Pulmonary rehabilitation outcome in chronic obstructive pulmonary disease patients with a different body composition

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Context Change in body composition is commonly present in chronic obstructive pulmonary disease (COPD) patients.

Aim The aim of this study was to investigate the effects of pulmonary rehabilitation program (PRP) on COPD patients who have a different body composition.

Materials and methods In this study, we measure;Deg;BM;Deg;I and fat-free mass index (FFMI) using a single-frequency bioelectrical impedance analysis apparatus to classify patients into three categories: Group 1 nonmuscle depleted;Deg;BM;Deg;I greater than or equal to 21 kg/m^2 and FFMI greater than or equal to 16. Group 2 muscle depleted;Deg;BM;Deg;I greater than or equal to 21 kg/m^2 and FFMI less than 16 in men or FFMI less than 15 in women. Group 3 muscle depleted with cachexia;Deg;BM;Deg;I less than 21 kg/m^2 and FFMI less than 16 in men or FFMI less than 15 in women. PRP outcomes were assessed by the improvement in pulmonary function severity, exercise capacity by 6-min walk test, dyspnea score by modified-British Medical Research Council, and health status by combined assessment test score and arterial blood gas improvements.

Results Forty-four patients with FFMI were measured by bioelectrical impedance analysis. The patients were mainly elderly men (*N*=35; 79%), who have a mean age of 65 years with different global initiative obstructive lung disease stage I–IV. In the nonmuscle depleted group, there were statistically significant improvements in the mean values of FFMI (kg/m^2) while in the muscle depleted group there were improvements as regards the mean values of dyspnea score by modified-British Medical Research Council; in the cachectic group there were statistically significant improvements in the mean values of BMI (kg/m^2), forced expiratory volume in the first second (FEV_1), forced expiratory volume in first second divided by forced vital capacity ratio, combined assessment test score after PRP.

Conclusions A comprehensive PRP outcome change in COPD patients with different body compositions.
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Introduction

Chronic obstructive pulmonary disease (COPD) is a common, preventable, and treatable disease that is characterized by respiratory symptoms and airflow limitation that is due to airway and/or alveolar abnormalities usually caused by significant exposure to noxious particles or gases [1].

Measurement of BMI may not accurately reflect changes in body composition in COPD. Body weight consists of fat mass and fat-free mass (FFM), which includes water and body cell mass (bones, internal organs, muscle). Measurement of body cell mass can be performed by measurement of fat-free mass index (FFMI) [2]. COPD patients have concomitant chronic diseases linked to the same risk factors, that is, aging, smoking, and inactivity, which may have a great impact on health status and survival in those patients. Skeletal muscle dysfunction is characterized by sarcopenia (loss of muscle cells) and abnormal function of the cells [3]. Inflammatory mediators may contribute to skeletal muscle wasting and cachexia. The association between low body cell mass and worsening prognosis is a common observation in COPD patients [4].

Cachexia and muscle depletion are characterized by FFM depletion, which can be estimated using skinfold anthropometric measurement and bioelectrical impedance analysis (BIA) [5]. FFM measurement by BIA is easy to perform and has shown significant correlations to reference measurements methods such as magnetic resonance imaging [6].

Pulmonary rehabilitation is a comprehensive intervention including exercise, nutritional counselling, psychological counselling, and education about the disease nature, progression, prevention of exacerbation, and breathing exercises, which lead to improvement in clinical outcomes such as quality of life, dyspnea score, and exercise capacity [7].

Thus, the aim of this study was to assess pulmonary rehabilitation outcome on COPD patients with different body compositions.

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Materials and methods

Materials

A retrospective, randomized, controlled study in the period from June 2016 to October 2018 .The study protocol was reviewed by the appropriate Ethics Committee, from Faculty of Medicine, Beni Suef University. All patients gave their informed, written consent before study inclusion.

The study population consists of 44 patients with a clinical diagnosis of COPD and confirmed by doing pulmonary function tests they were chosen from the Outpatient Clinic of Chest Diseases Department, at Faculty of Medicine, Beni-Suef University

Inclusion criteria

Diagnosis of COPD patients was established by full clinical history and examination, history of cigarette or shisha smoking or history of indoor biomass fuel exposure, and spirometric measurements that demonstrated irreversible airflow obstruction. All patients were required to fulfill the criteria of COPD according to latest global initiative obstructive lung disease (GOLD) 2019 classification. Patients must have had at least 3 months of smoking cessation.

Exclusion criteria

Patients with acute exacerbation; patients with acute respiratory failure; and patients with joint, muscle, and neurological disorders unable to do pulmonary rehabilitation exercises; patients with cardiac failure class III or IV NYHA, neoplastic disease, and hyperthyroidism were excluded, as these can be causes of weight loss. Patients who had contraindications for BIA measurement, such as those with defibrillator placement or pacemakers, were excluded from the study.

Study design

Patients were classified by body composition into three different groups based on BMI and FFM depletion:

(1) Group 1: nonmuscle depleted BMI greater than or equal to 21 kg/m^2 and FFMI greater than or equal to 16.
(2) Group 2: muscle depleted BMI greater than or equal to 21 kg/m^2 and FFMI less than 16 in men or FFMI less than 15 in women.
(3) Group 3: muscle depleted with cachexia BMI less than 21 kg/m^2 and FFMI less than 16 in men or FFMI less than 15 in women.

Study outcome

All tests were performed before and after pulmonary rehabilitation program:

(1) Assessment of exercise capacity by 6-min walk test (6MWT) [8].
(2) Assessment of symptoms by the Modified British Medical Research Council Questionnaire (mMRC) [9].
(3) Assessment of health status impairment in COPD by combined assessment test (CAT) score. which is an eight-item test [10].
(4) Arterial blood gas measurements where PO_2, PCO_2, and SpO_2 were measured [11].

Assessment of functional severity by spirometry [12].

This was performed by MasterScreen PFT. No.781040, where forced expiratory volume in the first second (FEV_1), forced vital capacity (FVC), and FEV_1–FVC were measured:

(1) Stage I: mild FEV_1/FVC less than 0.70 FEV_1 greater than or equal to 80% predicted.
(2) Stage II: moderate FEV_1/FVC less than 0.70 50% less than or equal to FEV_1 less than 80% predicted.
(3) Stage III: severe FEV_1/FVC less than 0.70 30% less than or equal to FEV_1 less than 50% predicted.
(4) Stage IV: very severe FEV_1/FVC less than 0.70 FEV_1 less than 30% predicted or FEV_1 less than 50% predicted plus chronic respiratory failure.

Methods

Pulmonary rehabilitation program

The pulmonary rehabilitation program (PRP) consists of a 1 h session three times a week for a 8-week period. Patients underwent strengthening, endurance exercise, and respiratory muscle exercises. They exercised on a treadmill and on a cycle ergometer. They also performed light floor exercises with and without weights and stretching exercises as per ATS guidelines for pulmonary rehabilitation [2].

BMI measurement is calculated by dividing the weight in kilograms by height in meters squared. FFMI measurement: The bioelectrical impedance technique is a reliable and valid approach for estimation of human body composition. This method is safe, noninvasive, and provides rapid measurements. The procedure involves sending a very small current of 800 μA at an alternating frequency of 50 kHz through the body and measuring its resistance. We used Body Fat Analyzer BT 905 (BIA BT-905) (Skylark Device Co., Taipei, Taiwan). Both instruments required electrode placements at specific sites on the wrist, distal second metacarpal, ankle, and distal second metatarsal. Therefore, ‘whole-body’ BIA was measured. FFMI is measured by dividing the FFM in kilograms by height in meters squared.

Statistical analysis

The statistical analysis was performed using SPSS 19 (SPSS, Chicago, IL, USA). Results are presented as the mean±SD, and proportional data are presented as percentages. Groups were compared using one-way analysis of variance. Two groups were compared using the independent samples *t*-test. Relevant indicators of COPD were correlated using Spearman's correlation or Pearson's correlation analysis.

A *P* value of less than 0.05 was considered statistically significant.

Results

This study was done on 44 COPD patients. The age of the patients ranged from 52 to 78 years with a mean age of 65 years. Of the patients 35 (79%) were men and nine (20%) were women. Clinical characteristics of the studied patients with different stages of COPD according to GOLD classification and 11 patients were nonmuscle depleted with a BMI more than or equal to 21 kg/m^2 and FFMI greater than or equal to 16 and 16 patients with muscle depleted BMI greater than or equal to 21 kg/m^2 and FFMI less than 16 and 17 patients with cachexia BMI less than 21 kg/m^2 and FFMI less than 16. The groups were well balanced in terms of comorbidities and age as in Table 1. Also, the sample size was determined according to the duration of the study.

In the nonmuscle depleted group, there were statistically significant differences as regards the mean values of FFMI (kg/m^2) mean±SD (64±22) to be mean±SD (68.10±15.10) after PRP but there were improvements regarding other variables but nonstatistically significant differences as shown in Table 2. In the muscle depleted group, there were statistically significant differences as regards the mean values of dyspnea score by mMRC mean±SD (2.93±1.1) to be mean±SD (2.37±0.78), but there were improvements regarding other variables but nonstatistically significant differences as given in Table 3. In the cachectic group, there were statistically significant differences as regards the mean values of BMI (kg/m^2) mean±SD (19.06±2.6) to be mean±SD (24.67 ±5.06), FEV_1 mean±SD (28.10±10.52) to be mean±SD (40.39±13.8), FEV_1/FVC mean±SD (42.56±15.97) to be mean±SD (48.85±14.63), CAT score mean±SD (12.56±5.28) to be mean±SD (18.31±6.63), but there were improvements regarding other variables but nonstatistically significant differences as in Table 4.

Table 1 Clinical characteristic of the patients

	Total (*n*=44) [*n* (%)]
GOLD	
Stage 1	4 (9.1)
Stage 2	8 (18.2)
Stage 3	12 (27.3)
Stage 4	20 (45.5)
BMI (kg/m^2) and FFMI (kg/m^2)	
Nonmuscle depleted	11 (25.0)
Muscle depleted	16 (36.4)
Cachexia	17 (38.6)

FFMI, fat-free mass index; GOLD, Global Initiative for Chronic Obstructive Lung Disease.

Table 2 Statistical comparison between different variables in the nonmuscle depleted group before and after pulmonary rehabilitation program

	Before PRP (mean±SD)	After PRP (mean±SD)	*P* value
Mean BMI (kg/m^2)	27.00±4.450	25.45±4.180	0.424
Mean FFMI (kg/m^2)	19.32±1.9	18.73±3.069	0.020
Mean PO_2	51.94±11.5	64.68±7.3	0.640
Mean PCO_2	44.32±7.5	40.82±5.27	0.071
Mean SpO_2	92.93±2.0	96.27±1.6	0.884
Mean FEV_1	64.2±22.9	68.10±15.10	0.070
Mean FEV_1/FVC	49.04±15.93	53.28±13.49	0.563
Mean 6MWT	291.82±88.6	326.82±58.13	0.757
Dyspnea (mMRC)	2.18±1.07	1.54±0.54	0.720
CAT score	24.45±8.8	27.09±5.5	0.995

6MWT, 6-min walk test; CAT, COPD assessment test; FEV_1, forced expiratory volume in the first second; FFMI, fat-free mass index; FVC, forced vital capacity; mMRC, Modified British Medical Research Council; PCO_2, arterial partial pressure of carbon dioxide; PO_2, arterial partial pressure of oxygen; SpO_2, oxygen saturation.

Comparison between nonmuscle depleted, muscle depleted, and cachectic group before PRP showed statistically significant difference as regards the mean values of BMI (kg/m^2), FFMI (kg/m^2), SpO_2, FEV_1, dyspnea (mMRC), CAT score as in Table 5, while after PRP there were statistically significant differences as regards the mean values of PCO_2, FEV_1, dyspnea (mMRC), and CAT score as in Table 6.

Regarding FFMI as the lowest mean values in the cachectic group 28±10 to be 40.39±13.81 after PRP, followed by the muscle depleted group 38±14 to be 47.87±13.60 after PRP and the highest value was in the nonmuscle depleted group 64±22 which was also found to be 68.10±15.10 after PRP, with statistically significant difference between them before PRP but nonsignificant after PRP.

In this study, the lowest mean values of FEV_1 found in the cachectic group 28±10 to be 40.39±13.81 after PRP, followed by the muscle depleted group 38±14

Table 3 Statistical comparison between different variables in the muscle-depleted group before and after pulmonary rehabilitation program

	Before PRP (mean±SD)	After PRP (mean±SD)	*P* value
Mean BMI (kg/m^2)	28.73±4.2	25.87±5.4	0.414
Mean FFMI (kg/m^2)	14.57±.75	15.20±1.897	0.527
Mean PO_2	48.68±10	63.9±11.1	0.421
Mean PCO_2	44.72±4.5	42.68±5.8	0.058
Mean SpO_2	93.25±3.3	94.87±2.4	0.153
Mean FEV_1	38.0±14.9	47.8±13.6	0.072
Mean FEV_1/FVC	45.54±14.71	51.07±12.90	0.165
Mean 6MWT	229.13±70.9	291.50±68.9	0.213
Dyspnea (mMRC)	2.93±1.1	2.37±0.78	0.024
CAT score	11.93±6.0	17.12±6.9	0.711

6MWT, 6-min walk test; CAT, COPD assessment test; FEV_1, forced expiratory volume in the first second; FFMI, fat-free mass index; FVC, forced vital capacity; mMRC, Modified British Medical Research Council; PCO_2, arterial partial pressure of carbon dioxide; PO_2, arterial partial pressure of oxygen; PRP, pulmonary rehabilitation program; SpO_2, oxygen saturation.

Table 4 Statistical Comparison between different variables in the muscle depleted group with cachexia before and after pulmonary rehabilitation program

	Before PRP (mean±SD)	After PRP (mean±SD)	*P* value
Mean BMI (kg/m^2)	19.06±2.6	24.67±5.06	0.023
Mean FFMI (kg/m^2)	13.75±1.16	20.03±1.77	0.211
Mean PO_2	44.92±10.1	56.93±10.4	0.515
Mean PCO_2	47.85±6.1	46.45±5.02	0.720
Mean SpO_2	92.56±2.9	93.86±3.2	0.970
Mean FEV_1	28.10±10.52	40.39±13.8	0.001
Mean FEV_1/FVC	42.56±15.97	48.85±14.63	0.000
Mean 6MWT	223.83±74.20	270.25±89.92	0.926
Dyspnea (mMRC)	3.44±.616	2.37±1.02	0.526
CAT score	12.56±5.28	18.31±6.63	0.000

6MWT, 6-min walk test; CAT, COPD assessment test; FEV_1, forced expiratory volume in the first second; FFMI, fat-free mass index; FVC, forced vital capacity; mMRC, modified British Medical Research Council; PCO_2, arterial partial pressure of carbon dioxide; PO_2, arterial partial pressure of oxygen; PRP, pulmonary rehabilitation program; SpO_2, oxygen saturation.

to be 47.87±13.60 after PRP, and the highest value was in the nonmuscle depleted group 64±22 which was also found to be 68.10±15.10 after PRP. Regarding FEV_1/FVC the lowest mean values in the cachectic group 42.56±15.97 to be 48.85±14.63 after PRP followed by the muscle depleted group 45.54±14.71 to be 51.07 ±12.90 after PRP and the highest value was in the nonmuscle depleted group 49.04±15.93 and then 53.28 ±13.49 after PRP.

In the current study, the lowest mean values of PO_2 were found in the cachectic group 44.92±10.1 to be 56.93±10.4 after PRP followed by the muscle depleted group 48.68±10 and 63.9±11.1 after PRP and the highest value was in the nonmuscle depleted group 51.94±11.5 which was also found to be 64.68±7.3 after PRP. The highest mean values of PCO_2 found in the cachectic group were 47.85±6.1 and 46.45±5.02 after PRP, followed by the muscle depleted group 44.72±4.5 and 42.68±5.85 after PRP and the highest value was in the nonmuscle depleted group 44.32±7.5 to be 40.82 ±5.27 after PRP.

The lowest mean values of SpO_2 was found in the cachectic group 92.56±2.9 to be 93.86±3.2 after PRP, followed by the muscle depleted group 94.87±2.4 to be 93.25±3.3 after PRP and the highest value was in the nonmuscle depleted group 96.27±1.6 which was also found to be 92.93±2.0 after PRP; the lowest mean values of 6MWT found in the cachectic group were 223.83±74.2 and 270.25±89.9 after PRP, followed by the muscle depleted group 229.13±70.9 and 291.50 ±68.9 after PRP and the highest value was in the nonmuscle depleted group 291.82±88.6 to be 326.82 ±58.1 after PRP. The highest mean values of dyspnea (mMRC) was found in the cachectic group 3.44±.6 and 2.37±1 after PRP, followed by the muscle depleted group 2.93±1 to be 2.37±0.7 after PRP and the highest

Table 5 Statistical comparison between non-muscle depleted, muscle depleted, and cachectic group before pulmonary rehabilitation program

	Nonmuscle depleted (mean±SD)	Muscle depleted (mean±SD)	Cachectic (mean±SD)	*P* value
Mean BMI (kg/m^2)	27.00±4.4	28.73±4.2	19.06±2.6	0.000*
Mean FFMI (kg/m^2)	19.32±1.9	14.57±.75	13.75±1.16	0.000*
Mean PO_2	51.94±11.5	48.68±10	44.92±10.1	0.216
Mean PCO_2	44.32±7.5	44.72±4.5	47.85±6.1	0.216
Mean SpO_2	96.27±1.6	94.87±2.4	92.56±2.9	0.001*
Mean FEV_1	64.20±22.9	38.09±14.9	28.10±10.5	0.000*
Mean FEV_1/FVC	49.04±15.93	45.54±14.71	42.56±15.97	0.554
Mean 6MWT	291.82±88.6	229.13±70.9	223.83±74.2	0.060
Dyspnea (mMRC)	2.18±1	2.93±1	3.44±.6	0.004*
CAT score	24.45±8.8	11.93±6	12.56±5.2	0.000*

6MWT, 6-min walk test; CAT, COPD assessment test; FEV_1, forced expiratory volume in the first second; FFMI, fat-free mass index; FVC, forced vital capacity; mMRC, modified British Medical Research Council; PCO_2, arterial partial pressure of carbon dioxide; PO_2, arterial partial pressure of oxygen; SpO_2, oxygen saturation.

Table 6 Statistical comparison between non-muscle depleted, muscle depleted, and cachectic groups after pulmonary rehabilitation program

	Non-muscle depleted (mean±SD)	Muscle depleted (mean±SD)	Cachectic (mean±SD)	*P* value
Mean BMI (kg/m^2)	25.45±4.18	25.87±5.47	24.67±5.06	0.785
Mean FMI (kg/m^2)	18.73±3.069	15.20±1.897	20.38±1.77	0.487
Mean PO_2	64.68± 7.3	63.9±11.1	56.93±10.4	0.054
Mean PCO_2	40.82±5.27	42.68±5.85	46.45±5.02	0.015*
Mean SpO_2	92.93±2.0	93.25±3.3	93.86±3.2	0.665
Mean FEV_1	68.10±15.10	47.87±13.60	40.39±13.81	0.000*
Mean FEV_1/FVC	53.28±13.49	51.07±12.90	48.85±14.63	0.651
Mean 6MWT	326.82±58.1	291.50±68.9	270.25±89.9	0.090
Dyspnea (mMRC)	1.5471±.5	2.3753±.7	2.3750±1	0.005*
CAT score	27.09±5.5	17.12±6.9	18.3±6.6	0.000*

6MWT, 6-min walk test; CAT, COPD assessment test; FEV_1, forced expiratory volume in the first second; FFMI, fat-free mass index; FVC, forced vital capacity; mMRC, modified British Medical Research Council; PCO_2, arterial partial pressure of carbon dioxide; PO_2, arterial partial pressure of oxygen; SpO_2, oxygen saturation.

value was in the nonmuscle depleted group 2.18±1 to be 1.54±0.5 after PRP. The lowest mean values of CAT score found in the muscle depleted group were 11.93±6 and 17.12±6.9 after PRP, followed by the cachectic group to be 12.56±5.2 and 18.3±6.6 after PRP and the highest value was in the nonmuscle depleted group 24.45±8.8 and 27.09±5.5 after PRP.

Discussion

PRP improves the health status and exercise capacity in COPD patients with different body compositions, but there was significant improvement in functional severity and health status in COPD patients with muscle depleted with cachexia while dyspnea score improved significantly in patients with muscle depleted without cachexia but FFMI significantly increased in the non-muscle depleted COPD patients. FFMI significantly correlated with dyspnea, exercise capacity, pulmonary function, and respiratory muscle function and may be a predictor of COPD severity due to enhanced protein catabolism in COPD patients with muscle mass depletion [13]. Previous studies have reported that the muscle mass depletion subgroup, defined as BMI less than 21 kg/m^2 and FFMI less than 16 in men or FFMI less than 15 in women, was more prevalent in COPD GOLD stage IV more than patients in GOLD stages II and III [14]. So our results agree with the previous work as muscle depleted with cachexia group with BMI less than 21 kg/m^2 and FFMI less than 16 with a mean FEV_1 of 28.1±10.52 which means that most of them are in stage IV but there was statistically significant increase after PRP as the mean FEV_1 reaches 40.39±13.81 [15].

Weight loss was particularly prevalent in COPD patients and was closely correlated with exercise capacity limitation, increased frequency of exacerbations, and decreased quality of life and mortality. Improvements in exercise performance, and quality of life and skeletal muscle function after exercise training in COPD patients are well reported. However, the effect of PRP on COPD patients with different body compositions has rarely been studied.

Previous studies hypothesized that FFM-depleted COPD patients are less likely to improve after pulmonary rehabilitation since exercise training can induce systemic inflammation and oxidative stress in COPD patients with muscle depletion [16].

Regarding FFMI the lowest mean values were in the cachectic group followed by the muscle depleted group and the highest value was in the nonmuscle depleted group with statistically significant difference between them before PRP but nonsignificant after PRP. So, these results agree with Jones *et al.* [15] as they found that patients who had sarcopenia had the same responses to pulmonary rehabilitation as those without muscle sarcopenia in terms of exercise performance (incremental shuttle walk) and quality of life (St. George's questionnaire). Tunsupon and Mador [17] found that body weight muscle depletion and muscle depletion had no effect on patients achieving the minimal clinically important difference for quality of life and exercise tolerance measures after PRP which is not in agreement with our results. Maltais *et al.* [18] performed aerobic exercise on patients with COPD and he found that COPD patients who had muscle depletion have weaker muscles than those who had not have muscle depletion.

In this study the lowest mean values of FEV_1 was found in the cachectic group, followed by the muscle depleted group and the highest value was in the non-muscle depleted group, regarding FEV_1/FVC the lowest mean values were in the cachectic group, followed by the muscle depleted group and the highest value was in the nonmuscle depleted group. Criner *et al.* [19] found that there were statistically significant improvements of the mean values of FEV_1, FEV_1/FVC but there were improvements in 6MWT but not significant after 8 weeks of pulmonary rehabilitation.In our study, the lowest mean values of 6 MWT were found in the cachectic group followed by the muscle depleted group and the highest value was in the non-muscle depleted group. The highest mean values of dyspnea (mMRC) was found in the cachectic group, followed by the muscle depleted group and the highest value was in the nonmuscle depleted group. The lowest mean values of CAT score was found in the muscle depleted group followed by the cachectic group and the highest value was in the nonmuscle depleted group.

In the study of Troosters *et al.* [20], 100 patients were assigned to receive the full exercise training program. Patients who completed the 6-month duration program of outpatient training resulted in significant and clinically relevant improvement in exercise performance, 6-minute walk distance, quality of life, and respiratory and peripheral muscle strength. In the study of Griffiths *et al.* [21] on 200 disabling chronic lung disease patients (the majority with COPD) who were assigned for a 6-week rehabilitation program also showed greater improvements in general and disease-specific health status and walking ability.

In the study by Ali *et al.* [22] nine sessions of PR exercises in COPD patients with acute exacerbation produced statistically significant improvement in FEV_1, 6MWT, exercise capacity, general well-being, and peak oxygen uptake.

In a study of Ries *et al.* [23] on 119 outpatients COPD with moderate to severe airflow obstruction were randomly assigned to an 8-week comprehensive pulmonary rehabilitation; there were significant improvement in clinical symptoms and exercise performance. Pulmonary rehabilitation improves COPD systemic manifestations and relieves dyspnea. These improvements are clinically important.

Study limitation

BIA is not a gold standard method for assessing body composition, but is safe and relatively available. The small number of patients is another important limitation of this study, which did not allow statistical analysis in some groups. Also, female participants were fewer due to the relatively low morbidity of COPD in women.

Conclusion

PRP improves different functional parameters, health status, and exercise capacity in COPD patients with a different body composition but there is significant improvement in functional severity and health status in COPD patients with muscle depleted with cachexia.

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Conflicts of interest

There are no conflicts of interest.

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