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ORIGINAL ARTICLE

Effect of physical training on fat-free mass in patients with chronic obstructive pulmonary disease (COPD)

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Abstract

Background. Weight loss and depletion of fat-free mass are common problems in patients with chronic obstructive pulmonary disease (COPD) and are related to muscular weakness and exercise intolerance. Physical training of COPD patients has good effect on exercise tolerance and quality of life. The aim of this study was to examine factors that affect change in fat-free mass after physical training, in patients with COPD.

Patients. Patients were examined before and after a 4-month exercise period. Weight and height were measured, and bioelectrical impedance was performed. Fat-free mass (FFM) was calculated, by a three-compartment model, and fat-free mass index (FFMI) was calculated as FFM kg/m² and body mass index (BMI) as kg/m². A symptom-limited ramp ergometer test and 12-minute walk test (12MWT) were performed. Dyspnoea score of daily activities was determined by Chronic Respiratory Disease Questionnaire (CRDQ). Blood was taken for analyses of C-reactive protein (CRP) and fibrinogen. Patients with a BMI <21 kg/m² were given nutritional support during the training period.

Results. A total of 27 patients completed the training (64 years, FEV₁ 31% of predicted). Patients with low FFMI gained 1.2 kg, whereas those with normal FFMI lost 0.7 kg ($p = 0.04$). In multivariate analyses high age ($p = 0.03$), low FEV₁ ($p = 0.02$), and a high level of dyspnoea ($p = 0.01$) at baseline were found to be negative predictors for increase in FFM.

Conclusions. Difficulties in increasing the fat-free mass in COPD patients by physical training seem to be associated with dyspnoea in daily life and impaired lung function (FEV₁).

Key words: *Chronic obstructive pulmonary disease, dyspnoea, exercise training, fat-free mass, nutrition*

Introduction

There is growing evidence that chronic obstructive pulmonary disease (COPD) is a multi-organ systemic disease. Skeletal muscle weakness, muscle wasting, and impaired exercise performance, which are poorly related to air flow limitation, have commonly been reported in COPD patients (1).

Exercise-limiting factors include muscular weakness (2), dynamic hyperinflation resulting in increased work of breathing (3), increased load on the respiratory muscles (4), and an intensified perception of

respiratory discomfort. In addition, symptoms perceived by the patients with anxiety and depression have impact on training tolerance and physical activity (5).

Loss of body weight is a common and serious finding in patients with COPD (6) and is associated with increased mortality and morbidity independent of gender, smoking, and lung function (7). Patients with low fat-free mass (FFM) often have muscular weakness, especially in the lower limbs (8). Low weight is also related to low health-related quality of life and worsening dyspnoea (9).

Pulmonary rehabilitation is an important component in the management of subjects with COPD (10) and is effective in improving exercise performance and health status (10). Exercise training is a core component of pulmonary rehabilitation and has been shown to be the best available means of improving muscle function, exercise capacity, and cardiovascular function (10). Exercise training has also been shown to result in less dyspnoea in daily life (11) and to less mood disturbance. Before training start, an adequate assessment including evaluation of body composition, i.e. FFM, needs to be performed in order to optimize intervention strategies (10). Body mass index (BMI) is a simple way to assess body composition. However, it is possible to have normal BMI and still be nutritionally depleted (12). FFM reduction is a better predictor of peak exercise performance than BMI (13), and it has been suggested that FFM is the best parameter to assess body composition.

A few studies have investigated the efficacy of multimodal intervention, including nutrition and anabolic steroids integrated into pulmonary rehabilitation for advanced COPD patients (14-16). Although the intervention was successful in improving body weight, FFM, and exercise tolerance, the influence of the various components could not be determined.

The underlying mechanisms contributing to depletion of skeletal muscle still remain unclear. Associations between various circulating markers of inflammation and the loss of muscle mass have been made in chronic inflammatory disease conditions, including COPD.

The aim of this study was to examine factors that affect change in fat-free mass after a period of physical training, in patients with COPD.

Material and methods

The study population was recruited from patients included in an exercise study comparing different training methods (17). Patients with moderate to severe COPD, according to the Global Initiative for Obstructive Lung Disease (GOLD) criteria, were consecutively invited to participate in the exercise study (1). Inclusion criteria were COPD with a post-bronchodilator FEV₁/FVC ratio <0.7 and a FEV₁ <60% of the predicted value. All patients ($n = 51$) included in the training study were asked if they wanted to participate in the current study. Forty-nine patients (96%) agreed to participate, of whom 27 patients completed the 4-month training period. Patients were considered drop-outs if they attended less than 75% of the training sessions. Reasons for drop-out were exacerbations ($n = 16$), other diseases ($n = 2$), and lack of motivation or transportation problems ($n = 4$).

Measurements were made before and after the 4-month training period. Information on smoking history was obtained using a structured interview. Informed consent was obtained from all the participants.

Exercise training

Exercise sessions were performed twice a week. Each session included cycle ergometer training at an intensity $\geq 65\%$ of baseline peak exercise capacity (W_{peak}) for 27 min. For warming up (6 min) and cooling down (6 min) the patients cycled at 30%–40% of baseline W_{peak} . After the cycling, once a week the session proceeded with flexibility and relaxation training, while the other session of the week proceeded with resistance training for upper and lower limbs as well as abdominal muscles (10 repetitions, two sets at about 70% of 1 repetition maximum). Exercise load was kept as high as tolerated at all times, above the target value when possible. Patients who desaturated on exercise ($\text{SpO}_2 < 90\%$) were given supplemental oxygen during training to keep $\text{SpO}_2 \geq 90\%$. All patients with BMI <21 kg/m² were given nutritional support ad libitum. The threshold of 21 kg/m² was chosen because mortality has been shown to be increased below this value in COPD populations (18).

Body composition

Body height was measured to the nearest 0.5 cm, and weight was measured on a balance scale to the nearest 0.1 kg. Bioelectrical impedance analysis was performed in the morning with patients in a fasting state using a Hydra EFC/ICF, model 4200, Xitron Tech (San Diego, CA, USA). FFM was calculated by a three-compartment model, and the fat-free mass index (FFMI) was calculated as FFM kg/body height m² and BMI as kg/m². Limits for depleted FFM were employed: FFMI ≤ 16 kg/m² was used for men and ≤ 15 kg/m² for women. The two outcome variables used were change in FFM, and FFM in per cent of baseline values (change in FFM of baseline).

Physical capacity

Peak exercise capacity in watt (W_{peak}) was determined by a progressive symptom-limited cycle ergometer test (Case 8000 Exercise Testing System, GE Medical Systems, Milwaukee, WI, USA).

Functional exercise capacity was measured by the self-paced 12-min walk test (12MWT) (19). The walking tests were performed in a level corridor, and the total distance walked (in meters) was measured. Two tests were performed both before and after the training period. The second test was repeated

on a different day within one week. The better of the two tests was used.

Dyspnoea

For evaluation of dyspnoea during activities in daily life the dyspnoea scale from the Chronic Respiratory Disease Questionnaire (CRDQ) was used (20). Patients scored dyspnoea experienced during five self-chosen activities of daily living. The scale for each of the five activities is 7-graded, and a higher score indicates less dyspnoea. The score from the five activities were combined, and the combined dyspnoea score thereby ranged from 5 to 35.

Systemic inflammation

Blood samples were taken for analyses of C-reactive protein (CRP) and fibrinogen. High-sensitivity CRP was measured with a two-point nephelometry method with a ProSpec instrument (Dade Behring, Marburg, Germany) using monoclonal mouse antibodies (Dade Behring, Marburg, Germany). The total analytical imprecision was 1.4% at 1.23 and 5.49 mg/L, with a lowest detectable level of 0.17 mg/L.

Measurement of fibrinogen was performed using a ProSpec instrument (Dade Behring, Marburg, Germany) with a rabbit antibody against fibrinogen (Dade Behring, Marburg, Germany). The total analytical imprecision was 5.7% at 2.2 g/L and 4.4% at 4.7 g/L.

Analyses were carried out at the Department of Clinical Chemistry at Uppsala University Hospital, Sweden.

Lung function

Forced expiratory volume in one second (FEV₁) was measured with a Jaeger master scope Spirometer (Jaeger, Höchberg, Germany). The best of three acceptable manoeuvres was used in accordance with the American Thoracic Society guidelines for standardization of spirometry (21). FEV₁ was expressed as a percentage of the predicted value using Swedish reference values (22,23).

The Ethics Committee at the Medical Faculty at Uppsala University approved the study (2002-07-02, Dnr 02-307).

Statistics

Results are expressed as mean \pm SD. Spearman rank correlation and multiple linear regression analysis were used when analysing the relation between change in FFM expressed in absolute values and per cent of the baseline values and baseline

characteristics. Spearman rank correlation was also used when analysing association between change in FFM and change in 12MWT and W_{peak} . Variables associated with change in FFM at $p < 0.10$ in bivariate analyses were included in the multiple linear regression model. CRP was log-transformed before being entered into the analyses. Statistically significant difference was assumed when $p < 0.05$.

Results

The study included 27 patients who completed the 4-month physical training period. The attendance rate was 29 ± 3 of 32 possible sessions. Patients with low FFMI at training start were more likely to gain weight than patients with normal FFMI (Table I). Nutritional supplementation during the exercise training period was given to all patients with BMI below 21 kg/m² at baseline; this meant that most patients with low FFMI received supplementation, whereas none of the patients with normal FFMI received supplementation (Figure 1).

The median change in FFM was 0.6 kg, while the median change in 12MWT and W_{peak} was 54 m and 10 W, respectively (Figure 2). Statistically significant correlations were found between changes in FFM and FEV₁, FFMI, dyspnoea score, and fibrinogen at baseline (Table II). There were no significant associations between change in FFM and change in 12MWT or change in W_{peak} .

In the multivariate analyses approximately 70% of the variation in FFM change was accounted for when age,

Table I. Baseline characteristics and changes in body composition and physical capacity, for patients with low or normal fat-free mass index (FFMI). Low was defined as FFMI ≤ 16 kg/m² for men and ≤ 15 kg/m² for women.

	Low FFMI (n = 15)	Normal FFMI (n = 12)	p
Female (%)	48	26	0.09
Age (years)	64 \pm 7	65 \pm 7	0.73
FEV ₁ % predicted	32 \pm 10	31 \pm 11	0.68
Fibrinogen (mg/L)	4.1 \pm 1	3.9 \pm 1	0.71
CRP (mg/L)	6.5 \pm 10.1	8.2 \pm 11.5	0.70
Pack-years	40 \pm 9	40 \pm 9	0.94
Dyspnoea score	17 \pm 4	17 \pm 3	0.90
Δ Weight (kg)	1.2 \pm 2.4	-0.67 \pm 2.1	0.04
Δ Fibrinogen (mg/L)	-0.3 \pm 0.9	-0.1 \pm 0.8	0.53
Δ CRP (mg/L)	-4.4 \pm 10.9	-1.4 \pm 12.9	0.58
Δ FFM (kg/m ²)	-0.2 \pm 2.4	1.3 \pm 1.6	0.07
Δ W_{peak} (watt)	20 \pm 28	11 \pm 10	0.40
Δ 12MWT (m)	99 \pm 90	35 \pm 66	0.06

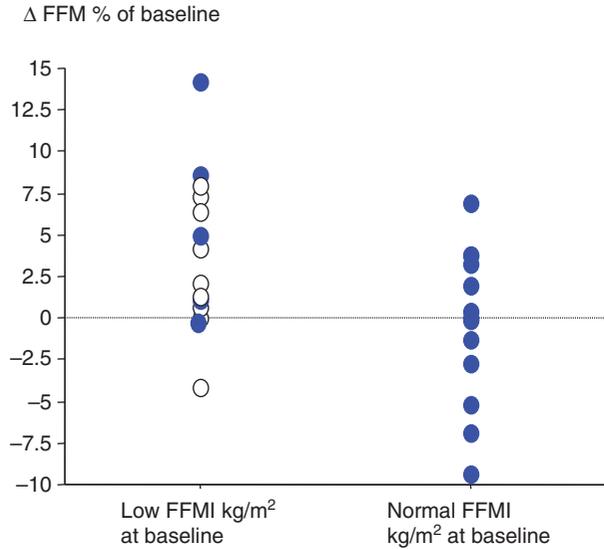


Figure 1. Changes in fat-free mass (FFM) in patients with low fat-free mass index (FFMI) and normal FFMI between baseline and four months of training. Low FFMI is defined as FFMI ≤ 16 kg/m² for men and ≤ 15 kg/m² for women. Filled-symbols = patients given no supplementation; open symbols = patients given supplementation.

sex, FEV₁, dyspnoea, and fibrinogen were combined in a multiple regression model (Table III). Change in FFM was negatively correlated with age and positively with FEV₁ and a higher dyspnoea score indicating less dyspnoea at the start of the training period.

Discussion

Our main finding is that patients with lower age, higher FEV₁, and a lower level of dyspnoea were more likely to increase in muscle mass during a 4-month physical training period.

Moreover, patients with a low FEV₁ were less likely to increase in FFM. It has been shown that muscle strength and FEV₁ are factors limiting exercise

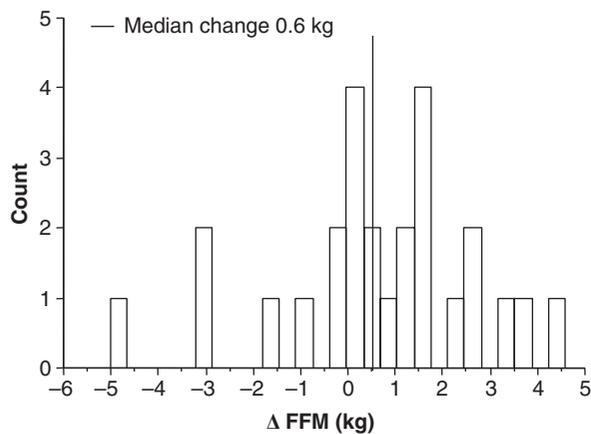


Figure 2. Distribution of changes in fat-free mass (FFM) between baseline and four months of training.

Table II. Associations between changes in fat-free mass (FFM), and variables showing lung function, body composition, systemic inflammation, physical capacity, and dyspnoea at baseline.

	Δ FFM		Δ FFM % baseline	
	rho	p	rho	p
Age (years)	0.06	0.76	0.09	0.66
Sex female	-0.003	0.99	-0.03	0.89
FEV ₁ % of predicted	0.48	0.01	0.48	0.02
Pack years (years)	0.09	0.65	0.09	0.64
BMI (kg/m ²)	-0.18	0.37	-0.26	0.19
FFMI (kg/m ²)	-0.35	0.07	-0.44	0.03
CRP (mg/L)	0.18	0.39	0.19	0.38
Fibrinogen (mg/L)	0.47	0.03	0.49	0.02
12MWT (m)	0.08	0.68	0.07	0.75
W _{peak} (watt)	0.20	0.30	0.16	0.42
Dyspnoea	0.48	0.02	0.44	0.03

capacity (2), and that expiratory airflow obstruction is a limiting factor to maximal ventilation and thereby limits exercise tolerance (24). There are multiple possibilities for the association between airflow obstruction and exercise limitation, for example dynamic hyperinflation (3) resulting in increased work of breathing, increased load on the respiratory muscles (4), and the intensified perception of respiratory discomfort. Another possible reason is that a low FEV₁ is related to hypoxic muscles due to insufficient oxygen caused by insufficient blood supply or hypoxemia (25).

We found that dyspnoea was a risk factor for not increasing FFM during an exercise programme. One recent study reported that dyspnoea on exertion is correlated with general anxiety, indicating that exercise training may be influenced negatively by anxiety-

Table III. Associations between changes in fat-free mass (FFM), and age, sex, lung function, dyspnoea, and fibrinogen. Estimates (beta coefficients) are adjusted for all the variables in the table.

	Δ FFM		Δ FFM of baseline	
	$R^2 = 0.697$		$R^2 = 0.682$	
	Coeff.	p	Coeff.	p
Age (years)	-0.120	0.03	-0.24	0.07
Female sex	-0.519	0.58	-0.658	0.77
FEV ₁ % of predicted	0.104	0.02	0.255	0.03
Dyspnoea CRDQ	0.336	0.01	0.661	0.03
Fibrinogen (mg/L)	0.588	0.16	1.63	0.11

worsened dyspnoea (26). As dyspnoea has been shown to be related to all subscores of St Georges Respiratory Questionnaire, a low health-related quality of life is obvious in subjects with dyspnoea (27). Dyspnoea can of course have many different explanations, and some of them can probably be treated. In malnourished patients with COPD nutritional interventions can improve quality of life (28). Strength training results in less dyspnoea during exercise, thereby making this strategy easier to tolerate than aerobic training (29).

Our finding that age is correlated with difficulties to increase FFM is consistent with the fact that cachexia is more common in older age (30). CRP in our patients with low and normal FFMI was within the normal range, and there was no significant correlation in the bivariate analysis between CRP at baseline and change in FFMI after training. This is in accordance with results of Eagan et al. who found, in a large COPD population, that CRP was positively associated with FFMI (31), thus CRP was not elevated in patients having lower FFMI. They concluded that CRP is not elevated in cachectic COPD patients. Our results and the results from Eagan et al. are in contrast to a prominent theory suggesting that pathological weight loss is at least partly explained by an increase in systemic inflammation reflected in enhanced plasma or serum concentrations of inflammatory markers (32). A probable explanation for increased CRP in COPD patients might instead be that active fat mass tissue in obese patients is associated to higher systemic levels of CRP (33).

There was a training response in our patients, which was seen in both increased maximal capacity (W_{peak}) and 12-min walk distance (34-36), and there was no significant difference in this response between the low FFMI group and the normal FFMI group. We found that FFM decreased slightly in the low FFMI group and increased in the normal FFMI group, but the difference between the two groups did not attain statistical significance. In accordance with our results, Berton et al. reported that both their depleted patients (who were given nutritional supplementation and endurance and strength training for 12 weeks) and their non-depleted patients (who just got the 12 weeks of training) slightly increased FFM and that there was no statistically significant difference between the groups (34). Two recent studies have shown improvements in FFM in depleted patients as a result of exercise training and nutritional supplementation, whereas depleted control patients who just received exercise decreased in FFM (36,37).

Our depleted patients received one oral nutritional supplementation after training, i.e. twice a week, whereas in the study by Berton et al. patients received

a daily polysaccharide supplementation if caloric ingestion was judged inadequate (34). In the two studies that improved FFM, one study gave essential amino acid supplementation twice a day for 12 weeks (37), and in the other study the patients were given three oral liquid supplements per 24 hours for four months (36). Thus, the amount and type of supplement may be an important factor to consider. As exercise capacity increases as a result of exercise training independently of BMI (38), we suggest that to improve FFM in depleted patients nutritional supplementation has to be extensive.

While muscle mass can be readily increased by progressive strength training, this would not be expected from an aerobic training programme such as ours. Strength training has been shown to have greater potential to improve muscle mass and strength than endurance training (39). In addition, it was recently shown that cachectic patients can retain the potential for skeletal muscle remodelling as a result of strength training (40).

It was not possible to study the effectiveness of supplementation during exercise training in patients with low FFMI because of our small number of patients. Another limitation is that potential confounding factors including physical activity and metabolic syndrome features were not measured. Our training programme was not primarily aimed at improving muscle mass but rather endurance capacity. Another limitation is that we did not control for daily caloric intake, i.e. patients might have dropped in the normal dietary intake.

Our conclusion is that in COPD old age, low FEV₁, and high level of dyspnoea in daily life were, independently of each other, related to less chance of increasing fat-free mass by physical training.

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