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Original Article

Effects of pulmonary rehabilitation in patients with mild-to-moderate chronic obstructive pulmonary disease: Bottom of an iceberg

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ABSTRACT

Objectives: This study aims to compare the effects of pulmonary rehabilitation (PR) in patients with mild-to-moderate and severe-to-very severe chronic obstructive pulmonary disease (COPD).

Patients and methods: Between January 2005 and December 2010, a total of 76 patients with mild-to-moderate (Global Initiative for Chronic Obstructive Lung Disease [GOLD] Stages I+II, n=33, mean age 66.0±8.6 years) and severe-to-very severe (GOLD Stages III+IV, n=43, mean age 63.5±8.8 years) COPD completed an eight-week outpatient PR program. Incremental and endurance shuttle walk tests (ISWT, ESWT), St. George's Respiratory Questionnaire (SGRQ), Chronic Respiratory Questionnaire (CRQ), and Hospital Anxiety and Depression Scale were assessed before and after PR. Changes after the intervention were compared between two groups.

Results: There were significant improvements in the ISWT and median 60 m [(-150)-(400)] in mild-to-moderate group and 70 m [(0)-(270)] in severe-to-very severe group (both, p<0.001). The ESWT time improved in both groups, 122s [(-279)-(665)] (p=0.002) and 61s [(-180)-(878)] (p<0.001), respectively. Significant effects were observed in all domains of the SGRQ except the impact score in mild-to-moderate patients. There were significant improvements in all domains except the symptoms score in severe-to-very severe patients. Using the CRQ, a significant improvement was shown in all domains of CRQ except the dyspnea score of mild-to-moderate patients. Anxiety and depression scores decreased after PR in both groups (p<0.05). According to changes in outcomes, there was no difference in any parameters between two groups.

Conclusion: This study demonstrates that patients with mild-to-moderate COPD benefit from PR comparably to patients with severe-to-very-severe COPD. Although patients with mild-to-moderate COPD are not usually symptomatic, our findings suggest that they should be included in PR.

Keywords: Anxiety; chronic obstructive pulmonary disease; depression; dyspnea; exercise; quality of life; rehabilitation.

Chronic obstructive pulmonary disease (COPD) is characterized by persistent airflow limitation and often coexists with comorbid diseases that may affect the prognosis significantly.[1] Although lung function measurement is essential for diagnosis, there is a weak correlation between outcomes such as dyspnea, fatigue, exercise intolerance and declined lung function.[2,3] It has been previously shown that peripheral muscle weakness contributes to exercise intolerance in COPD.[4] The pathophysiological changes cause exercise limitation and early activity restriction in the course of the disease. Additionally, they increase the progression of the disease.[5] Dyspnea and leg fatigue are major symptoms which limit exercise tolerance in COPD patients. These occur as a result of a complex vicious cycle which consists of impaired respiratory mechanics, gas exchange abnormalities, peripheral muscle dysfunction, limited ventilation, cardiac dysfunction and air trapping.[6] Elbehairy et al.[7] evaluated the underlying mechanisms of ventilatory impairment and exercise intolerance in patients with mild COPD. They showed that increased physiological dead space and wasted ventilation were the most consistent pulmonary gas exchange abnormalities during exercise in the patients with mild COPD. Despite of preserved forced expiratory volume in one

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second, these changes may result in early dynamic mechanical imbalance which causes dyspnea and exercise intolerance.

Recent evidences have demonstrated that quadriceps muscle strength and Health-Related Quality of Life (HRQOL) are impaired in patients with mild COPD.[8] Patients at early stages of COPD may benefit from pulmonary rehabilitation (PR), and the American Thoracic Society/European Respiratory Society recommends investigation of the potential effect of PR in patients with mild to moderate COPD.[9] The effect of exercise training in patients with mild COPD remains undetermined[10] and further studies are necessary to assess the benefits of physical activity.[11] Due to the limited results at early stages of COPD, in the present study, we aimed to analyze the effect of exercise training on patients with mild-to-moderate COPD and to compare the results with patients having severe-to-very severe COPD.

PATIENTS AND METHODS

Between January 2005 and December 2010, a total of 76 stable patients, who were referred from the COPD outpatient clinic had Global Initiative for Chronic Obstructive Lung Disease (GOLD) criteria[1] and completed the PR program, were included in this retrospective study at Ege University Hospital, Chest Department. In terms of illness severity, the patients were classified as patients with mild-to-moderate (GOLD Stages I+II) and severe-to-very severe (GOLD Stages III+IV) disease. All patients were accepted to the Pulmonary Rehabilitation Unit. Exclusion criteria: *(i)* Patients with disabling conditions (neuromuscular diseases, malignant disorders, unstable cardiovascular diseases, orthopedic problems, severe pulmonary hypertension), *(ii)* Patients unwilling to complete the program, *(iii)* Patients with lack of motivation or with poor compliance, *(iv)* Patients with acute exacerbation in the previous four weeks.

This study was approved by the Ethics Committee of Ege University School of Medicine. The study was conducted in accordance with the principles of the Declaration of Helsinki. A written informed consent was obtained from each patient. All patients were ex-smokers and were receiving optimal medical treatment which included inhaling long acting anticholinergic and corticosteroid/β_2-agonist according to the GOLD guideline.

The patients underwent an eight-week supervised outpatient PR program and received home exercise program once a week. The PR session consisted of education and exercise training. Exercise was started with a warm-up period followed by cycle ergometer (15 min) and treadmill training (15 min), upper and lower extremity strength training (5-10 min) and breathing and relaxation therapies (15-20 min, each) for 60-80 min/day twice a week. Breathing exercises consisted of diaphragmatic, glossopharyngeal, pursed lip and segmental breathing. Relaxation exercises were performed according to the Jacobson technique of progressive muscle relaxation.[12] Workloads for cycling and walking speed for treadmill ergometer were calculated with incremental shuttle walk test (ISWT) result (pikVO_2= 4.19 + [0.025 x distance of ISWT]).[13] All patients were trained at 60 to 70% of peak VO_2 that was calculated according to ISWT result. Exercise intensity was increased according to patient condition and exercise was applied continuously. Pulse oximetry was used during exercise, as the SpO_2 had to be above 90%. Resistance training was applied as one set with 8 to 12 repetitions, including the use of 8 to 10 muscles.

Dyspnea was assessed by the Medical Research Council (MRC) and Borg scales.[14] Exercise capacity was evaluated with ISWT and endurance shuttle walk test (ESWT).[15,16] Minimal clinically important significant differences for ISWT and ESWT were 47.5 m and 45-85 second, respectively.[17]

The HRQOL was assessed by the Turkish version of St. George's Respiratory Questionnaire (SGRQ) and Chronic Respiratory Questionnaire (CRQ). The SGRO consists of three domains: symptoms, activities, and impact with scores from 0 to 100, and the highest score represents poor quality of life (QoL). Change in score of four units for any domain is considered a clinically significant difference.[18,19] The CRQ is constructed by dyspnea, fatigue, emotional function, and mastery dimensions. The score range of each dimension changes 1 to 7 points. The low score points to poor QoL and change of 0.5 point is accepted as clinically significant difference for this questionnaire.[20]

The Hospital Anxiety and Depression Scale (HADS) was used to assess the presence of anxiety and depressive symptoms. It has been designed to measure symptoms for depression and generalized anxiety and is self-administered easily. Anxiety (HADS-A) and depression (HADS-D) are evaluated as separate components and each consists of seven items. Higher scores indicate more severe symptomatology. A cut off score of ≥8 for both scales is recommended for the evaluation.[21,22]

Table 1. Baseline characteristics of the mild-to-moderate patients and severe-to-very severe patients

	Mild-to-moderate patients					Severe-to-very severe patients					
	n	%	Mean±SD	Median	Range	n	%	Mean±SD	Median	Range	*p*
Age (year)			66.03±8.64					63.49±8.79			0.21
Gender											
Male	30					40					0.74
Female	3					3					
Smoking history (pack/year)				40	3-200				50	20-132	0.20
Patients on LTOT				1	3				11	25.6	0.008
Number of hospitalization				0	0-1				1	0-4	<0.001
Post. FEV_1 (predicted %)				55	50-87				35	15-49	<0.001
Post. FEV_1/FVC (%)			59.2±9.9					46.2±10.0			<0.001
PaO_2 (mmHg)*			79.8±13.6					67.9±11.6			<0.001
BMI (kg/m^2)				24.1	13.5-44.5				20.4	14.8-28.7	0.021
Comorbid illnesses											
Cardiovascular disease	7	21.2				14	32.6				0.31
Diabetes mellitus	4	12.1				1	2.3				
MRC				2	1-5				3	1-5	0.029
ISWT (m)				370	60-800				230	50-470	0.004
Exercise Borg (after ISWT)				3	0-7				4	0-9	0.026
ESWT											
Level				10	1-16				7	1-13	0.008
Speed (km/h)				4.36	1.80-6.00				3.60	1.78-5.14	0.01
Time (s)				420	110-1200				300	83-1293	0.032
SGRQ											
Total score				38.8	14.0-79.9				60.0	14.1-96.4	<0.001
Symptoms				52.8	4.0-90.5				62.9	2.3-100	0.007
Activity				53.4	29.6-93.3				73.2	23.6-100	<0.001
Impact				27.9	1.0-79.3				49.5	7.5-96.1	<0.001
CRQ											
Dyspnea				4.0	1.0-7.0				3.0	0.6-6.0	<0.001
Fatigue				4.5	1.8-6.3				3.5	1-5.5	0.011
Mastery				4.4	1.3-6.7				3.9	1.4-6.5	0.11
Emotional function				4.8	1.6-.7.0				4	1.0-7.0	0.13
HADS											
Depression				6	0-14				6	1-15	0.39
Anxiety				6	0-18				6	0-19	0.27

SD: Standard deviation; LTOT: Long term oxygen therapy; Post-FEV_1: Post bronchodilator forced expiratory volume in the first second of expiration; FVC: Forced vital capacity; PaO_2: Partial oxygen pressure in arterial blood gas; BMI: Body Mass Index; MRC: Medical Research Council Dyspnea Scale; ISWT: Incremental shuttle walk test; Borg: Borg Dyspnea Index; ESWT: Endurance shuttle walking test; SGRQ: St George's Respiratory Questionnaire; CRQ: Chronic Respiratory Disease Questionnaire; HADS: Hospital Anxiety-Depression scale.

Table 2. The comparisons of pre- and post-rehabilitation variables within the groups

	Mild-to-moderate patients					Severe-to-very severe patients				
	Baseline		After 8 weeks rehabilitation			Baseline		After 8 weeks rehabilitation		
	Median	Range	Median	Range	*p*	Median	Range	Median	Range	*p*
MRC	2	1-5	1	1-4	<0.001	3	1-5	2	1-5	<0.001
ISWT (m)	370	60-800	460	150-820	<0.001	230	50-470	290	140-610	<0.001
Exercise Borg	3	0-7	2	0-6	0.008	4	0-9	3	1-6	0.001
ESWT										
Level	10	1-16	12	2-16	<0.001	7	1-13	9	3-15	<0.001
Speed (km/h)	4.36	1.80-6.00	4.97	2.09-6.00	0.001	3.60	1.78-5.14	4.11	2.44-5.76	<0.001
Time (s)	420	110-1200	588	92-1295	0.002	300	83-1293	435	141-1301	<0.001
SGRQ										
Total score	38.8	14.0-79.9	31.5	4-68.5	0.003	60.0	14.1-96.4	47.0	20.0-87.3	<0.001
Symptoms	52.8	4.0-90.5	45.5	0-63.5	0.038	62.9	2.3-100	56.5	2.3-100	0.06
Activity	53.4	29.6-93.3	47.0	0-85.8	0.004	73.2	23.6-100	66.0	20.1-100	0.005
Impact	27.9	1.0-79.3	22.6	0-71.0	0.16	49.5	7.5-96.1	37.9	3.0-89.6	<0.001
CRQ						3.0	0.6-6.0	3.5	1.0-7.0	
Dyspnea	4.0	1.0-7.0	4.2	0-7.0	0.10	3.5	1-5.5	4.5	1.5-7.0	0.005
Fatigue	4.5	1.8-6.3	5.3	4.0-7.0	<0.001	3.9	1.4-6.5	4.8	1.0-7.0	<0.001
Mastery	4.4	1.3-6.7	6.0	3.5-7.0	<0.001	4	1.0-7.0	4.9	1.3-7.0	<0.001
Emotional function	4.8	1.6-.7.0	5.7	2.7-7.0	<0.001					<0.001
HADS-D	6	0-14	5	0-12	0.041	6	1-15	5	0-17	0.027
HADS-A	6	0-18	4	0-12	0.004	6	0-19	5	0-18	<0.001

MRC: Medical Research Council Dyspnea Scale; ISWT: Incremental shuttle walk test; Borg: Borg Dyspnea Index; ESWT: Endurance shuttle walking test; SGRQ: St George's Respiratory Questionnaire; CRQ: Chronic Respiratory Disease Questionnaire; HADS-D: Hospital Anxiety-Depression Scale Depression Score; HADS-A: Hospital Anxiety-Depression Scale Depression Score.

Apart from the exercise training program, the patients took part in monthly educational lectures with an interdisciplinary team on the various topics related with the disease.[23] The patients were assessed with aforementioned variables at baseline and after the intervention. The results obtained by mild-to-moderate patients were compared with the severe-to-very severe patients. All patient data were screened from their recorded rehabilitation files before and after PR.

Statistical analysis

Data were analyzed using IBM SPSS for Windows version 20.0 (IBM Corp., Armonk, NY, USA). Descriptive statistics were performed for all recorded variables. Parametric variables between the two groups (mild-to-moderate [GOLD I+II] patients versus severe-to-very severe [GOLD III+IV] patients) were compared by the Student's t-test. The Mann-Whitney U test was used to compare categorized or non-parametric variables between these groups. Non-parametric paired variables were analyzed with Wilcoxon test before and after PR. The results were shown as change between post-treatment and baseline levels (Δ values). A *p* value of 0.05 was considered statistically significant.

RESULTS

A total of 76 patients who completed the PR and had no exacerbation in four weeks before PR and during PR were enrolled in the study. Out of 76 patients, 33 were assessed as GOLD Stages I and II (mild-to-moderate) and 43 were in GOLD Stages III and IV (severe-to-very severe). The mean age was 66.0±8.6 years and 63.5±8.8 years, respectively. The groups were well-matched for sex, age, and smoking history at baseline. The mean Body Mass Index was 24.1 (range, 13.5-44.5) kg/m^2 in mild-to-moderate group and 20.4 (range, 14.8-28.7) kg/m^2 in severe-to-very severe group, respectively. Patients in the severe-to-very severe group had worse dyspnea, higher MRC and Borg scales (p=0.029, p=0.026) and poorer walking distance compared with the mild-to-moderate patients (p=0.004) (Table 1). The symptom, activity, impact and total scores of SGRQ, and the dyspnea and fatigue scores of CRQ were worse in severe-to-very severe patients than in mild-to-moderate patients at baseline (p<0.05). Baseline characteristics and demographic features of the patients are shown in Table 1.

Dyspnea, walking distance and endurance time, both anxiety and depression improved in mild-to-moderate and severe-to-very severe patients after the

Table 3. The comparisons of two groups for Δ median changes of variables

	Mild-to-moderate patients		Severe-to-very severe patients		
	Median	Range	Median	Range	*p*
ΔMRC	-1.00	-3.00 - 0	-1	-3 - 1	0.59
ΔISWT (m)	60	-150 - 400	70	0 - 270	0.52
ΔExercise Borg	0	-5 - 1	-1	-6 - 2.5	0.59
ESWT					
ΔLevel	2	-3 - 9	2	-3 - 6	0.25
ΔSpeed (km/h)	0.49	-0.79 - 2.49	0.60	-0.86 - 1.65	0.26
ΔTime (s)	122	-279 - 665	61	-180 - 878	0.45
SGRQ					
ΔTotal score	-5.1	-33.4 - 6.0	-6	-39 - 13.6	0.62
ΔSymptoms	-5.4	-55.9 - 29.5	-5.7	-43.4 - 21.9	0.60
ΔActivity	-6.1	-53.0 - 30.3	-6	-56 - 46.4	0.79
ΔImpact	-4.1	-38 - 25.0	-6	-37 - 9.5	0.19
CRQ					
ΔDyspnea	0.4	-2.2 - 3.6	0.6	-2.5 - 5.2	0.44
ΔFatigue	0.8	-1.5 - 4.0	0.8	-1.5 - 3.5	0.83
ΔMastery	0.5	-0.6 - 3.8	0.5	-1.3 - 2.5	0.39
ΔEmotional function	0.8	-0.6 - 4.9	0.7	-0.8 - 3.3	0.69
ΔHADS-D	-1	-7 - 3	-1	-6 - 7	0.63
ΔHADS-A	-1.5	-7 - 3	-2	-9 - 4	0.91

MRC: Medical Research Council Dyspnea Scale; ISWT: Incremental shuttle walk test; Borg: Borg Dyspnea Index; ESWT: Endurance shuttle walking test; SGRQ: St George's Respiratory Questionnaire; CRQ: Chronic Respiratory Disease Questionnaire; HADS-D: Hospital Anxiety-Depression Scale Depression Score; HADS-A: Hospital Anxiety-Depression scale anxiety score.

intervention. Exercise capacity increased after PR, with a mean score difference of 60 m and 70 m in the ISWT distance in both groups, respectively. Level, speed and endurance time increased significantly in both groups. All scores on SGRQ improved significantly from baseline to follow-up except the impact score in mild-to-moderate group and symptoms score in severe-to very severe group. Except for the dyspnea score of mild-to-moderate patients, there were also significant improvements in all domains of CRQ in both groups. Scores on dyspnea, exercise capacity, HRQOL, anxiety and depression before and after rehabilitation are shown in Table 2. The baseline HADS-D and HADS-A scores were 6 (0-14) and 6 (0-18) respectively in the mild-to-moderate patients; 6 (1-15) and 6 (0-19) in severe-to-very severe patients. The patients in both groups were not diagnosed with anxiety or depression. Comparisons for all changes at outcomes in both groups are summarized in Table 3. Participation in PR program led to decrease in dyspnea and improvement in exercise capacity and QoL. We observed same outcomes also in mild-to-moderate patients after rehabilitation, as there was no difference between mild-to-moderate patients and severe-to-very severe patients in terms of improvement. These results supported the benefits of PR at early stages of the disease.

DISCUSSION

Our study demonstrated that PR was an effective treatment for improving dyspnea, exercise capacity and HRQOL in patients with mild-to-moderate and severe-to-very severe COPD. In contrast to the belief that the patients at early stages are asymptomatic, MRC was already two in patients with mild-to-moderate disease and it was three in patients with severe-to-very severe disease at baseline. Observed improvements for dyspnea, exercise capacity and life quality were similar in two groups after the rehabilitation program.

In a recent guideline, PR has been considered as a component of the management of COPD. Indeed, the rehabilitation application has become routine care for individuals with moderate to severe disease[8] and it has been concluded that mild airway obstruction has only few clinical consequences and does not require any intervention.[24] However, according to the Burden of Obstructive Lung Disease (BOLD) study, patients with mild COPD constituted 45% of the whole COPD patient population, and the remaining patients were assigned to GOLD Stage II to IV.[25]

There is an increasing amount of data that mild airflow obstruction is also associated with a reduction in exercise capacity in patients with COPD.[26] Impairment in exercise capacity in mild-to-moderate disease is supported by the evidence that quadriceps muscle strength and QoL is already impaired in patients with mild COPD.[8] Even before the patients at early stages of the disease are aware of their illness, they subconsciously restrict activities and therefore patients become progressively sedentary.[27] O' Donnell et al.[28] found that symptomatic COPD patients with either mild or moderate airflow limitation had evidence of physiological impairment at rest and during exercise. They had more intense dyspnea and significantly lower exercise tolerance compared to healthy control group. Ofir et al.[3] compared the symptomatic smokers who had COPD and mild airflow limitation with healthy control group. Patients with mild airflow limitation had significantly reduced exercise capacity and their exertional dyspnea rate was higher than that of healthy individuals.

The improvement in walking distance in mild-to-moderate patients was 60 m in our study. Considering that 47.5 m is the minimum clinically significant difference for ISWT in patients with COPD,[17] this may be evaluated as an increase in functional capacity which resulted from PR in mild-to-moderate patients. In Jacome's study 10, the improvement in walking distance was 32 m after intervention although patients in the study had only mild airflow obstruction and the PR program was three times a week. Improvement exercise tolerance was maintained at six and nine months after 12-week PR program for patients with mild COPD.[29] Díaz et al.[30] also evaluated the main contributors to dyspnea intensity and exercise limitation using the 6-minute walk test (6MWT) in COPD patients with mild airflow limitation, with or without activity related dyspnea. They found that inspiratory capacity (IC) decreased during exercise in dyspneic patients with mild airflow limitation and the change in IC was not only the main contributor to dyspnea intensity, but also an independent determinant of exercise capacity.

Several guidelines for COPD recommend PR for all symptomatic patients regardless of disease severity.[1,31] These recommendations are mainly based on the evidence of improvement in dyspnea, QoL, exercise endurance and functional capacity. In our study, all HRQOL domains improved after PR in mild-to-moderate patients except for the impact domain of SGRQ and dyspnea domain of CRQ. Many studies used generic instruments for measuring HRQOL

in moderate or severe disease.[32,33] Only few studies compared HRQOL in COPD patients with healthy controls and included early disease stages which was often undiagnosed.[34] Wacker et al.[35] examined time trends in HRQOL for over ten years for middle-aged persons with early COPD stages, compared to controls without airflow limitation, and analyzed the effect of COPD in the context of common COPD-related comorbidities. They concluded that, despite small changes over a 10 year time period, it was important to prevent disease progression in patients with airflow limitation. Furthermore, awareness of HRQOL impairments at early stages is of vital importance for early identification of persons at risk and starting interventions earlier is important for preventing the progression of the disease. In our study, nearly all domains of SGRQ and CRQ were improved in severe patients with the effect of PR. Additionally, both dyspnea and impact domains improved in mild-to-moderate COPD patients, but they were not statistically significantly.

The improvement of QoL for patients with mild COPD was shown in two different studies.[36,37] These results demonstrated that health domains could be improved with PR programs. The results support the necessity for robust study designs to establish these benefits at an early stage of COPD. In addition, PR has been shown to have a beneficial effect in reducing anxiety and dyspnea, also reported to be common in mild-to-moderate patients.[14,38] We observed similar improvements in anxiety and depression scores in both groups after intervention.

Nonetheless, our study has some limitations. The study had a small sample size, as the patients with mild-to-moderate disease were not easily convinced to participate in a PR program. Additionally, in the current study, the muscle strength or respiratory mechanics during exercise, which would have contributed some additional information about the mechanism(s) of the observed improvement, were unable to be measured.

In conclusion, there is a need to improve awareness of functional limitations and compromised QoL at early stages of COPD. Implementing PR at early stages of COPD may improve dyspnea, exercise capacity, QoL and psychological situation. Future studies are needed to address the mechanism of improvement in mild-to-moderate patients with COPD.

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