group. The randomisation process was conducted by a member of the research team not involved in the study, before baseline assessment and following the screening visit. Both the outcome assessor and the participants were blinded to treatment allocation.

Intervention and control products

Intervention and control products were unlabelled and delivered directly to the participants' residential addresses with both researcher and participants being blinded.

The intervention was a 125 mL bottle of Fortisip Compact Protein (FCP; Nutricia, Zoetermeer, The Netherlands) that has 300 kcal, 24% protein, 41% carbohydrate and 35% fat. The control was a 200 mL bottle of PreOp (Nutricia) that has 100 kcal and 100% carbohydrate. Participants were instructed to consume two bottles each day: one bottle in the morning after breakfast prior to attending the pulmonary rehabilitation session and one bottle during the day after a meal.

Both the intervention and control products were used throughout the 6-week duration of the pulmonary rehabilitation programme.

Study conduct

All baseline measurements were conducted prior to starting pulmonary rehabilitation, these included ISWT distance, body composition, anthropometric measurements, handgrip strength and five-repetition sit-to-stand test (STS5) time. Additionally, participants were given a pedometer and instructions on its use and how to complete the supplement and step count diaries. Participants were required to complete the following questionnaires: COPD Assessment Test [9], Hospital Anxiety and Depression Scale [10], modified Medical Research Council dyspnoea scale [11], St George's Respiratory Questionnaire (SGRQ) [12] and Malnutrition Universal Screening Tool [8]. At the end of the study, the acceptability of the intervention was assessed by a survey (appendix S1 in the supplementary material). A full description of the methodology is presented in appendix S2 in the supplementary material.

Sample size

The power calculation was conducted using parameters from a previous study [13]. The clinical significance of further increases in ISWT performance resulting from treatment adjunctive to pulmonary rehabilitation is unknown but we judged *a priori* that an additional increase of 35 m in the ISWT distance would be of functional benefit. The sample size was calculated to have 90% power to detect such a difference between treatment arms at the 5% significance level (Type I error), assuming a standard deviation of 53 m (obtained from the same study [13]). We assumed a 29% dropout rate from rehabilitation (using data from a previous study in the same pulmonary rehabilitation class [14]). Therefore, our final desired sample size was 138 COPD patients, with 98 required to complete the study. The minimal clinically important difference (MCID) of the ISWT following pulmonary rehabilitation is now considered to be between 35.0 and 36.1 m [15], but was 47.5 m at the time the study was designed [16].

Statistical analysis

Data were analysed on a modified intention-to-treat basis which included all participants who completed pulmonary rehabilitation and used nutritional supplementation. Data were assessed for normality by visual inspection of histograms and the Kolmogorov–Smirnov test. Baseline characteristics of the intervention and control groups were reported using mean and standard deviation or median and interquartile range as appropriate. For the main outcome of the ISWT, between-group differences were compared by ANCOVA considering baseline ISWT as a covariate. Pre- and post-pulmonary rehabilitation measurements within the intervention and control groups were compared using the paired t-test for normally distributed data and the Wilcoxon signed-rank test for nonnormally distributed data. Independent t-tests were used to compare the mean difference between the two groups for normally distributed data and Mann–Whitney U-tests were used for nonnormally distributed data. Each participant in the intervention group was classified as a responder (improvement of >36.1 m in ISWT distance) or a nonresponder and baseline characteristics were compared. SPSS version 26 (IBM, Armonk, NY, USA) was used to analyse data.

Results

We approached and screened 221 consecutive patients referred to pulmonary rehabilitation between 7 January 2019 and 31 January 2020. The CONSORT diagram is provided as figure 1, and includes patients who were excluded, withdrew and completed the trial. 125 (56.5%) were ineligible and 28 (12.7%) declined to consent, resulting in 68 participants (male n=42 and female n=26) randomised to receive FCP (intervention n=36) or PreOp (control n=32) and who started pulmonary rehabilitation. Of the 68 participants, 44 (intervention n=22 and control n=22) completed 6 weeks of pulmonary rehabilitation

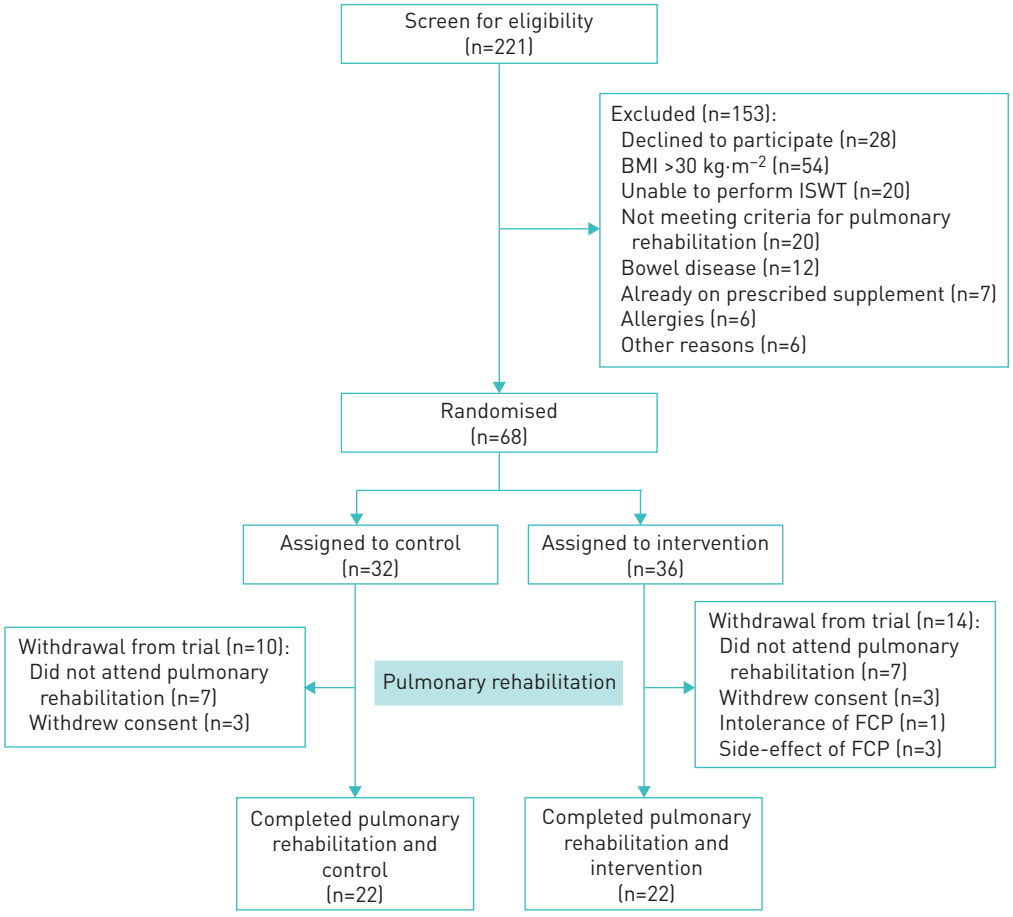

FIGURE 1 CONSORT recruitment diagram for enrolment and study completion. BMI: body mass index; ISWT: incremental shuttle walk test; FCP: Fortisip Compact Protein.

using nutritional supplementation and had both baseline and end of pulmonary rehabilitation measurements available. 14 participants (intervention n=7 and control n=7) withdrew from pulmonary rehabilitation. Four participants in the intervention arm withdrew due to side-effects/intolerance to the FCP supplement. There was no significant difference in dropout rate between the intervention and control groups. The compliance with supplements was calculated from the diary card, and was 96% (87–100%) in the control group and 97% (90–100%) in the intervention group. At this point, the trial was stopped due to the COVID-19 pandemic which closed the pulmonary rehabilitation class and analysis was performed.

The baseline characteristics of participants who completed *versus* those that did not complete pulmonary rehabilitation are presented in appendix S3 in the supplementary material. The baseline characteristics for those completing (control n=22 and intervention n=22) are presented in table 1. The intervention group was older than the control group (control 70±9 years *versus* intervention 75±6 years; p=0.04). There were fewer ex-smokers in the control group than in the intervention group (control 55% *versus* intervention 77%). A history of hospitalisation in the past year due to COPD exacerbation was significantly higher in the control group (control 0 (0–1) *versus* intervention 0 (0–0); p=0.03). SGRQ total, activity and impact domains showed a significantly higher impact of COPD in the control group compared with the intervention group (SGRQ total score 52±17 *versus* 41±13; p=0.02; SGRQ activity score 57 (57–86) *versus* 57 (53–69); p=0.03 and SGRQ impact score 38±19 *versus* 27±12; p=0.03).

Primary outcome: ISWT

Both the control and intervention groups experienced a significant improvement in ISWT distance following pulmonary rehabilitation (40±60 m; p=0.005 and 73±68 m; p<0.001, respectively). After adjusting for baseline ISWT distance, the post-walk distance for the intervention group was 342±149 m compared with 305±148 m in the control group. This difference did not meet the pre-planned statistical cut-off of 5% (p=0.10; ANCOVA). However, it did meet the *a priori* definition of functional benefit in the ISWT of >35 m. It also exceeds the MCID in the ISWT of >36.1 m, as the mean difference between arms

TABLE 1 Demographic data and baseline characteristics of the chronic obstructive pulmonary disease (COPD) patients who completed the study

	Control	Intervention	p-value[#]
Subjects	22	22	
Demographics			
Age years	70±9	75±6	0.04*
Sex			0.53
Male	13 (59)	15 (68)	
Female	9 (41)	7 (32)	
Active smoker	10 (45)	5 (23)	0.20
Ex-smoker	12 (55)	17 (77)	
Smoking history pack-years	39 (24–59)	45 (28–93)	0.41
Exacerbation within last year	1 (0–2)	0 (0–1)	0.21
Hospitalisation due to exacerbations within last year	0 (0–1)	0 (0–0)	0.03*
Medications			
SABA	15 (68)	15 (68)	0.81
LABA	15 (68)	9 (41)	0.09
SAMA	0	0	
LAMA	16 (73)	8 (36)	0.02*
ICS	12 (54)	7 (32)	0.16
Nonrespiratory medications	17 (77)	20 (91)	0.09
Diabetes	0	0	
Pulmonary function			
FEV_1 L	1.2 (1–2)	1.6 (1–2)	0.27
FEV_1 % pred	52±19	59±22	0.18
FEV_1/FVC %	54±12	53±13	0.90
Anthropometric measurements			
Weight kg	68±13	75±16	0.12
Waist circumference cm	92±14	96±15	0.46
Hip circumference cm	98±9	104±11	0.04*
Mid-thigh circumference cm	56±8	59±6	0.16
Body composition			
Fat mass kg	24±7	26±6	0.50
BMI $kg \cdot m^{-2}$	23±4	24±4	0.36
Fat-free mass kg	43±10	49±13	0.12
FFMI $kg \cdot m^{-2}$	15±3	16±3	0.17
Functional outcomes			
ISWT m	265±133	269±130	0.92
mMRC grade	3 (2–3)	3 (2–3)	0.87
Right handgrip kg	26±19	30±10	0.15
Left handgrip kg	25±9	29±9	0.16
STS5 s	11 (7–13)	10 (9–12)	0.94
Questionnaires			
CAT score	20±8	18±6	0.37
Anxiety (HADS) score	6 (4–9)	4 (3–10)	0.42
Depression (HADS) score	6±3	5±3	0.19
SGRQ total score	52±17	41±13	0.02*
SGRQ symptoms score	63±23	52±21	0.14
SGRQ activity score	57 (57–86)	57 (53–69)	0.03*
SGRQ impact score	38±19	27±12	0.03*
MUST score	0 (0–1)	0 (0–0)	0.50
Physical activity steps·day^{-1}	2663 (1947–4912)	4297 (1726–7211)	0.33

Data are presented as n, mean±SD, n (%) or median (interquartile range), unless otherwise stated. SABA: short-acting β-agonist; LABA: long-acting β-agonist; SAMA: short-acting muscarinic antagonist; LAMA: long-acting muscarinic antagonist; ICS: inhaled corticosteroid; FEV_1: forced expiratory volume in 1 s; FVC: forced vital capacity; BMI: body mass index; FFMI: fat-free mass index; ISWT: incremental shuttle walk test; mMRC: modified Medical Research Council; STS5: five-repetition sit-to-stand test; CAT: COPD Assessment Test; HADS: Hospital Anxiety and Depression Scale; SGRQ: St George's Respiratory Questionnaire; MUST: Malnutrition Universal Screening Tool. [#]: p-values were calculated using the Chi-squared, paired t-test for normally distributed data and the Wilcoxon signed-rank test for nonnormally distributed data, and represent a comparison between the control and intervention groups. *: $p<0.05$.

was 37 m. The variability between participants in the control and intervention groups (148 and 149 m, respectively) was considerably higher than that found in previous studies. This difference in the ISWT is illustrated in figure 2.

Secondary outcomes

The within- and between-group changes in functional, anthropometric, body composition and HRQoL measures following pulmonary rehabilitation are reported in table 2. Within the control group, there were significant improvements after pulmonary rehabilitation in right handgrip (3±4 kg; p<0.05), left handgrip (3±5 kg; p<0.05), STS5 time (−3 (−5–−1) s); p<0.01), body weight (1±2 kg; p<0.05) and mid-thigh circumference (2±4 cm; p<0.05).

Within the intervention group, there were significant improvements after pulmonary rehabilitation in right handgrip (2±3 kg; p<0.05), left handgrip (2±3 kg; p<0.01), STS5 time (−2 (−2–−1 s); p<0.01), body weight (1±2 kg; p<0.01) and mid-thigh circumference (1±3 cm; p<0.05). There were no significant differences between the intervention and control groups.

Participants taking the intervention supplement were divided into those who responded on the ISWT and those who did not respond. The baseline characteristics of responders and nonresponders are presented in table 3.

There were significant differences in baseline mid-thigh circumference (responders 62±4 cm *versus* nonresponders 55±6 cm; p=0.006) favouring the responder group and higher baseline depression scores (responders 7±4 *versus* nonresponders 3±2; p<0.04), although the latter were both clinically within the normal range and this difference is higher than the MCID of 1.4 points.

There were no significant differences between baseline characteristics between responders and nonresponders in the control group.

Patient experience

79% of participants were satisfied with the taste of the supplement. 43% of the participants in the intervention (FCP) group wished to continue taking the product and 57% did not due to flavour, sweetness, texture or inconvenience.

Three participants in the intervention group developed mild diarrhoea, all of whom discontinued the supplement. No other side-effects were reported.

Discussion

This study investigated the effect of high-protein supplementation during pulmonary rehabilitation in COPD. We show that in COPD patients enrolled in a 6-week pulmonary rehabilitation programme, high-protein nutritional supplementation was not associated with a statistically significant improvement in exercise capacity measured by the ISWT above that seen due to pulmonary rehabilitation alone. However, there was a clinically meaningful difference favouring the intervention group.

Our study was stopped because of the coronavirus pandemic and we therefore present this study as a pilot trial. Our results suggest that using a high-protein supplement might enhance exercise capacity gains during pulmonary rehabilitation, but that further research would be required to confirm this. Our data are in keeping with other randomised controlled trials that have examined diverse nutritional supplements, including creatine, high-carbohydrate and protein supplements [13, 17–20]. Our participants were very

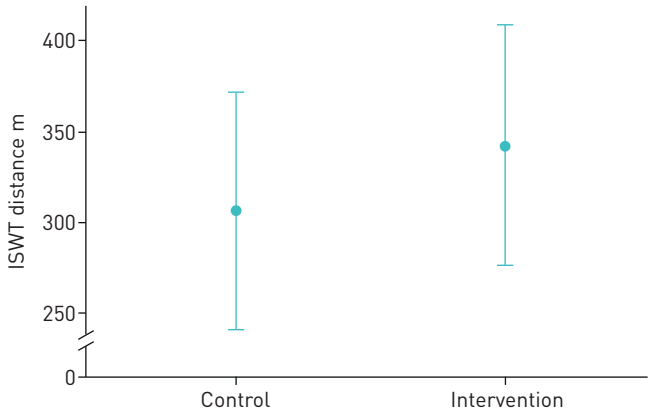

FIGURE 2 Post-pulmonary rehabilitation incremental shuttle walk test (ISWT) distance in the control (305±148 m) and intervention groups (342±149 m) (p=0.10). Data are presented as mean and standard deviation.

TABLE 2 Within- and between-group changes in functional outcomes, anthropometric measurements, body composition, health-related quality of life and physical activity following pulmonary rehabilitation[#]

	Control		Intervention		Between-group difference[¶]	95% CI	Effect size	p-value[+]
	Pre	Post	Pre	Post				
Functional outcomes								
ISWT m	265±133	305±148	269±129	342±149	32±85	−5–70	2.7	0.10
mMRC grade	3 (2–3)	3 (2–3)	3 (2–3)	3 (2–3)	0 (0–0)	0		1
Right handgrip kg	26±19	29±9	30±10	32±10	0.5±5	−2–3	1.5	0.44
Left handgrip kg	25±9	28±10	29±9	30±10	0.9±7	−2–4	0.5	0.33
STS5 s	10 (7–13)	8 (6–10)	11 (9–12)	9 (7–12)	−1 (−4–0.3)	−5–0.2	4	0.08
Anthropometric measurements								
Weight kg	68±13	69±13	75±16	76±16	0.4±2	−0.6–2	0.2	0.50
Waist circumference cm	94 (78–105)	94 (77–102)	93 (87–105)	96 (85–111)	1 (−3–1)	1–3	0.1	0.38
Hip circumference cm	98±9	98±9	104±11	103±9	2±6	−1–4	1.2	0.11
Mid-thigh circumference cm	56±8	58±6	59±6	61±5	0.4±6	−2–3	0.05	0.75
Body composition								
Fat mass kg	26 (18–30)	25 (18–30)	27 (21–32)	27 (19–33)	2 (−2–4)	−3–4	0.03	0.24
Fat-free mass kg	41 (34–52)	42 (34–56)	52 (37–61)	49 (38–59)	0.3 (−3–4)	−2–5	0.3	0.88
FFMI kg·m^{-2}	15±3	15±3	16±3	17±4	0.1±2	−1–1	0.001	0.38
Questionnaires								
CAT score	20±8	19±8	18±6	17±7	0.04±8	−3–3	0.12	0.98
Anxiety (HADS) score	7±4	6±5	6±5	5±5	0.4±3	−1–2	1	0.55
Depression (HADS) score	6±3	6±3	5±3	4±4	0.5±3	−1–2	0.03	0.39
SGRQ total score	52±17	51±17	41±13	43±16	2±15	−5–10	0.006	0.48
SGRQ symptoms score	63±23	57±20	52±21	49±27	3±28	−11–17	0.06	0.76
SGRQ activity score	72±18	71±19	60±17	66±21	6±21	−5–16	0.5	0.20
SGRQ impact score	38±19	36.6±20	27±12	28±16	0.5±18	−9–10	0.001	0.74
MUST score	0 (0–1)	0 (0–1)	0 (0–0)	0 (0–0)	0 (0–0)	0		1
Physical activity steps·day^{-1}	2663 (1947–4912)	2903 (1800–4753)	4297 (1726–7211)	5973 (2000–6812)	31 (−1421–1337)	−974–1369	0.04	0.88

Data are presented as mean±SD or median (interquartile range), unless otherwise stated. ISWT: incremental shuttle walk test; mMRC: modified Medical Research Council; STS5: five-repetition sit-to-stand test; FFMI: fat-free mass index; CAT: COPD Assessment Test; COPD: chronic obstructive pulmonary disease; HADS: Hospital Anxiety and Depression Scale; SGRQ: St George's Respiratory Questionnaire; MUST: Malnutrition Universal Screening Tool. [#]: control n=22 and intervention n=22; [¶]: mean difference for each group was calculated by subtracting baseline from post-rehabilitation measurements; [+]: p-values were calculated using the paired t-test for normally distributed data and the Wilcoxon signed-rank test for nonnormally distributed data, and represent the change between the mean differences in the control and intervention groups.

heterogeneous with variation in exercise capacity measured by the ISWT. This likely reflects variation in lower extremity strength, muscle weakness, baseline exercise tolerance and ventilatory limitation.

We found there was an improvement in handgrip strength noted in association with pulmonary rehabilitation, but no additional effect of protein supplementation, suggesting that supplementation may have different effects on different muscle groups. This is similar to results in previous studies [13, 21, 22]. For example, using carnitine for 8 weeks during pulmonary rehabilitation did not significantly improve handgrip strength when compared with a control group who received glucose [21].

The STS5 exercise assesses daily activities that rely on lower limb muscle performance. In COPD, STS5 correlates with HRQoL and lower limb strength [23]. We were unable to show a significant difference between groups, although there were significant improvements within each group in response to pulmonary rehabilitation, as would be expected in an effective pulmonary rehabilitation programme. In COPD patients who underwent outpatient pulmonary rehabilitation, STS5 was responsive and significantly correlated with exercise capacity [24].

Our data demonstrate that participants who received the intervention and reached or exceeded 36 m (MCID) in the ISWT had a larger mid-thigh circumference at baseline. Similar associations were reported in a study in which mid-thigh circumference was positively associated with exercise capacity in COPD [25]. Additionally, thigh muscle strength (*e.g.* quadriceps) has been positively associated with exercise capacity [26]. As muscle mass increased, strength and endurance improved [26]. This suggests that those who responded to the intervention might initially have higher muscle mass, especially in the lower limbs. We did not find any differences between the groups in hip or waist circumference.

TABLE 3 Baseline characteristics between responders and nonresponders to the incremental shuttle walk test (ISWT) in the intervention group

	Responders	Nonresponders	p-value
Subjects	13	9	
Demographics			
Age years	74±5	78±6	0.15
Sex			0.90
Male	9 (69)	6 (66)	
Female	4 (31)	3 (33)	
Ex-smoker	10 (77)	7 (78)	0.96
Smoking history pack-years	49 (28–105)	45 (21–49)	0.34
Exacerbation within last year	5 (38)	5 (56)	0.43
Hospitalisation due to exacerbations within last year	0 (0)	1 (11)	0.22
Anthropometric measurements			
Weight kg	78±14	71±18	0.32
Waist circumference cm	98±12	92±18	0.33
Hip circumference cm	106±8	102±15	0.44
Mid-thigh circumference cm	62±4	55±6	0.006*
Pulmonary function			
FEV_1 % pred	59±22	52±19	0.28
FEV_1/FVC %	53±13	54±12	0.75
Body composition			
BMI kg·m^{-2}	25±3	24±5	0.50
Fat-free mass kg	16±2	15±3	0.29
FFMI kg·m^{-2}	52±13	45±14	0.38
Functional outcomes			
ISWT m	265±134	274±132	0.88
mMRC grade	3 (2–3)	3 (2–3)	0.95
Right handgrip kg	32±12	28±8	0.45
Left handgrip kg	30±10	27±8	0.43
STS5 s	11±3	11±4	0.89
Questionnaires			
CAT score	19±6	18±7	0.78
Anxiety (HADS) score	6 (2–13)	3 (2–7)	0.26
Depression (HADS) score	7±4	3±2	0.04*
SGRQ total score	42±14	39±12	0.56
MUST score	0 (0–0)	0 (0–2)	0.36
Physical activity steps·day^{-1}	4909±2851	3930±3495	0.49

Data are presented as n, mean±SD, n (%) or median (interquartile range), unless otherwise stated. FEV_1: forced expiratory volume in 1 s; FVC: forced vital capacity; BMI: body mass index; FFMI: fat-free mass index; mMRC: modified Medical Research Council dyspnoea scale; STS5: five-repetition sit-to-stand test; CAT: COPD Assessment Test; COPD: chronic obstructive pulmonary disease; HADS: Hospital Anxiety and Depression Scale; SGRQ: St George's Respiratory Questionnaire; MUST: Malnutrition Universal Screening Tool. *: p<0.05.

We found that participants who exceeded the MCID in the ISWT with the supplement had a higher baseline depression score (although still within the normal range) and this was higher than in the nonresponder group by more than the MCID of 1.4 points [27]. In COPD patients, depression has a negative impact on pulmonary rehabilitation outcomes such as exercise capacity and dyspnoea which might unfavourably affect the distance walked in the ISWT during the baseline visit [28]. Our pulmonary rehabilitation programme involved exercise and education, including stress management. Treating depression might positively impact exercise capacity, allowing further improvement at the end of pulmonary rehabilitation.

We were required to stop recruitment due to the COVID-19 pandemic; consequently 44 subjects completed the study. Pulmonary rehabilitation in London was eventually transferred to an online service, preventing continuation of the study, and at this point we analysed our data. Our data can be used to inform the power calculation of a definitive study. The ISWT distances in the control and intervention groups after our pulmonary rehabilitation programme were 40±60 and 73±68 m, respectively. The dropout rate was 35%. A sample size calculation with 80% power at 5% significance level and standard deviation of 65 m (the average standard deviation of the ISWT distance for both groups) with 35% dropout suggests a study would need to recruit 190 COPD patients (95 per group), with 124 completing the study.

Limitations

We failed to recruit the required sample size because we were forced to stop the trial early. As such, we present this as a pilot trial. Additionally, the strict criteria for inclusion (*e.g.* BMI <30 kg·m^{-2}) limited recruitment. We did not assess muscle mass (*e.g.* with ultrasound) or measure quadriceps strength. This might more accurately quantify the effect of the intervention on lower limb muscles. Thigh circumference may not be the most accurate measurement, especially in obese patients. There were some differences between groups in baseline characteristics such as age, number of hospital admission and QoL which may have impacted outcomes. We could not provide a placebo identical to the intervention, but were able to relabel both products, and both the assessor and the patients were blind to this. There was heterogeneity in the exercise capacity measured by the ISWT between participants. We observed a larger standard deviation for the 6-week ISWT than expected. We were not able to collect empty bottles to verify compliance with the supplement, relying only on the diary card.

Conclusions

Using a high-protein nutritional supplementation in COPD patients who were enrolled in pulmonary rehabilitation, we were not able to identify a statistically significant difference between the intervention and control groups in exercise capacity measured by the ISWT or in other secondary outcomes, which is likely due to the small sample size. However, there was a clinically meaningful difference favouring the intervention and the individuals who reached that improvement had a larger mid-thigh circumference at baseline. Nutritional supplements were acceptable to patients. Further definitive research investigating the potential utility of nutritional supplements in this population is warranted.

Author contributions: The study was designed by A.M. Aldhahir, J.R. Hurst and S. Mandal. Data collection was led by A.M. Aldhahir with assistance from Y.S. Aldabayan and J.S. Alqahtani. A.M. Aldhahir led the data analysis, supervised by C. Smith. A.M. Aldhahir wrote the first draft of the manuscript. All authors revised the manuscript for important intellectual content and approved the final version for submission.

Conflict of interest: A.M. Aldhahir has nothing to disclose. Y.S. Aldabayan has nothing to disclose. J.S. Alqahtani has nothing to disclose. H.A. Ridsdale has nothing to disclose. C. Smith reports personal fees for educational materials from Gilead and grants from ViiV Healthcare outside the submitted work. J.R. Hurst reports support to attend meetings, and payment for educational and advisory work, personally, and University College London received payment for educational activity and advisory work from pharmaceutical companies that make medicines to treat COPD, outside the submitted work. S. Mandal has nothing to disclose.

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