Early View

Original article

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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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Take home message

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.

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Abstract

Background: Pulmonary rehabilitation (PR) 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 PR outcomes but rigorous evidence is absent. We aimed to investigate the effect of high protein-supplementation (Fortisip Compact Protein, FCP) during PR on exercise capacity.

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

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

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

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 (HRQL) [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 muscle further

deconditioning, reduced muscle strength and endurance [4]. Pulmonary rehabilitation (PR) is a multi-professional education and exercise programme that is a fundamental management strategy in COPD, resulting in improved exercise performance and HRQL, promoting self-dependency in relation to activities of daily living whilst reducing dyspnoea and the risk of exacerbation [5, 6]. Maximising the value and response to PR 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 PR. Several studies, summarised in a recent systematic review, have investigated the benefit of using nutritional supplementation during PR but yielded conflicting results [7] 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 PR would enhance benefits in exercise capacity.

Material and methods

Trial design

This double-blind, parallel group randomised control superiority trial was registered at clinicaltrials.gov (NCT04027413) [9]. The study was approved by a local ethics committee and UK Health Research Authority (HRA) (reference 18/LO/1842).

Participants

Participants with confirmed COPD (post-bronchodilator forced expiratory volume in 1 second (FEV_1): forced vital capacity (FVC) ratio <0.7) and an appropriate exposure history, enrolling on a PR programme were recruited from the Central and North West London NHS Foundation Trust, UK,

between 7 January 2019 and 31 January 2020, with the last visit for last participant completed on the 20 March 2020. At this point the study had to be suspended, a national 'lock-down' for the conronavirus-19 pandemic meant that the PR service was stopped.

Before starting PR, 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 (AA). 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) above 30 kg/m^2 without recent weight loss of more than 5% were excluded from the study.

Randomising and blinding

Participants were randomised (1:1) using a web-based service 'sealed envelope' with equal allocation concealment, block size 4, stratified based on BMI ≥ 20 kg/m^2 or < 20 kg/m^2, given that oral nutritional supplementation is recommended in COPD patients with a BMI <20 kg/m^2 or those who 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 outcome assessor and participants were blinded to treatment allocation.

Interventions

Both products were unlabelled and directly delivered to the participants' residential address with both researcher and participants being blinded.

The intervention was a 125 ml bottle of Fortisip Compact Protein (Nutricia, *Zoetermeer, Netherlands*) that has 300 kcal, 24% protein; 41% carbohydrate; and 35% fat. The control was a 200 ml bottle of PreOp (Nutricia, *Zoetermeer*, *Netherlands*) with 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 PR session, and one during the day after a meal.

Both the intervention and control products were used throughout the six-week duration of the PR programme.

Study conduct

All baseline measurements were conducted prior to starting PR, this included ISWT, body composition, anthropometric measurements, handgrip strength, and five-repetition sit-to-stand. 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 (CAT) [10], Hospital Anxiety and Depression Score (HADS) [11], Medical Research Council (MRC) [12], St. George Respiratory Questionnaire (SGRQ) [13], and Malnutrition Universal Screening Tool (MUST) [8]. At the end of the study, the acceptance of the intervention was assessed by a survey (Appendix 1). A full description of the methodology is presented in Appendix 2.

Sample size

The power calculation was conducted using parameters from a previous study [14]. The clinical significance of further increases in ISWT performance resulting from treatment adjunctive to PR is unknown but we judged *a priori* that an additional increase of 35m 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 [14]). We assumed a 29% dropout rate from rehabilitation (using data from a previous study in the same PR class [15]). 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 PR is now considered to be between 35.0 and 36.1 m [16], but was 47.5 m at the time the study was designed [17].

Statistical analysis

Data were analysed on a modified intention- to- treat basis which included all participants who completed PR and used nutritional supplementation. Data were assessed for normality by visual inspection of histograms, and the Kolmogorov-Smirnov test. Baseline characteristics of interventional and control groups were reported using mean and standard deviation or median and interquartile range as appropriate. For the main outcome of ISWT, between-group differences were compared by ANCOVA considering baseline ISWT as a covariate. Pre-and post-PR measurements within the intervention and control groups were compared using paired t-test for normally distributed data and Wilcoxon signed-rank test for data not normally distributed. Independent t-tests were used to compare the mean difference between the two groups for normally distributed data and Mann-Whitney U tests for data not normally distributed. Each participant in the intervention group was classified as a responder (improvement in the distance walked exceeded 36.1m on ISWT) or a non-responder and baseline characteristics were compared. The Statistical Package for the Social Sciences (SPSS), Version 26 (IBM Corp, Armonk, USA) software was used to analyse data.

Results

We approached and screened 221 consecutive patients referred to PR between 7 January 2019 and 31 January 2020. The CONSORT diagram is illustrated 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 (42 male, 26 female) randomised to receive FCP (intervention, n= 36) or preOp (control, n= 32) and who started PR. Of the 68 participants, 44 (intervention= 22; control = 22) completed six weeks PR using nutritional supplementation and had both baseline and

end of PR measurements available. Fourteen participants (intervention= 7; control= 7) withdrew from PR. Four participants in the intervention arm withdrew due to side effects/intolerance to the FCP supplement. There was no significant difference in drop out rate between intervention and control groups. The compliance with supplements was calculated from the diary card, and was 96 (87, 100) % in the control and 97 (90, 100) % in the intervention groups. At this point, the trial was stopped due to the COVID-19 pandemic which closed the PR class, and analysis was performed.

The baseline characteristics of participants who completed versus those that did not complete PR are presented in Appendix 3. The baseline characteristics for those completing (control: 22; intervention: 22) are presented in Table 1. The intervention group was older than the control group (control: 70 years ±9 vs. intervention: 75 years ±6; p = 0.04). There were fewer ex-smokers in the control than the intervention groups (control: 55%; 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) vs. intervention: 0 (0, 0); p = 0.03). SGRQ total score, activity, and impact domains showed significantly higher impact of COPD in the control group compared with the intervention group (SGRQ total: 52 ±17 vs. 41 ±13, p = 0.02; activity domain: 57 (57, 86) vs. 57 (53, 69), p = 0.03; impact domain: 38 ±19 vs. 27 ±12, p = 0.03).

Primary outcome Incremental Shuttle Walk Test

Both the control and intervention groups experienced a significant improvement in ISWT following PR (40 m ±60; p = 0.005 and 73 m ±68; p < 0.001 respectively). After adjusting for baseline ISWT, the mean (SD) post-walk distance for the intervention arm was 342 m ±149 compared to 305 m ±148 in the control arm. 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 ISWT of more than 35 m. It also exceeds the clinically meaningful difference (MCID) in ISWT of more 36.1 m, as the mean difference between arms was 37 m. The variability between participants in both arms of 149 and 148m was considerably higher than that found in previous studies. This difference in ISWT is illustrated in Figure 2.

Secondary outcomes

The within and between group changes in functional, anthropometric, body composition, and health related quality of life measures following PR are reported in Table 2. Within the control group, there were significant improvements after PR in right handgrip (3 kg ±4; $p <0.05$), left handgrip (3 kg ±5, $p <0.05$), STS5 (-3 sec (-5,-1)); $p <0.01$), body weight (1 kg ±2; $p <0.05$) and mid-thigh circumference (2 cm ±4; $p <0.05$).

Within the intervention group, there were significant improvements after PR in right handgrip (2 kg ±3; $p <0.05$), left handgrip (2 kg ±3, $p <0.01$), STS5 (-2 sec (-2,-1); $p <0.01$), body weight (1 kg ±2; $p <0.01$) and mid-thigh circumference (1 cm ±3; $p <0.05$). Between intervention and control groups, there were no significant differences.

Participants taking the intervention supplement were divided into those who responded on ISWT compared to those who did not respond. The baseline characteristics of responders and non-responders are presented in Table 3.

There were significant differences in baseline mid-thigh circumference (responder: 62 cm ±4 vs. non-responder: 55 cm ±6; p = 0.006) favouring the responder group, and higher baseline depression scores (responders: 6 ±4 vs. non-responders: 3 ±2; p < 0.04). Although the latter were both clinically within 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 non-responders in the control group.

Patient Experience

Seventy-nine percent of participants were satisfied with the taste of the supplement. 43% of the participants in the FCP (protein) 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 PR in COPD. We show that in COPD patients enrolled in a six-week PR programme, high protein nutritional supplementation was not associated with a statistically significant improvement in exercise capacity measured by ISWT above that seen due to PR 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. Our results suggest that using a high protein supplement might enhance exercise capacity gains during PR, but that further research would be required to confirm this. Our data are in keeping with other RCTs that have examined diverse nutritional supplements including creatine, high carbohydrate and protein supplements [14, 18-21]. Our participants were very heterogeneous with variation in exercise capacity measured by ISWT. This likely reflect variation in lower extremity strength, muscle weakness, baseline exercise tolerance, and ventilatory limitation.

In our study, there was an improvement in handgrip noted in association with PR, 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 [14, 22, 23]. For example, using carnitine for eight weeks during PR did not significantly improve handgrip strength when compared to a control group who received glucose [22].

The five-repetition sit-to-stand exercise assesses daily activities that rely on lower limb muscle performance. In COPD, STS5 correlates with HRQL and lower limb strength [24]. In our study, we were unable to show a significant difference between groups, although there were significant improvements within each group in response to PR as would be expected in an effective PR programme. In COPD patients who underwent outpatient PR, STS5 was responsive and significantly correlated with exercise capacity [25].

Our data demonstrate that participants who received the intervention and reached or exceeded 36 m (MCID) in the ISWT had 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 [26]. Additionally, thigh muscle strength such as quadriceps have been positively associated with exercise capacity [27]. As muscle mass increased, strength, and endurance improved [27]. 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 circumferences.

We found that participants who exceeded the MCID in ISWT with supplement had a higher baseline depression score (although still within normal range), and higher than in the non-responder group by more than the MCID of 1.4 points [28]. In COPD patients, depression has a negative impact on PR outcomes such as exercise capacity and dyspnoea which might unfavourably affect the distance walked in ISWT during the baseline visit [29]. Our PR programme involved exercise and education, including stress management. Treating depression might positively impact exercise capacity allowing further improvement at the end of PR.

We were required to stop recruitment due to the COVID-19 pandemic; consequently 44 subjects completed the study. PR in London was eventually transferred to an online service, preventing continuation of the study at this point we analysed our data. Our data can be used to inform the power calculation of a definitive study. The mean ±SD of the ISWT in the control group and intervention group after our PR programme were 40 ±60 m 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 65m (the average SD of ISWT 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, such as BMI < 30 kg/m^2, limited recruitment. We did not assess muscle mass, for example 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 quality of life which may have impacted outcomes. We could not provide a placebo identical to the intervention, but were able to relabel both products and both assessor and patients were blind to this. There was heterogeneity in the exercise capacity measured by 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, only provide a diary card.

Conclusion

Using a high protein nutritional supplementation in COPD patients were enrolled in PR, we were not able to identify a statistically significant difference between groups in exercise capacity measured by 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 individuals who reached that improvement had 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 are warranted.

Data availability statement: Data are available upon reasonable request to the corresponding author.

Conflict of interest:

JRH has received support to attend meetings, and payment for educational and advisory work, personally and to his employer (UCL) from pharmaceutical companies that make medicines to treat

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Table 1: Demographic data and baseline characteristics of COPD patients who completed the study divided into two groups; control and intervention.

Subjects Demographics	Control (22)	Intervention (22)	p-value
Age (years)	70 ±9	75 ±6	**0.04**
Male n (%)	13 (59%)	15 (68%)	0.53
Female n (%)	9 (41%)	7 (32%)	
Active smoker n (%)	10 (45%)	5 (23%)	0.20
Ex-smokers n (%)	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 n (%)	15 (68%)	15 (68%)	0.81
LABA n (%)	15 (68%)	9 (41%)	0.09
SAMA n (%)	0	0	^
LAMA n (%)	16 (73%)	Yes: 8 (36%)	**0.02**
ICS n (%)	12 (54%)	7 (32%)	0.16
Non-Respiratory medications n (%)	17 (77%)	20 (91%)	0.09
Diabetes n (%)	0	0	^
Pulmonary function			
FEV_1 (L)	1.2 (1, 2)	1.6 (1, 2)	0.27
FEV_1 (% predicted)	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	56 ±8	59 ±6	0.16

(cm)

Body composition			
FM (kg)	24 ±7	26 ±6	0.50
BMI (kg/m^2)	23 ±4	24 ±4	0.36
FFM (kg)	43 ±10	49 ±13	0.12
FFMI (kg/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
(R) Handgrip (kg)	26 ±19	30 ±10	0.15
(L) Handgrip (kg)	25 ±9	29 ±9	0.16
STS5 (sec)	11 (7, 13)	10 (9, 12)	0.94
Questionnaires			
CAT	20 ±8	18 ±6	0.37
Anxiety scores (HADS)	6 (4, 9)	4 (3, 10)	0.42
Depression scores (HADS)	6 ±3	5 ±3	0.19
SGRQ total	52 ±17	41 ±13	**0.02**
SGRQ symptoms	63 ±23	52 ±21	0.14
SGRQ activity	57 (57, 86)	57 (53, 69)	**0.03**
SGRQ impact	38 ±19	27 ±12	**0.03**
MUST	0 (0, 1)	0 (0, 0)	0.50
Physical activity (steps/ day)	2663 (1947, 4912)	4297 (1726, 7211)	0.33

Data are presented as n (%), mean ±SD, or median IQR. ^ No data to compare with.

p value was calculated using chi square, paired t-test for normally distributed and Wilcoxon signed-rank test for non-normally distributed data, and represented a comparison between control and intervention groups.

Abbreviations: SABA, Short-acting beta-agonists; LABA; Long-acting beta-agonists; SAMA, Short-acting muscarinic antagonist; LAMA, Long-acting muscarinic antagonist; ICS, Inhaled corticosteroids; FEV1, Forced Expiratory Volume in 1 second; FEV1%, Predicted Forced Expiratory Volume in 1 second; FEV1/FVC, calculated ratio between both measurements; BMI, Body Mass Index; FFM, fat-free-mass; FM, fat-mass; FFMI, fat-free-mass index; ISWT, incremental shuttle walk test; mMRC; modified medical research council dyspnoea scale; (R) handgrip, right handgrip; (L) handgrip, left handgrip; STS5, Sit to Stand– Five Test; CAT; COPD assessment test; HADS, hospital anxiety and depression scale; SGRQ, St. George's respiratory questionnaire; MUST, malnutrition universal screening tool.

Table 2: Within and between group changes in functional, anthropometric, body composition, HRQL, and physical activity following PR.

Outcomes	Control (22)		Intervention (22)		Between groups difference	95%CI	Effect size	p-value (The change between the mean differences)
	Pre	Post	Pre	Post				
Functional outcomes								
ISWT (m)	265 ±133	305 ±148	269 ±129	342 ±149	32 ±85	-5 to 70	2.7	0.10
mMRC grade	3 (2, 3)	3 (2, 3)	3 (2, 3)	3 (2, 3)	0 (0, 0)	0	^	1
(R) Handgrip (kg)	26 ±19	29 ±9	30 ±10	32 ±10	0.5 ±5	-2 to 3	1.5	0.44
(L) Handgrip (kg)	25 ±9	28 ±10	29 ±9	30 ±10	0.9 ±7	-2 to 4	0.5	0.33
STS5 (sec)	10.6 (7, 13)	7.5 (6, 10)	11 (9, 12)	9 (7, 12)	-1 (-4, 0.3)	-5 to 0.2	4	0.08
Anthropometric measurements								
Weight (kg)	68 ±13	69 ±13	75 ±16	76 ±16	0.4 ±2	-0.6 to 2	0.2	0.50
Waist circumference (cm)	94 (78, 105)	94 (77, 102)	93 (87, 105)	96 (85, 111)	1 (3, 1)	1 to 3	0.1	0.38
Hip circumference (cm)	98 ±9	98 ±9	104 ±11	103 ±9	2 ±6	-1 to 4	1.2	0.11
Mid-thigh circumference (cm)	56 ±8	58 ±6	59 ±6	61 ±5	0.4 ±6	-2 to 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 to 4	0.03	0.24
FFM (kg)	41 (34, 52)	42 (34, 56)	52 (37, 61)	49 (38, 59)	0.3 (-3, 4)	-2 to 5	0.3	0.88
FFMI (kg/m^2)	15 ±3	15 ±3	16 ±3	17 ±4	0.1 ±2	-1 to 1	0.001	0.38
Questionnaires								
CAT	20 ±8	19 ±8	18 ±6	17 ±7	0.04 ±8	-3 to 3	0.12	0.98

Anxiety (HADS)	7 ±4	6 ±5	6 ±5	5 ±5	0.4 ±3	-1 to 2	1	0.55
Depression (HADS)	6 ±3	6 ±3	5 ±3	4 ±4	0.5 ±3	-1 to 2	0.03	0.39
SGRQ total	52 ±17	51 ±17	41 ±13	43 ±16	2 ±15	-5 to 10	0.006	0.48
SGRQ symptoms	63 ±23	57 ±20	52 ±21	49 ±27	3 ±28	-11 to 17	0.06	0.76
SGRQ activity	72 ±18	71 ±19	60 ±17	66 ±21	6 ±21	-5 to 16	0.5	0.20
SGRQ impact	38 ±19	36.6 ±20	27 ±12	28 ±16	0.5 ±18	-9 to 10	0.001	0.74
MUST	0 (0, 1)	0 (0, 1)	0 (0, 0)	0 (0, 0)	0 (0, 0)	0	^	1
Physical activity (steps/ day)	2663 (1947, 4912)	2903 (1800, 4753)	4297 (1726, 7211)	5973 (2000, 6812)	31 (-1421, 1337)	-974 to 1369	0.04	0.88

Data are presented as n (%), mean ±SD, or median IQR.

Mean difference for each group was calculated by subtracting baseline from post rehabilitation measurements.

p value was calculated using paired t-test for normally distributed and Wilcoxon signed-rank test for non-normally distributed data, and represented the difference between the mean differences in control and intervention groups.

† p<0.05; ‡ p<0.01; α significant within the group.

Abbreviations: ISWT, incremental shuttle walk test; mMRC; modified medical research council dyspnoea scale; (R) handgrip, right handgrip; (L) handgrip, left handgrip; STS5, Sit to Stand– Five Test; BMI, Body Mass Index; FFM, fat-free-mass; FM, fat-mass; FFMI, fat-free-mass index; CAT; COPD assessment test; HADS, hospital anxiety and depression scale; SGRQ, St. George's respiratory questionnaire; MUST, malnutrition universal screening tool.

Table 3: Baseline characteristics between responders and non-responders to ISWT in the interventional group.

Subject Demographics	Responders (13)	Non-responders (9)	p-value
Age (years)	74±5	78 ±6	0.15
Male n (%)	9 (69%)	6 (66%)	0.90
Female n (%)	4 (31%)	3 (33%)	
Ex-smokers n (%)	10 (77%)	7 (78%)	0.96
Smoking history (pack-years)	49 (28, 105)	45 (21, 49)	0.34
Exacerbation within last year n (%)	5 (38%)	5 (56%)	0.43
Hospitalisation due to exacerbations within last year n (%)	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 (% predicted)	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
FFM (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
(R) Handgrip (kg)	32 ±12	28 ±8	0.45
(L) Handgrip (kg)	30 ±10	27 ±8	0.43
STS5 (sec)	11 ±3	11 ±4	0.89
Questionnaires			
CAT	19 ±6	18 ±7	0.78
Anxiety scores (HADS)	6 (2, 13)	3 (2, 7)	0.26
Depression scores (HADS)	6.5 ±4	3 ±2	**0.04**
SGRQ total	42 ±14	39 ±12	0.56
MUST	0 (0, 0)	0 (0, 2)	0.36
Physical activity (steps/ day)	4909 ±2851	3930 ±3495	0.49

Data are presented as n (%), mean ±SD, or median IQR.

Abbreviations: SABA, Short-acting beta-agonists; LABA; Long-acting beta-agonists; SAMA, Short-acting muscarinic antagonist; LAMA, Long-acting muscarinic antagonist; ICS, Inhaled corticosteroids; BMI, Body Mass Index; FFM, fat-free-mass; FM, fat-mass; FFMI, fat-free-mass index; FEV_1, Forced Expiratory Volume in 1 second; FEV_1%, Predicted Forced Expiratory Volume in 1 second; FEV_1/FVC, calculated ratio between both measurements; ISWT, incremental shuttle walk test; mMRC; modified medical research council dyspnoea scale; (R) handgrip, right handgrip; (L) handgrip, left handgrip; STS5, five repetition sit to stand; CAT; COPD assessment test; HADS, hospital anxiety and depression scale; SGRQ, St. George's respiratory questionnaire; MUST, malnutrition universal screening tool.
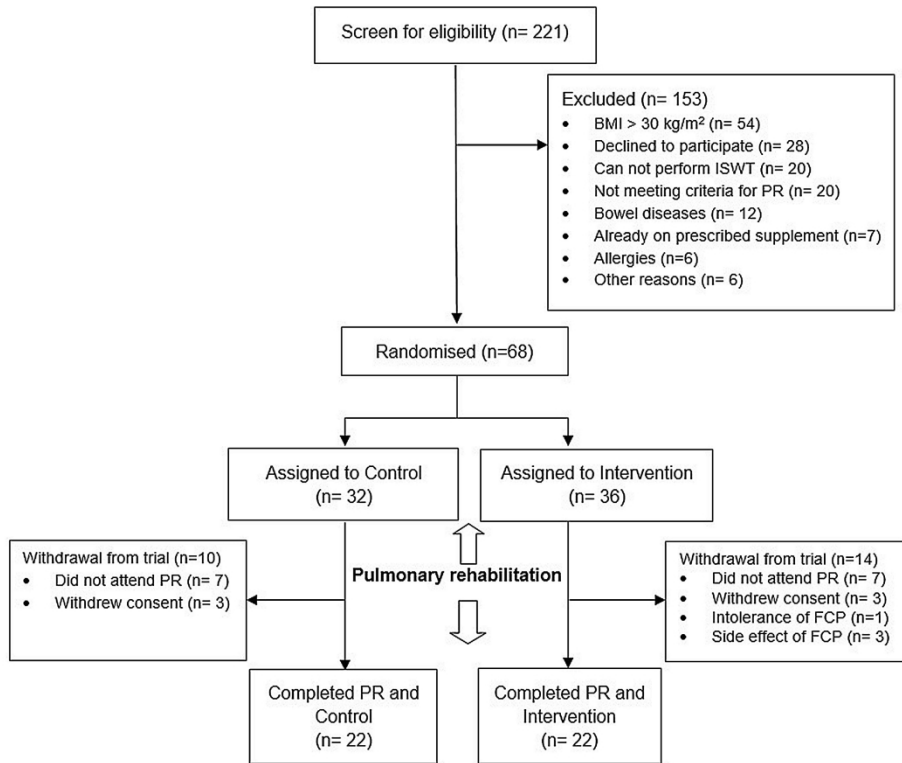
Figure 1: Consolidated Standards of Reporting Trials (CONSORT) recruitment diagram for enrolment and study completion.
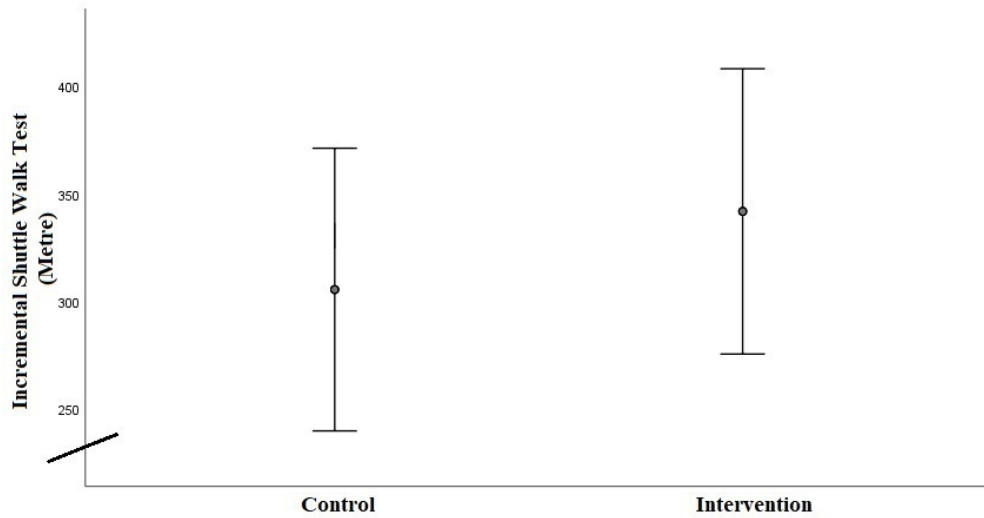
Figure 2: Post pulmonary rehabilitation mean ±SE of Incremental Shuttle Walk Test (ISWT) in the control and intervention groups. The mean ±SD of ISWT for the control group is 305 m ±148 and for the intervention group is 342 m ±149; p= 0.10.

Protein Supplementation to Enhance Exercise Capacity in COPD during Pulmonary Rehabilitation

SUPPLEMENTARY APPENDIX

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Appendix 1: supplement acceptability survey

UCL

Nutritional Supplementation to Enhance Exercise Capacity in COPD Patients

Thank you for taking part in this survey.

1. Since starting the supplement, which of the following applies to your appetite? Please circle below.

   1. Increased   2. Decreased   3. Stayed the same.

2. How satisfied are you with the taste of your supplement? Please Circle below.

   1 = Not satisfied at all   2 = slightly satisfied   3 = satisfied   4 = very satisfied

3. What did you like or dislike about the supplement?

4. If it was available, would you continue to take your supplement? Please circle below.

   1. Yes   2. No

5. What can be changed about the supplement to make you more likely to take it?

6. What do you think about having to take it twice a day?

Appendix 2: Pulmonary rehabilitation and methodology of outcome measures

Pulmonary Rehabilitation (PR)

PR is a comprehensive out-patient programme consisting of one hour of exercise training and one hour of education which participants attend twice a week for a total of 12 sessions. The PR programme is supervised by respiratory physiotherapists and follows the British Thoracic Society (BTS) guidelines (1). The exercise training portion starts with a warm-up and is followed by low intensity aerobic exercises such as cycling, treadmill walking and level walking, and resistance exercise, such as progressive resistance of upper and lower body with free weights, step up, thigh muscle training with or without weight cuffs and sit to stand. Intensity of exercises depended upon the tolerance of each individual. The education offer includes but is not limited to: stress management, signs of chest infection, early recognition of exacerbation, dyspnoea and symptom management, nutrition, techniques using inhalers and nebulisers, energy conservation, smoking cessation and chest clearance techniques. Education topics were delivered by a multidisciplinary team.

Outcome measurements

Spirometry (FEV_1, FVC and FEV_1/FVC ratio):
To confirm the diagnosis of COPD, post-bronchodilator hand-held spirometry was performed using a Micro 1 Handheld Spirometer (CareFusion, *Basingstoke*, UK), which follow the ATS/ERS standards of lung function (2). Participant were seated in upright position with the head slightly elevated during the test. Tests were repeated three times to conform with published quality-assurance criteria (3).

Primary outcome: exercise capacity

The primary outcome was the difference in change in ISWT distance (in meters) from baselines between groups. The ISWT was conducted based on European Respiratory Society and American Thoracic Society recommendations (4). Two cones were placed a distance of 9m apart. The course was 9m in length and the cones are placed with an inset of 0.5 m from either end. An audio recording has the test instructions played to avoid any variation in the test. Heart rate, blood pressure, level of dyspnoea using Borg scale, and oxygen saturation were measured prior and immediately after the test. Participants were required to perform the ISWT before enrolling in PR twice to overcome a learning effect and the higher distance was used in analysis.

Secondary outcomes

Questionnaires

CAT and SGRQ were used to assess health-related quality of life (5, 6), levels of anxiety and depression was assessed by HADS (7), breathlessness was assessed by mMRC and BORG (8), and the risk of malnutrition was assessed MUST (9).

Physical activity monitoring

Participants were asked to wear a step counter pedometer (Yamax Digi-walker SW-200) on the left side of waist (10), and recorded all daily steps for 14 days, except when showering and sleeping, before starting the PR program and for 14 days after PR completion. A diary card was provided for each period.

Sit to Stand – Five Test

Participants were instructed to sit on a straight-backed chair without arms, with feet flat on the floor and hands folded across the chest, and asked to stand up and sit down without using arm

support as fast as possible five times. A stop watch was used to count the time (11). For those who cannot do the manoeuvre, the test was terminated.

Handgrip strength

A Jamar smart handheld dynamometer (Patterson Medical Ltd, *Warrenville*, Illinois, USA) was used to measure the highest isometric strength of forearm muscles and the hand. The test was conducted by holding the device following specific guidelines (12). The average of the best two measurements were used for the analysis.

Body weight, height and composition

Body weight was measured in light clothing using a digital scale (EB4074C, *Anaheim*, US) while height was measured using a wall-mounted stadiometer without shoes.

To measure body composition, a Bodystat Touch 1500 (Bodystat Ltd, Douglas UK) was used. Participants were instructed to be in supine position and rest for three to four minutes. Two electrodes were placed on the anterior surface of the right hand and right ankle.

Waist, hip, and mid-thigh circumference

Participants were asked to stand up with feet closed together, both hands close to the body, and relaxed. A stretch- resistant tape was placed at the top of the iliac crest and the lower margin of the lowest palpable rib with the measurement taken at the end of normal exhalation to measure the waist. For the hip, the tape was used horizontally to measure the widest portion of the buttocks with the measurement taken at the end of normal exhalation. For the thigh, measurement was made directly under gluteal fold with tape horizontal to the floor. All measurements were repeated twice, and the mean was calculated with both measurements within 1 cm difference.

Participants experience using oral nutritional supplements (ONS)

At the end of the trial, participants were provided with a survey regarding their experience using nutritional supplementation during PR (Appendix 1).

Appendix 3: Demographic data and baseline characteristics of subjects with COPD divided into two groups; completers and non-completers.

The mean age of the participants was 72 ±8 years: 62% were male, and 62% were ex-smokers. The non-completers had a trend towards higher numbers of exacerbations and hospital admissions but these were not significant when compared with completers ($p >0.05$). Our participants were mainly GOLD 2 and 3, with median FEV_1 1.3L (57% predicted). There were no significant differences between the groups in the ISWT, weight, FFM, FM, physical activity measured by steps, CAT, anxiety and depression scores, risk of malnutrition, and STS5 ($p > 0.05$). A difference in the SGRQ scores between the two groups was not statistically significant ($p >0.05$). Overall, there were no statistical differences in baselines characteristics between completers and non-completers.

Table 1: Demographic data and baseline characteristics of subjects with Chronic Obstructive Pulmonary Disease (COPD) divided into two groups; completers and non-completers.

Subjects Demographics	Total population (68)	Completers (44)	Non-completers (24)	p-value completers vs. non-completers
Age (years)	72 ±8	73 ±8	70 ±9	0.16
Male n (%)	42 (62%)	28 (64%)	14 (58%)	0.67
Female n (%)	26 (38%)	16 (36%)	10 (42%)	
Active smoker n (%)	26 (38%)	15 (34%)	11 (46%)	0.34
Ex-smokers n (%)	42 (62%)	29 (66%)	13 (54%)	

Smoking history (pack-years)	41 (28-58)	45 (28-61)	39 (30-58)	0.75
Exacerbation within last year	1 (0 – 2)	1 (0 – 2)	2 (0 – 3)	0.09
Hospitalisation due to exacerbations within last year n (%)	15 (22%)	7 (16%)	8 (33%)	0.09
Medications				
SABA n (%)	44 (65%)	31 (70%	13 (54%)	0.18
LABA n (%)	40 (59%)	25 (57%)	15 (63%)	0.65
SAMA n (%)	0	0	0	^
LAMA n (%)	36 (53%)	24 (55%)	12 (50%)	0.70
ICS n (%)	33 (49%)	19 (43%)	14 (58%)	0.20
Other non-Respiratory medications n (%)	60 (88%)	38 (86%)	22 (92%)	0.52
Diabetes n (%)	0	0	0	^
Pulmonary function				
FEV_1 (L)	1.3 (1 – 1.9)	1.6 (1.1 – 2.4)	1.2 (1.1 – 1.2)	0.77
FEV_1 (% predicted)	58 (39 – 70)	64 (43 – 74)	49 (37 – 60)	0.89
FEV_1/FVC %	52 ±12	54 ±12	51 ±13	0.36
Anthropometric measurements				
Weight (kg)	69 ±14	71 ±14.6	66 ±12	0.13
Waist circumference (cm)	93 ±13	94 ±14	90 ±11	0.30
Hip circumference (cm)	100 ±10	101 ±10	98 ±8	0.33
Mid-thigh circumference (cm)	57 ±8	58 ±7	56 ±9	0.46
Body composition				

Fat mass (kg)	25 ±6	25 ±6	24 ±6	0.49
BMI kg/cm^2	24 (21 – 27)	24 (21 – 27)	24 (21 – 27)	0.98
FFM (kg)	45±11	47.9 ±12	41.9 ±3.7	0.11
FFMI (kg/m^2)	15.3 ±3	15.8 ±3	14 ±1	0.60
Functional outcomes				
ISWT (m)	266 ±134	267 ±130	264 ±144	0.94
mMRC grade	3 (2 – 3)	3 (2 – 3)	3 (2 – 3)	0.82
(R) Handgrip (kg)	27 ±9	28 ±10	24 ±7	0.09
(L) Handgrip (kg)	25 ±8	27 ±9	23 ±5	0.05
STS5 (sec)	10.3 (8.6 – 12.8)	11 (7 – 15)	9.8 (10 – 10)	0.70
Questionnaires				
CAT	20 ±7	19 ±7	21 ±7	0.34
Anxiety scores (HADS)	7 ±4	6 ±4	8 ±4	0.25
Depression scores (HADS)	6 (3 – 9)	6 (3 – 8)	7 (2 – 12)	0.45
SGRQ total	49 ±17	46 ±16	55 ±18	0.07
SGRQ symptoms	61 ±21	57 ±22	68 ±17	0.07
SGRQ activity	67 ±20	66 ±18	71 ±23	0.30
SGRQ impact	35 ±18	32 ±17	42 ±20	0.06
MUST	0	0	0	0.99
Physical activity (steps/ day)	3014 (1765 – 5914)	4102 (2148 – 6385)	3687 (1532 – 5841)	0.93

Data are presented as n (%), mean ±SD or median IQR. p value represent a comparison between completers and non-completers. ^ No data to compare with.

Abbreviations: SABA, Short-acting beta-agonists; LABA; Long-acting beta-agonists; SAMA, Short-acting muscarinic antagonist; LAMA, Long-acting muscarinic antagonist; ICS, Inhaled corticosteroids; BMI, FEV$_1$, Forced Expiratory Volume in 1 second; FEV$_1$%, Predicted Forced Expiratory Volume in 1 second; FEV$_1$/FVC, calculated ratio between both measurements; BMI, Body Mass Index; FFM, fat-free-mass; FM, fat-mass; FFMI, fat-free-mass index; ISWT, incremental shuttle walk test; mMRC; modified medical research council dyspnoea scale; (R) handgrip, right handgrip; (L) handgrip, left handgrip; STS5, five repetition sit to stand; CAT; COPD assessment test; HADS, hospital anxiety and depression scale; SGRQ, St. George's respiratory questionnaire; MUST, malnutrition universal screening tool.

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