

Original Article

Effects of whey protein complex combined with low-intensity exercise in elderly inpatients with COPD at a stable stage

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Background and Objectives: Previous literature mostly has demonstrated the efficacy of pulmonary rehabilitation (PR) combined with whole nutrition powder in patients with chronic obstructive pulmonary disease (COPD). However, the benefits of whey protein as an oral nutritional supplement (ONS) during PR are not clear. **Methods and Study Design:** It took 12 weeks to complete the trial, we divided 90 elderly patients with stable-stage COPD into a low-intensity exercise group (n= 30, PR group), PR plus whey proteins complex group (n= 30, PRWP group), and a control group (n= 30) randomly, and assessed index such as exercise capacity, mental health status, lung function, and body composition. Eventually, 84 people persisted until the end of the trial. **Results:** Compared with the control group, hand grip strength (HGS)(1.4 ± 0.6 kg, and 1.0 ± 0.2 kg respectively, $p < 0.05$) in the PRWP and PR group, 6 minutes of walking distance (6MWD)(14.1 ± 3.8 m, $p < 0.05$) in PRWP group improved. Furthermore, compared with the PR group, Medical Research Council Dyspnea Scale (MRC)(-0.2 ± 0.1 , $p < 0.01$), anxiety score (-1.2 ± 0.4 , $p < 0.01$), and body weight (2.0 ± 0.8 kg, $p < 0.05$) improved in the PRWP group. There were no inter-group differences in a fat-free mass index or appendicular skeletal muscle mass index. **Conclusions:** Muscle strength could be enhanced in both intervention models. Adding whey protein complex was additionally successful in rectifying dyspnea, anxiety, and weight loss caused by exercise. This rehabilitation pattern might be valuable in elderly patients with COPD.

Key Words: COPD, elderly patients, low-intensity exercise, whey proteins complex, muscle strength

INTRODUCTION

Chronic obstructive pulmonary disease (COPD) is characterized by limited airflow and chronic airway inflammation, along with anxiety and depression. Approximately 20%-50%^{1,2} of patients have malnutrition, atrophy, and loss of muscle groups in the diaphragm or limbs. It leads to pulmonary ventilation and cough expectorant dysfunction, progressive dyspnea, fatigue, and poor exercise tolerance, which ultimately affects the quality of life and survival rate.³ According to the latest international guidelines,⁴ pulmonary rehabilitation (PR) could improve exercise ability (muscle strength and endurance), and cardio-pulmonary function, and reduce the number of acute exacerbations or readmission rates. PR is a comprehensive intervention performed after a thorough, holistic assessment of the patient, including but not limited to exercise training, education, and behavior change. Among them, upper and lower limb endurance and resistance exercise had been confirmed as grade A evidence.^{5,6}

Although high-intensity exercise is more conducive to functional improvement, it is less durable and less adherent than low-intensity exercise for the elderly.^{7,8} Further

more, Steiner⁹ stated that patients undergoing PR were often in negative energy expenditure, that is, the daily diet was not enough to meet the high metabolic needs of training, especially for malnourished patients with COPD. Oral nutritional supplements (ONS) could rectify the negative energy expenditure and maintain patients' weight.¹⁰⁻¹³ However, there is still no consensus on other benefits of ONS in PR because of the heterogeneity of previous studies.¹⁴

Whey protein contains leucine, an essential amino acid (EAA) known to increase insulin secretion and affect molecular regulation. It stimulates muscle protein synthesis through the mTOR pathway and is often recommend-

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Manuscript received 21 February 2023. Initial review completed 30 April 2023. Revision accepted 06 September 2023.
doi: 10.6133/apjcn.202312_32(4).0001

ed for sarcopenia patients. Daily whey protein is effective in correcting lean tissue loss in resistance training in the healthy elderly, menopausal women, or patients with sarcopenic obesity, and also in improving tolerance to training in patients with COPD.^{15,16} However, there are still no studies in China on the combination of whey protein and PR for COPD patients, only the effect of taking whey protein alone had been reported in China.¹⁷ We thus investigated the effect of whey protein complex during low-intensity endurance or resistance exercise on patient outcomes such as improvement of weight, muscle mass, and muscle strength.

METHODS

This randomized controlled trial was registered at clinicaltrials.gov (NCT04741373), and ethical approval was granted by the Medical Ethics Committee of Huadong Hospital Affiliated with Fudan University (acceptance number: 2020K204).

Patients

Patients with COPD were consecutively recruited from March to September 2021, and all subjects gave their informed consent. The target sample size (alpha 0.05, power 80%) was calculated based on weight change was about 1.5 kg from the study of Sugawara¹¹ and accounted for a 25% drop-out.

Of the 263 patients screened at the Fourth Rehabilitation Hospital, Huadong Hospital, Hongqiao Community Health Service Center, Zhoujiaqiao Community Health Service Center, and three nursing homes in Shanghai, a final total of 90 were enrolled according to the following inclusion criteria randomly. Participants were assigned to the low-intensity exercise group (n= 30, PR group), PR plus whey proteins group (n= 30, PRWP group), and a control group (n= 30). Patients of both intervention groups received inpatient rehabilitation at the Fourth Rehabilitation Hospital. Patient data about COPD history, smoking history, comorbidity, medication, oxygen absorption, blood oxygen saturation, heart rate, and blood pressure were recorded.

Inclusion criteria

1. Age > 60 years old.
2. Patients diagnosis: after inhaling the bronchodilator, the forced expiratory volume in 1 s (FEV1)/forced vital capacity (FVC) ratio was < 0.7 by spirometric testing (Jaeger MasterScreen, Germany).
3. Disease severity was evaluated according to the Global Initiative for Chronic Obstructive Lung Disease (GOLD) Guideline. And they were at moderate (predicted FEV1 50-79%) or severe (predicted FEV1 30-49%) levels.
4. Stable patients who 1) had been admitted less than twice in the past two years due to acute aggravation, 2) had no change of sputum or other respiratory symptoms, and 3) had no drug adjustment in nearly one month.
5. Patients could complete lung function, 6-min walking distance, and grip strength assessments. During the past year, patients had not been enrolled in any form of PR and had not taken any kind of ONS.
6. Patients agreed to participate in the trial and gave their

informed consent and had good compliance.

Exclusion criteria

1. Patients with heart disease (e.g., ischemic heart disease with a history of angina).
2. Patients with cognitive impairment, kidney failure, and malabsorption syndrome.
3. Patients who could not exercise or complete the testing program due to intermittent claudication caused by peripheral artery disease or osteoporosis.
4. Patients whose arterial SpO₂ oxygen saturation was < 88% were in a quiet state.
5. Patients who received systemic steroids.

Intervention protocol

Only those in the PRWP group received whey protein supplements enriched with leucine.

The patients in both intervention groups underwent 12-week supervised low-intensity exercise. All subjects received usual care including routine education brochures, and medication including anticholinergic, β 2-agonist, or bronchodilators such as LAMAs, LABAs, or ICS.

Low-intensity exercise program

Exercise training included aerobic, resistance, and respiratory training. Aerobic exercise mode was upper and lower limb linkage via equipment named MOTomed viva2 (Jiangsu Tianrui Medical Device Co., Ltd). According to the maximum oxygen intake from the cardiopulmonary exercise test, the exercise intensity range was low to moderate, and the exercise duration was 20 min, 4 times/week. After a 10-minute warm-up, electrocardiogram (ECG), and oxygen saturation were monitored simultaneously during exercises. If oxygen saturation was < 85%, blood pressure > 200/100 mmHg, or heart rate reached 85% of the maximum heart rate, and training was stopped.

Before resistance training, a rehabilitation therapist tested the single repeated maximum load (1RM) and guided the correct use of weight-bearing tools (range 1-10 kg). The load was gradually increased to 70-85% of 1RM. The upper limb was exercised 4 times/week using a dumbbell, and 5 sets of movements each time. Respiratory training was processed 6 times/ week including lip contraction and abdominal breathing. About a 10-min break was allowed between the two training methods each time.

Oral nutritional supplement (ONS)

The ONS was a packet of powder containing 10g of whey protein with 0.2g leucine and 0.2g beta-hydroxy-beta-methylbutyrate (HMB) (Beijing Qiwang Nutrition Technology Co., Ltd).

HMB is an intermediate metabolite of leucine which plays an anabolic role in muscle, where it acts as a signaling molecule to stimulate protein synthesis. It reduces proteasome expression and proteasome enzyme activity, thereby reducing myocyte death. Patients in the PRWP group consumed ONS twice a day. They also were encouraged to eat the daily meals provided by the hospital.

Education

Hospitalized patients in all groups received health education brochures that emphasized correct methods of medication intake, oxygen absorption, self-assessment of nutritional status, diet, and a video about respiratory exercises. The PR and control groups did not have extra activities and ONS outside of the intervention as a result of health education under the supervision of medical staff.

Outcome assessments

Exercise capacity

Isometric handgrip strength (HGS) was measured using a handgrip dynamometer (Jamar® Hand Evaluation, USA) to represent upper limb muscle strength. Strength was measured twice in each hand, and the mean values were used. Meanwhile, 6 min walking distance (6MWD) was measured in a corridor to represent muscular endurance.¹⁸

Mental health status

The Chinese version of the Hospital Anxiety and Depression Scale (HADS) translated by Ye¹⁹ had good reliability and validity²⁰ and was used in our study. It comprised 14 items to evaluate anxiety and depression symptoms, with a score ≥ 8 denoting anxiety and depression.

Pulmonary function

Post-bronchodilator FEV1, FVC, maximal inspiratory pressure (P_Imax, which represents inspiratory muscle strength), and maximal expiratory pressure (P_Emax, which represents expiratory muscle strength) were assessed by standardized COPD diagnosis equipment (Jaeger MasterScreen, Germany), to evaluate lung function grade and respiratory muscle forces. Dyspnea at rest was evaluated by Medical Research Council Dyspnea Scale (MRC)²¹ and the cough sputum was assessed by COPD assessment test (CAT) score.²² The Global Initiative for Chronic Obstructive Lung Disease (GOLD) assessment consisted of the number of lung infections, MRC, and CAT scores.

Energy intake and body composition

Patients were asked to register their food intakes over 3 consecutive days at baseline. The information was analyzed by computer nutrient software (ver2.05 on DRIs 2018, SY, UIC, Shanghai, China). First, height and body weight (BW) were measured with the shoes off and light clothing using digital scales (Inbody BSM370, Korea), and body mass index BMI (kg/m²) was calculated automatically. Body composition including fat-free mass (FFM), fat mass (FM), and appendicular skeletal muscle mass (ASM) was measured using multi-frequency bioelectrical impedance analyzers²³ (Inbody S10, Korea) on an empty stomach in the early morning when no exercise was done, in a sitting position. Finally, the indexes of FMI(FM(kg)/height(m)²), FFMI(FFM(kg)/ height(m)²), and ASMI(ASM(kg)/height(m)²) were calculated.

Statistical analyses

Results were presented as mean \pm standard error ($X \pm SE$), median and interquartile range (IQR) (25-75th percentile). Intra-group changes were analyzed by paired

samples T-test for continuous normally-distributed data, or Wilcoxon rank-sum test for continuous non-normally distributed data. Among the three groups, parametric data were compared by one-way ANOVA-, and nonparametric data were compared by the Kruskal-Wallis H test taking the difference between the baseline and end of the test as a compare factor. Bonferroni tests were used to compare the two groups. Two-sided p -values < 0.05 were considered statistically significant. SPSS 24.0 for Windows (IBM Statistics SPSS, Chicago, IL, USA) was used for statistical analysis.

RESULTS

Baseline characteristics of patients

Mean age 82.5 years, height 162.8 cm, BMI 22.8 kg/m², FFMI 14.8 kg/m², FFMI was lower than normal in about 78.5% of cases (based on less than 18 kg/m² for males and less than 15 kg/m² for female).²⁴ Pulmonary function grade was moderate (69.1%) and patients in group D (GOLD subgroup) accounted for about 75%. Patients all received hospital-supplied meals and ate essentially the same amount of energy and protein on PR and non-PR days. Data from food intakes over 3 consecutive days showed that the actual baseline energy intakes for the three groups were 1599.8 kcal, 1626.5 kcal, and 1603.9 kcal while protein intakes were 62.9 g, 65.6 g, and 63.8 g respectively.

Indicators, such as age, gender, history of COPD, smoking history, type of comorbidity, oxygen flow, oxygen saturation, pulmonary function grade, and GOLD subgroup, were not significantly different at baseline. But there were differences in weight, BMI, FMI, P_Imax, and P_Emax among the three groups at baseline (Table 1). To avoid bias from baseline data, differences before and after the intervention was used for comparison among the three groups.

Outcome assessment

During the trial, the drop-out rate in the PRWP, PR, and control groups was 10%, 3.3%, and 6.6% respectively because of death and other side effects. All other patients had good compliance. Mean whey protein intake reached 1.89 ± 0.2 bags/day, and just 3 subjects reported side effects including stomachache, nausea, and diarrhea. A patient flowchart was shown in Figure 1. Mean changes after the interventions in PRWP, PR, and the control groups were shown in Table 2.

Exercise capacity

HGS ($+1.4 \pm 0.5$ kg, and $+1.1 \pm 0.6$ kg, $p < 0.05$) were significantly increased in both the PRWP and PR groups after the intervention, resulting in the improvement of HGS in both intervention groups when compared with the controls ($+1.4 \pm 0.6$ kg, and $+1.0 \pm 0.2$ kg, $p < 0.05$). Meanwhile, 6MWD improved from baseline in the PRWP group ($+16.1 \pm 3.6$ m, $p < 0.01$), resulting in a significant difference compared to the controls ($+14.1 \pm 3.8$ m, $p < 0.05$) (Figure 2). P_Imax in the PRWP group and P_Emax in the PR group at 12 weeks both increased, but there was no difference among the three groups ($p > 0.05$) (Table 2).

Table 1. The study procedure

Parameters	Mean (SE)			<i>p</i>
	PRWP (n = 30)	PR (n = 30)	Control (n = 30)	
General				
Gender (M/F), n	13/14	15/14	10/18	NS
Age, years	80.5 (1.4)	81.1 (2.2)	85.9 (0.9)	NS
Height, cm	163 (1.7)	161 (1.8)	162 (1.5)	NS
Weight, kg	57.9 (1.7)	64.8 (2.3)	58.6 (1.8)	0.035**
COPD history, year	9.6 (1.5)	7.8 (1.3)	6.7 (0.3)	NS
Smoke history, pack-year	13.7 (3.4)	12.8 (3.2)	6.4 (2.4)	NS
Self-report co-morbidities, n [†]	2 (1)	1 (2)	1 (0)	NS
Dietary intake				
Energy intake, kcal	1599 (57.3)	1626 (54.4)	1603 (51.9)	NS
Protein intake, g	62.9 (2.4)	65.6 (2.3)	63.8 (2.9)	NS
Lung function and symptom scores				
FEV ₁ , L, % predicted**	71.7 (1.4)	67.2 (2.3)	68.6 (1.2)	NS
FEV ₁ /FVC, %	63.3 (4.1)	61.8 (5.6)	62.4 (4.8)	NS
Frequency of acute exacerbation [†]	1 (2)	1 (1)	1 (1)	NS
MRC dyspnea scale	2.1 (0.1)	2.1 (0.2)	2.5 (0.2)	NS
CAT	17.0 (0.8)	17.9 (1.0)	16.6 (0.6)	NS
GOLD groups, A: B: C: D	0:10:0:17	2:6:0:21	0:10:0:18	NS
Nutritional and emotional status				
MNA-SF	7.2 (0.5)	7.2 (0.4)	11.7 (0.2)	0.0001**
Serum Albumin, g/L	37.9 (0.7)	37.7 (0.7)	36.5 (0.7)	NS
HADS-Anxiety	6.4 (0.5)	7.6 (0.4)	7.7 (0.4)	NS
HADS-Depression	12.2 (0.7)	13.3 (0.7)	13.4 (0.8)	NS
Muscle strength				
HGS, kg	14.3 (1.3)	13.4 (1.9)	15.1 (1.0)	NS
6MWD, m	138 (8.1)	135 (8.0)	166 (12.5)	NS
PI _{max} , cmH ₂ O [†]	33 (10)	32 (16)	51 (19)	0.003*
PE _{max} , cmH ₂ O [†]	40 (11)	37 (18)	67.5 (28)	0.004*
Body composition				
BMI, kg/m ²	21.6 (0.6)	24.6 (0.7)	22.1 (0.6)	0.003**
FMI, kg/m ²	7.4 (0.5)	9.7 (0.5)	7.6 (0.7)	0.013**
FFMI, kg/m ²	14.2 (0.3)	14.9 (0.5)	15.2 (0.4)	NS
ASMI, kg/m ²	6.1 (0.2)	5.9 (0.3)	6.4 (0.4)	NS

MNA-SF, Mini Nutritional Assessment-Short Form; HADS, Hospital Anxiety and Depression; FEV₁, forced expiratory volume in 1s; FVC, forced vital capacity; MRC, Medical Research Council; CAT, COPD assessment test; BMI, body mass index; FMI, fat mass index; FFMI, fat-free mass index; ASMI, appendicular skeletal muscle index; HGS, hand grip strength; 6MWD, 6 min walking distance; PI_{max}, maximum inspiratory mouth pressure; PE_{max}, maximum expiratory mouth pressure.

[†]Median (IQR) values, using Kruskal-Wallis H test, and **p*<0.05; the rest were normal data, using One-way ANCOVA, and ***p*<0.05

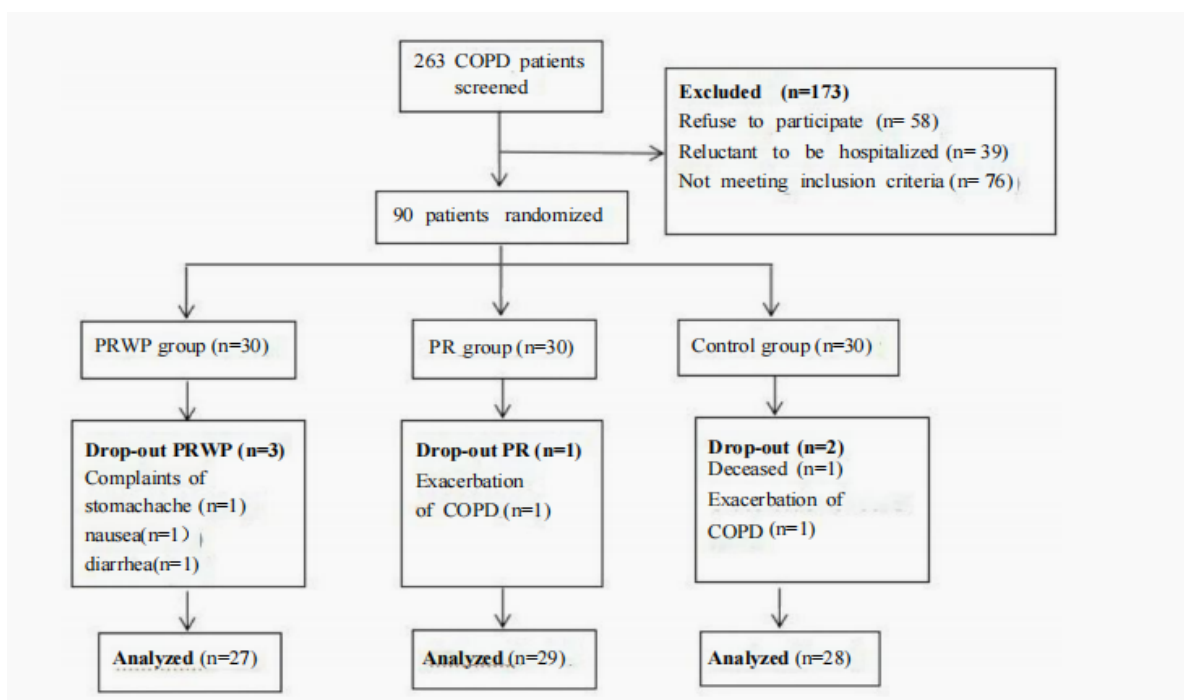
**Figure 1.** Patients flow diagram based on completion of body composition testing

Table 2. Outcome of the intervention

Parameters	PRWP (n=27)			PR (n=29)			Control (n=28)			Among group differences <i>p</i> -value
	Pre	Post	ΔPre-post	Pre	Post	ΔPre-post	Pre	Post	ΔPre-post	
Muscle strength and endurance										
HGS, kg	14.3 (1.4)	15.8 (1.4)**	1.4 (0.5)	13.4 (1.5)	14.5 (1.9)*	1.1 (0.6)	15.1 (1.1)	15.2 (1.1)	-0.02 (0.2)	0.031
6MWD, m	139 (8.6)	155 (8.3)**	16.1 (3.6)	135 (8.2)	140 (9.5)	4.9 (4.3)	167 (11.0)	168 (12.7)	1.9 (2.2)	0.023
PI _{max} , cmH ₂ O [†]	33 (10)	34 (10)*	1 (4)	32 (16)	33 (20)	1 (3)	51 (19)	52.5 (19)*	2 (4)	0.52
PE _{max} , cmH ₂ O [†]	40 (11)	43 (10)	2 (5)	37 (18)	38 (26)*	2 (5)	67.5 (28)	68.5 (32)	2 (6)	0.85
Mental health status										
HADS-A	6.4 (0.5)	6.4 (0.4)	-0.04 (0.3)	7.6 (0.4)	8.5 (0.3)**	0.9 (0.3)	7.6 (0.4)	7.8 (0.4)	0.2 (0.2)	0.022
HADS-D	12.2 (0.8)	11.8 (0.9)	-0.4 (0.7)	13.3 (0.7)	13.0 (0.7)	0.3 (0.03)	13.4 (0.8)	12.9 (0.8)	-0.4 (0.4)	0.865
Lung function and symptom scores										
%FEV ₁ , pred	71.7 (1.4)	71.9 (1.4)	0.3 (0.5)	67.2 (2.3)	66.8 (2.3)	0.4 (0.6)	68.6 (1.2)	67.5 (1.2)*	-1.1 (0.5)	0.242
MRC	2.1 (0.2)	1.8 (0.2)	-0.3 (0.1)*	2.1 (0.2)	2.3(0.2)	0.2(0.1)	2.5 (0.2)	2.5 (0.1)	0.04 (0.05)	0.003
CAT scores	17.0 (0.8)	16.4 (1.1)	-0.7 (0.7)	17.9 (1.0)	17.9 (1.0)	0.0 (0.35)	16.6 (0.6)	18.0 (0.9)	1.4 (0.9)	0.009
Body composition										
Weight, kg	57.9 (1.8)	59.2 (1.8)	1.2 (0.7)	64.8 (2.3)	63.5 (2.1)	-1.4 (0.7)	58.6 (1.9)	58.4 (1.9)	-0.1 (0.2)	0.03
BMI, kg/m ²	21.6 (0.7)	22.1 (0.6)	0.5 (0.3)	24.6 (0.7)	24.1 (0.6)	-0.5 (0.3)	22.1 (0.6)	22.1 (0.6)	-0.05 (0.07)	0.051
FMI, kg/m ²	7.4 (0.6)	8.3 (0.6)	0.9 (0.5)	9.7 (0.5)	8.9 (0.7)	-0.8 (0.5)	7.6 (0.7)	7.3 (0.7)	-0.3 (0.9)	0.137
FFMI, kg/m ²	14.2 (0.3)	13.7 (0.4)	-0.5 (0.4)	14.9 (0.5)	15.3 (0.6)	0.4 (0.4)	15.2 (0.4)	14.8 (0.6)	-0.4 (0.7)	0.419
ASMI, kg/m ²	6.1 (0.3)	5.6 (0.2)	-0.1 (0.3)	5.9 (0.3)	6.4 (0.3)*	0.5 (0.05)	6.4 (0.5)	6.1 (0.3)	-0.3 (0.5)	0.153

HADS, Hospital Anxiety and Depression; FEV₁, forced expiratory volume in 1s; MRC, Medical Research Council; HGS, hand grip strength; 6MWD, 6 min walking distance; PI_{max}, maximum inspiratory mouth pressure; PE_{max}, maximum expiratory mouth pressure; CAT, COPD assessment test; BMI, body mass index; FMI, fat mass index; FFMI, fat-free mass index; ASMI, appendicular skeletal muscle index

[†]Median (IQR) values, and within group changes compared using Wilcoxon signed ranks test, among group differences compared using Kruskal-Wallis test. and Bonferroni tests were further used for comparing the differences between the two groups.

p*< 0.05, *p*< 0.01.

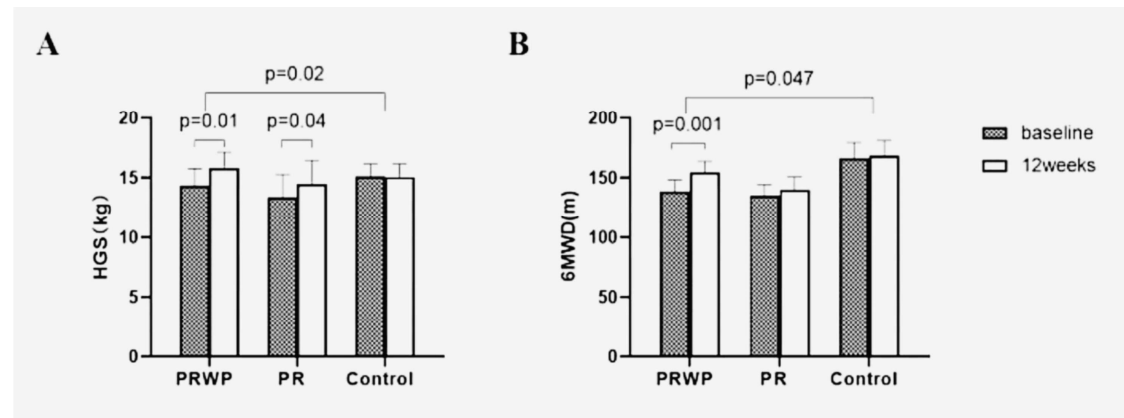


Figure 2. Mean baseline and 12 weeks values of A: Handgrip strengths (HGS); B: 6 min walking distance (6MWD). Data are presented as mean (SE). Within group changes were tested with the paired t test, between groups by linear regression (*p*<0.05).

Mental health status

At baseline, eight (26.6%) patients had anxiety, and twenty-five (83.3%) patients were depressive in the PRWP group, whereas seventeen (56.6%) patients had anxiety, and twenty-seven (90%) patients were depressive in the PR group. After the intervention, anxiety scores remained unchanged in the PRWP group but worsen in the PR group (0.9 ± 0.3 , $p = 0.01$). So anxiety was significantly improved in the PRWP group compared to the PR group (-1.2 ± 0.4 , $p < 0.01$). There was no statistically significant change in depression in any of the three groups before and after the intervention ($p > 0.05$).

Pulmonary function

In the PRWP group, the MRC score (dyspnea) decreased after intervention (-0.3 ± 0.1 , $p < 0.05$), so MRC and CAT scores (cough, sputum) were statistically improved (-0.2 ± 0.1 , and -2.1 ± 1.2 , $p < 0.05$) when compared with that of the PR group. There were also differences in the GOLD groupings determined by the frequency of respiratory infections, MRC, and CAT scores: 11 patients in the PRWP group changed from GOLD D to B, and 18 patients in the PR group. This resulted in a significant improvement compared to the control group ($p < 0.05$). There was no statistically significant difference in pulmonary function classification among the three groups ($p > 0.05$).

Body composition

From baseline to the end of the trial, BW (-1.4 ± 0.7 kg, $p = 0.054$) and FMI (-0.8 ± 0.5 kg, $p = 0.08$) had a decreased tendency in the PR group whereas BW ($+1.2 \pm 0.7$ kg, $p = 0.09$) and FMI ($+0.9 \pm 0.5$ kg, $p = 0.07$) had an increased tendency in PRWP group. These resulted in an improvement of BW ($+2.0 \pm 0.8$ kg, $p < 0.05$) in the PRWP group, compared with the PR group (Figure 3). There were no significant inter-group differences in FFMI and ASMI (Table 2).

DISCUSSION

High-intensity exercise, despite its ability to improve exercise capacity, cardiopulmonary function, and quality of life, is difficult to adhere to over the long term, limiting both the target subjects (hospitalized patients in the acute infection phase) and the duration of benefit (9-12 months).^{28,29} The reason might be the negative energy

expenditure caused by high-intensity exercise. Low-intensity exercise, which not only can have similar efficacy³⁰ to high-intensity, but also with better compliance and sustainability, is becoming a PR modality to change the daily activity patterns of patients, especially the elderly.³¹ In our trial, the benefit was only one person dropping out of the test and an increase in grip strength.

In addition to low-intensity PR, lots of studies investigated the influence of ONS during PR. The types of ONS were being explored, ranging from energy-only to those containing the functional ingredient Vit D-3, n-3 unsaturated fatty acids. The current consensus was weight gain, but the other outcomes such as lean tissue, muscle strength, or muscular endurance remain controversial.¹⁰⁻¹³ Whey protein and its functional components were used and improvement in both HGS (representing muscle strength) and 6MWD (representing muscular endurance) were observed in our study. The outcomes coincided with previous literature. Deutz's²⁶ found that supplementation with a high-protein oral nutritional supplement (ONS) containing HMB (HP-HMB) was associated with improved handgrip strength, and the body weight of malnourished, hospitalized patients with COPD. Lavolette¹⁶ stated pressurized whey supplementation, by its antioxidant and nutritional properties, may improve exercise tolerance and potentiate the effects of exercise training in patients with COPD. A significant increase in 6MWD was a marker for maintenance of daily activity after PR and distance differences greater than 30-50 m were highly correlated with 5-year survival.⁷

In addition to that, the improvement in dyspnea and anxiety in the PRWP group compared to the PR group was also similar to the previous findings. Korkmaz²⁷ showed that nutritional support with integrated PR significantly improved physical performance, dyspnea, and body composition in COPD patients. Jaatinen³² found that intake of yogurt enriched with a-lac, casein tripeptides may contribute beneficially to stress coping in stress-prone but healthy subjects. Its mechanism might be as follows: Individuals with high trait anxiety were characterized by functional shortages of 5-hydroxytryptophan (5-HT) during stress, which is a neurotransmitter that regulates mood, appetite, behavior, and sleep. Whereas tryptophan is a precursor to 5-HT, whey proteins that provide high tryptophan concentrations may bring benefits by modulating the body's acute stress response.^{33,34}

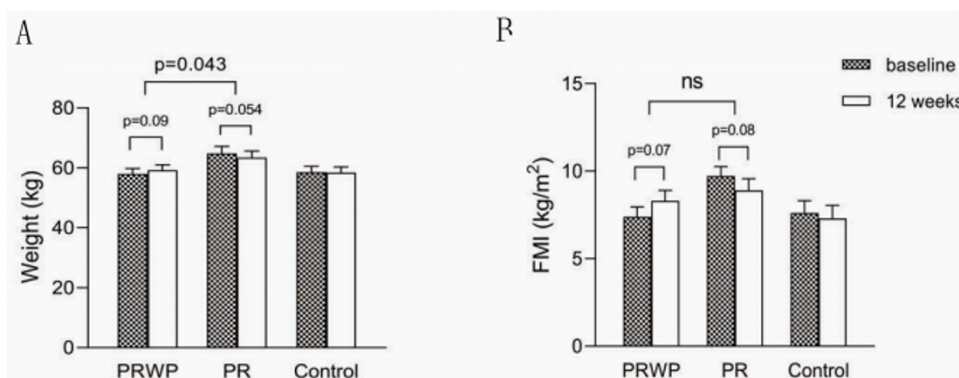


Figure 3. Mean baseline and 12 weeks values of A: Weight; B: Fat Mass Index (FMI). Data are presented as mean (SE). Within group-changes were tested with the paired t test, between groups by linear regression ($p < 0.05$).

Finally, changes in weight and FMI in the PRWP group were mentioned at the time of this trial, the weight gain in the PRWP group was caused by a rise in fat mass within the group, where the cause could be the supplement itself, or the supplement might promote appetite. Unfortunately, no difference in muscle mass gain between groups was observed. Depletion of muscle tissue was also considered an independent risk factor for a poor COPD prognosis and was positively associated with higher mortality. Muscle consumption was caused not only by an energy imbalance, but also by protein metabolism disorders due to muscle disuse, hypoxia, or drugs. Constantin³⁵ stated that protein supplementation after exercise in COPD patients was unresponsive to candidate genes and proteins regulating muscle protein breakdown and synthesis. Recent literature stated that antioxidant and anti-inflammatory markers inhibited muscle catabolism through functional component supplements, such as n-3PUFA, vitamin C, and creatine,^{11,25} which later experiments could focus on.

Limitations

Some limitations of our study were the small sample size and the lack of a non-nutritional placebo for the PR group. Adequate COPD clinical trials are needed to explore nutritional strategies to maintain the effect of exercise training after PR.

Conclusions

HGS improved in both intervention groups while 6MWD improved only in the PRWP group. Furthermore, the combination of whey proteins complex and exercise improved dyspnea, a symptom of cough, anxiety, and body weight loss caused by PR in stable elderly patients with COPD. In summary, whey protein complex combined with low-intensity exercise had good compliance in elderly patients to improve muscle function and pulmonary symptoms.

ACKNOWLEDGEMENTS

We would like to thank Shaowu Wang, and Ling Mao for assistance with supervising the resistance training, Yiru Zhao for assistance with dietary assessment, and Huili Zhu, Yinan Zhou, Weiping Jiang for counseling on the respiratory knowledge. Also we would like to thank Rufeng Jin for statistical knowledge guidance.

CONFLICT OF INTEREST AND FUNDING DISCLOSURE

The authors have declared that no competing interests exist. Shanghai Municipal Health System Important and Weak Discipline Project (Clinical Nutrition) whose funding number was No.2019ZB0102.

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