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Are the gains from pulmonary rehabilitation the same in idiopathic pulmonary fibrosis and other interstitial lung diseases?

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Abstract. *Introduction:* In addition to dyspnoea and cough in interstitial lung diseases (ILD), the main symptom is decreased effort capacity. Pulmonary rehabilitation (PR)is recommended besides medical treatment approaches in chronic respiratory diseases. PR programs include approaches such as exercise training, patient and family training, nutritional assessment and support, psychosocial assessment and support. COPD patients more often directed to PR programs, besides that PR is also recommended for ILD. In this study, we aimed to evaluate the PR-related gains in patinets with IPF and non-IPF ILD. *Methods:* This retrospective study that we evaluated the PR data, demographic features of the patients with ILD who completed PR program between 2017 and 2020. PR was an 8-week (2days) outpatient PR program including aerobic and strengthening exercises. The 6-minute walking test (6MWT) results, quality of life scores that were recorded at the beginning and end of the PR program were evaluated.The patients were evaluated in two groups, patinets with IPF and non-IPF ILD. *Results:* A total of 56 patients (30 IPF, 26 non-IPF) with mean age 62±10 were included in the study. Among IPF patients 23 (77%) of them were receiving antifibrotic drugs. Non -IPF patients were: Unclassified ILD 9(16%), nonspecific interstitial pneumonia (NSIP) 8 (14%), sarcoidosis 3(%5), fibrotic hypersensitivity pneumonitis (fHP) 3 (5%), sjogren 2 (4%), scleroderma 1(2%). Both in IPF and non-IPF groups improvement in 6MWT, SGRQ total score after PR were statistically significantly improved (p= 0.001, p=0.002), (p= 0.001, p=0.018). Inspiratory muscle evaluation, MIP statistically increased after PR both in IPF and non-IPF patients (p= 0.015, p=0.028). There no significant differences in gains after PR program in walking capacity, quality of life, maximum inspiratory pressure between IPF and non-IPF patients. *Conclusion:* PR programs provide significant gains both in patints with IPF and non-IPF ILD. It is important that patients should be directed to PR programs in the early stages of ILD.

Key words: pulmonary rehabilitation, idiopathic pulmonary fibrosis, interstitial lung diseases, antifibrotics, nonpharmacological IPF management, quality of life, 6MWT

Introduction

Interstitial lung diseases encompass a wide range of diseases that can be caused by different pathophysiologies, starting with lung parenchymal damage and resulting in fibrosis in some parts. ILD shares similar features like pulmonary deterioration and fibrosis that causes lung volume restriction and impairment in gas exchange (1,2).

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Shortness of breath, which initially occurs during exertion in patients, begins to occur at rest in the course of time. Shortness of breath causes limitation in daily life caused by cough and weakness resulting social isolation, decrease in quality of life, depression and increased anxiety. In addition to shortness of breath and cough, the main symptom in interstitial lung diseases (ILD) is decreased effort capacity (1,3).

All these factors poses exercise limitation and dyspnea, that are important symptoms that limit daily life activity and impairment in quality of life in ILD. There is a decrease in lung function and O2 transition due to O2 transmission decreases due to weakened gas exchange as a result of fibrosis (4,5).

Alongside pharmacotherapy with antifibrotics for IPF patients or corticosteroids in other ILD to slow down the progression of the disease, pulmonary rehabilitation has started to gain importance as a non-pharmacological approach to increase the decreased exercise capacity (6,7,8,9).

Pulmonary rehabilitation (PR) is an interdisciplinary program that is recommended in addition to medical treatment approaches in chronic lung diseases with reduced daily living activities, with the main goal of helping them to achieve the best functional level and quality of life they can have individually.PR programs mainly include approaches such as exercise training, patient and family education, nutritional assessment and support, psychosocial assessment and support (10,11).

In general, patients with chronic obstructive pulmonary disease are referred to pulmonary rehabilitation (PR) programs, PR is also recommended in interstitial lung diseases. It is recommended that patients be referred to PR in the early period in interstitial lung diseases. IPF guidelines recommend pulmonary rehabilitation (PR) as the main component of nonpharmacological therapy, however, the long term effects evidence is still contoversial (10,11). Studies comparing the gains of pulmonary rehabilitation of IPF and non-IPF interstitial lung diseases are limited (12).

In this study, it was aimed to evaluate the PR-related gains in ILD with idiopathic pulmonary fibrosis (IPF) and non-IPF patients.

Methods

This retrospective cohort study was designed in the pulmonary rehabilitation unit of a tertiary training hospital for chest diseases and thoracic surgery between January 2017 and December 2020.

The study was approved by the ethics committee (protocol code:116.2017.R-227) accordance with the Declaration of Helsinki. Informed written consent was provided from all patients.

The rehabilitation data and demographic characteristics of the patients with the diagnosis of interstitial lung disease who completed the 8-week (2 days per week) outpatient PR program were evaluated retrospectively.

Patients

Patients with ILD attended to outpatient PR program were evaluated for the study. The patients were evaluated in 2 groups as IPF and non-IPF patients.

Patients with ILD referred and completed the 8 week PR program, age over 18 years included and patients who discontinued the program, previously involved in PR program or can not perform the 6 minute walk test were excluded from the study.

IPF patients: Those diagnosed with IPF according to the 2022 ATS/ERS/ALAT/JRS IPF guideline were included (1).

Non-IPF patients: Patients with Interstitial lung diseases, other than IPF (Nonspecific interstitial pneumonia (NSIP), Sarcoidosis (satge 3), fibrotic hypersensitivity pneumonitis (fHP), scleroderma, sjögren and unclassified ILD) referred to PR program.

Patients demographics, type of ILD, comorbidities, treatment, presence of LTOT (long term oxygen therapy), dyspnea and fatigue score, exercise capacity, quality of life, anxiety and depression, muscle strength, body composition were evaluated from PR patient data.

The flowchart summerizes the study protocol (Figure 1).

Measurements

PR program data was collected in files including measurements performed before and at the end of the PR program (total 16 sessions).

Pulmonary function tests

Spirometry was carried out before and after PR with ZAN 300 and DLCO performed with Jaeger MS-PFT analyzer unit.

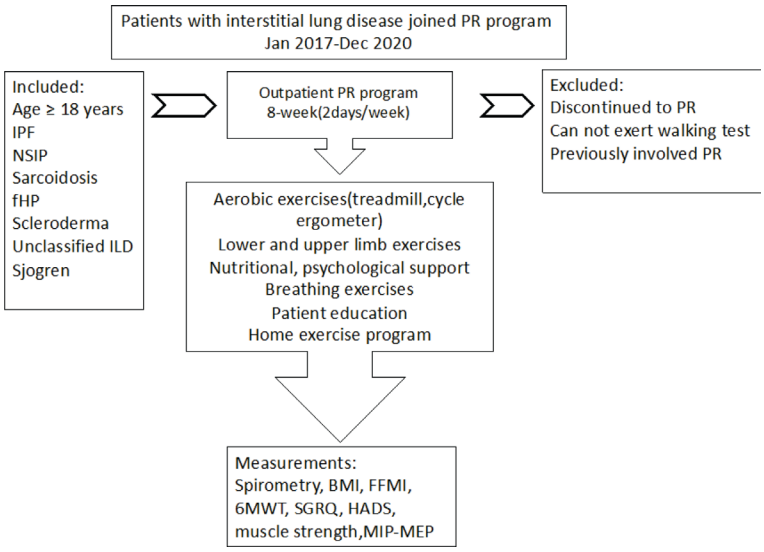

Figure 1. Summary of the study protocol.

Body composition measured bybioelectrical impedance analyzer (Tanita BodyComposition Analyzer, Model TBF-300), body mass index and fat-free mass index were recorded.

Dyspnea was evaluated with the Modified Medical Research Council (mMRC) (13).

The 6-minute walk (6MWT) test was performed to evaluate exercise capacity.6MWT was performed convenient to the guidelines ofthe American Thoracic Society. The test performed in a 30-m-long corridor, arterial blood pressure, Modified Borg score was asked to the patients to evaluate dyspnea and fatigue before and after the walking test. Oxygen saturation was followed during the test, the total walking distance was enrolled at the end of the test (14,15,16).

Muscle strength

Peripheral muscle strength: hand grip strength was measured by Baseline smedley digital hand dynamometer model 12-0286. Right and left side measurements were made, the best value of the three measurements was reported.

Respiratory muscle strength: Maximal inspiratory pressure (MIP) and maximal expiratory pressure (MEP) are evaluated with *MEC PFT Systems Pocket-Spiro MPM100* the best value of the three measurements was reported (17,18).

Questionnaires

The hospital anxiety and depression questionnaire (HADS) used to evaluate anxiety and depression level (19,20).

Health-related quality of life was assessed with the St. George'sRespiratory Questionnaire (SGRQ) (21).

PR program

The outpatient PR program was delivered by two physiotherapistsin 8 weeks (2 days/week). The sessions included aerobic exercises with treadmill, cycle ergometer, upper and lower limb (0.5-1 kg dumbbell / Cosfer dumbbell sets) and strengthening exercises. Exercise programs and workload intensity were targeted at 60%-85% of the maximal workload information optained from 6MWT measurements and increased in accordancewith each patient's improvement.Patients receiving long-term oxygen therapy (LTOT) also received O_2 during the sessions and if SpO_2 decreased below 90%. Breathing exercises and energy conservation techniques were also included in the PR program.

To improve patient compliance a written diary for home-exercise program (including exercise figures).

Psychological and nutritional support was given when patients' needed. Weekly information meetings

were held with patients and their relatives about their disease.

Outcomes

The primary outcome was the fulfillment of the PR program, improvement in exercise capacity, quality of life and anxiety depression scores.

Statistical analysis

The SPSS (Statistical Packege for Social Sciences) portable 20.0 package program (IBM Corp.; Armonk, NY, USA) was used for statistical analysis. Kolmogorov-Simirnov test was used to define non-parametric and parametric values. The Wilcoxon test was used to compare the non-parametric changes within the groups and the parametric changes within the groups were analyzed with the t-test. The median with interquartile range (IQR) was employed for non-parametric continuous variables, and mean ± standard deviation (SD) was used for parametric continuous variables. Count and percentage were used when applicable. A p value < 0.05 was accepted as statistically significant.

Results

A total of 56 patients (30 IPF, 26 non-IPF) with mean age 62±10 were included in the study. Among IPF patients 23 (77%) of them were receiving antifibrotic drugs.

Non -IPF patients were: Unclassified ILD 9(16%), nonspecific interstitial pneumonia (NSIP) 8 (14%), sarcoidosis 3(%5), fibrotic hypersensitivity pneumonitis (fHP) 3 (5%), Sjogren 2 (4%), scleroderma 1(2%).

Table 1 and Table 2 summarises the demographic characteristics of patients with ILD.

Table 3 shows the changes of IPF and non-IPF patients after PR program. Both in IPF and non-IPF groups improvement in 6MWT, SGRQ total score after PR were statistically significantly improved (p= 0.001, p=0.002),(p= 0.001, p=0.018). Inspiratory muscle evaluation, MIP statistically increased after PR both in IPF and non-IPF patients (p= 0.015, p=0.028).

Table 4 reveals the differences in gains after PR program in walking capacity, quality of life, maximum inspiratory pressure between IPF and non-IPF patients. In both groups there were no significant difference in gains (p=0.63, p=0.77, p=1.0).

Table 1. Demographic characteristics of patients with ILD

Demographic characteristics of patients N=56	
Age, (year) , mean±SD	62±10
Gender, (n%)	
Female	15 (27)
Male	41 (73)
IPF, (n%)	30 (54)
Antifibrotics	23(77)
Pirfenidone	17 (57)
Nintedanip	6 (20)
Non-IPF, (n%)	26 (46)
Unclassified ILD	9 (16)
Nonspecific interstitial pneumonia (NSIP)	8 (14)
Sarcoidosis (stage 3)	3 (5)
Fibrotic hypersensitivity pneumonitis (fHP)	3 (5)
Sjögren	2 (4)
Scleroderma	1 (2)
Pulmonary function tests	
FCV %, mean±SD	64.8 ± 19.6
DLCO %, mean±SD	47.5 ± 16.6
MRC, median (IQR)	3 (2-3)
Smoking status, n(%)	
Nonsmoker	16 (29)
Active smoker	3 (5)
Exsmoker	37 (66)
Smoking packyear, median (IQR)	30 (21-43)
BMI kg/m^2, mean±SD	28.44 ± 4.2
FFMI kg/m^2, mean±SD	19.9 ± 3.7
Comorbidities, n(%)	
Hypertension (HT)	18 (32)
Diabetes mellitus (DM)	10 (18)
Coronary artery disease (CAD)	8 (14)
Gastroesophageal reflux	7 (13)
Cardiac arrhythmia	4(7)
Hypothyroidism	3(5)
LTOT	20 (36)

ILD: Interstitial lung diseases, mMRC: modified medical research council dyspnea scale, BMI: Body mass index, FFMI: Fat free mass index, FVC: Force vital capacity, DLCO: Diffusing capacity for carbon monoxide, LTOT: Long-term oxygen therapy.

Discussion

In this study we aimed to evaluate the PR-related gains in IPF and non-IPF patients, and the results revealed that PR program provide significant

Table 2. Demographic characteristics of patients with ILD

Demographic characteristics of patients with ILD N=56				
	TOTAL	**IPF N=30**	**NON-IPF N=26**	***p***
Age, (year) , mean±SD	62±10	61±10	63±9	0.45
Gender, (n%)				
Female	15 (27)	1(3)	14(54)	*0.001*
Male	41 (73)	29(97)	12(46)	
Pulmonary function tests				
FCV %, mean±SD	64.8 ± 19.6	67.1±18.6	63±21	0.46
DLCO %, mean±SD	47.5 ± 16.6	47.3±16.6	48±17	0.98
mMRC, median (IQR)	3 (2-3)	3(2-3)	3(2-3)	0.41
Smoking status				
Nonsmoker	16 (29)	5(17)	11(42)	0.034
Smoking packyear, median (IQR)	30 (21-43)	38(20-40)	30(25-50)	0.55
BMI kg/m^2, mean±SD	28.44 ± 4.2	28.8±3.2	28±5	0.50
FFMI kg/m^2, mean±SD	19.9 ± 3.7	21±2.2	18.6±5	*0.02*
LTOT	20 (36)	11(37)	10(35)	0.87

Table 3. The changes of IPF and non-IPF patients after PR program

	IPF N=30			**Non-IPF N=26**		
	Before PR	**After PR**	***p***	**Before PR**	**After PR**	***P***
Exercise capacity						
6MWT (m) , mean±SD	366±133	421±141	**0.001**	340±118	402±156	**0.002**
Quality of life						
SGRQ, mean±SD						
Symptom	63.1±22.9	53.9±22.9	**0.019**	61.7±24.3	51.6±21	**0.004**
Activity	69.5±22.3	60.4±23.3	**0.015**	74.3±20.1	66.6±23.2	0.17
Impact	50.4±26.8	37.3±22.2	**0.001**	53.2±23.9	44.2±29.9	**0.044**
Total	59.4±21.8	47.0±20.5	**0.001**	60.9±19.8	49.3±25.1	**0.018**
HADS						
Anxiety, median(IQR)	7(3-10)	4(2-6)	**0.005**	8(4-11)	8(3-10)	0.22
Depression	7(3-13)	6(4-8)	**0.027**	8(3.5-10)	7.5(2.3-9.8)	0.17
Muscle strength, median(IQR)						
Hand grip,kg right	34.5(29.6-39.7)	35.2(30.2-41.3)	0.98	24.7(20.9-29.3)	28.1(22.5-31.1)	0.09
Hand grip,kg left	33.9(27-37.4)	32.8(27.9-40.3)	0.52	22.1(20-25.9)	25(19.3-26.5)	0.34
MIP cmH2O	74(62.5-97)	87(66-110.5	**0.015**	57(48-82)	69.5(56-134.5)	**0.028**
MEP cmH2O	94(73.5-118.5)	110(95.3-126.5)	0.07	83(55-110)	96(63.8-112.5)	0.27
BMI kg/m^2, mean±SD	28.8±3.3	28.6±3.3	0.16	27.4±4.7	26.3±7.0	0.45
FFMI kg/m^2, mean±SD	20.6±1.7	20.6±1.7	0.76	18.3±4.9	21.6±11.0	0.10
FVC %, mean±SD*	64.5(53-82.5)	59(42.3-78.5)	0.13	71(46-81)	70(49-85)	0.16
DLCO %, mean±SD**	42.5(34.5-59.5)	45.5(41-62.3)	**0.007**	43(30.5-48)	38(27-48.5)	0.68

6MWT: 6 minute walk test, SGRQ: St.Geaorge's respiratory questionnaire, HADS: Hospital anxiety and depression scale. Abbreviations: MIP: Maximum inspiratory pressure ,MEP: Maximal expiratory pressure,BMI: Body mass index, FFMI: Fat free mass index, FVC: Force vital capacity, DLCO: Diffusing capacity for carbon monoxide,*FCV and DLCO were avaible in 20 patients among IPF, and in 19 among non-IPFpatients.

Table 4. The differences in gains after PR program in walking capacity, quality of life, Maximum inspiratory pressure between IPF and non-IPF patients

	IPF	Non-IPF	*p*
Δ 6MWT(m), mean ±SD	59.1 ± 55.3	62 ± 81.1	0.63
Δ SGRQ total score, median(IQR)	13.1 (4.5 – 21.3)	5.5 (-2.8 – 15.9)	0.77
Δ MIP cmH2O, median(IQR)	6 (3 – 18)	7 (3 - 21)	1.0

Abbreviations: 6MWT: 6 minute walk test, SGRQ: St. Geaorge's respiratory questionnaire, MIP: Maximum inspiratory pressure.

gains in exercise capacity and quality of life both in IPF and non-IPF patients.

Interstitial lung diseases begin with lung parenchymal damage and can progress to fibrosis in some areas, abnormal gas exchange, rapid oxygen desaturation during exercise resulting in dyspnea, decreased exercise capacity and deterioration in quality of life and social isolation. Among other reasons that cause a decrease in exercise and functional capacity are; the onset of the disease at older ages, progressive and impaired gas exchange (22).

Nishiyama O et al also detected reduced quadriceps weakness correlated with exercise limitation and lung function impairment in IPF patients (23). Increased afferent reflexes originating from the lung or chest wall, thus limiting exercise tolerance may be attributed to higher respiratory drive during exercise (23). In a recent study we observed that pectoralis muscle strength was significantly decreased in elderly patients with IPF and pectoralis muscle strength was associated with pulmonary function as well as being an independent predictor for FVC% (24). Badenes-Bonet et al mentioned sedentary life in IPF patients with Gender-Age-Physiology) GAP III stage, BMI ≥ 25 kg/m^2 and lower lower quadriceps strength or lower maximum inspiratory pressure (25). In the present study the mean BMI of ILD patinets was 28.4 ±4.2 kg/m^2.

Both IPF and other interstitial lung diseases cause the development of hypoxia and pulmonary hypertension in the future with the restriction, progressive fibrosis, and gas exchange anomalies they create. This is very important in the management of the difficult disease process. In addition to medical treatments such as corticosteroids and antifibrotic drugs, exercise-based pulmonary rehabilitation programs are gaining importance as a non-medical treatment method. All these reasons reveal why rehabilitation should be included in IPF patient management (26).

In this study both IPF and non-IPF patients accomplished improvement in quality of life (SGRQ). Gains in 6MWT was improved in both groups, both groups achieved a better gain than minimaly significant value for chronic respiratory diseases (27,28,29). Tonelli et al. obtained gains in exercise performance, quality of life, symptoms for both IPF and non-IPF patients in a comprehensive PR program with 24 sessions (12).

PR is an interdisciplinary treatment approach, aiming to increase physical and social performance in patients who are symptomatic due to chronic respiratory disease, have reduced exercise capacity, have limitations in daily living activities and have impaired quality of life. It is structured in line with individual needs and aims to raise it to the best level the person can have. The most important component is exercise training, moreover, evaluation of body composition, nutritional support and treatment in necessary cases, psychosocial assessment and support, patient and family training, are also important components(30). Informing patients and their caregivers about the disease, raising awareness about exercise and making behavior change to improve the physical and psychological status in order to cope with the disease are among the achievable goals of PR. Comprehensive PR programs should include aerobic exercise, strengthening and relaxation exercises, energy conservation techniques, education of the patient and their family, nutritional and psychosocial support.

In daily practice, it is observed that some ILD patients develop rapid desaturation shortly after taking action, although there is no desaturation at rest. This situation requires more attention especially in exercise training of these patients, therefore physiotherapists experienced in cardiopulmonary rehabilitation is important. Dyspnea and cough are the main symptoms of ILD, which causes a decrease in exercise capacity, fear of movement, immobility, and deterioration in quality of life. Patients who develop pulmonary hypertension in the advanced stages of the disease can be included in the program by monitoring blood

pressure, SpO2 and pulse during exercise, ensuring safe conditions for the patient and paying attention to exercise intensity. Heavy aerobic exercises that will increase intrathoracic pressure should be avoided in these patients. Additionally, patients should be carefully monitored for the risk of dizziness and syncope, and they should be advised to pay attention to these issues during exercises they do at home.

Although antifibrotic treatment has an effect on survival in IPF, these patients may still be lung transplant candidates. Another issue that emphasizes the importance of PR is that it causes difficulty during exercise in patients with peripheral muscle weakness before lung transplantation, even though ventilatory limitation disappears after transplantation. A multidisciplinary individualized PR may provide improvement in 6MWT, quality of life, help to overcome postopertaive recovery and the stress of the procedure (31,32). Fortuna et al. point out that PR in anticipation of lung transplantation and education regarding the importance of peripheral muscle and exercise capacity for better transplant outcomes were motivating factors in their study, metioning that two-thirds of subjects completed the PR program.(33) The duration of pulmonary rehabilitation programs vary 3 to 48 weeks with the frequency of the sessions ranged between 2 and 7 days per week (12,34,35).

In daily life pulmonology practice, the patients most frequently referred to PR programs are COPD patients, and while planning this study, we aimed to emphasize the importance of PR as a nonmedical treatment as well as medical treatments in ILD. On the other hand, multicenter studies are needed to determine how long-term gains in COPD patients and ILD patients continue. The effectiveness of PR is shown for the short term, the gains are shorter-term than COPD (36,37,38,39). To ensure the long-term gains, home-based PR programs can be planned supported with new technological follow-up systems such as telerehabilitation.

Arizono S et al and than Nolan CM et al. and with larger patient group mentioned the similar PR complation rates and similar benefits in exercise capacity, dyspnea and quality of life (40,41).

In this study although exercise capacity and quality of life scores improved in both groups, anxiety and depression score improved better in IPF group. This revealed the need to provide more information about patients' fears and concerns, social limitations, assessment of family support, and the development of more psychologist support (42,43). In the PR program, besides exercise sessions patients and their relatives are frequently informed about the disease, treatment, devices (LTOT) and medications by education sessions. This provides both patients and their relatives with an understanding of the disease and a more positive outlook on the disease process. Therefore, it has a positive effect on anxiety and depression. In this study since the diagnosis of some of the patients in the non-IPF disease group was unclassified ILD, it might created a limitation in terms of anxiety and depression in those patients.

The limitations of this study are; this is an single center study, the number of patients is not large, this is a retrospective study, long-term follow-up results could not be added to the study due to distruptions in patient follow-up due to the Covid 19 pandemic, whereas this a real life observative study in a tertiary hospital for chest diseases.

Conclusion

As a result, PR programs provide significant gains in ILD with and without IPF. In the management of ILD, it is important to refer patients to PR programs in the early stages of the disease when the disease is diagnosed.

Acknowledgements: Some of the data from this study were presented at the 2020 European Respiratory Society (ERS) International Congress, and then the study was continued and the number of patients was increased.

Conflict of Interest: The authors declare they have no conflict of interest with respect to this research study and paper.

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